Comments received on discussion papers informing the report of the UN Interagency Coordination Group on AMR to the UN Secretary-General

- **Members States**
  - Australia
  - Brazil
  - Canada
  - Finland
  - France
  - Germany
  - Ireland
  - Japan
  - Morocco
  - Netherlands
  - Norway
  - Pakistan
  - Sweden
  - Switzerland
  - Turkey
  - Ukraine
  - United Kingdom
  - United States
- **CSOs and NGOs**
  - Antibiotic Resistance Coalition
  - American Society for Microbiology
  - Edinburgh Infectious Diseases
  - Global TB Caucus
  - Health for Animals
  - Infectious Diseases Society of America
  - International Union Against Tuberculosis
  - Médecins Sans Frontières Access Campaign
  - RESULTS UK
  - United States Pharmacopeial Convention
- **Private**
  - Aequor, Inc. and Aequor, Ltd
  - AMR Industry Alliance
  - Elanco
- **Individual**
  - Carol Geraldine C. Pablo
  - Melquiades Huauya Ore
  - Patricia Huijbers, Joakim Larsson, Carl-Fredrik Flach
  - Céline Pulcini
  - Natalie Schellack and Hannelie Meyer
  - Sara Tomczyk
- **Other**
  - Gavi, the Vaccine Alliance
  - Global Antibiotic Research & Development Partnership
  - Joint Programming Initiative on Antimicrobial Resistance
  - Medicines Patent Pool
  - South Centre
  - Wellcome Trust

Member States

Australia

From:	WHO
Sent:	16 July 2018 03:48
To:	IACG-secretariat
Cc:	WHO; RICHARDS, Laura; PATFIELD, Jack; HOLDWAY, Jacinta; HPPB Coord; VERCAMMEN, Laurence
Subject:	WHO - The UN Interagency Coordination Group on Antimicrobial Resistance [SEC=UNCLASSIFIED]
Attachments:	IACG_AMR_Invest_innovation_research_boost_RD_and_access_110618.pdf; IACG_AMR_National_Action_Plans_110618.pdf; IACG_Surveillance_and_Monitoring_for_AMU_and_AMR_110618.pdf
Follow Up Flag:	Follow up
Flag Status:	Flagged

Dear IACG Secretariat,

Thank you for providing us with the opportunity to comment on the first group of discussion papers.

Please find below comments from the Australian Government Department of Health. Our colleagues at the Australian Government Department of Agriculture and Water Resources have provided feedback through the OIE.

AMR: Invest in innovation and research, and boost R&D and access

International consensus is needed on what the prioritised international AMR R&D agenda is. Australia suggests that new antibiotic development should focus on priority pathogens, as identified by the WHO, and funding should be targeted to new innovative drug development, rapid diagnostics and vaccines that could be easily and cheaply used in various settings. Australia recognises the issues of driving development of new antibiotics, given the low market value (hence low return on investment), and supports the need for further work to examine market pull incentives as a valuable first step.

Australia supports measures to improve access to medicines, recognising that equitable and reliable access to safe, efficacious, quality, affordable medicines is fundamental to achieving Universal Health Coverage and the Sustainable Development Goals (SDG). There are many factors that impact on access to medicines across all stages of the medicines chain, from financing for research and development (R&D), to regulatory processes, manufacturing, supply, reimbursement arrangements and pricing.

The paper includes a brief suggestion that the use of “delinkage” mechanisms will drive R&D solutions and ensure greater and more equitable access to new and improved products that represent effective solutions to AMR. Australia’s position is that the link between medicine prices and R&D costs is not clear-cut and we do not support statements that imply that de-linking R&D costs and medicine prices will improve access to affordable medicines.

On Section 2.2, noting the range of existing initiatives already place, Australia considers that it may be most appropriate and efficient to extend the mandate of one or more of these fora to explicitly include AMR, rather than investing in the establishment of new, stand-alone mechanisms which could be costly, duplicative, and further contribute to siloed approaches.

Australia broadly supports the guiding principles as outlined in the paper, however we note that some flexibility may be needed in principle 1 ***Global public benefit***, to recognise and allow for national and regional resistance challenges to be appropriately prioritised and addressed. The principles could also be incorporated into the tripartite group’s upcoming framework and the mandate of the Global AMR R&D Hub.

AMR: National Action Plans

Australia supports the development of an investment framework, led by the World Bank Group (to be presented to the UN General Assembly in September 2019) as an important mechanism to help identify countries' planning to date and costed priority areas for action so that funding for countries needing assistance with implementing NAPs can be targeted. As the discussion papers note, Member States, particularly LMIC, face varied challenges when it comes to developing and implementing National Action Plans (NAP). Regional and global approaches should always consider the national circumstances of countries in implementing AMR policies. Australia supports the need for the 'decision tools' described on page 13, although it is unclear if these will be developed as part of the WB investment framework, or separately. Such tools and guidance on 'best buys' should also be mapped against the GAP objectives.

Australia supports information-sharing forums as a concrete capacity-building action to assist with developing NAPs through sharing insights into what worked well and what didn't. In addition to the tools and forums identified in the paper, Australia suggests that the AMR Action Package under the Global Health Security Agenda could play an important role in facilitating sharing of national experiences.

Both Universal Health Care (UHC) and the SDGs are concerned with the provision of health and wellbeing for all. These are multisectoral issues, that extend beyond traditional notions of healthcare and into other fields. As such, the multisectoral nature of AMR is an issue of great importance to the UHC and SDG agendas. Failing to adequately address AMR will impact on our collective ability to implement UHC and to achieve the SDGs, and as such, these broader agendas provide an important additional lens for further awareness raising and momentum for action on AMR.

Given this paper talks about the importance of 'awareness and political will', it would be valuable to mention the efforts of the G20 to keep AMR on the political agenda, including establishing a dedicated Health track, and AMR being a key focus on discussions in 2017, 2018 and 2019. G20 members committed to 'lead by example and to have in place multi-sectoral National Action Plans on AMR based on the One Health approach and in line with the WHO Global Action Plan on AMR' (2017 Declaration). In 2017 G20 Leaders committed to 'further examine practical market incentive options', in relation to the development of new antimicrobial medicines and diagnostics. It is important to ensure that this commitment is followed through and remains on the G20 agenda.

Surveillance and monitoring for antimicrobial use and resistance
Australia acknowledges that an integrated surveillance system built on a one-health approach and compatible with international data models is optimal. Australia also acknowledges that establishing a national surveillance system for AMR is complex and resource intensive. While Australia has established a system for antibacterial use and resistance in human health, it has not yet expanded into other antimicrobials, nor integrated animal or plant health or embedded surveillance in the community health sector. Australia would be very interested to learn from the experiences of countries which have successfully implemented a one-health surveillance system.

Australia supports the Joint External Evaluation assessment as a valuable process to assess existing systems.

Do not hesitate to contact us should you have any queries regarding our input, otherwise we look forward to seeing the second group of discussion papers once they are released.

Kind regards,

Jack

WHO Engagement — International, AHMAC and Digital Health Branch
Australian Government Department of Health

Brazil

MINISTÉRIO DA SAÚDE
Gabinete do Ministro
Assessoria de Assuntos Internacionais de Saúde

Discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General

(Brazil)

1. Antimicrobial resistance: national action plans (NAP).

The document is quite general and complete. It covers several critical issues for formulation and implementation of NAPs. About 100 countries already have NAPs and 67 more are in the process of formulation.

Regarding the listed implementation difficulties of the NAP, it is interesting to mention the issue of political awareness and decision making, as well as the historically difficult issues of financing and bureaucracy in developing countries. Before establishing sources of funding, AMR should be treated as a priority, as a public health issue. So, it is necessary to convince public opinion, the common citizen and also the authorities. In the case of Brazil, the option for fiscal austerity has been disabling some health care programs and public policies in general.

The text addresses the difficulties and tools for implementation of the NAP, but it doesn't clearly address the policy objectives: would it be the reduction of antimicrobial consumption? Prevention of bacterial infection? The development of more powerful drugs? The flow of AMR between humans, animals and plants?

"Building consensus among diverse stakeholders to raise awareness in the general public". The question of the difficult interaction with the different sectors involved in the formulation of the NAP: health, environment, agriculture and veterinary were conveniently addressed. Brazil is a big exporter of food, with highly represented economic interests, whose focus is agribusiness, income, foreign exchange and generated jobs. It contrasts with the focus of collective health, but specifically, on health surveillance, the risk mitigation. Are there other sectors that can be benefit from the use of antimicrobials like the pharmaceutical industry, especially in the case of generic or non-patent medicines? It is important to discuss the economic impact of AMR's actions. Dialogues with productive sectors are necessary, not only with big companies and their representatives.

The text talk about tools such as discussion forums among the various sectors and communication actions to raise awareness of the importance of the topic. It suggests that case studies and use of robust data and technical information as a means of convincing. But perhaps it should address more clearly arguments based on economic

rationality as a way of sensitizing productive sectors. How much resources would be saved with an effective AMR policy? How identifying opportunities to invest in AMR-sensitive? The text say that AMR's actions could be interesting for private health agents, in reference to NAP's financing possibilities: Countries should ensure the right investment and regulatory environment for, and develop partnerships with, the private sector to ensure that it contributes fairly to the cost of antimicrobial production and clean up (be it antibiotic agents, private health care provision or the food industry). It should be clearer. How it can be a good business? Which kind of industry could be interested?

In topics like this one: cannot access enough resources to finance the plan's activities, such as for the capacity and means for better infection prevention and control (in humans and animals) and resources for outreach, access to clean water, sanitation and hygiene (WASH), human and animal, waste management and building and equipping microbiological laboratories. The text touch the old discussion of basic attention in Health particularly in developing countries: cross-sectoral theme: basic education e sanitation. Sometimes an investment in education or basic sanitation can produce more impact in health indicators than a direct investment in health. Another structural challenge for low- and middle-income countries (LMICs) is that the difficult of access medicines is more dangerous than its excessive use.

The IACG document contemplated some points like the importance of international cooperation and collaboration to NAPs implantation like “Cooperation improves national, regional and institutional governance in addressing AMR”. It is important to make some pression in the politic level, inclusive with commitments and agreements. How to make NAP interesting for some agents or maybe obligatory?

One relevant point of this document is the thought about “Prioritize actions on the basis of what is feasible at local and national levels (including within existing programmes) and which actions likely to have the greatest impact on their own citizens and communities. It is interesting to source to convergence and respect the countries experiences. Regional cooperation includes shared platforms and joint initiatives in a range of activities, from funding to knowledge exchange, and economies of scale.

2. Surveillance and monitoring for antimicrobial use and resistance.

We understand that this document is a compilation of what already exists worldwide about AMR monitoring and surveillance, with the objective of identifying obstacles and opportunities for improvement. Regarding Brazil, most of the answers to the questions are political / economic. We refer the contributions to some questions.

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?

The biggest difficulty is the lack of a national database that receives resistance data from isolated micro-organisms of humans, animals and food. Moreover, despite the

various guides cited in the document, each area (clinical, animal and food) has a conception of risk and tries to establish its priorities in isolation.

How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?

Private sector data could be entered into public systems, provided that laboratories meet the same standards established for public laboratories and that these data are identified at private institutions. It is also important that filters are inserted capable of excluding private data, if it is necessary to carry out evaluation only of the public data.

3. Antimicrobial resistance: Invest in innovation and research, and boost R&D and access.

The document addresses obstacles and opportunities for the implementation of actions geared to the Strategic Objective 5 of the GAP. The document is very precise in identifying the obstacles, describing them and pointing out in which phases of research and development of health technologies such obstacles are present in the fields of human, animal and plant health.

In addition, it systematizes the opportunities for stimulating, fostering and financing R&D and access to health technologies, both globally and regionally, which may include AMR. The “de-linkage” incentive mechanisms proposed in the document are concrete and feasible, but there may be resistance from health authorities in countries where such mechanisms are in conflict with current legislation. Thus, the functioning of these mechanisms depends on the political awareness and engagement of the authorities and political commitment.

Canada

Combined input from the Government of Canada on IACG Reports

1) Antimicrobial resistance: Invest in innovation and research, and boost R&D and access

General Comments on the R&D/R&I Paper

- The document on R&D mainly emphasizes response to AMR in terms of antimicrobials, diagnostics and vaccines. The concept of "alternatives to antibiotics," although mentioned in the document, needs to be further developed. Biologic alternatives to antibiotics including phage-therapy, antimicrobial peptides and pre- and probiotic is an emerging focus in fundamental and pre-clinical science. These and other "alternatives" are promising areas for coordinated R&D investment; and this theme should be integrated into the document.
- The emphasis in the document for increased investment and coordination of R&D efforts should be reiterated, given that AMR research is tremendously underfunded and the global scale of the problem.
- The need for both push and pull mechanisms that support fundamental science should be reiterated.
- A greater alignment among research funders (e.g. JPIAMR).
- Open platforms for coordinating research efforts (e.g. JPIAMR Virtual Research Institute).
- Continue to follow a One Health approach.
- Reiterate the need for all types of health research including basic science, clinical science, health services and population health research.

a) Research and development:

How could R&D funding be better channeled?

- Coordination of research activities at a global level would increase the value of R&D outcomes relative to the funds invested.
- It may be helpful if organizations that establish priorities actually had funding to ensure the necessary R&D was undertaken. While the launch of the Global AMR R&D Collaboration Hub is encouraging, it is yet another organization (not a funding body) that will establish priorities in alignment with those of the WHO, FAO, and OIE to merely "inform and collaborate" on a global, political level; "identify and prioritise R&D gaps" and facilitate resources; and promote increased investments into AMR R&D, maintaining awareness at all levels.
- Greater coordination among existing funding organizations, perhaps even pooling resources, could ensure priority R&D is undertaken at the intensity required and that the "best in the world" are engaged to undertake it. At a minimum, ensuring each is aware of what the other is doing.
- Use dedicated Requests for Applications to fill the current AMR R&D gaps.
- Use the expertise and infrastructure of the existing funding agencies (such as NIH, MRC, Welcome Trust, Gates, etc.) to fund application, review and distribution.

- The WHO is encouraged to identify horizontal technologies, including AI and other digital technologies, as a most efficient means to develop solutions to address AMR across all diseases, and therefore as a way to channel resources more efficiently. Canada could leverage its strong expertise in academia and in clinical trials to further contribute to the global efforts to address AMR. Investments of $107 million, made through the Canadian Institutes of Health Research between 2012 and 2017, have contributed to strengthening research in areas such as antimicrobial discovery, target identification, alternatives, diagnostics, surveillance and stewardship.

What will it take to increase and sustain donor and private funding of R&D in AMR?

- Donor and private funding is likely to depend on two key factors: awareness of the issue and return on investment. Therefore, efforts should continue to raise national, regional and global awareness of the staggering consequences of diminished R&D to address AMR. Return on investment could be financial (for shareholders) or ease of disease burden (for philanthropists). For shareholders, discussions on economic incentives (i.e. market entry rewards and advance market commitments) should continue so that a financial benefit is perceived to be achievable. For philanthropists, R&D progress should be communicated broadly, including how such progress will be translated to aid low and lower-middle income countries.
- Private investment will depend on ROI – novel methods (as outlined in the report) are required.
- Donor funding likely dependent on demonstrating real results which would benefit from better channeling of R&D funding.

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

- Those identified in the report are all likely helpful.
- Five main challenges in human health have been identified. To address challenges 1 (There is uncertainty in the expected return on investment of antibiotics) and 2 (Unclear market potential), discussions should continue at the national and global level to identify appropriate economic incentives. With respect to challenges 4 (Clinical trials) and 5 (Regulatory pathways), international regulatory agencies should aim to develop harmonized clinical trial requirements, while also minimizing national regulatory burden through targeted review processes, to the extent possible. For challenge 3 (Scientifically complex fundamental research and costly preclinical research), the scientific complexity of R&D can only be addressed through additional resources for basic and preclinical research. Ideally, sustained funding for R&D coupled with appropriate incentives and reduced regulatory burden would be sufficient to attract and retain quality researchers in basic and preclinical science.

How should the design of incentive mechanisms be coordinated at the global, regional, and national levels?

- Incentive mechanisms are currently being examined at the national level by a number of countries and this should continue. However, appropriate market entry rewards have been estimated at approximately $1 billion (O'Neill report, DRIVE-AB report), a figure that is difficult for one country to put forward alone. Nor should a single country bear the burden of financing such incentives, given

the potential global benefit. Therefore, economic incentive mechanisms should be coordinated at the global level. Similarly, while steps can and should be taken nationally to address regulatory burden, harmonization of data requirements at the regional or global level, to the extent possible, would likely have the most impact.

- Possibly provide for some reciprocal recognition of antibiotic approvals among countries – i.e. if an antibiotic approved in one jurisdiction, approval in another should, if not automatic, be made easier.
- Better coordination between the various global initiatives would better support a more effective approach to dealing with AMR in order to ensure the alignment of efforts. Coordination across existing initiatives could be improved globally to avoid duplication. (Current global initiatives include CARB-X-Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, launched in 2016 (US$ 455 million over 5 years); GARDP: the Global Antibiotic Research & Development Partnership, established in 2016 by WHO and partners to support R&D on antibiotics (US$ 69 million raised by September 2017) and JPIAMR: Joint Programming Initiative on Antimicrobial Resistance, which finances basic and preclinical research (US$ 80 million to date)).
- Incentives mechanisms (push and pull mechanisms) at the national level may depend on the specific approach of that specific jurisdiction to encouraging the R&D pipeline (i.e. some countries may use more push incentives- i.e. tax credits- whereas other countries may prefer pull incentives –i.e. market rewards-). Globally, assuming a global fund would be established, issues may arise around what incentive mechanisms would be used, how is effectiveness measured, and how would access to any new drugs be administered (especially to low and middle income countries).

How could current efforts in R&D coordination be strengthened?

- Increased support from national leaders.

b) Access:

Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

- Thinking outside the box in terms of relevant technologies – surveillance is critical - potential application for artificial intelligence in analyzing surveillance data, for example.
- Better sharing / coordination of surveillance data/best practices – creating global networks.
- Requiring companies to put in place access and stewardship plans before a new product enters the market to mitigate development of resistance (see 2018 Benchmark AMR report at: https://amrbenchmark.org/key_finding/antibiotics-in-clinical-development/)
- Delinking sales bonuses from antibiotics (also 2018 Benchmark AMR report).
- “Pooled procurement” at the international level should be further examined. Supporting pooled procurement would not only to reduce prices but, also, act as a way to enlarge market opportunities for companies involved in AMR, and as a way to respond to the “small market” challenge which limits incentives for private companies to invest in this sector. Canadian companies in AI and AMR diagnostics/prevention could greatly benefit from global procurement initiatives.

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

- If the question relates to the creation of a new initiative around access to medicines, this is a broader, cross-cutting issue that would require additional consultations and discussions before any decision could be reached. There is a need to ensure alignment with broader positions and discussions in this area.
- Regulators should continue to update their regulatory systems to expand access to AMR-related health technologies and address the challenges identified. As a specific example, Health Canada is currently looking at improving the regulatory review of drugs and devices by rethinking its regulatory system so that it adapts to changes in health care delivery while giving people faster access to the drugs and medical devices they need.
- This plan includes providing more timely access to drugs and devices, including drugs for the treatment of AMR and other unmet medical needs by:
    - Expanding the priority review process, to decrease review time for products needed by the health care system.
    - Aligning our reviews with Health Technology Assessment.
    - Renewing the Special Access Programme to improve access to products that are not authorized for sale in Canada.
    - Early scientific advice to manufacturers of drugs and medical devices.
    - Building better access for AMR diagnostic kits and expediting these applications.
    - Formalizing pre-submission scientific advice for the medical devices industry to define specific review requirements.
    - Making better use of real-world evidence to support regulatory decisions across a product's lifecycle for both drugs and medical devices. Real-world evidence is data collected outside the strictly controlled environment of clinical trials (for drugs) and investigational testing (for devices) once the product is marketed.
- The early scientific advice to manufacturers initiative is intended to have the regulator and Health Technology Assessment (HTA) organizations working together to improve and expand access to AMR-related health technologies and other unmet medical needs.
- Before discussing the expansion of existing initiatives to include AMR, or the creation of new initiatives, a thorough understanding of what current initiatives are covering and where there are opportunities for synergy or linkage would be helpful, to avoid the proliferation of initiatives in this space.
- There could be an international database of who is doing what and more importantly sharing of results of R&D.

c) Cross-cutting topics in R&D and access:

How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

- Nil

d) One-health approach:

Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

- Data integration and analysis under One Health lens.
- Unified global surveillance systems tracking AMR pathways and providing real time “alerts”.

How and which organization(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?

- Close coordination and collaboration between the global agencies such as WHO, FAO and OIE and with other global funding agencies such Bill and Melinda Gates Fund and Wellcome Trust.
- Establish scholarship and postdoctoral training programs through professional societies and government funding agencies to ensure opportunities to train in multidisciplinary approaches to “one health”

2) Antimicrobial Resistance: National Action Plans

a) Mainstreaming:

What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?

- In this big puzzle of AMR, many pieces are still missing, and any regulations at this time may be misleading considering that the focus of work may be limited to adherence to regulations than to really understand and fill the gaps to gauge the contributions from each sector to the development of AMR in humans. Measures in place to prevent contamination by pathogenic organisms do not address spread of mobile elements containing genes conferring AMR in normally benign bacteria. We currently have a very limited understanding of the role of foods in the spread of AMR.
- Access to health care varies within and across countries. In countries with universal health coverage (UHC), the models vary widely as well. Nevertheless, UHC offers important opportunities to drive progress in AMR, for example by:
    - Including infection prevention and control measures such as vaccinations and good hygiene practices that reduce the need for antimicrobials
    - Regulating access to antimicrobials and promoting their rational use by patients.
    - Improved AMR governance and stewardship
- While implementation of IHR by each country can accelerate AMR action at global and national levels through timely monitoring, detection and reporting of public health events/emergencies of international concern, this could pose a challenge for some countries where surveillance infrastructure is fragmented across various tiers of government leading to lack of harmonized systems and data.

What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development?

- Under One Health approach, the experts from all walks of life need to understand the contribution they make, and the preventive measures they can adopt to mitigate the risks of AMR. Although political and financial support are required, a clear disconnection between policy makers and scientific community exists due to the lack of information in certain areas.
- Research and Innovations to inform evidence based AMR policies and interventions and updated international standards, guidance and tools are needed.

What forces maintain national responses to AMR in silos, and how can we overcome them?

- Some forces that could maintain national responses to AMR in silos include:
    - Lack of coordination across government line ministries/jurisdictions and between human health, animal health, agri-food and environment sectors and stakeholders.
    - Overlapping mandates and accountabilities leading to lack of clarity on who is responsible for what and a fragmented approach to tackling AMR.

    - In cross cutting areas, the will to take the leadership role and own responsibilities has been left to “others”, resulting in leaving the issue in the lurch.
- Some ways to overcome these silos:
    - Fostering a One Health approach to address AMR and improving coordination across jurisdictions, sectors and stakeholders
    - A coordinated approach that leverages comparative advantages of diverse stakeholders across sectors
    - Integrated data platforms, information/knowledge exchange/sharing
    - Leadership/ Champions
    - Education, awareness raising
    - Incentives to farming and pharmaceutical industry to fight AMR at ground level can make a difference.

How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?

- Nil

b) Financing:

What support do countries need to translate information on the global impact of AMR into a country-specific case?

- There is an urgent need to share the data. Global travel and export/import of food has already changed patterns of AMR transmission from various human, animal, food and environmental sources to humans. With a change in the status of animal health, the export and import trends will keep changing, resulting in fluctuating AMR status/trends in a country.
- Education, training, capacity building, resources.
- Leadership, political will, capacity.
- Research to generate country-specific evidence on the burden and impacts (social/economic) of AMR.

How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners?

- AMR needs to be associated and the plans should be made along the food production line that should be mirroring the detection of pathogens. The contribution to the AMR due to environment and use of disinfectants can be well accounted.
- Making AMR a public health and political priority by building country-specific evidence on the social and economic impacts on AMR (e.g. on national GDP).
- Advocacy, education, awareness raising among policy makers.

What is the role of the international community in supporting international public goods such as AMR surveillance data?

- Countries have been under pressure to provide information to multiple fora, but many have limited tools and negligible support on diagnostic or lab capabilities. Animal health surveillance is missing either due to cost or lack of infrastructure within the countries to conduct such tests.
- Encourage country participation in global surveillance systems such as WHO's GLASS.
- Build/support country surveillance infrastructure and capacity.

How can we support decisions to balance the portfolio of investment in AMR-specific and AMR-sensitive interventions, particularly in LMICs that need support in developing public health, animal health, plant health, and environmental support services across the regulatory and operational domains?

- Nil

Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)

- Integrated surveillance models and incorporation of advanced information (Whole Genome Sequencing) into the existing data is still challenging. There should be data hubs/centres working under One Health leadership so that the scientific community does not need to work in silos.

c) Regional Cooperation:

What are the highest priorities for training in Member States with respect to NAP implementation?

- Infection Prevention and Control
- Antimicrobial Prescription Practices
- Designing surveillance based on the basic knowledge on the status of AMR. Countries should focus on how the animals are housed, how the food is processed and where the AMU is mostly used.

What platforms would be most useful for sharing success stories, example of best practice and lessons from experience in NAP development and implementation?

- OIE and WHO should be the platforms for Animal/food and human respectively.
- Regional exchanges (e.g. South-South) – online, conferences, meetings etc.
- Global, regional, national - shared online repositories.
- Centres of Excellence, Virtual Networks

What sensitivities should be considered when encouraging regional cooperation on AMR?

- Trade is one of the most sensitive issues.
- Recognition that countries are at different stages vis a vis resources and capacity to respond to AMR

- Responsibility for AMR may lie with one of more line ministries; governance arrangements are not uniform across countries.

What role should regional economic communities play in developing regional cooperation platforms? And how can they be supported?

- Regional Economic Communities such as the BRICS could play a leadership and convening role to make AMR a regional priority.
- Commit to concrete measures (resources, benchmarks, etc.) to jointly tackle AMR at country and regional levels.
- Collaborative research, tools, guidance documents, infrastructure support, etc.

3) Surveillance and monitoring for antimicrobial use and resistance

a) Integration:

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?

- Obstacles include:
  - Lack of good harmonized data for integration.
  - Lack of technical expertise (capacity) and knowledge to integrate data across sectors.
  - Lack of examples around the world on the spectrum of possibilities for data integration (which should range from basic summaries to simple figures to complex analyses - options for countries to implement according to their needs and capacities).

How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?

- Given the ease with which plasmids can move among bacteria, focus should be on the resistance markers rather than the host organism in all the streams that contribute to human AMR. Global data sharing initiatives such as the GMI (Global Microbial Identifier) should be supported. Interoperability of data should be considered, with prioritization of resources for standardization of surveillance data. Existing platforms for sharing and storing data can be leveraged.
- Canada currently includes antimicrobials sold for use on crops in our human/animal AMU comparisons. The common metric used by the Public Health Agency of Canada for reporting across these three sectors is kilograms of active ingredients.

How can initiative involving surveillance data held in the private sector be integrated into global, public reporting systems?

- Each sector should have its own set of data that can be shared on a 'need' basis. Private sectors can be encouraged to share data through the negotiation of agreements that would minimize the impact of the data sharing on the submitting organization.
- France has some examples. Transparency is key.

b) Prioritization:

What further support do countries that are establishing systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

- Financial in the form of diagnostic capacity and opportunities to work with developed countries to identify the specific issues related to the country.
- Countries need epidemiological technical expertise. That way the system can be designed from the beginning with capacity for integration or to best meet national needs. The team developing the surveillance system also needs to have both expertise in human medicine, veterinary medicine, and microbiology.

How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

- Most of the initiatives focus on sharing the information among countries at different fora. However, the group of countries usually work in silos e.g. G7, G20. Except OIE AND Codex there does not exist any international fora where the technical discussions are held on AMR. The regulatory aspect should be strengthened by investing in the alternatives.

What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?

- The data from the pharmaceutical companies should be reviewed and verified to determine the real impact these types of drugs have on AMR. This have never been discussed or identified in any global fora.

c) Comparability:

What support do Member States need to strengthen national surveillance systems and improve the quality, collection, and submission of their data to global surveillance databases?

- Political will
- Fundamentally, human resources and funding are required.

What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?

- Strengthen the AMU data and AMR data in food producing animals. Standardization of ontology used to ensure data interoperability.

What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?

- For WGS, guidance is required on how to use the sequence data in integrated analysis with:
    - AMU, and
    - identifying similarities of isolates across sectors (animal, food, humans - how similar is enough to call the isolates similar?).

d) Availability:

What support do countries require to develop and report accurate national data and share them on global surveillance systems?

- WGS data is extensive, and there do not seem to be any directions on how to use data in integrated assessment. A lot of work needs to be done in this area.

What data formats and visualization tools are most useful for reporting and further analysis?

- Canada could provide information regarding a situation in which data integration led to a successful intervention in the poultry industry with respect to resistant *Salmonella* Heidelberg.

How can lessons be learned from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?

- Nil

e) Sustainable investment:

How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?

- It may not be necessary for each country to develop these - a few good case studies pertinent to the different ranges of economic situations might be enough.

What tools are required to address the investment required for surveillance of AMR and AMU?

- Examples of the costs of incremental surveillance systems. If the new Codex work on AMR with respect to integrated surveillance systems develops a solid approach for incremental surveillance, the next step would be to add in what the potential resources might be for each increment.

What role can the private sector play in financing surveillance?

- Nil

Canada

ADDITIONAL COMMENTS FROM CANADA ON THE IACG SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE REPORT

(June 2018)

Page/Paragraph	Addition/Deletion/Quoted text	Comment
p.3/Fig.1		I quite like this figure. The only thing that is missing is that surveillance data is intended to be linked to action. This concept is part of the basic definition of surveillance. I think this point needs to be even more explicitly stated than just publication and knowledge sharing.
p.5/2nd para under 'integration across sectors'		Consider adding the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) as an example in the list of surveillance programs.
p.6/1st para under 4.1	Sample sources, microorganisms, scenarios for integration, and antimicrobial classes should all be prioritized.	For example, integration of data on AMR in generic *E. coli* could be achieved across humans, animals, and the environment.
p.6/1st para under 4.1	Effective prioritization on AMR should aim to generate the most relevant ~~public~~ health indicators	Delete 'public.' There may also be animal or environmental health indicators that could have a very important role to play in either transmission of AMR or use of antimicrobial agents.
p.6/1st para under 4.1	"…but there is no equivalent tool for countries to prioritize AMR surveillance."	Michael Garner et al developed a tool to prioritize AMR risks from a public health perspective that might be relevant to this discussion: 'An Assessment of Antimicrobial Resistant Disease Threats in Canada' (April 2015) http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0125155
p.6/1st para under International lists	"These include ….the OIE List of Antimicrobial Agents of Veterinary Importance. Both can be used in setting up and implementing national antimicrobial stewardship…"	Can the OIE list in its current format be used for stewardship?
p.9/Standardized methods for surveying AMR and AMU (entire section)		Information from AGISAR that could be added here (WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance)
p.9-10/2nd para under Alternatives to continuous surveillance	"For example, a PPS protocol for determining antimicrobial prescribing practices in hospitals….other regions"	Are there examples of similar PPS that could be mentioned here on the animal side of things?

ADDITIONAL COMMENTS FROM CANADA ON THE IACG SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE REPORT

(June 2018)

Page/Paragraph	Addition/Deletion/Quoted text	Comment
p.10/1st para under Availability	"Another major challenge, particularly in LMICs, is moving from generating data to translating it into useful information and then policy."	This is not just a challenge for LMICs, but for higher income countries as well.
p.11/3rd para under Publication of data	"For example, no information is available on AMU in plants…."	Canada has these data (plants, humans and animals), and some other countries do as well, however we only report on the percentage of total kilograms distributed for use in plants in comparison the total kilograms distributed for use in humans and animals.

Finland

Comments of the IACG discussion papers

Jari Jalava, PhD, Senior Expert

National Institute for Health and Welfare

Chairman of the MTKA

and

Nina Kaario, Senior Veterinary Officer

Ministry of Agriculture and Forestry

Food Department , Food Safety Unit

These comments are presented on behalf of the **Finnish National Expert Group on Antimicrobial Resistance Control and Prevention (MTKA)**

https://thl.fi/fi/web/infektiotaudit/yhteystiedot/asiantuntijatyoryhmat/mikrobilaake-resistenssin-torjunnan-kansallinen-asiantuntijaryhma

IACG discussion papers:

Antimicrobial resistance: Invest in innovation and research, and boost R&D and access

Antimicrobial resistance: national action plans Antimicrobial resistance: national action plans

Surveillance and monitoring for antimicrobial use and resistance

General comments

The conclusions and key messages presented in these documents are solid and realistic. Implementation of National Action Plans on Antibiotic resistance is the key issue. Despite the fact that awareness of the AMR has increased, the political commitment is still missing of which consequences are the insufficient financial resources, inadequate coordination and lack of interventions.

Specific comments

Invest in innovation and research, and boost R&D and access

Prevention and control of infections (IPC) are important measures to resists AMR as mentioned also in the IACG discussion paper dealing with surveillance. In this context, development of accurate and fast diagnostics and development of new vaccines are as important topics as is the development of new antimicrobial agents. It can be noted that development of diagnostics is not as resource intensive as development of new antimicrobials. Also research in the field of hospital hygiene and AMR epidemiology should keep in mind. If new antimicrobials are developed, IPC is the key measure to maintain their effectiveness. It is very true that R&D should be coordinated to ensure appropriate priority setting, funding allocation and unproductive duplication of activities. AMR is at the moment very popular topic, which is good, however there is a risk that resources are spread so thinly that nothing can be finalized.

National action plans Antimicrobial resistance (NAP)

As already mentioned, it is true that "In most countries, the greatest challenge is not writing a NAP but implementing it and demonstrating sustained action." This is not only problem in LMICs but also in HICs where the political commitment is missing. Mainstreaming is an important concept. More practical guidance how mainstreaming can be done is needed. Behavioral change is a concept that could also be included in the toolbox enabling implementation of NAP.

Surveillance and monitoring for antimicrobial use and resistance

This is a well written document. However, discussion of the Data Protection Regulation (like the new EU-wide data protection instrument) is missing, although this regulation has profound impact on all surveillance done at least in EU. This is especially important if a case based data is collected and submitted to the international databases like TESSy and GLASS.

It is excellent that the Tripartite is working to promote the harmonization of data from different AMR and AMU surveillance systems (TISSA). There is also need for harmonized report for policy-makers and other stakeholders in a simple format that are not too information-dense but highlight the resent development of AMR and AMU.

AMR and AMU surveillance are important and a good starting points, but alone surveillance will not stop the increase of AMR.

France

We thank IACG to give stakeholders the opportunity to share our view on the discussions of IACG group.

The key messages and questions raised by the IACG group are very interesting and challenging. You may find here the contribution of the French Ministry for Agriculture and Food.

1. Observations regarding Doc « Antimicrobial resistance: invest in innovation and research, and boost R&D and access ».

It might be interesting to also mention the JPI-AMR and EJP –One Health at the beginning of the page 8, for the R&D initiatives in animal health.

2. Observations regarding Doc « Antimicrobial resistance: national action plans ».

- **What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas? <u>No observation</u>**

- **What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development? <u>No observation</u>**

- **What forces maintain national responses to AMR in silos, and how can we overcome them?**

The way curriculum is organized in disciplines (agronomy, ecology, medicine, veterinary sciences, etc.) builds a gap between these disciplines. Competent authorities are also organized in different fields: ministry for agriculture, ministry for health, etc.

To overcome this silo effect, it is necessary to have people working together. In France, the roadmap to fight against AMR is common to several ministries. Since 2013, Ministries of Agriculture, and Health organize each year a Congress on the fight against antimicrobial resistance. They were recently joined by the Ministries of Research and Environment. Those common projects are important because meeting and discussing regularly are keys to begin overcoming the silos.

- **How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?**

It is important to enroll local partners who need to be part of the process in order to shape tailored and sustainable NAPs, as already mentioned in the document.

- **What support do countries need to translate information on the global impact of AMR into a country-specific case? No observation**

- **How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners? No observation**

- **What is the role of the international community in supporting international public goods such as AMR surveillance data? No observation**

- **How can we support decisions to balance the portfolio of investment in AMR-specific and AMR-sensitive interventions, particularly in LMICs that need support in developing public health, animal health, plant health and environmental support services across regulatory and operational domains? No observation**

- **Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)**

It is urgent to have strong scientific evidence of the efficacy and toxicology of alternatives to antimicrobials, such as herbal plants. It would also be of great help to know the economic model of impact of AMR and potential benefit of NAP.

- **What are the highest priorities for training in Member States with respect to NAP implementation?**

It is of tremendous importance to train the future pharmacists, physicians, farmers, veterinarians and the agents who inspect them to good practices of AMU. Young children should also receive intensive education on hygiene at school.

- **What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?**

A website could be efficient for countries to look for best practices or lessons that could fit their situation. It would be helpful to have a contact available for each story, in order to know in detail how good practices were successfully implemented.

- **What sensitivities should be considered when encouraging regional cooperation on AMR? No observation**

- **What role should regional economic communities play in developing regional cooperation platforms? And how can they be supported?**

Economic communities should keep in mind that harmonization in the fight against AMR is really important to avoid competitive distortions inside a region. When professionals have the feeling that they make more effort than professionals from other countries, they lose motivation and get reluctant to keep on their effort.

3. Observations regarding Doc « Surveillance and monitoring for antimicrobial use and resistance ».

- **What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?**

There are technical obstacles: how to collect and shape data given that the bacteria to target can be different. The fact that few firms are manufacturing and saling antimicrobials in the world could be an opportunity to facilitate the collection of use data.

- **How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance? No observation**

- **How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems? No observation**

- **What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU? No observation**

- **How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?**

Experts specialized in AMR surveillance strategies can help countries by working with them during the first years of surveillance implementation. Experts are able to adjust to national contexts, and to design surveillance system enabling comparable data.

- **What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?**

Sales of drugs by internet is a very complicated issue for countries, because it is difficult to track the companies and to sue them.

- **What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases? No observation**

- **What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?**

It is necessary to reconsider dosage for each "combination" bacteria – animal - antibiotic. Harmonized optimized dosages would help the collection of data of AMU.

- **What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?**

It is also necessary to set standards for antibiograms adapted to each animal species, by independent experts, such as Vetcast.

- **What support do countries require to develop and report accurate national data and share them on global surveillance systems? No observation**

- **What data formats and visualization tools are most useful for reporting and further analysis?**

It is necessary to set easy formats for data reporting. The more complicated the format is, the less chance we have that people will report data.

- **How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU? No observation**

- **How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors? No observation**

- **What tools are required to address the investment required for surveillance of AMR and AMU? No observation**

- **What role can the private sector play in financing surveillance? No observation**

Germany

From: Müller Dr., Susanna -Z23 BMG
Sent: 09 July 2018 16:45
To: IACG-secretariat
Cc: Z23 BMG
Subject: GER comments on the discussion papers prepared by the IACG

Follow Up Flag: Follow up
Flag Status: Flagged

Dear colleagues,
thank you for sharing the IACG documents and the possibility to send our comments on this papers.
Please find attached the German comments:

1. **AMR: national action plans and**
2. **Surveillance and monitoring for antimicrobial use and resistance:**

General comments:

- The document mainly refers to the situation in LMIC and therefore does not fully apply to the situation in Germany. The German Antimicrobial Resistance-Strategy "DART 2020" has been adopted in 2015 and its implementation is well underway with yearly interim reports on the implementation.
- Regarding "Regional Cooperation" are the German activities well embedded in the activities on the EU level.

From a human medical point of view, it is important to establish a stronger link to the sustainable development goals, in particular SDG 3 and universal health coverage. Surveillance and medical care, especially in the area of AMR, cannot be seen separately. In our view, it will only be possible to establish surveillance systems when it becomes clear how useful the generation of surveillance data has for immediate patient care and empirical evidence-based treatment recommendations for improving patient management. Effective health systems with appropriate core capacities for the prevention and treatment of infectious diseases are indispensable for successfully combating AMR. These include u. a. reliable information systems, availability and access to effective medicines and diagnostics (laboratories), the availability and implementation of evidence-based guidelines and treatment recommendations, well-trained and motivated medical staff, and functioning surveillance systems.

The responsibility for health systems is primarily in the hands of the public authorities. For clinical patient management as well as for the generation of surveillance data the establishment and strengthening of laboratory capacities for patient care as well as an approach that incorporates clinical, laboratory diagnostic, hospital hygiene and surveillance aspects in the form of an integrated stewardship are the prerequisite. Aspects such as access to and financing of diagnostics and antibiotics needs to be considered. If patients spend a high proportion of their income on laboratory testing and medication, there is a risk that adequate diagnostics and therapy will not take place, with concomitants of missing surveillance data and AMR development.

Answers on the guiding questions:

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?
At the meeting of the Public Health und Veterinary Health Institutes of the G20 in October 2017 among others the need for "evidence beyond ecological studies" (e.g., link sequencing and epidemiological data) was highlighted. The following issues were listed under "challenges": sampling schemata / approach, voluntary versus compulsory (coverage, representativeness), routine surveillance data versus monitoring (overestimation), differences in private / public sector, different agencies involved for AMR / AMC".

How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?

A key concept of GLASS is the availability of and access to surveillance data for public health and policy to inform and implement national measures. When integrating data into global systems, it should be considered that this is done with the involvement of relevant national institutions and does not bypass them.

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?
As shown above, the basis for surveillance is a functioning health system. Surveillance for AMR requires laboratories integrated into the hospitals that can perform valid manual species identification and resistance testing. The establishment of such laboratories and laboratory training including pre- and post-diagnostics is necessary, where this is not yet the case.

What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?
Page 9 refers to the importance of internationally recognized standards such as CLSI and EUCAST for data quality. The same section refers to national recommendations as an alternative; additionally only the recommendations of the Russian Federation are mentioned. Harmonization and adaptation to the special needs of LMIC is needed. Good coordination and communication as well as the avoidance of parallel transmission paths and double messages increase the acceptance of global surveillance and monitoring systems.

How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?
As mentioned above, surveillance must be seen as part of a functioning health system. Most of the generated data comes from routine medical care and routine medical care benefits from the data.

3. AMR: Investment in innovation and research and boost R&D and access

General comments : We are not in favour of creating a new initiative due to possible fragmentation of funding and the resulting additional administrative structures and expenses which would reduce the available financing for the intended purpose. Besides, as it is stated in the document immediate action is required whereas launching a new initiative would take considerable time.

- Chapter 1, p. 8, delinkage: that the text as it is now gives the impression that delinkage mechanisms are distinct from pull- or push mechanisms. However, push- and mechanisms can be designed (and used) in a way to create delinkage. The para should be revised in this regard.
- Chapter 2, p. 4-6, description of challenges: Some of the challenges (e.g. 3 and 5) do not seem to be restricted to AMR, but valid for other indications where we do not see a lack of products on the market.
- Chapter 1, p. 8-9, paras on push and pull mechanisms: Currently, push and pull mechanisms seem to be portrayed in an unbalanced way with too much weight on pull. Push mechanisms address more challenges than just the mentioned challenges 3 and 8. E.g., they are successfully used in supporting clinical trials. Likewise pull mechanisms might not address all the challenges mentioned. While acknowledging the still existing funding gap, the recent considerable increase in R&D funding on national and international level should be mentioned.
- Chapter 1, p. 9: The role of the Global AMR R&D Hub (so far on p. 10) should be mentioned before JPI-AMR and STAR-IDAC IRC, which are both not coordinating instruments in the stronger sense. The Hub should be portrayed more adequately. It is the first high level coordination tool addressing most of the main gaps mentioned in section “R&D coordination” on p. 9.
- Chapter 1. p. 9 last para, JPIAMR: Suggestion to change wording: Instead of ”JPIAMR coordinates national research programs…” “JPIAMR <u>helps</u> coordinating national research programs to <u>reduce</u> duplication in…”
  <u>Rationale</u>: While completely acknowledging the valuable work of JPIAMR it must be clear that JPIAMR has no active coordinating role for the establishment of national programs.
- Chapter 2, p. 11- 12. Some of the challenges listed are not specifically addressing access issues (but inappropriate use, falsified drugs etc.). The chapter should be revised and better structured. Most of the challenges mentioned are not specific to the problem of AMR, but are linked to the general question of establishing resilient health systems. An AMR-specific approach might even not be necessary. On page 12, Challenge 1 is too general and should be rephrased: “Not all health technologies meet the needs of LMICs”.
- Chapter 3, p. 15: The guiding principles as detailed on page 15 seem unclear. E.g. it is not explained how conflicting legitimate interests (e.g. between LMICs and high-income countries or between different

stakeholders) should be balanced. To address R&D *solely* from a "utilitarian" point of view of benefit and value for money does not seem adequate with respect to the freedom of research. Some aspects mentioned in the guiding principles, such as global R&D priorities, efficiency or the needs of LMICs will also be addressed by the Global AMR R&D Hub. The Hub not only aims to increase coordination in R&D investments on a political level. It also strives for an increasement of investments, in particular for global health priorities.

Remarks regarding the „open questions" cited in the working document:

1. **Research and development**

Summarizing answer to questions pertaining to chapter 1:
Addressing the identified gaps and finding tangible solutions to the questions above needs a platform for high level coordination between representatives of the most relevant donor countries and organisations. To this purpose, 15 countries, the European Commission and two philanthropies have created the "Global AMR R&D Hub" which will give evidence based guidance for funding decisions while completely respecting the members' sovereignty. It will follow the One Health approach and will be guided by the global priorities set by WHO, FAO, OIE and other relevant intergovernmental organisations. The Hub will also advocate for increased investment in R&D for AMR among its members and beyond.
It is clear that the challenges described in the report can only be tackled using a wide variety of funding instruments and incentives – there is not *the one* incentive or delinkage mechanisms that solves all the problems. The increased coordination through the Global AMR R&D Hub will make it possible to combine different funding instruments (both push and pull) from different funders more effectively, thereby lifting the potential of the whole toolbox of incentives. The Hub will also be the place to pave the ground for multi-donor support for expensive activities such as pull mechanisms.
With regards to the design of new incentive mechanisms, it seems important to address different levels (national, regional, global) and take into account the needs and requirements of both developers/implementers and donors. As stated already in the report, future efforts need to build on the work that has already been done (e.g. reports by DRIVE AB and OECD/ WHO/OIE/FAO).

2. **Access**

Comment on question 2: In line with the argumentation on p. 14, we would prefer using existing initiatives and supporting them instead of setting up new ones leading to even morefragmentation. Moreover, most of the challenges mentioned are not specific to the problem of AMR, but are linked to the general question of establishing resilient health systems. An AMR-specific approach might therefore not be necessary.

3. **Cross-cutting topics in R&D and access**

As a general statement, we are neither supportive of any attempt for creation of new supranational R&D funding entities nor of mandatory financial obligations for donor countries nor of the creation of an international framework regulating R&D and education. While there are of course some internationally recognized (scientific, ethical) standards that R&D and education should adhere to, it lies within the national responsibility to set the frame for R&D. In Germany, these frameworks have to align in particular with the freedom of research guaranteed by the German constitution.

Best regards
Susanna

Yours sincerely

Dr. Susanna Müller

_____

Z 23 – Global Health
Federal Ministry of Health

Ireland

From: Doyle, Rob
Sent: 11 July 2018 12:59
To: IACG-secretariat
Cc: Blake, Martin
Subject: IACG consultation documents

Hi
Apologies for the slightly late response.
The Irish Department of Agriculture, Food and the Marine, Antimicrobial Resistance team have read the documents we have no specific comments on the individual documents
We believe that the IACG discussion papers on Antimicrobial Resistance are useful documents and that we support their aims and intentions.

Kind Regards

Rob Doyle SSVI

Head of Division Veterinary Medicines and Antimicrobial Resistance.

Japan

From: 駒田 謙一/Kenichi KOMADA
Sent: 09 July 2018 10:42
To: IACG-secretariat
Subject: Comments for publiuc consultation on the IACG document "3. Surveillance and monitoring for antimicrobial use and resistance "

Dear Secretariat,

I am Kenichi KOMADA, a medical officer in the National center for Global Health and Medicine, Japan.
I would like to send the following comments on the IACG document "3. Surveillance and monitoring for antimicrobial use and resistance ".

To establish the effective and sustainable surveillance system, it is indispensable to develop the laboratory capacity especially in low and middle income countries.
Accurate diagnosis will be one of the foundations for the surveillance but many LMICs don't have enough capacity.
To collect accurate information from the front line and improve the quality of report for global surveillance system, each country should have strong system to detect AMR correctly, to report the results timely and to maintain those qualities.
LMICs need a lot of support for that including strengthening national reference laboratory, organizing well-coordinated laboratory network, establishing and maintaining external quality assurance assessment scheme.
In this regard, I would like to suggest the document should focus more on strengthening laboratory capacity and give clear guidance.

I hope those will help.
Best regards,

Kenichi KOMADA

//
KOMADA Kenichi, M.D., M.P.H.

Medical Officer
Bureau of International Health Cooperation
National Center for Global Health and Medicine, Japan (NCGM)

Morocco

Moroccan National Office of Food Safety (ONSSA)

ANTIMICROBIAL RESISTANCE: INVEST IN INNOVATION AND RESEARCH, AND BOOST R&D AND ACCESS

How could R&D funding be better channeled?

- International and national projects
- Building priorities taking into account national authorities issues

What will it take to increase and sustain donor and private funding of R&D in AMR?

- Raise awareness
- Demonstrate research impacts on return of investment

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

- Encourage public services for research and development in order in create new AM molecules and alternatives
- Encourage targeted research

How should the design of incentive mechanisms be coordinated at global, regional and national levels?

- Answers to global problematic

How could current efforts in R&D coordination be strengthened?

- Expand the research field
- Increase coordination meetings frequencies

Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

- Nothing to report

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

- projects funding vaccine development can be expanded to include antimicrobial R & D as it complements antibiotic therapy

How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

Global public benefit:

- Investment should take into account national sanitary authority needs and start from prioritized health issues
- Criteria definition in financing specification for R&D
- Tax exemption for corporations
- Private-public partnership
- Access to food without risk of AMR transmission through the food chain
    - Encourage research in order to develop a farming system
    - Insure sustainable farming systems without AMU

Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

- Practical case study trainings
- Inter-agencies communication

How and which organization(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?

- Cotutelle of all stakeholder organizations aiming to responsibility equity
- Create a ***One Health*** service

Morocco

Moroccan National Office of Food Safety (ONSSA)

NATIONAL ACTION PLAN

3.1. Mainstreaming:

What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?

- International health regulations

What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development?

- Standardized interpretation of the monitoring results

What forces maintain national responses to AMR in silos, and how can we overcome them?

- Essentially the difficulties in terms of inter-sectoral coordination;
- A poor understanding of the risks and issues;
- Facilities solutions allowing some stakeholder's categories to blame others rather than to question themselves.

We can overcome this through international advocacy highlighting:

- ''One Health'' approach
- Each stakeholder category is a part of the problem and a part of solution
- Encourage inter-sectorial coordination through mixed organized workshops and trainings
- Development of an integrated computer system enabling each stakeholder to introduce and share specific data.

How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?

- ensuring the existence of coordination mechanisms
- ensuring that every stakeholder category is integrated in funding

3.2. Financing:

What support do countries need to translate information on the global impact of AMR into a country-specific case?

- Expert workshops

How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners?

- In the general budget of the country at the level of specific budget lines

What is the role of the international community in supporting international public goods such as AMR surveillance data?

- Through international organisations (OIE, FAO, OMS), to develop standardized tools for data collection

How can we support decisions to balance the portfolio of investment in AMR-specific and AMR-sensitive interventions, particularly in LMICs that need support in developing public health, animal

health, plant health and environmental support services across regulatory and operational domains?

- on the basis of each ''country situation'', identifying the categories A B C D of each country

Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)

- Firstly, the One Health epidemiological model of attribution for resistance development and transmission, because a better understanding of the Health epidemiological model will allow to adapt the fight
- Secondly, the economic model of impact and potential benefit, because this will give arguments to justify the budgets

3.3. Regional cooperation

What are the highest priorities for training in Member States with respect to NAP implementation?

- Regulation and code of ethics
- Respect of the indications contained in the notices.
- Good practices for the use of the veterinary medicinal product, and in particular antimicrobial agents.
- Distribution channel
- Sensitization of private veterinary practitioners on antimicrobial resistance
- Dangerous practices
- Role of biosafety and alternative methods
- Role that the veterinarian can play to fight against antimicrobial resistance.
- Items to be checked during inspections (National Orders, competent authorities).

What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?

- International organizations websites (OIE,..etc.) regularly consulted by members

What sensitivities should be considered when encouraging regional cooperation on AMR?

- Through previous experiences with international organisations (OIE, OMS…etc.), few risks may occur if we focus on technical thematic for technical resources. If this operation is of a higher level, do not forget bodies in charge of diplomatic actions such as the Ministry of Foreign Affairs which facilitate regional meetings and workshops progress.

Morocco

Moroccan National Office of Food Safety (ONSSA)

SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE

4. INTEGRATION:

WHAT ARE THE OPPORTUNITIES FOR, AND OBSTACLES TO, INTEGRATING DATA ANALYSES WITHIN AND ACROSS SECTORS?

Opportunities:

- Approaches harmonization
- Stakeholders sensitization
- Data synthesis
- More informations regarding AMR circulation and evolution

Obstacles:

- Lack of communication between sectors
- Each department want to take the lead
- Departments which want to take the lead and beat the other departments
- One-way communication
- One sector puts the blame on another sector

How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?

Designate national pilots who have structures or who support follow-up :

Plant production: quarantine system, research laboratories, government laboratories for monitoring plant health

Environment:

AMR surveillance in soil, water and industrial waste

How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?

- Regulation
- Communication to the authorities → Data synthesis → integration to the national/global action plan

4. 1. Prioritization

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

- Capacity building
- Workshops in order to learn more about AMU
- Sensitization
- Punishment, penalization designated in regulatory system

How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

- Training, national strategy sensitization
- Audit system and international guides development

What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data ?

- Laboratory of control and surveillance plan
- Develop a computer platform to synthesize the results of each sector
- Régulation

4.2. Comparability

What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?

- Expertise in order to assess the implemented collection system
- Workshops to learn and harmonize data collection

What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?

- Harmonized system for data collection

What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?

- Molecular biology , genetics, phylogenetics
- Automating system

4.3. Availability:

What support do countries require to develop and report accurate national data and share them on global surveillance systems?

- Computer plateform adapted to each country context
- Workshops to sensitize and to train stakeholders in order to act

What data formats and visualization tools are most useful for reporting and further analysis?

- Easy to use and specific software
- Each stakeholder should get access to this software and introduce information according to a harmonized system

How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?

- Nothing to report

4.4 sustainable investments:

How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?

- Demonstrate the new AM molecules invention potential

What tools are required to address the investment required for surveillance of AMR and AMU?

- Provision of ready to use tools (accessible, easy to use and adapted to country context)

What role can the private sector play in financing surveillance?

- Research and development
- Training : for example industrial waste treatment
- Antimicrobial molecules productions monitoring and surveillance
- Add AMR surveillance to the auto control system of each pharmaceutical establishment
- Cleaning procedures validation

Netherlands

From: Grand, M.J.F. le (Maria)
Sent: 09 July 2018 15:21
To: IACG-secretariat
Subject: RE: WHO - The UN Interagency Coordination Group on Antimicrobial Resistance

Dear IACG secretariat,

Thank you for the three IACG discussion papers and the opportunity to provide feedback via this consultation procedure. I am writing you on behalf of the Netherlands Ministry of Health, Ministry of Agriculture and National Public Health Institute. Our main comments apply to the paper on National Action Plans, since we feel this is the main area where the IACG has a mandate and clear complementary function. In general we think the paper provides clear and good key messages for the UN Secertary-General that we adhere to and thus support your line of argument towards world leaders in the UN GA. Consequently, we do feel that the other papers on surveillance and R&D are somewhat duplication of effort that should be avoided since important work is already being done at the global level by e.g. WHO and the G20 R&D hub.

