Investing in the Development & Conservation of New Antibiotic Treatments: DNDi’s Engagement
Origins of DNDi

1999
- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND Working Group
- JAMA article: ‘Access to essential drugs in poor countries - A Lost Battle?’

July 2003
- Creation of DNDi
- Founding partners:
  - Institut Pasteur, France
  - Indian Council of Medical Research, India
  - Kenya Medical research Institute, Kenya
  - Médecins Sans Frontières
  - Ministry of Health, Malaysia
  - Oswaldo Cruz Foundation/Fiocruz, Brazil
  - WHO – TDR (Special Programme for Research and Training in Tropical Diseases) as a permanent observer

AMR: In turn, DNDi is ready for history to repeat itself based on what we have learned.
Address Immediate Patient Needs & Deliver Innovative Medicines: Short- and Long-term

Long-term projects
- New chemical entities (NCEs)
- New formulations
- New indications for existing drugs

Medium-term projects
- Completing registration dossier
- Geographical extension

Short-term projects
- Research: > 5 years
- Translation: 3-5 years
- Development: 1-2 years
- Implementation: 1-2 years
In a decade of R&D, 6 new treatments delivered

- 30 projects, 6 diseases areas
- 15 entirely new chemical entities (NCEs)
- Over 130 partnerships, most in endemic countries
- 150 staff, half in endemic countries & 600 people working on DNDi projects
- Over EUR 350 million raised equally from public and private sources
- 3 regional disease-specific clinical trial platforms and 2 technology transfers

✓ Easy to use
✓ Affordable
✓ Field-adapted
✓ Non-patented
DNDi Portfolio: A mix of existing drugs & NCEs

6 new treatments delivered
15 NCEs

- **HAT**
  - Nitroimidazoles
  - Oxaleish
  - Amino pyrazoles
  - Leish H2L
  - SCYX1330682
  - SCYX1608210

- **Leishmaniasis**
  - Nitroimidazoles
  - Fexi sulfate
  - Fexi/MF combo
  - New treatments for HIV/VL
  - PKDL Asia/Africa
  - New VL Treatments Latin America

- **Chagas**
  - Chagas H2L
  - Biomarkers
  - New Benz Regimens/Combos
  - Fexinidazole

- **Filaria**
  - Macro Filaricide 2
  - Emodepside

- **Paediatric**
  - HIV
  - Two ‘4-in-1’ LPV/r based FDC granules
  - LPV/r pellets with dual NRTI FDC
  - Superbooster HIV/TB

- **Mycetoma**
  - Fosravuconazole

- **Malaria**
  - ASAQ FDC
  - Artesunate-Amodiaquine
  - ASMQ FDC
  - Artesunate-Mefloquine

- **New NCEs**
  - NECT
    - Nifurtimox-Eflornithine Combination Therapy
  - SSG&PM
    - Africa
  - New VL Treatments
    - Asia

- **Research**
  - Screen
  - Hit to Lead
  - Pre-clinical
  - Phase I
  - Phase IIa/PoC

- **Development**
  - Phase IIb/III
  - Registration
  - Access

- **Implementation**
  - NECT
    - Nifurtimox-Eflornithine Combination Therapy
  - SSG&PM
    - Africa
  - New VL Treatments
    - Asia

- **HIV**
  - New Benz Regimens/Combos
  - Fexinidazole

- **SCYX1330682**
  - SCYX1608210

- **Nitroimidazoles**
  - Fexinidazole

- **Fexi sulfate**
  - Fexi/MF combo

- **New treatments for HIV/VL**
  - PKDL Asia/Africa
  - New VL Treatments Latin America

- **Leish H2L**
  - SCYX1330682
  - SCYX1608210

- **Oxaleish**
  - SCYX7158

- **Amino pyrazoles**
  - CPGD35 (CL)

- **Anfoleish (CL)**
  - New CL combos

- **New CL combos**
  - New VL Treatments Latin America

- **Benznidazole**
  - Paediatric Dosage Form

- **Biomarkers**
  - Fexinidazole

- **Biomarkers**
  - Emodepside

- **Macro Filaricide 2**
  - Two ‘4-in-1’ LPV/r based FDC granules

- **Superbooster HIV/TB**
  - LPV/r pellets with dual NRTI FDC

- **Fosravuconazole**
  - Fosravuconazole
DNDi’s success is only possible through innovative partnerships.

**CRITERIA FOR SUCCESS**
- Share the same vision
- Mutual understanding
- Involvement throughout the whole process
Industrial Partnerships at All Stages of Development

Research
Screen Hit to Lead Lead Opt. Pre-clinical Phase I Phase IIa/PoC Phase IIb/III Registration Access

Development

Translation

Implementation

HAT
- AbbVie
- Advinus
- Anacor
- Astellas
- AstraZen.
- Bayer
- BMS
- Eisai

Leishmaniasis
- AbbVie
- Advinus
- Anacor
- Astellas
- AstraZen.
- Bayer
- BMS
- Eisai
- GSK
- MSD
- Novartis
- Pfizer
- Sanofi
- Shinogi
- Takeda

Chagas

Filaria
- AstraZen.
- Astellas
- Bayer
- BMS
- J&J
- Novartis
- Pfizer
- Sanofi

Paediatric HIV

Mycetoma

Malaria

AbbVie
- Cipla

Eisai

Bayer
- Gilead
- Gland Pharma
- Lafepe
- Sanofi
- Mundo Sano /ELEA

AstraZen.
- Astellas
- Bayer
- J&J
- Novartis
- Pfizer
- Sanofi

Abbott
- J&J

Scynexis

Eisai

Gilead
- Gland Pharma
- Sanofi

GSK
- MSD
- Novartis
- Pfizer
- Sanofi
- Takeda

AbbVie
- Advinus
- Anacor
- Eisai
- Scynexis

Astellas
- Gilead
- Gland Pharma
- Sanofi

BMS
- GSK
- MSD
- Novartis
- Pfizer
- Sanofi
- Takeda

AbbVie
- Advinus
- Anacor
- Eisai
- Scynexis

AstraZen.
- Astellas
- Bayer
- J&J
- Novartis
- Pfizer
- Sanofi

Abbott
- J&J

Cipla

Farmanguinhos
- Cipla
- Zenufa

Sanofi
- Cipla
- Zenufa
Combating malaria resistance: 2002 WHO recommendations

ASAQ FDC: > 400 Million Treatments Distributed

- Pre-qualified by WHO in 2008
- <1 USD for adults, < 0.5 cents for children
- Easy-to-use, non-patented
- Registered: 30 African countries, India, Ecuador, Colombia
- First Risk Management Plan with MMV and Sanofi
- Transfer of technology to Zenufa (Tanzania)

In partnership with Sanofi
Creating large-volume drug screening capacity: Institut Pasteur Korea

- Access to screening capacity (HCS technology) for VL and Chagas since 2008
- >1.5 Mio compounds screened to date in collaboration with multiple Pharma partnerships
e.g. for VL and Chagas: 20,000 compounds/month
- Pasteur expertise in infectious diseases
- Technology developed as a public good

Automated image analysis on Operetta
Exploring more open, collaborative drug discovery models

- A shift from bilateral to **multilateral collaboration**
- Companies working together on a **shared project**
- Ownership and intellectual property rules agreed in advance
- Three year countdown to launch in April 2015
- Project now underway and new companies ready to join
Partnering and research capacity building with MoHs and National Control Programmes

Major Role of Regional Disease Platforms:

- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
- Defining patients’ needs and target product profile (TPP)
For each disease, a Target Product Profile to guide all decisions (example of paediatric HIV)

**IDEAL CHARACTERISTICS (TPP)**

- 4 ARVs in one
- Simple to open and use with water, milk, food
- Good taste
- No fridge needed
- Suitable for infants (<2 months - 3 years)
- TB-treatment compatible
- Affordable for governments
Our new Business Plan 2015-2023:
A dynamic approach to address patient needs

Pipeline focus can quickly be adapted to:

• stay aligned with changes in the environment

• rapidly respond to urgent patient needs

• address specific regional needs

Disease Portfolio

New Opportunities

Completion & exit
Most neglected diseases remain at the core, with new diseases taken on progressively.

