Report on Immunization and Vaccines related Implementation Research Advisory committee meeting

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Contents

Abbreviations

BOD	Burden of Disease
BMGF	Bill and Melinda Gates Foundation
EPI	Expanded Programme on Immunization
CFR	Case Fatality Rate
FPHVV	full public health value of vaccines
GAVI	The Vaccine Alliance (Global Alliance on Vaccines and Immunizations)
GoC	Grade of confidence
HPV	Human Papillomavirus
ICAN	Immunization Costing Action Network
IHME	Institute for Health Metrics and Evaluation
ICVA	International Collaboration for Vaccine Acceptance Initiative
IP	Intellectual Property
IVB	Department of Immunization, Vaccines and Biologicals
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
JHU	Johns Hopkins University
JRF	Joint Reporting Form
MCEE	Maternal and Child Epidemiology Estimate
MCV1	Measles containing vaccine first dose
MCV2	Measles containing vaccine second dose
MI4A	Market Information for Access to Vaccines
MoH	Ministries of Health
PAHO	Pan American Health Organization
PDVAC	Product Development for Vaccines Advisory Committee
QUIVER	Quantitative Immunization and Vaccines-related Research Advisory Committee
SAGE	Strategic Advisory Group of Experts
SDG	Sustainable Development Goals
UHC	Universal Health Coverage
UNICEF	United Nations Children's Fund
WG	Working Group
WHA	World Health Assembly
WHO	World Health Organization
WUENIC	WHO/UNICEF Estimates of National Immunization Coverage

Introduction

Dr Katherine O'Brien, Director of the Department of Immunization, Vaccines and Biologicals (IVB) of the World Health Organization (WHO) welcomed the Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC) members and provided a status update on the WHO transformation. She invited IVIR-AC members to provide input and feedback on the action plan that is being developed to follow the Global Vaccine Action plan (which ends in 2020) up to 2030. Dr O'Brien then welcomed Professor Walter Orenstein as the new chair of the IVIR-AC, replacing Professor Robert Breiman.

Walt Orenstein welcomed new IVIR-AC members Julie Leask, Paula Mendez, Virginia Pitzer, and Joseph Wu, after which Committee members and meeting participants introduced themselves.

Dr Raymond Hutubessy then provided an introduction to the focus and functions from the IVIR-AC. IVIR-AC has no executive, regulatory or decision-making function. Its role is to provide advice and recommendations to the Strategic Advisory Group of Experts (SAGE) and IVB Director of WHO.

The key objectives of IVIR-AC are:
- To appraise methods to estimate disease burden and resolve differences in disease burden estimates.
- To appraise guidance documents including methods to estimate disease and economic impact of vaccines.
- To advance techniques to assess cost-effectiveness of vaccines.
- To develop behavioural research to facilitate optimal and timely acceptance of vaccines.
- To define how disease and post-marketing surveillance should be conducted.

Session 1: WUENIC vaccine coverage methods and estimates

Introduction

The production and dissemination of health statistics is a core WHO activity mandated to WHO by its Member States in its Constitution. Since 2000, WHO and United Nations Children's Fund (UNICEF) have made annual estimates of national infant immunization coverage for selected vaccines. The WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) are informed by data officially reported to WHO and UNICEF by Member States, surveys as well as data reported in the published and grey literature. Based on the available data, consideration of potential biases, and contributions from local experts, the most likely level of immunization coverage is estimated. This approach is strongly based on data provided by countries and allows for countries to be involved in the development of the estimates, and to see their data reflected in the estimates[1,2,3].

WUENIC methods were updated after discussion at the October 2011 meeting of the Quantitative Immunization and Vaccines-related Research (QUIVER) Advisory Committee (the predecessor of the IVIR-AC). [4,5] WUENIC was also checked against the 18 items to be reported under the "Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement" (GATHER). Even though the GATHER guidelines were not designed for health service delivery coverage indicators, such as vaccination coverage, they provide a useful framework. WUENIC meets all GATHER criteria except item 11, as no formal comparison with other "models" has been undertaken. Item 16, "Report a quantitative measure of the uncertainty" is not fully applicable, as WUENIC uses a rule-based approach and not a mathematical model, thus it presents a Grade of Confidence on the estimates instead.