Input on the discussion paper on AMR national action plans:

- In general we feel this is a good paper and we recognize the line of argument as the one we also would follow/support. We compliment you on the broad perspective, highlighting access to financial resources as an obstacle and describing AMR sensitive (infection prevention) and AMR specific (prudent use) measures.
- We feel that solid recommendations are laid down in this paper however followed by a weaker evidence base. As you may know, we do not recognize that weak evidence base in the Netherlands, where for example veterinary policy on AMR is based upon advice of Health Council – an important independent scientific board.
- By choosing the focus of national action plans and thus starting from national level perspective, we maybe miss insight in opportunities of global level interagency coordination – e.g. what are possibilities of global level interagency coordination and cooperation to stimulate action on prudent antibiotic use in the agricultural sector at state level in the interest of public health. Maybe the gaps and challenges at global level would then suggest or read an option that global targets are needed for national levels to act properly.
- In paragraph 2 on *Gaps & Challenges* and paragraph 3 on *Enabling implementation* the paper mentions tools and best practices available to help countries; mentioning the work by the tripartite and ReAct. There are many more resources worth mentioning! E.g. ECDC has countries best practices and communication tools, lots of information on country experiences have been shared via numerous conferences over the past few years and via cooperation mechanisms such as the EU Joint Action or the GHSA AMR work package and the WHO SPP portal.
- In paragraph 2.2 on *Public and private sector financing* we suggest that you could add that we need to frame AMR as a threat to achieving SDG's at UN and national level – in order to access the development start-up funds which is now difficult.
- In paragraph 2.3 on *Coordination across sectors and stakeholders* we notice that you do not mention the yearly tripartite self-assessment as an opportunity for countries to contact other stakeholders and sectors and seek for cooperation on AMR. We have heard that if this proves to be difficult this is also a trigger to ask for help at WHO Regional Offices which we see as a positive signal and development, which might be useful to add.
- On paragraph 2.5 on *Data and technical capacity* we agree that data provide evidence required to persuade politicians and policy makers to take action. However, we would like to add on the other hand that we know already a lot on AMR, we feel that there is a global sense of urgency and we can act already because we know the main no-regret measures: improving infection prevention and prudent use of antibiotics. Therefore there is no need to wait for more surveillance data to take action. Main reason to also work on surveillance, especially in LMIC, is that insight in the local situation is necessary to take tailor-made measures and to monitor progress.
- Finally, in paragraph 3.2 on *Financing*, we would like to draw attention to the GHSA AMR work package progress made in stimulating bilateral cooperation. It might be worth exploring if the initial mapping done in

the WHO SPP portal could be extended and used more by organizing brokerage between countries offering support and countries requesting support on (implemention of) AMR NAPs via WHO?

Kind regards,

Maria le Grand
Ministry of Health, Welfare and Sport
Public Health department | Infectious diseases

Norway
Institute of Public Health

From: Littmann, Jasper
Sent: 09 July 2018 15:28
To: IACG-secretariat
Cc:
Subject: Feedback Discussion paper 1 "Antimicrobial resistance: invest in innovation and research, and boost R&D access"

Dear IACG Secretariat,

please find below feedback from the Norwegian Institute of Public Health on the first discussion paper "Antimicrobial resistance: invest in innovation and research, and boost R&D access". Feedback is provided for each of the three sections of the paper, and where specific questions from the report have been answered, these questions are repeated in italics below.
Thank you for the opportunity to provide comments and feedback on this report.

Best wishes

Jasper Littmann
Director – Centre for Antimicrobial Resistance
PhD, MPH
Norwegian Institute of Public Health

NIPH

Feedback IACG Discusssion Paper 1: Antimicrobial Resistance: invest in innovationa and research, and boost R&D access
(Author: Dr. Jasper Littmann, Director, Centre for Antimicrobial Resistance at the Norwegian Institute of Public Health: on behalf of the Norwegian Institute of Public Health)

1. R&D challenges

The report highlights the importance of de-linkage, as a method of separating expected returns on investment from the volume of sales, and summarises the most relevant push and pull incentives. In light of the considerable financial burden of around $1 billion per developed drug, pull incentives should not be the first priority. Their use would also presuppose a full de-linkage of profits from sales to ensure equitable access and rational use.
We agree strongly with the need for research coordination to avoid the duplication of research projects. However, coordination must not come at the cost of diversity in research approaches. This applies in particular to the use of the WHO's Priority Pathogen List (PPL), which not based on the current or projected public health impact of bacterial pathogens but the relative lack of available treatments. Many drug-resistant bacteria with a high disease

burden are not included in the list, and it would be problematic if they were excluded from future research funding as a result.
An additional point, which the report does not touch on but which appears important in the context of this discussion is that most pharmaceutical companies have by now exited the field of antibiotic development. It will therefore be relevant to evaluate for whom some of the proposed mechanisms (such as large pull incentives) would be relevant in practice.

Open Questions in the report:
How could R&D funding be better channelled?
Currently, there seems to be no clear agreement on how R&D funding should be allocated, and whether to prioritise new classes of drugs over the development of new treatments (e.g. combination therapies). While the latter could potentially be more limited in their application and future utility, the former come with the problem of long development times. In the medium run, a focus on new treatments may be a more pragmatic approach.

What will it take to increase and sustain donor and private funding of R&D in AMR?
See previous question. Also note that a focus on large pull incentives limits the number of potential donors.

How should the design of incentive mechanisms be coordinated at global, regional and national levels?
Different incentive mechanisms would ideally need to agree on a universal access policy to avoid competition based on profitability.

How could current efforts in R&D coordination be strengthened?
International coordination efforts will require comprehensive overviews of research activities and stakeholders at the national level. Many countries would currently struggle to identify all research activities at the national level, which means that effective international coordination is made more difficult. In addition to developing international coordination mechanisms, it will therefore be important to assist countries with the implementation of suitable national monitoring and evaluation tools to track ongoing research and research gaps.

2. Access

The report points out that the lack of access to essential antimicrobials contributes to more deaths in low and middle-income countries than AMR. This should lead us to prioritise the improvement of access to antibiotics in these countries. Access should not only take into account the existence of a stable and reliable supply chain, but also the use of adequate supply channels, which ensure that patients are given the correct drug. The improvement of access to antibiotics is therefore inextricably linked to access to universal health coverage.

Open Questions in the report:
Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?
The report summarises the most important challenges to access and the existing mechanisms to address them, and explicitly states the importance of UHC to establishing equitable access to antibiotics. The discussion of access to antibiotics for animals appears to require an additional analysis.

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?
Since AMR is a problem for the treatment of many infectious diseases, the inclusion into existing mechanisms and funding initiatives appears to be a more pragmatic approach. This is further supported by the fact that forming and securing funding for a new international initiative would take considerable time and political resources. However, this inclusion may prove difficult in the animal and environmental sector, where there are potentially fewer funds that could expand their work on AMR.

3. Cross-cutting topics in R&D and access

Open Questions in the report:

How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

The guiding principles for funders that the report provides are a useful and concise summary of important action points. Adding further to the list may complicate operationalisation.

Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

Examining the transmission of resistance genes via animals and / or the environment would help in highlighting the importance of a One Health approach and allow policy makers to identify priorities that help to curb the emergence of resistance. Currently, the potential complexity of a fully integrated One Health approach makes it difficult to fully appreciate its long-term benefits or to plan its implementation. A more narrow focus on aspects that may e.g. be of clinical relevance would help to establish the practical importance of the One Health approach.

Norway

Institute of Public Health

From: Littmann, Jasper
Sent: 09 July 2018 15:33
To: IACG-secretariat
Cc:
Subject: Feedback Discussion paper 2: "Antimicrobial Resistance: National Action Plans"

Dear IACG Secretariat,

please find below feedback from the Norwegian Institute of Public Health on the second discussion paper "Antimicrobial resistance: national action plans".
Feedback is provided for each of the three sections of the paper, and where specific questions from the report have been answered, these questions are repeated in italics below.

Best wishes

Jasper Littmann
Director – Centre for Antimicrobial Resistance
PhD, MPH
Norwegian Institute of Public Health

www.fhi.no

NIPH

Feedback IACG Discussion Paper 2: Antimicrobial resistance: national action plans (Author: Dr. Jasper Littmann, Director, Centre for Antimicrobial Resistance at the Norwegian Institute of Public Health: on behalf of the Norwegian Institute of Public Health)

General comment:
This discussion paper offers an excellent summary of the main challenges of implementing national action plans, and highlights how the process differs between countries and regions.
Below are comments and responses to the questions posed in the text.

1. Mainstreaming

Open Questions in the report:
What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?
AMR has been described as a barrier to the implementation of numerous SDGs, including, health food security, ending poverty and sustainable consumption. Consequently, AMR could be included into many of the activities in these fields. The rational use of antibiotic is antibiotics, is for example one of the important cornerstone of many

NAPs, but it requires the correct diagnosis of an infection by a trained health professional and the subsequent prescription of antibiotics. This makes the achievement of UHC effectively a precondition for implementing rational use policies globally.

What forces maintain national responses to AMR in silos, and how can we overcome them?
While AMR is often described as a One Health challenges, veterinary and clinical sectors do not always cooperate fully in addressing the problem. Part of the challenge may be the inherent complexity of AMR and the difficulty of understanding the interaction between different sectors. Joint education for pharmacists, physicians and veterinarians is an example of overcoming parts of this challenges. Similarly, it will be important to make explicit the potential gains from better cooperation (see also questions on financing below).

2. Financing

Open Questions in the report:
What support do countries need to translate information on the global impact of AMR into a country-specific case?

Global AMR-figures tend to be too abstract for many policymakers, and – at worst – may lead to shifting blame between countries. A prerequisite will be industry and disease-burden adjusted information, which can be used to develop scenarios that are of importance to each country wishing to implement AMR policies. This should include estimates of the financial consequences of inaction for the health care and agricultural sectors.

What is the role of the international community in supporting international public goods such as AMR surveillance data?
The international community should in the first instance aim to:

1) Assist LMICs with the collection, quality assurance, and analysis of data
2) Make both, country-specific and aggregated international data freely available
3) Provide assistance with visualisation tools that explain changes to the AMR burden over time

Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)
For many countries, the calculation of the future cost of inaction will be an important initial step to develop comprehensive policies and justify the prioritization of work in the field of AMR.

3. Regional cooperation

Open Questions in the report:
What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?
Independent and widely known platforms, such as WHO's website, which offer information in a range of languages.

What sensitivities should be considered when encouraging regional cooperation on AMR?
Countries within the same region may occasionally view cooperation on AMR as a matter of competition. While this can have a positive impact in encouraging countries to implement policies and set the standard for a given region, it may also complicate the frank discussion and evaluation of shortcomings, challenges or failures among regional partners.

Norway

Ministry of Climate and Environment

From: Lindstad Torstein
Sent: 09 July 2018 04:22
To: IACG-secretariat
Cc: Crompton Solveig; Wathne Karl-Olaf
Subject: IACG Public Consultation

Dear IACG Secretariat,

The Ministry of Climate and Environment of Norway welcomes the opportunity to provide some comments to the discussion documents as inputs for the Report of the Inter-Agency Coordination Group to the UN Secretary General.

It is clear that the environment is playing an increasingly important part of the global AMR discussion, but it still seems to be at an early stage. The IACG group on National Actions Plans points out on page 5 of its consultation note*: "Some agendas, such as the environment are still evolving, and it is not yet clear what the priority actions for countries are, so whilst the involvement of the environment is critical to the multisectoral approach, it is not yet always clear who should be involved, and what the focus should be."* Based on our experiences thus far in the implementation of the Norwegian National Strategy, we would agree with the observation and suggest that it would be useful for the IACG to identify appropriate actions in this respect. This is an issue we believe is cross-cutting and should require both a consideration of the focused contribution of environment organizations, such as UN Environment, as well as how to integrate the relevant environmental aspects into work of the other sectoral organizations.

We hope that the work of the IACG can bring the discussion forward by, for example, identifying some of the concrete environmental issues that is directly linked to the challenge of AMR and point to which international actors and/or global framework (UN organizations, conventions, etc.) that can be best suited to take the lead and do something about it.

It is in and of itself telling that we do not have more specific inputs to make, or answers to provide to the questions raised in each of the discussion documents. This is no doubt indicative that it would be useful to consider the role of the environment sector in the fight against AMR in a deliberate and consolidated way, if we are to succeed.

Best Regards,

Torstein Lindstad

Deputy Director General
Department of Nature Mangement
Ministry of Climate and Environment
Norway

Pakistan

Ministry of National Health Services, Regulation & Coordination

Comments on Discussion Papers on AMR

S. No	Discussion Paper Title	Pakistan status	Comments on the Discussion Paper
1.	**Antimicrobial resistance: National Action Plan**	Pakistan has developed and endorsed NAP with "One Health" approach. The Ministry has also provided technical support for developing Provincial Action Plans. The Pakistan NAP has following 7 strategic priorities: i. Development and implementation of a national awareness raising and behavioral change strategy on antimicrobial resistance; ii. Establishment of an integrated national AMR surveillance (human, animal usage and resistance monitoring); iii. Improve prevention & control of infections in health care, community, animal health, food, agriculture and environment; iv. Update and enforce regulations for human and veterinary antimicrobial utilization; v. Phase out use of antimicrobials as Growth Promoters and provide appropriate alternatives (such as prebiotics, probiotics); vi. Integration of AMR in all public health research agendas including research on vaccines; and, vii. Estimation of health and economic burden of AMR for decision making.	The discussion paper is very comprehensive and addresses major concerns, needs and updates on initiatives being taken at global level, However, some of the comments on discussion paper are as follows: • There is a need for incorporating AMR in the public health initiatives such as UHC, IHR, SGD and food security since AMR is cross-cutting multi-sectoral issue directly linked to health security. • Needs more clarity on AMR-specific and AMR-sensitive activities and may be defined in the discussion paper with examples. • Fragmented health systems keep AMR in silos. This can be overcome by adopting integrated one health approach. Strong national focal points with mandate to implement, monitor and report back to global community may overcome national response to AMR in silos. • International development partners may provide technical assistance to the member states as well as support to the countries for creating/ enhancing political will and advocacy for senior policy makers across sectors. • Sharing best practices through regional forum may help in translating information on global impact of AMR into country specific case. • AMR may be included into National Action Plan for Health Security (NAPHS) being developed by the countries following Joint External Evaluation (JEE) of IHR-GHSA core capacities. The member states should provide seed money for AMR as an emerging problem for priority areas. Partners may contribute with additional funds based on gap analysis.

		Pakistan is in process of costing the NAP and mobilize the indigenous resources for AMR and IPC. Pakistan is among the category "C" countries as described in the discussion paper facing challenges for NAP implementation.	• A standardized costing tool may be developed to help countries cost the NAP, carry out gap analysis viz-a-viz the existing resources. • International community should highlight the critical findings of surveillance data at global and regional conferences/ symposia and also consider predictive modeling based on genetic analysis of MDR pathogens based on transmission dynamics. • International partners may provide legal expertise and technical assistance to low and middle income countries (LMIC) in drafting legal frameworks and their implementation for AMR containment. • For country like Pakistan as a LMIC, developing economic case of impact and potential benefits will help in resource mobilization. • Trainings on tools for AMR utilization/ consumption, stewardships activities for health workforce and community awareness may be considered. • Mechanisms for regional consultations of countries to share lesson learnt in NAP development and implementation may be established. • Regional economic countries may provide financial resources for regional platforms.
2.	**Antimicrobial resistance: Invest in innovation and research and boost R & D and access**	AMR related R&D has been included in the NAP as a key priority with the aim to integrate AMR in all public health research agenda including vaccines and diagnostics	The discussion paper is very comprehensive and addresses major concerns, needs and updates on initiatives being taken at global level, However, some of the comments on discussion paper are as follows: • Countries should be encouraged to establish / strengthen research councils with the mandate and resources to carry out R&D for AMR.

			• There is need to establish linkages between developed countries having basic research facilities with LMIC for clinical trials of new/ novel drugs and vaccines. • Global AMR, R&D blue prints may be developed and reviewed yearly by panel of experts. The drug-bug combination may be prioritized for resource allocation for R & D. • Global and Regional R&D platforms may be established to increase and sustain donor and private funding for R&D. • Keeping in view the fact that AMR has broader public health impact and involves diverse stakeholders, a new R&D access initiative may be created. • Guiding principles should be based on evidence, best practices and must have consensus of all the member states. • Surveillance for different drug-bug combination and antimicrobial utilization based on One Health approach may impact R&D. • WHO, FAO and OIE together with NGOs may take lead to train next generation of scientists on AMR in collaboration with national Governments.
3.	**Surveillance and monitoring for antimicrobial use and resistance**	Surveillance has been identified as key strategic priority in the NAP Pakistan has been enrolled in GLASS with identified sites contributing to the national data A national plan for AMR sentinel surveillance in human health sector is being developed in collaboration with development partners including WHO, US CDC and Fleming fund, UK.	The discussion paper is very comprehensive and addresses major concerns, needs and updates on initiatives being taken at global level, However, some of the comments on discussion paper are as follows: • Lack of coordination among sectors is key impediment for integrated data analysis. • One Health hubs should be established by the member states with defined mechanism for data sharing across sectors.

			• Necessary legislative framework may be developed and implemented to integrate private sector into national and global reporting system. • Standardized tool should be developed for different sectors for assessment purposes alongwith standardized protocol for surveillance in the respective sectors. • Mechanism of AMR surveillance strategy in the NAP aimed at capacity building of the laboratories to generate reliable data with the capacity to analyze, interpret and disseminate integrated data. • Well equipped Drug Surveillance Units/ Labs may be established with the mandate to operate in all sectors. Drug Regulatory bodies must reinforce strict regulation for manufacturer providing falsified and substandard medicines. • On site trainings for the member states to facilitate data collection, clearing and submission to global surveillance database by "Super-users" of software like WHONET. • Capacity building of lab, epi and data staff, drug inspectors using standardized tools. • National or Regional laboratories may be established to provide support to the countries for advance molecular studies such as Whole Genome Sequencing (WHS) or Next Generation Sequencing (NGS). • Quality assurance system for maximum number of laboratories for ensuring quality data. Regional networks may be established to share/ support countries for reporting on AMR. • Autobiograms, tables and graph on priority pathogens may be useful for reporting. • Early implementation of surveillance to generate evidence is critical to develop economic case to attract investors.

Sweden

From:	Mårten Kivi
Sent:	28 June 2018 17:11
To:	IACG-secretariat
Cc:	Anders Nordström; Martin Jeppsson; Anna Brådenmark; Jenny Fernebro; Maria Wallin
Subject:	Public consultation Discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General
Attachments:	Sweden_IACG draft work plan_online consultation.pdf
Follow Up Flag:	Follow up
Flag Status:	Flagged

Dear IACG-secretariat,
Thank you for initiating the public consultation to inform the IACG report to the UN Secretary-General. We would like to take this opportunity to reiterate some previous input prepared in Government Offices of Sweden (enclosed). In particular:

1. Sweden's view is that the focus of the IACG should be to advise the Secretary-General on high level strategic policy issues. There is concern that the work of the IACG may become too technical rather than focusing on providing the political platform needed and envisioned. There are actors in the system who are well suited to do the more detailed work.
2. There is a need to reach out and communicate the aim and importance of the IACG-process. Such communication should consider both the overall strategic direction and the concrete IACG activities, and should take into account the short- and long-term perspectives.

We look forward to further dialogue regarding the task of the IACG that is of great importance to us.

Best regards,

Dr Mårten Kivi
Deputy Director
Division for Public Health and Health Care
Ministry of Health and Social Affairs
Government Offices of Sweden

Government Offices of Sweden

Memorandum

31 August 2017
S2017/04470/FS

Online consultation with regard to the draft work plan of the Interagency Coordination Group (IACG) on AMR

With reference to the online consultation with regard to the draft work plan of the Interagency Coordination Group (IACG) on AMR[1], this is to provide feedback prepared within the Government Offices of Sweden. Different sectors concerned with AMR-related policies have been involved in the preparation of the present feedback, in line with the One Health concept.

The Swedish Government is highly committed to the fight against AMR. The establishment of the IACG is welcomed and supported. This is also reflected by previous letters sent to the WHO Director-General and the UN Secretary-General regarding the establishment of the IACG, including a letter on behalf of the Alliance of Champions against AMR.[2] The IACG is expected to be instrumental to boost coordination and commitment across the UN system and beyond.

The draft work plan generally describes a number of relevant activities. We appreciate and would like to take this opportunity to provide and reiterate some comments:

The high-level meeting of the General Assembly on AMR and the political declaration was a great success. It provides a basis and starting point for comprehesive action against AMR through a multisectoral One Health approach. As reflected in the draft work plan, the work of the IACG should be firmly linked with the political declaration in order to ensure legitimacy.

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[1] http://www.who.int/antimicrobial-resistance/interagency-coordination-group/online-consultation/en/

[2] S2016/02698/EIS and S2017/00383/EIS

The commitments made in recent years must result in concrete and effective actions worldwide, in different sectors and at different levels. These actions should be monitored to support follow up on progress and exchange of experiences.

The focus of the IACG should be coordination between different stakeholders and sectors. Based on the present draft work plan there is concern that the work of the IACG may become too technical rather than focusing on providing the political platform needed and envisioned. The group must not take over the normative and technical roles of the respective UN agencies. The political focus of the mandate of the IACG was for example underlined in a recent letter from the WHO Director-General.[3] The need for a political focus in the present process does not mean that formal intergovernmental negotiations should be initiatied, at least not at this stage before recommendations emanating from the IACG are available.

UN agencies and other international organisations have key roles to play in the joint task to advance positions and build capacities. Leadership, particularly at the highest level, is crucial to engage and build partnerships between different stakeholders and sectors and to mobilise resources. Leadership is also important to ensure legitimacy for low-, middle- and high income countries. Moreover, valuable partners include but are not limited to civil society and the private sector, as outlined in IACG's terms of reference and draft work plan, e.g. activity 1.2 (4).

In order to ensure sustained global actions against AMR as per the political declaration it is important to maintain momentum within and beyond the UN system. Thus, the draft work plan should further highlight and elaborate on the need for a longer term perspective, also after the 73rd session of the UN General Assembly.

Needless to say, it is important to ensure links to ongoing activities, regarding AMR in specific as well as health and veterinary systems, the environment and sustainable development in general. In some respects the draft work plan emphasizes that activities should be coordinated with, complement and not duplicate ongoing work by the tripartite and others. This notion is welcomed and should characterize the work of the IACG

[3] D4-180-15

overall. As indicated in the draft work plan, the above needs to be considered in relation to the proposed activity 4.2 that refers to a roadmap with quantitative targets. This should be rephrased/reconsidered in the light of the coordination role of the IACG and the presence of other relevant fora and frameworks.

Last but not least, it is positive that the draft work plan recognizes the need for a an inclusive and transparent approach with for example regular updates and MS briefings. We look forward to further dialogue in this regard.

Switzerland

From: Perez-La Plante Miguel EDA PERMI
Sent: 10 July 2018 10:37
To: IACG-secretariat
Subject: Comments Switzerland AMR

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Sir, Madam,

I apologize the message below was supposed to reach you yesterday. I hope that our comments below can be considered.

We have read these different documents and find in general that they give a good vision of the problems to be solved by asking the relevant questions. We would like to contribute the following remarks:

Invest in innovation and research, and boost R&D and access:

- This document gives a very useful and comprehensive overview of existing R&D initiatives and further remaining challenges for new antimicrobials, diagnostics and vaccines.
- Regarding the challenge for a better coordination of R&D to ensure appropriate priority setting, funding allocation and unproductive duplication of activities, the document should stress the fact that the G20 Global AMR R&D Collaboration Hub (mentioned on page 10) has been set up with this very ambition.
- Under chapter 3 “Cross-cutting topics in R&D and access”, it is mentioned (on top of page 15) that “there is no guidance on mobilizing further investment to fill the gaps”. While this is true for now, it could be tackled by the Hub recently created.

National Action Plans:

3.1.

- What forces maintain national responses to AMR in silos, and how can we overcome them?
- Different implementation cultures and financial structures and procedures within each department and office can make it difficult to coordinate and dedicate enough personnel and resources in order to align joint activities to a common timeline. One solution is to coordinate only as much as needed (e.g. in terms of joint communication towards stakeholder and the public; and in surveillance), and leave as much as possible under the lead of each department/office, but under a commonly defined NAP. Essential for a minimum of coordination across sectors is budgeting for national AMR coordination activities (including personnel), for example in a way that the lead, capacity building and budget for this is allocated to one domain/department.
- How can international development partners support full integration of the AMR programs they fund into sustainable initiatives in beneficiary countries?
- See above (Budgeting for national AMR coordination activities (including personnel), for example in a way that the lead, capacity building and budget for this is allocated to one domain/department.)

3.2.

- What is the role of the international community in supporting international public goods such as AMR surveillance data?
- Establishing mathematical models such as for the burden of disease related to AMR for example is very costly and cannot be afforded by all countries. Knowledge transfer and sharing of established procedures is very valuable.

Surveillance and monitoring for antimicrobial use and resistance:

4.4.

- What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?
- International guidelines on targeted inclusion of whole genome sequencing (WGS) for public health needs (surveillance, outbreak investigation and management) would help to guide countries in priority setting and resource allocation.

With kind regards,

Miguel Perez-La Plante
Counsellor
Permanent Mission of Switzerland to the UN in Geneva

www.dfae.admin.ch/geneve

Turkey

From:	TUGBA ATAMAN ATAK
To:	VERCAMMEN, Laurence; IACG-secretariat
Cc:	YUSUF IRMAK
Subject:	Ilt: ILT:WHO - The UN Interagency Coordination Group on Antimicrobial Resistance: second set of discussion papers are out
Date:	01 August 2018 16:18:55

Dear IACG Secretariat,

I'm writing on behalf of Ministry of Health of Turkey, first of all, we appreciate all your efforts.

The documents which you mentioned in your first e-mail reviewed by our technical departments. We find the documents to be quite detailed and appropriate.

Now, we are working on the new documents mentioned your second e-mail. I hope we will send our views no later than 31 August.

Kind regards,

Ukraine

From: катерина сояк
Sent: 12 July 2018 16:29
To: IACG-secretariat
Cc: Viktor Liashko; Ігор Кузін
Subject: Discussion papers. Antimicrobial resistance: Invest in innovation and research, and boost R&D and access

Ministry of Health of Ukraine together with National Public Health Center being a responsible bodies for control of antimicrobial resistance (AMR) are deeply interested in discussion of papers provided by Interagency Coordination Group on Antimicrobial Resistance (IACG) as well as in fruitful collaboration in developing of One Health approach for achieving objectives that were indentified in Global Action Plan on Antimicrobial Resistance.

All countries are facing the great challenge of antimicrobial resistance. The basis for all research and innovations is human resources. Without building a generation of scientists that are enthralled with idea of combating antimicrobial resistance (as it was at the beginning of XX century that revolutionized approach to infectious diseases) we will not be able to control AMR effectively. Despite the fact that Global society recognize the problem of AMR only few countries have courses that exist on regular basis at the undergraduate level and address such areas as antimicrobial stewardship, infection prevention and control etc. One of the important steps for promotion of research in antimicrobial resistance should be inclusion of comprehensive courses that are focused on the various topics regarding AMR in the curriculum of students, postgraduates whose specialties are related to AMR problem.

Public Health Center
Ministry of Health of Ukraine
Сайт: http://phc.org.ua/

Ukraine

From: катерина сояк
Sent: 12 July 2018 16:32
To: IACG-secretariat
Cc: Viktor Liashko; Ігор Кузін
Subject: Discussion papers. Antimicrobial resistance: national action plans

Ministry of Health of Ukraine together with National Public Health Center being a responsible bodies for control of antimicrobial resistance (AMR) are deeply interested in discussion of papers provided by Interagency Coordination Group on Antimicrobial Resistance (IACG) as well as in fruitful collaboration in developing of One Health approach for achieving objectives that were indentified in Global Action Plan on Antimicrobial Resistance.

We have read the document and want to express our gratitude for the work done. Also, we would like to give a brief description of those problems with which Ukraine faced when developing the National Plan. Perhaps these problems have standard solution mechanisms and this will be added to your document.

We all know that cross-sectorial involvement in AMR National plans development is crucial for its success. But it could be a challenge for countries where One Health approach is only being developed. Unfortunately, from our previous experience, similar documents after approval at all levels remain ineffective. Examples from leading countries how to include all National stakeholders in AMR plan development and implementation could be beneficial for countries that experience problems with finding ways for effective dialogue and collaboration in actions for combating AMR.

Public Health Center
Ministry of Health of Ukraine
Сайт: http://phc.org.ua/

Ukraine

From: катерина сояк
Sent: 12 July 2018 16:24
To: IACG-secretariat
Cc: Віктор Ляшко; Ігор Кузін
Subject: Discussion papers. IACG Surveillance and Monitoring for AMU and AMR

Ministry of Health of Ukraine together with National Public Health Center being a responsible bodies for control of antimicrobial resistance (AMR) are deeply interested in discussion of papers provided by Interagency Coordination Group on Antimicrobial Resistance (IACG) as well as in fruitful collaboration in developing of One Health approach for achieving objectives that were indentified in Global Action Plan on Antimicrobial Resistance.

Surveillance is a key component for combating antimicrobial resistance. Lack of proper surveillance programs is one of the reasons why levels of AMR are so dramatically increased during last decades. Nowadays our surveillance programs are focused mostly on antibiotic resistance and resistant bacteria. However, antimicrobial surveillance implies more wider spectrum of antimicrobials, such as antifungal drugs. We can`t ignore the fact that we face a lot of new fungal infections with high level of resistance (for instance infections caused by Candida auris, Candida glabrata etc). We need to remember that we have fewer groups of antimicrobials to combat fungal infections comparing with antibiotics and any postpone in actions now could result in serious threats for public health care in future. So, we want to emphasize a big need to include surveillance for antifungal resistance as a essential part of surveillance for antimicrobial resistance in Global and National action plans.

As it was mentioned in the paper, low and middle income countries (LMICs) do not have robust systems for collecting and analysing data on AMR and AMU because of lack of resources and capacity. One of the important issues that contribute to unsatisfied level of surveillance in LMICs are non-availability of molecular techniques that allowed obtaining information about genomic background of resistance, patterns of transmissions etc. Formidable lack of equipment for molecular detection of resistant strains even at the level of national reference laboratories in LMICs makes surveillance programs incomplete.

Focus on molecular techniques in surveillance for AMR as effective and informative methods should be made and support programs for strengthening lab capacity of LMICs should be considered.

Public Health Center
Ministry of Health of Ukraine
Сайт: http://phc.org.ua/

United Kingdom

Department of Health & Social Care

UK Government response to the Antimicrobial resistance: Invest in innovation and research, and boost R&D and access IACG discussion paper

The following UK Government departments and organisations contributed to this response:

- Department of Health and Social Care
- Department for International Development
- Department for Environment, Food and Rural Affairs
- Veterinary Medicines Directorate
- Medical Research Council (on behalf of the Cross-Council Initiative)

Question 1: How could Research and Development (R&D) funding be better channelled?

1. Antimicrobial Resistance (AMR) arises from a complex interplay between biological, economic, social, cultural, environmental and technical factors and can rapidly spread from one system (human, animal, food and environment) and country to the next. Tackling AMR therefore requires an increase in coordinated cross-disciplinary 'One Health' and global R&D.

2. In our view, the R&D response needs to be embedded within the full breadth of the IACG framework. It should not be restricted to solely basic research - applied and interventional research should also be considered as critical - or limited to supporting the development of medical countermeasures (therapeutics, vaccines, diagnostics and alternative remedies). While such countermeasures have an important role to play, they are neither sufficient nor always required – for example, improvements in Infection Prevention and Control (IPC) and targeted prescribing have a significant impact on AMR, in the absence of new countermeasures.

3. It is vital to take a varied and comprehensive approach to R&D funding to address AMR. We need to support research to identify, prioritise and understand the drivers of AMR, whether biological, economic, cultural, environmental or technical; and support the development of cost-effective and sustainable interventions (policy, practice or product-based) that target these. This will require providing support for coordinated 'One Health' interdisciplinary efforts and funding/incentives for the development of interventions, from the early stages right through to clinical/evaluative trials and beyond.

4. It is important that we fund not only novel research, but also the improvement and implementation of existing interventions and technologies. Although improving existing technologies may not be the most attractive proposition for researchers, it could lead to quick wins for AMR, for instance in the case of vaccines and reformulation of existing molecules and treatment protocols.

5. Alongside this, it is essential that sufficient applied research is undertaken alongside intervention development to ensure that solutions are well-adapted to local contexts, and to maximise their uptake by health/food/environmental systems and in local communities. It is vital to ensure that we have a broad range of social science that considers the following in different contexts and, where appropriate, across the One Health spectrum:

    a. the role of gender;
    b. WASH practices, including handwashing practices;
    c. the political will and business/market environment;
    d. use of drugs, including traditional medicines, and of modern health technologies and the impact of medicalisation;
    e. behavioural change among health/veterinary practitioners and the public.

6. In the UK, we work hard to coordinate our research investments domestically and internationally. For example, the AMR Cross-[Research] Council Initiative funds a wide spectrum of AMR research, encouraging scientists and researchers to come together from a very diverse range of academic disciplines, including social and economic sciences, arts and humanities and engineering. The UK is also funding the development of the next generation of AMR academics through the AMR PhD Training Programme.

7. The Cross-Council Initiative feeds into the AMR Funders' Forum (where it meets a number of other funders, including Department of Health and Social Care and Department of Business, Energy and Industrial Strategy-managed programmes). These relationships in turn influence the UK's position within the Joint Programming Initiative on AMR (JPIAMR), led by the Medical Research Council, and other international collaborative efforts. This increases the UK's impact in coordinating efforts internationally. It is important that countries first coordinate at the national level to effectively coordinate at the international level.

8. More effective co-ordination of research activities at a global level will help to reduce potential duplication of effort to address priority evidence gaps. It is therefore vital that R&D funding efforts are joined up and that both positive and negative findings feed into the wider international research picture. This must include ensuring the use of ethical research methodologies and the open-access publication of findings. The UK research councils have an open-access policy, which aims to make findings of publicly-funded research freely available as soon as possible.

9. We should support the development of the research base (especially human capital) around the world, but particularly in the Global South. We need to expand the capacity for LMIC researchers on the ground – this will lead not only to a developed research industry in the Global South, but also potentially to greater uptake of any successful intervention.

10. It is also important for countries to collaborate on research projects, to share experience, learning and data / information to help foster good working relationships on AMR. Cross-border collaborations and partnerships are vital to develop context-specific innovations and solutions that address the challenges on the ground. This is also a means of leveraging more funding for research projects. The UK has leveraged many millions of pounds of funding into AMR through research partnerships with other countries. The UK Department for International Development has significant investments in CGIAR, as the largest research organisation working on tropical livestock health, which could be an avenue for further AMR research. The UK's Newton Fund and Global Challenges Research Fund are other channels

for research funds, especially for multi-disciplinary applied and operational research. Finally, the UK's Global AMR Innovation Fund has sought to not only fund neglected areas of AMR R&D but to leverage additional funding from other donors. Within its portfolio, it is running joint research competitions with China and Argentina, with the International Development Research Center of Canada and has invested in CARB-X, which is majority-funded by the US Government.

11. An example of research partnerships that address challenges on the ground is the Fleming Fund collaboration. The Fleming Fund has worked with the MRC and the DHSC Global Health Research Team to align with a £10 million call for research on AMR in low and middle income countries. Now that grantees have been selected, they will be matched with the Fleming Fund country grants teams. Fleming Fund-built surveillance infrastructure will thereby benefit the research projects. On the other hand, data and findings from the research projects will inform the work of Fleming Fund country grants, either in real time or in exploring possibilities for the future.

12. The recently-announced Global AMR R&D Hub led by Germany must be supported to play a prominent role in encouraging coordination and facilitating collaboration in international research efforts in AMR, particularly at a political level, building on existing efforts and adding value to the system. The UK hopes that the Hub will provide a forum which makes the case for continued high-level investment in AMR R&D and strengthening of research partnerships, especially with leaders and researchers in the Global South. Alongside this, we expect it to facilitate global conversations on R&D priorities which will help avoid duplication and identify complementarity, thereby boosting research into areas of AMR that are currently under-resourced. It will be important for Hub governance and outreach to properly reflect the needs and priorities of emerging economies and low/lower middle income countries. We recognise the Hub's role as one of coordinating and advocating, however, rather than funding.

13. There is a significant research void in understanding and communicating the impact of the colonisation and infection of humans and animals by resistant microbes (for example, calculated values for complications from routine surgeries: death, illness, lost productivity and healthcare costs). This lack of burden evidence limits our ability to make a compelling case for action to policy makers and to prioritise intervention strategies.

14. The role of the environment in AMR transmission and the impact of AMR on the environment is poorly understood. There is currently negligible research investment in considering the impact of AMR and associated antimicrobial pollution on ecosystems, for example soils. Human health research on AMR should include indirect effects. The example of neonicotinoids and bee health illustrates why it is important to evaluate risks of pollution in a wide context. More investment and coordination is needed for this to happen.

15. We understand that other IACG discussion papers consider other responses to AMR, and we would suggest considering the cost and impact of each intervention that collectively the IACG will recommend next year. Our response to AMR needs to extend well beyond the development of new antibiotics, diagnostics, vaccines and alternatives. Efforts are also needed in other areas, including infection prevention and control, farming practices, environmental management, and behaviours within healthcare settings and beyond. We need to consider whether research into new health technology solutions represents the best value for money, in terms of improved outcomes. For example, the UK has decreased the harm done by *Clostridium difficile* through improved prescribing, rather than the development and use of new drugs.

Question 2: What will it take to increase and sustain donor and private funding of R&D in AMR?

16. It is important that we secure balanced support for R&D funding across the full spectrum of R&D needs, as described above. While funding for therapeutics, vaccines, diagnostics and alternative remedies is important, it should not come at the expense of consideration and support for the wider needs. In the absence of such support we are at risk of introducing new therapies to which resistance will inevitable rapidly emerge and spread. This will require us developing and making the economic case for benefits arising from new medical countermeasures and from other interventions including, for instance, the economic benefits of improvements in animal husbandry on food security, at a country level, and financial returns, at the producer level.

17. In the UK, we are working on remodelling reimbursement for antibiotics to ensure that their price reflects their value to society, and to effectively de-link profits from the volume of product sales. It is important ensure that other countries are also engaged in equivalent work, in a way that is tailored to their specific healthcare system whilst also ensuring global coherence, especially in relation to IP management, rules on appropriate use, access and affordability. The UK's model will be but one form of financial incentive for developing new antimicrobials.

18. However, we must not rely solely on governments to provide the financial incentives for bringing new products to market. Many reports have advocated for governments to pool funding into a large incentive to develop new antimicrobials. While there has been support for these suggestions on the global stage, no practical market incentive options have been trialled on a regional or international scale. It needs to be made clear to pharmaceutical companies that, in the absence of swift collaborative action from global leaders, the call for funding will fall to donors, private funders and pharmaceuticals themselves. Given the urgency of this issue, industry cannot simply continue to divest from this R&D area and rely on action at the state level.

19. To increase R&D funding, we need to accelerate the communication of the economic case for investment in AMR, which has been clearly laid out in several reports to date, including the 2016 Review on AMR[1] and the World Bank's 2017 report[2]. More analysis remains to be carried out on the impact and value of investment into vaccines and diagnostics.

20. Pharmaceutical company shareholders should continue to push for greater investment into R&D into new drugs from industry as a form of corporate social responsibility, and also as a means of protecting their profits. Other treatments that are often used alongside antibiotics, for example cancer drugs, will become redundant if resistance continues to grow. Pharmaceutical companies should invest in new antibiotics to ensure continued profit from existing investments. In addition, developing a global public good could be badged as a corporate social responsibility contribution.

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[1] O'Neill J (chair). Review on antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014. Available at http://amr-review.org/

[2] World Bank. 2017. "Drug-Resistant Infections: A Threat to Our Economic Future." Washington, DC: World Bank. License: Creative Commons Attribution CC BY 3.0 IGO. Available at www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

21. UK funding for the new AMR Benchmark describes pharma investment in AMR-relevant research, which is almost always publically financed, at least in part. Governments supporting product development partnerships (PDP), including the UK, could do more to use the Benchmark data and influence increased company investments, and shape access and stewardship frameworks. The Access to Medicines Foundation, publisher of the Benchmark, is working effectively with investor platforms to influence fund manager decisions, and there is scope to do more with this stakeholder group.

22. Countries could also encourage more co-funding from pharmaceutical companies, for example through a Pay or Play scheme.

23. To attract more donor funding, it would be useful to not only continue to emphasise the economic case for investment, but also to look at the human cost of failure to act. To do this effectively, we should work with existing national and international communications campaigns to highlight how AMR-associated morbidity and mortality psychologically, economically and socially affects individuals, their families and healthcare systems as well as national economies. Civil society has a greater role to play here, and there are lessons to be learned from successful campaigns in HIV/AIDS.

24. AMR is a development issue: low-income countries stand to be particularly hard hit by the social and economic burden of AMR, with food security threatened, increased numbers of people living in extreme poverty and the progress made thus far reversed. For this reason, there should be greater investment in AMR from philanthropic organisations that address the development agenda.

25. Awareness-raising campaigns and associated calls for increased donor and private funding should build towards the next key milestone: the Secretary General's report back to the UN General Assembly in September 2019.

26. We need to promote the development of global Target Product Profiles (TPPs)[3] to guide R&D efforts relevant to human and animal health. Funding for new antimicrobials, new therapies, vaccines and diagnostics must be fully aligned with existing global public and animal health priorities for AMR prevention, to steer R&D towards the areas with the highest public and animal health need. TPPs need to be updated on a regular basis to keep them current with evolving public and animal health needs. The development of TPPs for antimicrobials needs to be based on a classification of pathogens by threat level. At the global level, the WHO has developed a list of priority pathogens, which will inform global R&D priorities for effective antibiotic treatments and TPPs for human health. The US Centre for Disease Control and Prevention (CDC) completed a comprehensive antimicrobial resistance threat assessment specifically for the US. An equivalent list should be produced for pathogens or bacteria of importance for animals taking into account both their animal and public health relevance.

[3] A TPP defines the minimal/ideal profile of the final marketed product and shows the ultimate goals of the proposed product development effort such as disease indication, population, delivery mode, treatment duration and regime (in the case of new antimicrobials), and standards for clinical efficacy or diagnostic use. Cost of the final product or specific technical requirements may also be included in the TPPs. It is a key strategic document for drug and diagnostic developers as it helps them to align their needs with current public and animal health priorities. TPPs may be used to assess the value and novelty of an antibiotic (or an antibiotic regimen) or a diagnostic test and thus help select those that qualify for funding

27. Accurate TPPs would represent one way of improving the uptake of new products related to AMR. Another way to improve uptake would be to clearly state the associated risks of an intervention as against the clinical benefit. Guidance on the acceptability of the risk / benefit ratio would be useful for researchers to develop user-friendly products. In addition, research into new products and interventions (including behaviour change) needs to sit alongside implementation research that considers how interventions can be implemented effectively in different settings.

Question 3: Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

28. Currently, there is a lot of theory about 'pull' incentives and de-linkage mechanisms, but very little practical action. To solve this impasse, we need technical expertise on the practical options for implementing financial incentives and de-linkage mechanisms, backed by sustained high-level political commitment from the international community.

29. There is limited analysis of how 'pull' and 'push' mechanisms reinforce each other (e.g. through models such as product development partnerships – where the focus is on developing new products with a public health (not profit) focus). The UK is a leading investor in successful PDPs - including in GARDP - and continues to strongly support the model on which they are based. It is also important to understand how any new incentives would complement the current 'high volume-low price' drug market model. Any alternative model would need to avoid recourse to high prices to restrict use; rather, incentives should be used to ensure new products are reserved for use only as appropriate.

30. The UK believes that a fully-resourced high-level working group of eminent experts dedicated solely to providing practical market incentive options would be able to provide recommendations to country leaders and finance ministers that are tailored to different regional settings, and can be taken to the piloting and implementation stage. The group would need to include experts in health systems, health economics, international finance mechanisms, drug development, drug regulation, purchasing and intellectual property and stewardship. We need to take care that this does not replicate the WHO process for the Consultative Expert Working Group (CEWG) report on more funding for R&D for neglected diseases, but also applies to AMR. The UK has proposed such a step forward to the G20 but has not yet been able to reach consensus with other G20 member states and are looking to explore alternative ways to deliver on the G20 commitments.

31. It is increasingly critical we find a solution to stimulating the pipeline for antimicrobials. Pharmaceutical companies continue to pull out of the antibacterial and antiviral market leaving a stark gap in the pipeline; it was only last week that Novartis AG shut down its antibacterial and antiviral research operations, joining other pharmaceutical companies that have pulled out of the field in recent years such as AstraZeneca.

32. To be successful, this working group would need to have international political support at the highest level. This means clear and sustained support from leaders, especially of high-income countries, and commitments to provide financial backing to overcome the existing market failures which prevent the end-stage development of new antimicrobials. This support needs to be One Health, covering human, animal and environmental health.

Question 4: How should the design of incentive mechanisms be coordinated at global, regional and national levels?

33. This answer to this question best falls to a working group of eminent experts, as proposed above. If the mechanism is to be global or regional, then the design must be coordinated at the level also. If it is to be national, then it will have to be tailored to the specific country context. What is clear is that incentive mechanisms – whilst implemented nationally or regionally – need to share common principles around stewardship, access and affordability. Both high-income countries and the Global South need to be committed to, and involved in, finding a solution so as to avoid a 'tragedy of the commons' along the lines of climate change.

34. In the 2017 Hamburg declaration, G20 leaders committed to *"further examine practical market incentive options"*. The IACG should call upon G20 leaders to implement these commitments.

Question 5: How could current efforts in R&D coordination be strengthened?

35. The WHO Blueprint on R&D is broadly valued as setting out the consensus on priorities in pandemic preparedness. There may be a case for WHO (or even the Global AMR R&D Hub) to coordinate information about 'best in class' proposals against AMR priorities across the globe and support the development of portfolios where unsuccessful work can be stopped early and resources reallocated to more promising options. A focus on individual funders/country-based funding will favour work in that country, which is not necessarily going to support the best science. Mechanisms for coordination need to agree global portfolio approaches and collaboration rather than competition to succeed. A new global resource pooling mechanism would be politically challenging.

36. One suggestion would be to establish a One Health AMR Secretariat where the strategic research priorities on human, animal and environmental health could be agreed, promoted, and reported. This would help move the conversation beyond the human-health led work undertaken by WHO in Geneva and promote strong, multidisciplinary, cross-organisational working beyond the current siloes.

Question 6: Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

37. High-income countries should do more to invest in vaccines, diagnostic technologies and surveillance systems for use in low and middle-income countries, including developing and providing products in partnership that are appropriate for the setting, and running locally-tailored awareness-raising programmes about the benefits of both. This could include for example expanding the existing WHO programme on the detection of substandard and falsified medicines.

38. It is important to conduct behavioural research on uptake and adoption and then develop interventions that are specific to certain populations, for example gender-specific interventions in animal husbandry in LMICs where women are most likely to manage animal welfare. Or interventions with new health technologies that specifically target women in LMICs, where women are less likely than men to access modern health technologies.

39. High income countries should help to build capacity in LMICs where the value of AMR-related products is understood to ensure that the population is aware of new products and the ways in which they could benefit from them.

40. We would also support the streamlining of regulatory processes and pathways for both animal and human medicine, which would allow innovations to reach the people (and the livestock/fish) who need them faster.

41. Access to, and responsible use of, essential, effective antimicrobial treatments, vaccines and diagnostics and prevention of AMR are one of WHO's core health system building blocks, critical for making progress on universal health coverage and strengthening health systems sustainably and equitably. The UK and other governments should ensure that the health systems and UHC agendas integrate AMR-specific and -sensitive interventions into policy dialogue for improving quality and effective coverage.

42. At country level, we need innovation and demonstration with government partners and others to explore and promote use of new and existing diagnostic technologies, linked to effective treatments, and best possible drug selection to minimise the development of AMR, and ensure those with resistant infections are on appropriate treatment (examples include VL testing, and effective 2L treatment for HIV, supporting the use of Genexpert and bedaquiline for MDR TB treatment, use of dispersible amoxicillin for pneumonia, ensuring access to BP for syphilis treatment, and others); and reducing misuse of antibiotics (for example scaling access to Zn/ORS for treatment of diarrhoea along with CME for providers).

43. The barriers to the effective use of vaccines and therapeutics are not the same in livestock and humans. Farming is an entirely private-sector activity, and commercial distribution networks need viable markets for products. The biggest issue in getting vaccines into use is the lack of a financially sustainable business model for rural areas. These models work well in areas close to cities, with strong demand, good infrastructure, access to finance and animal health support etc. The PDP GALVmed is testing five different private sector-led distribution approaches, providing de-risking finance in the hope this will provide proof-of-value for these markets.

Question 7: Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

44. To avoid duplication of work, existing funds should be extended to include AMR. Teams within funds working on AMR should liaise regularly to ensure that work is complementary and covers the whole breadth of the One Health agenda. Gavi, the Global Fund, the Global Financing Facility and Unitaid all recognise and are taking action to address AMR in their national programme funding, and work with AMR bodies within the UN Tripartite. Medicines supplied through such global funds for HIV, malaria and TB have to be effective or to have options for where there is resistance. UK and other funding partners need to continue to push for AMR-sensitive programming in country national strategies.

45. Innovation plays an essential role in tackling AMR. Unitaid, for example, explicitly works to overcome barriers to access to new tools and fast-tracking innovation to prevent, diagnose and treat HIV/AIDs, TB and malaria. Up to half its current portfolio supports innovative grants to stop bacteria, viruses, fungi and parasites from becoming resistant to the antimicrobial drugs used to treat the infections

they cause. Unitaid's work on fever management for example, is linked to AMR as it responds to the critical gaps in innovation and access to improved diagnostic tools to distinguish between bacterial and non-bacterial infections.

46. There is scope for expanding investment in developing effective and scalable innovations for the small scale private sector which is responsible for significant prescribing and OTC distribution, and where the majority of poor clients first seek care in developing countries. Evidence based interventions to improve responsible practice are limited, with most progress in TB (e.g. public private mix in India).

Question 8: How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

47. The UK would support the following additions to the guiding principles:
    a. Partnership / collaboration: Ensure that a specific percentage of all R&D projects are conducted as collaborative projects between researchers in different countries in order to ensure context-specific interventions and high uptake
    b. Interdisciplinarity: Because AMR is an interdisciplinary issue that affects all different settings, ensure that, where appropriate, R&D projects engage researchers from across disciplines

48. The UK supports exploring the idea of global guiding principles in R&D funding for AMR. This could be operationalised through an agreed 'charter' or similar non-binding instrument agreed at member state level. However, we would need to ensure it lines up with UK guiding principles in other areas of market failure, for example products for tropical diseases.

49. We consider it important to also strengthen global consensus on ensuring all publically funded research is made available as open-source, that both positive and negative findings are published in a timely manner, that all research, and especially clinical trials, are carried out according to the highest ethical standards and that funding flows are transparent.

Question 9: Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

50. Strengthen analysis and sharing of international scientific evidence on the development, transmission and control of antimicrobial resistance in food, agriculture and the environment, including making data openly available and encourage the transfer of technology in this area.

51. Support the development of new effective preventive vaccines for animals and increase the knowledge base concerning the barriers that influence the wider use of vaccination and diagnostics in veterinary practice.

52. Increase funding for R&D into improving husbandry practices at low cost to farmers to prevent infection and reduce the amount of antimicrobials used prophylactically, for example, with more research into building design. This should also include research into the feasible and uptake of biosecurity measures in the event of an outbreak of drug-resistant disease. This research should be carried out in different resource settings and take into account the financial capacity for intervention uptake.

53. One of the most pressing research pieces in One Health is examining the potential impact of environmental pollution with antimicrobials, active pharmaceutical ingredients, resistant pathogenic microbes, resistance genes and other determinants (e.g. heavy metals) on rates of resistance microbes in humans and animals, and the resulting health, social and economic impacts. This is mentioned in the paper by IACG sub-group on 'Reduce unintentional exposure and the need for antimicrobials, and optimize their use', but is worth reiterating in the context of research. The UN Environment Agency should be supported to follow up on the commitments made in the UNEA-3 resolution to respond to this question by UNEA-5, and held accountable for their responses.

54. Member States must likewise be supported and encouraged to implement the call to put in place appropriate discharge control measures, perhaps through a programme similar to the UN Tripartite questionnaire on National Action Plans, whereby countries self-assess their progress against this commitment and the results are published publicly.

Question 10: How and which organisation(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?

55. The Tripartite (WHO, FAO and OIE) should lead on this work as per their commitments in WHA68.7, on the condition that they continue to strengthen their inter-organisation collaboration.

56. High-income countries (HICs) should be encouraged to use their Official Development Assistance to build research and development experience and expertise both in other HICs and in low and middle income-countries, through sustainable, productive and equitable research partnerships and consortia. They can also promote this through their investments in existing R&D and PDP activities – many of the organisations supported are involved in building capacity for R&D, access to products, tech transfer for manufacture etc.

United States

IACG AMR: Invest in innovation and research, and boot R&D and access

US Government Comments

This is an area that has been the subject of multiple papers and reports already. Consider outlining 1-3 key actions or clear recommendations for each section.

In regards to 'Open questions': The U.S. government subject matter experts would gladly participate in submitting input to these and other questions outlined in the report. It would be helpful to understand when the IACG process will allow an opportunity to offer this input.

Throughout the paper, suggest replacing 'tackle' with 'address' when discussing the issue of AMR. Tackle is slang and misrepresents the appropriateness of the work we are doing to combat AMR.

There is only a cursory discussion about the need for stewardship programs. Certainly in this document it's important to mention it as a key program needed to sustain activity of new drugs.

The primary focus of this document seem to be related to development of new antimicrobials (and brief mention of diagnostics and ATA). Other areas of research could have been included, for example:

- More basic research on AMR pathways and attribution studies.
- Addressing prevention of AMR development and transmission.
- Research related to reviving the use of 'old'/ current antimicrobials (given that there seems to be limited promise in the pipeline of new product development); i.e., are there ways to optimize the use of what is currently available.

In Key messages 'addressing multiple challenges in R&D': One of the largest challenges is the negative return on investment. We find it very odd that this is not mentioned in key messages.

Comment for 3rd bullet, first sub-bullet 'coordinated to ensure…': The term "coordinated" needs to be better defined since NIH would not have outside agencies or organizations determine what projects/grants should/should not be funded or how much is allocated for AMR research. In addition as researchers cannot survive on one NIH or IMI grant we maintain that duplication is not always a bad thing. Funding from multiple mechanisms is typically necessary.

Comment for Introduction and Scope title, line 4 & 5, '… and the pipeline of new treatments…': This is an inaccurate statement. Donors make decision based on their priority diseases.

Page 2

Comment for first paragraph, line 8, 'promoters': Although the document focuses on product development, initially noting that research needs are broader would be useful, including research on improved methods and strategies to prevent AMR development and transmission, as well as implementation research on how to promote spread of effective methods and strategies. After noting the broader research needs, a statement could be added to indicate that the document's research section will focus on product development. Suggest adding: In addition, prevention of AMR development and transmission must be addressed, including research to improve methods for interrupting transmission, promoting appropriate antibiotic use, and preventing healthcare associated infections, as well as research on how to promote implementation broadly.

Comment for third paragraph, line 7, 'the R&D process end-to-end': As does the appropriate use of antibiotics and antimicrobials. (Stewardship)

Page 5

Comment for Fig. 1: In item# 10, HH needs to be defined.

Page 6

Comment for point 9, 'While this applies…': Even if regulatory burden is relatively low, a key challenge for "minor species" or minor uses" is the low market potential (i.e., low ROI) – and therefore, limited incentive for companies to develop.

Comment for point 10, 'restricted for use in humans…': Not necessarily true, though there may be more data requirements to assure reasonable certainty of no harm (with respect to AMR potential), in order to approve use of a critically important human AB in animals.

Comment for point 11, 'the cost of discover…': This is unclear. We assume this means collective costs associated with developing "alternatives to antibiotics" – not costs associated with developing individual products.

Page 7

Comment for point 12 title 'preclinical': Preclinical research is not the appropriate terminology for plant protection products. Suggested phrase: **Research, development, regulation and market launch of plant protection products are costly, time-consuming and complex.**

Comment for point 13, 'heavy metals or polychlorinated biphenyls': Why are heavy metals and polychlorinated biphenyls and their impact on health singled out here? Is this the consensus or official recommendation by the IACG subgroup? If so, it should be documented. If this is an example of lower priority projects, that could be explained more here or elsewhere in the report.

Page 8

Comment for Fig. 2: De-linkage can be used for multiple mechanisms and it would be best to define what is meant here. For example: delinking IPR or delinking profit when public funds are used neither of which the U.S. would support. The U.S. may agree with delinking the profit from the number of pills sold. 2. This paper consistently calls for funding based on global priorities. Domestic priorities should also be included as it is critical for nations to address controlling infection in their own localities.

Page 9

Additional bullet under 'funding for priorities could be optimized', please add: Funding levels and the intensity of research efforts should be accordance with priorities as determined by accepted risk analyses.

Comment for last paragraph, 'delinking incentives to R&D': We disagree this is an incentive. How would this encourage industry to remain in R&D and if they do not who is going to actually do the R&D? Academia is excellent for research but who would take it to clinical trials, manufacturing, and to market? If you are going to recommend delinkage you should explain how and who this will incentivize.

Page 10

Comment for first sentence, 'concept of delinkage': This misrepresents what is supported in the UN and G20 AMR declarations which is very specific in regards to AMR and does NOT include IPR or setting cost/price.

Page 11

Comment for title 'R&D coordination': This term needs to be clearly defined… It is one thing to share information on what NIH is funding and altogether something else to have an outside group such as the IACG on AMR determine what NIH should support.

Page 12 (mislabeled pg10)

Comment for 6th paragraph, 'limited transparency': We disagree there is limited transparency. NIH's Report includes a category for "Antimicrobial Resistance" which could be cited as transparent sharing of the NIH-sponsored portfolio in the research area.

Page 13 (mislabeled pg11)

Comment for second paragraph, third line, 'to more deaths…': Is this for susceptible infections? Otherwise this sentence does not make sense.

Comment for second paragraph, fourth line 'LMICs': These should be spelled out the first time.

Comment for Fig. 3: Item #4 needs to include the symbol for diagnostics. Since lack of diagnostics contribute to inappropriate use of antibiotics.