<table>
<thead>
<tr>
<th>Portfolio</th>
<th>Disease areas</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current portfolio</td>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric HIV</td>
<td></td>
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<tr>
<td></td>
<td>HAT</td>
<td></td>
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<td></td>
<td>Chagas</td>
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<td></td>
<td>Filariasis</td>
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<tr>
<td></td>
<td>Leishmaniasis</td>
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<td></td>
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<tr>
<td>New diseases</td>
<td>Hepatitis C</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Mycetoma</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>Potential diseases (illustrative)</td>
<td></td>
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</tr>
</tbody>
</table>

Legend:
- Full portfolio (multiple projects at different phases)
- Development
- Implementation
- Disease strategy complete
- Incubator

DNDi (Drugs for Neglected Diseases initiative)
How we will do it… operationally

**Idea sourcing**
- Consultation Process

**Idea translation**
- Exploratory
- Feasibility
- Concept validation

**Selection of appropriate model**
- Include in DNDi Portfolio (Full or mini)

**Implementation of disease programmes**
- **FULL PORTFOLIO**
  - Research
  - Development
  - Implementation
  - €100 + million
- **MINI PORTFOLIO**
  - ~ €25 million
- **SUPPORT**
  - Up to €1 million

**Range of support models**
- **Light role**
  - Knowledge sharing
  - Advocacy push
  - Advisory role
- **Active role**
  - Build resource platform
  - Incubator

**Patients’ needs**

**Implementation & exit**
Next steps for DNDi to incubate the facility

- Board decision in December 2015: go/no go

- Need for securing political support and stakeholder input

- We are prepared to incubate the Facility, in the same way MSF incubated DNDi, and WHO/TDR incubated FIND and MMV

THANK YOU!
Investing in the Development & Conservation of New Antibiotic Treatments
Global Antibiotic Research & Development Facility

Vision and Strategy
In cooperation with the public and private sectors:

• *develop new antibiotic treatments* addressing AMR
• *promote their responsible use* for optimal conservation
• *while ensuring equitable access* for all

by setting up a not-for-profit product development partnership that will focus on *global health needs*, while ensuring any new product is *adapted to resource-limited settings*. 
The context

- Lack of sufficient **investment and incentives** for the development of antibiotic treatments
- WHA GAP requests WHO Secretariat to work on the creation of **new partnership(s) to address R&D gap**
- Many initiatives have been launched, but overall remain insufficient: **complementarity is key**
- Market-driven approaches are not structured to address **responsible use** and some of the unmet needs
The Role of WHO

- Take part in the set-up of the new partnership
- **Report on the antibiotic pipeline** to feed into the Global Health R&D Observatory
- Provide input on **priority setting**, target product profiles and overall direction
- Facilitate coordination with other initiatives, e.g. G7 global network meeting of researchers and experts in 2016/17
- Develop and pilot conservation approaches
- Develop options for a global framework for development and conservation (WHA68.7)
## Existing & upcoming AMR R&D initiatives

<table>
<thead>
<tr>
<th>Task</th>
<th>Developer</th>
<th>Developer/ Funder</th>
<th>Funder</th>
<th>Funder</th>
<th>Funder</th>
<th>Funder</th>
<th>Funder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Focus</td>
<td>Product develop.</td>
<td>AMR basic research Prod. Develop.</td>
<td>Early stage research &amp; early stages of product develop.</td>
<td>Product development (market entry rewards)</td>
<td>AMR Basic &amp; preclinical research product develop.</td>
<td>Product develop.</td>
<td>AMR Basic research Product develop.</td>
</tr>
<tr>
<td>Specific public health needs</td>
<td>Global health needs &amp; suitability for resource poor settings</td>
<td>Based on WHO’s priority medicines report</td>
<td>Yes</td>
<td>Rewards linked with unmet global needs</td>
<td>JPI AMR Strategic Research Agenda</td>
<td>Unmet medical need in US</td>
<td>Medical needs in Europe &amp; globally, incl. LMIC</td>
</tr>
<tr>
<td>Products submitted to conservation strategies?</td>
<td>Yes</td>
<td>No</td>
<td>--</td>
<td>Yes, rewards linked with stewardship</td>
<td>No</td>
<td>Possible for ‘pull incentives’</td>
<td>--</td>
</tr>
<tr>
<td>Target product profiles?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Possibility to link with other initiatives?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>If eligible under EU programme</td>
</tr>
</tbody>
</table>
Guiding Principles

1. Antibiotic development should be financed partly through a global funding mechanism and should experiment new models for conservation and access.

2. Sustainable investment should be coordinated at country and international levels.

3. R&D should focus on the significant bacterial infections with an emphasis on global needs.

4. Scientific relevance shall guide choices.

5. New antibiotics must be affordable for all and subject to a global conservation agenda.
Three-Pronged Approach

1. Research and Development
   - Conduct antibacterial research both with academia and the private sector, including paradigm-shifting approaches for antibiotic treatments.
   - Support rapid and (near) point-of-care diagnostics as an essential component of the product development strategy.

2. Conservation
   - Implement and test new incentive models, including de-linkage of R&D cost from price of product, to support responsible use initiatives.

3. Access
   - Promote equitable, responsible access: ensuring access to all in need, while minimizing unnecessary use.
Short-Term Goals

1. Identify needs, gaps, top priorities for development of new antibiotics/antibiotic regimes unaddressed by other actors, ensure complementarity

2. Establish partnerships with existing R&D networks

3. Launch short-term projects to deliver needed therapeutic solutions (e.g. appropriate paediatric formulations or improved regimens of existing antibiotics)

4. In doing so, immediately test existing conservation and access proposals applied to short-term projects.
Long-Term Goals

1. Build, with partners, a solid antibiotic R&D portfolio to respond to longer-term needs to address AMR

2. Support the framework for the effective conservation (stewardship) of antibiotics, with WHO and countries

3. Secure funding sources to sustain continuous pipeline replenishment and test incentive mechanisms
Deliverables and Timelines

Five-Year Plan
Years 1-2

• Set up a core team and working network of public and private partners
• Finalize a business plan and establish budget for a minimum of five years
• Engage additional founding partners and funders for long-term support

• Establish **priority target product profiles** (TPPs)
Years 1-2 continued

- Establish governance, including scientific advisory board and international network of scientific experts
- Set up a independent legal entity
- Identify short- and long-term research projects
- Initiate 1-3 short term projects, for example:
  - improved paediatric formulations (form, dosage, shelf-life)
  - new formulations of existing drugs (appropriate dosage, administration route)
  - combinations of existing drugs to address AMR
  - establish feasibility of innovative projects (e.g. adjuvants’, anti-virulence, dormancy breakers)
Years 3-5

- Continue initiated short-term projects and implement new projects
- Implement the business plan, including funding of innovative R&D proposals and of pilot conservation projects
- Secure long-term funding
- Launch long-term projects, for example:
  - combination screening platforms
  - platform for improved formulations;
  - support disruptive scientific approaches (e.g. anti-virulence)
Start-up and launch: no time to waste

Seed funding of 3+ million USD is required for:

Within 2 years, to become an independent organization focused on providing tools to fight AMR

- 4-6 FTEs for core team (DNDi to provide 1 FTE and infrastructure)
- Raise further funding for new projects
- Set up initial projects

START-UP PHASE
People and Projects

~

2 Yrs

3-5 Yrs
What commitments are needed today?

- Financial and political support – steering role
- Contribution of expertise – working groups
- Partnerships with your ongoing initiatives – complementarity!