Because of the availability of new modelling approaches and tools as well as new usage of the estimates, WUENIC is again reviewing its approach and WHO and UNICEF are exploring alternative methods and inputs. There are, for example, new thoughts and modelling approaches, including the onset of big data analytics, artificial intelligence, machine learning and geospatial analysis. Furthermore, WHO and UNICEF should continue efforts to further improve the transparency of data inputs as well as the estimation process. In addition, other uses of WUENIC estimates demand that estimates be provided with even greater accuracy, precision and immediacy. Consistent with the Sustainable Development Goal (SDG) theme of "leave no one behind" there is increasing attention towards subnational estimates that are current, independent and objective. Finally, there is a desire to incorporate new data sources such as vaccine supply and disease surveillance, but it is not yet clear whether value would be added by including these new data given that these input data are also of unknown and varying quality.

IVIR-AC was informed of the timeline for soliciting alternative approaches for WUENIC and was requested to provide input on the WUENIC methods and approach.

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[1] AbouZahr C, Boerma T, Byass P. Bridging the data gaps: do we have the right balance between country data and global estimates? Glob Health Action 2017; 10 (sup 1):1299978

[2] AbouZahr C, Boerma T, Hogan D. Global estimates of country health indicators: useful, unnecessary, inevitable? Glob Health Action 2017;10(sup 1):1290370

[3] Boerma T, Mathers CD. The World Health Organization and global health estimates: improving collaboration and capacity. BMC Med 2015;13:50

[4] Burton A, Monash R, Lautenbach B, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bulletin of the World Health Organization 2009, 87:535-541. https://www.who.int/bulletin/volumes/87/7/08-053819/en/

[5] Burton A, Kowalski R, Gacic-Dobo M, Karimov R, Brown D. A formal representation of the WHO and UNCIEF Estimates of National Immunization Coverage: A computational logic approach. PLoS One 2012,7(19): e47806.

Review

Although the WUENIC methods are not perfect, they are still relevant. The WUENIC estimates provide information on trends in vaccination coverage and also encourage countries to measure and report data on immunization coverage.

While recognized that more than three-quarters of WUENIC estimates are based on reported country data, concerns remain around the perceived subjective nature of some WUENIC decisions when the working group chooses to "override" a rule. These situations are reduced but not fully overcome by the computational logic approach, which still requires human judgement when producing estimates. IVIR-AC remains concerned with the approach taken to convey uncertainty in the WUENIC. Although WHO and UNICEF have noted that there is no underlying probability model upon which the WUENIC are based and therefore they do not present classical measures of statistical uncertainty, e.g., confidence intervals, and they have chosen not to make subjective estimates of plausibility or certainty ranges around WUENIC, the Grade of Confidence (GoC) approach that leverages the accumulation of endorsements has limitations. The lack of ranking of the quality of data assessed and the absence of potential data, such as disease surveillance evidence (though disease surveillance data are also subject to error), is a concern. However, WHO and UNICEF noted these limitations in the GoC description (see Brown et al 2013[6]) and continue to refine the approach.

The availability and quality of empirical data, including country contextual data, is crucial for the development of immunization coverage estimates. It remains important to invest in better methods for collecting empirical data at country level. However, for any data collected, it is important to think about measurement bias (e.g. number of doses administered are not appropriate for the reported number of children vaccinated). Furthermore, care should be taken not to burden the Expanded Programme on Immunization (EPI) staff with excessive data collection requirements.

Discussion

Quality of data is very important; modelling based on poor data is not going to give good coverage estimates. Information from several sources / tools is needed and triangulation is required. No source of data should be discarded.

The challenge with estimating immunisation coverage is that there is no gold standard. The limitations of surveillance data depend on how the information is collected but might include recall bias and any problems with registered data. Surveillance data can be checked with surveys, but these also have limitations. They may for example be exclusively done in the capital and as such not be representative of rural areas.

Studies are available in which sero-surveillance, home based immunization records and parent recall were compared which allowed for bias in home based records and parent recall to be estimated[7]. Such studies might be available for more countries and it could be interesting to systematically identify these. Instead of ad-hoc studies, it might be possible to establish enhanced surveillance sites where several methods are used systematically.