Page 14 (mislabeled pg12)

Please provide more explanation for point 1, final bullet, 'packaging…'

Please specify drug(s) for point 2, second paragraph, '41% of drug samples…'

Comment for point 4, final paragraph, 'as growth promoters…': This statement may need further qualification. Medically important antibiotics are no longer approved for growth promotion use in the US. Such uses have also been banned in other parts of the world.

Page 16 (mislabeled pg14)

Comment for point 6, 'high cost': Cost is not the only limiting factor in using new plant protection products but accessibility to new modes of action of these products. Hence, suggested sentence: **Use of new plant protection products is limited by their high cost and accessibility to new modes of action**.

Page 18 (mislabeled pg16)

Comment for fifth paragraph, 'Extending the mandates of existing funds to include AMR': Please elaborate. These funds already cover the resistant HIV, TB, malaria. It is our understanding these funds are not interested in covering the gram negatives because when compared to the others they do not have as high of a global burden.

Comment for sixth paragraph, 'Creating a new access initiative': Where will the funds for the new initiative come from? And what would be its mandate to cover pathogen wise?

Comment for 'Open questions' topic: Consider: How can the risk assessment process be used to prioritize individual and coordinated efforts?

Comment for first sentence under title ‘Cross-cutting’, ‘…the need for additional guidance for funders’: For or from? It is not clear which funders would not understand the issues. If you are providing guidance to find more funders that could have value.

Page 19 (mislabeled pg17)

Comment for ‘Gaps: absence of…’: While NIH can receive outside advice and guidance on research priorities, ultimately, NIH sets its own scientific priorities and determines how its funds for AMR are used for specific projects/grants.

Comment for ‘Open questions’ topic: The principles would need to be agreed to before they could be operationalized.

Comment for first paragraph under ‘Gaps: further…’: Increased understanding of plant and environmental sectors need to be emphasized on research needs and gaps under the One Health approach.

Page 20 (mislabeled pg18)

Comment for ‘Open questions’ topic: In response to the 2nd question, NIH supports numerous training programs and ensures sufficient resources are targeted to attract researchers to this field. We would defer this responsibility to another organization.

United States

IACG AMR: National Action Plans

US Government comments

The document does a good job of giving examples where it can of resources, lessons learned, and what has worked well. If it's possible, links to actual national level NAP might be a helpful addition.

Regarding the 'Questions for stakeholders' throughout the document: The U.S. government subject matter experts would gladly participate in submitting input to these and other questions outlined in the report. It would be helpful to understand when the IACG process will allow an opportunity to offer this input.

Throughout the paper, suggest replacing 'tackle' with 'address' when discussing the issue of AMR. Tackle is slang and misrepresents the appropriateness of the work we are doing to combat AMR.

Please define acronyms when used for the first time, comment on first bullet 'Key messages': NAP – National Action Plan

When discussing concerns about the environment, please use 'environmental issues' rather than 'the environment' in order to better address aspects of the environment rather than it as a whole. Too general.

Please consider using words like 'inclusion of' rather than 'involvement of' as to better describe the collaborative nature we are trying to maintain.

Please also use 'public health' rather than just 'health' to address strategies and plans to better address the audience.

Please include 'human and animal health' when discussing sectors involvement in AMR as we use a One Health approach to discuss AMR

Please made sure to address monitoring and evaluation together throughout the paper. It is important that both are included to understand progress and areas of strength/weakness

Page 2

Comment on last paragraph, last line, 'triangular': Please clarify. Is this one health?

Page 3

Comment for Fig. 1 'Key Challenges…': Under the category of "Data and Technical Capacity", the narrative should be revised to "Countries need data on antimicrobial use, access, and resistance…" Under the category of "Finance", the narrative should be modified to "Public and private sector….and use of antimicrobials, diagnostics, and vaccines".

Page 5

Comment for first paragraph, line 4, 'In all cases…': Consider adding statement about potential benefits (cost-saving) over time, if AMR is addressed effectively.

Comment for fourth paragraph, line 4, 'food chains, and environment.': This is a rather broad and vague term (here and throughout the document). Can this be made more clear? Some suggestion of what this would mean on a practical level?

Page 6

Comment for third paragraph, under title 2.4, 'specify targets': Suggest using the term goals, objectives, or milestones along with or instead of "targets". It is not clear what "targets" means and is not described in the WHO GAP as something agreed to.

Comment for fourth paragraph, 'countries a questionnaire…': What were the results/findings from the survey? A high level summary would be useful. Or a link to the WHO results page..

Page 9

Comment for second paragraph, third line, 'promoting implementation…': Guidelines are not sufficient to promote broad implementation. Efforts focused on implementation are greatly needed.

Page 12

Comment for Fig. 3: Why are PPPs listed twice? The organization of the "Sources" is unclear?

Sentence restructure for final paragraph, second to last sentence, please add: It is now on an investment framework to help countries to identify where resources will have the greatest impact is urgently needed.

Page 13

Comment for last bullet in 'Questions' box, 'transmission': This is intended to include understanding of improved methods and strategies for preventing AMR, as well how to promote their implementation. Please consider adding: "For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission development of improved methods for combating AMR and conducting antibiotic stewardship as well as strategies to promote implementation or the economic…"

United States

IACG Surveillance and Monitoring for AMU and AMR

US Government Comments

Throughout the paper, suggest replacing 'tackle' with 'address' when discussing the issue of AMR. Tackle is slang and misrepresents the appropriateness of the work we are doing to combat AMR.

The document provides useful considerations for how to prioritize pathogens, data sources, etc and when and how to integrate surveillance across multiple platforms and systems (e.g. plant, animal, human). A country example of process and outcome would be helpful, and, barring that, a roadmap of how to use the tools to identify pathogens and next steps for surveillance and integration could be helpful.

In regards to the Questions for Stakeholders: The U.S. government subject matter experts would gladly participate in submitting input to these and other questions outlined in the report. It would be helpful to understand when the IACG process will allow an opportunity to offer this input.

Page 1

Section on Monitoring: The vast majority of this section discusses surveillance, not monitoring. It would be helpful to define each term, explain how they differ (if they do), and if they are different, clearly explain when each is needed.

Key Messages 7th bullet comment 'AMR containment': Please clarify what "AMR containment" means in this context as this term of art can differ depending on human, animal,….

Page 2

Addition of more detail in line 6 under Barriers to effective surveillance topic to more directly address what we are talking about in addition to understanding this specific topic on a national level: A further barrier may be difficulty in implementing international guidelines for surveillance of AMR and AMU at the national level.

Page 9

Comment for topic title Standardized: CLSI publishes international standards for susceptibility testing of bacteria from animal origin in the following document: *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals, 5th Edition*. This should be included as a reference in the document.

CSOs and NGOs

Antibiotic Resistance Coalition and Civil Society

ANTIBIOTIC RESISTANCE COALITION AND CIVIL SOCIETY INPUT TO THE INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE

May 2018

Signatories:

African Christian Health Association Platform
Alliance to Save Our Antibiotics
American Medical Student Association
Center for Indonesian Veterinary Analytical Studies
Center for Science and Environment
Consumers' Association of Penang
Ecumenical Pharmaceutical Network
Food Animal Concerns Trust
Health Action International
Health Care Without Harm
Health Justice Philippines
IFARMA
Initiative for Health & Equity in Society
Institute for Agriculture Trade and Policy
National Resources Defense Council
Oceana Chile
Pan-African Treatment Access Movement
People's Health Movement
Public Citizen
ReAct – Action on Antibiotic Resistance
ReAct Africa
ReAct Asia Pacific
ReAct Europe
ReAct Latin America
ReAct North America
Sahabat Alam Malaysia (Friends of the Earth Malaysia)
Society for International Development
Sustainable Food Trust
Third World Network
Universities Allied for Essential Medicines
US Public Interest Research Group
What Next Forum
Yayasan Lembaga Konsumen Indonesia (Indonesian Consumer Organization)

Introduction:

As the work of the UN Interagency Coordination Group on Antimicrobial Resistance proceeds, we would like to share some inputs into these important deliberations. Members of the Antibiotic Resistance Coalition and its civil society partners convened for a meeting co-organized by ReAct, the South Centre and Third World Network, *Charting a Future Free From the Fear of Untreatable Infections: A Civil Society Agenda*, from May 7 to 9 in Geneva, Switzerland. Drawing from these discussions and building on the unifying principles laid out in ARC's Antibiotic Resistance Declaration and its previous policy statements, we have put forward some considerations for the IACG's recommendations. These points also underscore the charge laid down by the UN Political Declaration on AMR that led to the creation of the IACG.

Given that the IACG's work currently is organized into six Subgroups, we have prepared our inputs into the six thematic areas, although we anticipate that these inputs may well feed into the work of multiple Subgroups and the consideration of the IACG overall. As the IACG's work in these areas becomes available for public consultation, members of the Antibiotic Resistance Coalition look forward to providing additional feedback. In the process of generating these inputs for the IACG, over fifteen civil society groups provided feedback to the Antibiotic Resistance Coalition's Secretariat for consideration.

Subgroup 1: Communication, public awareness, behavior-change, professional education and training

- Effective communication involves more than just broadcasting information: it should mobilize key constituencies. In such public awareness campaigns, civil society should be recognized and included for its critical role as a vehicle for communicating for public awareness and behavior change over AMR, and this should be an integral part of the implementation of National Action Plans.
- Communication for behavior change should involve empowering local champions, both among providers and patients as well as communities and civil society. Any NAP implementation or global strategy on AMR should acknowledge the importance of rooting such efforts more sustainably in networks of local champions and advocates. The work on AMR will not be a short sprint, but a marathon.
- Professional associations and industry groups should be encouraged to come out with position statements, if not codes of conduct, for its members regarding antibiotic use, marketing and AMR. These position statements and codes of conduct can be tools to induce behavior change—even if they are not legally enforceable--in these groups.
- Specific training modules could be developed for engaging professional groups, and efforts should be made to increase awareness through short training sessions. There should be a clear action plan in place, regarding development of these modules and administering them.
- AMR and Infection Prevention and Control (IPC) integrated modules should be incorporated in curricula of prescribers and other healthcare groups, those should include a focus on communication skills to empower health professionals to challenge misuse or overuse of antibiotics in practice
- Regulatory bodies should be engaged in ensuring AMR modules are included in recertification and continuing professional education for all health professional groups.
- The public narrative for addressing antimicrobial resistance should move away from the war metaphor to one that recognizes more holistically the ecological interplay between humans and bacteria in the environment. This has significance in how we approach this challenge, from the overuse of antibacterial agents in our built environment to the need for greater understanding of how a healthy microbiome might resist infection by bacterial pathogens.
- Especially given limited resources, targeting communication efforts is key. In the short and medium term, focusing on raising awareness in specific interest groups can be a potentially high impact activity. It can help in channeling resources to achieve specific objectives in raising awareness among these groups, which can lead to behavior change. Context specific and culturally appropriate communication mechanisms

should be adopted to convey and create a sense of urgency and mobilize societal action for AMR

- Low- and middle-income countries suffer from weak health systems and other practices that can potentially drive up the rate of AMR, such as poor conditions of sanitation and environmental hygiene. Some of these countries are still grappling with other endemic disease challenges as well as the HIV and AIDS pandemic. There is need for special focus on these countries to ensure that the threat of AMR is adequately communicated to all relevant sectors, and that national and regional responses against AMR are initiated and maintained.
- Targeting the focus of AMR behavior change efforts is also strategic. The example of Thailand's Antibiotic Smart Use project is instructive. By focusing on three conditions—cold, cough and diarrhea—the messaging is clear, and impact, more easily measurable. By providing an herbal treatment alternative for palliating viral causes of fever, the project also took into account the sociology of the doctor-patient encounter.
- The Tripartite Agency Monitoring & Evaluation framework for AMR must include indicators that are transparent, actionable, and focused on measurable changes in behavior, not just attitudes or knowledge.
- Monitoring for accountability can give important impetus for motivating behavior change. Such monitoring requires effective surveillance and data collection as well as a commitment to making such information transparent and actionable by the public, civil society and policymakers.
- Effective monitoring systems will produce data that—when placed into the hands of civil society or the public—will yield policy triggers. For example, antibiotic residues or drug-resistant pathogens on retail grocery shelves can serve to alert the public and regulatory authorities alike.
- There is a risk of groups with commercial interests (like pharmaceutical companies or organizations funded by them) taking over the campaign and orienting it in ways which can benefit them or their interests. There should be an institutional mechanism to evaluate potential partners regarding their commercial interests and funding channels. This would be an institutional safeguard against conflict of interest in addressing AMR.
- The IACG should encourage collaboration between governments and civil society organizations towards public education efforts. While governments can reach local institutions, government officers, and political and regulatory bodies, CSOs have the capacity to connect with opinion leaders, local actors and communities where governments may have limited reach.
- The work of the IACG itself must reflect the principles of transparency, accountability, broad consultation including with civil society, and conflict of interest disclosure in all of its deliberations, so that the communication

of its findings and recommendations will be credibly received.

Subgroup 2: National Action Plans, including measurement and surveillance

- National Action Plans (NAPs) should make clear and concrete commitments to the principles in the UN Political Declaration on AMR, including but not limited to the charges to
    - "Develop multisectoral national action plans, programmes and policy initiatives in line with a One Health approach and the global action plan on antimicrobial resistance…" and
    - "Take steps to ensure that national action plans include the development and strengthening, as appropriate, of effective surveillance, monitoring and regulatory frameworks on the preservation, use and sale of antimicrobial medicines for humans and animals that are enforced according to national contexts and consistent with international commitments."
- The IACG should provide a clear roadmap to "mobilize adequate, predictable and sustained funding and human and financial resources and investment through national, bilateral and multilateral channels to support the development and implementation of national action plans, research and development on existing and new antimicrobial medicines, diagnostics, vaccines and other technologies and to strengthen related infrastructure, including through engagement with multilateral development banks and traditional and voluntary innovative financing and investment mechanisms, based on priorities and local needs set by governments, and ensuring public return on investment." These resources should not only be limited to human health sectors, but also span animal, agricultural, and environmental sectors. Similarly, the IACG's roadmap should recommend resource mobilization not only for the development of new technologies, but also for innovation of practice, which includes stewardship in the healthcare delivery system and sustainable farming to mitigate the overuse or misuse of antimicrobials across sectors. Animal, agriculture and environment sectors should receive adequate attention.
- NAPs on AMR must recognize the challenge of underuse, not just overuse, of antibiotics and anticipate as well as support the transition of livelihoods, particularly of those marginalized or engaged in small-scale agricultural operations, in implementing these policy initiatives.
- The implementation of NAPs must recognize how the local context varies, and those providing technical support should work to develop approaches that are culturally sensitive and context specific. This will require investing in the innovation of local approaches to access and stewardship of antibiotics in both healthcare delivery and in food

production as well as in the sharing and adoption of best practices.

- The NAP process should not only take a One Health approach and involve key stakeholders from the healthcare delivery, food production and environment sectors, but also must engage civil society for effective implementation, assessment and reporting of NAP progress. The implementation of NAPs will require rooting these efforts in the mobilization of key constituencies best reached by enlisting civil society.
- Harnessing the potential of civil society and other actors may be helpful in building political will and momentum and would increase transparency of national progress on AMR.
- Given limited resources, support should be provided to country governments, so that they may assess what measures or interventions to prioritize in addressing AMR. These priority-setting approaches should be transparent to the public along with the data driving these decisions. Governments should be supported to cost action plans and build the economic case--factoring in both direct and indirect benefits--for informed decision making among competing priorities to address AMR.
- In order to derive maximum effectiveness of AMR containment efforts in the short-term, IACG should consider focusing on select high-priority countries. The criteria for selection could include the extent of antimicrobial use and production; consumption, export and import of meat and other food animal products; and infectious disease burden.
- The NAP process should ensure that policymaking is not distorted by financial conflict of interest. Implementation of the NAP will require receiving input from a broad range of stakeholders, including those with commercial interests; however, this can and should be done without compromising the public's interest and without having public policy decision making influenced unduly by those commercial interests. This is a clear signal that the IACG should communicate in its recommendations as well as its own deliberations.
- Many of the members of the Antibiotic Resistance Coalition work on AMR as part of a larger set of development concerns cutting across sectors. From this experience, it is clear that NAPs too must integrate the work of AMR into larger development concerns, as recognized in the Sustainable Development Goals and Universal Health Care Agenda 2030 as well as AMR-sensitive efforts like WASH, and not just rely on vertical programs focused on AMR.
- Irrational antibiotic use is driven by health system issues with many countries having a largely unregulated and heterogenous private health sector with over-the-counter sale of antibiotics (including irrational FDCs, which should be clearly differentiated from rational FDCs included in the WHO's EML). NAP implementation would be very difficult unless the health system issues

are concurrently addressed through Universal Health Coverage and SDGs.

- The IACG should specifically provide a clear approach to harnessing technical support from WHO, FAO, OIE and other intergovernmental stakeholders such as UNEP, UNICEF, and UNDP for supporting NAP implementation. The IACG should recommend an approach that ensure coordination, consensus and coherence in guidance and communication at the global, regional and country level. Similar to how the WHO, FAO, and OIE are operating at the global level, there should be similar coordination at the regional and country levels between their respective offices in close collaboration with other key partners, including other UN agency offices and civil society within the region and in country.
- In the wake of the limited focus so far on environmental aspects of AMR, the IACG should push for collective efforts for global guidance, standards and capacity to manage waste from farms, industry and healthcare settings. It should expedite effective integration of UNEP across all potential sectors and involve other environmental groups to fill the gap and leverage local expertise. AMR should no longer remain a mandate specific to the tripartite and move beyond to include environmental agencies. In addition, the tripartite monitoring and evaluation framework needs to evolve to include suitable environmental indicators.
- Monitoring and evaluation of progress on implementing national actions plans should build on the WHO's M&E framework, but reviews of progress should also take stock of the gaps, bottlenecks and barriers to implementation in countries and elevate such findings to the appropriate political level for consideration on how to address these.

Subgroup 3: Reduce need for antimicrobials and unintentional exposure, and optimizing use

- The indisputable need for innovation to bring new antimicrobial medicines to market has overshadowed the importance of other forms of innovation. These include the repurposing of older antibiotics and development of effective combination products; R&D of new diagnostic and vaccine technologies that would reduce the need for antimicrobials; and the piloting and scaling of improved antimicrobial use practices, both in stewardship in healthcare delivery and in animal husbandry and aquaculture practices in food production systems. Global financing and coordination of innovation to address AMR must extend to these other priorities.
- Access and stewardship should be recognized as twin goals, and there must be efforts to address the challenge of lack of access to antimicrobials, particularly for people living in areas with weak health systems, not just overuse of these life-saving drugs. Efforts should also more fully appreciate

the role that diagnostic support can play in allowing the appropriate use of antimicrobials.

- Substandard and falsified antibiotics contribute to the challenge of rational use of antibiotics in healthcare delivery and subsequently to antimicrobial resistance. They are a major issue that needs to be urgently tackled in many developing countries. The regulatory agencies of each country should be given the mandate and adequate budget to conduct inspections. Ensuring access to safe, effective antibiotics and diagnostics requires well-resourced quality assurance mechanisms. The use of traceability mechanisms from production to dispensing, secure packaging, pharmacovigilance, including postmarketing surveillance systems, and technological measures to prevent falsified medicines can possibly reduce the burden of the issue.
- Also problematic is the illegal marketing of unregistered, fixed-dose combination antibiotics by multinational companies, such as those identified in a recent study of the Indian marketplace.
- Better training of health professionals could help curb excess use through non-commercial, evidence-based programs, including those that emphasize the importance of infection prevention and control practices in healthcare facilities. Private healthcare providers and low-skilled and/or informal providers should also be included in these efforts.
- Payment incentives for healthcare professionals should be aligned, so as not to exacerbate inappropriate use of antimicrobials, but rather to support appropriate access and to incentivize effective stewardship. Educational programs or marketing on antibiotic use sponsored by drug companies pose a financial conflict of interest that should be avoided.
- Manufacturers and those selling antibiotics to providers, farmers, consumers and others in both the healthcare delivery and food production systems should be prohibited from marketing for inappropriate uses or incentivizing medical and veterinary personnel to overuse or inappropriately prescribe antibiotics.
- Professional associations and organizations and collectives of hospitals and healthcare providers should play an important part in all initiatives for reducing antibiotic use, in the human, animal and environmental sector.
- A major part of the strategy in reducing the reliance on antimicrobials in the food system requires reforming food production systems using innovative strategies and agro-ecological approaches that do not harm the health of people or the planet. Lowering stocking densities, providing access to the outdoors, using more resilient breeds are all farming practices which are known to reduce the need for antibiotics and should be encouraged.
- As stated by the European Food Safety Authority and the European Medicine Agency, “In some farming systems, much reliance is placed on the routine use of antimicrobials for disease prevention or for the treatment of

avoidable outbreaks of disease, such that these systems would be unsustainable in the absence of antimicrobials. The stress associated with intensive, indoor, large scale production may lead to an increased risk of livestock contracting disease." According to EFSA and the EMA, "Farming systems with heavy antimicrobial use should be critically reviewed, to determine whether/how such systems could sustainably reduce the use of on-farm antimicrobials. If a sustainable reduction in the use of on-farm antimicrobials is not achievable, these systems ideally be phased out." The IACG should support policies aimed at phasing out any farming practices or systems which are unsustainable in absence of high levels of antibiotic use.

- Antibiotics should be available to treat diseased animals. But antibiotics considered critically important for humans must not be used for animals, except under veterinarian oversight for very narrowly defined circumstances treating diseased animals to save lives or prevent serious suffering when no alternatives exist.
- Food produced without routine use of antibiotics and without antibiotic residues should be labelled through reliable, certified schemes to facilitate consumer choice. Food produced with routine use of antibiotics must be clearly labelled, until effective prohibition of such antibiotic use can be introduced.
- By choosing to purchase food produced without the routine use of antibiotics, both consumers and procurers of food can play an important role in shaping how suppliers use antibiotics in bringing their product to market.
- The IACG's recommendations should include the recent WHO guideline on the use of medically important antimicrobials in food-producing animals in its report for the consideration of, and support by, Member States at the UN General Assembly and relevant international bodies. These guidelines represent an important step in curbing the use of antimicrobials for growth promotion and preventative use in the food system.
- Feed containing antibiotics and its labelling, marketing and imports remain largely unsupervised. There is a need for oversight mechanisms of the claims being made, of the online marketing and of the importing of feed and premixes. There is also a need for policy frameworks to be created for data disclosure on antibiotics used and sales of feed.
- Several alternative products (such as probiotics, prebiotics) are already being used in food animal production. Their potential role in reducing the need for antibiotics needs to be included in the global discussion on antibiotic resistance reduction.
- The potential environmental impact of antibiotics does not stop with discharge from manufacturing plants, but also extends to the run-off from agricultural operations and to point source pollution such as hospitals where these antibiotics are used. Studies have shown that the prevalence of antibiotic resistance in bacteria of public health importance can

be increased by this antibiotic pollution. Therefore, antibiotic resistance should be included in environmental risk assessments of human and veterinary antibiotics. Measures to reduce agricultural antibiotic pollution, such as proper composting of manure or treatment of slurry, should be introduced.

- There is now clear scientific evidence (Sandegren, 2014) that the "minimum selective concentration", above which an antibiotic selects for resistant bacteria, can be many times lower (in some cases hundreds of times lower) than the minimum inhibitory concentration (MIC). This has important implications for the setting of Maximum Residue Limits (MRLs) for residues of antibiotics in foods. The current method for setting MRLs assumes that no selection for resistance can occur below the MIC. There is, therefore, a need to revise the method for setting MRLs, which may need to be significantly reduced in many cases in order to avoid residues selecting for resistance in the human gut.
- Ensuring effective stewardship of antimicrobial use in both the healthcare delivery and food production systems requires a monitoring system with data collection and transparency.
- The pharmaceutical industry can play its role in supporting effective stewardship by disclosure of data on antibiotic production and sales and on the disclosure of antibiotic API discharged as effluents from manufacturing plants.
- To reduce antibiotic pollution, the pharmaceutical industry could take greater responsibility in the safe disposal of unused or expired antibiotics across the supply chain, such as through antibiotic take-back programs from consumers, retailers, and bulk drug dealers.

Subgroup 4: Invest in innovation and research, and boost R&D and access

- The IACG should be guided by the principles laid out in the UN Political Declaration on AMR: "all research and development efforts should be needs-driven, evidence-based and guided by the **principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility…**" [emphasis added].
- Similarly, the UN Political Declaration notes, as should the IACG in its findings: "we acknowledge the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access…"
- For delinkage to ensure access and stewardship, healthcare delivery system actors that engage in stewardship of and provide access to antimicrobials, not just drug companies, must be involved in constructing the arrangements.
- R&D incentives should foster R&D collaboration and accelerate delivery

time of a new product from "bench to bedside," through the sharing of research results, clinical trial data, and compound libraries, as well as the pooling of intellectual property rights. Such approaches have the potential to speed up development, reduce costs, and increase efficiency.

- Funding incentives, whether push or pull funding, should be aligned to ensure that public resources are invested in a coordinated fashion so that when developers receive sufficient incentives to develop new medical tools, they are not paid twice, once upfront with push incentives and again upon market entry, through pull incentives or high prices of the final product.
- In designing incentives for antibiotic, vaccine or diagnostic innovation, key operating principles should include:
    - Delinkage of a drug company's return on investment from the price and volume of antibiotic sales;
    - Transparency of R&D costs (delineated by product and clinical trial phase), clinical trial data and prices;
    - Fair and sustainable return on public investment, as benchmarked against prices obtained under generic competition or through alternative approaches such as a product development partnership; transparency on cost of goods and R&D funding; or prices achieved in a setting where the intellectual property is publicly owned and licensed;
    - Commitments to achieve affordable access and effective stewardship of these drugs; and
    - An end-to-end approach whereby, upstream incentives in the R&D pipeline should be coupled to shaping access and stewardship downstream.
- Certain incentives run contrary to the principle of delinkage and risk exacerbating the misalignment of economic rewards and antimicrobial stewardship. Such incentives include efforts to extend patent, data or market exclusivity.
- The proposal of awarding vouchers for transferable IP exclusivity for antibiotic innovation imposes an additional financial burden on important medicines needed for others, like cancer patients.
- Late stage market entry rewards will not address adequately the serious scientific bottleneck in the discovery of novel classes of antibiotics nor improved access to old, existing drugs
- To ensure this scientific bottleneck is addressed, incentives should move beyond bets on individual companies, drug by drug, to investments that transform the innovation ecosystem, from pre-competitive inputs to clinical trial platforms.
- If life-saving antibiotics are not affordable, then they will not be available to those in need. It is important for the IACG to describe policy options for ensuring the affordability of both novel and existing antibiotics,

particularly of those in short supply. The WHO-Health Action International Medicine Prices project, the WHO Vaccine Product, and the Price and Procurement (V3P) project provide useful lessons in how a standardized instrument might support greater transparency of pharmaceutical product pricing, offer a measure of affordability, and take stock of availability.

- Investments in R&D and innovation should not focus exclusively on bringing new antimicrobial drugs to market, but also on other areas of innovation that are needed to most effectively combat antimicrobial resistance, including repurposing of older antibiotics, adapting existing drugs to specific local needs, exploring the role of combination products, R&D of new diagnostic and vaccine technologies, and piloting and scaling of improved antimicrobial use practices.

Subgroup 5: SDG alignment, Global Governance post 2019, and UN role and responsibilities

- The proposed system of global governance over AMR efforts should build upon, as the UN Political Declaration on AMR does, the Tripartite blueprint for tackling AMR of the Global Action Plan on antimicrobial resistance, the Universal Healthcare Agenda, and the 2030 Agenda for Sustainable Development.
- Certain principles importantly would undergird an effective system of global governance on AMR:
    - Intersectoral collaboration, including the healthcare delivery system, food production and the environment
    - Integration of AMR into existing programs, frameworks and initiatives, while looking for specific AMR results
    - Alignment of the work of Tripartite agencies, other UN agencies and other multilateral organizations to address priority areas for AMR
    - Broad participation among countries, particularly low- and middle-income countries
    - Solicitation of inputs from various stakeholders across sectors including civil society organizations
    - Avoidance of any conflicts of interest especially among those who might shepherd a global governance process.
- Integrating AMR into the relevant international indicator frameworks, including the Global Burden of Disease Study, and into the voluntary national reviews of the implementation of Sustainable Development Goals would usefully contribute to global efforts to tackle this challenge.
- Monitoring and evaluation of progress towards an effective response to AMR is essential to ensure accountability. Such monitoring requires governments to ensure collection and public transparency of relevant data as well as the complementary efforts of civil society to hold key stakeholders

accountable. Indicators can play a useful role in holding stakeholders accountable and trigger much needed regulatory changes.

- The Tripartite Agency Monitoring & Evaluation framework for AMR must include indicators that are transparent, actionable, and focused on changes in behavior, not just attitude or knowledge.
- Global governance must include leadership in environmental AMR monitoring and surveillance, with effective integration of UNEP alongside the work of WHO, FAO and OIE.
- Tangible measures to mobilize financial and technical assistance for global and national implementation of efforts to tackle AMR; set specific indicators, milestones and targets for achievement; and put forth mechanisms for sustainable political commitment and lasting global coordination are needed.
- Efforts should be made to secure commitments towards addressing AMR from country governments in such a way that would enable low- and middle-income countries that bear a disproportionate burden in tackling AMR can do so equitably.

Subgroup 6: Surveillance and monitoring for antimicrobial usage and resistance

- Surveillance and monitoring are key to ensuring accountability in making progress towards an effective response to AMR.
- Effective surveillance systems (using quality-assured tools) must provide monitoring integrated across sectors, including the healthcare delivery system, food production and the environment.
- Concrete plans for mobilizing both financial and technical resources, including laboratory resources, for implementing local surveillance systems, particularly in low- and middle-income countries, are critical.
- While standardization is important, the design of surveillance and measurement approaches should be tiered to the stage of development or level of resources in that country setting. This tiered approach might enable broader participation among less well-resourced countries and provide steppingstones to deeper engagement as local infrastructure and capacity grow.
- Surveillance and monitoring must not only measure efforts to use antibiotics more appropriately and to avoid overuse, but also must safeguard against underuse. To ensure access, it is necessary to monitor antibiotic price, stock outs, access to second-line antibiotics, and quality of medicines sold on the market. It is crucial to involve the public and healthcare providers and put a mechanism in place to allow them to report on prices and stockouts, including those of essential diagnostic tests.
- For surveillance in human health, it is critical to ensure that national data are reflective of the resistance patterns in the community hospitals, clinics and rural areas. Access to diagnostic tools and quality-approved microbiology laboratories, hardly available in low-resource settings currently, is a crucial

element of this. Relying on data derived solely from tertiary care hospitals can overestimate resistance rates and misguide national guideline development and monitoring processes.

- Monitoring efforts should also pay attention to conflict of interest issues, both in the healthcare delivery and the food production systems. In healthcare delivery, conflict of interest can arise from misaligned financial incentives for providers to prescribe or dispense antibiotics or mispromotion of antibiotics. In the food production system, these concerns can arise when veterinarians face incentives to overprescribe antibiotics or to use antibiotics for non-therapeutic indications.
- Surveillance of antibiotic use in agricultural crops and AMR in agricultural environment and commodities should be integrated into the overall surveillance efforts. Countries need to be supported to better understand and address emergence and spread of AMR from agricultural systems, judicious antibiotic use practices and risk reduction approaches along with enforcement of standards for antibiotic residues in agricultural food products.
- Where possible, countries should collect and publish data on antibiotic use in livestock by species, and by farming system used (intensive, free-range, organic). The transparency of such data can help motivate reductions in antibiotic misuse and overuse.
- In the spirit of a true One-health approach, understanding and addressing the environmental dimension of AMR must receive greater focus at the global level and ensure that environment is adequately reflected and effectively integrated into the guidance across sectors linked directly or indirectly to AMR and lead to a greater buy-in of the environmental policy makers at a national level.
- The NAP surveillance efforts for example should encompass use and sales of antibiotics for crops and Active Pharmaceutical Ingredient levels in waste from farms, industry and health care facilities.
- Surveillance systems should take into account the evidence that the "minimum selective concentration", that is, the level at which an antibiotic selects for resistant bacteria, is many times lower than the minimum inhibitory concentration (MIC). This finding should prompt efforts to reduce the Maximum Residue Limits of antibiotics in food that assume that no selection for resistance occurs below the MIC.
- Discharge limits of antibiotics in effluents such as from pharmaceutical manufacturing, hospitals and food processing units must be determined. Waste management strategies should be formulated to reduce microbiological contamination from food animal farms and healthcare settings. AMR-centric approach should be adopted and embedded into the environmental regulations across food, feed, drug and healthcare sectors. For example,

presence of antibiotics in industrial waste or effluents such as from pharmaceutical industry should be considered as a hazardous chemical, and policy changes made accordingly.

- As part of a long-term AMR containment strategy, AMR surveillance in the environment including that of antibiotic residues, resistant bacteria and other determinants must be integrated with surveillance in human, animal and food sectors. Apart from the framework for integrated surveillance, standards and guidelines that help harmonization of testing methods, analysis and reporting across different sectors, sub-sectors and geographies should be formulated and disseminated into the country-level surveillance systems along with technical support to build capacity.

From across the spectrum of civil society engaged in antimicrobial resistance, we hope that these collective reflections will make a constructive contribution to the IACG's process in arriving at recommendations for the UN Secretary-General on this intersectoral challenge. For each Subgroup, we have sought to lay out a framework of important principles that might serve as a useful guidepost to your deliberations. We would be pleased to connect the IACG's Subgroups to parts of the Antibiotic Resistance Coalition and its civil society partners that might share further perspective on these issues.

Antibiotic Resistance Coalition

ANTIBIOTIC RESISTANCE COALITION RESPONSE TO THE INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE PUBLIC CONSULTATION

INVEST IN INNOVATION AND RESEARCH, AND BOOST R&D AND ACCESS

July 2018

Signatories:

Alliance to Save Our Antibiotics
American Medical Student Association
Consumers Association of Penang
Ecumenical Pharmaceutical Network
Food Animal Concerns Trust
Health Action International
IFARMA
Institute for Agriculture and Trade Policy
ReAct – Action on Antibiotic Resistance
ReAct Africa
ReAct Asia Pacific
ReAct Europe
ReAct Latin America
ReAct North America
Public Citizen
Sahabat Alam Malaysia
Society for International Development
Sustainable Food Trust
Universities Allied for Essential Medicines (Europe & Brazil)
US Public Interest Research Group

Introduction:

The IACG commendably has taken up the critically important and linked issues of innovation and access and the need to invest in such efforts to tackle AMR in the healthcare delivery system, the food system and the environment. Interested members of the Antibiotic Resistance Coalition (ARC) convened to develop this joint response to the questions posed to stakeholders and to provide useful input to IACG's discussions of recommendations. We understand that this discussion paper represents the work of a subgroup of the IACG members and that its work is ongoing. This discussion paper's analysis is quite limited; the questions posed, wide ranging; and the public consultation period, too short to generate analyses across the breadth of issues raised. So we trust this will be just the beginning of a process of engaging stakeholder inputs as the IACG focuses on more specific, potential recommendations. We also hope this will complement the earlier sent input, particularly on the work on *Innovation, R&D and Access*, by 28 ARC members and its civil society allies around the time of the Divonne meeting.

1. **Policy coherence with the UN Political Declaration on AMR, which gave rise to the IACG, and with the Global Development and Stewardship Framework under development by the Tripartite agencies would be important. The UN Political Declaration on AMR[1] provides a guiding beacon to what the IACG should address in its recommendations in channeling R&D funding.**

1.1 Certain key principles should underpin the IACG's proposals on research and development. This will require an end-to-end approach, whereby these principles are an integral part of the target product profiles, public financing of R&D and licensing of these products, not an afterthought upon market entry.

"…all research and development efforts should be needs-driven, evidence-based and guided by the **principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility…**[emphasis added]"

1.2 The attention of the discussion paper to the important concept of delinkage—and the failure of some potential approaches like market exclusivity to reflect this core principle—could be clearer.

"…in this regard, we acknowledge the importance of **delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales** so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines, and other results to be gained through research and development…[emphasis added]"

[1] Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. Available at: https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

1.3 *The need to create an enabling environment, infrastructure and financing for piloting new innovation models, notably those that embrace delinkage, would also be key.*

"all relevant stakeholders, including Governments, industry, non-governmental organizations and academics, should continue to explore ways to support innovation models that address the unique set of challenges presented by antimicrobial resistance, including the importance of the appropriate and rational use of antimicrobial medicines, while promoting access to affordable medicines.

1.4 *The Global Framework for Development and Stewardship to Combat Antimicrobial Resistance will be a critical instrument to steer the design and coordination of an end-to-end approach to supporting R&D, including incentive mechanisms.*

As described in the Global Framework, its reach spans from bench to bedside:[2] "As mandated in WHA68.7, the framework will support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries and in line with the Global Action Plan on Antimicrobial Resistance (GAP-AMR)."

2. Recognizing that the IACG's work continues in this area, we would flag that priority setting and financing for R&D and access can be better coordinated.

2.1 *In establishing a "Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics," WHO has provided the basis for measuring whether R&D funding is 'needs-driven' in the area of new antibiotic drugs.*

2.2 *Investments in R&D should not focus exclusively on bringing new antibiotic drugs to market, but also on other areas of innovation that are needed to more effectively combat AMR.* As acknowledged in the discussion paper, a successful response to AMR will also need to address vaccines and diagnostics. In these areas, further work is needed to set global priorities in order that R&D funding can be aligned.

2.3 *In funding R&D, supporting a portfolio of approaches remains important, but all parts of that portfolio should strive to adhere to principles of delinkage, transparency of R&D costs, fair return on public investment, and an end-to-end approach in safeguarding access and stewardship.* Product development partnerships like DNDi have a track record of setting target product profiles with affordability as a key criterion, negotiating arrangements with drug manufacturers consistent with the aims of meeting the needs of resource-limited settings, and investing in local

[2] WHO. *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance: Draft Roadmap* (WHO/EMP/IAU/2017.08). Geneva, Switzerland: WHO, 12 May 2017. Available at: http://www.who.int/phi/implementation/research/WHA_BackgroundPaper-AGlobalFrameworkDevelopmentStewardship.pdf

infrastructure like clinical trial networks. This approach is being further developed and applied to AMR by The Global Antibiotic Research & Development Partnership (GARDP), a joint initiative of DND*i* and the WHO, which aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. However, we are unclear whether the significant public investment that CARB-X has managed through drug-by-drug, company-by-company investments follows these principles. The IACG should recommend that all public funding for antibiotic R&D be evaluated and held accountable to these core principles.

The product development partnership model, as reflected in DNDi's approach with treatments for neglected diseases and through GARDP, is one that might be emulated for innovation of diagnostics and vaccines in the animal health sector.

2.4 *In financing access to health technologies to address AMR, extending the mandate of already existing funds, such as UNICEF, Global Fund, UNITAID, GAVI, would be most efficient and effective in the short term.* In the long term, as the capacity and structures grow within the existing mechanisms, there might be an opportunity to split off these parts into a self-sustained and dedicated AMR fund. Over time, it could further grow to cover needs in animal, plant and environmental health.

- If several different funds extended their missions to include AMR, it would be important to have some strategy for how to coordinate and base the funding on some common principles and guidance on how to include considerations of stewardship.
- A review of previous and ongoing funding initiatives might have value in shaping how AMR-related funding might be directed. The Fleming Fund's experience in setting priority country targets might offer useful insights. The EU model of co-funding of animal health measures to monitor, control and eradicate zoonoses could be an approach to be explored and expanded further.[3] National funds for animal health and welfare can also take a larger responsibility to address AMR.

2.5 *The discussion paper takes as given the "limited expected return on investment (ROI) of antibiotics," but this claim deserves more careful and empirical analysis than presented.* While the pharmaceutical industry has worked to keep actual R&D costs and drug-specific returns on investment non-transparent, peak revenue can be compared between first-in-class antibiotics and me-too antibiotics. First-in-class antibiotics such as linezolid and daptomycin both placed in the top 100 drugs by sales in the United States.[4] Tygacil, an antibiotic with a poor benefit-risk ratio and mortality risk, nonetheless commanded global revenues of $323 M, $304 M and

[3] Report from the Commission to the European Parliament and the Council on the outcome of the EU co-financed programmes for the eradication, control and monitoring of animal diseases and zoonosis over the period of 2005-2011. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014DC0115

[4] Based on data from Evaluate Pharma

$274 M in the years 2014-2016.[5] The uncertainty of investment seems to describe largely non-novel classes of antibiotics, which the drug industry continues to bring to market. In a study of systemic antibiotics approved by the U.S. FDA over a two-decade period (1980-2009), over 40% were withdrawn from the market.[6] Twenty out of 26 of these withdrawals were not for safety reasons. This raises the question whether the lower net present value for antibiotics is driven primarily by shorter treatment times to cure or just remarkably high failure rates because drug companies were given the wrong incentives to bring me-too drugs to market with little value added.

3. R&D funding could be significantly better channeled.

3.1 *R&D should follow an end-to-end approach, from bench to bedside, by which upstream incentives are coupled with access and stewardship measures downstream.* The value chain depicted in this discussion paper stops short of making this connection. The full value chain spans from bench to bedside, not just from fundamental research to approval. This requires engaging actors in healthcare delivery systems, not just drug companies, in designing such incentives. Delinkage is only part of this end-to-end approach, but to ensure access and stewardship of new antibiotics, providers, payers and patients have to be involved.

Shaping such a model requires a combination of push and pull incentives, rather than a focus on pull incentives such as late stage market entry rewards or extended market exclusivity which increase the cost of antibiotics, often fail to deliver affordability or availability of products to those in need, and do not ensure antibiotic stewardship. Transferable IP exclusivity proposals that transfer monopoly pricing from antibiotics to other medicines also may reduce access to patients in need when they cannot afford those medicines as a result of delayed generic entry or extended monopoly pricing.

3.2 *To be clear, every dollar paid for the purchase of antibiotics is a pull incentive. For the public sector, the key issue is targeting--where and how to invest those monies for R&D. The key bottleneck in the antibiotic R&D pipeline is upstream in the drug discovery phase, where public investments could help transform the innovation ecosystem.* Bringing a new drug to market can take upwards of a decade, so time discounting can seriously erode the value of public monies put in as pull incentives as opposed to push incentives upfront. In fact, a study authored by those closely tied to industry modeled this problem and concluded: "However, an analysis by Sharma

[5] Copenhagen Economics. *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe. Final Report,* May 2018. Available at: https://www.copenhageneconomics.com/dyn/resources/Publication/publicationPDF/5/445/1527517171/copenhagen-economics-2018-study-on-the-economic-impact-of-spcs-pharmaceutical-incentives-and-rewards-in-europe.pdf

[6] Outterson K, Powers JH, Seoane-Vazquez E, Rodriguez-Monguio R, and Kesselheim AS. Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S., 1980-2009. *Journal of Law, Medicine & Ethics* Fall 2013, pp. 688-696.

and Towse found that a key pull incentive—extended market exclusivity—had minimal impact on improving the net present value (NPV) of antibiotics. By contrast, push incentives may be of greater value. Because pull incentives should result in larger amounts of revenue than push incentives, the assertion that pull incentives are less economically valuable than push incentives may be counterintuitive. However, as we show below, **push incentives may be 95% smaller than pull incentives and still yield similar value**. [emphasis added]"[7]

3.3 *Expectations of industry returns on investment of new antibiotics should not be benchmarked against blockbuster drugs like cancer.* Such returns are, in significant measure, a result of the industry's own lobbying for extended exclusivity on these products that result in monopoly pricing. Fairer benchmarks might include what the public sector would pay if there were generic competition, an alternative pathway with a product development partnership bringing the drug to market, or a marginal cost plus model for establishing appropriate pricing.

3.4 *Target product profiles set by the public sector can play an important role in better channeling R&D funding and coordinating R&D efforts globally.* This receives little attention in the IACG discussion paper. First of all, target product profiles should enable more effective delivery in resource-limited settings. Heat stability, for example, can obviate the need for a cold chain for vaccines. Secondly, target product profiles should also include affordability as a criterion. After all, an innovation that is not accessible by those in need has no value at all.

Product development partnerships such as the Drugs for Neglected Diseases Initiative and Medicines for Malaria Venture include target price points for products they develop. The Boston Consulting Group failed to do so on the premise that "Most high-need drugs developed as a result of this initiative will be needed in both low-/middle-income countries and high-income countries, allowing for significant price differentiation in many cases. Because pricing is critical from an access perspective in low- and middle-income countries and, as many would argue, from a stewardship perspective in high-income health systems, we propose to define differentiated pricing and access requirements for new drugs in all funding contracts entered into with GUARD."[8] We believe the Boston Consulting Group analysis is seriously wrong on this key point:

- High prices are certainly a deterrent to access, but to suggest that high prices would ensure appropriate stewardship in high-income health systems is just erroneous. Effective diagnostics might improve stewardship, ending misaligned economic incentives might help, but high drug prices paid by public and private insurers and patients have no clear and consistent connection to enabling effective stewardship.

[7] Spellberg B, Sharma P, Rex JH. The critical impact of time discounting on economic incentives to overcome the antibiotic market failure. *Nature Reviews Drug Discovery* 2012; 11(2): 168.

[8] Boston Consulting Group. *Follow-up Report for the German GUARD Initiative. Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development.* Berlin, Germany: German Federal Ministry of Health, February 2017, page 20.

- The BCG report does not provide evidence, example or clarity that its proposed funding contracts could make good on differentiated pricing and access requirements. In fact, the report states: "Profit potential may be slightly reduced via price and availability obligations, but the recipient would maintain the right to market the antibiotic in the major markets (with some minor restrictions (see 7.1.6)."[9]
- Time and again, civil society has shown that voluntary, tiered pricing is insufficient to ensure affordability of life-saving drugs, neither for patients in low- and middle-income countries nor in industrialized countries. Patients have died for lack of affordable insulin prices in the United States.

Relying largely on "differentiated pricing and access requirements" to ensure affordable access is a useful example of how NOT to coordinate design of incentive mechanisms globally. An end-to-end approach signals the market, beginning with target product profiles, at the start of the R&D process.

3.5 *Moving beyond bets—drug by drug, and company by company—the IACG should consider public investments that transform the R&D innovation ecosystem. In the short term, there should be an increased focus on push incentives.* With an empty pipeline in AMR related research for now, the major challenge and opportunity lies within innovation and research rather than the development and production phase. The success rate of high-throughput screens to leads is very low, in the neighborhood of 7% in the experience of leading pharmaceutical companies.[10] This is ten-fold lower than therapeutic classes overall. The fact that first-in-class antibiotics can command top sales figures on the U.S. market, yet this is not sufficient incentive to bring forward novel classes of antibiotics suggests a scientific bottleneck. Investments for breakthrough R&D should consider how to recruit a wider array and non-traditional entrants in the drug discovery process and how to build and scale innovation platforms that might enrich, for example, publicly available compound libraries with promising natural products as future classes of antibiotics and clinical trial platforms and specimen repositories that might speed the development of drugs and diagnostics.

Pooling the building blocks for enabling R&D into these health technologies is another key investment approach to transforming the innovation ecosystem. The Medicines Patent Pool has importantly shown its value in pooling the licenses of end-products that might be used in combination, notably for AIDS, TB and hepatitis C. Pooling of reagents, research tools, innovation platform technologies and compound libraries also could play an important role in lowering the barrier to new

[9] Boston Consulting Group. *Follow-up Report for the German GUARD Initiative. Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development.* Berlin, Germany: German Federal Ministry of Health, February 2017, page 41.

[10] So, AD, Gupta N, Brahmachari SK, Chopra I, Munos B, Nathan C, Outterson K, Paccaud JP, Payne DJ, Peeling RW, Spigelman M, Weigelt J. Towards new business models for R&D for novel antibiotics. *Drug Resistance Updates* 2011;*14*(2), 88-94.

entrants to R&D or to allowing other companies to take the risks of breakthrough innovation.[11]

3.6 *To ensure sustainable financing, there must be ongoing assessment of the technology landscape, an economic case made for continued strategic investments in R&D, and monitoring for accountability (including early signs) by both government and non-governmental watch efforts.*

Various ongoing efforts can help complete an assessment of the technology landscape. On the human health side, through the Global Observatory on Health R&D, WHO has begun to track the R&D pipeline for novel antibacterial drugs. Their snapshot released in September 2017 reveals a persistent dearth of novel antibiotics, particularly targeting Gram-negative pathogens.[12] Only one or two novel antibiotics are expected to enter the market over the next 5 years, far too few to address the growing challenge of drug-resistant bacterial infections. Most are only modifications of existing classes of antibiotics. Similarly, WHO also recently published an Essential Diagnostics List and has plans to update it annually.[13] While the first list focuses on *in vitro* diagnostics, subsequent editions will expand to cover additional areas such as antimicrobial resistance. Complementing these efforts, WHO has worked to identify priority pathogens affecting human health.[14] However, there remain gaps to be filled.

The economic case for continued strategic investments in R&D builds upon the needs assessment and anticipated return on investment from the resulting technologies developed and distributed. Intergovernmental agencies, funders and country governments all would benefit from a priority setting framework and a project that would effectively model the anticipated benefits and returns on investment in various AMR-related interventions. SimSmoke served a useful role in projecting country-wide prevention gains from different kinds of tobacco control programs, from advertising restrictions to tobacco taxes, that would take years to show returns in health or lowered healthcare expenditures.[15] By supporting the development of

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[11] So AD, Stewart E. "Sharing Knowledge for Global Health" in *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors.* Washington, DC: Committee on the U.S. Commitment to Global Health, Institute of Medicine, 2009, Appendix F Commissioned Paper.

[12] Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Licence: CC BY-NC-SA 3.0 IGO. Available at: http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf?ua=1

[13] World Health Organization Model List of Essential In Vitro Diagnostics, First Edition (2018). Geneva, World Health Organization; 2018. Available at: http://www.who.int/medical_devices/diagnostics/EDL_ExecutiveSummary_15may.pdf

[14] Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery and Development of New Antibiotics, World Health Organization, 2017. Available at: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1

[15] Levy DT, Mabry PL, Graham AL, Orleans CT, Abrams DB. Exploring Scenarios to Dramatically Reduce Smoking Prevalence: A Simulation Model of the Three-Part Cessation Process. *American Journal of Public Health* 2010;100(7):1253-1259.

simulation modeling, governments and funders alike could gauge what mix of interventions would be worthwhile and lead to hoped-for gains in addressing AMR.

3.7 *HIV/AIDS, tuberculosis and vaccines reveal the challenges and the successes in mobilizing and sustaining donor and private funding for R&D and for ensuring affordable access to these products. In these efforts, a key component to sustainable financing was affordable pricing (to be discussed below), and a key player in keeping the pressure up for continued funding was civil society.* The IACG should consider how to create an enabling environment for both of these key factors.

The Stop TB Partnership provides support to civil society groups working at the country level through its Challenge Facility for Civil Society. Funding agencies like the Global Fund dedicate seats on their governance boards to civil society representation.

3.8 *Better channeling of R&D funding also means targeting the players which might make the most difference in bringing forward innovation.* For example, would small and medium-sized enterprises be more likely to take up truly novel classes of antibiotics, and could designing targeted incentives to these firms work better? Might they also have lower expectations of return on investment, and if so, would that also make public investment more cost-effective?

In LMICs, POC diagnostics compete for limited space in the laboratories of peripheral clinics and secondary hospitals. Local healthcare delivery systems cannot afford to purchase, let alone maintain, parallel laboratory equipment for a basic battery of diagnostic testing. Are some manufacturers more willing to invest in an interoperable diagnostic platform into which their diagnostic test would plug and play? Efforts to advance such a vision and targeting financing for diagnostic R&D accordingly might also make it possible to evolve the diagnostic testing technology more quickly, without having to replace the equipment with each advance. A WHO consultation on in June 2015 began discussions along these lines on diagnostic interoperability standards,[16] but rekindling this process and focusing it on the urgent need for POC diagnostics to address AMR could be another area for IACG recommendation.

4. Both to safeguard and expand access, several types of mechanisms would be critical to creating the enabling policy environment to achieving these aims—those mechanisms assuring access to the product, those that safeguard affordability, and those that enable monitoring for access.

4.1 *Access to product, in part, refers to the challenge of underuse, quality antibiotics, and drug shortages.*

[16] WHO. Global consultation on diagnostics interoperability standards. Geneva, Switzerland: WHO, 11-12 June 2015. Available at: http://apps.who.int/iris/bitstream/handle/10665/181059/9789241509305_eng.pdf?sequence=1

Underuse as well as overuse of antibiotics costs lives. The Monitoring and Evaluation Framework for benchmarking progress on antimicrobial resistance must include indicators that capture access, such as to second-line antibiotics, and affordability of these life-saving drugs. Otherwise this will communicate to key actors in the healthcare delivery system that governments or intergovernmental agencies care about complying with stewardship measures to preserve the effectiveness of antibiotics, but not whether those same settings have access to life-saving antibiotics. And that is no foundation upon which to build a shared commitment to tackling AMR.

Access to quality antibiotics is important as well. Strategies to empower drug regulatory agencies as well as consumer groups with tools to monitor for substandard and falsified drugs should be developed. A University of Edinburgh study commissioned by WHO models the human toll if we fail to address the use of substandard and falsified antibiotics to treat childhood pneumonia.[17]

Finally access to antibiotics can be compromised by drug shortages. The fragility of the supply chain, particularly for old antibiotics that may provide last-line defense against drug-resistant pathogens, must be addressed with 1) sentinel warning system when existing suppliers might exit, 2) demand forecasting and pooling procurement so that suppliers can reliably count on year-to-year sales, and 3) a financing mechanism that can boost reimbursement when margins are too thin, support entry of generic suppliers to meet GMP requirements, and provide wider margins on international procurement tenders. These steps might be taken through a pooled procurement mechanism. The experience of procurement agents, from UNICEF to the Global Drug Facility for TB drugs, could usefully be tapped to propose how the procurement of antibiotics might be better coordinated across key public sector buyers, from church-based healthcare systems to these global procurement agents.

In a recent *Lancet Infectious Diseases* commentary, several strategies to ensure availability of old, effective antibiotics were put forward, including the "formation of a multidisciplinary working group that would identify obstacles and solutions; disclosure and mapping of current production and supply chains; agreements on quality criteria, continued production, and stock management; collaboration between national regulatory agencies to secure the availability of effective antibiotics; predictable joint procurement that might result in an incentive for producers."[18]

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[17] A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva, Switzerland: World Health Organization, 2017. Available at: http://www.who.int/medicines/regulation/ssffc/publications/SE_Study_EN.pdf?ua=1

[18] Tängdén T, Pulcini C, Aagard H, Balasegaram M, Hara GL, Nathwani D, Sharland M, Theuretzbacher U, Cars O. Unavailability of old antibiotics threatens effective treatment for common bacterial infections. *Lancet Infectious Diseases* 2018; 18(3), 242-244. Available at: https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(18)30075-6.pdf

4.2 Affordability of products, both in LMICs and in high-income countries, remains a concern. Safeguards against high pricing that goes well beyond marginal cost plus might include ensuring multiple generic suppliers in the procurement scheme and benchmarking against what a product development partnership might be able to do to bring the drug to market.

Fulfilling the goals of sustainable innovation and access requires transparency about R&D costs, clinical trial data, and prices, fair return on public investment, and R&D that takes an end-to-end approach, by which upstream incentives are coupled with access and stewardship measures downstream. Such transparency requirements could be made at the national level or by procurement agents as a requirement of those drug companies submitting bids for tenders. Claims of commercial sensitivity over such information seem to have little foundation, and the burden of proof should be on manufacturers to prove how such disclosure does not serve an overriding, public interest purpose.

Where other approaches like pooled procurement fail to result in affordable pricing, the use of TRIPS flexibilities and compulsory licensing should be an option. Even the threatened use of compulsory licensing has resulted in more reasonable pricing behavior by drug manufacturers, both in the country in question and sometimes more globally. Brazil, for example, threatened to use compulsory licensing for the AIDS medication, Efavirenz by Merck and Nelfinavir by Roche. After negotiations with the pharmaceutical industry between 1999 and 2001, Merck and Roche reduced their drug prices by 59% and 40%, respectively. In the end, Brazil did not use a compulsory license, but still saved tens of millions of US dollars.[19] Thailand actually used a compulsory license to lower the price of Abbott's Kaletra HIV drug, and as a result, Abbott responded by cutting its price in over forty countries.[20]

Pooling of building blocks for health technologies or of the health technologies themselves can also help facilitate market entry of firms that might either provide a more efficient market price or a more competitive price that ensures greater affordability. The Medicines Patent Pool has expanded its mandate to include patented medicines of WHO's Model List of Essential Medicines in its patent pooling and voluntary licensing initiative and could be a good vehicle to promote access, and ensure good stewardship through its licensing, of novel antibiotics.[21,22]

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[19] Guennif, S. (2017). Evaluating the usefulness of compulsory licensing in developing countries: a comparative study of Thai and Brazilian experiences regarding access to AIDS treatments. *Developing world bioethics*, *17*(2), 90-99. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/dewb.12124

[20] Public Citizen, Kaletra – Abbott's Abusive Practices. Available at: https://www.citizen.org/our-work/access-medicines/kaletra-campaign/kaletra-abbotts-abusive-practices

[21] Medicines Patent Pool, Exploring the expansion of the Medicines Patent Pool's mandate to patented essential medicines. Available at: https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf

[22] Medicines Patent Pool Foundation – TB Stewardship Report (2016) Available at: https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf

4.3 *Monitoring for access by government and non-government actors can play an important part.* As noted, the need to monitor for access, not just stewardship, has already been noted. The twin goals of access and stewardship come together in the guiding principle of delinkage—separating drug company investment into R&D from the price and quantity of drug sold. Delinking on price assures affordability; delinking on quantity of drug sold, stewardship. Delinkage mechanisms cannot be struck with drug companies alone, but rather must involve those in the healthcare delivery system. In fact, the obligations of stewardship must be carried out at the level of the encounter between healthcare provider and patient, and neither drug companies nor healthcare professionals would likely support a delinkage approach whereby drug companies reached into that relationship to shape clinical decision making.