Thank you!
Review of possible funding/incentive mechanisms and opportunities

TECHNICAL CONSULTATION JOINTLY HOSTED BY THE WORLD HEALTH ORGANIZATION AND THE DRUGS FOR NEGLECTED DISEASES INITIATIVE

November 13, 2015

John-Arne Røttingen
Norwegian Institute of Public Health
University of Oslo
Harvard T.H. Chan School of Public Health
Our understanding of the Partnership’s Proposed Scope

• Address global public health and specific needs of developing countries, targeting products that industry will not undertake due to lack of profitability, for example:
  – Pediatric formulations
  – Combination therapies for Typhoid fever
  – New chemical entity for melioidosis
  – New chemical entity for gonorrhea (for HIV-positive)

• Ensure that new antibiotics are affordable to all and are subject to a global conservation agenda

• NOT novel antibiotics targeted for high income markets
There is a role for global public goods, especially for incremental innovation.

prescribed separately, the two drugs together would cost no more than $20 or $40 a month. By contrast...[the new combination pill]...costs about $1,500 a month."
Focus on antibiotic innovation

To produce analysis of the global problems of antimicrobial resistance (AMR), and to propose concrete actions to tackle these internationally.

To explore novel economic strategies and reward models both to promote the development of new antibiotics and to bolster appropriate consumption of existing antibiotics.
Convergence of principles

- Need for both “push” and “pull” mechanisms
- Delinkage (i.e., revenues delinked from volumes sold) built in
- Access and responsible use are integral considerations for all mechanisms
- Global collaboration and financing necessary
R&D allocation mechanisms

Push mechanisms

- Grants
- Milestone prizes
- Subsidies
- Tax breaks
- Open knowledge innovation

Pull mechanisms

- Public-Private Partnerships
- Advance Market Commitment (AMC)
- Milestone and end prizes
- Volume guarantees
Trends in antibiotic consumption

“Two trends are contributing to a global scale-up in antibiotic consumption. First, rising incomes are increasing access to antibiotics. That is saving lives but also increasing use—both appropriate and inappropriate—which in turn is driving resistance. Second, the increased demand for animal protein and resulting intensification of food animal production is leading to greater use of antibiotics in agriculture, again driving resistance.”

CDDEP’s The State of the World's Antibiotics Report, 2015
New paradigm in financing

• Existing health R&D financing mechanisms are either:
  – Financed through development aid
  – Focus on stimulating national/regional research with no agreed priority-setting and no linkages to responsible use and access

• Yet for this model:
  – Greatest need in middle-income countries
  – Advantages for all countries regardless of economic status (e.g., combination therapies, pediatric formulations, etc.)
  – Advantages across diseases (e.g., diagnostics for fever)
Current financing environment

• Need to build on existing mechanisms and organizations
• DNDi has 10+ years experience developing drugs for neglected diseases.

• Landscape already contains BARDA, JPIAMR, IMI, UK-China Fund, Wellcome Trust
• None focus specifically on the needs of LMICs, where resistance is growing fastest.
Financing – raising funds
## Potential financing

<table>
<thead>
<tr>
<th>Payer</th>
<th>Mandatory</th>
<th>Voluntary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals</td>
<td>Tax</td>
<td>Gifts, donations, voluntary levies on tickets, phone bills etc.</td>
</tr>
<tr>
<td></td>
<td>• Direct</td>
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<tr>
<td></td>
<td>• Indirect – Sales taxes, “Sin taxes”, Antibiotic consumption, Airline tax</td>
<td></td>
</tr>
<tr>
<td>Companies</td>
<td>Corporate tax</td>
<td>• Investment based upon expected ROI</td>
</tr>
<tr>
<td></td>
<td>Financial transaction tax</td>
<td>• Corporate social responsibility</td>
</tr>
<tr>
<td>Countries</td>
<td>Legally binding agreements Membership fees</td>
<td>Political allocation</td>
</tr>
</tbody>
</table>


Potential financing sources

Base financing:

- Voluntary governmental and/or foundation financed

Investor-based financing:

- Social impact bonds based upon revenues from patented technology contracts in high and middle income countries
- Licensing revenues from private companies (with stipulations regarding responsible use and access)
- Loans from EIB’s IDFF

Grant-based research funding:

- Apply for funds from BARDA, JPIAMR, IMI, UK-China Fund, UNITAID, Wellcome Trust
Investing in the development of new antibiotics and their conservation: A proposal for a global antibiotic research and development facility

Dr Manica Balasegaram, Executive Director
MSF Access Campaign, November 2015
MSF and AMR

MSF can no longer safely assume the efficacy of simple antibiotics

• Bacterial infections one of the most common presentations in MSF projects
  – Including lethal invasive bacteria infections (IBI) such as bacteremia, meningitis, pneumonia and dysentery

• Risk of ineffective initial antibiotic treatment higher in MSF set-ups
  – Patients present later, with advanced disease, fewer safety nets for those inappropriately managed

• Antibiotic resistance (ABR) has emerged in most contexts where MSF works

• ABR is growing in severity; all regions of the world are affected to varying extents
  – High, middle and low IC countries affected
  – Many of the gaps in ABR surveillance exist where MSF operates
  – This in turn makes it difficult to understand true needs and gaps
Key problems

• Field surveillance

• Diagnostics
  – Especially to promote rationale use

• Drugs
  – Better formulations, combinations, regimes and new treatments/protocols where there is resistance
Key problems: diagnostic tools

In the field settings MSF cannot diagnoses bacterial infections with a high degree of sensitivity or specificity

Not enough national data exists to guide empirical choices

Lack of tools to distinguish bacterial infections from mycobacteria and non bacterial pathogens (eg viruses, parasites)
Cannot distinguish infections caused by sensitive / ABR bacteria

Microbiological capacity very limited in most MSF contexts (eg gram stain or blood culture not available)
Key problems: drugs

Marked increased in broad-spectrum antibiotics use:
- 3rd generation cephalosporins: ceftriaxone
- Fluroquinolones: ciprofloxacin
- β-Lactam/β-lactamase inhibitors: amoxicillin-clavulanate

This strategy has major costs:
- May drive further ABR
  - Most children leaving MSF ITFC are colonized with ESBL-producing gram negative bacteria (Niger, 2011)
- Unsustainable “arms race”
  - Bacteria evolve new resistance mechanisms
  - Highly ABR strains emerging in L&MICs eg Enterobacteriaceae strains expressing NDM-1
  - Few antibiotics in the development pipeline

However, improving access & patient care is our priority!
Recent MSF field experience

CNS infection study, Mbarara, Uganda (2011)
• S pneumo with intermediate sensitivity to PCN, resistant to cotrimoxazole
• H influenzae resistant to amoxicillin, chloramphenicol
• ESBL E coli and Kleb pneumo
• Salmonella typhi resistant to cipro

Diarrhea, Niamey & Maradi, Niger (2009)
ESBL Salmonella documented
1/3 bacteria were resistant to all antibiotics available in Niger
What is needed?

- Strong global health perspective: defined priorities, TPPs etc
- Monitoring & surveillance
- Diagnostics (new tools, improved lab capacity)
- Updated guidelines and policies (international and national)
- Education and local capacity
- Regulation
- Rational use linked with access strategies
- Coordinated procurement and supply
- Appropriate uptake, compliance
- Clinical research capacity and platforms
- Alternative incentives to promote innovation and conservation
What is needed?