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[6] Brown D, Burton A, Gacic-Dobo M, Karimov R. 2An Introduction to the Grade of Confidence Used to Characterize Uncertainty Around the WHO and UNICEF Estimates of National Immunization Coverage. The Open Public Health Journal, 2013, 6, 73-76.
7 Dansereau E, Brown D, Stashko L, Danovaro-Holliday MC. A systematic review of the agreement of recall, home-based records, facility records, BCG scar, and serology for ascertaining vaccination status in low and middle-income countries. Gates Open Research 2019;3:923.

A continuous challenge is the work pressure on health staff, who are often overwhelmed and do not have time to record vaccination.

It was noted that the ultimate outcome of interest is not vaccination coverage, but the prevention of diseases. By looking at disease surveillance data it might be possible to capture whether there are places with high vaccination coverage but where outbreaks did materialize. Outbreaks in high coverage areas raise questions about whether this is due to vaccine failure or whether immunization coverage data are inaccurate. While this is being done, it is not systematically studied. A systematic review might be done on this. A potential challenge is that vaccination status of cases is often unknown.

In evaluating the methodology, it is important to consider what level of accuracy is expected for these data, i.e. is it required to capture a 1% coverage difference from year to year, or rather to get a broader idea about trends.

There are increasing needs to understand immunization coverage at subnational level. Current data collected may in broader sense / under certain circumstances be used for subnational level, but not for district level.

A proposal was made to set-up an IVIR-AC Working Group (WG) to work closely with the WHO secretariat on the evaluation of new information sources and modelling approaches as they are considered. The Institute for Health Metrics Evaluation (IHME) methods is one of possible alternative methods and strengths and weaknesses of all alternatives should be considered.

Questions to be answered

- Are the WUENIC methods still relevant, given the WHO's constitutional mandate to produce statistics in order to monitor immunization programme performance?
- Are there any constraints to the current WUENIC approach?
- Under what conditions should the current WUENIC method be adapted or adopt existing alternative methods?
- How should WHO and UNICEF handle situations where observed data or trends contradict immunization data such as doses administered or survey results?

Summary and Recommendations

Since 2000 the WHO and UNICEF have made annual estimates of national infant immunization coverage for selected vaccines. The WUENIC are based on data officially reported to WHO and UNICEF by Member States, surveys and other data reported in the published and grey literature.

A review of the WUENIC methodology, exploring alternative methods and inputs as well as improving upon existing processes, was started. IVIR-AC was informed of the timeline for soliciting alternative approaches for WUENIC and was requested to provide input on the WUENIC methods and approach, focusing on the relevance and possible constraints. IVIR-AC was furthermore asked to comment on the conditions under which the current WUENIC methods should be adapted or adopt existing alternative methods, and how WUENIC or alternative methods should handle situations where observed data or trends from data such as doses administered or survey results contradict each other.

Recommendations

- Given the time constraints before any new methods can be adopted we should continue to rely on the current WUENIC methods in the near future.

- In the meantime, we should evaluate the strengths and weaknesses of alternative methods including the IHME model and what comes out of the three Expression of Interest letters.

- Having high quality data for estimating coverage is critical for evaluating programme performance and stimulating improvements where and when needed.

- A problem in estimating coverage is there is no gold standard against which different methods can be compared therefore there will still be need for human judgement. However, if finances allow, sites, in which there is comprehensive and accurate data available to determine true immunization coverage, should be set up to assess the feasibility and accuracy of various data collection methods to better refine vaccine coverage estimates.

- The Committee noted that refinements to country immunization coverage reports such as use of coverage surveys also involve subjective judgement as to how to use the supplementary information to adjust coverage estimates.

- Uncertainties in the methods should be described (e.g., when using alternative data such as surveys to adjust the estimates based on administrative methods). Some ranking of the quality of data used for adjustments should also be described.

- While coverage is important, it is no substitute for actual measurement of disease reduction as a result of immunization. Thus, disease surveillance would be the best indicator of programme performance but given the difficulties in establishing comprehensive systems capable of detecting all vaccine-preventable diseases it is difficult at this point; hence, we have to rely on coverage as the primary outcome measure for most immunization programmes.