Drug companies should be prevented from mispromoting health technology products, in particular antibiotics. Drug company manufacture and marketing of unregistered combinations of antibiotics should be stopped.[23] Prohibitions against such mismarketing should be enforceable in local statute, and a system that makes such problems transparent might serve to speed local enforcement, both by governments and the drug companies involved.

Finally, we might note that monitoring for access gained an important tool in the WHO Essential Medicines List's Access, Watch and Reserve designations of antibiotics. But this tool is also one which we need further work and guidance to operationalize.

5. Guiding principles for investing in R&D and access should build upon those laid out in the UN Political Declaration on AMR and the Global Development and Stewardship Framework process.

5.1 *The principles of delinkage, transparency of R&D costs, fair return on public investment, and an end-to-end approach in safeguarding access and stewardship would be important to build into the design of public efforts to invest in R&D and access.* Global public benefit, equity, gaps in response, and value for money are certainly a useful starting point for evaluation criteria for return on investment from public investments in R&D and access.

5.2 *There needs to be an intersectoral, interagency, intergovernmental coordination body that can take in an overview of the whole AMR field.* There is a need for R&D to be seen as an integral component within the larger cycle of needs and priority setting, R&D and public health action, and monitoring, evaluation and review towards progress of commitments.

[23] McGettigan, P., Roderick, P., Kadam, A., & Pollock, A. (2018). Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India. British journal of clinical pharmacology. Available at: https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bcp.13503

5.3 Monitoring and transparency for accountability will be necessary to ensure that R&D and access principles are operationalized. External stakeholders such as governments, civil society and the public should have access to open data to be able to conduct the evaluation of progress of government and company benchmarking.

6. *To have the greatest impact on One Health, one must better prioritize innovation of both technologies and of practice in the food production sector and the environment.*

6.1 *It may be challenging to model the return on making AMR-related investments in healthcare delivery, food production and the environment together.* Admittedly, averting the use of a widely used, old antibiotic against avoiding the overuse of a last-line, novel antibiotic is not easily reducible to a common metric. However, the opportunities to avert unnecessary use of antibiotics are so much larger—from the near elimination of the use of antibiotics in salmon aquaculture as in Norway[24,25] to halving the number of antibiotic treatment days in children under age 5 with universal pneumococcal vaccination.[26]

6.2 *Making the calculus for specific interventions in differently resourced settings should not be a static exercise, but rather the IACG should consider what enabling, systemic factors might tip this calculus radically in favor of adoption.* For example, might product development partnerships which have begun to show success for bringing to market treatments for neglected diseases in humans be applied as a model for bringing public goods, like diagnostics and vaccines, in the food production system?

6.3 *For some areas of technology, the IACG may call for additional mapping of the landscape, from technologies for the removal of antibiotic pollution from the environment to the reengineering of medical instrument surfaces to make them resistant to bacterial colonization.* At a time when the pharmaceutical industry is calling for billions of dollars in additional incentives to bring new antibiotics forward, the benefits and costs of making breakthrough improvements in efforts to address AMR through these approaches should be weighed against the societal benefit and cost of bringing a new drug to market.

6.4 *Training the next generation of scientists in the One Health approach and finding sufficient resources to attract such researchers involves more than boosting near*

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[24] WHO. "Vaccinating salmon: How Norway avoids antibiotics in fish farming," October 2015. Available at: http://www.who.int/features/2015/antibiotics-norway/en/

[25] Use of Antibiotics in Norwegian Aquaculture. Oslo, Norway: Norwegian Veterinary Institute, 2016. Available at: https://www.vetinst no/rapporter-og-publikasjoner/rapporter/2016/use-of-antibiotics-in-norwegian-aquaculture/ /attachment/download/03528c2b-8849-4a07-bbe8-98358aceb176 f8e3f50d9442a35da57158ce9b5d0c43f165ce53/2016_22_Use%20of%20Antibiotics%20in%20Norwegian%20Aquaculture.pdf

[26] Laxminarayan, R, Matsoso, P, Pant, S, Brower, C, Røttingen, JA, Klugman, K, & Davies, S (2016). Access to effective antimicrobials: a worldwide challenge. *The Lancet*, *387*(10014), 168-175.

term educational opportunities and research funding, and a systemic solution likely will not come from investing in one or more organizations to take lead. Taking a systems approach, the IACG might consider what points of intervention will drive sustained change and demand for this knowledge that such scientists might generate. Does credentialing of veterinarians and physicians in One Health competencies feed a system demand for designing interventions with such research insights? Would the advent of product development partnership focused on bringing much needed veterinary diagnostics and vaccines excite a new generation of scientists? The IACG needs to move beyond patching the innovation system with a fix and a fund here and there when more systemic change is needed.

Antibiotic Resistance Coalition

ANTIBIOTIC RESISTANCE COALITION RESPONSE TO THE INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE PUBLIC CONSULTATION

NATIONAL ACTION PLANS

July 2018

Signatories:

Alliance to Save Our Antibiotics
American Medical Student Association
Center for Science and Environment
Consumers Association of Penang
Ecumenical Pharmaceutical Network
Food Animal Concerns Trust
Health Action International
IFARMA
Institute for Agriculture and Trade Policy
ReAct – Action on Antibiotic Resistance
ReAct Africa
ReAct Asia Pacific
ReAct Europe
ReAct Latin America
ReAct North America
Sahabat Alam Malaysia
Society for International Development
Sustainable Food Trust
US Public Interest Research Group

Introduction:

The IACG has importantly focused on the role of National Action Plans in advancing efforts on AMR. Interested members of the Antibiotic Resistance Coalition (ARC) convened to develop this joint response to the questions posed to stakeholders and to provide useful input to IACG's discussions of recommendations. We understand that this discussion paper represents the work of a subgroup of the IACG members and that its work is ongoing. We have focused our response around the three sets of questions laid out in the paper (mainstreaming, sustainable financing, regional coordination), but recognize that the paper itself is organized around five areas (Awareness & political will, Data & technical capacity, Monitoring, Coordination, and Finance). ARC responses to other discussion papers will more directly address some of these issues, and we anticipate that those responses will also be of interest to IACG members focused on feedback to this discussion paper. We trust this will be just the beginning of a process of engaging stakeholder inputs as the IACG focuses on more specific, potential recommendations. We also hope this will complement the earlier sent input, particularly on the work on *National Action Plans*, by 28 ARC members and its civil society allies around the time of the Divonne meeting.

1. **Mainstreaming AMR into broader universal health coverage, sustainable development, food system and environment agendas is key, both to scaling and to sustaining efforts to address AMR. Setting targets and integrating this intersectoral work within the National Action Plans**

1.1 *As a starting point, NAPs on AMR must better incorporate sustainable food production and animal health as well as environmental issues. Without these issues being better woven into the implementation of NAPs, one cannot expect reciprocal commitment from these sectors.* Among the first 25 NAPs posted in the WHO Library, most were from industrialized countries and make mention of biosecurity and how inspection, prevention and control could reduce the need for antimicrobials.[1] However, few countries address antibiotic pollution or discharge from healthcare settings or food animal production settings. Efforts to grow the role of other UN and intergovernmental agencies, alongside the Tripartite agencies, would be important to ensuring this integration and intersectoral collaboration and coordination. The UN Environment Program should be encouraged to take a stronger role with the Tripartite agencies in forging a One Health approach to tackling AMR.

1.2 *AMR-sensitive interventions, from WASH (water and sanitation for health), maternal and child health, and improving vaccination rates to improved animal husbandry practices, have significant potential to reduce the burden of bacterial infections.* Lowering the burden of viral illness can also reduce the unnecessary use of antimicrobials. Similarly, adoption of more sustainable agricultural practices can diminish reliance on antibiotics in intensive farming operations. To give priority to

[1] Centre for Science and Environment. *National Action Plans on Antimicrobial Resistance: Need for Greater Focus on Environmental Spread,* 2016. Available at: https://cdn.cseindia.org/userfiles/factsheet-national-actionplan.pdf

such interventions, countries would benefit from modeling that could project the return on investment through the lens of AMR. The IACG could also work with other UN and intergovernmental agencies, both represented in its membership as well as others like UNDP and UNESCO, to make more concrete how AMR-sensitive interventions would benefit from taking on AMR, and vice versa. This process as well as the recommendations that might follow from the IACG should help with the process of better realigning UN and intergovernmental agency activities to bolster efforts to address AMR.

1.3 *AMR-specific interventions can decrease the burden from drug-resistant infections, driven in part by antibiotic treatments of presumptive or diagnosed bacterial infections.* The relative benefits and costs of mounting AMR-specific vs. AMR-sensitive interventions are likely context-dependent. Ensuring that the return on investment for AMR-specific interventions can also be modelled alongside AMR-sensitive interventions will help integrate these efforts. Similarly, the IACG might also propose the development of a toolkit that might quantify how large a "drag effect" AMR will place on the country's achievement of Sustainable Development Goals.

1.4 *At the national level, an inter-Ministerial committee that meets regularly typically is the approach taken to ensure intersectoral coordination to tackle AMR. However, this must be paralleled by similar intergovernmental and international agency coordination at the global level and by their in-country focal points working together at country level.* Such integration across AMR-specific and AMR-sensitive initiatives at the global level will enhance how these programs, particularly those supported through overseas development assistance, are implemented at the country level.

1.5 *By setting country-level targets for AMR, governments working with different assets and resources might chart different pathways to the same goals.* Flexibility in adapting the modalities of tackling AMR to the local context is key. For example, a One Health approach requires an integrated surveillance system, attention to environmental discharge of antibiotics from hospitals and agricultural operations, and investment in interventions that curb antimicrobials in both the healthcare delivery system and the food production system.

However, for countries to go the distance, AMR-sensitive and AMR-specific programs must offer a tiered approach. Rather than a "one size fits all" approach, both indicators and programs could lay out a series of steppingstones, with expectations growing as local infrastructure and capacity do and as external technical and financial support is received. These steppingstones would take into account the country's stage of development, level of resources, and local context such as the size of the livestock industry. By offering a tiered approach, lower-resourced countries might participate in the global reporting system at an earlier stage. To be clear, we are not suggesting that a tiered approach should enable some countries to delay or even not to commit to targets.

Effective AMR mainstreaming into multiple national and global programs should adopt and be held accountable to a time-bound, outcome-based approach and move beyond mere planning and integration with few activities. This could, for example, in the case of WASH, mean setting a target for increased supply of clean water such as for drinking, irrigation and aquaculture. In the case of nutrition programs that are based on public food distribution schemes, it could mean a set annual increase in sourcing of foods grown without antibiotic use; and when it comes to linking with responsible production, it could mean a designated increase in area covered under sustainable agriculture, say organic or non-chemical farming.

1.6 *Intergovernmental agencies must not only develop guidance on specific competence areas and for specific groups of workers (as usefully laid out in the WHO Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance), but also define what areas of competence for such workers are needed to bridge across sectors.* Beyond pointing to the need to define these areas of competence, the IACG might a) encourage education, training materials and treatment guidelines reflect this inter-sectoral guidance; b) support platforms that would collect and curate such materials, share best practices and disseminate these through professional society, government and church-based healthcare delivery systems, key actors in the food supply chain, and civil society; and c) urge the development of intervention approaches that can be tailored and implemented in differently resourced settings.

1.7 *Mainstreaming AMR will require communicating greater understanding of this One Health challenge to the public and to other sectors into which these issues might be integrated.* Ensuring this inter-sectoral understanding will require ensuring that professional education, on-the-job training and capacity building carries this integrated understanding of AMR and other development issues.

2. Sustainable financing for AMR should include support for the implementation of stepwise approaches, prioritization of resources, and access to essential antibiotics.

2.1 *Country governments have limited resources but face many policy options for implementation National Action Plans on AMR. To direct their investments in the most strategic way, the IACG could call upon intergovernmental agencies to help provide a prioritization framework to assist with this country-level decision making.* Such modeling could help make the economic case for return on investment in AMR. Still all countries, even those with minimal domestic resources, can commit to a core set of actions on AMR, such as the establishment of an Inter-Ministerial Committee to coordinate implementation of the NAP on AMR.

2.2 *The economic case should be made that high-income countries supporting the implementation of NAPs in low- and middle-income countries is a highly cost-effective investment.* The World Bank report argues that:[2]

> …our analysis shows that action on AMR constitutes one of the highest-yield development investments available to countries today… Different countries stand to benefit from AMR control in different ways. Low-income countries will see substantial economic payoffs, relative to the size of their economies. The largest absolute and per capita gains, however, will actually flow to upper middle-income and high-income countries. Assuming, very conservatively, that only 10 percent of the modeled costs were averted through AMR containment measures, high-income countries would still obtain benefits of $0.9 trillion and $2.7 trillion, in the low AMR-impact and high AMR-impact cases, respectively. This is four times and thirteen times more than the global investment cost of $0.2 trillion.

Such analysis might be further refined and detailed, making the case for specific countries and/or regions.

2.3 *Financing for implementation of NAPs is seriously lacking, but so is financing for access to antibiotics and other health technologies critically important to saving lives in low- and middle-income countries (LMICs).* Of course, the challenge of high drug prices is a global one, not limited to LMICs, but the challenge of underuse of antibiotics and other life-saving health technologies may claim more lives than overuse at this time in some resource-limited settings. The IACG should be clear on the paramount importance of ensuring affordable access to all those in need.

2.4 Global financing priorities must also be set, such that:

Financing for innovation of technologies to address AMR (drugs, diagnostics, vaccines) must also be tied to target product profiles that include affordability as a criterion and that ensure the end-products are suited to use in resource-limited settings, so that NAPs at the country level can be carried out effectively.

Financing for innovation has to go beyond innovation of technologies for healthcare delivery, but also must support the development of vaccines and diagnostics that counter the reliance on antimicrobial use in food animal production.

A globally coordinated research agenda also must support the innovation of practice, both for antimicrobial stewardship in the healthcare delivery system and for curbing antimicrobial use in the food production system.

2.5 *Sustainable financing may require recommending a financing mechanism that could provide lasting support such as that adopted by 196 parties to the Montreal Protocol.*

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[2] World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future.* Washington, DC: World Bank, 2017. Available at: http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf

One of the most successful international treaties has been the Montreal Protocol, which has phased out 98 percent of ozone-depleting substances and has put the world on the path to closing the hole in the ozone layer over Antarctica. Mexico was originally the only developing country to have ratified the agreement, but, by 2013, the Multilateral Fund had provided financial assistance to 147 of the 196 parties to the Protocol and all developing countries had complied with their obligations by 2013. The Fund has funded 144 country programs since 1991, providing $3.6 billion to projects ranging from industry conversion and technical assistance to training and capacity building efforts. The UN Environment Program, the UN Development Program, UN Industrial Development Organization and the World Bank collectively coordinate the implementation of the Montreal Protocol. Thirty years after its signing, the Montreal Protocol remains a valuable model example for sustainable financing, developing country support and participation, and inter-agency coordination.

3. Regional cooperation should be expanded to international cooperation, include setting targets for AMR, and enable mechanisms of monitoring for accountability.

3.1 *International, not just regional, cooperation is necessary, and action by industrialized countries, not just LMICs, is important.* Examining the highest users (by DDD per capita in healthcare delivery or by antibiotics consumed by biomass in food production) by country, clearly the responsibility is a shared one, and this paper seems to focus largely on bolstering the infrastructure needed for NAP implementation in LMICs. Important as that is, there also must be commensurate action among industrialized countries, which also carry responsibility for much of today's and tomorrow's projected usage.

3.2 *Targets are both aspirational and operational. The gap between the two reflects often a resource gap. The timeframe for accomplishing such targets, however, must take into consideration the resources mobilized.* The goals for target setting, therefore, are at least twofold. On the one hand, the setting of targets and the sizing up of the gap between aspirational and operational targets provide a useful guide to how resources, both global and domestic, might be directed. On the other hand, such targets also provide benchmarks towards which countries might strive to achieve.

Concurrently, there should be targets for access to antibiotics, curbing excessive use, and lowering drug resistance levels. This will require triangulating carefully, especially in countries where there are both challenges of access and excess. Such targets should avoid unadjusted approaches like the global median of antimicrobial consumption in a country, where there may be both underuse and overuse present.

Monitoring for accountability can be a powerful tool to leverage policy change. For example, regional cooperation might be strengthened and encouraged through self-reporting and benchmarking against comparison scorecards.

3.3 *Countries at a similar resource and asset level and leading the way could help the global community to gauge what aspirational goals are feasible and appropriate.* Not all LMICs are the same in their capacity, flexibility and political will in what they can do. It would be useful to identify the progress made by countries--given different levels of assets and resources--on implementation of NAP AMR goals.

3.4 *The impact of AMR-related trade restrictions by importing countries on export markets can also play an important role in shifting consumer demand and also production practices.* The IACG could analyze how such patterns in trade restrictions might align with efforts to work with countries to advance their NAPs on AMR. Some countries might be motivated by their exports facing increasing trade restrictions; others might be usefully targeted because they are significant importers of such food animal products.

3.5 *At the global level, AMR should be recognized as an integral part to achieving the Sustainable Development Goals. Setting AMR goals at the global level can serve as a benchmark for countries developing and implementing their NAPs.* The UN High Level Political Forum's yearly progress review and country voluntary reporting provides an important opportunity for Member States to discuss their efforts towards these AMR-related goals. Several country governments, notably Germany, Ghana and Norway, have called upon the WHO to rally key stakeholders in support of the SDG 3 goals and to develop a joint "Global Action Plan for Healthy Lives and Well-Being for All." In so doing, AMR-specific indicators in the Sustainable Development Goals could be added in the 2020 review process. For SDG3, such an AMR-specific SDG indicator might address access issues to life-saving antibiotics.

Antibiotic Resistance Coalition

ANTIBIOTIC RESISTANCE COALITION RESPONSE TO THE INTERAGENCY COORDINATION GROUP ON ANTIMICROBIAL RESISTANCE PUBLIC CONSULTATION

SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE

July 2018

Signatories:

Alliance to Save Our Antibiotics
American Medical Student Association
Center for Science and Environment
Consumers Association of Penang
Ecumenical Pharmaceutical Network
Food Animal Concerns Trust
Health Action International
IFARMA
Institute for Agriculture and Trade Policy
ReAct – Action on Antibiotic Resistance
ReAct Africa
ReAct Asia Pacific
ReAct Europe
ReAct Latin America
ReAct North America
Sahabat Alam Malaysia
Society for International Development
Sustainable Food Trust
US Public Interest Research Group

Introduction:

The IACG commendably has taken up the important concerns over surveillance and monitoring for antimicrobial use and resistance in the healthcare delivery system, the food system and the environment. Interested members of the Antibiotic Resistance Coalition (ARC) convened to develop this joint response to the questions posed to stakeholders and to provide useful input to IACG's discussions of recommendations. We understand that this discussion paper represents the work of a subgroup of the IACG members and that its work is ongoing. Some of more technical questions posed would require either further study, dedicated expert consultations, and/or a longer timetable for response. We urge the IACG not to leave such technical questions to be answered by web-based technical consultation, but to stage the needed expert consultations to find the best answers (e.g., How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?). We also trust this will be just the beginning of a process of engaging stakeholder inputs as the IACG focuses on more specific, potential recommendations. We also hope this will complement the earlier sent input, particularly on the work on *Surveillance and Monitoring for Antimicrobial Use and Resistance*, by 28 ARC members and its civil society allies around the time of the Divonne meeting.

1. **Surveillance information needs to be channeled in strategic ways that inform other areas, from R&D needs to measuring the effects of stewardship. The discussion paper provides a useful framework for considering how to address challenges in mounting effective surveillance and monitoring over antimicrobial use, but could focus more purposefully on the key goal—to inform and help drive public health action.**

1.1 *In the healthcare delivery system, surveillance might address clinical demands, public health demands and infection control demands.*[1] Clinical demands refer to using surveillance data to improve patient treatment by optimizing the empirical antibiotic treatment choices based on local epidemiology. Public health demands refer to using surveillance data to generate reliable estimates to determine the size of ABR as a national and international public health problem. Infection control demands refer to using surveillance data to track transmission and outbreaks and to uncover origins of high-risk strains.

1.2 *On the food system side, the importance of surveillance to guide policy action also holds. There are clear examples from the US and Europe.* Development of resistance in *Campylobacter* to fluoroquinolones led to a ban on the use of this

[1] Grundmann H. Towards a global antibiotic resistance surveillance system: a primer for a roadmap. *Ups J Med Sci* 2014 May; 119(2): 87-95. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034565/

class of antibiotics in poultry.[2] Detection of cephalosporin resistance in the US led to an extra-label restriction[3]; detection of MRSA in pigs led to action in EU[4]; and in Canada, the detection of cephalosporin resistance in chickens and people in *Salmonella Heidelberg* led to a voluntary ban on the use of the drugs in hatcheries.[5]

1.3 *These connections between surveillance and policy action do not come across clearly in this discussion paper, but we hope they will be the foundation of the IACG's recommendations in this area.* Moreover, the promotion of surveillance systems should be tied to parallel efforts to promote regulation that allows for action when problems are detected. All of the Tripartite agencies (WHO, FAO and OIE), as well as bodies like the Codex Alimentarius Commission, have important roles in defining legal frameworks that could support such regulatory systems at the country level and the normative basis for what are not non-technical barriers to trade at the global level.

1.4 *Importantly, the impact of antibiotic use and discharge into the environment, from point source pollution from manufacturing plants to agricultural run-off and hospital wastewater, warrants attention in an integrated surveillance system.* Environmental surveillance should not just be limited to AMR in pharma manufacturing waste, but also include food production settings (farms, slaughterhouses, processing units), healthcare settings (human health and animal health), waste treatment facilities.

2. Effective surveillance and monitoring begins with availability of surveillance and monitoring data, laboratory infrastructure, and standardized instruments.

2.1 On the healthcare delivery side, surveillance and monitoring can capture a) antimicrobial consumption and use, resistance levels and appropriateness of use; b) antimicrobial prices and affordability, availability and stockouts, by area (urban vs. rural); or c) pharmacovigilance, quality (substandard and falsified) and marketing of illegal drug combinations.

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[2] Price, Lance B., et al. "The persistence of fluoroquinolone-resistant Campylobacter in poultry production." *Environmental Health Perspectives* 115.7 (2007): 1035. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913601/#b11-ehp0115-001035

[3] Food and Drug Administration, Department of Health and Human Services, New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition Cephalosporin Order of Prohibition, January 2012. Available at: https://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf

[4] European Food Safety Authority. "Analysis of the baseline survey on the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in holdings with breeding pigs, in the EU, 2008-Part A: MRSA prevalence estimates." *EFSA Journal* 7.11 (2009): 1376. Available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1376.pdf

[5] Government of Canada, Reductions in Antimicrobial Use and Resistance: Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine, Available at: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-program-antimicrobial-resistances-surveillance-bulletin.html

We welcome that the IACG has noted point prevalence surveys as an alternative to continuous surveillance, and hope to see this lifted as a key message in the final recommendations. Sentinel point prevalence studies are key to overcome some of the barriers for surveillance in low resource settings, and importantly, should not occur in isolation from already ongoing global surveillance efforts.

A standardized protocol to carry out sentinel point prevalence studies, particularly in low- and middle-income countries, is needed. Such studies can help establish case definitions for disease and serve as a baseline for subsequent full-scale surveillance efforts. While such sentinel point prevalence studies should be encouraged and supported, the trade-offs such as between scaling these efforts and building local infrastructure and capacity must be considered. Important lessons might be garnered from the experience and assessment of national TB prevalence surveys.[6]

Part of making surveillance more feasible low- and middle-income countries (LMICs) is increased support for: more robust and affordable tests better adapted to the needs of low-resource settings, including with longer shelf-life and stability at ambient temperatures; quality assurance and sustainable implementation of such tests both at point-of-care and centralized laboratories; training for the interpretation of results and/or simplification of reporting; and support for the analysis and publication of the results. In addition, when new technologies are available (e.g. mass spectrometry, rapid tests, WGS), they are often too complex, expensive or not sufficiently validated in low-resource settings to be used in local microbiology labs, thus further impeding equitable access to the best technologies.

2.2 *On the food system side, surveillance and monitoring can capture: a) drug resistance and resistance gene levels, antibiotic residues in food and the environment, and antimicrobial consumption or use by livestock species, and b) products on the market, including unregistered or irrational drug combinations.* The availability and use of combination antibiotics varies by country. In the United States, these concerns can arise from animal drug compounding, but are the subject of FDA regulation.[7] In India, antibiotic combinations—some containing drugs critically important for treating human infections--have been approved for veterinary use in poultry.[8]

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[6] Stanecki K, Binkin N, Hoa NB, et al. Independent Assessment of National TB Prevalence Surveys Conducted Between 2009-2015. Washington, DC: US Agency for International Development, February 2016. Available at: https://www.usaid.gov/sites/default/files/documents/1864/TB-prevalence-surveys-assessment-2016-508-final.pdf

[7] Janice Steinschneider, US FDA. Compounding Regulatory Perspective. USP Veterinary Drugs Stakeholder Forum, November 9, 2012. Available at: https://www.usp.org/sites/default/files/usp/document/get-involved/stakeholder-forums/6a-animal-drug-compounding-fda-perspective-2012-11-09.pdf

[8] Pearson NO, Limaye S. Antibiotic Apocalypse Fear Stoked by India's Drugged Chickens: Feeding chickens antibiotics may speed diseases costing $100 trillion. Bloomberg News, March 29, 2016. Available at: https://www.bloomberg.com/news/features/2016-03-29/antibiotic-apocalypse-fear-stoked-by-india-s-drugged-chickens

Similarly, a standardized survey approach would be useful in surveillance of food systems. Some countries have already collected national data on antimicrobial use by livestock species. This shows that it can feasibly be done. It should be done because antimicrobial use varies widely by species, and the distribution of livestock by country also varies widely.

Publishing such data by farming system and by small-scale and large-scale producers would provide much needed insight into planning. How much to invest in looking at specific farms in point prevalence surveys and how much to invest in a sustainable and continuous national data collection system will depend on available resources and the local context.

2.3 *Harmonizing testing to enable comparison across countries is very important to create the enabling policies for curbing antimicrobial use.* On the animal side, for example, the EU introduced harmonized testing for antibiotic resistance in *E. coli*, *Campylobacter* and *Salmonella* in poultry and pigs for EU Member States and a few additional non-EU countries like Iceland, Norway and Switzerland. All the data are then published in reports by the European Centre for Disease Prevention and Control and European Food Safety Authority (EFSA), compared to results of resistance testing in humans.[9] The testing reveals huge differences in antibiotic resistance between different European countries, as there are huge differences in antibiotic use. For example, in the 2016 report, approximately 80% of the E. coli from Iceland, Finland and Norway were sensitive to all 14 antibiotics tested, whereas in 15 countries this percentage was 10% or less. Denmark and the Netherlands have also started to collect data tracking antibiotic-usage by species.[10,11] In the UK, the poultry council and the pig industry have established voluntary industry schemes for collecting usage data, which have already contributed to major cuts in antibiotic use.[12,13] These voluntary industry schemes, however, should only be a steppingstone towards statutory data collection.

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[9] EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2018. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. EFSA Journal 2018;16 (2):5182, 270 pp. https://doi.org/10.2903/j.efsa.2018.5182

[10] DANMAP 2016 Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032. Available at: https://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP_2016_web.ashx

[11] SDa, Netherlands Veterinary Medicines Authority. "Usage of antibiotics in agricultural livestock in the Netherlands in 2016." (2017). Available at: http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/Eng%20rapport%20AB%202016/engels-def-rapportage-2016-deel-1-en-2-22-09-2017.pdf

[12] British Poultry Council, Antibiotic Stewardship Report 2018. Available at: https://www.britishpoultry.org.uk/bpc-antibiotic-stewardship-report-2018/

[13] Agriculture and Horticulture Development Board, UK Pig Industry Halves Antibiotic Usage in Two Years, May 2018. Available at: https://pork.ahdb.org.uk/news/news-releases/2018/may/uk-pig-industry-halves-antibiotic-usage-in-two-years/

2.4 *Availability of laboratory infrastructure is also essential to carry out these surveys, and such facilities might be regional.* In some areas, regional labs capable of whole genome sequencing might provide such services. Such a strategy could help leapfrog surveillance systems forward. Carrying out an assessment of where such regional capacity might be best positioned could be done at the global level.

2.5 *AMR surveillance programs should begin by building upon the existing infrastructure.* For example, there would be strategic value in integrating the AMR surveillance component into ongoing, national level infectious disease control programs such TB/HIV control programs. AMR surveillance data generated as part of these programs should also feed into the overall AMR surveillance database. Lessons and best practices adapted from other successful AMR surveillance programs should be shared.

3. Integrated AMR surveillance should be a key goal of such systems.

3.1 *Across sectors, the WHO AGISAR, WHO GLASS's ESBL E. coli Tricycle AMR Surveillance project, and the ECDC/EFSA/EMA integrated surveillance efforts might provide useful lessons for scaling such efforts.* The work of the WHO Advisory Group for Integrated Surveillance of Antimicrobial Resistance (AGISAR) provides Member States with technical assistance on conducting integrated AMR surveillance programs.[14] The WHO Global Antimicrobial Resistance Surveillance System (GLASS) has embarked on a demonstration project to develop a global protocol for a simplified, integrated surveillance approach focused on extended-spectrum beta-lactamase *E. coli* across three settings—the healthcare delivery system, the food system and the environment.[15] The project is training personnel from pilot countries across the WHO regions. The European Centre for Disease Prevention and Control, European Food Safety Agency, and European Medicines Agency also has engaged in integrated surveillance of AMR in humans and food animals.[16,17]

3.2 *Within the healthcare delivery system, an integrated surveillance system should capture not only measures of antimicrobial stewardship, but also of antibiotic access.* Striking the right balance in ensuring that curbing overuse does not

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[14] *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach: Guidance from the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).* Geneva, Switzerland: World Health Organization, 2017. Available at: http://apps.who.int/iris/bitstream/handle/10665/255747/9789241512411-eng.pdf?sequence=1

[15] Matheu J, Aidara-Kane A, Andremont A. The ESBL Tricycle AMR Surveillance Project: A Simple, One Health Approach to Global Surveillance. *AMR Control*, July 31, 2017. Available at: http://resistancecontrol.info/2017/the-esbl-tricycle-amr-surveillance-project-a-simple-one-health-approach-to-global-surveillance/

[16] ECDC. EU integrated surveillance of antimicrobial resistance. Available at: https://ecdc.europa.eu/en/infectious-diseases-public-health/microbiology/eu-integrated-surveillance-antimicrobial-resistance

[17] ECDC/EFSA/EMA. Second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA Journal*, 2017; *15*(7): 4872 (135 pages).

exacerbate underuse would be important. Failing to do so sends the wrong message to those in resource-limited settings where both underuse and overuse remain challenges.

4. Transparency of surveillance and monitoring data must follow from availability. Making the data publicly available would allow for analysis, comparison, and accountability from these findings.

4.1 *At the country level, non-transparency sometimes results not from lack of capacity to collect such data, but concerns of commercial confidentiality. Public health concerns should override concerns over commercial confidentiality.* While the IACG paper focuses on low- and middle-income countries, there is also notable lack of public transparency of data—even when such data are collected--in high-income countries where such infrastructure for surveillance exists.

In the United States, the Food and Drug Administration collects data on antibiotic sales, by livestock species, from drug companies, the US Department of Agriculture conducts voluntary farm surveys through the National Animal Health Monitoring System, and the Agricultural Resource Management Survey captures limited data on whether a farm used antibiotics for a particular purpose. Collectively, however, such data are inadequate for tracking trends and changes in AMR from the food system.[18] Without transparency of collected data, efforts to ensure accountability for AMR benchmarks will be slowed.

The failure to disclose data on grounds of commercial confidentiality should be justified in terms of a public benefit test. The default should be public disclosure unless a compelling and overriding reason not to disclose is made. In setting such data access policies, the burden should be on those seeking to withhold such information to justify why the public's interest is not better served in knowing such information and holding such actors accountable.

4.2 *At the global level, non-transparency of surveillance and monitoring data also exists.* OIE, for example, reported that 10 countries mention colistin as an antimicrobial agent authorized for use of growth promotion, but OIE does not disclose which countries permit this use, perhaps concerned that doing so would jeopardize country participation in this global reporting system.[19] The IACG should consider a recommendation that protects the integrity of such reporting system, but

[18] Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. *Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock.* Washington, DC: Antibiotic Resistance Action Center, George Washington University Milken Institute School of Public Health and Natural Resources Defense Council, 2017, p. 24.

[19] World Organization for Animal Health. *OIE Annual report on the use of antimicrobial agents in animals: Better understanding of the global situation.* Paris, France: OIE, 2016. Available at: http://www.oie.int/fileadmin/Home/fr/Our_scientific_expertise/docs/pdf/AMR/Survey_on_monitoring_antimicrobial_agents_Dec2016.pdf

does not compromise the public disclosure of such information. One approach would be to release the data unless a country specifically requests that it not be done.

4.3 *Civil society and academic institutions should be supported to conduct independent investigations using alternative data collection approaches to provide transparency of such findings. Such snapshots might prompt greater transparency at a systemic level.*

For example, Consumers Union analyzed pork samples from six U.S. cities as part of their Consumer Reports, and found harmful *Yersinia enterocolitica* in 69 percent of samples. A majority of these pathogens were resistant to medically important antibiotics. Based on these findings, Consumers Union put forth tips for consumers and launched its Meat Without Drugs campaign urging supermarkets to stop selling meat raised with routine antibiotics.[20] The Center for Science in the Public Interest also conducted analyses of antibiotic-resistant *Salmonella* outbreaks in the U.S. linked with meat and poultry to pressure the government to label antibiotic resistant *Salmonella* a food adulterant.[21] The Center for Science and Environment also conducted independent analyses on the antibiotic policies of major fast food chains, revealing the double standards held by fast food companies which are making commitments to reduce the routine use of antibiotics used for their food animal products in the United States, but not in India.[22]

4.4 *Public procurement agencies might also play an important role in encouraging greater transparency of such data.* They could insist on disclosure of whether drug companies have manufactured and/or licensed drugs for dual markets, that is, for both human and veterinary use as well as where and what antibiotic sales were made.

5. Prioritization is key in channeling global resources to where the return on investment would be greatest. The baseline consumption of antimicrobials in healthcare delivery and in the food system, the trajectory of growth, and the concentrated flows of export and import of food animal products could factor into a prioritization framework for policy interventions.

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[20] Consumers Union, New Study: Consumer Reports finds antibiotic-resistant bacteria in pork products, 2013. Available at: https://consumersunion.org/news/new-study-consumer-reports-finds-antibiotic-resistant-bacteria-in-pork-products/

[21] Center for Science in the Public Interest, Petition for an Interpretive Rule Declaring Antibiotic-Resistant *Salmonella* Heidelberg, *Salmonella* Hadar, *Salmonella* Newport and *Salmonella* Typhymurium in Meat and Poultry to be Adulterants, October 2014. Available at: https://cspinet.org/sites/default/files/attachment/oct-14-abr-petition.pdf

[22] Chandra Bhushan, Amit Khurana and Ananya Tewari 2017. Double Standards, Antibiotic Misuse by Fast Food Companies, Centre for Science and Environment, New Delhi. Available at: http://cdn.cseindia.org/attachments/0.68707600_1520933761_double-standards-antibiotic-misuse-by-fast-food-companies-20171113.pdf

5.1 *By developing standardized data collection and reporting approaches, countries would be better supported in developing sustainable national or regional AMR surveillance strategies.* Much of this work is ongoing. The Tripartite agencies' work on the Monitoring and Evaluation Framework provides a useful starting point as do efforts like WHO's Global Antimicrobial Resistance Surveillance System, WHO's Advisory Group on Integrated Surveillance of Antimicrobial Resistance, the Global Action Plan's Country Self-Assessment, FAO's ATLASS assessments, and OIE's country survey of antimicrobial use in animals. More work to integrate AMR-sensitive indicators from other UN and international agencies, from UNICEF to GAVI, requires a system-wide approach to coordinating such data collection beyond the Tripartite agencies. While some of these data points can be collected by country contact points, others will require fielding an instrument adaptable to the national and local context.

There may be useful lessons to be drawn from the work of the WHO-Health Action International (HAI) project on Medicines Prices and Availability[23]. It developed a simple, gold standard methodology to collect evidence on the price, availability, affordability and price components of medicines. The instrument focuses on up to 50 essential medicines. It allows for benchmarking retail prices against the MSH reference index, enables comparisons between urban-rural and public, private and mission sector medicine outlets, and captures measures of availability and affordability of a treatment course.[24] The methodology has been fielded in over 120 countries and has been adapted to measure the price, availability and affordability of other commodities. The instrument has been widely emulated for its effectiveness in reliably measuring medicine prices and availability in a standardized way, thereby facilitating national and international comparisons.

In a staged approach, resources should go to where there continues to be demonstrable need, so a country's commitment to AMR surveillance and monitoring could be tied to sustaining these efforts.

5.2 *Baseline data on antimicrobial consumption and related patterns can provide initial direction of resources to where surveillance and monitoring efforts would have the greatest potential impact.* The IACG could, with the assistance of Tripartite agencies, develop a prioritization framework, where higher antimicrobial consumption (both measured in terms of aggregate and per capita/by biomass), the country's role as key exporter or importer of food animal products or as provider of medical tourism services, and infrastructure (e.g., laboratory testing, supply of

[23] World Health Organization, Health Action International. Measuring medicine prices, availability, affordability and price components. 2nd ed. Geneva: World Health Organization; 2008.

[24] Niëns LM, Cameron A, Van de Poel E, Ewen M, Brouwer WB, Laing R. Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. *PLoS Med* 2010; *7*(8). Available at: http://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1000333&type=printable

prescribers in both healthcare and food production sectors), and of course, baseline efforts already dedicated to AMR monitoring and surveillance factor into where resources might be prioritized.

5.3 *Surveillance systems can also help identify substandard and falsified medicines in the supply chain, and developing mobile kits and systems for reliable reporting of such findings could help equip both government authorities and civil society in monitoring for these problems.* Track-and-trace systems provide ways to ensure the integrity of drug product packages from the point of manufacture to the point of dispensing. However, substandard and falsified antimicrobials likely fall outside of these voluntary, track-and trace systems, and sampling pharmacy dispensing outlets and farming operations could be a considerable undertaking. Even where such sampling for surveillance and monitoring already exists, piggybacking the testing for substandard and falsified medicines requires both technical and financial resources. A useful steppingstone would be the development of a low-cost, easily implemented, mobile test kit for identifying key substandard and falsified antimicrobials and guidance on how to report reliably and credibly such findings. Such a test kit could then be integrated into surveillance and monitoring efforts carried out by governments, civil society or healthcare delivery systems. Safeguards and conflict of interest requirements would have to be put into place, so that such approaches were not used for branded, commercial marketing efforts to discredit quality generic suppliers. We would also note that "counterfeit" is no longer a recognized definition as it can lead to confusion between substandard and falsified products and the protection of intellectual property rights. The WHO definition of substandard and falsified products should be used.[25]

Concerns have arisen that some published research has sought to raise doubts over the quality of generic medicines as being truly bioequivalent (as measured by drug regulatory agency established criteria of pharmaceutical equivalent, pharmacokinetic equivalence, or in vitro susceptibility testing). We also caution that the testing to identify substandard or falsified medicines carefully adhere to validated methods of establishing drug quality.

5.4 A systems perspective should be taken in designing surveillance and monitoring efforts. Steps should be taken to mitigate problems that might come with prioritization, such as the neglect of tracking drug resistance to older antibiotics when focused on newer antibiotics for priority pathogens. Surveillance should also consider tracking not just the most worrisome, drug-resistant pathogens, but also trends of inappropriate use (e.g., using antibiotics for viral disease or uncomplicated diarrhea).

In both healthcare delivery and especially in food production, older antibiotics may still be widely used. So integrated surveillance and monitoring efforts need to

[25] WHO, Definitions of Substandard and Falsified (SF) Medical Products. Available at: http://www.who.int/medicines/regulation/ssffc/definitions/en/

ensure that these drivers of drug resistance that tilt usage towards newer antibiotic alternatives are not neglected.

We would also caution against adopting the Drug Resistance Index,[26] a composite measure "that combines the ability of antibiotics to treat infections with the extent of their use in clinical practice" until it is more robustly tested. The benefits of a composite index over tracking separately resistance to the top drug-bug combinations are not obvious, but the risks of a composite index in masking important underlying trends are.

5.5 *Prioritizing efforts to integrate the environmental aspect of AMR into ongoing surveillance and monitoring systems is critical to ensuring greater policymaker buy-in to addressing these concerns in National Action Plans on AMR.*

We would emphasize that environmental surveillance for AMR should not just be limited to antibiotic pollution from pharmaceutical manufacturing plants, but also should include both food production settings (farms, slaughterhouses, processing units) as well as healthcare settings (hospitals) and waste treatment facilities.

Surveillance of antibiotic use in the agricultural sector, surrounding environment and food products should also be integrated into the overall surveillance efforts. Countries need to be supported to better understand and address emergence and spread of AMR from agricultural systems, judicious antibiotic use practices and risk reduction approaches along with enforcement of standards for antibiotic residues in agricultural food products.

There is a need for greater global guidance for environmental surveillance for AMR. Defining the optimal methods, tools, breakpoints, sampling design and locations, and priority bacterial pathogens and antibiotics all require considerable work. A roadmap for scaling up such efforts is also much needed.

6. Comparability enables cross-country and cross-setting comparisons important for both prioritizing resources and policymaker attention. The development of standardized instruments, of course, need to accommodate implementation in differently resourced settings, but also should spur stepwise adoption of surveillance and monitoring approaches that only be possible with greater technical and financial inputs over time.

6.1 *To advance efforts to ensure comparability in surveillance and monitoring systems across countries and similar settings, there will need to be a globally coordinated training and capacity building effort. The design and scale-up of such an effort should draw upon the lessons and many years of experience of similar efforts in public health and agricultural extension services.* Best practice networks, learning

[26] Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. *BMJ Open* 2011; 1:e000135. Available at: https://bmjopen.bmj.com/content/bmjopen/1/2/e000135.full.pdf

collaboratives, and twinning programs are just some of the various tested approaches that might be emulated.

6.2 *Conflict of interest in setting standards for comparability must be avoided.* For example, breakpoints for establishing antimicrobial susceptibility of bacterial pathogens are critical to determining what the levels of local drug resistance are. These breakpoints are set by committees, such as those of EUCAST or the Clinical Laboratory Standards Institute (CLSI). A study from Johns Hopkins flags concern how these antimicrobial susceptibility criteria are set. Investigators found that if the breakpoint for ceftriaxone were lowered as CLSI had recommended, they would have been a 300% increase in the number of cases classified as drug resistant, a finding that would prompt many healthcare providers to switch to more expensive, broader spectrum antibiotics. However, the investigators note that such a switch would have not made any difference in saving the lives of children treated for these infections. Worrisomely, around that time and still today, a majority of members of the CLSI Committee setting these antibiotic breakpoints reported potential financial conflict of interest or ties to the pharmaceutical industry.[27] So it would be important that conflict of interest safeguards are in place wherever the process of setting standards for comparability is underway.

6.3 *Systematic reviews of published studies on magnitude and trends of antimicrobial resistance reveal a need for minimum reporting guidelines.* Academic institutions and other research groups could contribute more meaningfully not only to the literature, but also to surveillance and monitoring systems if the quality of reporting their findings met minimum standards. Reviewing 40 years of AMR research on enteric pathogens in East Africa, the authors of this systematic review concluded:[28]

> The majority (98%) of human studies were based on hospital- (rather than community-wide) sampling and although they report high levels of antimicrobial resistance in the region, study design and methodological differences preclude conclusions about the magnitude and trends of antimicrobial resistance. To remedy this, we discuss and propose minimum reporting guidelines for the level of detail that should be explicitly provided for antimicrobial resistance study designs, testing of samples and reporting of results that would permit comparative inferences and enable meta-analyses. Further, we advocate for increased focus on community- rather than hospital-based sampling to provide a better indication of population-wide trends in antimicrobial resistance. This approach, together with the establishment of a robust regional surveillance network, should over time build a pool of evidence-based data useful for policy decisions and interventions aimed at controlling antimicrobial resistance.

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[27] Clinical and Laboratory Standards Institute, Subcommittee on Antimicrobial Susceptibility Testing—Disclosure Summary, 5/17/2016. Available at: https://clsi.org/media/1794/disclosure-of-interest.pdf

[28] Omulo S, Thumbi SM, Njenga MK, Call DR. A review of 40 years of enteric antimicrobial resistance research in Eastern Africa: what can be done better? *Antimicrobial Resistance and Infection Control* 2015; 4:1. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4339253/pdf/13756_2014_Article_41.pdf

The Tripartite agencies engaged in joint monitoring and evaluation efforts would be well positioned to convene expert groups to define these minimum reporting guidelines for such studies, and groups like the International Council of Medical Journal Editors could support their adoption.

7. Sustaining investment in surveillance and monitoring systems requires a multi-pronged strategy of making the economic case for such funding and ensuring the value-added use of these data by governmental policymakers and non-governmental actors.

7.1 *At the country level, a framework for making the economic case for prioritization of AMR surveillance and monitoring, alongside antimicrobial stewardship and other interventions, could be important to ensuring the sustainability of these efforts.* Such a framework might include a model that allows country-level estimation of the World Bank's projected toll on economies, if AMR goes unchecked, in terms of increased drug resistance, losses in livestock productivity, and numbers pushed into poverty.[29] Complementing this picture, the framework might also consider the likely impact of restrictive antibiotic policies on food exports from the country and food imports into the country.[30] Emulating the impact model conducted the University of Edinburgh for WHO, another module in this framework might document the potential, anticipated country-level impact of substandard and falsified antibiotics in treating an index infection like pneumonia in children.[31]

7.2 *At the global level, the World Bank's analysis of drug-resistant infections suggests a significant economic toll globally, disproportionately falling on low- and middle-income countries.* The World Bank report argues that:[32]

> …our analysis shows that action on AMR constitutes one of the highest-yield development investments available to countries today… Different countries stand to benefit from AMR control in different ways. Low-income countries will see substantial economic payoffs, relative to the size of their economies. The largest absolute and per capita gains, however, will actually flow to upper middle-income and high-income countries. Assuming, very conservatively, that only 10 percent of the modeled costs were averted through AMR containment measures, high-

[29] World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future.* Washington, DC: World Bank, 2017. Available at: http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf

[30] Johnson R. "Potential Trade Implications of Restrictions on Antimicrobial Use in Animal Production." Washington, DC: Congressional Research Service, July 11, 2011. Available at: http://nationalaglawcenter.org/wp-content/uploads/assets/crs/R41047.pdf

[31] A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: World Health Organization, 2017. Available at: http://www.who.int/medicines/regulation/ssffc/publications/SE_Study_EN.pdf?ua=1

[32] World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future.* Washington, DC: World Bank, 2017, page xx. Available at: http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf

income countries would still obtain benefits of $0.9 trillion and $2.7 trillion, in the low AMR-impact and high AMR-impact cases, respectively. This is four times and thirteen times more than the global investment cost of $0.2 trillion.

The IACG could make the clear case as to how high-income countries would benefit disproportionately from investing in AMR and why they should make such an investment now rather than at some date in the future. In addition, positioning AMR as a development aid issue could mainstream this work into these funding streams.

7.3 *Ensuring that surveillance and monitoring data are transparent, actionable, and serve as policy triggers will also engage policymakers and enlist civil society in supporting sustainable investment in such systems.* Making sure that these data serve a continued, useful purpose is key to maintaining investment in their collection. This means that governmental agencies AND non-governmental groups should be encouraged to use these data as tools for accountability—creating scorecards, profiling institutions and providers, making comparison across farming operations. The more key actors are invested in the use of these data, the more likely investment will continue. The Yellow Card system in Denmark and the Chain Reaction report each represent examples of how such collected data can be made actionable.

The Yellow Card Initiative led by the Danish Veterinary and Food Administration (DVFA) incentivizes pig farmers to adhere to antibiotic consumption reduction targets in order to reach Denmark's goal of reducing antibiotic consumption in pig farms by 15% from 2015 to 2018. Each year, the DVFA establishes antibiotic consumption thresholds. Compliance occurs in a three-step process, starting with a yellow card for failure to comply. The measures escalate, and in the final stage, farms that do not reach the target threshold for antibiotic consumption receive a "Red Card," are fined a third time, and must make additional changes to their practice such as reducing their stocking density. Consequently, this strategy successfully led to decreased antibiotic consumption in the pig production sector.[33] The Yellow Card initiative is a valuable example of how enhanced surveillance of antibiotic use and resistance can facilitate the implementation of targets by targeting top users.[34]

Another example is the *Chain Reaction* report, which is a scorecard developed by a coalition of consumer groups to benchmark progress towards a demand for socially

[33] Danish Veterinary and Food Administration (2017). Special provisions for the reduction of the consumption of antibiotics in pig holdings (the yellow card initiative). Available at: https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/Dyrevelfaerd%20og%20veterinaermedicin/Veterin%C3%A6rmedicin/Yellow%20Card,%20English%20version,%20180517.pdf

[34] Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. COMBATING ANTIBIOTIC RESISTANCE A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C. Available at: http://battlesuperbugs.com/sites/battlesuperbugs.com/files/Final%20Report%208.25.17.pdf

responsible antibiotic policies in the U.S. fast food industry.[35] The coalition recruited data and ranked the United States' top 25 restaurant chains on their antibiotic use policies. Based on networks of consumers, students, healthcare professionals and the public, this information was then leveraged through consumer demand to compel restaurants to make changes to their antibiotic policies and impose such requirements on suppliers of food animal products. Transparency allows these actions to be reflected back in the data put forth to civil society and consumers, who can subsequently hold companies accountable for the promised change.

[35] Friends of the Earth, Consumers Union, NRDC, Center for Food Safety, FACT, & U.S. PIRG (2017). Chain Reaction III: How Top Restaurants Rate on Reducing Use of Antibiotics in Their Meat Supply. Available at: https://uspirgedfund.org/sites/pirg/files/reports/ChainReaction3_Report_final.pdf

AMERICAN SOCIETY FOR MICROBIOLOGY

American Society for Microbiology

9 July 2018

UN Interagency Coordination Group on Antimicrobial Resistance
World Health Organization
Geneva, Switzerland

Dear Members of the Interagency Coordination Group on Antimicrobial Resistance:

On behalf of the American Society for Microbiology (ASM), we congratulate the Interagency Coordination Group (IACG) on its vision for global surveillance and monitoring of Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR). We agree with the IACG that a roadmap requires coordination across countries and sectors to establish, scale, and sustainably maintain such systems. As described in the IACG paper, the majority of at-risk geographies for AMU and AMR are also confronted with minimal health infrastructure. Over the past decade, ASM has supported efforts strengthening laboratory capacity for HIV, TB, AMR, and global health security programs in these types of settings and shares some lessons-learned and recommendations for IACG to consider within this commentary.

AMU and AMR surveillance will undoubtedly include a network of laboratories. ASM's efforts have shown that one broadly-applied solution will likely not meet the needs of global or national stakeholders if specific country requirements are not considered. Minimally-resourced human and veterinary health programs often under-resource laboratory services resulting in understaffed and unreliable infrastructure, and presenting a weak-link in any surveillance system. Local ownership of the solution is necessary for sustained implementation. Our approach is to collaborate with country partners to develop and support their own public health solutions through a range of programs aiming to strengthen laboratory infrastructure or develop and implement national actions plans.

ASM recommends that IACG consider components of the laboratory and data workflow that are often neglected in most surveillance roadmaps, and should be assessed, improved, and monitored as part of any system deployed to a minimally-resourced setting. Any solution must utilize a framework to classify laboratory readiness that permits comparison between countries while also assessing distinctive characteristics and infrastructure of the implementing country. Laboratories charged with surveillance responsibilities should, at minimum, be assessed for the following: workforce capacity, data quality, partner coordination, and political will.

Workforce Capacity
ASM has found that one common limiting factor for laboratory readiness in a minimally-resourced setting is the capability of an existing workforce, to include community health extension workers and national program managers. In most instances, we have found public health and veterinary laboratories lacking expertise and staff capacity to develop and/or adhere to protocols necessary for robust surveillance systems. In addition to laboratory workflow and

methods, these individuals play an essential role ensuring the quality and timeliness for collecting, analyzing, and reporting data.

ASM addresses this challenge through long-term assessments and monitoring of laboratory staff and personnel through continuous in-country and virtual mentorship programs. These programs are led by global health microbiology experts who follow an approach to increase local expertise by cascading training through "training the trainers" approaches. As one example, ASM's five-year collaboration with the Government of Zambia and the US Centers for Disease Control and Prevention on a targeted mentorship program has resulted in improved capacity of national laboratories to perform TB diagnostic services, as measured by South African Development Community Accreditation Services.

Data Quality

Poor-quality data can result in a missed AMU or AMR event, or alternatively, in unnecessary expenditure of program resources. One challenge for increasing quality is the lack of electronic reporting tools - many countries still rely on paper-based documentation for reporting surveillance data. In addition to technologies, there also lacks standardized data architecture. This vulnerability results in inconsistent submission of reports oftentimes fraught with incomplete or incorrect data.

Through its work supporting HIV, TB, and malaria programs, ASM has implemented innovative technology solutions that are user-friendly and can be used offline in regions with intermittent internet connectivity, such as phone or tablet-based apps. In addition to technologies, ASM has also implemented a check-list that documents resources necessary for any operational microbiology laboratory.

ASM recommends the use of standardized data architecture and user-friendly technologies to permit integration within a surveillance system, so that timely decisions can be made at the country-level as well as by international AMR/AMU partners. One example of an international laboratory data platform is WHONET from the World Health Organization's Collaborating Centre for Surveillance of AMR.

Partner Coordination

In addition to directly improving laboratory and workforce infrastructure, a governance framework should be enforced to coordinate well-intentioned partners operating within the same geography. AMR and AMU surveillance systems will also likely require cross-sector collaboration (human, agriculture, environment) in a way that is different than many existing health programs, such as those targeting infection by HIV, TB, and malaria.

Targeted countries often have existing partnerships with donors and non-government organizations tasked as implementing partners on vertical health programs, often with disproportionate availability of resources compared to the smaller contribution committed to an

AMR and AMU threat. Leveraging infrastructure established by other support mechanisms may be an important consideration for sustaining an AMR and AMU systems. However, ASM has also found that in many instances different tools and resources for education and implementation assistance are used within a country, even for the same disease program. This lack of coordination decreases a government's ability to effectively integrate the diversity of projects for maximum public health impact.

ASM recommends that an IACG roadmap includes supporting country leadership to develop, maintain, and enforce a governance framework that coordinates partner activity, standardizes tools and approaches, and ensures consistent communication.

Political will

The laboratory workflow starts with planning and continues with engagement between program and individual patient, collection and transport of a specimen, laboratory analysis, data reporting, and interpretation for a prescribed decision or action. AMR and AMU surveillance also requires a multi-sectoral collaboration that includes coordination within each sector, such communities, clinicians, laboratorians, and national reference centers as well as the education system and peripheral institutions to sensitize patients and their families, as well as train data generators, collectors, and analysts. This workflow crosses national, state, provincial/district, and household boundaries, requiring a spectrum of political will and incentives to sustain stewardship and mitigate anticipated challenges.

The rate of presumptive treatment, in absence of diagnostic data, remains high in many public and private healthcare settings, particularly in countries with limited resources. ASM continues to develop methods to incentivize clinicians to request and act-on laboratory data derived from patient samples. In addition to the physician-patient encounter, local healthcare management may discourage diagnostic testing by not supporting operational needs of a laboratory. Within some countries, there may also be distrust between state and national health authorities. Data-sharing between countries can also be politically challenging as many governments may be reluctant to share data if there is risk for alternative interpretations. For example, data might adversely affect local agriculture and tourism industries or result in public concern and unrest. These considerations complicate rapid dissemination of data and will likely impede an AMR/AMU response.

ASM recommends that any roadmap consider sensitization and relationship building between actors responsible for collecting, processing, interpreting, and sharing AMR/AMU data to emphasize each contribution towards quality and timely data, as well as ensure that proper protocols along the workflow are adhered. IACG's roadmap should also consider efforts to build trust between governments, non-government partners, donors, private sector, and the global community to encourage responsible data collection, use, and sharing limited to public health purposes. To encourage reporting and responsible data-use, ASM recommends that technical

assistance be available to countries to pro-actively monitor and respond to potential irresponsible use of data.