Issues for the facility

- Strong global health perspective: defined priorities, TPPs etc
- Monitoring & surveillance
- Diagnostics (new tools, improved lab capacity)
- Updated guidelines and policies (international and national)
- Education and local capacity
- Regulation
- Rational use linked with access strategies
- Coordinated procurement and supply
- Appropriate uptake, compliance
- Clinical research capacity and platforms
- Alternative incentives to promote innovation and conservation
The facility: scientific added value

- R&D that will not be taken by other actors; improved formulations, combinations and updated dosing schedules – DNDi already has a track record
- Focus on specific diseases, especially where trials needed in LMIC context
- Potential focus on upstream ideas where risk taking can be encouraged
- PDPs (eg DNDi) have significant space to work on research, policy and early implementation in tandem with others including WHO and multilaterals (GF, UNITAID)
The facility: conservation and access

- Critical to have strong focus on LMIC and most vulnerable population access
- Diagnostics key in improving rationale use
  - improved integrated approach of fever management can significantly aid conservation
- Key role of essential medicines list (to ensure best policy) and WHO PQ (to promote uptake of best quality products)
- Facility could play similar role to The GDF for TB drugs (eg linking drug demand to supply and monitoring)
- Specific country level strategies need to be developed through further consultations
- Traditional incentive systems do not work: conservation & access promoted by different model based on de-linkage. Plenty of proposals that are ready for implementation!
The facility: set up

Real potential to develop a facility that will be global health focussed

Governance is key:
• Mandate and involvement of WHO but outside formal WHO structure (for flexibility)
• DNDi board/SAC serving as starting models (and allows time to develop the final governance structure)
• Governance not just a round table of donors
  – Independence must be ensured
  – Needs to ensure stays true to mission; takes and mitigates risks
  – Needs to provide required strategic technical and political input
  – Developing country presence is important
  – Technical expertise from a wide range of actors

Financing:
• Long term and sustainable
• Country commitments & contributions
Challenges for the facility

• Good understanding of needs and gaps for developing countries
  – Implementation of all aspects of GAP is therefore important to ultimately drive R&D agenda

• Political support and member state buy-in
  – Willingness of global health community and member states to implement something different to go beyond just talking about “alternative business models”
  – Sustainable, long term financing (including from developing countries)

• Identifying and implementing conservation strategies
  – Link with WHO critical
  – Important that WHO also has member state’s support to play a key role in AMR

• Creation of an open source and knowledge innovation model
When are we entering the post-antibiotic era?

For some diseases we have already entered!

Fatal pneumonia because antibiotics are not working (K. pneumomiae)

Fatal infection with Neisseria gonorrhoeae
13/38 countries reported inter-regional spread of or an endemic situation for CPE
What is the cost of not taking action?

By 2050, AMR could lead to

- 10 million deaths every year
- reduction of 2%-3.5% in GDP globally

AMR Review

Between now and 2050, the world can expect to lose US$ 600 to US$ 100 trillion worth of economic output
Global Action Plan on Antimicrobial Resistance
One year in development

World Health Assembly, May 2014
Requests the Director General to develop a global plan

WHO leads development of the plan, May to Dec 2014
With advice from experts, Member States, forums and web consultations

WHO Executive Board, Jan 2015
Expresses strong support to take plan to World Health Assembly

World Health Assembly, May 2015
Adopts the Global Action Plan – over 50 supporting statements
Passes new resolution to support action – over 60 country sponsors
Increase in WHO organization-wide budget for AMR

Global action plan on antimicrobial resistance
Financial projections for 2016-2017: distribution by WHO Regional Office

Total: USD 53,792,873
Five strategic objectives:

1. Improve awareness and understanding (WAAW)
2. Strengthen knowledge through surveillance & research
3. Reduce the incidence of infection (IPC)
4. Optimize the use of antimicrobial medicines
5. Ensure sustainable investment (R&D)

National Action Plans
Implementation GAP: Guiding Principles

1. Realistic & achievable objectives
2. Take into account different capacities of Member States
3. Involve FAO and OIE, where appropriate
4. All-inclusive approach (HIV, TB and malaria)
5. Joint ownership between HQ and Regions
6. Communication!
Core value: together aligned
GAP is a big thing
GAP organizational structure

Global Technical Coordination Group

HQ & RO staff

Global Policy Group

Steering Group
ADGs & DPMs

AMR Coordinating Secretariat

Marc Sprenger, Director
Liz Taylor, Monitoring & Reporting Officer
Eileen Jameson, Management Officer
Ellen Attafuah, Assistant
Pravarsha Prakash, Technical Officer
Katie Barker, Technical Officer

Global action plan on antimicrobial resistance
AMR secretariat

Global action plan on antimicrobial resistance
AMR Steering Group

1. Agree WHO work plan
2. Implementation plan proposal for donors & partners
3. Organization-wide resource mobilization strategy
4. Prioritize activities and budget and funding allocation

Meet quarterly
# Implementation GAP: 10 work streams

1. Global communications campaign (Liv Lawe-Davies)
2. Support National Action Plans of MS (Carmem Pessoa)
3. Global Antimicrobial Resistance Surv System (Carmem Pessoa)
4. Support measures to improve IPC (Benedetta Allegranzi)
5. Monitor use & enhance stewardship of antibiotic use (Gilles Forte)
Implementation GAP: 10 work streams

6. Encourage R&D and explore new business models (Peter Beyer)
7. Improve point of care diagnostics (Francis Moussy)
8. Address the environmental drivers (Kate Medlicott)
9. Engage the United Nations General Assembly
10. Vaccines in order to prevent AMR (Martin Friede)

One Health liaison: Awa Aidara
Additional: HTM, STI, Maternal Health, etc
Global action plan on antimicrobial resistance

**ANTIBIOTIC RESISTANCE**

*Antibiotic resistance* happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause. This is compromising our ability to treat infectious diseases and undermining many advances in medicine.

We must handle antibiotics with care so they remain effective for as long as possible.

**WHAT POLICY MAKERS CAN DO**

1. Ensure you have a robust [national action plan](https://www.who.int/drugresistance) to tackle antibiotic resistance
2. Improve surveillance of antibiotic-resistant infections
3. Strengthen policies and implementation of infection prevention and control measures
4. Regulate and promote the appropriate use of quality medicines
5. Make information on the impact of antibiotic resistance available

[World Health Organization](https://www.who.int)

*AntibioticResistance*

---

**CAUSES OF ANTIBIOTIC RESISTANCE**

*Antibiotic resistance* happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

- Over-prescribing of antibiotics
- Patients not finishing their treatment
- Over-use of antibiotics in livestock and fish farming
- Poor infection control in hospitals and clinics
- Lack of hygiene and poor sanitation
- Lack of new antibiotics being developed

[World Health Organization](https://www.who.int/drugresistance)

*AntibioticResistance*
Global Antimicrobial Resistance Surveillance System (GLASS)
Lead: Carmem Pessoa

Goal
To achieve a monitoring capacity to capture essential information on the global situation of antimicrobial resistance and inform decision making.
Global Antimicrobial Resistance Surveillance System (GLASS)
Lead: Carmem Pessoa
GLASS future directions

Integrated foodborne AMR surveillance
- Food-animals
- Food
- Humans

Monitoring of antimicrobial use or consumption

Surveillance of bacterial resistance in humans

Environmental AMR surveillance

... other types of AMR surveillance

Global action plan on antimicrobial resistance
R&D and explore new business models
Lead: Peter Beyer

Global Antibiotic Research and Development Facility
In a decade of R&D, 6 new treatments developed

- 30 projects, 6 diseases areas
- 15 entirely new chemical entities (N CEs)
- Over 130 partnerships, most in endemic countries
- 150 staff, half in endemic countries & 600 people working on DNDi projects
- Over EUR 350 million raised equally from public and private sources
- 3 regional disease-specific clinical trial platforms and 2 technology transfers

✓ Easy to use  
✓ Affordable  
✓ Field-adapted  
✓ Non-patented
DNDi’s success is only possible through innovative partnerships

CRITERIA FOR SUCCESS
• Share the same vision
• Mutual understanding
• Involvement throughout the whole process
Improve point of care diagnostics
Lead: Francis Moussy

Point-of-Care Dx for LMICs for treatment, surveillance
Many areas with no elec, no refrige, no trained medical staff…
New PoC Dx suitable for LMICs need to be developed
New approach Dx Local Health Care Centres

Low-cost, robust and open PoC diagnostics platforms

Instrument including Reader/transmitter

Cartridges for multiple diseases and health conditions
Engage United Nations General Assembly
Global action plan on antimicrobial resistance
Shift Words into Action
Shift Words into Action
Shift Words into Action: UN General Assembly 2016
One Health, liaison FAO / OIE
Lead: Awa Aidara
ANTIBIOTIC RESISTANCE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

The over-use and misuse of antibiotics in livestock, aquaculture and crops is contributing to antibiotic resistance and its spread into the environment, food chain and humans. This is compromising our ability to treat infectious diseases and undermining many advances in medicine.