- IVIR-AC recommends setting up an IVIR-AC WG to allow continuing dialogue between IVIR-AC and the WUENIC WG on the best ways to estimate vaccine coverage.

Session 2: Human Papillomavirus (HPV) vaccine coverage methods

Introduction

Since their first licensure in 2006, HPV vaccines have been progressively introduced in many countries, mainly targeting young adolescent girls between ages 9 to 14 years. However, the production of comparable coverage estimates has been limited by the many changes in the recommendations, resulting in changes in dosages (e.g. from 3 to 2 doses), multiple variations in timing and/or schedule (e.g. 6-month schedule versus 12-month schedule), and the targeting of multiple and different cohorts (e.g. all girls aged between 9 and 14 years old, sometimes with catch-up vaccination at 14 years, with or without the inclusion of 9-year old girls, etc). Notably, these differences do not only occur between countries, but also within the same country over multiple years.

WHO developed two measures of HPV vaccine coverage:
1. **The percentage HPV vaccination programme coverage**. This is the vaccination coverage according to the national schedule in a specific calendar year. This target serves to assess programme performance in the previous calendar year;
2. **The percentage protection by 15 years of age**. This is the vaccination coverage in a 15-year-old cohort which is vaccinated any time between 9-14 years of age. This target serves to assess countries' population protection level at 15 years of age through a standardized cohorts-based measure, independent of vaccination strategy and allows for comparison of vaccine coverage trends over time and across geographical regions

IVIR-AC was asked to comment on the methodology to develop the coverage estimates, which is based on the available data collected through the Joint Reporting Form (JRF) and additional data sources which are used for cross-checking. UN population estimates are used for the denominator. IVIR-AC was furthermore asked for suggestions on how to calculate uncertainty.

Review

Both indicators are valuable and useful for variety of purposes including monitoring, cross-country comparisons, market intelligence, modelling etc. The programmatic performance measure (indicator 1) is most useful to evaluate programme performance and compliance. However, to make useful comparisons between countries, the second indicator is required. These are thus complementary indicators with distinct purpose.

It would be helpful to clarify how the reporting of indicator 1 on programme performance would work in practice, for example, whether countries should monitor this indicator themselves. It might also be useful to link the indicator to the cervical cancer elimination strategy, which includes a target on the vaccination coverage of girls.

The second indicator, percentage protection by 15 year of age, is complex to produce but very valuable and informative. By 15 years of age, all members of the target population should have been offered the vaccine. The indicator allows for reporting of changes in coverage over time.

Further clarification in definitions might be useful, for example that separation by sex is always required. A definition for catch-up vaccination would also be useful.

The summary measures are appropriate but do not capture many important nuances. For example, HPVc based on the national schedule (2-dose or 3-dose) makes an artificial distinction that has no immunological basis; it would be better to report 1-, 2- and 3-dose coverage separately so that information is available on the number of doses each individual has received (although HPVc may be a useful process indicator). Another example relates to catch-up beyond age 15, which is important in MICs where many doses are bought by older people in the private sector. China for example has an indication for Gardasil for 20-40y olds only. Therefore it would be important to make the raw JRF data available, in addition to the summary outcome indicators (HPV1, HPVc).

It was not clear whether doses given at age 15 should be included in the indicator. It might be useful to consider revision of the JRF to allow separate recording / break down of doses given at age 15 and each year beyond as currently all doses given at age 15+ are grouped together.

It is indicated that the estimates are the results of a mixture of official JRF estimates and "other additional data sources" e.g. survey data, literature, government websites, etc. which are used for validation. It is not clear how this is done and it was proposed whether some kind of cross-validation or even triangulation could be conducted.

Alongside actual numbers it would be useful to strengthen information on HPV "programme characteristics" i.e. vaccine policy. The current description / mapping is ambiguous because "HPV in national immunization programme" can mean many different things. It would be useful to distinguish between licensure, recommendation, covered by insurance, completely free at point of vaccination, etc. For example, in Japan HPV vaccine is nominally still in the national programme but the government has suspended its recommendation and coverage has dropped below 5%. Thus, just reporting whether or not the vaccine is included in the national programme is not very meaningful.