National Action Plans
National Action Plans (NAPs) are essential for moving a global AMR/AMU agenda forward by clarifying country policy and coordinate resource allocation. ASM has worked with the governments of Tanzania, Ethiopia and Bangladesh in various capacities to support development of their own AMR NAPs. For example, we have provided technical assistance on topics such as Monitoring and Evaluation, and laboratory information systems and reporting.

ASM continues to work with country partners to develop their own NAPs across various health interests and has learned that success requires careful consideration of available resources, including workforce and supply chain, as well as realistic appreciation of challenges for implementing large-scale programs. We have found that robust and implementable NAPs take significant time and dedication by key opinion leaders to develop, unfortunately some have yet to be finalized in some of our partner countries.

Thank you for this opportunity to comment and contribute to the IACG vision of a robust monitoring and surveillance system. ASM is excited at IACG's leadership and looks forward to opportunities to support our global partners in the fight against AMR and AMU. Should you have any questions or require additional information, please contact Mark Lim, Assistant Director of International Affairs at ASM, at mlim@asmusa.org or +1.202.942.9306.

Sincerely,

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Mark David Lim, Ph.D.
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Edinburgh Infectious Diseases

IACG Consultation on AMR: Discussion Paper on Innovation and Research

Response from Edinburgh Infectious Diseases, Edinburgh, UK

We welcome the IACG's focus on research and innovation. We agree that there are numerous research and development gaps relating to AMR and that addressing these gaps will be essential for combatting AMR in the short, medium and long terms.

The IACG paper pays most attention to product development. This is clearly a key area and we welcome the emphasis given to diagnostics as well as drugs and vaccines. However, we note that there are many other areas where research and development (or, more broadly, translation) can contribute to the global response to AMR, and these could have been given greater emphasis.

Key areas where further research is needed include:

- Behavioural changes and other approaches to reducing antimicrobial usage;
- More intelligent usage of antimicrobials;
- Quantifying sustainable levels of usage of antimicrobials.

None of these (necessarily) require new products, but all have the potential to help maintain the effectiveness of existing products.

The IACG paper says little about basic science. However, basic scientific research will be crucial for any long term solution to the AMR crisis, particularly for providing alternatives to conventional antimicrobial drugs as therapies and prophylactics. Given the anticipated escalation of AMR in coming decades, and the complete absence of readily scalable alternatives to conventional antimicrobials, this is major cause for concern and should be an incentive for significantly greater investment in biomedical research worldwide.

We welcome the IACG's emphasis on access to antimicrobials. We note that improving access is expected to lead to increased usage, and this is entirely appropriate and desirable. However, improved access will increase the need to better manage AMR. In that context, as health systems improve there may be opportunities to increase control of antimicrobial usage, e.g. through phasing out over the counter access in favour of prescribing by clinical services.

In addition, we note that by itself prescribing evidently does not prevent misuse and overuse. Equally, many antibiotics acquired over the counter are needed and are being used appropriately. We suggest that value-laden terminologies are unhelpful and should be changed, e.g. essential versus avoidable usage.

We note and welcome the IACG's call to operationalise a One Health approach to AMR. There are a number of outstanding questions in this area, particularly the problem of quantifying the extent and the route of the transfer of resistance determinants from food animals to humans. One practical step to addressing this would be to call for the routine genome sequencing of bacterial isolates from both humans and food animals as part of national surveillance systems, wherever this is practical and can be done to scale (hundreds or thousands of isolates per year). Genomic data – appropriately analysed – is the most reliable way of tracking the transfer of bacteria and resistance determinants between populations.

M.E.J. Woolhouse (on behalf of Edinburgh Infectious Diseases)

Edinburgh 05/07/18

Edinburgh Infectious Diseases

IACG Consultation on AMR: Discussion Paper on Surveillance and Monitoring

Response from Edinburgh Infectious Diseases, Edinburgh, UK

We welcome the IACG's focus on surveillance and monitoring. We agree that these are critical pillars of the global response to AMR. However, surveillance and monitoring are frequently given less attention – by both health agencies and research funders – than other topics such as the development of new therapies or preventives.

The IACG paper notes that surveillance and monitoring of AMR are often inadequate, particularly in LMICs. We agree, but believe that this observation could be given far greater emphasis. Surveillance data are extremely poor and often non-existent (as revealed by the WHO document '*Antimicrobial Resistance: Global Report on Surveillance*' in 2014), and the problem is not confined to LMICs. One direct result of this deficiency is that we do not currently have a robust estimate of the global health burden of AMR – this remains an impediment to prioritisation and budget allocation. We suggest that filling this gap could act as a key driver and unifying motive for concerted global action on AMR surveillance and monitoring.

The IACG paper says little on diagnostics technologies, even though diagnostics is the cornerstone of any disease surveillance system and is a recurring theme in the '*Antimicrobial resistance: Invest in innovation and research, and boost R&D and access*' IACG discussion paper. Naturally, there is considerable overlap between the roles of diagnostics for patient care and diagnostics for public health surveillance, and obvious efficiency gains when the same test fulfils both purposes. Nonetheless, there may also be important differences in the design criteria (e.g. the need for rapid test results is not so critical for surveillance purposes). We recommend that the IACG reviews the use of diagnostics for surveillance.

The IACG paper notes that many countries do not have appropriate systems in place for the sustainable collection of good quality surveillance data on AMR. In this respect, we consider the recently released, revised International system for the Classification of Diseases (ICD-11) a huge missed opportunity. ICD-11 (like its predecessors) makes minimal provision for reporting treatment failures (specifically for antimicrobials) that could have provided valuable data for monitoring the global impact of AMR. We recommend that this is revisited as soon as possible.

The IACG makes some general observations about the design of surveillance systems. Designing effective but efficient surveillance systems that meet both local and international needs is not straightforward: AMR is very complex, highly heterogeneous and variable over small spatiotemporal scales. We consider that surveillance system design needs to be recognised as an important research gap in its own right and needs to be given similar attention as is given to topics such as the design of vaccination or treatment programmes.

Under 'Prioritization' the IACG paper makes reference to exercises including the WHO Priority Pathogens List for R&D of New Antibiotics. We broadly agree with this exercise for its specified purpose. However, this list does not – in our view – constitute a sound basis for either surveillance priorities or research priorities more generally. We note that penicillins remain the most widely used class of antibiotics worldwide, yet very little attention is paid to managing penicillin resistance. It is

likely that achieving a small decrease in rates of penicillin resistance would have a far greater global impact than preventing a much larger increase in resistance to a last-line antibiotic. We suggest that volume of usage should be one criteria used to establish surveillance and research priorities alike.

Surveillance clearly needs to be integrated across humans, farm animals and the wider environment. An important component of an integrated surveillance system ought to be the routine genome sequencing of bacterial isolates from all sources, wherever this is practical and can be done to scale (hundreds or thousands of isolates per year). Genomic data – appropriately analysed – is the most reliable way of tracking the transfer of bacteria and resistance determinants between population compartments.

Finally, we welcome the IACG's comments on the importance of data sharing. More consideration on how best to achieve this is needed. For example, it might be possible to make data sharing a condition of receipt of funds to support surveillance programmes.

M.E.J. Woolhouse (on behalf of Edinburgh Infectious Diseases)

Edinburgh 05/07/18

Global TB Caucus

From: Rosanna Flury
Sent: 06 July 2018 15:09
To: IACG-secretariat
Subject: Feedback - IACG consultation, combined brief feedback for papers 1, 2, and 3

Follow Up Flag: Follow up
Flag Status: Flagged

Dear IACG Secretariat, please find the comments from the Global TB Caucus below:

Full name, title and affiliation: Ms Rosanna Flury, European Regional Director, Global TB Caucus
Title of the discussion paper on which you are submitting comments in the subject line of the email. We recommend one email feedback per discussion paper; * We have provided combined comments as our comments to Paper 1 (Research and Development), and Paper 3 (Surveillance and Monitoring) are fairly brief. Please see below.

IACG consultation 2018
Discussion papers for development of IACG recommendations

1. Antimicrobial resistance: Invest in innovation and research, and boost R&D and access

Global TB Caucus

Overall Comments:

- Drug-resistant tuberculosis (TB), which has been estimated to cause a third of deaths globally associated with AMR, does not feature appropriately in the paper in line with the content of the UN political declaration on AMR. It is instead grouped with HIV and Malaria - both of which have less drug-resistance associated deaths than TB.
- The paper gives the indication that there is no improvement needed to global access initiatives on HIV, TB and Malaria. This gives the impression that coordination around R&D for these diseases may not need to be a continued priority. This view is flawed.
- R&D for TB has a double challenge in that there are little commercial incentives for the pharmaceutical sector to invest due to the challenges that are faced in the general development of all antimicrobials, but also in that the drugs must be accessible to patients of all incomes and sold at a very low price, as many of those who need DR-TB drugs are from low income groups. Hence, innovative solutions such as prizes are particularly important for drug-resistant diseases that are widespread and affect people living in poverty, such as TB.
- Many leading infectious (HIV, TB and malaria) and non-infectious (cancer) killers are treated with combinations of drugs, this protects against resistance and results in quicker, safer treatment. Monotherapy is a leading driver of resistance in all microbial infections, and any solution to AMR R&D market failure should, therefore, include more focus on developing efficient ways to create new regimens of drugs.

2. Antimicrobial resistance: national action plans discussion paper

Global TB Caucus

Chronological Comments:

- 2.1 The document states that political will is critical in ensuring an effective response, but then states that 'it can only take a country so far', this statement could be misinterpreted so we suggest rephrasing to: *Although political will is critical, it must be underpinned by broader support. For real engagement with and uptake of a NAP, the general public must also understand it and want to implement it. Building coalitions is a tried and tested method of building consensus among diverse stakeholders to raise awareness in the general public, advocate for policy and regulatory change and lead antimicrobial stewardship on the ground.*
- 2.1 For engaging the general public, there may not need to be new coalitions built. There will already be networks who are aware of drug resistance when it comes to certain infections and diseases - for example of TB or HIV. These civil society actors/networks communities would also be useful to engage in awareness building on AMR and more effort should be made to engage them.
- 2.2 This paragraph states there is a 'lack of adequate evidence about the cost of doing nothing' - but in fact, there is evidence that has been collated at the national, regional and global level on the predicted costs of MDR-TB

based on 'business as usual' *Find report here: Price of a Pandemic*. However, further research is still needed in this area to ensure a robust evidence base in order to make the case for prioritization from governments.

- 2.3 It is also important that there are accountability measures included in addition to coordination.
- 3. 'Enabling Implementation' - in order for implementation to be supported and carried out, there must be political will and strong support from government and the Ministry of Health. This is mentioned earlier in the document, but should be emphasized in these three areas of intervention as well.
- 3.1 There is an argument to be made with regards to extending vaccination, that a priority would be to increase R&D to accelerate development of effective vaccinations for the most prevalent drug-resistant infections such as TB.
- 3.1 'Champions' - political actors can also be very effective champions in this context and existing networks of political champions, such as the Global TB Caucus, could be engaged more proactively in addressing MDR/AMR.
- 3.1 The IACG should look toward the 2018 UN High-Level Meeting on TB and the 2019 High-Level Meeting on UHC as opportunities to integrate TB into broader AMR interventions and broader AMR interventions into action on UHC. The IACG should also consider both High-Level Meetings as a chance to increase political support for action on AMR, and to ensure further integration. The IACG takes into account the importance of other intergovernmental forums at the regional level in 3.3, but also needs to take into account global forums, for example the G20 or the BRICs.
- 3.1 There needs to be better integration of responses to infections that are susceptible to resistance, and AMR should be built into the individual national strategies to combat these infections, for example, between TB and HIV
- 3.1 The paper mentions the need to both raise public awareness of AMR and involve civil society organizations in the response as a stakeholder group. Involving local civil society and communities in programmes to address AMR can help ensure sustainability by embedding public awareness and support.
- 3.2 The investment framework presented to UNGA in 2019 should align with the AMR UN High-Level Meeting political declaration but also investment targets set out in the UN High-Level Meeting on TB, in particular with regards to domestic investment in national TB responses and investment in TB R&D, and furthermore with any investment targets focusing on address drug-resistance as a result of the UN High-Level Meeting on UHC.
- 3.2 Further evidence is needed to convince governments of the need to intervene to the extent suggested. We would highlight country level economic data and projected economic losses as particularly important, as this will be needed not just to convince Ministries of Health, but also of finance.
- 3.3 Intergovernmental political forums and dialogue (in addition to multi-stakeholder forums) is missing from regional cooperation initiatives. For example, many intergovernmental forums regularly discuss health issues, for example the African Union, the European Union, the Council of Europe and so on. These political platforms can underpin incentive mechanisms for R&D, and help ensure political accountability, coordination and collaboration on AMR.

3. Antimicrobial resistance: surveillance and monitoring for antimicrobial use and resistance

Global TB Caucus

Overall Comments:

- In order for AMR surveillance and monitoring to be effective, it must be comprehensive. Some initiatives to contribute to surveillance have excluded major drug-resistant infections, which depletes overall effectiveness - for example, the Fleming Fund (an initiative of the UK government to address AMR) specifically excludes drug-resistant TB from its scope. Although there are programmes in place to address DR-TB, AMR interventions should take into account all drug-resistant infections, and not contribute to further silos. As the paper recommends, surveillance systems should be integrated, build on systems that already exist (such as those for tuberculosis) and not be exclusive.

With many thanks, and please don't hesitate to contact us should you need clarification.

Rosanna Flury on behalf of the Global TB Caucus Secretariat

Rosanna Flury | **Regional Director - Europe and Central Asia** | **Global TB Caucus**

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Health for Animals

HealthforAnimals input into the IACG public consultation on **"Invest in innovation and research, and boost R&D and access IACG discussion paper"**. HealthforAnimals www.healthforanimals.org is the international non-profit association that represents the animal health sector - manufacturers of veterinary vaccines, pharmaceuticals and other animal health products. We represent 200+ companies on all continents - 85% of the animal health sector.

PAPER 1: Invest in innovation and research, and boost R&D and access IACG discussion paper

1. How could R&D funding be better channeled?

The best channel for developing new medicines to address disease that are currently managed with medically important antibiotics is the private sector and incentives to support private investment. Incentives such as improved exclusivity, protection of data, and R&D tax credits enable investment in new products.

Funding for AMR must be driven by better outcome objectives that have society action/motivation principles as the key driver. Doing R&D just for science objectives will not move the improvement of AMR forward at the pace needed to get societies to make needed changes in using and demanding use of Antibiotics. So, a stronger collaboration with industry, policy makers and academia must be one of the initial steps.

In 2017, a report entitled "*Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*" was produced by the US Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf The report features a One Health approach that provides, at least within the United States, a path forward for the human and animal sector needs by covering economic, research and development, regulatory and behavioral incentives. The IACG would find useful approaches that would be applicable to many of the questions posed in the Public Consultation.

Of note for the animal sector, to supplement the discussion paper entitled "Antimicrobial resistance: Invest in innovation and research, and boost R&D and access", specifically on page 5, the PACCARB proposes the formation of an Innovation Institute as a coordinating center to enable early phase researchers and start-up companies to generate data and apply for funding to advance their technology. Extrapolation of this proposal to an international level would be enabling for universities government researchers and private enterprise, in LMICs or other countries, to work together in the spirit of One Health toward finding, developing and deploying practical, effective disease interventions and novel non-antibiotic treatments.

2. What will it take to increase and sustain donor and private funding of R&D in AMR? Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

AMR breaks the basic rule of discovery, manufacturing and then marketing the end product. New antibiotics that are really excellent discoveries will need to be protected by using them sparingly. So private funding will not commit to R&D unless there are financial reasons to get and stay involved. It may mean public money being designated for specific objectives that private industry can see business advantage prospering as a result of engagement.

Innovations should also be targeted at non-antibiotic therapeutics for infectious disease. Not all therapy options for bacterial infections are antibiotics. There are modes of action that can prevent infections from occurring and thus obviate the need for antibiotics.

Governments should provide guidance and designate areas that innovation in antibiotics can be welcomed. In animal health, there are classes of antimicrobials that are not medically important and deliver significant health benefits for animals. There are also diseases in animal health that only a medically important antimicrobial is appropriate. Unfortunately, future

innovation for unmet needs in antibiotics for animal health are very difficult to justify because of unclear guidance from global organizations and national authorities. Designated areas and types of molecules, including antibiotics, would be helpful.

3. How should the design of incentive mechanisms be coordinated at global, regional and national levels?

There are models around the world that use a public pool of resources to accomplish very specific goals to improve society and quality of life. These same models will likely need to be used for AMR. An example is public transportation resourcing. Contractors bid and use these transportation resourced pools and mapped out objectives to bid on projects. Some type of objectives to get competitive bidding from private and academic sectors will need to be deployed in AMR incentives.

4. How could current efforts in R&D coordination be strengthened?

A new type of partnership will need to be developed where private enterprise and academia actually figure out how to work side by side with each other. Industry will embrace this if outcomes are well defined with time parameters for success.

5. Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

Objectives that are able to show success quickly will encourage many to see the possibilities of the new model. Trying to do too much initially, will strangle the energy to continue to go forward with the model. All models need to begin, will need adjustment frequently and continue to show success, quickly.

6. Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

National research efforts plan an important role in developing new technologies, medicines, and diagnostics for human and animal health. These should continue. There is little evidence that a new organization can successfully replace the existing national programs

7. How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

AMR is very complicated even in affluent countries. But to make measurable progress consistently, most of the medical professionals will need to begin the journey locally in their own domain. First show progress locally with customized objectives that can be accomplished with current local resources and experience. As the early victories become the culture then adapt these principles to a broader region with expanded (and now more justified) guiding principles. It will be messy as one-size-fits-all will not be possible but everyone, if prioritized properly can make progress locally.

8. Which practical One Health activities would have the greatest impact on R&D and access and would be most feasible?

Focus on zoonotic disease. One Health should be a strong and energized collaboration between medical disciplines that have influence on improving people, animals and our environment. However, currently each sector is trying first to cast more responsibility to the others as a way of protecting status quo. We should determine those objectives that demand a true collaboration between these disciplines (human, veterinary, and environment) to find constructive actions to improve the AMR challenges.

9. How and which organization(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?

This is a national competence. This answer is really challenging to consider. We are not sure there are any agencies currently set up to accomplish a One Health approach. For decades human and veterinary medicine has went down their own path. Each knowing of the other but not really

considering how to partner. Today, there are signals for improvement here. Soon, there will be institutes that are set up with the lead recruits in science, policy, information technology and finance all understanding that medicine (and life partners from environment and engineering) in all disciplines must work together for best way forward in sustaining people in our limited resource world. Until this paradigm changes however, we will need to use the current system (with its collaboration flaws) to make improvements and learn the paths for sustainable One Health success.

Health for Animals

HealthforAnimals input into the IACG public consultation on **"National Action Plans"**. HealthforAnimals www.healthforanimals.org is the international non-profit association that represents the animal health sector - manufacturers of veterinary vaccines, pharmaceuticals and other animal health products. We represent 200+ companies on all continents - 85% of the animal health sector.

PAPER 2: Antimicrobial resistance: national action plans

1. **What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?**
   Currently, there is only the early discussion about One Health, with little actual scope of collaboration between human and veterinary disciplines (the other groups, above, are even more recent to these discussions). Frequently, teams of scientists and committees having these discussions are top heavy with either human or veterinary professionals, depending on which group was the organizing faction. AMR is a strategical demand and as such, it's very difficult to get resources committed to prioritize it higher on current agendas.

2. **What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development?**
   We believe Member States should first figure out early success strategies locally before they spend lots of time trying to organize global guidance in these areas. It is much more efficient to succeed locally, using customized approaches before trying to impose bigger ideas (with bigger resource needs) onto a global platform.

3. **What forces maintain national responses to AMR in silos, and how can we overcome them**
   Overall national protectionism is a major limitation. Human medicine disciplines have a massive footprint with massive numbers of medical professionals, they have created a level of attitude that everyone else should fall in line behind their needs and ideas. So, AMR national response silo roadblocks is heavily in their sector. Only recently have the medical community and some of their big thinkers begun to realize that they need many partners to fully comprehend and understand the scope of food, environment, animal health and policy and the true need for partners from each sector.

4. **How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?**
   International organizations are most effective when they are in their primary area of competence and fulfill needs of a government or major stakeholder. For example, WHO's GLASS and AGISAR programs are far more capable than Codex Alimentarius Commission to provide guidance on surveillance. Any guidance from Codex on surveillance will only confuse countries and has little ability to maintain timely guidance. Codex moves very slow on areas outside its primary competency.

   Again, every nation has customized needs in AMR. One-size fits all is not the answer. Just like managing water and hygiene needs across the many diverse countries, so too, AMR demands customized decisions to harness customs and resource limitations.

5. **What support do countries need to translate information on the global impact of AMR into a country-specific case?**
   As with so many societal challenges, the strongest resourced countries will have to begin solving their local challenges in AMR, first. As these better resourced countries are able to get a better AMR path sorted out, then they will provide trained 'agents of change' to assist less resourced countries. Imposing rules on countries that have little enforcement ability is not good use of engaged people in this AMR journey.

6. **How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners?**

   Policy makers in every country need persuasion (and constant reminders) that AMR is a challenge that must be tackled. Budgets get set according to priority. AMR must be in the top 5 in any country to get resources into budget. Regular and effective persuasion to policy makers is essential to progress on getting agenda priority.

7. **What is the role of the international community in supporting international public goods such as AMR surveillance data?**

   If a country gets serious about improving their local AMR challenges, they will put in place adequate surveillance systems if they have the resources to do so. Once these systems are deployed and collecting relevant and actionable data, medical professionals will be motivated to collate and study the data to stay on a continuous improvement pathway. International rules are not likely to be enforceable, anytime soon.

8. **How can we support decisions to balance the portfolio of investment in AMR-specific and AMR-sensitive interventions, particularly in LMICs that need support in developing public health, animal health, plant health and environmental support services across regulatory and operational domains?**

   Available clean water, sanitation and hygiene (WASH) is first prior and largest priority of these LMICs. As professionals and organizations committed to WASH, work towards their goals, AMR improvement steps will naturally come along as a consequence of higher health in the LMICs.

9. **Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)**

   Research into transmission pathways - which are the most important, enables targeting of actions where most effective. Currently, it is convenient for policy makers and many medical professionals, to target legislation to limit volume of use of antibiotics. It is very hard scientific work to show actual risk of antibiotic use in food sources getting into the human medicine chain of risk. One Health and what it represents, must sort out where the lowest hanging opportunities are to show quick progress on AMR issues, most relevant today to human health impact. Targeting general reductions of use of antibiotics as the way to battle AMR, is a very poor way to get to the core challenges of managing AMR.

10. **What are the highest priorities for training in Member States with respect to NAP implementation?**

    Highest priorities must be to get medical professionals, at the patient level, to engage every day in AMR process and decisions to improve the AMR situation. Rules enacted far away from the patient interface will be poorly implemented as medical professionals will first protect the patient as their professional oath demands.

11. **What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?**

    Again, local success stories are most effective. Social media can be a friend to science as these types of stores are shared. Expecting medical conferences to change public culture and opinion in AMR is not likely to happen. Unfortunately, not using Antibiotics by medical professionals is still seen by the public (and insurance analysts) as a type of bad decision by the attending medical professional.

12. **What sensitivities should be considered when encouraging regional cooperation on AMR?**

    There are different disease challenges and legal frameworks for medicines in each countries and global institutions, such as WHO, FAO, or OIE, should not assume that these disease and legal frameworks fit together easily. Efforts to recommend elimination of medicines should

careful consider health, zoonotic, and welfare consequences of these actions. For example, the word ‘therapeutic’ has several different definitions - in some countries this can mean clinical outcome while in others it can mean a specific disease modifying outcome. Local and regional cultures, access to available healthcare and population dynamics all are working to dictate any level of cooperation on AMR. So again, empowering and training medical professionals, well versed in the local societal culture, is best way to make real progress at the patient level.

13. **What role should regional economic communities play in developing regional cooperation platforms? And how can they be supported?**

IACG would be wise to guide countries to use GLASS and AGISAR and delete any reference to Codex Alimentarius Commission’s potential guidelines on surveillance. Countries, especially LMIC, value clear, timely, and meaningful guidance for implementing surveillance of AMR with their limited resources. Codex does not have primary competence in this area and cannot complete updates in timely manners. The scientific basis and governance for the AGISAR and GLASS are far better suited to perform this function.

Surveillance programs assessing AMR in the regions is a first step in understanding the regional risk and being able to formulate any cooperation platforms.

Health for Animals

HealthforAnimals input into the IACG public consultation on "**Surveillance and monitoring".** HealthforAnimals www.healthforanimals.org is the international non-profit association that represents the animal health sector – manufacturers of veterinary vaccines, pharmaceuticals and other animal health products. We represent 200+ companies on all continents – 85% of the animal health sector.

PAPER 3: Surveillance and monitoring for antimicrobial use and resistance

1. **What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?**

   Much of this function is best driven by national programs (i.e. CIPARS, NARMS) and international organizations (GLASS, AGISAR, OIE) working together to share findings, outcomes, and learnings to adapt resistance surveillance programs for the best public health outcomes.

   Countries and international organizations need to focus more on resistance surveillance. There are many inputs that contribute to resistance and the more we understand the ecology through resistance monitoring, the better equipped countries will be to adopt appropriate risk management measures.

   Academic and professional opportunities are well established for new and effective scientific discoveries. Medicine is highly motivated to make a difference in helping people and their health, so data that shows progress in AMR and resultant improved patient outcome, will be enough to sustain progress across all sectors.

   To date there has been a nearly exclusive focus on "animals" by national AMR surveillance programs that collect and test food borne bacteria originating from food animals or meat products. Bacteria of interest (typically enterococci, *E. coli*, salmonella and campylobacter) are zoonotic and thus the approach is appropriately using "human" antimicrobial susceptibility testing (AST) methods, no matter whether the isolates came from animals, food or other non-human origins. Since the interest in public health centers on which antibiotic treatment options are available for human disease intervention this is an appropriate practice. The Clinical Laboratory Standards Institute (CLSI) standards for AST as well as those of European Unioin Committee on Antimicrobial Susceptibility Testing (EUCAST) are already in use on a global basis and provide a good start for AST harmonization, although some breakpoints differ due to pharmacologic aspects of patient dosing. An overview of the many national food borne bacteria AMR programs was compiled by the CLSI Veterinary Antimicrobial Susceptibility Testing (VAST) subcommittee that published VET05-R in 2011 a document entitled "Generation, Presentation, and Application of Antimicrobial Susceptibility Test Data for Bacteria of Animal Origin; A Report" (https://clsi.org/standards/products/veterinary-medicine/documents/vet05/). This report provides a practical outline that illustrates best practices for obtaining samples, conducting testing, presenting data and summary statistics, as well as other useful information that contributes to the harmonization of programs conducted in countries around the world.

   An important gap in the Surveillance paper provided by the IACG is that the data generated from testing of a limited number of zoonotic bacteria in these programs is frequently misinterpreted as indicative of the entire AMR situation in the animal pathogen sector. Indeed, there have been very few national surveillance programs that collect *pre-treatment bacterial pathogens* of food animals (or other animals for that matter) to conduct susceptibility testing that generates data that is required in veterinary antibiotic stewardship protocols and responsible use guidelines. While OIE has general antimicrobial susceptibility testing methods within the Terrestrial Code and Terrestrial Manual, they do not include bench-level methods for fastidious pathogens of animals and do not include clinical breakpoints. The only international standards setting organization that has established both AST methods and breakpoints for animal pathogens is the CLSI whose internationally constituted VAST subcommittee continues its 25 years of work on methods and breakpoints (https://clsi.org/standards/products/veterinary-medicine/documents/vet01/). This standard is already in use in many countries by veterinary diagnostic laboratories (and even some "human" labs that test animal isolates from a One Health perspective). Veterinarians rely upon the laboratory reports to guide

their selection of appropriate antibiotics to consider for administration to the animals under their care. Thus, VAST harmonization of animal pathogens is already in progress and can be further adopted by other veterinary diagnostic laboratories to begin to organize data collection on a national basis. Indeed, there is already a workable program in Europe that can serve as a template for countries or regions to implement (deJong *et al*. 2013. Pan-European resistance monitoring programmes encompassing food-borne bacteria and target pathogens of food-producing and companion animals. International Journal of Antimicrobial Agents 41 (2013) 403–409. (https://www.sciencedirect.com/science/article/pii/S0924857912004372). The IACG needs to recognize this significant gap in national programs to generate animal pathogen AST data that are essential to veterinarians who need to make antibiotic use decisions as a component of responsible use practices and antibiotic stewardship programmes.

2. **How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?**
   As said earlier, getting a team together that includes these sectors, with well defined objectives of the team efforts, is the best way forward. The secret to making this team most effective is to "define the problem" very well that needs to answered.

3. **How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?**
   Artificial Intelligence is bringing tremendous tools forward that can get this accomplished. Working through the private data protection challenges can be accomplished through data blending processes that will mask data identity privacy issues.

4. **What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?**
   Many developing countries should be encouraged to work with the private sector to help facilitate resistance monitoring. In LMIC, there are very limited resources at the government level, but the companies have labs and capacity to support this type of monitoring. International organizations should encourage countries to work with the private sector to help facilitate antimicrobial resistance monitoring program.

   Diagnostic technology must be discovered that allows quicker and more convenient patient side answers. This will move surveillance systems to a much better coordination and data availability status.

5. **How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?**
   AMR improvement needs a strong local set of motivations to be useful to the medical professionals deploying antibiotics in their day to day execution of medical decisions.
   If surveillance strategies give actionable local answers the national context will be very well served.

6. **What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?**
   Many false medicines enter international commerce/are traded as chemicals and not medicines. Better training of customs officials to ensure appropriate designation at export and import can help.

   Each country must sort out relevant and enforceable policy that tests and certifies substandard medicines in all sectors. Well enforced processes country by country is necessary to make progress here. Black market and substandard products are a reality of living so constant evolution of these certification and enforcement processes is necessary.

HealthforAnimals has developed a detailed report in 2017 with a series of recommendations. It is here. https://www.healthforanimals.org/component/attachments/attachments.html?id=301&task=download

7. **What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?**
   Global surveillance databases are probably an outgrowth of national security issues for each country. Trying to set up global databases at this point in AMR strategy is likely not a good use of current resources. If very high risk issues are uncovered, countries will quickly deploy necessary actions to mitigate risk as best they can.

8. **What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?**
   Harmonization across sectors is a noble aspiration at this point. We believe progress must be made at the local and patient level that improves life in the AMR challenges. Harmonization is a natural step in later phases of broadening the success of what is positively happening at the local patient interface.

   Simplify the bodies that provide guidance to countries, especially countries with limited resources.

9. **What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?**
   Improved patient side tests to give actionable answers is needed for next phase of understanding resistance challenges. Oftentimes when there is 24 hour+ delay in understanding possible resistance challenges, patient decisions can't wait that long.

10. **What support do countries require to develop and report accurate national data and share them on global surveillance systems?**
    This seems, at several levels, seems to be a likely national security issue.

    It is unlikely that countries will want to share these data unless risk of doing so is mitigated and managing very well. There are many pathways between cooperating countries to share sensitive data. Each country will need to sort this out on a customized decision basis.

    So, countries that are resourced and motivated to improve the AMR issues in their country will work across borders with other medical professionals to sort out new thoughts in continuously improving their progress in AMR.

    Countries should also consider focusing surveillance systems on areas of greatest risk for introduction of a pathogen to a patient or a consumer. Presenting data in a equal way may not help because some data points may reveal a greater risk to public health than others – for example, nosocomial infections versus consumption of a cooked food item.

11. **What data formats and visualization tools are most useful for reporting and further analysis?**
    Using advanced medical reporting tools is already a normal process in managing and understanding emerging infectious diseases that are highly risky from country to country. These reporting and analyzing tools are being adapted already for AMR resistance reporting.

12. **How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?**
    See answer above for similar thoughts.

13. **How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?**

Business models and investor enthusiasm are beginning to show signs of interest. AMR is not yet a worldwide immediate tragedy that encourages world citizens to have it top of mind. Models for success for business will come about as local success enterprises show the measured value of improving AMR at the local level.

14. **What tools are required to address the investment required for surveillance of AMR and AMU?**
    Better actual risk models must be developed that have immediate, local actionable outcomes. It is very hard to prioritize resources for AMR unless everyone involved can see very clear outcomes as a result.

15. **What role can the private sector play in financing surveillance?**
    The private sector will be key to many discoveries necessary to show success in better diagnostics, new antibiotic compounds and delivery of these to patients. Medicine is very motivated to harness science and know how to improve patient lives. Business is motivated to use business principles to help medicine. Without the private sector, countries will not succeed in this AMR journey.

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IDSA
Infectious Diseases Society of America

Infectious Diseases Society of America

July 9, 2018

Haileyesus Getahun, MD, PhD, MPH
Coordinator and Head
UN Interagency Coordination Group on AMR Secretariat

Dear Dr. Getahun:

The Infectious Diseases Society of America (IDSA) greatly appreciates the work of the Interagency Coordination Group (IACG) on Antimicrobial Resistance (AMR) and the opportunity to help inform its efforts. IDSA represents over 11,000 physicians and scientists. Our members care for patients with or at risk of infectious caused by multidrug resistant organisms; lead antimicrobial stewardship programs and infection prevention and control programs; conduct basic, translational and clinical research on AMR and on the development of new vaccines, diagnostics and therapeutics; and drive public health interventions to prevent, detect and track resistance.

IDSA strongly supports international efforts to advance comprehensive solutions to AMR, including stimulating research and development for urgently needed new antibiotics and diagnostics, implementing infection prevention and stewardship programs, and strengthening surveillance. IDSA has been sounding the alarm on AMR for well over a decade and has helped inform, advance and secure federal funding for the US National Action Plan on Combating Antibiotic Resistant Bacteria. We continue working to advance antibiotic research and development (R&D) incentives in the US Congress. IDSA is eager to assist the IACG, World Health Organization (WHO) or other global partners on any aspect of global AMR efforts. Below please find responses to questions posed by the IACG.

Research & Development

How could R&D funding be better channeled?

It is important to direct limited resources to the areas of greatest unmet medical need—serious or life-threatening infections with few or no existing treatments. The WHO Priority Pathogen List provides a good set of targets for R&D. New agents with activity against these pathogens would be tremendously beneficial for patients. Well-defined, predictable targets are essential to encourage private investment in antibiotic R&D.

What will it take to increase and sustain donor and private funding of R&D in AMR?

There is currently little to no opportunity for industry and investors to earn a return on investment for antibiotic R&D. Traditional models reliant on high sales volume of a new drug are not feasible for an antibiotic, as public health realities demand that antibiotics be used judiciously. A "pull" incentive that provides a predictable return on investment that is de-linked from antibiotic sales and use is necessary to spur R&D.

While many conversations about incentives are focused on antibiotics, it is also important to spur the development and appropriate use of rapid diagnostics. Diagnostic tests are essential for guiding appropriate antibiotic use, but diagnostic developers face a host of challenges in developing tests (including securing specimens and expert laboratories for validation as well as regulatory burdens). Once a diagnostic is approved, much more work is needed to ensure its clinical uptake.

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

Push and pull incentives are needed to support early discovery and the full spectrum of clinical development of new antibiotics. Predictability is a priority, and multi-year funding arrangements can be powerful push incentives. Efforts such as CARB-X are very important push incentives, and more resources should be invested into these approaches.

However, it will remain challenging to draw more pharmaceutical company and venture capital resources to antibiotic R&D without a strong pull incentive. IDSA and others have proposed a market entry reward that would be paid out over a period of years to an antibiotic developer. In return, the developer would need to commit to antibiotic stewardship and access for those who truly need the drug.

Research and modeling conducted by DRIVE-AB—a project of the European Union's Innovative Medicines Initiative involving multiple countries, academic institutions, and industry— developed the following estimates to demonstrate the likely impact of market entry rewards for new antibiotics that target a WHO priority pathogen.

Post-Approval Payments	Total New Antibiotics for Unmet Needs Over 30 Years	First in Class New Antibiotics*for Unmet Needs Over 30 Years
$0	23	4
$400 million	27	6
$600 million	46	11
$1 billion	74	19

*First-in-class, new antimicrobials are especially sought as they are the most likely to have durable efficacy against multidrug resistant organisms

How should the design of incentive mechanisms be coordinated at global, regional and national levels?

At a global level, it would be useful to build agreement upon the same or similar target pathogens. As discussed above, the WHO Priority Pathogen List is an appropriate start. This agreement will provide clarity and predictability for developers and ensure that incentives are targeted to the areas of greatest unmet medical need.

There are other opportunities for international collaboration that should be further explored. For example, clinical trial networks across multiple country sites may facilitate studies of new drugs with more speed and less cost. To maximize the potential of such an approach it would be important to streamline administrative processes for each site. It would also be useful to provide further opportunities for cross-approval of antibiotics by different regulatory bodies (e.g. the U.S. Food and Drug Administration and the European Medicines Agency) using data from multi-country studies to approve drugs more rapidly. Current attempts to do so are hindered for many indications by different regulatory agencies' guidance documents for the appropriate trial endpoints.

While it is important to aim for global coordination to ensure that priorities are accurately reflective of global needs and to leverage resources and strengths wherever possible, we must also recognize that some nations may be able to act more quickly than others or may need to utilize different financing mechanisms. We should not allow the push for multi-national coordination to slow or stymie progress

Access

Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

Access for new and existing technologies, including vaccines, diagnostics and antibiotics, is an essential component of the broader strategy to combat AMR. Access to antimicrobial drugs in particular poses some unique challenges due to the need for stewardship. Currently, over the counter availability of antibiotics in some countries is leading to significant misuse and overuse of these precious drugs. Efforts to expand access to antimicrobial drugs must be coupled with efforts to ensure a stable workforce of healthcare providers in all countries who are trained on appropriate antibiotic use.

R&D and Access

How should the guiding principles (global public benefit, equity, gaps in response, value for money) be operationalized?

As discussed above, it is important to focus new incentives for antibiotic R&D on the WHO Priority Pathogen List to ensure that funding is aimed toward the most serious gaps and toward products that will provide the greatest public benefit. Wherever feasible, incentives should be de-linked from sales volume or use, to ensure that developers have the opportunity for ROI without compromising appropriate use or access. IDSA also recommends that developers receiving

incentives should be required to make commitments regarding stewardship and appropriate access.

One Health Approach in the Context of R&D and Access

How and which organization(s) could take the lead to ensure that the next generation of scientists is trained in the One Health approach and that sufficient resources are allocated to attract researchers?

WHO should take the lead given its expertise and ongoing efforts in the global AMR response. Without WHO's leadership, continued progress would likely be at risk. Collaborative centers that include multiple institutions across multiple countries may be a cost-efficient way to provide sustained paths for AMR researchers.

IDSA is dedicated to ensuring the next generation of scientists to address infectious diseases threats, including AMR. We routinely lobby the US Congress to increase funding for biomedical research to attract new scientists. We host an annual meeting with the National Institutes of Health for medical students, residents and fellows interested in pursuing an ID research career to provide them with opportunities to engage with senior researchers and to learn about career development. We also provide mentorship opportunities at **ID**Week, our annual scientific meeting, and provide research funding to support young investigators. We would welcome the opportunity to explore more global engagement on supporting the next generation of scientists and attracting more AMR researchers.

National Action Plans

What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development?

Stakeholders in member states need support to bring AMR to their national agendas. While health ministers in many countries are already engaged, the World Organization for Animal Health (OIE) and the Food and Animal Organization of the United Nations (FAO) should help bring additional relevant ministers to the table.

Member States also need help to make a compelling economic case for animal and environmental health and AMR. More data is needed to demonstrate the economic reasons for investments in combating AMR, including how investments can be made in an affordable and feasible manner and the economic costs of inaction. These data should be communicated in a clear manner that is compelling to the public. Increasing public pressure on individual governments will be an important tool to advance AMR solutions.

WHO, OIE and FAO should provide additional opportunities for stakeholders within various countries to discuss common challenges and share lessons learned. IDSA conducted successful advocacy campaigns in the US to advance several AMR activities on the national agenda, and we would welcome the opportunity to share our insights and learn from others.

What forces maintain national responses to AMR in silos, and how can we overcome them?

The political silos at country level make national responses to AMR fragmented. FAO and OIE, as well as UN environment (which should significantly increase its response and involvement in the global AMR agenda) have a significant role to play in bringing relevant ministers to the AMR table with ministries of health. Economic cases will also assist in breaking down political silos at country level.

How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners?

AMR is a cross-cutting issue that spans multiple sectors as well as multiple Sustainable Development Goals (SDGs). Failure to successfully address AMR will have devastating impacts for health systems, public health, food supply and even entire economies. Leveraging the SDGs and SDG agendas can get help secure additional funding for AMR activities across different sectors.

What is the role of the international community in supporting international public goods such as AMR surveillance data?

Global AMR surveillance data is absolutely essential for the international community, especially within the Global Health Security Agenda. Without these data, we cannot effectively target interventions or evaluate their impact. Increased investments in infrastructure and training for public health practitioners and other implementers at the country level are needed to support good quality national surveillance data that spans the human, animal and environmental sectors.

What are the highest priorities for training in Member States with respect to NAP implementation?

Stewardship in human and animal health and surveillance are high priorities for training. These activities are essential in all countries to effectively identify and track AMR and to promote appropriate use of antibiotics. Within human health, it is distressing that antibiotics are still available over the counter in some countries. In order to remedy this substantial challenge, efforts to ensure the availability of health care providers trained in appropriate antibiotic use will be essential. Even in countries with large numbers of healthcare providers, many still lack stewardship training.

In the US, IDSA is launching a new curriculum to train all infectious diseases fellows on stewardship. Some of our members are utilizing telemedicine or other means to provide stewardship training to providers in other countries. We would welcome the opportunity to connect with additional providers in other countries to provide support wherever it may be useful.

What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?

Online platforms such as the community of practice for National Action Plan development hosted by WHO is a very useful example. Such communities should be made available to individuals involved in the animal health sector of NAP development. Additional topics that can be explored include securing national funding to support NAP implementation, and breaking silos in AMR response on the national level.

Surveillance

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?

Obstacles include the diverse backgrounds and varying levels of expertise in different countries. This difference is very pronounced in the animal and agricultural sector where very little surveillance is done globally. Lack of agreement on antibiotic consumption indicators is another challenge for appropriate monitoring.

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

Through the Global Health Security Agenda, the US and other countries and partners are providing resources to help low- and middle-income countries establish surveillance systems for AMR and other emerging infectious disease threats. US funding for the GHSA is scheduled to end in 2019 unless the US government acts to extend it. IDSA is advocating for continued investment, and urges other partners to continue investing as well.

What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?

Further training and increased laboratory capacities in all sectors to identify counterfeit, falsified and substandard meds is essential. Regional cooperation can be leveraged for an improved surveillance platform.

What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?

Additional financial resources are needed to support these activities. For example: in the US the National Action Plan sets a goal for the vast majority of hospitals to report antibiotic use and resistance data to the Centers for Disease Control and Prevention National Healthcare Safety Network by 2020. Unfortunately, progress on this metric has been very slow. This program at CDC has not received the increased funding necessary to provide the technical support that healthcare facilities need to begin reporting. IDSA continues to advocate for these resources.

What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?

Multinational agreement on antimicrobial use measures and a global antimicrobial use index would allow for comparison across countries and sectors (human, animal, environmental). Such measures would also allow for targets to be set and progress to be measured. As data collection and reporting hopefully drive all countries to reduce inappropriate use, we must also be cautious to ensure that appropriate access to antibiotics is not impeded.

What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?

Currently there may be a significant gap between when a new antibiotic is approved and when antimicrobial susceptibility testing guidelines are made available to clinical microbiology laboratories. Pharmaceutical companies and test developers must be supported in their efforts to work together to coordinate development. Regulatory barriers to susceptibility test device development must be addressed. Incentives should be provided to susceptibility test developers to begin test development earlier in the process in order to address the higher level of risk assumed by beginning to develop a test before the antibiotic has received regulatory approval.

What tools are required to address the investment required for surveillance of AMR and AMU?

We need to develop and publicize a strong economic case in support of AMR surveillance in order to drive increased interest in investment by additional countries and non-government donors. Better economic arguments can also help sustain investment in the Global Health Security Agenda, which is supporting the establishment of surveillance systems.

What support do countries require to develop and report accurate national data and share them on global surveillance systems?

Many countries require training for health providers and public health practitioners to learn how to conduct surveillance. Additional investments in sustainable surveillance platforms is also needed.

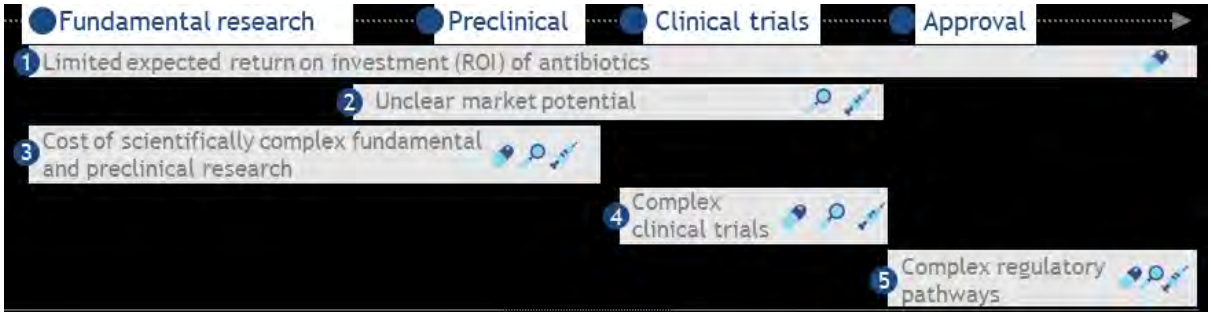
Once again, IDSA thanks all members of the IACG for your commitment to advancing robust global efforts to address AMR. We look forward to additional opportunities to assist with this important work.

Sincerely,

Paul G. Auwaerter, MD, MBA, FIDSA
President, IDSA

International Union Against Tuberculosis and Lung Disease

The International Union Against Tuberculosis and Lung Disease response to Antimicrobial resistance: Invest in innovation and research, and boost R&D and access IACG discussion paper.



Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

Tuberculosis is a WHO priority AMR pathogen and suffers the same market failure as the other AMR priority pathogens. Despite greater than 10million people a year developing active TB, it is not seen as a profitable area for investment by private industry[1]. Both TB and other AMR priority pathogens currently rely on antibiotics/antimicrobials for treatment, however, TB requires combinations of drugs to successfully treat it and therefore not only is drug development important, but also, how new drugs work in combination with others in the development of TB regimens. This requires that regimen development is prioritised early in the development pathway. The broad barriers and gaps in TB R&D outlined in the IACG discussion paper are similar for TB.

For TB, the Life Prize is a proposed de-linked model of R&D that not only ensures that the final product (a TB regimen not just new TB drugs) developed answers the public health need but is affordable and accessible in a sustainable way to all those who need it. The Life Prize de-linked model of R&D includes:

- Awarding prizes to researchers with drugs entering clinical development (phase one entry/IND or equivalent). This Prize will recoup R&D costs to that point (for TB, estimated to be between $30 - $40M USD) . This helps to move preclinical compounds into clinical development. This also helps incentivise new actors into TB R&D as there is a shorter time line for a return on their investment (ROI) and is associated with very clear criteria for the ROI which is independent of marketing and registration. (helping with barriers 1-3)
- The Prize is awarded to compounds that fulfil a predefined Target Product Profile as well as ensuring that all data and Intellectual Property (IP) (for the indication of TB) are made available/open.
- The data and IP is pooled for these new products to allow for easier and faster combination development for treatments that will improve the outcomes, duration and side effects of the current TB treatment. This facilitates and speeds up the clinical development phase and potentially decreased costs associated with data and IP agreements.
- Development from phase one onwards will be through donor grant funding with the commitment to continue to pool data and IP, so that it is available to others developing regimens as well as allowing other scientific questions to be addressed using the data. (barrier 4)

[1] http://www.treatmentactiongroup.org/sites/default/files/TB_FUNDING_2017_final.pdf

- By rewarding and recouping R&D with prizes and then paying for the research with grants into new drugs and treatments, all the treatments that are developed through The Life Prize framework will be affordable and accessible to all those who need them through this delinked model. The R&D costs are recouped through the R&D process.
- It has been developed with the input of key stakeholders in TB – academic institutes, biotech companies, pharmaceutical industry, national programmes and patient representatives to ensure that the incentives not only incentivise actors currently in TB R&D but has the potential to bring new investment (both financial and scientific)
- Currently the Life Prize is investigating resource mobilisation for the pull funding (prizes) for TB R&D.

The innovative use of prizes and grants, coupled with IP access strategies can help overcome the challenges and barriers for antibiotic development. Placing prizes earlier in the pipeline is a lower cost as the donors take on more of the risk. It is important to establish if the incentives are adequate and in the right place of the R&D cycle to incentivise the actors required and have provisions to ensure end product access. Using WHO Target Product Profiles and Target Regimen Profiles can ensure that the genuinely new products/modes of action are rewarded.

Data pooling and working closely with the WHO and regulatory authorities can allow for a smoother regulatory process with regulators confirming the type of data required so that this can be planned for in all donor agreements. (barrier 5)

TB R&D is mainly undertaken by small and medium sized entities and academic institutions and feedback from these groups was that a end-stage market entry reward is not an incentive as it occurred too late in the pipeline with too much up front investment required whereas an earlier reward coupled with increased donor funding for the later stage clinical development could ensure that these groups could develop their products faster and stay involved in the R&D of the products for longer. IP also plays a key role, particularly in any area requiring combination development but also for access and stewardship. Innovative IP strategies, including IP pooling (using organisations like the Medicines Patent Pool) can remove barriers to collaborative R&D as well as ensuring quality products with sustainable access provisions. (see Medicines Patent Pool Stewardship report)[2]

Using prizes, grants and pooling mechanisms can address the challenge and barriers outlined in the IACG report but it is unlikely there is a “one size fits all” approach for drugs, diagnostics and vaccines. Looking at the gaps and establishing the role of IP and data access in these gaps will be key to designing the right combination of push and pull funding with consideration of the added value of innovative IP strategies to ensure a de-linked model of R&D.

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

There are a number of different groups that may be able to support access and investment in AMR and it is likely to be more cost effective to expand their mandate to include AMR technologies rather than setting up new initiatives. Organisations like Unitaid may be able to help support market access work for new antibiotics for priority pathogens. Initiatives like the Global Drug Facility for TB could support procurement of quality assured antibiotics, utilising their pooled procurement to help with forecasting and economies of scale for price reductions. The Medicines Patent Pool can support the IP components of access and organisations like the Critical Path Institute that have developed data sharing platforms that can be expanded for AMR.

[2] https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf

The role of the G20 AMR collaboration Hub may be key to playing the coordinating role in AMR technology development, providing a platform for donors to plan and collaborate to overcome specific financial barriers.

MSF Access Campaign

Response by MSF Access Campaign to the consultation on IACG discussion paper, 'Antimicrobial resistance: Invest in innovation and research, and boost R&D and access'

Existing response to R&D challenges, remaining gaps and open questions to bridge those gaps

1. How could R&D funding be better channelled?

1.1. The framework for R&D funding has been set by the United Nations Declaration on AMR (2016). This states clearly that all R&D funding should be 'needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility.' It further acknowledges, 'the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development…'

1.2. In establishing a 'Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics' (global PPL), WHO has provided the basis for measuring whether R&D funding is 'needs-driven' in the area of new antibiotic drugs including TB. All funding for new antibiotics should therefore follow this guide to ensure it is aligned with the UN Declaration.

1.3. However, it is important to note that investments in R&D should not focus exclusively on bringing new antibiotic drugs to market, but also on other areas of innovation that are needed to most effectively combat AMR. As acknowledged in the discussion paper, a successful response to AMR will also need to address vaccines and diagnostics, as well as developing novel approaches and clinical algorithms that are adapted to specific local contexts. In these areas, further work is needed by WHO to set global priorities in order that R&D funding can be aligned with unmet needs.

1.4. The principle of affordability can be ensured by attaching conditions for access to R&D funding. Funding for upstream R&D can and should be coupled with access and stewardship requirements downstream as these products enter the market. AMR products and technologies that have benefited from significant public support should be considered public goods, and a public return on investment, through affordability and accessibility for all, should therefore be ensured. To this extent, public funders should ensure the traceability of taxpayer money invested in R&D. This is a necessary prerequisite for providing transparency and building public accountability for R&D as a shared responsibility.

1.5. The principle of efficiency can be ensured by fostering collaboration in order to accelerate delivery time of new treatments from 'bench to bedside' through the sharing of research results, including clinical trial data, providing access to well characterized sample banks and compound libraries, as well as the pooling of intellectual property rights as needed to further optimise development. These conditions will speed up development, reduce costs, and increase efficiency. The IACG should recommend incentives that foster these approaches.

1.6. In order to ensure the principle of equity is addressed in R&D, funding must be specifically made available for adapting drugs to the needs of specific patient populations that are often overlooked. This includes providing funding for the development of heat-stable, paediatric and oral formulations of existing and new antibiotics.

1.7. There is also a need to look at recommendations for how to address the following areas of innovation: repurposing of older or withdrawn antibiotics; exploring the as-yet-untapped potential of combination products (rational fix dose combinations (FDCs)); sustainable implementation of new technologies within health programmes; and piloting, evaluating and scaling-up improved practices for infection control and antimicrobial use.

1.8. Finally, all R&D funding should operationalize the principle of delinking investment in R&D from the expectation of high prices and volume of sales, as set out in the funding framework provided by the UN Declaration on AMR.

2. What will it take to increase and sustain donor and private funding of R&D in AMR?

2.1. Increasing and sustaining donor funding of R&D on AMR requires political will. One way to build political will is to increase public support for the issue. In this regard the traceability of public funding is critical as it allows the public to see whether they are getting a return on their investment in the form of the development of new technologies to meet their needs at prices they and their governments can afford.

3. Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

3.1. The 5 challenges identified in the human health R&D value chain set out clearly the barriers to product development for new antibiotics, diagnostics and vaccines. The paper then identifies where existing initiatives contribute in part to addressing each of these challenges. This is useful, but it omits two important elements of analysis that are needed to get a full picture of the global response: an indication of the scale of the challenge versus the scale of the response; and the extent to which existing initiatives are aligned with the key principles outlined in the UN Political Declaration on AMR.

3.2. The question of scale is important because a particular initiative may contribute to ameliorating a particular challenge, but perhaps only with a fraction of the necessary budget to do this sufficiently. It is important to present the estimated scale of the *required* response against the scale of the *existing* response in order to see the size of the gap to be filled.

3.3. Analysing the extent to which existing and future initiatives address a specific challenge (such as challenge 1: the uncertainty in the expected return on investment of antibiotics) in isolation does not provide a necessary qualitative assessment of whether these initiatives operationalize the principles set out in the UN Political declaration on AMR. For instance, it may be possible to address the uncertainty in the expected return on investment in antibiotics by providing large financial rewards for any new antibiotic successfully completing phase 2 studies and entering the market without attaching any conditions to ensure affordability or stewardship. This type of incentive is clearly not fit for purpose and could lead to a perpetuation of the cycle of profit focus, expensive drugs, and limited patient access, at the expense of public finance.

3.4. Rather than looking to add incentive after incentive to address discrete challenges in isolation, as the framing of this question encourages, the IACG should look to support an investment framework from bench to bedside to ensure that clinical benefit, access and stewardship are guaranteed throughout the entire product development process. This would begin with defining target product profiles (TPPs) for priority unmet needs (based on the global PPL in the area of new antibiotics, for example); ensuring that access and affordability are set out as key target characteristics within these TPPs, including target price points to guide investment choices; and then seeing products through to the bedside by supporting the sustainable implementation of new AMR technologies within health systems.

3.5. Moreover, approaches that foster collaboration through the sharing of research results should be supported, as they will speed up development, reduce costs, and increase efficiency. This includes sharing clinical trial data, providing access to well characterized sample banks and compound libraries, as well as the pooling of intellectual property rights, as needed, to further optimise development. In this light, the Medicines Patent Pool should be looked at as a suitable mechanism for promoting collaborative research through the pooling of intellectual property rights during the development phase, while ensuring populations in need globally can benefit. This can be particularly useful in facilitating the development of rational FDCs, and improved combination regimens for drug resistant TB, for example.

4. How should the design of incentive mechanisms be coordinated at global, regional and national levels?

4.1. As stated above in 1.1, coordination starts with adhering to the framework set by the UN Declaration on AMR. If incentives are built on these principles[1] and follow the needs-driven prioritization set by the global PPL, coordination should follow and research and development efforts will be more successful. The Global Development and Stewardship Framework (GDSF) under development by the WHO, FAO and OIE should also provide a more tangible coordination framework, once agreed. The GDSF seeks to follow the entire value chain of product development from bench to bedside and, as such, should provide clear guidance to coordinate incentive mechanisms at the national, regional and global level.

4.2. Mechanisms that promote transparency and traceability of funding will allow donors and implementers to see where the gaps are in the response and provide the first building blocks for coordination. Without transparency on the R&D portfolios and funding flows the risk of overlap and duplication remain.