We must handle antibiotics with care so they remain effective for as long as possible.

WHAT THE AGRICULTURE SECTOR CAN DO

1. Ensure that antibiotics given to animals—including food-producing and companion animals—are only used to treat infectious diseases and under veterinary supervision.
2. Vaccinate animals to reduce the need for antibiotics and develop alternatives to the use of antibiotics in plants.
3. Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
4. Adopt sustainable systems with improved hygiene, biosecurity and stress-free handling of animals.
5. Implement international standards for the responsible use of antibiotics, set out by OIE, FAO and WHO.

Global action plan on antimicrobial resistance
International context

1. Global Health Security Agenda
2. G7
3. TATFAR
4. AMR review
5. Joint Programming Initiative AMR
6. Etc
7. Etc
International Initiatives: align
After 20h flight: reality check
No prescription needed, just take 2
No knowledge, no instruction
After 10h flight: reality check

Courtesy: FAO, HJ Ormel DVM
After 10h flight: reality check

Courtesy: FAO, HJ Ormel DVM
What did they tell me…

No medical microbiology lab in main hospital
No infection and prevention control in hospital
No drug regulation
No knowledge, no awareness
No money for GP

But committed local people and Country Office WHO
She is the champion!
No comment....
Miracle...after 1 day

Global Antibiotic R&D Facility
Conclusion

1. Global Action Plan AMR is ambitious
2. Global Action Plan AMR: joint responsibility
Thank you
Antimicrobial Resistance in Developing Countries

Prof. Nirmal Kumar Ganguly
Visiting Professor of Eminence
Policy Center for Biomedical Research
THSTI, Faridabad, India
Former DG ICMR, India
Global Trends
Deaths attributable to antimicrobial resistance every year compared to other major causes of death

- Tetanus: 60,000
- Cholera: 100,000 - 120,000
- Measles: 130,000
- AMR in 2050: 10,000,000
- Road traffic accidents: 1,200,000
- Diarrhoeal disease: 1,400,000
- Diabetes: 1,500,000
- Cancer: 8,200,000

Source: Review on Antimicrobial Resistance 2014
Deaths attributable to antimicrobial resistance every year by 2050

Asia: 4,730,000
Europe: 390,000
North America: 317,000
Latin America: 392,000
Africa: 4,150,000
Oceania: 22,000

Source: Review on Antimicrobial Resistance 2014
Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries.
Antibiotic consumption is increasing in developing countries...

**Per capita total antibiotic use, retail sector, 2005-2010**

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
Once an antibiotic is introduced, resistance is not far behind...


CDDEP
THE CENTER FOR DISEASE DYNAMICS, ECONOMICS & POLICY
WASHINGTON, DC • NEW DELHI

PUBLIC HEALTH FOUNDATION OF INDIA
Non-prescription use of antimicrobials

Figure 2: Frequency of non-prescription use of antimicrobials in the general population based on published works. In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

Morgan et al, Lancet ID, 2011
Hospital use of carbapenems is rapidly growing

**Per capita total carbapenem use, hospital sector, 2005-2010**

Source: Based on data obtained under license from IMS Health MIDAS™ (January 1999-December 2010); IMS Health Incorporated. All Rights Reserved.
Potential loss of in GDP, % fall compared to baseline scenario in 2050

Source: KMPG project
INDIA
Status Paper: Rationalizing antibiotic use to limit antibiotic resistance in India+
Global Antibiotic Resistance Partnership (GARP) - India Working Group

Determinants of antibiotic prescribing

- Lack of appropriate knowledge
- Lack of trust in or delayed lab results
- Desire to meet patient demand
- Fear of clinical failure
- Economic incentives
- Unstable/inadequate drug supply
- Peer norms
- Marketing influence
- Traditional beliefs about antibiotics

Number of studies that identified these determinants

Indian J Med Res 134, September 2011, pp 281-294
Action needed a global level to tackle emerging threats like NDM-1

<table>
<thead>
<tr>
<th>Isolate and resistance determinants</th>
<th>Total (%)</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<td><strong>Escherichia coli</strong></td>
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<td></td>
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</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;SHV&lt;/sub&gt;</td>
<td>27 (26)</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;TEM&lt;/sub&gt;</td>
<td>16 (69)</td>
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<td>7</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;OXA&lt;/sub&gt;</td>
<td>8 (35)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;CTXM&lt;/sub&gt;</td>
<td>20 (87)</td>
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<td>6</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
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<td>5 (19)</td>
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</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
<td>6 (22)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Negative for all determinants</td>
<td>4 (15)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
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<tr>
<td><em>bla</em>&lt;sub&gt;SHV&lt;/sub&gt;</td>
<td>68 (65)</td>
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<td>12</td>
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<td>15</td>
<td>11</td>
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<td>8</td>
<td>11</td>
<td>4</td>
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<td><em>bla</em>&lt;sub&gt;OXA&lt;/sub&gt;</td>
<td>30 (47)</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;CTXM&lt;/sub&gt;</td>
<td>58 (91)</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>14</td>
<td>10</td>
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<tr>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
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<td>0</td>
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<td>Negative for all determinants</td>
<td>4 (6)</td>
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<td>1</td>
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<tr>
<td><strong>Enterobacter cloacae</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;SHV&lt;/sub&gt;</td>
<td>8 (7.6)</td>
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<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;TEM&lt;/sub&gt;</td>
<td>7 (87)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<td>1</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>2</td>
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<tr>
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<td>3 (37)</td>
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<tr>
<td>Negative for all determinants</td>
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<td>0</td>
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doi:10.1371/journal.pone.0112101.t002

Prevalence of NDM-1 in a NICU over 5-Year Period  Source: Sulgana Basu  NICED
ICU
Jan., 2008 - Dec., 2010 Blood Isolates
3 Yrs. (n = 1928)

- Candida sps, 522
- Staphylococci, 506
- Klebsiella, 245
- Acinetobacter, 210
- Enterococci spp., 135
- E. coli, 116
- Pseudomonas aeruginosa, 90
- Enterobacter, 38
- Staph. aureus, 37
- Strept. pneumoniae, 18
- Salmonella typhi, 11
- Salmonella, 11
- Staphylococci, 506

Table I: Trends of isolation rates, antimicrobial consumption and resistance *K.pneumoniae*

<table>
<thead>
<tr>
<th></th>
<th></th>
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<td>98</td>
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<td>77</td>
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<td>89</td>
<td>76</td>
<td>59</td>
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<td>80</td>
<td>64</td>
<td>83</td>
<td>82</td>
<td>66</td>
<td>81</td>
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<td>64</td>
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<td>Piperacillin+ Tazobactum</td>
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<td>71</td>
<td>51</td>
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<tr>
<td>Amp C</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>8%</td>
</tr>
<tr>
<td>Carbapenemase producer</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
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<th>(%) resistance</th>
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<th>2004</th>
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<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>p value</th>
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<td>63</td>
<td>68</td>
<td>87</td>
<td>75</td>
<td>69</td>
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<td>Piperacillin+ Tazobactum</td>
<td>53</td>
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<td>47</td>
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<td>30</td>
<td>27</td>
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<td>15%</td>
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</table>