It is not possible to calculate statistical uncertainty of HPV coverage because admin data are used. It might be more useful to think about uncertainty in relation to how data are collected, robustness of reporting data, distinguish between vaccination and natural infection, correct age to assign a vaccination to, etc.

Several other suggestions were made:
- Reporting of Year of Birth rather than age at dose in the JRF.
- Consider the potential impact on reporting if in future only one dose of HPV vaccine is required. This might simplify information collection (and calculations). But it requires the reporting of coverage with 1 dose.
- Need to clarify how subnational programmes and private sector purchases will be captured.
- Better to avoid the term "HPV vaccination protection by age 15" since vaccination is not immunisation (e.g. cold chain failure, vaccination after sexual debut) and suggest replacing by "HPV vaccination received by age 15".
- Measure of vaccinated at age 15 (prevalence) and vaccinated at each age (incidence) will be different due to deaths, migration - hence registers not equal admin coverage. There may not be a big difference in most countries but it is important to note.
- Coverage indicators needs to be supplemented with data on reasons for low vaccination update.

Discussion

The school-grade approach of converting school grade to a normative age was discussed, since this approach may mean that the numerator and denominator do not refer to the same population. While the concern was understood, it was highlighted that the school grade system was for purpose of delivery of the vaccine (and not for measurement). So although countries target schools for delivery of the vaccine, population is still used as the denominator because the interest is in population level coverage. Because in many countries there are multiple ages in a certain school grade, the conversion used is an estimate / approximation of the coverage by age.

Survey data will be used to validate administrative data. A number of potential issues with surveys were highlighted. First, recall bias might be a problem in surveys. If vaccination cards are available, these should be used to confirm the vaccination status. Second, the question was raised whether it is appropriate to ask the mother about the vaccination status of their daughter, or whether the girls should be asked themselves.

It was questioned whether the JRF captures whether someone has received the first or second dose? Perhaps a quality check can be added that checks if there are more 2nd or 3rd doses than 1st doses. Since some countries vaccinate by means of campaign (1st campaign, 2nd campaign) there might be some girls who are vaccinated in the 2nd campaign who did not have their first dose.

The ultimate question is what the impact of vaccination is on the development of cervical cancer. It is important to consider the age of sexual debut and accumulation of infection over time. If sexual debut is before age 15, then opportunities to prevent disease are missed.

Questions to be answered

- Does IVIR-AC have any comments on the HPV vaccine coverage methods, its validity and interpretation for guiding HPV vaccination programme monitoring?
- Does IVIR-AC have suggestions on how to calculate uncertainty?

Summary and Recommendations

Until now the production of comparable coverage estimates has been limited by the many changes in the recommendations and the variety of national HPV vaccination policies. Notably, differences do not only occur between countries, but within the same country over the years.

WHO has developed two measures of HPV vaccine coverage: One indicator was receipt of complete HPV vaccination by 15 years of age. The other was receipt of complete immunization according to country recommendations for age at receipt of HPV vaccines.

IVIR-AC was asked to comment on the methodology to develop these estimates, which is based on the available data collected through the JRF and additional data sources. IVIR-AC was furthermore asked for suggestions on how to calculate uncertainty.

Recommendations

- IVIR-AC appreciates the importance of the exercise and endorses the approach. It is useful for a variety of purposes including monitoring, cross country comparisons, market intelligence, and modeling.

- IVIR-AC agrees that both indicators are valuable, but full data (number of doses received by a person by age and year) collected in JRF should be made available, as well as a quality assessment of the data.

- Where grade-based reporting is currently used, efforts should be made to convert to an age-based reporting system.

- In the long run, assuming country-specific recommendations are tailored to maximizing reductions in HPV infection and related cancers that HPV causes, the programme indicator may eventually be the most valuable. There may be other measures that may be programmatically useful in some circumstances (e.g. catch up vaccination of older cohorts) but the one measure that is most critical is compliance with country programme recommendations. However, at the present time both indicators should be measured and reported.