Existing response to challenges of access, gaps identified and open questions to bridge the gaps

5. Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

5.1. The mechanisms described in the paper are limited to the following:

- Specific 'global' funds for certain diseases and certain LMICs (such as Gavi, the Vaccine Alliance, the GFATM and UNITAID)
- The WHO's Essential Medicines List
- Voluntary licensing, including patent pooling
- Implementation research

As the paper notes, the global funds identified lack a specific focus on AMR. Moreover, the scope of countries covered by these initiatives is limited and differs from one to the other. In recent years these funds have insisted on 'transitioning' or 'graduating' middle-income countries out of eligibility for support. As such the usefulness of these funds to address the access issues of a wider range of countries is further diminished. The IACG should recommend that any mechanism to expand access to AMR-related health technologies be global in scope. This could start with revisiting and reversing the current trend towards restricting support for LMICs through 'graduation' and 'transition'.

[1] 'needs-driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility… the importance of delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results to be gained through research and development…'

5.2 In the area of vaccines this is particularly pertinent. Increasing affordable access to vaccines should be a high priority within the global AMR response as there is overwhelming evidence supporting vaccination as an effective, safe, low-cost measure to reduce the burden of both infectious diseases and AMR at every level[2]. For example, it has been estimated that introduction of Haemophilus influenzae type b (Hib) conjugate vaccine and pneumococcal conjugate vaccine (PCV) to 75 developing world countries could reduce antibiotic use for these diseases by 47% and avert 11.4 million days of antibiotic use in children younger than 5 years old each year [3]. Other vaccines for diarrhoeal and respiratory infections, in particular, have similar potential. Yet, currently, vaccination coverage is unacceptably low in many countries where MSF works. PCV, to take one example, remains unaffordable for a number of LMICs. By May 2018, globally 53 countries (27%) had not introduced a PCV vaccine in their national immunisation programme[4]. Of these 53 countries only 7 are Gavi-eligible countries[5], which illustrates a trend seen for years whereby low-income countries are introducing new vaccines at a faster pace than middle-income countries (MICs) due to availability of international donor financial support. The lowest price of ~USD 10 per child is available to those countries that are subsidised by Gavi, the Vaccine Alliance and, since 2017, to humanitarian organizations through the Humanitarian Mechanism, a mechanism for accessing affordable and timely supply of vaccines for use in humanitarian emergencies[6]. Even some Gavi-supported countries are not scaling up PCV coverage in their immunisation programmes for fear that they won't be able to sustain an affordable supply once they transition out of Gavi funding and have to pay much higher prices. The IACG should recommend measures to address this situation as a priority.

5.3 Governments must be supported to address situations of monopolies and high prices where these are barriers to access for needed AMR technologies. This involves avoiding the granting of poor quality patents as well as making use of compulsory licensing to overcome unaffordable prices of monopoly products.

5.4 Pooled procurement, as specifically modelled by the Global Drug Facility (GDF), should be explored as a key mechanism for ensuring both lower prices for antibiotics and improved stewardship. The GDF represents a large portion of the market for TB drugs and diagnostics, and uses this to negotiate prices with companies based on larger volumes. GDF's international tenders allow both generic and innovator companies to compete in supplying quality-assured TB health products. It rejects tiered pricing; encourages suppliers to enter

[2] Kathrin U Jansen & Annaliesa S Anderson (2018): The role of vaccines in fighting antimicrobial resistance (AMR), Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1476814

[3] *Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, Davies S. 2016. Access to effective antimicrobials: a worldwide challenge. Lancet 387:168 175.doi:10.1016/S0140-6736(15)00474-2*

[4] WHO Data, statistics and graphics , http://www.who.int/immunization/monitoring_surveillance/data/en/
Access 5th July 2018

[5] IVAC's digital platforms contain downloadable vaccine introduction maps : http://view-hub.org/viz/
Access 5th July 2018

[6] Accessing Affordable and Timely Supply of Vaccines for use in Humanitarian Emergencies: the Humanitarian Mechanism
http://www.who.int/immunization/programmes_systems/sustainability/The_Humanitarian_Mechanism_ToRs.pdf?ua=1

into markets; provides forecasting to suppliers as well as providing governments with forecasting assistance and orders (which is important given different shelf lives). It anticipates and addresses global supply issues and provides advice to countries on switching to optimal from sub-optimal formulations. In the area of diagnostic tools, GDF has been able to negotiate improved service and maintenance terms from companies.

Cross-cutting topics in R&D and access

6 How should the guiding principles be operationalized? Are there additional relevant guiding principles to be considered?

6.1 The guiding principles are set out clearly in the UN political declaration on AMR, as referenced in the paper on page 15 and noted in this submission under point 1.1. It is unclear why one of those principles, 'Equity' has been expanded upon in the consultation paper, and three new 'guiding principles' (Global public benefit, Gaps in the response and value for money) have been added. The IACG takes its mandate from the UN Declaration on AMR and, as such, should focus on these globally agreed principles to guide its work.

6.2 Please see answers 1.1 to 1.8 for MSF's response on how to operationalize the principles of the UN Declaration on AMR.

MSF Access Campaign

Response by the MSF Access Campaign to the consultation on IACG discussion paper, 'Surveillance and monitoring for antimicrobial use and resistance'

The MSF Access Campaign welcomes the discussion paper on surveillance and monitoring and agrees that it is an important area of work requiring the commitment of funding and resources by donors and governments to facilitate the monitoring of antimicrobial use and resistance to track the epidemiology of AMR and the appropriate use of medicines, which is a necessary and important baseline for targeting areas of necessary and appropriate intervention. Crucially, the development and provision of tools and know-how required to feasibly and sustainably implement surveillance and monitoring in low-resource settings must be prioritized, and all data be made publicly availably, preferably following normative guidelines in terms of the methodology of collection.

The MSF Access Campaign would like to add the following considerations to improve the discussion paper:

Upfront key message could be extended to include:

- Priorities for surveillance in the context of human health should also be based on GLASS.
- Local surveillance data may also be used to inform clinical guidelines that may still be based on syndromic diagnosis.

Within the main text, the following points could be made clearer or amended:

- Agree that surveillance data should be made available via easily accessible, publicly available sources but this does not come through strongly enough.
- Agree that the variables and recommendations for harmonization – or equivalence – should preferably be evidence-based and set by a normative body, such as WHO

GLASS, for the standardization of surveillance in the context of human health, and should be further emphasized.

- "Counterfeit" is no longer a recognized definition as is can lead to "confusing the phenomenon of substandard and falsified products with the protection of intellectual property rights"; thus the WHO definition for substandard and falsified products should rather be used: http://www.who.int/medicines/regulation/ssffc/definitions/en/

Answer to some of the questions posed:

- **"What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?"** Part of making surveillance more feasible and likely in LMICs is increased support for (i) more robust and affordable tests better adapted to the needs of low-resource settings, including with longer shelf-life and stability at ambient temperatures, (ii) the sustainable implementation of these at both point-of-care and more centralized laboratories, along with quality-assurance, (iii) training for the interpretation of results and/or simplification of reporting, and (iv) support for the analysis and publication of the results. This could be made apparent as part of the "recognized barriers for LMICs". In addition, when new technologies are available (e.g. mass spectrometry, rapid tests, WGS), very often they are too complex, too expensive or not sufficiently validated in MSF-type settings to be feasible in microbiology laboratories there, thus impeding equitable access to the best technologies even further.

RESULTS UK

From: Janika Hauser
Sent: 09 July 2018 20:02
To: IACG-secretariat
Subject: Re: Public Consultation: Discussion Paper 1 (RESULTS UK)

To whom it may concern,

my sincere apologies, I just spotted a small copy & paste error on my part. Please disregard the previous email and use the comments below, which have been slightly amended to expand our comments on the role of PDPs.

With kind regards,

Janika Hauser

Innovation, research and development

- We welcome this discussion paper and the due attention given to both R&D and access, and their respective overlap.
- Within the discussion paper, tuberculosis (TB) generally and drug-resistant TB (DR-TB) specifically is currently considered as part of the 'three diseases' (HIV, TB and malaria). While resistance is becoming a growing concern for all three infectious diseases, the size, spread and complexity of the DR-TB epidemic, cause of 1-in-3 AMR-associated deaths, warrants further and specific attention within discussion papers and the work of the IACG moving forward.
- We would also recommend including an acknowledgement of the importance of R&D and access to improve the AMR response to uphold human rights, most notably the right to health and the right to science (articles 12 and 15, respectively, of the International Covenant on Economic, Social and Cultural Rights).
- The discussion paper identifies five challenges in the antibiotic value-chain that have hampered investment in R&D.
    - Uncertainty in the expected return on investment: this point currently only refers to limited purchasing volumes on account of increased stewardship measures. It fails to recognise the significant impact of weak healthcare systems unable to diagnose and guarantee access to treatment for common microbial infections, including TB. It also does not recognise the impact of poverty among affected populations more widely, which, in the case of TB, HIV and malaria is also a factor hampering investments in R&D.
    - Unclear market potential: the current language suggests that the unclear market potential is solely the result of LICs and LMICs making poor public health investments. The experience in TB has shown this to be far more complex, with the roll-out of the GeneXpert diagnostic module alone having been hampered by a lack of operational research, difficulties in re-allocating multi-year grants to large-scale and unforeseen infrastructure investments, and uncertainty over potential beta-versions of the test becoming available.
    - Clinical trials: the absence of reliable biomarkers for conditions like TB require clinical endpoints that make trials larger and lengthier. Poor lab capacity in countries make research more complicated by necessitating sample cohorts, while low site capacity makes trials enrol more slowly. Low regulatory capacity can lead to further delays. Ethical issues also emerge where Institutional Review Boards are not well informed about the appropriate inclusion of women/children/other vulnerable populations in research, and inadvertently lead to the exclusion of these populations from benefitting from scientific progress.
    - Regulatory pathways: The discussion paper only goes so far as to suggest additional research, which, while useful, does not build on the conclusions of existing research that clearly points to the potential value of regulatory harmonisation efforts. The expansion and improvement of existing harmonisation pilots, such as those coordinated by the World Health Organization and regionally driven harmonisation, should be explored more proactively by the IACG.
    - Further clarification is needed about the distinction between 'uncertainty in the expected return on investment of antibiotics' and 'unclear market potential'.
- Further attention should be given to the role of social science research in understanding consumption, prescription and treatment patterns and broader health system economies.
- We strongly support the call for increased clarity over funding priorities and encourage the proactive use of coordination mechanisms such as the G20 AMR R&D collaboration hub. Wide participation and the transparent publication of funding details are considered to be particularly important.

- The need for coordination and collaboration of research itself, as opposed to solely the appropriate targeting of investments, is not adequately discussed in the paper. Many leading infectious and non-infectious diseases are treated using a combination of drugs, which protects against the emergence of resistance and ensures quicker and safer treatment. Monotherapy is a leading driver of resistance in microbial infections and solutions to AMR should therefore focus on delivering whole treatment regimens as opposed to single agents alone. Where products are developed in isolation from one another, their impact on treatment outcomes will be limited and the duration from bench to bedside will be extended due to the need for additional trials (see experience with bedaquiline and delamanid). This requires data sharing, as proposed by the Life Prize for TB's push/pull/pool model. This would also ensure improved access to the products of innovation.
- When discussing public and philanthropic funding for R&D, the discussion paper defines the only gap as being in the 'optimizing funding for priorities', which creates the false impression that improved coordination will resolve AMR R&D challenges. The funding gap for AMR R&D is well established and both increased investments and the coordination thereof will be essential moving forward. Any discussion on AMR R&D requires acknowledgement of and consideration of models to secure additional investments from both public and private sector.
- If PDPs are to be individually named, we would encourage a more universal approach, including recognition of the work of AERAS, TBVI, IAVI and others. PDPs have developed significant expertise, particularly in translational research, and a variety of products (including diagnostics, drugs and vaccines) will be needed to combat AMR in the long term. Many of the issues raised in the paper - notably R&D gaps, lack of funding, delinking research costs from end user costs - can be addressed by PDPs. PDPs can bridge gaps between basic research and late-stage clinical trials, leveraging both public and private funding to ensure tools are developed for which there may not be a ready market.
- We welcome the discussion of delinkage and the explicit reference to the commitments made by UN Member States to expand R&D efforts that are 'needs-driven, evidence-based and guided by the principles of affordability effectiveness and equity". The discussion paper moves on to outline some of the key incentivisation mechanisms piloted thus far, including advance market commitments, priority review vouchers and market exclusivity rewards The discussion paper does not pay adequate attention, however, to the criticism these mechanisms have come under, particularly on account of their limited impact on stimulating innovation while in some cases also restricting access.

Access

- Limited health system capacity should be considered first and foremost when discussing access issues in AMR. Only 1 in 5 people with MDR-TB can expect to be appropriately diagnosed and treated. Requiring patients to travel long distances and miss work to get medicines is a huge barrier to receiving and staying in care, and thus fosters the development or amplification of AMR.
- The discussion paper notes that over-the-counter sales of non-prescribed antibiotics in LMICs contribute to the emergence and spread of AMR. The discussion paper does not recognise, however, that even in the public sector, inappropriate antibiotics are often prescribed out of keeping with WHO recommendations.
- When describing existing global access initiatives, the discussion paper should recognise the work of the Global Drug Facility, a pooled procurement mechanism for TB drugs that has facilitated a more stable and appealing market for manufacturers while also providing technical assistance to countries to support forecasting and supply management. This approach could be a model for other disease areas.
- We welcome the mention of the Essential Medicines List as an important initiative for access. The discussion paper should also recognise the Essential Medicines List for children and the recently released Essential Diagnostics List.
- It is notable that the discussion paper creates the impression that access initiatives for HIV, TB and malaria have been able to resolve access issues for the three diseases, require no improvement, and should therefore act as a model for AMR initiatives. While progress has been made and important lessons can be learnt from the global response to HIV, TB and malaria, much work remains to be done.
- The discussion paper proposes the expansion of mandates of existing funds such as the Global Fund and UNITAID to include AMR. It is important to note that many of these funds already include AMR within their mandates through the funding of diagnosis and treatment of both drug-sensitive and drug-resistant strains of disease. It should also be emphasised that at current funding levels, these funds are already unable to meet the total need for financial support and any expansion of mandates could only be considered in the event of commensurate funding increases.
- Additionally, co-financing and transition plans among donors, particularly the Global Fund and GAVI, are placing increasing importance on domestic financing for the response to AMR. Yet many national policies regarding tendering and local registration prevent the procurement of quality-assured health products. IACG should include the importance of donors' ensuring that countries have appropriate policies and laws in place to continue the procurement of quality-assured health products before domestic financing for procurement begins.

RESULTS UK

From: Janika Hauser
Sent: 09 July 2018 19:49
To: IACG-secretariat
Subject: Public Consultation: Discussion Paper 2 (RESULTS UK)

To whom it may concern,

This email responds to the request for feedback on the IACG's discussion paper 2 ('Antimicrobial Resistance: National Action Plans').

We thank the IACG for the opportunity to provide feedback on the discussion papers. Our comments, made on behalf of RESULTS UK, can be found at the bottom of this email.

As requested, an individual email has been sent with comments for each of the three discussion papers.

With kind regards,

Janika Hauser

Antimicrobial Resistance: National Action Plans

- When discussing coordination across sectors and stakeholders, the discussion paper only references human health, animal health, plant health, food chains and environment. Multisectoral leadership also necessitates the appropriate involvement from Ministries of Finance (for funding), Ministries of Education (awareness raising, research and innovation) and Ministries responsible for social care among many others, to ensure holistic interventions. Ultimately, the convening power for this number of actors requires leadership from Heads of State or Government.
- Members of parliament, civil society organisations and bi- and multi-lateral partners have a demonstrable track record of championing action and high-level political leadership. The IACG discussion document should explicitly recognise these and encourage their active involvement.
- The active involvement of civil society organisations in national action planning and in the implementation of interventions will facilitate sustainability and public awareness.
- The discussion paper rightly places significant emphasis on the role of regional platforms as a place for knowledge sharing. However, such platforms should not only be conceived of as places for sharing best practice, but also for driving leadership and holding governments to account for implementing appropriate policies. AMR does not respect borders and with the need for national leadership recognised throughout this paper, national, regional and global accountability measures (e.g. AMR as a standing agenda item at regional leaders' meetings such as the AU Summit, and economic blocs such as BRICS and G20) should be more proactively explored by the IACG.
- The UN High-Level Meetings on TB and UHC offer an opportunity to further integrate AMR with these agendas and increase political support for global and national action on AMR.
- The financial case for investing in AMR should align with those outlined in the UN High-Level Meeting political declarations on AMR, TB and HIV. A national breakdown of up-front costs and the cost-of-inaction should be included to encourage leadership and shape national action planning.
- The World Health Organization's Global TB Programme encourages countries in low-, middle- and high-income countries to develop National TB Research Plans, outlining research needs, priorities and funding. The plans encourage coordination of research investments globally and facilitate priority setting and strengthen research networks, while being appropriate to national resource and research capacities. Programmatic action on AMR should not be conceived of as separate from

research, and synergies between the two investments should be recognised through the full integration of AMR research into national action planning.

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Janika Hauser | **Parliamentary Advocacy Officer (TB)** | **RESULTS UK – you have the power to end poverty**

| www.results.org.uk

RESULTS UK

From: Janika Hauser
Sent: 09 July 2018 19:49
To: IACG-secretariat
Subject: Public Consultation: Discussion Paper 3 (RESULTS UK)

To whom it may concern,

This email responds to the request for feedback on the IACG's discussion paper 3 ('Surveillance and monitoring for antimicrobial resistance').

We thank the IACG for the opportunity to provide feedback on the discussion papers. Our comments, made on behalf of RESULTS UK, can be found at the bottom of this email.

As requested, an individual email has been sent with comments for each of the three discussion papers.

With kind regards,

Janika Hauser

Surveillance and monitoring for antimicrobial resistance

- Barriers to effective surveillance include the lack of effective diagnostic tools. In the case of DR-TB, the continued absence of a point-of-care rapid diagnostic test for MDR-TB has undermined surveillance and monitoring efforts, underlining the need for further investments.
- The paper should recognise the importance of basic infrastructure investments, particularly in low-income countries where tools, basic infrastructure such as power and internet supply and sophisticated data management platforms remain sparse. Given overstretched programmatic budgets which see health services unable to provide even basic diagnosis and treatment to their populations, it is difficult to justify investments into advanced surveillance systems. There is a clear need, therefore, for broader investments that don't come out of limited programmatic budgets. Importantly infrastructure investments should not contribute to disease-silos by restricting their scheme of work to individual diseases, and instead prioritise based on need and/or epidemiological impact

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Janika Hauser | **Parliamentary Advocacy Officer (TB)** | **RESULTS UK – you have the power to end poverty**

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SOUTH CENTRE

South Centre Submission to IACG on "Antimicrobial Resistance: National Action Plans"

12 July 2018

This is a South Centre submission in response to the public consultation by the Interagency Coordination Group on Antimicrobial Resistance (IACG) on "**Antimicrobial resistance: national action plans (NAPs)".**

General comment

Developing countries face many challenges in addressing AMR. There is a lack of awareness, expertise, funds, technical equipment, personnel and political will to take the range of actions required. These are serious obstacles to the implementation of AMR action plans. Developing countries also face a number of obstacles in health and other areas (climate change, volatility of food prices, unemployment, poverty) that compete with AMR for resources. AMR is a complex issue and difficult to show its direct impact. It is also less visible than other health issues such as specific disease outbreaks and epidemics. In the competition for scarce funds and personnel, it is difficult for AMR to obtain the resources and attention it deserves.

Developing countries need to give higher priority to AMR. They also need to receive more support to increase their capacity to develop and implement inter-sectoral national action plans to combat AMR.

Response to questions:

What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?

The integration is essential for a comprehensive response. AMR should be integrated into existing health programs, including child and maternal health, TB and HIV programs, as well as agendas on sustainable agriculture and environment.

Targets on AMR can also be included in the reporting on national progress towards achievement of Sustainable Development goals, including Goal 2: zero hunger, Goal 3: Good Health and Well-Being, Goal 6: Clean Water and Sanitation. This would encourage continued political attention to AMR at national level.

The achievement of Universal Health Coverage and its sustainability would be under threat if AMR was not addressed as part of a broader health systems issue. Countries should be encouraged to strengthen their primary care as part of a broader development agenda and integrate measures to combat AMR. In this regard WHO is correctly positioning AMR as part of UHC.

What support do Member States need to build AMR-specific and AMR-sensitive activities into national strategies for public health, animal health, plant health, food security and sustainable economic development?

Key areas of support are technical and financial.

Countries will need support to expand nationally to all areas, including remote and rural, infection prevention and control (IPC) and water, sanitation, and hygiene (WASH) as key interventions on AMR.

To understand the threat of AMR in the local context, build surveillance capacity is critical.

Countries also need support to formulate and implement a comprehensive national policy for rational and appropriate use of antimicrobials. This will include regulating marketing practices by companies in human and animal health to support appropriate use and address perverse incentives to sales personnel and to medical and veterinary personnel that are linked to high volume of antibiotic sales.

The WHO guidelines on antibiotic use in animals are useful and important reference that countries can implement from the human health perspective. This should be supplemented by guidelines jointly issued by WHO, FAO and OIE.

Developing countries will also need support in implementing measures to reduce the routine use of antibiotics in animal production and transition into more sustainable production systems.

An international fund, or a number of funds, should be established to assist developing countries to meet the costs of addressing AMR, without overly straining their public health budgets that could skew their priorities and reduce their ability to tackle other critical public health challenges.

What forces maintain national responses to AMR in silos, and how can we overcome them?

Coordination among the different government sectors at the country level is one of the main challenges that developing countries face in implementing NAPs. Therefore, supporting countries to set up national inter-ministerial committees that involve agriculture and health for implementation of NAPs could help break the silos. Integrating the environmental ministry at the national level would also help to make sure that this aspect is also addressed. This committee may be hosted at the Ministry of Health to ensure that there is a clear lead. Inter-sectoral expert working groups can also be established to carry out coordinated work. Part of the support to establish these national committees and working groups could be delivered through technical assistance provided by the tripartite (WHO-FAO-OIE) at the regional/national level. At the same time, commitment is needed to make the committees functional.

International recognition of efforts and good examples of countries that have established functional inter-sectoral coordination and collaboration on AMR could serve as a positive incentive to help maintain momentum. The recent joint publication by the tripartite offers

useful reflections on this topic drawn from country lessons on how to establish and sustain the multisectoral collaboration needed to develop and implement NAPs[1].

How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?

Part of the support for full integration should include technology transfer and the provision of technical equipment including diagnostics and know how to developing countries on grant or concessional terms.

Also, there is a need to ensure that there will be strong international cooperation for building capacity of developing countries to address AMR.

What support do countries need to translate information on the global impact of AMR into a country-specific case?

Support at the global level in providing guidelines or regulations for medical personnel, hospitals and clinics on the appropriate use of antibiotics, and on relations with industry sales representatives.

Countries will also benefit by having access to therapeutic guidelines that could help provide guidance on treatment particularly for resource poor setting with limited access to appropriate laboratory and diagnostics tools.

Continual sharing of information between countries will add to encouragement and partnership in sharing the responsibility for the control of AMR and the implementation of antimicrobial stewardship.

How can AMR be integrated into the plans and budgets of governments and, where appropriate, development partners?

The development of a technical tool and global road map for mobilizing funding for implementation of NAPs that would allow countries to assess their own resource capacities against existing plans and budgets and to access the additional funding that they need. Development partners need to be aware of the specificities of each setting and be flexible in their approach to support NAPs that should count with domestic ownership in the design and implementation as well as targets and monitoring mechanism to ensure success.

What is the role of the international community in supporting international public goods such as AMR surveillance data?

Where there are no data currently kept, priority must be directed at supporting the maintenance of records at all levels; patient records including all necessary patient, diagnosis and treatment details; laboratory records of all necessary details of tests and results. Without these data, surveillance is not possible and stewardship is also not possible.

The international community should provide technical and financial support to developing countries for capacity building and financing of the comprehensive range of activities to

[1] Tackling antimicrobial resistance (AMR) together. Working paper 1.0: Multisectoral coordination. Geneva: World Health Organization; 2018 (WHO/HWSI/AMR/2018.2).

address AMR at national level, including prevention of infections, appropriate use of antibiotics, improvement of practices in hospitals and clinics, new regulations including on marketing, prescription and dispensing of medicines and their enforcement, interventions to control antibiotic use in agriculture and animal health, improvement of practices in hospitals and clinics, educating the public, community workers and health professionals, etc.

How can we support decisions to balance the portfolio of investment in AMR-specific and AMR-sensitive interventions, particularly in LMICs that need support in developing public health, animal health, plant health and environmental support services across regulatory and operational domains?

The countries should be supported to establish as part of NAPs an inter-Ministerial committee that ensures a one-health approach. Each country depending on the context will identify what are the priorities for interventions. At the same time, there is need for global guidance on interventions, and the FAO-WHO-OIE collaboration is critical to lead the way on how to ensure that interventions are complementary across the sectors (which for example is not evident to date in the animal health sector). There is also need to have a space for coordination among various agencies providing support or operating at country level which can be supported by regional focal point offices that are of tripartite nature and also involve UNEP.

Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform?

The selection of an antimicrobial for the specified indication that is consistent with appropriate clinical guideline recommendations. There is a need for up to date standard treatment guidelines which are based on appropriate laboratory surveillance specific for the setting.

What are the highest priorities for training in Member States with respect to NAP implementation?

The priorities should be identified as part of a national process for definition of NAPs, based on assessment that is context-specific. The mechanism for transmitting the needs assessment should be through the tripartite plus UNEP, either through national or regional focal points. This information could also be made more widely available for other donors, development agencies, civil society organizations and other stakeholders to enhance resources and improve coordination. More resources should be made available to provide training to developing countries in particular least developed countries.

What platforms would be most useful for sharing success stories, examples of best practice and lessons from experience in NAP development and implementation?

Platforms at global, cross-regional, regional, national and community level that are sustainably funded and staffed (may be part of a regional organization or regional representative office of the tripartite), specify stakeholders involved and type of intervention, in addition to the lessons learned and what has been identified as a best practice in a particular context. Stakeholders at country level are seeking examples of what works in similar contexts, high-impact, cost-effective, rather than an overall approach that may be impractical in some settings. Digital tools can support information sharing and success stories shared. Civil

society are key stakeholders in this process of dissemination of practices. The tripartite plus UNEP should play a leading role in developing a global platform for this purpose.

What sensitivities should be considered when encouraging regional cooperation on AMR?

Regional ownership, inclusion. Identification of national champions that act as focal points for interaction with regional and global platforms. National ownership of NAPs is critical for making regional platforms a supportive tool for NAP implementation.

United States Pharmacopeial Convention

Interagency Coordination Group to the UN Secretary-General on Antimicrobial Resistance (IACG) Public Consultation, Feedback on IACG Working Paper: National Action Plans

July 6, 2018

The United States Pharmacopeial Convention would like to thank the Interagency Coordination Group to the UN Secretary-General on Antimicrobial Resistance (IACG) for the opportunity to comment on the IACG's discussion paper titled Antimicrobial *Resistance: National Action Plans*. We recognize the IACG's mandate to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance and to report back to the UN Secretary-General in 2019.

USP is a non-governmental organization (NGO) that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements worldwide. As an NGO in Consultative Status with the United Nations Economic and Social Council, and in Official Relations with the World Health Organization, we are committed to the global fight against Antimicrobial Resistance (AMR).

The global burden of substandard and falsified medicines presents a potential danger to realizing a key pillar of AMR global strategy: medicines stewardship. The WHO estimates that one in ten medicines in Lower/Middle Income Countries (LMICs) are substandard and/or falsified, with antimicrobials representing a significant proportion of the total[1]. This categorization— which can be broadly referred to as poor quality medicines—means that these medicines are out of specifications and will be ineffective as intended treatments. Poor quality medicines create an environment that foster AMR by encouraging the mutagenic potential of microbes. Poor quality medicines also hamper providers' ability to properly treat patients with available medicines even under the best of care guidelines; damage patients' trust in the health system; and cost lives [2].

Strengthening national medicines quality surveillance systems, combined with targeted sentinel surveillance of critical antimicrobial medicines, would help to illuminate the true burden of poor quality medicines within an AMR context. Current evidence suggests that the burden likely varies depending on the country and the types of medicines, with potentially more devastating health effects in places where health and regulatory systems are already weak.

In the IACG call for comments, the question was posed: "*What sensitivities should be considered when encouraging regional cooperation on AMR?"*

National Action Plans currently have vastly varied approaches to priority setting and depth of planning under the broad pillars set forth by the AMR Global Action Plan. Though this diversity can mean appropriate adaptation to local contexts, it can present a challenge to regional cooperation, especially where country level approaches, capacities, and resources are less aligned. A more specific, commonly accepted set of priorities is needed if regional cooperation is to be further employed to tackle transnational issues in AMR. Any regional cooperation approach needs to take into account the variability in both the burden of poor quality medicines and the burden of AMR, and the capacity of health systems to respond on both fronts.

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Already within AMR National Action Plans, many LMICs are incorporating elements of strengthening systems to address poor quality medicine threats. Too often, plans do not translate into action due to a lack of specificity and resources. However, under the WHO's Substandard and Falsified medicines (S&F) framework, specific interventions like strengthening and supporting regional networks of medicines quality laboratories provide an excellent opportunity to facilitate national and regional capacity strengthening, information sharing and best practices required to detect poor quality medicines. These efforts can also help build on best practices for transnational AMR disease surveillance.

The WHO's S&F framework exists as a set of agreed-upon, technical-to-policy principles to prevent, detect, and respond to substandard and falsified medicines. These systems level approaches build on lessons learned from global experiences on good medicines supply stewardship. They are applicable across human and animal health medicines quality challenges in AMR.

To better enable regional cooperation, the IACG should recommend countries to more formally incorporate the WHO's S&F framework into their AMR strategies. Countries working from this framework can better plan regional collaborations at the intersection of quality of medicines issues and AMR, with aligned goals, targets, and approaches to substandard medicine issues. Tackling medicines quality across regions can thus decrease one factor contributing to AMR and allow countries to lay the ground work for securing quality medicines supply chains that cut across geography and health programs. These efforts can address not only AMR but potentially other health systems' needs.

USP remains committed in our support of the public health mission and the ongoing leadership of the IACG on these matters. We look forward to serving as a resource to the IACG in providing ongoing guidance to ensure sustained effective global action to address AMR and reporting to the UN Secretary-General in 2019.

For more information, please contact:

Dr. Phillip Nguyen M.D. DABFM | Dr. Katherine C. Bond Sc.D.
International Public Policy &Regulatory Affairs
US Pharmacopeial Convention

"WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Reports and Executive Summary." World Health Organization. Nov. 2017. http://www.who.int/medicines/regulation/ssffc/capacity-building/en/

2. Nwokike, Jude; Clark, Aubrey; Nguyen Phillip P.; "Medicines quality assurance to fight antimicrobial resistance." Bulletin of the World Health Organization 2018; 96:135-137. doi: http://dx.doi.org/10.2471/BLT.17.199562

Private

Aequor, Inc and Aequor, Ltd

From: Marilyn Bruno
Sent: 06 July 2018 02:27
To: IACG-secretariat
Cc: Cynthia Burzell
Subject: SUBJECT - INVESTMENT IN INNOVATION AND RESEARCH - AEQUOR feedback on AMR global action guidance

COMMENT SUBMITTED BY Marilyn Bruno, Ph.D., J.D. - CEO of Aequor, Inc. and Aequor, Ltd., representing a woman-owned small business incorporated in the U.S. with a wholly-owned subsidiary in the UK.

COMMENT - I read with interest that the Interagency Coordination Group on Antimicrobial Resistance (IACG) is seeking feedback on global action. I was the State Department point person on U.S. interagency meetings during the bird flu crisis in the '00s, and have remained very familiar with the issues as CEO of a company that has developed novel remedies for AMR, Aequor, Inc., member of BIO, signatory of the Davos Declaration on AMR, speaker at the UN High level meeting on AMR, tasked by the Commission on One Health to promote International One Health Day, etc.

We are closely following US, EU, and UK trends in investment in innovation and research for new remedies, diagnostics and vaccines. However, still missing is mention of the fundamental facts about **biofilm.** As known for decades by microbiologists, biofilm is the first resistance response of bacteria and fungi to environmental stressors: heat, biocides, UV rays, the human, plant and animal immune systems, antibiotics, and vaccines. The bacteria and fungi form biofilm first as a glue-like matrix that facilitates attachment to surfaces and colonization, and then an impenetrable shield that grows thicker and faster in proportion to the environmental stressers. The biofilm matrix also captures other species of pathogens and facilitates horizontal gene transfer, which leads to accelerated mutations and new Superbugs.

Sadly, there are still no diagnostic tests for biofilm. No known biocide, antibiotic, vaccine, etc. that work *in vitro* can work *in vivo*, in the presence of biofilm. Further, biofilm testing is not part of the pre-clinical or clinical trial testing regimes of any regulatory agency overseeing new drug and vaccine candidates. This is a serious and potentially deadly oversight, as most bacteria and fungi are biofilm formers. In fact, it is no coincidence that every pathogen on the WHO and CDC lists of urgent, pandemic, bioterrorist threats and AMR strains are biofilm-formers.

Aequor's founder, Cynthia Burzell, Ph.D., is an expert on biofilm, having developed over the past 16 years a portfolio of inexpensive, non-toxic small molecules that remove biofilm without triggering a resistance response. Some kill the AMR pathogens alone. Others "potentiate" existing antibiotics. For example, even a low dose of *Penicillin* kills MRSA, VRSA and other AMR pathogens in combination with Aequor's molecules.

In order to achieve results for the public funding and invesments for AMR remedies, biofilm must be addressed. Please let us know if you would like further information on the role of biofilm in AMR, why the development and prescription of all antibiotics will trigger thicker biofilm, training in biofilm testing, or biofilm testing services. We look forward to working with you.

Respectfully submitted,

Marilyn J. Bruno, Ph.D., J.D.
CEO, Aequor, Inc.

Aequor, Inc and Aequor, Ltd

From: Marilyn Bruno
Sent: 06 July 2018 02:40
To: IACG-secretariat
Cc: Cynthia Burzell
Subject: SUBJECT - NATIONAL ACTION PLANS - AEQUOR feedback on AMR global action guidance

COMMENT UBMITTED BY Marilyn Bruno, Ph.D., J.D. - CEO of Aequor, Inc. and Aequor, Ltd., representing a woman-owned small business incorporated in the U.S. with a wholly-owned subsidiary in the UK.

COMMENT - I read with interest that the Interagency Coordination Group on Antimicrobial Resistance (IACG) is seeking feedback on global action. I was the State Department point person on U.S. interagency meetings during the bird flu crisis in the '00s, and have remained very familiar with the issues as CEO of a company that has developed novel remedies for AMR, Aequor, Inc., member of BIO, signatory of the Davos Declaration on AMR, speaker at the UN High level meeting on AMR, tasked by the Commission on One Health to promote International One Health Day, etc.

We are closely following global trends to develop national actions plans to combat AMR. We applaud progress to develop practical guidance for effective global action on antimicrobial resistance, including surveillance and communications infrastructure, official point people and institutions identified in every country to quickly disseminate information on outbreaks, ways to contain them, emergency phone numbers and computer links, etc.

However, still missing is mention of the fundamental facts about **biofilm.** As known for decades by microbiologists, biofilm is the first resistance response of bacteria and fungi to environmental stressers: heat, biocides, UV rays, the human, plant and animal immune systems, antibiotics, and vaccines. The bacteria and fungi form biofilm first as a glue-like matrix that facilitates attachment to surfaces and colonization, and then an impenetrable shield that grows thicker and faster in proportion to the environmental stressers. The biofilm matrix also captures other species of pathogens and facilitates horizontal gene transfer, which leads to accelerated mutations and new Superbugs. Biofilm quickly spreads in air and water, carrying the AMR colony to new locations.

Sadly, there are still no diagnostic tests for biofilm. No known biocide, antibiotic, vaccine, etc. that work *in vitro* can work *in vivo*, in the presence of biofilm. Further, biofilm testing is not part of the pre-clinical or clinical trial testing regimes of any regulatory agency overseeing new drug and vaccine candidates. This is a serious and potentially deadly oversight, as most bacteria and fungi are biofilm formers. In fact, it is no coincidence that <u>every</u> pathogen on the WHO and CDC lists of urgent, pandemic, bioterrorist threats and AMR strains are biofilm-formers.

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In order to develop effective national plans to combat bacterial and fugal AMR, biofilm must be addressed. Please let us know if you would like further information on the role of biofilm in AMR, why the

development and prescription of all antibiotics will trigger thicker biofilm, training in biofilm testing, or biofilm testing services. We look forward to working with you.

Respectfully submitted,

Marilyn J. Bruno, Ph.D., J.D.
CEO, Aequor, Inc.

Website: www.aequorinc.com

Aequor, Inc and Aequor, Ltd

From: Marilyn Bruno
Sent: 06 July 2018 02:49
To: IACG-secretariat
Cc: Cynthia Burzell
Subject: Fw: SUBJECT - SURVEILLANCE AND MONITORING - AEQUOR feedback on AMR global action guidance

COMMENT SUBMITTED BY Marilyn Bruno, Ph.D., J.D. - CEO of Aequor, Inc. and Aequor, Ltd., representing a woman-owned small business incorporated in the U.S. with a wholly-owned subsidiary in the UK.

COMMENT - I read with interest that the Interagency Coordination Group on Antimicrobial Resistance (IACG) is seeking feedback on global action. I was the State Department point person on U.S. interagency meetings during the bird flu crisis in the '00s, and have remained very familiar with the issues as CEO of a company that has developed novel remedies for AMR, Aequor, Inc., member of BIO, signatory of the Davos Declaration on AMR, speaker at the UN High level meeting on AMR, tasked by the Commission on One Health to promote International One Health Day, etc.

We are closely following global efforts to improve surveillance and monitoring of AMR outbreaks. However, still missing is mention of the fundamental facts about **biofilm.** As known for decades by microbiologists, biofilm is the first resistance response of bacteria and fungi to environmental stressers: heat, biocides, UV rays, the human, plant and animal immune systems, antibiotics, and vaccines. The bacteria and fungi form biofilm first as a glue-like matrix that facilitates attachment to surfaces and colonization, and then an impenetrable shield that grows thicker and faster in proportion to the environmental stressers. The biofilm matrix also captures other species of pathogens and facilitates horizontal gene transfer, which leads to accelerated mutations and new Superbugs. Biofilm spreads rapidly in air and water, carrying the pathogens to new locations.

Sadly, there are still no diagnostic tests for biofilm. No known biocide, antibiotic, vaccine, etc. that work *in vitro* can work *in vivo*, in the presence of biofilm. Further, biofilm testing is not part of the pre-clinical or clinical trial testing regimes of any regulatory agency overseeing new drug and vaccine candidates. This is a serious and potentially deadly oversight, as most bacteria and fungi are biofilm formers. In fact, it is no coincidence that <u>every</u> pathogen on the WHO and CDC lists of urgent, pandemic, bioterrorist threats and AMR strains are biofilm-formers.

Aequor's founder, Cynthia Burzell, Ph.D., is an expert on biofilm, having developed over the past 16 years a portfolio of inexpensive, non-toxic small molecules that remove biofilm without triggering a resistance response. Some kill the AMR pathogens alone. Others "potentiate" existing antibiotics. For example, even a low dose of *Penicillin* kills MRSA, VRSA and other AMR pathogens in combination with Aequor's molecules.

In order to undertake effective surveillance and monitoring of AMR outbreaks, recognizing and containing the presence of biofilm is critical. Recognizing its source is also critical. MRSA and other AMR pathogens, for example, are spread in hospitals but are also found on all surfaces in communities (playgrounds, schools, markets, water faucets, shower heads, food, etc.) and spread through human and animal contact (even domestic pets).

Please let us know if you would like further information on the role of biofilm in AMR, why the development and prescription of all antibiotics will trigger thicker biofilm, training in biofilm testing, or biofilm testing services. We look forward to working with you.

Respectfully submitted,

Marilyn J. Bruno, Ph.D., J.D.
CEO, Aequor, Inc.

Website: www.aequorinc.com

AMR Industry Alliance

IACG Consultation

IACG Working document: Discussion paper with preliminary analysis
Antimicrobial resistance: Invest in innovation and research, and boost R&D and access

I. Key messages

- **Barriers to investments on AMR R&D:**
  - Novel antibiotics are generally undervalued by reimbursement systems relative to the benefits they bring society. Uptake of novel antibiotics is slow, since they are usually used sparingly to preserve effectiveness when resistant infections are relatively rare and there may be limited availability of appropriate diagnostics and surveillance data.
  - The primary barrier for diagnostics R&D is restricted market potential, given the under-utilization of existing diagnostic tests. Diagnostics often are undervalued by health care systems relative to their essential role in providing quality care, and therefore may seem expensive or burdensome when compared to the simple practice of giving an antimicrobial agent empirically.
  - There needs to be a sustainable Return on Investment (ROI) for diagnostic systems and a balanced division of value between therapeutics and diagnostics, especially when used in antibiotic stewardship programs helping to reduce inappropriate antibiotic use.
  - New clinical studies must be designed to reflect the value of diagnostics, when used alone or in combination with other health products and technologies.

- **The need for novel incentives:**
  - The progress made on push incentives in encouraging: While push mechanisms are valuable and should be continued, on their own they will not be sufficient to address the AMR innovation gap. These “push” incentives subsidize R&D efforts, whether successful or not; while this helps reduce the upfront spend needed to be invested in development, it does not have a significant impact on the potential returns from the investment of company or investor funds.
  - Pull incentives are urgently needed: Pull mechanisms reward successful delivery of innovation with funding that increases the return on investment and improves the predictability of the return. They incentivize pharmaceutical companies to take on the necessary risk and uncertainty that comes with the research and development of novel products to address AMR. Pull incentives are critical to maintaining a healthy investment ecosystem.
  - To develop new, innovative health products, collaboration must be fostered through public-private partnerships involving all stakeholders, including pharma, drug, vaccines and diagnostic companies, as well as surveillance networks.
  - In spite of high-level statements and commitments from political leaders on the urgent need for new treatments, diagnostics, and vaccines, current reimbursement systems send wrong signals:

        - Reimbursement reform is needed to enable appropriate access to novel antibiotics and stabilize the economics of antibiotic R&D. Reimbursement reform can complement and reinforce key antimicrobial stewardship components, including the use of diagnostics, de-escalation, regimen monitoring, and surveillance.
        - Novel antibiotics prices are often pegged to older generic antibiotics. Payer reform is needed to better capture the societal value of antibiotics in Health Technology Assessments (HTA).
        - The level of reimbursement for a diagnostic test is an important driver of utilization. While a diagnostic test may add expense to the laboratory, it can save money for the overall health system and have a broad impact on decreasing AMR.
        - There is a need to assess the health and medical value of diagnostics through evidence-based studies on a local and global basis. Reimbursement practices need to be aligned with public health goals to drive more timely and accurate diagnosis of infectious diseases
    - A suite of incentives including both push and pull incentives, is needed. These incentives should be sustainable and sufficient to stimulate R&D across the full R&D lifecycle, from discovery through development, to see an impactful long-term change on the pipeline of new products.
    - A global pull mechanism for antibiotics R&D is unlikely to be created and would not provide sustainable solutions. We believe in a local/regional solution tailored to countries specificities rather than a global coordinated model. Different models may be appropriate for different countries/health systems, funding/reimbursement systems, challenges, products.

- **Access:**
    - Given that health care financing and delivery is managed at the national- or subnational-level, a sustainable and sufficient global pull mechanism for antibiotics R&D is unlikely. We support local/regional solutions tailored to countries' specificities rather than a global model. Different models may be appropriate for different countries/health systems, funding/reimbursement systems, challenges, products.
    - Rational order for prescription of antibiotics: The paper states that Stewardship and Rational Use are not in scope for this paper (are addressed by another IACG group). However, it is imperative that to preserve the efficacy of antibiotics, we must ensure increasing access to the right antibiotics in a rational order. Determining global best-practices in prescribing antibiotics and ensuring a rational order in which older generations are prescribed first would allow for later/newer generations to be saved as treatments of last resort.
    - Access to responsibly-made, high-quality antibiotics: A focus on simply increasing access to antibiotics will contribute to AMR if the production processes are not clean and sustainable. The language should specify that we aim to ramp up access to responsibly-made, high-quality antibiotics produced ideally based on the best practices from the

Common Manufacturing Framework produced by the AMR Industry Alliance. This supports the IACG's One Health approach by including the impact to environmental health as well. It would be helpful for the IACG paper to highlight the work made by the Industry Alliance such as the creation of the first Common Manufacturing Framework.

- Geographic scope: Analysis of barriers leading to access issues in HICs: There is little reference to access issues (incl. shortages) in HICs besides the mention that it was not considered for this iteration of this document. It is imperative that procurement processes (incl. government tenders) and market dynamics be highlighted as potential barriers to access in HICs. Some analysis has been done with the work of the Access to Medicine Foundation as well as in a recent survey by WHO. This should be featured under "Supply and Delivery" in a chart for HICs.
- Greater focus on older, generic antibiotics: Little reference and guidance is given on how to increase access to existing generic antibiotics (while a large marjority of volume is generic antibiotics).
- **S**trengthening health system capacities is key to improve access to antimicrobials consistently with rational use guidelines. National, regional, and local laboratory capacity needs to improve so that there is enhanced access to diagnostic tests and testing facilities in all countries. Provide support to resource-limited settings and health care facilities on training for performing tests, analyzing the results, and issuing report.

II. Specific comments on the draft paper

Page, column, paragraph	*"Specific Text" from the draft paper* **and/or Comment**	**Suggested Edit**	**Importance L, M, H**
p. 1, Key Messages	There is no specific comment that a pull incentive is needed. While there are a number of push incentives experts agree that pull incentives are needed to support a strengthened R&D pipeline.	A new bullet should be added: Without concerted action by a subset of member states to implement a pull incentive tailored to their specific context there will be a global crisis due to the absence of available antibiotic, vaccines, and diagnostics.	High
p. 2	*"Plan to also consider access issues in high-income countries (HIC)".* We welcome the recognition that there are also access issues in high-income countries, particularly through shortages.	We urge UN IACG to also explore how reimbursement reform for hospital-administered antibiotics would enable appropriate access to novel antibiotics by removing barriers posed by bundled-payment mechanisms.	Medium
p. 4, challenge #1	"*low prices, due to the availability of generic alternatives …*"	… and because novel antibiotics are approved on the basis of non-inferiority trials (see Challenge 4 below)."	Low
p. 5, challenge #7	Which reimbursement policies exist for animal health products?		Low
p. 5, figure, challenge #6	As depicted in the figure regulatory pathway only shows impact on approval; however, regulatory changes have significant impact throughout the clinical pipeline. For example, due to complexities in regulatory environment it can cost over $100,000 to recruit each individual patient. Regulatory reform could decrease this cost burden.	The regulatory pathways also impact clinical trials, not just approval. Therefore, its impact should be shown throughout the clinical pipeline.	Low
p. 6, column 1, Unclear market potential.	The text focuses on cost of vaccines and willingness of patients to pay for the vaccines. However, especially for vaccines that will have an impact on AMR a specific challenge with vaccines beyond the traditional challenge is having systems in place that support and pay for the use of vaccines in adult	Suggest adding text that highlights the challenges in getting regulatory approval for vaccines that can be used in adults and vaccine access programs that will be impactful in adults.	Medium

	populations. Many of the vaccines that could be developed for AMR would be targeted for adult use; however, vaccination systems are largely designed globally to support access for children and not adults.		
p. 7, section 1.2	The paper should acknowledge that the private sector is currently the largest funder of AMR-relevant R&D. and that the current public/philanthropic investments have not been sufficient to address the innovation gap. The weaknesses and insufficiencies of relying on public/philanthropic funding for R&D should be acknowledged. One of the explicit objectives of the public investment in AMR-relevant R&D should be to enable/support sustained or increased private investment. The Novo REPAIR fund is not public or philanthropic fund, it is a private, return-seeking investment fund focused on AMR. In general, this section does not refer to the limited engagement of private capital funds.		
p. 8, Proposal for advance market commitment	*Some of these [pull] mechanisms are monetary in nature…like advance market commitments, which allow developers of new products to sell a defined volume of their products to funders at a pre-specified price*	We propose that the advance market commitment be considered for forgotten antibiotics, in the first instance. The challenge for	Medium

(AMC) for novel antibiotics		forgotten antibiotics[1] is different and specific compared to that of essential or novel antibiotics. As demand for forgotten antibiotics falls below a certain level, it is not sustainable for manufacturers to continue producing them. The AMC creates a market guarantee to secure supply and this incentivizes manufacturers to continue producing them. In countries with centralized medicine procurement system, essential and forgotten antibiotics could also benefit from AMC. For example, the UK's National Health Service could be considered an AMC. While there is a contract/agreement with government to purchase and prices are fixed, the volumes purchased are variable.	
p. 8, "delinkage" Mechanisms + p. 8, figure 2, column 1 + p. 9, column 1, para 5	*"One way of optimizing and increasing the impact of funding for R&D could be by use of "delinkage" mechanisms. As stated above, there is little expectation that price- and volume-based sales will drive R&D in solutions to tackle priority pathogens. By disconnecting the cost of investment in R&D from the expected price and volume of sales of the products, delinkage incentivizes R&D while ensuring that priorities are targeted."* • We welcome the UN IACG's recognition that the current R & D environment for antibiotics is financially unattractive.	• *By partially decoupling ~~the cost of investment in R&D~~ developer revenue from the ~~expected price and~~ volume of sales of the products, AMR delinkage incentivizes R&D for public health priorities while ~~ensuring that priorities are targeted~~ supporting appropriate use.* • Edit "delinked" to "decoupled", this should be edited for the entire paper.	High

[1] Pulcini, C., Bush, K., Craig, W. A., Frimodt-Møller, N., Grayson, M. L., Mouton, J. W., … Gyssens, I. C. (2012). Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia. Clinical Infectious Diseases, 54(2), 268–274. https://doi.org/10.1093/cid/cir838

	Reducing the link between antibiotic **revenue** and **volume** will make antibiotic innovation more attractive to developers while at the same time encouraging appropriate use. • Using the term "delinked" causes confusion as there are multiple definitions for the term. In the IP community there is a very different definition that implies access to IP. Given the confusion caused by this term it is important to use "decoupled" or another term that implies mechanisms to reduce and partially uncouple the proportion of manufacturer revenue that is derived from antibiotic sales volume.		
p. 8, column 2, para 5 Pull mechanisms	For a pull incentive to be impactful it should meet a set of common principles. These principles should be added to the document.	Suggest adding the principles to the document. Key principles when developing policies to incentivize antimicrobial R & D • There is no one-size-fits-all solution • Clear definitions for products that would earn a pull reward are needed • Market-based models should be retained to allocate limited resources and reward successful innovation • Predictable and sustainable funding is critical • The impact of the incentive must be sufficient to support sustainable on investment in R&D	High

		• Reduce and partially uncouple the proportion of manufacturer revenue that is derived from antibiotic sales volume • Align with stewardship principles that support global access	
p. 8, column 2, para 5 + p.9 Pull mechanisms/monetary pull mechanisms	In addition to MERs and AMCs, a bullet should be added for HTA and reimbursement reforms. A reference to TEE (Transfer Exclusivity Extension) should also be added. This paper should not be setting policy that will need to be implemented by governments, but offering suggestions on the various options. The pull incentive should be tailored to the individual market, which should be highlighted. As written the section specifically excludes an important incentive option that is being considered in the U.S. and also being studied by the E.C., transferrable exclusivity incentives. To date the only proposal that has been formally proposed by a government is a transferable exclusivity extension-the U.S. government. Unlike a market entry award TEE does not require any upfront government funds, and therefore may be the preference of some governments. Exclusion of this on the list could negatively impact governments considering all options.	The paper says that there is "limited" experience with these non-monetary incentive mechanisms. However, several concrete examples are given in the following paragraph. The sentence should therefore be: *Several of these non-monetary pull mechanisms have been implemented in different contexts, but have had a limited impact on R&D investment.* A bullet point should also be added that states: "Transferrable Exclusivity Extension (TEE): Company awarded with a market exclusivity voucher than can be used for any other product or sold to other companies. TEEs would be useful for stimulating R&D for both pharmaceutical and biotechnology companies by transferring the value of a product in another therapeutic area to antimicrobial agents."	High

p.9, Consideration of streamlined clinical trials as a pull mechanism	*"….Other pull mechanisms are not monetary. These include: streamlined clinical trials, such as a requirement for smaller test populations;"*	The life sciences Industry does not consider streamlined clinical trials to be a pull mechanism. Streamlining clinical trials will reduce the costs and time for drug but, exercised in isolation, this would not be sufficient to incentivise industry. Because there will still be significant risk and investment – and lack of predictable market still exists. A suite of incentives - both push and pull incentives - is needed with the most urgent action needed on pull incentives. These incentives should be sustainable and sufficient to stimulate R&D across the full R&D lifecycle, from discovery through development, to see an impactful long-term change on the pipeline of new products.	Low
p. 9 footnote No. 32 Longitude Prize for diagnostics as an example of a market entry reward	*"…Only very small [market entry] rewards have been offered in recent years [including the Longitude Prize and the Brucellosis Vaccine Prize]"*	We appreciate the UN IACG's recognition that for any pull incentive to be effective it must reflect the societal value of the product and be predictable and sustainable.	Low
p. 10, column 1, para 1	States: "*There is limited experience in use of these mechanisms, and the debate with respect to AMR is on use of market entry rewards*."	Edit sentence to read: "Despite consensus in the community that pull incentives are needed to strengthen R&D, no government has yet taken action to implement a new incentive and only the U.S. has proposed a formal policy option (REVAMP Act as of June 2018	High

	This is not an accurate statement. As the following set of references shows there is consensus among stakeholders that there is a need for a pull incentive. Despite this consensus in the community there has been no pull incentive implemented by any government. • Frank Mueller-Langer (2013) Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research? Health Econ Policy Law. 2013 Apr; 8(2): 185–208. • O'Neill, J. (2016). Tackling Drug-Resistant infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. • Daniel, G.W., Lavezzari, G., Qian, J., McClellan, M.B., Schneider, M. (2016). Tracking the Progress of Economic Incentives for Antimicrobial Drug Development in the U.S. and Across the Globe. Duke-Margolis Center for Health Policy. Available from: https://healthpolicy.duke.edu/sites/default/files/atoms/files/Antimicrobial%20Economic%20Incentives%20Landscape%20Analysisv2.pdf • PACCARB. (2017). Recommendations for Incentivizing the Development of Therapeutics, Diagnostics, and Vaccines to	is available here : https://www.congress.gov/bill/115th-congress/house-bill/6294/text).	

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	• Ferraro, J., Towse, A., and Mestre-Ferrandiz, J. (2017) Incentives for New Drugs to Tackle Anti-Microbial Resistance. Office of Health Economics Working Paper. Available from: https://www.ohe.org/publications/incentives-new-drugs-tackle-anti-microbial-resistance • Outterson, K. & McDonnell, A. (2016). Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy. Health Aff. (Millwood) 35, 784–790 • Duke-Margolis Center for Health Policy. 2017. Value-based Strategies for Encouraging New Development of Antimicrobial Drugs. https://healthpolicy.duke.edu/sites/default/files/atoms/files/value-based_strategies_for_encouraging_new_development_of_antimicrobial_drugs.pdf • Outterson K. (2018). Innovative ways to pay for new antibiotics will help fight superbugs. Retrieved from https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/ • DRIVE AB: http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf • Outterson K. (2014). New business models for sustainable antibiotics. Chatham House: London.		