Association between carbapenem consumption and resistance in *P. aeruginosa* and *A. baumannii* (SGRH)

$p$ value for *A. baumannii* $< 0.5$

Goel & Wattal, JAC, May 17;2011
"The Chennai Declaration" named after the city where the meeting took place, is the consensus evolved out of the meeting and co-authored by representatives of various medical societies. The document is based on realistic goals and objectives, with a deep understanding of the background Indian scenario.
Antimicrobial Resistance Research and Surveillance network: India

Indian Council of Medical Research

Source: Dr. Kamini Walia ICMR
Antimicrobial Research and Surveillance Network at ICMR

- Antimicrobial Resistance Research and Surveillance
- Antimicrobial Stewardship Program
  - Treatment guidelines
  - Infection control policy document
  - Prescription practices
  - Focus on infectious diseases
Antimicrobial Research and Surveillance Network at ICMR

- Nodal centres are focal points for six pathogenic groups:
  - *Enterobacteriaceae / sepsis* (PGIMER)
  - Fungal pathogens (PGIMER)
  - Gram negative non-fermenters (CMC)
  - Enteric fever organisms (AIIMS)
  - Diarrhoeagenic organisms (CMC)
  - MRSA, Enterococcus (JIPMER)

- 15 Regional Centres (RC) proposed

**Major imperatives:** Standardisation and uniformity
Updates.....

- Data collection at nodal centers initiated on September 1, 2013
  - Almost 18,000 isolates tested
- SOPs (bacteriology and mycology) available at ICMR website
- Data managed by the Bioinformatics team at ICMR HQs
Shigella spp

- High resistance to nalidixic acid
- 50% R to norfloxacin and ampicillin
- Association of ESBL genes with qnr genes – rare among Indian isolates
- $\text{bla}_{\text{CTX-M-15}}$ occurrence in Shigella spp increases the threat for spread of cephalosporin resistance among Enterobacteriaceae

<table>
<thead>
<tr>
<th>Organism</th>
<th>Genes for sulfonamide resistance</th>
<th>Genes for β-lactam resistance</th>
<th>Genes for quinolone resistance</th>
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<tbody>
<tr>
<td>S. flexneri (n = 22)</td>
<td>dhfr1a 22, Sul II 15, bla$<em>{\text{OXA}}$ 12, bla$</em>{\text{TEM}}$ 4</td>
<td>bla$_{\text{CTX-M-15}}$ 2, AmpC 2</td>
<td>qnr A, B, S 6</td>
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<tr>
<td>S. sonnei (n = 6)</td>
<td>dhfr1a 6, Sul II 5, -</td>
<td>bla$_{\text{TEM}}$ -</td>
<td>qnr - 1</td>
</tr>
</tbody>
</table>
Salmonella typhi

**S. typhi** multidrug resistance (MDR) : ampicillin, chloramphenicol and trimethoprim – sulfamethoxazole - downward trend
• High resistance to **FQ, cephalosporins** in **S. typhi** is increasingly reported
Non-fermenting gram negative bacilli (NFGNB)

- *Acinetobacter* species 60% isolates, *Pseudomonas* species 24%, *Stenotrophomonas* species 4%, *Burkholderia* species 4%.
- All isolates of *P. aeruginosa* were susceptible to colistin, followed by imipenem (85%), amikacin (80%), ciprofloxacin (80%), piperacillin-tazobactam (58%) and meropenem (50%)
- *A. baumannii* isolates showed maximum susceptibility was to colistin (99%) followed by imipenem (53%) and meropenem (53%).
## No. of genes identified in CRO multiplex PCR reaction

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>NC</th>
<th>‘n’</th>
<th>SPM</th>
<th>IMP</th>
<th>VIM</th>
<th>NDM</th>
<th>OXA-48 Like</th>
<th>KPC</th>
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<tbody>
<tr>
<td>P. aeruginosa</td>
<td>CMC</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>0</td>
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<tr>
<td></td>
<td>AIIMS</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>JIPMER</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Acinetobacter sp.</td>
<td>CMC</td>
<td>30</td>
<td>0</td>
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<td>4</td>
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<tr>
<td></td>
<td>AIIMS</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
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</tr>
</tbody>
</table>
ICMR Antimicrobial Stewardship Program: Survey of Practices, 2014

- 20 Hospitals: 13 public and 7 private
- AMSP documents in 4/20 hospitals
- Accreditations better in private hospitals
- Infection control document in 20/20
- Comprehensive treatment guidelines missing in most hospitals
  - Syndrome specific guidelines frequently available
- AMSP not linked with IT system in most hospitals
- Most hospitals do not have infectious disease physicians and clinical pharmacists
### Antimicrobial Surveillance and Research network

**E. coli from blood**

<table>
<thead>
<tr>
<th></th>
<th>PGIMER</th>
<th>CMC Vellore</th>
<th>JIPMER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>&lt;10</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Cef-sulbatam</td>
<td>50</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Amikacin</td>
<td>78</td>
<td>&gt;90</td>
<td>83</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8</td>
<td>25</td>
<td>30</td>
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</table>

**Klebsiella spp from blood**

<table>
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<th></th>
<th>PGIMER</th>
<th>CMC Vellore</th>
<th>JIPMER</th>
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</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>&lt;10</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Cef-sulbatam</td>
<td>20</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt;40</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Pip-Tazo</td>
<td>30</td>
<td>45</td>
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</tr>
</tbody>
</table>
Trends in Anti-microbiome Pan Indian Distribution of Pneumococcal Serotypes

PIDOPS study: Dr. K L Ravi

Multidrug Resistance: 26%
Trends in Anti-microbiome

PIDOPS study: Dr. K L Ravi
Foreign collaborations

- **National Institute of Allergy and Infectious Diseases, NIH, USA**
  - Systems biology
  - Epidemiology of neonatal sepsis
  - Clinical trials for new entities
- **Center for Disease Control, USA**
  - Strengthening infection control
- **Research Council Norway, Norway**
  - Methods for assessment of the burden of resistance
  - Integrated project surveillance systems for AMR and antibiotic use in humans and/or animals.
  - Ecological, evolutionary and molecular studies of AMR in clinical and non-clinical environments.
Antimicrobial Resistance – Cadila Approach

Collaborative effort with UK organization

- Develop antibiotic resistance breakers (ARB) to rejuvenate known – approved antibiotics.

- Antibiotic Resistance Breakers
  - Improves efficacy of approved antibiotics
    - Effective against resistant organism
    - Faster killing
    - Least Chance of developing resistance
    - Effective against multiplying as well as non-multiplying organisms
    - Known compounds (approved drugs) as well as Novel compounds with no/minimal antibacterial activity
ARB and MDR Gram –ve organisms

Faster Killing of resistant organisms
ARB and MRSA infection

Faster Killing of resistant organisms

Log CFU/ml vs Time (Hr)

- Approved Antibiotic
- ARB – Novel compound
- Approved Antibiotic + ARB

Faster Killing of resistant organisms
Need for proactive actions to assist developing countries in strengthening systems to address AMR risks

- Strengthening national and international interdisciplinary cooperation and developing holistic strategies and action plans
- Improving regulatory frameworks based on internationally agreed principles and standards (Codex, OIE)
- Reducing the need for antimicrobials in animal husbandry, by improving animal health disease prevention and good practices along the chain
- Strengthening food and human surveillance systems for AMR and the quantities of all antimicrobials being used at the national level
- Raising awareness (among veterinarians, value chain actors including producers and the public) about AMR
- Developing appropriate policies/guidance on the prudent and responsible use of antimicrobials in animal husbandry
- Supporting research to generate data on the prevalence and trends in AMR, as well as supporting risk assessment, risk management and risk communication in the AMR area
Find new antibiotics