Session 3: Global vaccine acceptance and demand

Introduction

IVIR-AC WG on demand and acceptance

The IVIR-AC WG on demand and acceptance was created in March 2018 to serve as a link between IVIR-AC and the International Collaboration for Vaccine Acceptance Initiative (ICVA). The Terms of Reference for the IVIR-AC WG on vaccine acceptance and demand were agreed on during the September 2018 IVIR-AC meeting. During this meeting IVIR-AC also reviewed a conceptual framework on vaccine acceptance and demand which had the purpose to guide IVIR-AC in this area.

Demand data expert WG

The demand data expert WG was launched in October 2018 to support the WHO EPI. The objective of the demand data expert WG is to provide a set of tools and guidance for programmes and partners to boost the availability, quality, and use of local and global data on acceptance and demand, including supporting assessments of under-vaccination, facilitating the design and evaluation of interventions and tracking trends over time. The expected outputs include: 1) modular and comprehensive package of quantitative and qualitative tools, targeted to caregivers and community health workers, and 2) user-friendly practical guidance for local data collection, analysis and use. In 2019 the demand data expert WG aims to develop the tools and carry out Phase 1 of the testing of the tools, followed by Phase 2 testing of the tools in the first and second quarter of 2020 and finalization and roll-out of the tools later in the year.

IVIR-AC was asked to comment on the proposed workplan of the demand data WG .

Review

Demand data expert WG

The proposed process for tool development seems feasible. Selecting low-income countries in the African region for piloting should take into consideration language and geographical distribution.

There are other groups within WHO involved in coverage surveys. E.g. Coverage Evaluation Surveys for Preventive Chemotherapy: Field guide for Implementation (2016), in addition the site for Vaccination Coverage Surveys - Technical Resources contains information (questions, tools, etc.) that could inform the data.

Demand tends to be lower in relatively remote and insecure areas. Challenges could include logistics (access, security, etc.).

There are local research institutions that can and should be partners. It is important to build local capacity and to work with social scientists in countries in order to get the project to scale and also to provide valuable contextual information. Equally important is working with the National Health Ministry and agency responsible for immunization. Programme managers should be integrated in this WG since they know the challenges.

In order to balance quality, practicality and timeliness it was proposed to have regular consultations and review of the processes, to work closely with the countries where data are collected, to coordinate the approach between the different groups, and to have a realistic planning (considering constraints and planning for them).

Proposed ways for the dissemination of the tools include online platforms, regional and sub-regional offices/programmes, and ministry of health sites for the different countries.

Discussion

IVIR-AC WG on demand and acceptance

The data demand WG has picked-up on the framework which was developed by the IVIR-AC WG and presented to IVIR-AC in September 2018, but is also looking at other frameworks and is in the process of developing a new framework that integrates the framework proposed by the IVIR-AC WG .

The South Africa research proposal to investigate HPV vaccine acceptance and demand, which was presented to IVIR-AC in September 2018 has been put on hold for financial reasons but is still planned to take place.

The role of IVIR-AC, and the IVIR-AC WG on vaccine acceptance and demand, is unclear. The strength of the IVIR-AC is in research and modelling. The secretariat is requested to specify better where IVIR-AC can contribute.

Demand data expert WG

Vaccine hesitancy is one of many barriers to vaccination. Reasons for under-vaccination vary widely between countries, within countries, and according to social-economic status. Some reasons for under-vaccination may be related to hesitancy of parents to vaccinate, but others relate to the health system and/or health providers. They are also differ according to vaccine, e.g. BCG coverage might be 95% (at time of birth) while measles coverage is 60% because it takes place at an older age and requires parents to take time off work etc. For this reason it might be challenging to develop standardized tools that work across the board and are applicable to these different contexts.

Questions to be answered

1. Does IVIR-AC have any inputs in relation to the demand data work stream
   a. What are IVIR-AC's comments on the proposed approach
   b. What can we learn from other efforts to standardize data collection, e.g. coverage?
   c. What issues should we anticipate, e.g. data collection, capacity, update of tools?
   d. How can these issues be best addressed?
   e. How can we balance quality, practicality and timeliness?
   f. What is the best way to disseminate such tools?
2. Does IVIR-AC have any inputs in relation to the proposed priority activities for the demand sub-group?