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	RE%20GENERATIONS%20FINAL%20WEB_0.pdf • DRIVE AB: http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf • O'Neill, J. (2016). Tackling Drug-Resistant infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. • Boston Consulting Group (2017).Breaking through the wall: A call for concerted action on antibiotics research and development. Retrieved from: • https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf • Review on antimicrobial resistance. (2015)Securing new drugs for future generations: the pipeline of antibiotics. Retrieved from https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf • Seabury S., Sood N. (2017). Toward A New Model For Promoting The Development Of Antimicrobial Drugs, Health Affairs Blog. Retrieved from		

	https://www.healthaffairs.org/do/10.1377/hblog20170518.060144/full/		
p. 10, column 1, para 1	*"It has been suggested that the value of an innovation for society should be reflected in its price. Others have estimated that a prize of US$ 1 billion."* However, per the above reference list the consensus is that there is not consensus on the value of a pull incentive needed. The range is from $1-$4B.	Suggested edit "a prize of at least $1B" supported by the following references. • O'Neill, J. (2016). Tackling Drug-Resistant infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. • Boston Consulting Group (2017).Breaking through the wall: A call for concerted action on antibiotics research and development. Retrieved from: • https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf • Review on antimicrobial resistance. (2015)Securing new drugs for future generations: the pipeline of antibiotics. Retrieved from https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf • Seabury S., Sood N. (2017). Toward A New Model For Promoting The Development Of Antimicrobial Drugs, Health Affairs Blog. Retrieved from https://www.healthaffairs.org/do/10.1377/hblog20170518.060144/full/	Medium
p.9, column 1, para 3	*"Experience in use of these mechanisms is also limited. Market exclusivity and fast-track reviews are available, for example, under legislation in the European Union, Japan and the USA. Additionally,*	Suggest adding the following text to the end of the paragraph. *"Despite these policies the existing pipeline is not nearly large enough to keep up with the current pace of the emergence of resistance. Over the past two decades, there has been a significant*	Medium

	law in the USA includes the following incentives: the Generating Antibiotic Incentives Now Act, under which an additional exclusivity period can be awarded to foster investment into new antibiotics; the Food and Drug Administration Revitalization Act, which established transferable priority review vouchers for all drugs to treat neglected tropical diseases or rare paediatric diseases; and streamlined clinical trials, also for high-priority antibiotics in terms of resistance, through the Limited Population Antibacterial Drug Act."	*decline in the number of large pharmaceutical companies conducting antibiotic R&D. Today, only five of the top 50 pharmaceutical companies have antibiotics in clinical development. Within the last two years, four large pharmaceutical and many biotechnology companies have exited this space due to the scientific, regulatory, and economic challenges posed by antibiotic discovery and development."*	
p. 10, column 1, para 4 R&D coordination	The text should be careful to allow governments flexibility to tailor a set of priority pathogens that is consistent with other lists, but also can meet the specific public health priorities.		Low
p. 10, open questions		Suggest adding question about scaling up private investment: *What will it take to increase and sustain donor and private sector funding of R&D in AMR?*	Low
p. 12, challenge #4 OTC	The structure of the intro paragraph makes it seem that inappropriate use is only an issue in the private sector or with OTC antibiotics. It should be clear that the bullets below apply to both the public and private sector.		Medium
p. 12, challenge #5	The actual capacity of the health system to deliver appropriate use of antimicrobials is not addressed (first bullet focuses on human and financial resources only).	Suggest additional bullets: • *The limited health system capacity to diagnose and treat infectious diseases appropriately in both the public and private sectors.*	Medium

		• *Limited access to health care, particularly for rural communities, contributes to underuse or inappropriate use of vaccines, diagnostics, and antimicrobials.*	
p.14 Proposal for pooled procurement of medicines	*…pooled procurement of medicines to support uninterrupted access to high-quality medicines and technologies, with potential to drive down prices…*	We are supportive of pooled procurement for medicines and technologies, particularly for essential and forgotten antibiotics. Antibiotics offer slim financial margins; R&D is risky and expensive; and, growth in demand comes mainly from the poorest. One of the manifestations of these issues is that antibiotics have fragile supply chains, with shortages and stock outs occurring. For essential antibiotics and forgotten antibiotics, predictability and/or guaranteed demand is key to ensuring manufacturers engage in the antibiotics business. Pooled procurement would support thus, particularly if purchases/procurement entities allow competitive pricing. Current pooled procurement mechanisms are not well-suited for novel antibiotics. The issue with novel antibiotics is different to that of essential or forgotten antibiotics in that their true societal value is not reflected in their prices. To make any pooled procurement system for novel antibiotics proposed viable to industry, its first considerations should be on how to properly assess and reflect the true societal value of antibiotics [For further context, see comments on advance market commitment in this submission]	Medium

p. 14, column 1, para 1	Investments in infrastructure are needed to strengthen access.		Low
p. 14, column 2, para 3 Medicines Patent Pool	The paragraph describes the Medicines Patent Pool as an option. However, this approach may not be appropriate for antibiotics for the following reasons: (i) nearly all antibiotics on the WHO EML are off-patent, including all of those antibiotics categorized as "Access" antibiotics; (ii) the increased availability of low-priced newer antibiotics addressing resistance could accelerate the development of AMR, especially if deployed in weak health systems with limited capacity to deliver care appropriately or outside of carefully managed vertical programs (which do not exist today for antibiotics); and (iii) the antibiotic market is small, fractured, and unattractive for generic manufacturers and there is no centralized, donor-funded global buyer to facilitate procurement.		High
p. 14, open questions		Suggest additional open questions: *What are the access barriers that are specific to antibiotics (vs other therapeutic areas)? How to balance the need to expand access to antibiotics while limiting inappropriate use (access/excess tension)? Are different mechanisms needed to expand appropriate access to novel antibiotics, generic antibiotics, vaccines, and diagnostics?*	Medium
p.16 Addressing access challenges	*…There might be ways to address similar challenges to access in human and animal health simultaneously, by common training for doctors and veterinarians…*	This approach would have to be carefully assessed and delivered. The basic challenges are common but the behaviour and incentives to be changed are different.	Low

common to human and animal health by training doctors and veterinarians simultaneously			

III. Response to open questions posed by the UN IACG

a. R & D

- What will it take to increase and sustain donor and private funding of R&D in AMR?

  Private investment in antibiotic research and development (R & D) is relatively unattractive. Many large pharmaceutical companies have stopped investing in this area altogether, and the pipeline is considered a concern. Low sales of newly-approved antibiotics that address resistance discourages further investment. Adoption by governments of sustainable and substantial pull incentives, as part of a suite of incentives including push mechanisms, robust pull incentives and reform of reimbursement and Health Technology Assessment (HTA) systems, must be achieved if industry is to continue to invest and take on the risk in research, development, and commercialization for new medicines and vaccines to address AMR. The key gap is currently on pull incentives.

- Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

  IFPMA member companies are aligned on the need for at least one of the two following high-impact novel pull incentives to address the innovation gap:
  - Transferrable Exclusivity Extension (TEE): Company awarded with a market exclusivity voucher than can be used for any other product or sold to other companies. TEEs would be useful for stimulating R&D for both pharmaceutical and biotechnology companies by transferring the value of a product in another therapeutic area to antimicrobial agents.
  - Market Entry Rewards (MERs): A single or series of payments given to a company that launches a product addressing a pre-identified medical need. Market entry reward would provide significant revenue early in the product lifecycle when product sales volumes are generally low.

- How should the design of incentive mechanisms be coordinated at global, regional and national levels?

  A suite of incentives is needed but the key gap is on pull incentives. There is no “one-size-fits-all” solution, models need to be tailored to national specificities. What is urgently needed is action at national level to progress the design and implementation of these pull incentives. We call on governments to move forward with the adoption and implementation of these programs within their national context and this can initially be coordinated between governments and national trade associations.

  AMR is a global problem and no country can solve it on its own. What is ultimately needed is a coordinated global approach where risks are shared. The global governance and coordination could be supported by a High-Level AMR Commission, as proposed by the UN IACG recently, to ensure long-term international standards and norms are locked in.[2]

b. Access

- Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

  [See our response in the table above on this proposal for a new access initiative]

[2] Rochford, C., Sridhar, D., Woods, N., Saleh, Z., Hartenstein, L., Ahlawat, H., … Davies, S. (2018). Global governance of antimicrobial resistance. The Lancet, 391(10134), 1976–1978. https://doi.org/10.1016/S0140-6736(18)31117-6

AMR Industry Alliance

IACG Consultation

IACG Working document: Discussion paper with preliminary analysis
National Action Plans

I. General comments:

Governments have a key role to play to slow the spread of AMR and create an environment that supports sustainable investment in AMR-relevant innovation access. Overall, most countries have not formally (or informally) involved the private sector in NAP development in spite of WHO's calls for multi-sectoral collaboration. The IACG paper should stress the important role the private sector plays in addressing AMR and that it should be formally included as a partner.

II. Specific comments on the draft paper:

Page, column, paragraph	*"Specific Text" from the draft paper* **and/or Comment**	**Suggested Edit**
P.5 3rd Paragraph		~~*AMR should not be financed only by the public sector.*~~ *Both the public and private sectors have a role to play in addressing AMR. Countries should ensure the right investment and regulatory environment for, and develop productive partnerships with, the private sector to jointly address AMR. Key private sector stakeholders include: manufacturers, distributors,* ~~*ensure that it contributes fairly to the cost of antimicrobial production and clean up (be it antibiotic agents,*~~ *private health care providers,* ~~*provision or*~~ *the food industry, and farmers*~~*)*~~*. To build support and facilitate implementation, these private sector stakeholders should be formally involved in NAP development and execution processes.*

AMR Industry Alliance

IACG Consultation

IACG Working document: Discussion paper with preliminary analysis
Antimicrobial resistance: Surveillance

Overarching comments:

As drafted the paper does not fully highlight the investment that some companies make in supporting surveillance programs and how those programs can complement or strengthen government initiatives. It is important that as policies are implemented and surveillance programs established that they are done so through a multi-sectorial and cross functional process.

The integration of surveillance systems and subsequent data while a novel and ambitious idea, the ability to do so across all platforms will make it difficult to achieve without some worry on quality and sensitivity in the data. Not all surveillance programs are created equal. It is important to consider the objectives of strengthened surveillance and how the community can support these objectives in a phased manner to ensure improved data is available to inform health care practice and policy. For examples, the ability to leverage current surveillance programs and their respective data is a first step that should be considered in bringing alignment to the data and to the public. This issue has been discussed at the Welcome Trust and ODI initiative, which serves as an important venue to continue this dialog. Further, since bringing LMICs up to speed will require time and investment, a short term solution may be to conduct point prevalence studies either using a portable lab or shipping specimens to a central lab.

The ability to strengthen individual local country surveillance programs will require more heavy investment at the country level than what is currently available. However, the ability to transform surveillance laboratories for routine testing in emergency situations could allow to justify such investment. If this is truly seen as top level emerging initiative then countries will need to respond in kind in the budgeting for such. Guidance should be provided on the appropriate framework necessary in each country to support surveillance and highlight the value proposition of investing already limited resources to strengthen programs. For example, priority should be given to expanding laboratory capability/ training locals as reliable in vitro data is the foundation of surveillance - human, animal, plant or environment. Methods must be standardized but also low and interoperable tech, sustainable with a reliable supply chain for reagents and equipment.

Answers to Questions Posed:

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?
The primary challenge is related to consistency in methodologies. Surveillance programs currently underway utilize different collection methodologies, data capture parameters, and testing requirements. ODI is creating a comprehensive portal which lists all surveillance programs for easy access.

How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?
No comment

How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?
Many pharmaceutical companies collect global surveillance data, including from sites in LMICs, that is publicly available and can be useful in identifying trends in pathogen incidence and AMR and provide early indicators of the emergence of resistant strains Some examples include MSD's Study for Monitoring Antimicrobial Resistance Trends (SMART), Pfizer's Antimicrobial

Testing Leadership and Surveillance (ATLAS), and GSK's Survey of Antibiotic Resistance (SOAR). Several companies (bioMerieux, GSK, MSD, Pfizer) are currently partnering with Welcome Trust, Open Data Institute (ODI), and IHME on providing access to their respective programs data.

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

The ability to strengthen individual local country surveillance programs will require investment at the country level as well as alignment and consistency in testing methodology – to enable integration of data nationally and globally. If this is truly seen as top level emerging initiative then countries will need to respond in kind in the budgeting for such.

How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

Priority should be given to expanding laboratory capability/ training locals as reliable in vitro data is the foundation of surveillance - human, animal, plant or environment. As mentioned methods must be standardized but also low tech, sustainable with a reliable supply chain for reagents and equipment.

Since bringing LMICs up to speed will require time and investment, a short term solution may be to conduct point prevalence studies either using a portable lab or shipping specimens to a central lab.

What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?

Per the document: The quality of data on AMR can be improved by the use of standardized methods for determining susceptibility to antimicrobial agents.

What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?

Per the document: The quality of data on AMR can be improved by the use of standardized methods for determining susceptibility to antimicrobial agents.

What more can be done to harmonize collection of data on AMR and AMU among sectors and levels?

Per the document: The quality of data on AMR can be improved by the use of standardized methods for determining susceptibility to antimicrobial agents.

What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e. g. WGS)?

The Center For Disease Dynamics, Economics & Policy has done a lot of work related to AMR (https://www. cddep. org/tools/) . Further both governments and the private sector should be viewed as important stakeholders with common goals of informing the appropriate use of medicines, for example government agencies such as the CDC, ECDC or even CFDA.

What support do countries require to develop and report accurate national data and share them on global surveillance systems?

Consider centralized reporting platform such as that available through ATLAS public web site that enable centralization of data and easy analyses and output of data for reporting

What data formats and visualization tools are most useful for reporting and further analysis?

Consider centralized reporting platform such as that available through ATLAS public web site that enable centralization of data and easy analyses and output of data for reporting

How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?

No comment

How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?

No comment

What tools are required to address the investment required for surveillance of AMR and AMU?

No comment

What role can the private sector play in financing surveillance?

Rather than solely focusing on the role the private sector should have in financing surveillance, it is important to recognize the significant investment that large multinational pharmaceutical companies already make each year to monitor surveillance globally in all regions of the world.

Pfizer's database, Atlas, was initiated in 2004 to monitor real-time changes in pathogen resistance and detect trends in multi-drug resistance longitudinally over time. It represents the integration of three surveillance programs (TEST, AWARE, INFORM), and collectively has generated 14 years of continuous global bacterial susceptibility data versus a panel of antibiotics. It includes source information from more than 760 sites across 73 countries, with data encompassing more than 556,000 isolates. Since 2004, publicly reported findings from these surveillance programs have been made available through over 50 published journal articles and over 750 medical congress presentations. Pfizer provides access to cumulative ATLAS surveillance data through a publicly available website (www. atlas-surveillance. com). The site supports an interactive platform enabling physicians to evaluate data, conduct analyses, and export tables and figures that include parameters such as organism, region, specimen source and in vitro susceptibility data. Pfizer also offers ATLAS as a mobile application to enable rapid access. Both the ATLAS webs site and App are regularly updated with new and emerging data from the active surveillance program. Pfizer believes in sharing surveillance data and endorses integration of our surveillance data into these reporting systems. Pfizer (through ATLAS) makes a significant investment each year to monitor surveillance globally in all regions of the world and continues to make the data fully accessible to the public and health authorities around the world at www. atlas-surveillance. com. In addition, we are working directly with key stakeholders at various government agencies to integrate ATLAS data into coordinated and/or integrated surveillance programs.

GSK's SOAR focuses on the effectiveness of antibiotics in the treatment of community-acquired respiratory tract infections, which are a major burden for healthcare systems. This includes pathogens such as Streptococcus pneumoniae and Haemophilus influenzae. SOAR tracks the effectiveness of the most commonly-used antibiotics (beta-lactams,

cephalosporins, macrolides and fluoroquinolones), based on three different breakpoints, through a quantitative method for determining antibiotic susceptibility in areas where resistance data can be scarce and more is needed to understand the local trends and inform appropriate prescribing. Studies cover the Middle East, Africa, Latin America, Common Wealth of Independent States, Asia, China and Eastern Europe.

More information: https://academic.oup.com/jac/issue/71/suppl_1

MSD's SMART is a worldwide surveillance study monitoring in vitro susceptibility patterns of clinical Gram-negative bacilli to 12 commonly-used antibiotics. Over 200,000 clinical samples have been collected from patients with complicated intra-abdominal infections since 2002 and from patients with complicated urinary tract infections since 2010, and analyzed for their in vitro susceptibility to 12 commonly used antibiotics in different regions of the world to monitor changing trends in antibiotic susceptibility. Currently, 192 hospital sites in 54 countries participate in SMART. MSD plans to expand the SMART program from 54 to 59 countries and from 192 to 222 sites, with a focus on developing countries by 2018. More information: panthe SMART program from 54 to 59 countries and from 192 to http://partnerships.ifpma.org/uploads/documents/196_1472569317.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3854014/

Global-Point-Prevalence-Survey (G-PPS) piloted by the University of Antwerp and funded by the diagnostic company bioMerieux.The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (GLOBAL-PPS) coordinates surveillance of antimicrobial prescribing and resistance in hospitalised adults, children and neonates worldwide. The first Global-PPS was conducted in 2015 and included 335 hospitals in 53 countries of six continental regions, using a standardised and validated method. It included the following antimicrobial agents: Antibacterials, antimycotics and antifungals for systemic use, antibiotics used as drugs for treatment of tuberculosis, intestinal antiinfectives, nitroimidazole derivatives and antimalarials according to the WHO ATC classification .

It is important that that the paper recognize the role that private sector surveillance can have to complement and strengthen government programs, and explore opportunities to improve coordination collaboration between the public and private sectors. For example, Pfizer currently contributes to financing surveillance programs in emerging markets including China government surveillance program and various independent surveillance programs in LATAM and Russia. This is done through a grants program.

George Tice, Elanco

From: George Anthony Tice
Sent: 08 July 2018 20:23
To: IACG-secretariat; SG_IT
Cc: Shabbir Simjee
Subject: Comments for IACG.

Dear Sir,

This is a brief response to the invitation to contribute, as a veterinarian, to the innovation and research report and I believe, this along with the other three reports are focussed and complete.

On AMR surveillance I do have a comment , and I copy my colleague, Elanco's Head of Microbiology, himself an infectious disease physician with a great deal of experience in the area – Dr. Simjee. He, I know, has contributed extensively to the FAO work as well as other consultative bodies.

I feel very strongly that in animal health we have to make surveillance and usage monitoring simple and doable for LMIC and it is NOT at the moment. The effort to develop the JIACRA and ESVAC reports was simply immense and way beyond the capability of LMIC. What does this mean? We must focus on the bugs and the drugs that are most likely to cause a human health concern because of zoonosis or other transfer mechanisms, and then measure those both in terms of usage and in terms of bacterial resistance. The various lists available are very very long, meaning that LMICs have to spend inordinate resource trying to find a little data on many many molecules, rather less, but more high quality data on a few molecules (which will also indicate responsible use) in a few organisms.

For example why get LMICs to spend time trying to find data on compounds that are never used in human health, or compounds that are of negligible importance. Rather focus on 4th generations cephalosporins and floroquinolones for example. Also in terms of bacteria – why go beyond Salmonella typhimurium/entertidis, E. Coli (subtype to be defined) and E. faecium.

I know by colleague Dr. Simjee has a great deal of experience here and would like to offer more insight from his extensive experience.

Kind regards

George Tice
Sr. Director, Market Access Europe, Middle East, Africa and Asia

Elanco Animal Health

www.elanco.com

Individual

Carol Geraldine C. Pablo

From: CAROL GERALDINE C PABLO
Sent: 09 July 2018 17:49
To: IACG-secretariat
Subject: SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?

1) A sole functioning agency to monitor use and resistance.
AS stated, cross-sectoral issues or impacts that may pose significant barriers to coordinated surveillance can impede a more efficient gathering of data that will efficiently monitor antimicrobial use and resistance. An agency, that will solely function to address the use and resistance of antibiotics should be coordinated directly international group that will collectively monitor the trends and problems. This group will also coordinate with different groups, health services/agencies and organizations.

2) Recognition of health services that directly distribute antibiotics for public consumption and the role they play in misuse, resistance and education to patients/consumers. Trainings has been for in hospital medical staff but not community based professionals who deal with consumers and ambulatory patents. this should be addressed as well.

How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

1) Research not on /clinical but more on social science. To determine practices/ behaviours and movement of antibiotic in the health practice and market. This evidence-based research output will determine the gap in practices, education and behaviour that will contribute to a sustainable education and shift of action to prevent antimicrobial misuse, identify resistance.

2) Training and education. This training should be given even for community based health professionals who directly communicate with consumers/patients who use antimicrrobials. The training should not only focus on the knowledge but also the impact of practice and behaviours. This should also include primary health care givers.

3) The participation and commitment of professional medical and health allied organization in the proper dissemination of knowledge and practice. They can include as part of their continuing education program and should have continues updates on the trends, practices, guidelines and regulation.

4) Inclusion in the academic curruculum for medical and health allied courses. This will not only focus on the knowledge of antimicrobials but societal impacts and practices as well.

5) A more detailed regulatory ordinances on the marketing, import and distribution of antimicrobials

What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data ?

The FDA counterpart of each country should have an intensive training for regulatory inspectors on identification of fake and substandard antimicrobials.
The marketing and distribution of antibiotic should have a stricter guideline to facilitate monitoring of marketing and administration to regional hospitals, primary health care centers and non traditional outlets of drugs. sticter penalties should also be imposed in the incorrect prescribing and dispensing of these drugs.

CAROL GERALDINE C. PABLO, Msc, RPh
Assistant Professor V / Associate Researcher
Faculty, Faculty of Pharmacy
University of Santo Tomas

Research Center on Social Sciences and Education
University of Santo Tomas

Melquiades Huauya Ore

From: melquiades huauya ore
Sent: 09 July 2018 18:05
To: IACG-secretariat
Cc: Ashley Enning; Zoe Adams
Subject: FEEDBACK on Surveillance and Monitoring for Antimicrobial Use and Resistance - Melquiades Huauya Ore

Dear IACG Secretariat,

My name is Melquiades Huauya Ore and I am a survivor of multi-drug resistant tuberculosis (MDR-TB) from Lima, Peru, and an associate of The Strongheart Group, a social change and impact NGO. I am very grateful to you for the opportunity to submit my feedback on this discussion paper about AMR surveillance, since the **resistant TB bacteria almost took my own life and continues to be the major contributor of AMR deaths globally. Eliminating TB is crucial for improving the global AMR situation.**

As allocating resources to containing AMR is one of the highest yield investments that can be made to minimize the impact of AMR, and **since TB is the main contributor to the spread of AMR, I feel that it is of utmost importance to focus on solutions and investments in addressing drug-resistant TB** in the context of the proposed open questions:

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?

As someone who survived MDR-TB, I can say that community health workers (CHWs) can help people recover from drug-resistant infections like MDR-TB, help make communities aware of the threat of drug-resistance and provide on-the-ground support with the surveillance, diagnosis and monitoring of AMR directly within communities.

When I was sick, a CHW came directly to my house to bring me my MDR-TB medicines, help me fight the resistant bacteria and help me and my family understand drug-resistance. When I didn't want to go on any longer, the CHW explained that I had to keep taking my medicines because if I stopped taking them, I could relapse, become even more sick and make the bacteria even more resistant. I understood then that if I relapsed, there probably would not be other stronger medicines that could kill the resistant bacteria that was causing me harm. The CHW provided monitoring and surveillance on my progress in my recuperation and fight against the resistant bacteria.

I strongly believe that formalized community health worker programs, where CHWs are trained and remunerated to provide direct support to people affected by TB, as part of a country's health system, should be considered as a core component of implementing AMR surveillance systems. CHWs can be integrated into an AMR surveillance system at the community level and therefore help curb AMR as they can:

- Find, diagnose resistance and monitor people with TB.

- Collect data about drug-resistant TB at the community level to inform national, regional and international responses to AMR

- Help people affected by TB and their families understand the risk of drug resistance

- Support people with TB in their treatment so that they adhere to their treatment, recover and eliminate the resistant bacteria and risk of its spread.

I am grateful for your consideration of these feedback points and for considering community-based solutions to resistant TB as an important focus of approaches to the containment of AMR globally.

Respectfully,
Melquiades Huauya Ore

_____

Estimado Secretariado del Grupo de Coordinación Interagencial (IACG),

Mi nombre es Melquiades Huauya Ore y soy un sobreviviente de la tuberculosis multi-droga resistente (MDR-TB) de Lima, Perú, y asociado del Grupo Strongheart, una ONG de cambio social e impacto. Estoy muy agradecido a ustedes por la oportunidad de entregar mi retroalimentación sobre este documento de discusión sobre la vigilancia de la RAM, ya que **la bacteria de TB resistente casi tomó mi propia vida y sigue siendo el mayor contribuidor a muertes por el RAM a nivel global. Eliminar la TB es esencial para mejorar la situación de RAM en el mundo.**

Ya que la inversión en la contención de la RAM es una de las inversiones de alto rendimiento que se puede hacer para minimizar el impacto de RAM, y **ya que la TB es el mayor contribuidor a la extensión de la RAM, me parece que sea de muy alta importancia enfocar en soluciones e inversiones de la TB droga-resistente** en el contexto de las preguntas propuestas:

> Cuales otros apoyos necesitan países que están estableciendo sistemas de vigilancia (también con herramientas existentes) para implementar un sistema de vigilancia nacional para RAM y el uso de los antimicrobianos?
>
> Como se puede aprender de iniciativas en VIH, tuberculosis y malaria para mejorar la vigilancia de RAM y el uso de antimicrobianos?

Como alguien que ha sobrevivido la TB-MDR, puedo decir que agentes de salud comunitario (CHWs) pueden ayudar en la recuperación de las personas por infecciones de bacteria resistente como la TB-MDR, brindando a las comunidades orientación sobre la amenaza de la droga-resistencia, y brindando apoyo directamente en las comunidades con la vigilancia, diagnóstico y el monitoreo del RAM.

Cuando estaba enfermo, una CHW venía directamente a mi casa para llevarme mis medicinas de MDR-TB, ayudarme a luchar contra la bacteria resistente, y darme a mí y a mi familia orientación sobre la resistencia. Cuando no quería seguir, me explicaba que había que tomar las medicinas porque si no las tomara, podría recaer, ponerme mucho más enfermo y hacer el bacilo aún más resistente. Entendía entonces, que si recayera, probablemente no hubiera habido otras medicinas más fuertes para matar el bacilo que me estaba dañando. Daba seguimiento y vigilancia de como evolucionaba en mi recuperación y lucha contra el bacilo resistente.

Creo firmemente de que programas formalizados de agente de salud comunitaria, en los cuales CHWs estén capacitados y remunerados para proveer apoyo directo a personas afectadas por la TB, como parte del sistema de salud de un país, se debería considerar como un componente clave de implementar sistemas de vigilancia de la RAM. CHWs pueden ser un parte del sistema de vigilancia de RAM y por lo tanto ayudar de poner alto a la RAM, por, a nivel comunitaria:

- Encontrar, diagnosticar la resistencia y monitorear personas con TB

- Coleccionar datos sobre la TB resistente a nivel comunitario para informar respuestas nacionales, regionales e internacionales a la RAM

- Orientar personas afectadas por la TB y sus familias sobre el riesgo de la resistencia

- Apoyar a personas con la TB en su tratamiento para que se adhieren al tratamiento, se recuperen, y se elimine el bacilo resistente y el riesgo de su extensión.

Agradezco mucho su consideración de estos puntos de retroalimentación y por tener presente soluciones basadas en la comunidad a la TB resistente como un enfoque importante en cuanto abordajes a la contención de la RAM a nivel mundial.

Respetuosamente,
Melquiades Huauya Ore

--
Melquiades Huauya Ore
Associate
Strongheart Group

Patricia Huijbers, Joakim Larsson, Carl-Fredrik Flach

From: Patricia Huijbers
Sent: 10 July 2018 07:26
To: IACG-secretariat
Cc: Joakim Larsson; Carl-Fredrik Flach
Subject: Discussion paper 3 Surveillance and monitoring for antimicrobial use and resistance

Dear Members of the IACG,

In response to your call for public consultation on the discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General from June 2018, we would like to provide input for discussion paper three entitled 'Surveillance and monitoring for antimicrobial use and resistance'. Specifically, we could like to address the second question for stakeholders under sub-heading '4. Integration' which reads 'How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?'.

As mentioned in the discussion paper, there are countries in the world which have a particular need for surveillance but little capacity for doing it due to constraints on infrastructure and resources. The paper goes on to suggest a sentinel surveillance system, with step-wise increases in the numbers and scope of participating sites, as the most appropriate approach to facilitate AMR surveillance in these countries. Sentinel surveillance in this case is taken to mean collection of data from individual patients on bacterial diseases and their causative organisms by a limited network of carefully selected reporting sites. We argue that this approach still requires considerable infrastructure and resources due to the need for sampling individual patients and suggest that a complementary strategy to collect information about the prevalence of antibiotic resistant bacteria in human populations could be through the analysis of wastewater. Specifically, urban wastewater from the inlet of municipal wastewater treatment plants contains bacteria from thousands of individuals in the community connected to a particular wastewater system. Wastewater-based epidemiology has already been successfully used to obtain information about pharmaceutical and illicit drug use (reviewed in Choi PM, Tscharke BJ, Donner E, et al. 2018. Trends in Analytical Chemistry. 105:453-469) and has great potential for generating knowledge on antibiotic resistance (reviewed in Fahrenfeld N, Bisceglia KJ. 2016. Environmental Science: Water Research and Technology. 2:788-799).

From studies performed by our group (in preparation for publication), where we have isolated E. coli from untreated wastewater from ten different European countries and compared antibiotic resistance prevalence in these isolates to prevalence in E. coli from bloodstream infections in the same countries compiled by ECDC (EARS-net), we have seen that there is good correlation between prevalence in wastewater and prevalence in the hospital. Implementation of surveillance through urban wastewater and start of data generation could potentially be faster than GLASS, since sample collection and processing can be concentrated in time and should require considerably less infrastructure and human and economic resources. The advantage of a culture-based compared to a metagenomics approach, as suggested in the Global Sewage Surveillance Project, is that that antibiotic resistance genes can be linked to their hosts. This is crucial for the use of this data for antimicrobial stewardship and guidance of empirical therapy. Our culture-based approach and the metagenomics approach proposed by others could complement each other, however, for the analysis of spatiotemporal trends in antibiotic resistance prevalence.

We suggest conducting further research on directed surveillance using untreated wastewater, including further validation to existing clinical monitoring, as a way to begin generating antibiotic resistance data in countries where there is none available. A sentence added to the text of the discussion paper on page 5 to reflect this might read 'If validated against clinical resistance data, monitoring of untreated sewage might also be used for surveillance of AMR and AMU in human populations'. Following from this, a bullet could be added under 'Questions for stakeholders' reading 'Can monitoring of untreated sewage be used for surveillance of AMR and AMU in human populations?'.

If you have any questions or feedback please do not hesitate to contact us.
Kind regards,
Dr. Patricia Huijbers, Dr. Carl-Fredrik Flach, Prof. Joakim Larsson Centre for Antibiotic Resistance Research (CARe) and Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg Guldhedsgatan

Céline Pulcini

From: Celine Pulcini
Sent: 26 June 2018 08:36
To: IACG-secretariat
Subject: Feedback on: Antimicrobial resistance: Invest in innovation and research, and boost R&D and access IACG discussion paper

Follow Up Flag: Follow up
Flag Status: Completed

To whom it may concern

I would like to congratulate you on the quality of the Discussion papers. I would like to provide feedback, on my individual capacity, on the "Antimicrobial resistance: Invest in innovation and research, and boost R&D and access" IACG discussion paper.

I agree that better Diagnostics are needed. However, standards defining Diagnostics that have real clinical added value are needed. As an example: we might not need a test that differentiates between viral and bacterial infections, but rather that differentiates between self-limiting (viral or bacterial) infections (not needing an antibiotic prescription) and the bacterial infections that require an antibiotic treatment because the treatment significantly improves relevant clinical outcomes. Moreover, how often and well the test is used in real clinical practice must also be assessed (combination of different factors: frequency of use when indicated, correct interpretation of the result...).

Best regards,

Prof. Céline PULCINI
MD PhD https://apemac.univ-lorraine.fr/node/536

Member of the executive committee of the French Infectious Diseases society (http://www.infectiologie.com/site/_spilf_presentation.php)
Chair of ESGAP (ESCMID Study Group for Antimicrobial stewardship) (https://www.escmid.org/index.php?id=140)
Associate Editor for Clinical Microbiology and Infection (http://www.journals.elsevier.com/clinical-microbiology-and-infection/)

CHRU de Nancy, Service de Maladies Infectieuses et Tropicales

Hôpitaux de Brabois, Bâtiment des spécialités médicales

Natalie Schellack and Hannelie Meyer

Questions for stakeholders WHO UN Professors Natalie Schellack and Hannelie Meyer

What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?

Challenges from a Low Income Country such as South Africa

Obtaining reliable antimicrobial consumption data in South Africa's two-tiered human healthcare system has been especially challenging. The public sector caters for the majority of South Africans (approximately 84% of the population; 42 million people), while private healthcare is affordable only to a minority (approximately 16% of the population; 7 million people)

Recording of antimicrobial consumption in the public sector is in its infancy requiring manual computation from aggregate data methods to elucidate antimicrobial consumption in healthcare facilities. Accurate consumption data from communities was precluded by fluid catchment populations. A lack of reliable data hampers antimicrobial stewardship efforts and evaluation of stewardship interventions. So for this country recording data is already challenging even before analysing the data.

One such constraint was the availability of procurement data from Intercontinental Marketing Services (currently, IMS Health), which was only forthcoming from the private sector, and focused exclusively on antibiotics. Infection forms the major burden of disease in SA, comprising largely of HIV and tuberculosis, as well as high rates of community and hospital-acquired infections. As of 2017, an estimated 7.06 million people are living with HIV in SA with an overall estimated HIV-prevalence rate of 12.6% (STATS SA, 2017). Hence, the data from the IMS in 2011 analysis fell short of the realistic picture of antimicrobial consumption in SA.

Although the private sector does have some data available, the quality or 'completeness' of the data is most often a problem e.g. omission of ICD10 coding, which means the diagnosis cannot be identified.

South Africa does not have any patient-level data available across the private and the public sectors. Development of such an integrated data management system would be essential for the National Health Insurance implementation.

Using an integrated electronic data management system for the entire medicines management cycle (selection, contracting, supply chain management, contract management and medicine use) would be ideal i.e. holistic value chain approach. This is however NOT the case in South Africa. There are certain factors contributing to medicines availability, which should be taken into consideration when interpreting surveillance data in the public sector, as the use of medicines, is often influenced by the unpredictable demand or unpredictable supply, which could originate at an international, national or local level. Examples include the following: Suboptimal implementation of Standard Treatment Guidelines (introduction or removal of medicines); Unanticipated changes to disease patterns; Trends in private sector demand and payment patterns resulting in unexpected changes to private sector demand; Demander performance management; Irrational prescribing or dispensing; Inappropriate infrastructure for storage skewing demand patters; Poor demand planning; Availability of raw materials; Intellectual property restrictions resulting in limited suppliers; changes to local regulatory requirements or amendment e.g. GMP; Changes to national contracting processes, including changes to conditions of award and contract; Supplier performance management; cash-flow and disbursement problems resulting in delayed payment of service providers; Suboptimal inventory and replenishment management; Unpredictable delivery or supply from internal suppliers (e.g. provincial warehouses); Weak contracting mechanisms for third party logistics (distribution); Poor supply planning; Poor distribution planning.

Challenges which limit the availability of sufficient information and resources to be able to design interventions: Non-standardised protocols; poorly resourced facilities; varying human resource capabilities.

Within the changing landscape of the National Health Insurance is a Visibility and Analytics Network (VAN) envisaged for the future with ongoing quality improvement. This would mean appropriately skilled people, enabled policy, processes and technology are combined to have a responsive approach to service delivery which is data driven. A National Surveillance Centre with dashboards and early warning system would be essential.

How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?

The data sources presented for antimicrobial procurement differ between the public and private health sectors. Variations in presentation of antimicrobial data are largely based on the differences in patient management systems – mostly manual/ paper-based in the public sector, compared to electronic record- keeping for the private sector. Private sector data were obtained from IMS Health. Although IMS Health does not report in standard units of consumption, i.e. DDDs, their units do help to show trends over time. IMS Health collects data from a variety of sources of healthcare information, including sales, de-identified prescription data, medical claims, electronic medical records, and social media. Conversely, public sector data were obtained from contract data arising from tenders from wholesalers (an open Request for Proposal, RFP) where the NDOH solicits bids from suppliers and publishes this on the NDOH website (National Department of Health, 2017). However these data reflect only what has been awarded on the basis of the tender (i.e., quantities forecasted for use), rather than what is actually used. Different tenders are awarded based on their descriptions and may be awarded for different time periods, although it does appear that most contracts currently awarded are for a 2-year time period (e.g., October 2015 to September 2017) in the current contracting process (National Department of Health, 2017). Presenting surveillance data on antimicrobial use in these two sectors can identify and target practice areas for quality improvement. The DDD (the usual adult dose of an antimicrobial for treating one patient for one day) has been considered useful for measuring antimicrobial prescribing trends within a hospital, including the various denominators from hospital.

Initiatives can include AM utilisation rates using more effective tools such as new mHealth and other approaches across public healthcare sectors linked to knowledge of resistance rates. Subsequently, use the findings to plan, implement and analyse the impact of future interventions to reduce inappropriate AM use and AMR rates. This includes using mHealth approaches to improve adherence to STGs, especially in PHC centres where most antibiotics are dispensed, reduce patient requests for antibiotics for viral infections in ambulatory care as well as improve the empiric use of AMs in hospitals. mHealth and other techniques can also be used to monitor future AM prescribing alerting key stakeholders to the need for future interventions if needed. **mHealth** is an abbreviation for **mobile health**, a term used for the practice of medicine and public health supported by mobile devices. The term is most commonly used in reference to using mobile communication devices, such as mobile phones, tablet computers, for health services and information, but also to affect emotional states. The mHealth field has emerged as a sub-segment of eHealth, the use of information and communication technology (ICT), such as computers, mobile phones, communications, patient monitors, etc., for health services and information. mHealth applications include the use of mobile devices in collecting data on antimicrobial use, delivery of healthcare information to practitioners with regards to appropriate use of antimicrobials using the Standard Treatment Guidelines (STG). Further to this, vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use. As a result, this will reduce future morbidity, mortality and costs in SA from AMR to enhance future sustainability of the public health system.

What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?

Pharmacists can play a key role in the implementation of and establishing surveillance systems for AMR and AMU. Further to this, support could be directed to formal training for surveillance in pharmacists training. Pharmacist can play an integral role in the surveillance of antimicrobial use but this will depend on support received, and depend on the level of training that he/she has received. As custodians of medicines, pharmacists are well placed to lead and drive the antibiotic surveillance initiative, not only through audit and data collection but through relationship building and working in multi-disciplinary teams.

How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

What data formats and visualization tools are most useful for reporting and further analysis?

In South Africa we have developed an application for surveillance. Point Prevalence Surveys (PPS) are well established surveillance methods for the monitoring of antimicrobial prescribing in hospitals. In the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global PPS) a web-based application was used for data-entry, validation and reporting. The web-based application allowed the global PPS to stretch over 53 countries and included 335 hospitals in 2015.

For the purpose of ongoing Point Prevalence Surveys, a web-based application was developed in South Africa as part of the ENAABLERS project. The web-application allows for anonymous patient data entry directly into the application via any mobile device connected to the web. The data encryption is done with both secure hash algorithm-256 (SHA-256) and Advance Encryption standard-265 (AES-256); these are the strongest encryption available and the same level of encryption used by international banks.

The data backups consist of both active and manual Backups, and both the active back-up and archives use the same encryption as the database. To minimize the risk of data mitigation failure, the data is stored in different geographic locations. The infrastructure is powered by Amazon Web Services (AWS) the industry leader in cloud services and is trusted by organizations like DOW Jones, Pfizer and the CDC. Every access to the data is logged and time-stamped and a log-file can be provided in the unlikely case.

Only authenticated users can access the database, various passwords protect the application, and passwords are protected by double encrypted password technology.

The raw data can be exported in comma separated values (.csv) text (.txt) a JavaScript object notation (.json) formats to Microsoft Excel for data analysis and statistical purposes.

Data collection within the ENAABLERS application consists of the following fields.

- *Hospital code, ward code, patient code, admission date, age, sex, employed, transferred.*
- *Hospitalization in past 90 days, Antimicrobial use past 90 days, duration and names of antibiotics in past 90 days.*
- *Catheterization, Intubation.*
- *Pre-existing medical conditions.*
- *Prescriber classification, Antimicrobial prescribed, indication, dose, frequency, route,*
- *Date, missed doses, out of stock,*
- *CST results, Bacterium name, sensitivity, IV to oral switch.*
- *Prescribed in INN, according to SEDL*
- *Unrelated surgery, prophylaxis,*
- *Hospital Questionnaire.*

Furthermore, no patient sensitive data is stored directly within the ENAABLERS application and patient confidentiality is maintained through the use of anonymous coding system build directly into the application.

An advantage of the ENAABLERS application is that the data is automatically exported to an Ms Excel® spreadsheet which provides automatically generated tables and graphs to summarise the data.

Sara Tomczyk

Full name: Sara Tomczyk
Title and Affiliation: Epidemiologist, ANDEMIA Project (African Network for Improved Diagnostics, Epidemiology and Management of Common Infectious Agents), Robert Koch Institute (representing self in addition to institute's official response)

Surveillance and monitoring for antimicrobial use and resistance

4. Integration
What are opportunities for, and obstacles to, integrating data analyses within and across sectors?
How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?
How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?

RESPONSE: The definition of "integration" should be expanded upon. I agree that it is more likely to be a "mosaic" in practice but more examples of what "successful integration" looks like in the WHO AMR resources could be given such as types of trend analyses, annual feedback sessions across sectors, etc particularly for low-resource settings. Antimicrobial resistance data collection grants (i.e. novel data collection sources, harmonization, etc.) from the Welcome Trust Grants or Gates Foundation that have come out in the last year should give regular and timely updates of the progress made in order to document these examples in a transparent way. I found the past AMR surveillance proof-of-principle (PoP) protocols/studies (with form templates in the annexes) from Eastern Europe that were published on the WHO website quite helpful to provide guidance in implementing human AMR surveillance in low-resource settings. The PoP concept could be used to showcase integrated data collection/analyses across sectors, particularly in low-resource settings.

4.1. Prioritization
What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?
How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?
What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal, and plant sectors and leverage the resulting data?

RESPONSE: Sufficiently detailed international AMR surveillance guidelines are not possible due to the diverse national contexts. However, tiered guidelines or grouping recommendations according to resource setting (i.e. basic, intermediate and advanced settings) could be useful. One example of how these tiered recommendations are presented is the US National Quality Partners Playbook for Antibiotic Stewardship in Acute Care (e.g. see page 6 - http://www.qualityforum.org/Publications/2016/05/National_Quality_Partners_Playbook__Antibiotic_Stewardship_in_Acute_Care.aspx). Similarly, stepwise priority step checklists linked to resources for AMR surveillance should be offered. This could be done by adapting the GLASS AMR surveillance checklist to give more visual scores and link to practical resources (e.g. WHO hand hygiene tool - http://www.who.int/gpsc/5may/hhsa_framework/en/ or the WHO national level IPC assessment excel-based tool - http://www.who.int/infection-prevention/tools/core-components/en/). Currently, it generally refers the reader to the national GLASS guide but this is high-level and doesn't help the implementer through the difficult practical questions concerning how to ensure quality bacteriology first and deciding on susceptibility definitions, types of sampling, etc., particularly for low-resource settings although the integrated surveillance of AMR in foodborne bacteria gets at some more of these practical

questions - http://www.who.int/foodsafety/publications/agisar_guidance2017/en/. I have heard from various partners in low- and middle-income countries that the AMR national action plan situational assessment was a comprehensive exercise which then identified many gaps but it was then difficult to know how to prioritize and take the next more practical steps; thus, it should be better linked to practical support tools, such as a stepwise AMR surveillance checklists.

There continue to be critical gaps in basic bacteriology in low-resource settings that rely on culture and manual testing. Implementation of AMR surveillance in these settings need to be better linked to existing lab bacteriology and quality management resources. Ideally this could also include a list of bacteriology experts with different language proficiencies to access when countries need to identify additional expert support in the local adaption process.

The animal and environmental sectors are wide and diverse but "low-hanging fruit" and high-impact priority areas should be better articulated, i.e. beef, dairy, poultry, turkey, small-companion animals, waste-water systems, selected streams near farms or run-off areas.

For all of these resources, a better and more-accessible inventory needs to be compiled, e.g. a simple list of resources, examples, PoPs, etc organized according to thematic area and shown with hyperlinks (this could also be better linked to the national action plan situational assessments). Numerous resources are still found on different areas of the WHO website which can be overwhelming and partners are often unaware of how to find them or that they exist. Dissemination strategies should be improved to share better summarized resources with country partners at key meetings, targeted listservs, strategic work between WHO and member states, etc. Our projects are in Francophone West Africa and finding available resources in French is still a challenge. WHO and other partners should also improve the timeliness of translated resources in selected languages to better serve the global population.

4.2. Comparability
What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?
What more can be done to harmonize collection of data on AMR/AMU among sectors and levels?
What additional work is needed on methods for testing antimicrobial susceptibility or to include new technologies in existing systems (e.g. WGS)?

RESPONSE: In Figure 1, the keys words for "Comparability" should include "standardized methods" as this is a key point, particularly for comparability of data across different country settings. As mentioned above in the response to question 4.1, the current Global AMR Plan resources are high level and it is harder to find guidance on practical steps on ensuring quality bacteriology (linking to quality management resources), deciding on susceptibility definitions, types of sampling, comparable groups that can be used for trend analyses across sectors, and finding antibiogram templates, etc, particularly for low-resource settings.

For low-resource settings, the decision on how to use EUCAST versus CLASI definitions can be one challenging example. There are some regional examples of health care associated infections (HAI) definition prioritization workshops (particularly in Latin America) where country experts (including experts in the local health system as well as HAI experts) gather to do a thoughtful prioritization exercise to decide on HAI definitions that can be used for surveillance that adapts to the local setting but in a meaningful way that still allows quality data that can be compared. Guidance for similar exercises for AMR would be useful, using benchmarking from the Global PPS or GLASS.

Guidance is also needed in the area of point prevalence surveys (PPS) for low-resource settings including questions such as how often one should conduct PPS, period vs point prevalence, and how to integrate HAI PPS guidance with AMR/AMU data collection. This could be done through a Proof-of-principle (PoP) protocol or other published examples.

The manuscript by de Kraker et al showing a narrative review of methods to evaluate stewardship interventions (https://www.sciencedirect.com/science/article/pii/S1198743X17302793?via%3Dihub) one example of what could be offer ed to review methods for AMR integrated analyses, of which may be something that the Tripartite Integrated Surveillance System for AMR/AMU (TISSA) could compile.

4.3. Availability
What support do countries require to develop and report accurate national data and share them on global surveillance systems?
What data formats and visualization tools are most useful for reporting and further analysis?
How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?

RESPONSE: In Figure 1, the key word "Feedback" should be included under the short description of "Availability." Feedback of AMR surveillance to human and animal health clinicians is critical but this emphasis or distinguishing between individual-level and aggregated feedback does not come out strongly in the currently elaboration on "Availability." It was mentioned that publishing data in a format that enables further manipulation and analysis such as in a spreadsheet is valuable. Excel tables with pre-formulated equations/macros to allow for automatic result visualization would be helpful (e/g. antibiogram templates, excel analysis templates, etc). In terms of use of modern web-based tools, other templates via Tableau for partners could also be explored. As mentioned above, the manuscript by de Kraker et al showing a narrative review of methods to evaluate stewardship interventions https://www.sciencedirect.com/science/article/pii/S1198743X17302793?via%3Dihub) also shows an example of what could be offered to review methods for AMR integrated analyses.

4.4. Sustainable investment
How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?
What tools are required to address the investment required for surveillance of AMR an AMU?
What role can the private sector play in financing surveillance?

RESPONSE: Antimicrobial susceptibility testing should be integrated with budget line items in general laboratory and bacteriology capacity building efforts with Ministries of Health and National Reference laboratories. It should be made explicit in financial programme planning and action plans. As much as possible, AMR surveillance should also be integrated in funded projects for HMIS and IDSR.

The WHO One Health tool which allows for forecasting of costs and health impacts at the national context could be used to support economic case studies. This could be a component of a thoughtful Proof-of-Principle (PoP) for integrated AMR surveillance in a low-resource setting as mentioned above that could provide a valuable example for other countries.

Other

Gavi, the Vaccine Alliance

From: Sophie Mathewson
Sent: 16 July 2018 10:32
To: IACG-secretariat
Subject: FW: Gavi response to the first IACG discussion paper: Antimicrobial resistance: Invest in innovation & research, and boost R & D and access

Follow Up Flag: Follow up
Flag Status: Flagged

As outlined below.

From: Sophie Mathewson
Sent: 16 July 2018 10:22
To: Claire Ward (External Consultant) ; GETAHUN GEBRE, Haileyesus

Cc: Tania Paratian Wilson Mok ; Austin Liu (External Consultant) Wilson Mok ; Gaurav Garg ; Claire Ward (External Consultant)
Subject: Gavi response to the first IACG discussion paper: Antimicrobial resistance: Invest in innovation & research, and boost R & D and access

Dear Dr Getahun,

Please find enclosed comments in response to the first IACG paper *Antimicrobial resistance: invest in innovation & research, and boost R & D and access* submitted on behalf of the Gavi Secretariat. Comments in response to the second and third papers will follow in separate emails.

We are grateful for the extension and the opportunity to give feedback.

Kind regards,
Sophie

Public consultation of the discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General

Responses have been included where they directly relate to Gavi's mission or mandate and relevant examples are available. For further information or clarification, please contact the Gavi Secretariat.

Discussion paper 1 - Antimicrobial resistance: Invest in innovation and research, and boost R&D and access (http://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_AMR_Invest_innovation_research_boost_RD_and_access_110618.pdf?ua=1)
R&D (p.10)

3. Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

Gavi's experience in market-shaping activities provides examples of approaches to address some of the challenges and barriers to R & D for new interventions for AMR, particularly vaccines. As an Alliance, Gavi creates a healthy market for vaccines, which plays a role in incentivising investment in vaccine research and product development, and ensuring that populations in low-income countries can access life-saving vaccines.

One of the challenges highlighted is the limited market for new products to address AMR, which deters R & D investment and can also affect supply of licensed products. In terms of its operating model, by aggregating demand from developing countries and pooling donor support for immunisation, Gavi has created a viable vaccine market in low and middle income countries.

With regards to specific mechanisms, Gavi's pneumococcal Advance Market Commitment (AMC) mechanism provides an example of an approach that could be adapted to incentivize the development of new products that would not otherwise be considered commercially viable such as certain vaccines and diagnostics to address AMR.

Access (p.14)

6. Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified (health technologies do not meet the needs of LMICs; substandard or falsified health products; limited use of diagnostics and vaccines; inappropriate use of antibiotics; limited health system capacity)?

7. Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

The following response addresses questions 6 & 7.

Integrating AMR within the mandate of existing organisations provides opportunities to leverage existing programmes, funding and networks in support of global efforts to address the threat that AMR poses to global health and human development. AMR is a cross-cutting issue and can be integrated with existing streams of work. This would also create opportunities for synergies and delivering on core principles (such as access, stewardship, coverage and equity).

Within Gavi, efforts are underway to consider how best to integrate AMR-related priorities across the organisation. For example in terms of mechanisms to expand access, Gavi is currently engaged in the Vaccine Investment Strategy (VIS) process which takes stock of available and expected vaccines for potential investment. AMR is included as a criteria for the VIS 2018 vaccine evaluation framework under 'Global Health Security Impact'. In the assessment of the potential importance of investments for AMR the approach has considered both direct effects (e.g., potential to reduce incidence of drug resistance disease) and indirect effects (e.g., reduction in antibiotic use from viral infections and improved diagnostic practices) of prospective vaccine investments. Through this process consideration of AMR will determine access to new vaccines through Gavi.

Sophie Mathewson

Research Specialist
Vaccines & Sustainability

Gavi, the Vaccine Alliance

From: Sophie Mathewson
Sent: 16 July 2018 10:39
To: IACG-secretariat
Cc: Tania Paratian; Wilson Mok; Austin Liu (External Consultant); Wilson Mok; Gaurav Garg; Claire Ward (External Consultant)
Subject: RE: Gavi response to the second IACG discussion paper: Antimicrobial resistance: national action plans

Follow Up Flag: Follow up
Flag Status: Flagged

Dear IACG Secretariat,

Please find enclosed comments in response to the second IACG paper *Antimicrobial resistance: national action plans* submitted on behalf of the Gavi Secretariat. Comments in response to the third paper will follow in a separate email.

Public consultation of the discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General

Responses have been included where they directly relate to Gavi's mission or mandate and relevant examples are available. For further information or clarification, please contact the Gavi Secretariat.

Discussion paper 2 - Antimicrobial resistance: national action plans (http://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_AMR_National_Action_Plans_110618.pdf?ua=1)

Mainstreaming (p.11)

1. What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?

AMR touches a number of different global agendas related to health and human development.
The 1 billion target on universal health coverage is one of the priorities in the 13th General Programme of Work (GPW) of WHO approved by the World Health Assembly in May 2018. The GPW recognises that immunisation "constitutes a strong platform for primary care upon which UHC can be built". With immunisation come supply chains, trained health-care staff, medical record keeping, community outreach, data monitoring and disease surveillance, which can be a platform for AMR related programmes such as awareness and access to antibiotics. At the same time immunisation is also a cost-effective and high impact strategy for infection control and disease prevention which are key objectives of the Global Action Plan on AMR by reducing the use and misuse of antibiotics.
To ensure global health security it is essential that countries have the capacity to detect and report emerging resistant diseases that may constitute a public health emergency of international concern, as required under the International Health Regulations. It is also important to promote the research and development of new vaccines against AMR to enable prevention and effective response to outbreaks of drug-resistant diseases.
AMR is an intersectoral problem that could derail our efforts to achieve the 2030 Agenda for Sustainable Development. On the other hand it is also important to recognise the joint contribution being made by other sectors to address AMR, such as the prevention of AMR with infection prevention and control (ICP) and water, sanitation, and hygiene (WASH) programmes.

4. How can international development partners support full integration of the AMR programmes they fund into sustainable initiatives in beneficiary countries?

At the global level, greater engagement of a wide range of development partners across sectors with the AMR agenda will sustain political visibility in different policy platforms. In terms of evaluation, coordinated and detailed reporting of contributions to AMR goals from international development partners will also support integration.

Gavi's support to health system strengthening builds country capacity (strategic, managerial and operational) that can support AMR programmes. Its co-financing policy encourages governments in Gavi-supported countries to invest in the introduction and roll out of new vaccines with high coverage, enhances country ownership of vaccine financing, and helps them plan for financially sustainable immunisation programmes.

Financing (p.13)

5. What support do countries need to translate information on the global impact of AMR into a country-specific case?

In response to question 5, countries need to have sufficient information on their own circumstances to understand how the global agenda relates to their own context.
However, there is also a need to ensure that information on the impact of AMR in countries supports global prioritisation and agenda setting.

We are grateful for the extension and the opportunity to give feedback.

Kind regards,
Sophie

Sophie Mathewson

Research Specialist
Vaccines & Sustainability

Gavi, the Vaccine Alliance

From: Sophie Mathewson
Sent: 16 July 2018 10:57
To: IACG-secretariat
Cc: Tania Paratian; Wilson Mok; Austin Liu (External Consultant); Gaurav Garg; Claire Ward (External Consultant); Lee Hampton
Subject: RE: Gavi response to the third IACG discussion paper: Antimicrobial resistance: Surveillance and monitoring for antimicrobial use and resistance

Follow Up Flag: Follow up
Flag Status: Flagged

Dear IACG Secretariat,

Please find enclosed comments in response to the third IACG paper *Antimicrobial resistance: Surveillance and monitoring for antimicrobial use and resistance* submitted on behalf of the Gavi Secretariat.

We are grateful for the extension and the opportunity to give feedback.

Kind regards,
Sophie

Public consultation of the discussion papers informing the report of the Interagency Coordination Group to the UN Secretary-General

Responses have been included where they directly relate to Gavi's mission or mandate and relevant examples are available. For further information or clarification, please contact the Gavi Secretariat.

Discussion paper 3 - Surveillance and monitoring for antimicrobial use and resistance
(http://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_Surveillance_and_Monitoring_for_AMU_and_AMR_110618.pdf?ua=1)

Integration (p.6)

1. **What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?**

Monitoring and Evaluation of Gavi activities, including country health surveillance are core functions for generating evidence to promote system learning, accountability and improved outcomes. It is important that the introduction of a vaccine or other interventions, such as antimicrobials, are integrated with monitoring and evaluation functions that provide feedback, at the regional, national and global levels, with real-time data on performance, impact and sustainability.
Data can either by integrated by a specialist monitoring group in ministry of health or by private sector actors. In addition, there needs to be a stronger emphasis on the uses and value of AMR and AMU surveillance data. The basis for establishing surveillance systems are stronger if the data generated can be specifically linked to key policy and decision-making processes.
With the over prescription of antimicrobials and other interventions driving the spread of drug resistant bacteria, data collection also needs to include information on laws and regulation of antimicrobial sales, e.g., whether or not prescriptions are required. This information and the governance of antimicrobials is highly important for understanding the regulatory landscape and the possible drivers, barriers and enabling environment for access, or excessive use, of antimicrobial interventions.

Prioritisation (p.8)

4. What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?
In order to successfully develop surveillance functions, countries require the generation of relevant data that is responsive to health needs and country context. In addition to tools, establishing surveillance

depends on setting priorities which should also take laboratory capacity into consideration. Once priorities have been identified, appropriate guidance, training and sustainable funding is needed for all stages of the surveillance chain from case detection through to testing, confirmation and reporting.

5. How could countries be better supported in developing sustainable national or regional AMR surveillance strategies that are adapted to national contexts but still can inform national policies and contribute to international containment of AMR?

A country-centric approach is crucial for adapting systems to meet the needs of local health needs, contexts and populations. Drawing on Gavi's experience in immunisation, the establishment of sustainable national or regional AMR surveillance strategies needs to be facilitated by adequate training, robust data quality and integrity practices and, sufficient resources. The following three practical suggestions are recommended:

- the development of forms, protocols, SOPs for countries to use in AMR surveillance;
- the adaptation of global guidelines to match the specificity of country contexts;
- surveillance strategies with sustainable financial support that is conditioned on some degree of co-financing and gradual transition of donor support to national governments.