THANK YOU
Access Innovation and Conservation

The experience of ReAct

Otto Cars MD PhD
Professor Infectious Diseases
Uppsala University, Sweden
Founder and senior adviser ReAct

“A future free from the fear of untreatable infections”
Antibiotic Resistance: A silent tsunami

Modern medicine

Child and maternal health

Basic medicine
Figure 1

Occurrence of carbapenemase-producing Enterobacteriaceae based on self-assessment by national experts, 38 European countries, May 2015
The shortfall of the R&D pipeline

EMA-ECDC-ReAct pipeline analysis

- 90 anti-bacterials against organisms of public health importance
- 66 new active substances
- 27 with new targets or new mechanisms of action
- 15 are systemic
- 4 against gram-negative
- 2 act on new targets
- 0 with new mechanism of action
“The infrastructure of antibiotic discovery both in academia and in industry is at a dangerously low level and needs to be rebuilt”
A leaking system

New antibiotics

Marketing

Volume sales

Misaligned financial incentives

Irrational use
“Nobody likes to lose business. We give whatever they ask. Competition, location of shops, license issues...everything has become commercialized”
- Urban pharmacist

“Even reputed companies offer complimentaries. If you prescribe more, they offer air conditioned car or free tickets.... Of late, we are forced to try new antibiotics”
- Urban doctor
Typical Pharmaceutical Economic Model:
Return is driven by sales volume

Investment
Preclinical and clinical development.
Demonstration of safety & efficacy

Return of Investment
Price (somewhat) controlled by authorities/payers
Volume (somewhat) driven by company and competition
3Rs for innovating novel antibiotics: sharing resources, risks, and rewards

The stream of new antibiotics is struggling to keep up with emerging bacterial resistance. Anthony So and colleagues examine what can be done to increase innovation.
Innovative financing to achieve de-linkage

WHO Consultative Expert Working Group on R&D Financing and Coordination

Delinkage: Divorcing R&D Funding from Product Pricing

Product Price

Delinkage: Divorcing ROI from volume-based sales

Revenue

Price X Quantity

R&D Investment

Antibiotic Innovation Policy Discussions
WHO Global action plan:
“The cost of investment in research and development may need to be de-linked from price and the volume of sales to facilitate equitable and affordable access to new medicines”
Innovative Medicines Initiative
New Drugs for Bad Bugs (ND4BB)

US Biomedical Advanced Research and Development Authority
BARDA
Innovative Medicines Initiative
New drugs for Bad Bugs (NB4BB)

“Public investment into development of new antibiotics should come with appropriate obligations to governments, regulators, producers, and distributors with respect to the marketing and responsible use of these new products to avoid the rapid build-up of drug resistance”.
(WHO/DNDi concept note: Guiding principles)

US Biomedical Advanced Research and Development Authority
BARDA
Innovative Medicines Initiative
New drugs for Bad Bugs (NB4BB)

Both IMI and BARDA are supporting pivotal trials of the Astra-Zeneca combination avibactam-aztreonam.
A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics

Matthew J Renwick¹, David M Brogan¹,² and Elias Mossialos¹
Universal Access to Effective Antimicrobials: An Essential Feature of Global Collective Action against Antimicrobial Resistance

Nils Daulaire, Abhay Bang, Göran Tomson, Joan N. Kalyango, and Otto Cars

Journal of Law, Medicine & Ethics, 2015
High Proportion of Intestinal Colonization with Successful Epidemic Clones of ESBL-Producing Enterobacteriaceae in a Neonatal Intensive Care Unit in Ecuador

Viveka Nordberg¹,²*, Arturo Quizhpe Peralta³,⁴, Telmo Galindo³, Agata Turlej-Rogacka⁵,⁶, Aina Iversen⁵,⁶, Christian G. Giske⁵,⁶, Lars Navér¹,²
Availability of old antibiotics

C. Pulcini et al. CID 2012;54:268

Ongoing Update 2015: Availability decreases, common long lasting shortages
Antimicrobial Stewardship:

The South African Perspective

Precious Matsoso
Director General; National Department of Health;
South Africa
13th November 2015
Why do we need an AMR strategy and implementation plan?

South Africa’s triple burden of AMR Multidrug resistant organisms

Multidrug resistant TB (MDR TB)

Drug resistant HIV (DRHIV)

Multi drug resistant organisms (MDR)

The AMR strategy and implementation plan focuses on multi drug resistant organisms

Bacteria and Fungi
How serious is AMR in SA?

SAMJ situation analysis 2011
The situation analysis identified numerous concerns and resource constraints limiting implementation of good infection control practices and antimicrobial stewardship programs
More recent studies are showing similar high rates of HAI’s
The Journey towards South Africa’s AMS Strategy

2009 - 2011

GARP places an AMR co-ordinator in SA

GARP - SA Situational analysis on AMR – Published Feb 2011 in SAMJ

SA Antibiotic Stewardship Partnership (SAASP) clinicians group launched

2012

2013

October 2013 Antimicrobial Resistance working group established and meetings held (Feb 2014)

April 2014 Antimicrobial Resistance Stakeholder Consultative meeting.

2014

Oct 2014 AMR summit launch’s AMR strategic framework and background document

Feb 2015 – Norms & standards draft published along side for AMR quality standards

June 2015 SA AMR implementation plan and MAC approved

2015

Jan & May 2014 WHA resolution “Combating AMR including Antibiotic resistance

Feb & Nov 2014 FPGH in Oslo on consultation of member of states

6 – 8 May 2015 – WHO Africa region hosts experts consultative conference on AMR in Brazzaville, DRC

19 May 2015 – FPGH side event at 68th WHA in Geneva

Background situational analysis

Strategy and policy outlining begins

AMR strategy launched

Implementation plan and stakeholder commitments defined

Department: Health

REPUBLIC OF SOUTH AFRICA
The South African AMR initiative started at the summit in October 2014.

Brought together key stakeholders from government, laboratory services, clinician societies, civil societies and regulatory bodies.
The summit culminated in all stakeholders signing a commitment to ......

Antimicrobial Resistance National Strategy Framework Commitments

The purpose of the Antimicrobial Resistance National Strategy framework is to provide a framework for managing Antimicrobial Resistance (AMR), to limit further increases in resistant microbial infections, and improve patient outcomes.

Governance Structures

- Strengthen, coordinate and institutionalise interdisciplinary efforts through national and health establishment level governance structures.
- Surveillance: Optimize surveillance and early detection of antimicrobial resistances to enable reporting of local, regional, and national resistance patterns to optimise empiric and targeted antibiotic choice.
- Infection Prevention & Control: Enhance infection prevention and control of the spread of resistant microbes to patients in healthcare settings, focusing on improvement in hand hygiene and the identification and isolation of patients with resistant organisms. Community measures include preventing infection through wide-reaching vaccination programmes and improvements in water and sanitation.
- Antimicrobial Stewardship: Promote appropriate use of antimicrobials in human and animal health through antimicrobial stewardship, including: Effective policies and protocols; Stewardship at point-of-care; National prescribing guidelines; Appropriate antibiotic choice.

Commitments

1. To collaborate as intersectoral, interdisciplinary organisations and departments to strengthen, co-ordinate and institutionalise efforts to address Antimicrobial Resistance.
   - Short term - March 2015: Establishment and initial meeting of National Ministerial Advisory Committee.
   - Short to medium term 2015 - 2019: Strengthen governance at Health Establishment levels.

2. To establish a national surveillance system to track and report resistant organisms and Antimicrobial use in agriculture and human health.
   - Short term 2015: Develop an Antimicrobial Resistance map for South Africa through data sharing between the private and public sector laboratory services.
   - Medium term 2015 – 2019: All Health Establishments meeting compliance of the National Core Standards relating to Antimicrobial Stewardship and Infection Prevention & Control.

3. To enhance the processes, structures, resources and supplies needed for effective Infection Prevention & Control.
   - Short term 2015: Ensure the equipment and Infection Prevention & Control resources required to practice effective hand hygiene are available at all times in all Health Establishments.

4. To promote the appropriate use of Antimicrobials in human and animal health through antimicrobial stewardship in facilities and suitable enabling legislation and regulations.
   - Short term 2015: Ensure availability of Antimicrobials according to Essential Medicines List in all Health Establishments.

5. To build the expertise and strengthen the competency of health and veterinary professionals and improve the staffing levels of the workforce in Antimicrobial Resistance and Infection Prevention & Control.
   - Medium term 2015 – 2019: Development of strategy and operational plan for the integration and implementation of Antimicrobial Resistance and Infection Prevention & Control training into the undergraduate and postgraduate medical curriculums of health care professionals in South Africa.

6. To increase the community awareness of Antimicrobial Resistance.
   - Short term 2014 – 2015: Design of an awareness campaign relating to Antimicrobial Resistance based on past successful campaigns.

7. To promote research into novel diagnostics and clinical trials in Infection Prevention & Control and Antimicrobial Resistance.

National Department of Health of the Republic of South Africa
Participating Stakeholders from Various Sectors, each Company represented herein as follows:

Signed on this 16th day of October 2014 in Johannesburg as The Antimicrobial Resistance National Strategy Framework Commitments.
Pillars of the South African AMR Strategy Framework

Impact: Rational Antimicrobial use and improved patient outcomes

**Strategic objective**

- **Antimicrobial resistance Governance**
  - Diagnostic stewardship
  - Enhance Surveillance
  - Antimicrobial Stewardship
  - Prevention including IPC and vaccination

**Enablers**

Health systems strengthening, research, education and communication
Objectives of the South African AMR Strategy Framework

**Strategic objective**

1. Strengthen, coordinate and institutionalize interdisciplinary efforts through national and health establishment level governance structures

2. Improve the appropriate use of diagnostics to identify pathogens and guide treatment

3. Optimise surveillance and early detection of antimicrobial resistances to enable reporting

4. Enhance infection prevention and control of the spread of resistant microbes to patients in healthcare settings, wide-reaching vaccination programmes and improvements in water and sanitation; and

5. Promote appropriate use of antimicrobials in human and animal health through antimicrobial stewardship.

**Strategic Enablers**

- Legislative and policy reform for health systems strengthening to support the quality of antimicrobials and to enable control over prescribing of antimicrobials in the animal health sector

- **Education** of all levels of health providers in human health and agriculture in the critical concepts of antimicrobial stewardship, infection control, infectious diseases, microbiology and pharmacology

- **Communication** to educate the public, create awareness and enhance patient advocacy of the dangers of inappropriate antimicrobial use

- **Research** into novel diagnostics such as point of care testing and clinical trials of treatment duration, antimicrobial consumption plus new antimicrobials.

The AMR implementation plan describes the activities needed to effect the strategy.
Implementation plan for AMR

Implementation plan has been approved

Each province must report quarterly on progress
Implementation plan Monitoring & Evaluation

Indicators for monitoring impact:

• Reduction in key resistant organisms:
  – *Escherichia coli*—bacterial bladder infections (UTI’s) and common infections in the community
  – *Staphylococcus aureus*—common cause of skin and soft tissue infections as well as bacteraemia in people of all ages
  – *Klebsiella pneumoniae*—common cause of severe infections of patients in hospitals that require treatment with carbapenem).

• Reduction in national consumption of antibiotics linked to key resistant organisms

• Reduction in maternal mortality from infectious diseases

• Reduction in neonatal mortality from infectious diseases
Ministerial Advisory Committee on AMR being appointed

MAC on AMR

Veterinarians

Laboratories – NHLS/NICD, SASCM and private

Clinicians, family Dr’s, pharmacists, microbiologists and nurses

Regulators and policy makers

DTI, DBE, DAFF, Military, DCS

HIV, TB representatives

NHC has approved the MAC and the call for nominations is imminent
AMR MAC: Proposed reporting and communication lines
Partnerships

• Partnership between the following parties which:
  – Center for Disease Dynamics Economics and Policy (CDDEP)
  – South African Society of Clinical Microbiologists (SASCM)
  – National Institute for Communicable Disease (NICD)
  – South African Antibiotic Stewardship Programme (SAASP)
  – Best Care Always!
# AMR MAC: Proposed membership

<table>
<thead>
<tr>
<th>Core members (25)</th>
<th>Co-opted members</th>
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<tbody>
<tr>
<td>Department of Agriculture, Forestry and Fisheries</td>
<td>Nominated representatives from:</td>
</tr>
<tr>
<td>Department of Science and Technology</td>
<td>• Basic Education</td>
</tr>
<tr>
<td>Department of Health:</td>
<td>• Trade and Industry</td>
</tr>
<tr>
<td>• Sector Wide Procurement;</td>
<td>• Correctional Services</td>
</tr>
<tr>
<td>• Communicable Diseases;</td>
<td>• Military Services</td>
</tr>
<tr>
<td>National Health Laboratory Services</td>
<td>Department of Health:</td>
</tr>
<tr>
<td>National Institute for Communicable Disease</td>
<td>Hospital Services and Health Workforce</td>
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<tr>
<td>Microbiologists/Pathologists</td>
<td>Primary Health Care</td>
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<tr>
<td>Infectious Disease Specialist</td>
<td>HIV drug resistance committee</td>
</tr>
<tr>
<td>Infection Control Specialist</td>
<td>TB drug resistance committee</td>
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<tr>
<td>Veterinarian</td>
<td>Malaria committee</td>
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<tr>
<td>Paediatrician specialised in Infectious Diseases</td>
<td>Regulatory bodies:</td>
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<tr>
<td>Hospital (clinical) Pharmacist Community</td>
<td>Medical Control Council</td>
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<tr>
<td>Pharmacists</td>
<td>South African Nurses Council</td>
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<tr>
<td>District Pharmacist</td>
<td>Health Professional Council of South Africa</td>
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<tr>
<td>Information systems or data warehouse specialist</td>
<td>South African Pharmacy Council</td>
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<tr>
<td>(communicable diseases)</td>
<td>South African Veterinary Council</td>
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<tr>
<td>Family Physicians</td>
<td>Others:</td>
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<tr>
<td>Epidemiologist</td>
<td>Civil Societies</td>
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<td>Health Economist</td>
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</table>
Antibiotic-resistant bacteria are increasing in prevalence worldwide, resulting in infections that are difficult and expensive to treat.

Laboratory surveillance data in South Africa show that from 2012 to 2014 (Drug-Bug combinations for tracking):

- *Escherichia coli (E coli)* resistant to fluoroquinolone is at 27% over this period;
- *Staphylococcus aureus* – MRSA rate is 30%, though slight decline has been noted (from 35% in 2012 to 28% in 2014).
- *Klebsiella pneumoniae* carbapenems resistant is at 3.2% rate and showed increase from 2.9% to 4.2% over this period.

All three organisms-antibiotic combinations show no statistically significant change in proportion of resistance from 2012 to 2014.
SA’s consumption alone increased by 175% when trimethoprim is included.

**Antibiotic Use in South Africa**

Source: IMS Health

- **Total consumption – 175% incr**
  - Trimethoprim – 2164% incr
    - (Pub 360%, priv 21%)

- **Consumption excl trimethoprim – 58% incr**
  - (Pub - 104% excl trimethoprim, Priv 18%)
Next steps and activities

- Line item AMR surveillance data to be collected by all the labs by province and by facility
- Animal health consumption and surveillance data to be sourced through partnerships with the Dpt of Agriculture (DAFF) and the Veterinary Societies
- Province departments being tasked to set out their implementation plans against the national AMR strategy
Thank you

National Department of Health
South Africa