6. What more can be done to facilitate the surveillance of falsified and substandard medicines in the human, animal and plant sectors and leverage the resulting data?

The Gavi Alliance relies heavily on population surveys to monitor immunisation coverage, and such surveys could be adapted to offer a means for periodically assessing the prevalence of falsified and substandard medications in a population. For example, medicines of interest (i.e., individual pills) could be collected from individuals in surveys such as DHS surveys and either inspected or tested to see if they meet quality standards. If medication pills were taken for testing, individuals who provided pills for testing would be provided replacement pills of the relevant medicines. Conducting such an assessment as part of a survey would ensure that the results were generalisable across a population while taking advantage of the existing survey infrastructure.

<u>Comparability (p.10)</u>

7. What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?

Gavi's experience has shown that the increased effectiveness and efficiency of interventions is achieved by developing programmes through an integrated health system strengthening approach, which is also relevant for AMR. In addition this requires engagement of civil society, private sector and other partners to contribute to a comprehensive surveillance system. To achieve and maintain a surveillance system further requires strengthening government teams at the national level (or subnational level where relevant) with the aim of improving structures, capabilities, processes and practices, and reporting to national and global surveillance databases.

Gavi support for countries is based across five bases to develop national systems, and a similar design could also provide a framework for the strengthening of a surveillance system:

a) Investing in demand, education and awareness programmes;
b) Helping to build the evidence base;
c) Ensuring adequate technical support;
d) Developing relevant guidelines and resources; and
e) Supporting innovative approaches and partnerships.

<u>Availability (p.12)</u>

10. What support do countries require to develop and report accurate national data and share them on global surveillance systems?

Timely, fit-for-purpose data is vital component of health activities and for countries to plan and monitor their health programme in an effective way. Gavi, the Vaccine Alliance works with WHO, the Global Fund and other agencies to strengthen countries' health information systems. In particular, Gavi supports improving Vaccine-Preventable Disease (VPD) surveillance. This area of work helps countries to strengthen their surveillance systems and use disease data to target and improve health programme interventions. Importantly, national surveillance systems also operate as a vital part of ensuring global health security and outbreak preparedness.

Gavi supports data collection practices to develop national systems, and a similar design could also provide a framework for the surveillance system date collection:

Data availability:

- Implement continuous improvements of surveillance data, information collection and management systems, based on the results of recent assessments and a sufficiently-funded data improvement plan that all relevant partners agree to support collaboratively;
- Implement national representative coverage surveys (conducted at least every five years);
- Establish or enhance electronic and paper data reporting systems for health care providers at service delivery points to report on disease indicators and other relevant data, e.g. antimicrobial use and resistance
- Conduct training for health care providers on reporting

Data quality:

- Identify mechanisms to increase the accuracy of denominators for use by immunisation programmes and disease surveillance systems, such as use of spatial demography;
- Implement annual data desk reviews, including triangulation analyses using data from different sources such as administrative, antimicrobial stock, surveillance, and survey data;
- Implement in-depth data assessments of the routine reporting system and disease surveillance, antimicrobial use and resistance (conducted at least every five years);
- Establish or enhance access to reliable international or national laboratory capacity that can meet diagnostic and confirmatory laboratory testing requirements for suspected disease cases.

Data use:

- Enhance the skills and knowledge of health workers at all levels in the continuous collection, analysis, use, and communication of immunisation, AMR and AMU following training needs assessment.
- Identify priority research topics related to improving immunisation and surveillance data as well as use of such data, and support in-country research on those topics
- Conduct and use relevant analyses to inform investments, targeting and tailoring for routine services.

11. What data formats and visualization tools are most useful for reporting and further analysis?
Gavi recognises the need for good quality data, and the importance of consolidating data sets, that are inter-operable with existing systems, generating robust evidence for health-, system- and policy- decision-making. To this end, Gavi has supported new immunisation registries linked to national multi-program DHIS2 platforms, with linkages to other systems where appropriate for the country context. Equally, the DHIS2 module could also be further used for reporting AMR and/or the integration of AMR data into the DHIS2 program.

12. How can lessons be learnt from initiatives in HIV, tuberculosis and malaria to improve surveillance of AMR and AMU?
Sustainable investment (p.14)
13. How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?
14. What tools are required to address the investment required for surveillance of AMR and AMU?
15. What role can the private sector play in financing surveillance?

Sophie Mathewson

Research Specialist
Vaccines & Sustainability

Global Antibiotic Research & Development Partnership

The Global Antibiotic Research & Development Partnership's comments on the IACG discussion paper 'Antimicrobial resistance: Invest in innovation and research, and boost R&D and access'

The Global Antibiotic Research & Development Partnership (GARDP) is a joint initiative of the World Health Organization (WHO) and the not for profit Drugs for Neglected Diseases *initiative* (DNDi). GARDP is a not-for-profit research and development (R&D) initiative that addresses global public health needs by developing and delivering new or improved antibiotic treatments while endeavoring to ensure sustainable access. GARDP builds on DNDi's track record of developing, delivering, and implementing seven new treatments since 2003 for neglected diseases and a pipeline of new chemical entities, using an alternative needs-based collaborative partnership model, as well as from WHO's technical expertise and leadership.

GARDP's vision is a world where everyone in need of antibiotics receives effective, appropriate, and affordable treatment, irrespective of where they live. At present, it has four global programmes: Antimicrobial Memory Recovery and Exploratory ,Sexually Transmitted Infections, Neonatal and Paediatric, seeking innovative ways to fight drug resistant infections.[1]

GARDP welcomes the opportunity to comment on the discussion paper, and the recognition by the IACG of the need to address innovation and access to existing and new health technologies, as part of sustained effective global action to address antimicrobial resistance.

GARDP's response will primarily focus on R&D for human health, while recognizing and supporting the need for a One Health approach for R&D for human, animal and environmental purposes, and the potential for synergies between approaches taken. We note that the IACG's work is ongoing, and hope that there will be further opportunities to engage with all stakeholders, as the IACG seeks to develop specific recommendations.

General Comments

Drug-resistant infections are now outpacing drug discovery at an alarming rate. The current pipeline for new antibiotics is weak as has been shown in the recent WHO pipeline report[2] in addition to already identified priority needs in TB and, to a large degree, does not reflect global public health priorities. This calls for coordinated, prioritized support for basic research and early stage discovery as well as for bringing new drugs through clinical trials and optimizing the use of existing drugs. Current incentives for new drugs and diagnostics to address antimicrobial resistance are inadequate to address public health needs.

The Political Declaration of the High-level Meeting on Antimicrobial Resistance, [3]which established the IACG, cautioned that success in the fight against antimicrobial resistance cannot be achieved with the current health tools and technologies, and that new approaches were necessary where *'all research and development efforts should be needs-driven, evidence-based and guided by the principles of*

[1] More information of GARDP's programmes available at : https://www.gardp.org/programmes/

[2] Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Licence: CC BY-NC-SA 3.0 IGO. Available at: http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf?ua=1

[3] Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. Available at: https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility.' and that there is '*a public return on the public investment on R&D'* ' It also acknowledged the importance of reactivating the R&D pipeline through incentive mechanisms that avoid the reliance on high price/volume combinations and the need to promote appropriate use of antibiotic by '*delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines, and other results to be gained through research and development '*

Any new approach must address the complex issues of stewardship as well as sustainable, equitable, and affordable access to existing and new antibiotic drugs. These must meet patients' needs from low-middle- and high-income countries, and take into account the diversity of national health systems challenges, and levels of economic development.

The overall objective for R&D development to address antimicrobial resistance is not an easy one, but it is vital - to ensure that existing health tools get to those who need them; that any new tools are designed from the start to meet health priority needs, reflect the realities of clinical practice, and ensure access but not excess. The IACG has an important role in ensuring that its recommendations focus on actions that implement the direction given by the AMR Declaration, and that can help meet this objective.

A global, collective and coordinated effort is required to tackle the many challenges related to delivering effective, appropriate and affordable antibiotic treatments to people in need. The discussion paper identifies a several of these challenges, however in its further work we would encourage the IACG to more adequately address and further develop a number of issues including:

- How to specifically implement the key principles, contained in the Political Declaration of the UN General Assembly (rather, than just being guided by them) when applying funding and designing incentives. This is further developed in the specific comments below.

- Further development of an end to end analysis - from the bench to the bedside - of the life cycle of new health technologies. This should be based on and seek to support the further development of the Global Framework for Development and Stewardship to combat Antimicrobial Resistance currently under development by the Tripartite agencies. [4] Such a comprehensive analytical base is critical to identify gaps, and design and evaluate appropriate interventions, targeted at the right actors. It must include, unlike the present discussion paper, stewardship (to preserve the effectiveness and impact of any new drugs developed) as well as sustainable, equitable, and affordable access to existing and new antibiotic drugs for those in need, as an integral part of the R&D process.

- Ensuring access with appropriate use/stewardship and sustainable access measures. New drugs alone are not enough. Identifying the best use of new drugs through public health studies is essential to guide appropriate use and stewardship.

- Furthermore, optimizing the use of existing drugs will be critical to protect the efficiency of such drugs over time. This can be achieved by improving the use of old and existing drugs,

[4] WHO. *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance: Draft Roadmap* (WHO/EMP/IAU/2017.08). Geneva, Switzerland: WHO, 12 May 2017. Available at: http://www.who.int/phi/implementation/research/WHA_BackgroundPaper-AGlobalFrameworkDevelopmentStewardship.pdf

including by generating evidence-based treatments for important diseases and syndromes with bacteria as causative agents, and introducing appropriate diagnostics to guide selection of the most appropriate agent. Unfortunately, there is little interest to support downstream development in this space. The IACG should consider making recommendations to support such development.

- Ensuring supply security and affordability of both old and new antibiotics needs to be addressed. This should also include active pharmaceutical ingredient (API) production as well as ensuring quality and compliance to environmental issues (such as waste management). Support for the conducting of market analyses of key antibiotics (including those on or of interest to the essential medicines list - EML) to identify gaps and liabilities around API and finished drug product manufacturing should be considered as part of the IACG's ongoing work. Building regional strategic production networks should also be considered.

- A recent *Lancet Infectious Diseases* commentary, proposed several strategies to ensure availability of old, effective antibiotics, including the "formation of a multidisciplinary working group that would identify obstacles and solutions; disclosure and mapping of current production and supply chains; agreements on quality criteria, continued production, and stock management; collaboration between national regulatory agencies to secure the availability of effective antibiotics; predictable joint procurement that might result in an incentive for producers."[5] Supporting strategies to secure access to existing antibiotics and provide treatment to patients, should also be seen as an essential element for the development and availability of any new health technologies. Effective strategies for access to existing antibiotics can provide important lessons, and help build a public health pathway for the sustainable supply, access , affordability and stewardship of new antibiotic drugs.

- Pro public health licensing of any intellectual property or other rights to develop and manufacture, and, stewardship provisions for developed products, must be considered together. These can facilitate additional essential R&D in particular public health segments (for example children under five) and ensuring sustainable access. Public funders of R&D should consider how suitable contractual measures (including through licensing agreements) can be put in place with private -sector actors receiving public support. This may enable both public and private sector actors to successfully and suitably roll out new treatments in the future. Not for profit drug developers, can play a role in implementing such condition, for example, GARDP includes clauses that ensure affordability and appropriate use of any new products developed by GARDRP in any partnership agreement. While developers can and should play a part in sustainable access, there remains a crucial role for governments, WHO, and other agencies to set the appropriate polices and standards at the national, regional, and global level.

- Building joint strategies and partnerships between drug and diagnostic developers to ensure rational use needs to be catalyzed (e.g. such as development of a point of care Sexually Transmitted Infections test in tandem with the development of a new drug against drug resistant gonorrhoea).

[5] Tängdén T, Pulcini C, Aagard H, Balasegaram M, Hara GL, Nathwani D, Sharland M, Theuretzbacher U, Cars O. Unavailability of old antibiotics threatens effective treatment for common bacterial infections. *Lancet Infectious Diseases* 2018; 18(3), 242-244. Available at: https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(18)30075-6.pdf

- **Emphasis on a global approach, that takes into account the particular needs in low- and middle-income countries (LMICs).** Meeting global health needs means developing drugs aimed at not only targeting priority pathogens (as designated by WHO in their Priority Pathogen List[6]) but also meeting the needs of specific high-risk populations (such as new born babies) and treating under-served diseases and syndromes. This ensures that any new health tools are designed from the start to address priority needs. GARDP's choice of initial programmes follows from these principles and has been supported by expert reviews and input from the World Health Organization (including priority pathogens, pipeline and landscape analyses).

- While multidrug-resistant pathogens are found globally, LMIC country needs must be met as AMR is largely impacting LMIC's, where health systems are often weak, and where out of pocket expense for healthcare are high. Furthermore, diagnostics and treatments must address specific contexts, population needs and epidemiological trends. It is of critical importance to ensure regulatory and public health-oriented trials are undertaken as early as possible in appropriate developing country contexts (where need and capacity exist).

- **Harnessing and building R&D capacity and linking appropriate actors in low-and and middle-income countries.** LMICs needs, as well as capacities, are insufficiently addressed in the AMR field. Many current incentives for R&D, and discussions for future ones are also primarily focused in the US and the EU. However, addressing antibiotic resistance is a shared responsibility, if solutions to contain antibiotic resistance are to make a difference globally, then low- and middle- income countries must be part of developing them, so solutions are developed **by, with** and **not** just **for** these countries.

- Understanding market dynamics in LMIC's, including for existing antibiotics, is needed to better assess how realistic and appropriate access and stewardship measures can be put in place. In addition to governments, local actors such as civil society organizations can play an important role in building understanding of needs and ultimately contribute to delivery and impact.

- Strong involvement of national authorities and drug regulatory bodies to better understand national priorities as well as ensure collaboration for downstream development and implementation is required. More work is needed to understand the requirements of LMIC regulators prior to registration of a new chemical entity (NCE) and label extension of existing drugs. In this area support from WHO will be critical.

- Building research networks including clinical trial networks that can integrate drug and diagnostic development is crucial. This needs to be done while ensuring country level ownership. GARDP is actively working with countries and existing actors to develop such a network for pediatric and neonatal antibiotic development. [7]

[6] Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Available at: http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf?ua=1

[7] On 3 July 2018 in New Delhi GARDP launched an observational study which is being carried out in hospitals/neonatal units in Bangladesh, Brazil, China, Greece, India, Italy, Kenya, South Africa, Thailand, Vietnam, and Uganda. The study focuses on collecting clinical information on babies with significant/clinical sepsis. It will generate a robust evidence base on how neonatal sepsis is managed which can be used as a basis for evaluating future interventions in neonates.. More information can be found here. https://www.gardp.org/2018/news-resources/press-releases/researchers-gather-new-delhi-kick-off-study-newborns-sepsis/

- Building partnerships with national research initiatives and funders will therefore be important. This includes the potential to work in partnership with drug discovery initiatives as well as supporting private sector actors.
- Harnessing existing capacities and strengths particularly in chemistry, manufacturing and controls(CMC), API and pharmaceutical development should be enhanced. There is a real opportunity to build an innovative value chain through linking biotech/small pharmaceutical companies, academia, not for profits and generic companies. GARDP is actively piloting such an approach such an approach through its STI Programme, where as a first approach, by 2023 GARDP seeks to register a new drug for gonorrhoea new drug for gonorrhoea in a number of high burden countries, ensure its integration into relevant policies and guidelines, and initiate its implementation together with a suitable treatment conservation and access strategy.[8]
- Ensure policy coherence of IACG recommendations. The IACG has, and will, also produce further discussion papers which focus on different elements of the response to antimicrobial resistance, such as national plans, and on surveillance. These and other essential aspects such as infection prevention control and public awareness raising are also relevant for R&D. Developers need to take into account the diversity of national health systems challenges, national plans, and levels of economic development. Surveillance activities not only serve epidemiological purposes but should link to R&D efforts in a mutually reinforcing way – country or regional-specific R&D programmes should address the resistance profiles and can feed back into surveillance efforts. It is therefore important that the IACG, as part of its review of each element, recognizes that there are overlaps between them, and that in its final recommendations, seeks to ensure coherence both within and between elements.

Specific comments on some of the open questions raised in the discussion paper.

1. Research and development. How could R&D funding be better channeled? What will it take to increase and sustain donor and private funding of R&D in AMR.

R&D requires adequate, sustainable funding, which is a shared responsibility of all Governments and should be available at the national, regional, and international levels. Such funding is only likely to increase and be sustained if funders are convinced that existing and future funding will ensure a public return on public investment made.

The IACG should include in its analysis, and critically review ways, to mobilize new funding, in addition to incentives that apply such funding. This should include proposals for taxes such as the pay and play model suggested in the O'Neill report, social impact bonds, development banks and funding, both in cash and in-kind from additional countries to the traditional donors.

[8] With WHO, GARDP devised short- and long-term target product profiles (TPPs) to guide the development of an R&D strategy for STIs with support of gonorrhoea experts the world over. It entered into its first partnership with Entasis Therapeutics (a biotech) to co-develop zoliflodacin – a novel first-in-class antibiotic for the treatment of uncomplicated gonorrhoea for **global** use, that includes provisions on access and stewardship and licensing of existing and future intellectual property to enable development and registration. A phase III clinical trial is planned in multiple countries including South Africa, Thailand, the EU and the United States. GARDP is also implementing a chemistry and manufacturing and controls plan that includes developing a commercial formulation of zoliflodacin for use in clinical trials and beyond. With WHO and relevant countries, GARDP aims to build on and develop appropriate access and stewardship plans. Both GARDP and Entasis are committed to affordable and equitable pricing in their respective license territories. More details can be found here: https://www.gardp.org/programmes/stis/

Any existing or new funding should be channeled to supporting a bench to bedside approach, which is focused on global public health priorities. The WHO's Global Health Observatory and WHO's priority pathogen list, provide an important base for such priority setting.

To best direct funding to agreed priorities, at least some portion of health R&D funding should be pooled, this could be done virtually where governments commit to allotting certain amount of funding to global priority projects.

Funding should have critical safeguards, based on the principles in the AMR Political Declaration in place to ensure a public return on the investment made, and monitoring and evaluation of the application of those safeguards. These should include:

• Sustainable Access, meaning equitable accessibility, availability, affordability and stewardship of health technologies for individuals and the health systems that serve them;

• Openness, transparency, and access to knowledge, meaning the greatest possible sharing of research knowledge to ensure efficiency and collaboration, and transparency of R&D costs;

• Pro-public health IP management and equitable licensing – concerning the availability, scope, and use of research tools and affordability of end products – to enable research and the fruits of innovation to be global public goods;

• Scientific and technological cooperation to harness expertise in both developed and developing countries, encourage collaboration between research centers, and facilitate technology transfer.

The discussion paper highlights GARDP's role, both in funding research and working throughout the drug pipeline to patient access, to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. It is important to clarify that GARDP is not just a research funder, rather it actively drives research that addresses public health priorities. In doing so GARDP seeks to build on, and adapted where necessary, for AMR the lessons learned from DNDI when seeking to apply such norms. These include building access into the R&D process from the beginning, to facilitate access to new treatments and their appropriate use, including through the use of clear target product profiles (TPPs) that consider the needs of the patients and the characteristics of the related health system.

As partnerships are key to DNDI and GARDP programmes it is important, and has been possible to included, contractual arrangements with pharmaceutical companies, research institutions, and academic partners that secure freedom to operate and ensure sustainable access.

Further activities that could be consider by the IACG include:

Expanding the remit of existing pooled funds, or develop funds to cover all areas of need, tied to agreed priorities and norms. The discussion paper also raises the possibility of extending the mandate of already existing funds, such as UNICEF, Global Fund, GAVI and UNITAID to finance access to health technologies. While their institutional experience and skills applied strategically, could provide added value in additional key areas of AMR R&D, both by their own interventions and by encouraging and leveraging partnerships with others. Some caution and further evaluation is needed. Any extension of mandate would need to come with additional funding, so as not to distract from the fulfillment of their existing mandates, and to ensure that the pressing needs for AMR are met. Funding should also not be diverted from existing AMR initiatives. There would need to be coordination between the different funds and the use of common principles to ensure sustainable access.

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

To implement the needed end to end approach, a combination of ways to apply and attract financial investments in research and development ('push and pull incentives') are likely to be required to effectively stimulate antibiotic innovation.

In seeking to evaluate the most appropriate delinkage mechanism (s) it is important that the IACG follows the definition established by the UN General Assembly 2016 Declaration, where the cost of investment in research and development are separated from both unit prices and sales volumes, in order to avoid high sales or prices that could undermine stewardship and affordable access.

There is also a misconception in the discussion paper that push mechanisms can only '*directly address challenges… related to the complexity of basic research and the cost of preclinical research'*. Product developers, such as DND*i* and MMV, which are primarily funded by up front 'push' payments, have successful track records of delivering, recommending, and implementing new treatments. DNDi alone, since 2003, has delivered seven new treatments for neglected diseases, and importantly a pipeline of new chemical entities. Both push and pull mechanisms can be designed for different actors, non- and for profit, and for stages of development.

However, focusing too strongly on types of financial incentives (push and pull) is not the most appropriate way to frame the issue. It is of crucial importance to identify at which stage in the R&D pipeline funding should be focused. Additionally, identifying the most appropriate private or public-sector actors, which in turn should then drive the type of funding approach adopted, is vital. As much of the current innovation in the field of antibiotics takes place in academia and in small and medium enterprises (SMEs), incentives need to be designed to meet their needs.

Significant resources (such as through IMI, CARB-X and Repair Impact Fund) are now being placed in the early translation space (lead optimization to phase 1). However, there is still a serious lack of funding for early discovery and conducting appropriate clinical trials, including post-regulatory trials. The latter is important as regulatory requirements for a new drug may drive development for certain indications (such as Hospital Acquired Pneumonia) on relatively small patient populations (1000 in number).

Funding and incentive mechanisms should promote open, collaborative approaches that aim from the start to efficiently deliver affordable products. For example, supporting mechanisms such as access to multiple compound libraries, data sharing, including pooling of intellectual property rights, as is currently being explored by the Medicines Patent Pool in relation to AMR, should be considered.

To ensure a public return on public investments. any incentive should include a contractual relationship between payer(s) and recipient(s) with strong governance, definitions around what constitutes innovation (based on public health priorities), and a clear agreement on sustainable access provisions

How could current efforts in R&D coordination be strengthened?

Collaboration between all existing and new AMR R&D related initiatives is essential to maximize the effort directed towards stimulating R&D for new antimicrobials in the fight against multi-drug resistance. The discussion paper identifies several existing mechanisms that could be built on. Additional information approaches should be considered that provide the basis for better coordination include information on the complete chain of research and development for new antimicrobials, diagnostics, and prevention measures/technologies including vaccines.

Joint Programming Initiative on Antimicrobial Resistance

From: Laura Marin
Sent: 09 July 2018 16:32
To: IACG-secretariat
Subject: RE: IACG Subgroup 4 interviews - follow-up and discussion papers

Dear IACG Secretariat

First of all we would like to congratulate you for such a paper. Especially relevant for us is your last open ended questions.

We just have 2 minor comments (in red) in the sentence describing JPIAMR at the paper on R&D, Page 9:

"JPI-AMR coordinates national research programmes on AMR and funds basic and preclinical research in the human, animal and environmental sectors through a strategic research agenda that maps its members' initiatives. Established in 2011 by 15 European countries, JPI AMR has grown into a global institution, with a diverse membership of 27 high- and middle-income countries."

With best regards
Laura

Laura Marin
Head of Secretariat
Joint Programming Initiative on Antimicrobial Resistance
Swedish Research Council

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Medicines Patent Pool

Medicines Patent Pool Submission to the discussion paper "Antimicrobial resistance: Invest in innovation and research, and boost R&D and access"

The international community has stressed the imperative of increased research and development (R&D) of new antimicrobials, access strategies as well as fostering better stewardship in order to preserve their effectiveness. The discussion paper on AMR prepared by the Inter-Agency Coordination Group recognizes some of the main challenges along the R&D value chain. Voluntary licensing, including patent pooling instruments such as the Medicines Patent Pool (MPP), is suggested as a mechanism that may contribute to addressing some of these challenges.

This submission will focus on the potential role that the Medicines Patent Pool (MPP) could play as part of the AMR response, with a particular focus on how the MPP could contribute to innovation, affordable access and good stewardship of new antimicrobials.

The MPP's Experience in Patent Pooling for HIV, hepatitis C and tuberculosis

The MPP is a United Nations-backed public health organization funded by Unitaid, working to improve access to affordable and appropriate HIV, hepatitis C and tuberculosis medicines in low- and middle-income countries. The experience of the MPP in HIV has provided a concrete example of how patent pooling can contribute to addressing some of the innovation and access challenges relating to health technologies. While the design of the HIV patent pool was guided by the specific circumstances in HIV, some of these circumstances might also apply to other areas in public health such as AMR, although the model would likely require adaptations to align with international public health objectives in the field of AMR.

In the field of HIV, the MPP's work on access relied on the fact that there were multiple new HIV medicines already on the market and a need for access in developing countries that could best be met though competition among multiple manufacturers to reduce the price to affordable levels. From an innovation perspective, the model sought to address the need for follow-on innovation in relation to products needed mostly in developing countries (e.g. pediatric formulations) and for products that require combining medicines patented by more than one entity (e.g. fixed dose combinations).

In November 2015, the mandate of the MPP was expanded to hepatitis C and tuberculosis (TB) and the model evolved to meet the needs in these therapeutic areas. In terms of innovation, while there had been multiple new hepatitis C treatments reaching the market, investments in tuberculosis R&D had been very limited, with only two new products reaching the market in the past forty years. Thus, while the first MPP license in HCV was for a marketed medicine with the aim of facilitating affordable access, the first MPP license in TB was for a medicine that had been stalled in clinical development for a number of years. The MPP license was expected to contribute to accelerating its development by facilitating access to the intellectual property by other potential developers promoting collaborative research and the development of new TB regimes.

Part of the work of the MPP in HIV, hepatitis C and TB was also relevant to concerns relating to antimicrobial resistance. For example, in HIV, the MPP holds numerous licenses on second-line

antiretrovirals – i.e. antiretrovirals used in patients whose HIV infection has developed resistance to first-line treatment – as well as products such as dolutegravir, which is recommended by the WHO for first-line use in countries with high levels of pre-treatment resistance to one class of medicines. The MPP is already implementing, monitoring, and enforcing stewardship-related obligations in its current licenses with drug manufacturers in the fields of HIV, hepatitis C and TB. These practices include the careful evaluation and selection of licensees through its Expression of Interest system, strict quality requirements, and provisions for pharmacovigilance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has demonstrated success in ensuring its licensees adhere to such obligations and has sought remedies up to and including termination of licenses for those who fail to perform.

In the field of TB, patent pooling could also play an important role in facilitating the development of new treatment regimens, by pooling the necessary intellectual property and clinical data that may be needed. Combining patent and data pooling with push and/or pull incentives could contribute to the development of new regimens that are needed in the field of TB to improve current treatments for multi-drug resistance TB in particular.

Currently, the MPP holds licenses on 16 medicines with nine patent holders, including pharmaceutical companies, universities and public research organizations. These licenses enable 25 partner generic companies and one product development partnership to develop, register, manufacture, and supply WHO-recommended products in a large number of LMICs. The MPP's work has delivered 17 million patient years of treatment and resulted in $535 million in savings from the procurement of more affordable quality-assured medicines.

The potential role of the MPP in contributing to innovation, access and stewardship for new antimicrobials, including new antibiotics

Recent high-level reports have recommended that the MPP could play an important role in new mechanisms for financing antimicrobial R&D. The Review on Antimicrobial Resistance chaired by Jim O'Neill recommended that incentive mechanisms such as market entry rewards should be linked to requirements to ensure access and stewardship – for example, by requiring recipients of payouts to license their discovery to the MPP under appropriate provisions.[1] Analyses from Chatham House, a prominent international affairs think tank based in the United Kingdom, and DRIVE-AB, a consortium supported by the European Innovative Medicines Initiative, made similar recommendations.[2] [3]

Last May, the MPP released the results of a feasibility study exploring the possibility of expanding its mandate to work on other patented essential medicines, including new

[1] The Review on Antimicrobial Resistance Chaired by Jim O'Neill. Tackling drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (accessed Feb 18, 2018).
[2] Chatham House. Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: Report from the Chatham House Working Group on New Antibiotic Business Models. 2015.
[3] DRIVE-AB. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access. 2018. http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf (accessed Feb 19, 2018).

antibiotics of public health priority.[4] The feasibility study provided the technical analysis for the MPP to expand its mandate beyond HIV, TB and hepatitis C. Over the coming months, the MPP will be working on prioritizing possible candidates for in-licensing, including exploring its possible role in relation to new antibiotics for combatting AMR.

In its feasibility study the MPP looked at its role in relation to new antibiotics taking into consideration the categorization made by the WHO Committee on the Selection and Use of Essential Medicines on antibiotics for Access, Watch and Reserve.[5] MPP licenses could be tailored to the specific public health needs that a new antibiotic can contribute to addressing while ensuring a proper balance between innovation, access and stewardship.

Linking patent pooling to new financial incentives for R&D for antibiotics

In the ongoing discussion on possible new incentive mechanisms that would contribute to strengthen the current antibiotic pipeline there is a general agreement, as approved by Member States at the UNHLM on AMR in 2016, that incentives should be designed "delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales so as to facilitate equitable and affordable access" and should consider innovation, access and conservation holistically.[6] Public health-oriented patent pooling can contribute to de-linking the cost of R&D funding from sales and a number of proposals have identified patent pooling as a way in which IP on new antibiotics could be managed in a public health-oriented manner.

Licensing to the MPP could similarly be included as a possible requirement in milestone prizes offered by different innovative R&D financing mechanisms. Indeed, should a large end-stage prize for the development of antimicrobials eventually be established, the MPP could play an important role as the mechanism to ensure equitable access and responsible stewardship, particularly in LMICs, by manufacturers for any new antimicrobial that is awarded an end-stage prize. For antibiotics that are meant to be kept as last resort or for limited use (e.g. *Watch* and *Reserve* categories*)*, additional incentives may be required for licensees to develop and manufacture them and make them available to those in need without largescale use that may result in the development of resistance.

The MPP could also work closely in collaboration with recent mechanisms established to support R&D for new antibiotics, such as CARB-X or GARDP. CARB-X, an initiative to stimulate the early-stage pipeline for antimicrobials targeting priority pathogens, has indicated that it would contractually require its grantees to develop an access and stewardship plan for its drug candidates that advance through the pipeline, and viewed licensing to the MPP as one key

[4] The Medicines Patent Pool Foundation. Exploring the expansion of the medicines patent pool[s mandate to patented essential medicines: a feasibility study of the public health needs and potential impact. https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf (accessed July 9, 2018)

[5] World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/ (accessed July 6, 2018).

[6] United Nations General Assembly. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. 2016. http://www.un.org/ga/search/view_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E (accessed July 6, 2018).

option for grantees to fulfil this requirement. Likewise, the Global Antibiotic Research & Development Partnership (GARDP) envisioned a role for MPP in AMR, both as a potential in-licensor of promising candidate compounds for further development, as well as a licensee of products successfully developed by GARDP.[7]

An access and stewardship licensing framework for the AMR context would build upon the substantial work that the MPP has already completed in exploring how stewardship-related practices could be integrated into its licensing model.[8] The development of such a framework would begin with the recognition that many of the most important measures for ensuring proper stewardship of new antimicrobials lie outside of the licensing context; for example, strengthening regulatory systems in LMICs, expanding the availability of proper diagnostics, and developing and implementing sound treatment guidelines will be key to achieving good stewardship but cannot be addressed in a license agreement with a manufacturer. However, MPP could nevertheless make an important contribution by addressing certain aspects of stewardship that can be influenced through licensing agreements, while contributing to facilitating access to needed new antibiotics in LMICs. Potential areas in which antimicrobial stewardship could be promoted through MPP licensing are explored further below:

- *Quality standards*

Ensuring that a drug meets quality standards, that it is safe and effective, contains the correct amount of active ingredient, has a stable shelf-life, and is manufactured in accordance with current Good Manufacturing Practices (cGMP) – is a central pillar of ensuring responsible antimicrobial stewardship[9]. In its licenses for HIV and HCV products, the MPP requires that all licensees manufacture the product in a manner consistent with WHO pre-qualification (PQ) or stringent regulatory authority (SRA) standards, or approval through an Expert Review Panel (ERP).[10] This is consistent with the standards used by the Global Fund, Unitaid and the Global Drug Facility (GDF). The MPP would continue to implement strict quality standards in any licenses for new antibiotics.

- *Release of active pharmaceutical ingredients into the environment*

[7] The Medicines Patent Pool Foundation. Exploring the expansion of the medicines patent pool's mandate to patented essential medicines: a feasibility study of the public health needs and potential impact. https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf (accessed July 9, 2018)

[8] The Medicines Patent Pool Foundation. TB Stewardship Report. 2016. https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf (accessed March 8, 2018)

[9] Laxminarayan R, Duse A, Wattal C, *et al.* Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; **13**: 1057–98.

[10] For example, the quality provision in the MPP-ViiV Form Sublicense for dolutegravir, in section 4.2, provides as follows: *"Licensee agrees that it will manufacture Raw Materials and Product in a manner consistent with (i) World Health Organization ("WHO") pre-qualification standards; or (ii) the standards of any Stringent Regulatory Authority ("SRA"), defined as regulatory authorities which are members, observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, as may be updated from time to time. Where such approvals are not yet available, the Licensee will obtain temporary approval through a WHO Expert Review Panel, as appropriate and if applicable."* A similar provision could be included in MPP licences covering other antimicrobials.

The O'Neill Review on AMR observed that improper treatment of wastewater by manufacturers of antimicrobial active pharmaceutical ingredients (APIs) and the resultant release of the APIs into the local environment can act as a "driver for the development of drug resistance, creating environmental 'reservoirs' of antibiotic-resistant bacteria." MPP licenses in antimicrobials could seek similar commitments from its licensees regarding environmental discharge and incorporate rigorous standards for acceptable levels of discharge once these are developed in the coming years.

- *Marketing and promotional practices*

It would be appropriate to have strict controls on the sublicensee's promotion and marketing for antibiotics that have been (or are likely to be) classified as "Watch" or "Reserve" in the WHO EML. In order to ensure that MPP sublicensees do not engage in inappropriate promotional activities, the MPP could, as part of its Expression of Interest (EOI) process, ask potential sublicensees to submit marketing plans that are in line, for example, with the recommendations in the WHO's Ethical Criteria for Medicinal Drug Promotion, or other relevant standards, and in line with national laws and regulations. Such plans could then become binding obligations as part of the licensing agreement.

- *Selection of licensees and affordability*

Unlike with MPP-licensed products with high sales volumes, such as medicines used in first-line HIV treatment, where the MPP seeks a large number of licensees in order to generate market competition, in antimicrobials the MPP may need to limit the number of licensees in order to better control the medicines' use in line with good stewardship. Under this practice, because the number of licensees – and thus competition – would be limited, there may be a need for additional measures to ensure that the end product is made available at an affordable price. This could be done, for example, by specifying a 'cost-plus' formula that establishes the maximum allowable price based on the manufacturer's production costs, while ensuring a sustainable profit margin for the licensee.

- *Definition of permissible buyers*

If guidelines such as the WHO EML recommend that an antimicrobial licensed to the MPP is used only in restricted settings (e.g. only in hospitals), it may be appropriate for the MPP to define in sublicence agreements the types of entities to whom sub-licensees may sell the product. This would be in line with the AMR Industry Alliance Roadmap, in which the signatories have committed to "collaborate with governments, their agencies and other stakeholders to reduce uncontrolled antibiotic purchase, such as via over-the- counter and non-prescription internet sales".[11]

- *Limitations on irrational combinations and use*

The inappropriate use of antimicrobials, including in irrational combinations, can contribute to the development of resistance. Recently, for example, an alarming proliferation of irrational

[11] Industry Roadmap for Progress on Combating Antimicrobial Resistance –September 2016. 2016.

fixed-dose combinations of antibiotics has been reported in India.[12] New antimicrobials may also have potential applications in veterinary use, but such use may not be conducive to good stewardship. In close consultation with the WHO and other experts, MPP licences could define permissible uses and permissible combinations.

Conclusion

While the patent pool model has so far only been applied to specific diseases, the model can be adapted to other areas beyond HIV, HCV or TB. As demonstrated in the case of HIV, non-exclusive voluntary licensing through a patent pool can be a cost-effective mechanism to enhance access to needed health technologies in developing countries and facilitate innovation, such as the development of needed formulations, such as medicines for children or new fixed dose combinations.

The increased focus on the need to respond to rising antimicrobial resistance will likely translate to a growing pipeline of new drug candidates to target priority pathogens in the coming years. Within the new categorization systems for antibiotics adopted in the Essential Medicines List in 2017 the MPP may be uniquely positioned to implement and enforce access and stewardship obligations which can contribute to support the appropriate use of antibiotics for newly developed antibiotics. Licences could be tailored to different antibiotics of public health priority depending on whether they fall under the Access, *Watch* or *Reserve* categories of the WHO. New incentive mechanisms for the development of new antibiotics could be linked to licensing via the MPP to support access and stewardship of the end of the product.

The MPP is already implementing, monitoring, and enforcing stewardship-related obligations in its current licenses with drug manufacturers in the fields of HIV, hepatitis C and TB. These practices include the careful evaluation and selection of licensees through its EoI system, strict quality requirements, and provisions for pharmacovigilance. Through these binding requirements and close monitoring of licensees' compliance, the MPP has demonstrated success in encouraging its licensees to adhere to such obligations. Further areas would likely need to be considered in the AMR context, as described above.

In the context of efforts to support the development of new antibiotics it is important that due consideration be given to ensuring that any new antibiotics of public health priority are available to those who need them in LMICs. Support to overcome innovation challenges in AMR should therefore integrate access considerations, as well as considerations relating to appropriate use, from the outset. Public health oriented licensing via the MPP can be a mechanisim to supporting these objectives, particularly if combined with incentives for the clinical development and manufacturing of new antibiotics.

[12] McGettigan P, Roderick P, Kadam A, Pollock AM. Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship. *Lancet Glob Heal* 2017; **5**: e1075–6.

Wellcome Trust

Interagency Coordination Group Consultation Paper 1 – response from the Wellcome Trust

This response sets out the views of the Wellcome Trust, responding to the work of the Inter-Agency Coordination Group (IACG) on Antimicrobial Resistance (AMR) in relation to R&D for new antimicrobials. We are a UK-based global charitable foundation, politically and financially independent, which has made a major multi-year commitment to supporting the global response to AMR.

Within this broader programme of work, we have committed up to $155m over five years to support antibiotic development through CARB-X, as well as a smaller contribution (£1m/$1.32m) to support the mobilisation of the Global Antibiotic R&D Partnership (GARDP). Our responses here thus draw on our role as one of the world's leading non-government funders of antibiotic R&D, as well as our organisation's wider, longstanding experience as a funder of biomedical R&D in other fields.

We commend the work of the IACG in developing this and other consultation papers, and we value the opportunity to comment on and provide input to such a vital process in the emerging worldwide response to the challenges of drug-resistant infections.

What will it take to increase and sustain donor and private funding of R&D in AMR?

Open funding partnerships which offer established, efficient, and effective routes for investment in AMR R&D can remove barriers to participation and facilitate the impactful use of increased donor funding. An example is CARB-X, which was established as a partnership with funding from the Wellcome Trust and the US Government Biomedical Advanced Research & Development Agency (BARDA), and now also includes funding from the Bill and Melinda Gates Foundation and UK Government. GARDP, initiated by the World Health Organization and Drugs for Neglected Diseases Initiative (DNDI) similarly provides a mechanism to direct donor funding towards prioritised R&D activities. While such initiatives have been highly effective over a short period (two to three years) in catalysing fresh activity in early stage antibiotic development, there remains both the scope and the need to substantially increase the scale of their activities and the resources made available to research in this area.

We recommend that the IACG should consider how it can encourage governments and other donors to utilise the opportunity afforded by the establishment of initiatives such as GARDP and CARB-X to make investments in R&D into new therapeutics for AMR via well-established vechicles..

While initiatives such as GARDP and CARB-X are providing important mechanisms to effectively direct donor funding towards R&D into new antibiotics, other crucial areas of R&D remain less well-served – across animal as well as human health. *The IACG should consider how other areas of AMR R&D might benefit from the development of platforms to support increased (and effective use of) donor funding.*

We believe that private sector participation in AMR R&D is necessary, and that the healthiest future for the field (and antibiotic development in particular) lies in having a sustainable balance between public, philanthropic and private investment and risk-taking. However,

private funding of R&D in the field (and in antibiotics in particular) is demonstrably hindered by low and unpredictable return on investment.

To enable an increase private investment, governments must consider a suite of policy interventions to decrease private funders' outlays by sharing R&D costs, and guarantee or increase the revenue from new antibiotics. Together with public and philanthropic funding, these actions can provide the incentives necessary to stimulate and sustain private investment. These incentives should be attached to certain conditions (mentioned below). In turn, increasing private investment in late-stage antibiotic development will give public and philanthropic donors the confidence to invest and support the highest risk, early stages of the pipeline.

There are already multiple initiatives in place to address gaps in R&D coordination and progress new incentive mechanisms for antimicrobials. These include action by the WHO, the G20, and the recently-established Global AMR R&D Hub (of which Wellcome is a member) and JPIAMR. We recommend that the IACG should focus on highlighting where there are substantial gaps in the remits of these initiatives, and seek to set out high-level principles which new incentive models and R&D coordination mechanisms should abide by to ensure that they meet global needs in an efficient manner.

Which incentives and de-linkage mechanisms could best address each of the challenges and barriers identified?

Challenge: cost of fundamental and preclinical research

The cost of scientifically complex fundamental and preclinical research needs to be shared between public and private funders through funding partnerships such as CARB-X. This will de-risk the riskiest and least commercially attractive stage of research, and populate the pipeline with antibiotic candidates.

Challenge: complex clinical trials

65% of the cost of bringing an antibiotic to market is related to clinical trials. This is because even those antibiotics intended only as back-ups must demonstrate clinical noninferiority, if not superiority, to current treatments. This requires the challenging task of identifying and enrolling large numbers of people with drug-resistant infections, when such populations are typically small, dispersed and difficult to enrol in trials.

To reduce this cost, funders and industry should develop and invest in innovative clinical trial models which lower the barriers to conducting trials – for instance through the establishment of global, standing clinical trial networks – without compromising patient safety or the robustness of the trial process.

Challenge: low return on investment for antibiotics

To increase private investment, public and philanthropic funders need to guarantee or increase the revenue from new antibiotics. This can be through policies that accelerate the regulatory pathway, extend market exclusivity or offer premium pricing, which are collectively termed lego-regulatory pull incentives, or via direct monetary contribution, known as outcome-based pull incentives.

Many different forms of pull mechanisms have been proposed, and it is likely that a mix of complementary incentives will prove the long-term outcome. Lego-regulatory pull mechanisms may be integral to this for some products or in some territories. But they run into issues given unpredictable demand and do not offer mechanisms to better enable access or strengthen stewardship because normal market forces deliver a return to industry.

Outcomes-based pull incentives potentially offer a highly effective mechanism to guarantee a return on investment to industry and, with appropriate calculation, can provide value-for-money for health service providers. These might include market-entry rewards (which offer large lump-sum payments to the successful developers of a new product meeting certain well-defined criteria) or insurance-based systems whereby healthcare systems pay for the right to access a product rather than for each unit they use. Importantly such incentives can be tied to mechanism to enable access and improve stewardship. Such models must be the priority for further development.

Any pull incentives which are developed should embody the following principles:

- An appropriate reward size that adequately incentivizes private-sector investment while not resulting in governments and/or health service providers overpaying.
- An appropriate balance of risk between the private and public sectors that incentivizes efficient development and encourages private investment.
- Prioritizing, through eligibility criteria or a tiered reward system, the development of antibiotics that meet the most urgent needs.
- Enabling stewardship through alternative reimbursement models independent of sales volumes, reward of positive marketing practices, or transfer of intellectual property to the public sector.
- Enabling availability and access by establishing manufacture and distribution of products and ensuring economic barriers to access are low

How should the design of incentive mechanisms be coordinated at global, regional and national levels?

Implementation of effective and efficient pull incentives, and the improved coordination of R&D efforts, will require some degree of global alignment and coordination. However, this alignment should still permit flexibility at the national or regional level, as well as recognising that national governments and other donors will often wish to maintain control over the use of their funds.

Multiple global initiatives and forums already exist to support the coordination, alignment and prioritisation of R&D efforts at a technical level (e.g. the JPIAMR) and the strategic level (e.g. the recently-established Global AMR R&D Hub.) This diversity of initiatives, in addition to the role of global groups such as the G20, can be considered to already provide an adequate basis for establishing the type of global coordination of incentive mechanisms outlined above. *The IACG should consider how and where the roles of these existing bodies and initiatives can be extended, and how any ongoing UN process for overseeing a global response to AMR can complement and strengthen their work, rather than duplicate it.*

Are there other mechanisms that should be considered to expand access to AMR-related health technologies and address the challenges identified?

If pull mechanisms are introduced to incentivise private investment in antibiotic development, they should be contingent upon adherence to strong access conditions. These conditions could address some of the barriers to access, including price, registration, and distribution, by making use of existing private sector capabilities.

Such access conditions should be developed in tandem with pull incentives. Given the current commercial environment, private investors may leave the AMR R&D space if they perceive that they may become subject to access-related liabilities without the security of adequate reimbursement.

As one example of this, the Medicines Patent Pool (MPP) has effectively worked with the private sector before to increase access. Mechanisms such as the MPP should be supported to explore whether they can apply their model to increase access to antibiotics, and funded to deliver this work if it is feasible.

The development of access plans needs to include a long-term continuity model to maintain availability of antibiotics once they go off patent, and also consider what steps can be taken by manufacturers, suppliers and distributors to support and incentivise proper antibiotic stewardship.

Access conditions, the MPP, and continuity models cannot address all the barriers to access. Governments and other funders need to support implementation research to identify delivery challenges and effective interventions to overcome them. *The IACG should consider how it can encourage global bodies and national governments to do more to identify and address system-level barriers to access to antibiotics.*

Should the mandates of one or several existing funds be extended to include AMR? Or should a new access initiative be created?

Ultimately the global community should support any initiative which can deliver sustainable, global, equitable access to innovative and established antibiotics. But the current political climate is more conducive to the consolidation, as opposed to fragmentation or proliferation, of global health initiatives. Given this, the extensions of existing institutional remits and funding streams seem a more viable approach than the establishment of new global bodies. *The IACG should use the opportunity presented by its report to the Secretary General to encourage national governments and relevant global institutions to go further and faster in building on existing initiatives and mechanisms, so as to address key strategic gaps in the AMR R&D landscape, and to support the identification of further funding to address remaining unmet needs (such as pull incentives) in this space. The building on existing initiatives should include a mandate to strengthening the approaches to achieve equitable access.*

London, July 2018

Wellcome Trust

Interagency Coordination Group Consultation Paper 2 – response from the Wellcome Trust

This response sets out the views of the Wellcome Trust, responding to the work of the Inter-Agency Coordination Group (IACG) on Antimicrobial Resistance (AMR) in relation to National Action Plans. We are a UK-based global charitable foundation, politically and financially independent, which has made a major multi-year commitment to supporting the global response to AMR.

Within this broader programme of work, we aim to support implementation of National Action Plans and enhanced global governance for AMR; for example, through activity such as the 'Call to Action' conference series, bringing together global representatives to encourage high level political dialogue and multi-sectoral collaboration. Our responses here thus draw on our role in facilitating partnership and advancing dialogues on key AMR issues to help move from discussion to implementation.

We commend the work of the IACG in developing this and other consultation papers, and we value the opportunity to comment on and provide input to such a vital process in the emerging worldwide response to the challenges of drug-resistant infections.

Mainstreaming

- **What scope is there to incorporate AMR into broader universal health coverage, international health regulations, sustainable development, food system and environment agendas?**

  There is scope to more strongly align AMR with the sustainable development agenda and Sustainable Development Goals (SDGs), particularly given that many of the SDGs are dependent on addressing AMR despite there currently being no AMR specific targets. There could be scope to create AMR specific targets to align with the SDGs, or even incorporate such targets into the goals themselves when they are reviewed.

  AMR could also be more strongly incorporated in the food system and environment agendas, particularly if we are to approach AMR in a truly 'one health' manner. While the FAO is a member of the tripartite, more could be done to mainstream AMR across other key players within the food system, particularly focusing on working with food producers and suppliers to enhance options for avoiding disease – whether in crops, livestock or fisheries – and alternatives to antimicrobials. *The IACG should consider ways to strengthen the one health approach embodied by the existing tripartite relationship, as well as considering how this can be extended – possibly by inclusion of the UN Environmental Programme (UNEP) as an additional member.*

- **What forces maintain national responses to AMR in silos, and how can we overcome them?**
  Breaking down of silos could be supported through appointment of champions prioritising and promoting AMR on a national level. Such leaders should have

oversight of national activity and a clear mandate to identify and join up activity from across sectors and silos. At a national level, leadership from the top of government – a Prime Minister or President, for instance – can be a highly effective means to break down siloes between policy-making departments. Senior buy-in to National Action Plan implementation within governments is essential to resolve competing interests between different parts of government, and ensure adequate accountability and financing for implementation of truly 'one health' strategies. *The IACG should consider how a UN-led process can support more consistent buy-in from heads of government as champions and leaders of national-level action against AMR.*

Financing

- **What support do countries need to translate information on the global impact of AMR into a country-specific case?**
  The economic case for acting on AMR has been firmly established through the work of the Review on AMR, and subsequently by the work of the World Bank. These projects have set out clearly that AMR represents a threat to global economic prosperity and development, although have not in general sought to identify macroeconomic impacts at a country level. However, while this economic evidence of the *need* to act is compelling, it does not assist global and national-level policy-makers in the prioritisation of interventions to tackle AMR.
  We suggest that the IACG should seek to encourage a focus amongst researchers on building the economic evidence base about the effectiveness and cost effectiveness of policy measures to tackle AMR at a national and global level, in preference to continued exploration of the macroeconomic impact of inaction. This will help ensure that policy-makers are able to make better decisions about the prioritisation and funding of measures to combat AMR.

- **Which elements of basic scientific understanding most urgently require work to ensure a strong, evidence-based policy and investment platform? (For example, mechanisms of resistance, the One Health epidemiological model of attribution for resistance development and transmission, or the economic model of impact and potential benefit?)**
  In LMICs in particular, efforts to take prioritised and evidence-based action against AMR will frequently be significantly challenged by gaps in national-level understanding of the primary causes of the development of drug resistance and their modes of transmission (within and between sectors.) Improvements to surveillance, and the strengthened evidence for decision-making that this will provide, will therefore provide significant benefits to national governments and their partners in the implementation (and monitoring) of national action plans. *The IACG should emphasise the importance of this element of scientific understanding in informing the national and global policy response to drug resistance.*

The Wellcome Trust very much looks forward to the publication of recommendations form the IACG and is committed to supporting their development and implementation over the next year and into the future.

London, July 2018

Interagency Coordination Group Consultation Paper 3 – response from the Wellcome Trust

This response sets out the views of the Wellcome Trust, responding to the work of the Inter-Agency Coordination Group (IACG) on Antimicrobial Resistance (AMR) in relation to Surveillance and monitoring for antimicrobial use and resistance. We are a UK-based global charitable foundation, politically and financially independent, which has made a major multi-year commitment to supporting the global response to AMR.

Within this broader programme of work, we run a number or initiatives focused on generation and sharing of epidemiological and surveillance data, including establishment and ongoing support for the Surveillance and Epidemiology of Drug Resistant Infections Consortium (SEDRIC) and facilitating the greater use of open surveillance data to improve our understanding of the development and spread of drug-resistant infections. Wellcome is working closely with the UK Government's Fleming Fund, and the Bill and Melinda Gates Foundation as co-funders of the AMR components of the major Global Burden of Disease project. In addition, Wellcome is supporting the Open Data institute to engage with the pharmaceutical industry to facilitate open sharing of otherwise proprietary post-marketing patient-level surveillance data generated by companies.

Acknowledging the need to address AMR via a 'One Health' approach, and considering that there are still many gaps in our scientific understanding of AMR transmission between animals and humans, we are currently supporting the California Senate Bill project, led by George Washington University, which is assessing (via the collection of genome sequencing and the monitoring of health records) the impact of introducing a ban on non-therapeutic antibiotic use in livestock on the emergence of resistance and human health.

Our responses here thus draw on our role as a key funder, partner and facilitator of surveillance and monitoring initiatives.

We commend the work of the IACG in developing this and other consultation papers, and we value the opportunity to comment on and provide input to such a vital process in the emerging worldwide response to the challenges of drug-resistant infections.

Integration

- **What are the opportunities for, and obstacles to, integrating data analyses within and across sectors?**
  A considerable volume of AMR-relevant data is available globally, however standards for collection often differ significantly both within and across sectors meaning integration of data is not readily possible. There is a need to drive progress in the development of shared global protocols for data collection, for which integration is likely required. At their core, such protocols should focus upon identifying key, common metadata which allow inferences to be drawn about levels of pathogen resistance across different countries and settings. The ultimate aim should be to generate datasets that are fit for purpose to allow the monitoring of the development and spread of drug-resistant infections on a global scale.

- **How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?**

  At present, systems for collecting and utilising surveillance data frequently operate in siloes across the human, animal and plant health sectors. Communication and collaboration between these sectors – nationally, regionally and globally – needs to be significantly improved in order to improve our collective understanding of AMR and embody a true 'one health' approach. The IACG should promote opportunities for these barriers to be broken down, and to establish high-level protocols which promote (and where necessary enforce) the routine sharing of relevant surveillance data in common and standardised forms between different sectors.

- **How can initiatives involving surveillance data held in the private sector be integrated into global, public reporting systems?**
  Significant volumes of data are generated in the private sector – particularly by pharmaceutical companies working in human health, but also in hospitals and other private healthcare facilities – which could be of practical use to improve surveillance of drug-resistant infections. Many companies have already committed to releasing such data to support public health surveillance efforts, as part of the September 2016 'industry roadmap', now being taken forward by the work of the AMR Industry Alliance.
  Wellcome is already working with the Open Data Institute, Institute of Health Metrics and Evaluation (IHME) and a small number of global pharmaceutical companies to identify practical opportunities for (and barriers to) sharing post-marketing surveillance data in an open way to benefit the wider public health community. This work has identified that more remains to be done to establish appropriate platforms and governance arrangements to support the routine sharing of this data by a broader range of companies.
  The IACG should consider endorsing these and other voluntary efforts by the private sector to share data of relevance to AMR surveillance, and encourage more companies to go further and faster in opening up the data that they currently hold. Beyond these voluntary efforts, the IACG should consider asking governments, regulators and other actors globally to consider how they can do more to either encourage – or even mandate – companies to make more accessible the surveillance data they generate, where there are compelling benefits to that data being in the public domain.

Prioritization

- **What further support do countries that are establishing surveillance systems need (in addition to existing tools) to implement a national surveillance system for AMR and AMU?**

  There is need for the development and dissemination of **standardised methods of data collection and analysis** to strengthen the way AMR and antimicrobial usage are recorded in clinical and community settings, including agriculture usage. Global norms and best practice should be established and embedded within national-level AMR action plans.

  There is an urgent need for systematic capacity development based on **training** modules that are tailored to the local country context. Training should not be a one

off undertaking – but should be designed to allow refresher courses to keep pace with changing technology / tools which might need to change based on changing AMR levels and disease epidemiological patterns. *The IACG should highlight a continued emphasis on such training as a key component of effective National Action Plans, and encourage donors and development agencies globally to play a greater role in supporting capacity building in this respect.*

Comparability

- **What support do Member States need to strengthen national surveillance systems and improve the quality, collection and submission of their data to global surveillance databases?**

  Countries that have surveillance systems in place would need to develop tools that support data capture, standardisation and harmonisation to increase data quality and depth, and to generate additional knowledge. Surveillance is only possible and effective in countries where the laboratory systems are well developed. A global standard needs to be established for what is or is not a standard microbiology laboratory for AMR collection. Member states where laboratory systems are lacking should be supported to develop this area.

Availability

- **What data formats and visualization tools are most useful for reporting and further analysis?**
  Maps and tools for presenting data can be very powerful. However the IACG should advocate for the principle that wherever possible, raw data should be made available to relevant public health communities and bodies, rather than just post-analysis summary, aggregated or processed data.

Sustainable investment

- **How can countries be supported in doing economic case studies to demonstrate the costs and benefits of surveillance and to attract investors?**
  There have been studies and publications looking at the economic case for surveillance primarily for pandemic preparedness. However, this has not been linked to AMR in terms of death avoided and burden alleviated. Considering that human death attributed to AMR is not well documented and at times missing (with the cause death attributed to the underlying disease rather than the infection), countries should in the first instance have agreed ways of capturing and recording causes of death, including co-morbidities, nationally.

- **What role can the private sector play in financing surveillance?**

  The private sector can play a vital role in supporting the development of innovations and technologies that can be embedded within national and global surveillance

systems. Working in a private public partnership would help modernise surveillance systems in place while making sure data captured is of high quality and impact.

The Wellcome Trust very much looks forward to the publication of recommendations form the IACG and remains committed to supporting their development and implementation over the next year and into the future.

London, July 2018