Summary and Recommendations

The Terms of Reference for the IVIR-AC WG on vaccine acceptance and demand were agreed on during the September 2018 IVIR-AC meeting. For 2019, the proposed priority activities for the WG are to agree on the conceptual framework / model to guide IVIR-AC in this area, and to provide methodological input into relevant activities such as methods for developing and testing tools to assess reasons for under-vaccination.

A demand data expert WG was established in October 2018, to provide a set of tools and guidance for programmes and partners to boost the availability, quality, and use of local and global data on acceptance and demand, including supporting assessments of under-vaccination, facilitating the design and evaluation of interventions and tracking trends over time. IVIR-AC was requested to comment on the demand data workstream, particularly with regard to the proposed approach and priority activities.

Recommendations

- The focus of IVIR-AC is on implementation research and modelling where results can be used to inform programmes and policies.

- IVIR-AC requests the WHO secretariat to provide further clarity about the role for IVIR-AC in implementation research and methods for enhancing vaccine acceptance and demand.

- There should be clarity of terminology and assurance that the terminology reflects the reasons for under-immunization. These reasons include hesitancy which is a motivational construct influenced by confidence in vaccines and perceptions of benefit. However, there may also be practical and programmatic issues such as: being aware a vaccine is due, knowledge on how to access a service, difficulty accessing a service, non-availability of sought vaccine, missed opportunities in healthcare settings, etc.

- IVIR-AC noted that vaccine acceptance and demand is a diverse and complex topic, and reasons for under-vaccination can vary by vaccine, location and time. Tools to be developed need to take into account this diversity and be adaptable to the different situations.

- IVIR-AC should consider the range of frameworks explaining vaccination behaviour, including those previously presented.

- The IVIR-AC supports the WG on Data Demand Workstream and its present plans. The IVIR-AC Acceptance and Demand sub-group should continue to provide review of the WG plans and methods.

- Given the importance of the hesitancy issue, identified by WHO as one of the top 10 global health threats for 2019[8], it is critical that adequate resources are made available to address this and other barriers to vaccination.

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[8] https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

Session 4: Market Information for Access Methodology (MI4A) for HPV vaccines

Introduction

The Market Information for Access to Vaccines (MI4A) was launched by WHO to contribute to the achievement of Strategic Development Goal 3.8 (Universal Health Coverage target) by enhancing access to safe, effective, quality, and affordable vaccines for all. MI4A responds to requests from Member States and the WHO SAGE to address vaccine market information gaps. MI4A focuses on vaccines that have availability constraints, affordability issues, or that are subject to important policy or vaccine pipeline changes. The purpose of MI4A is to address affordability and availability issues through enhanced market information, particularly targeting countries not receiving UNICEF, GAVI, or PAHO support.

In September 2018, MI4A published the global market study for HPV vaccines. Annual demand was forecasted by country for 2019 to 2030 based on target population, number of doses, an analog for coverage / update, vaccine wastage and a buffer. It highlights expected increase in demand due to the cervical cancer elimination initiative by at least 100M doses over the next 10 years. Supply was defined as the number of doses available for sale at global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events), and is estimated based on information from key manufacturers and the triangulation of several different information sources. A base scenario and several supply scenarios for available supply for commercialization were then estimated. The supply-demand balance is influenced by demand stability and predictability. IVIR-AC was requested to comment on the methodology, data and assumptions underlying the estimates of global demand and global supply presented in the HPV vaccine market information.

Review

General considerations

This is a vital and unique piece of work. Efforts to gather and share information on the supply and demand of different vaccines are critical for ensuring that suboptimal vaccine supply situations and supply shortfalls are prevented. Each piece (supply and demand, the supply-demand balance and pricing) are important - the most useful analyses will require all three pieces. The product is a valuable public good with the potential to shape markets and ultimately save lives if greater transparency and less information asymmetry generally leads to more efficient markets. The emphasis on making the methods for the estimation of supply and demand both transparent and replicable should be applauded. The initiative deserves IVIR-AC's full support.

Demand model

In terms of the data inputs, the use of UNPD population estimates seems appropriate as this is widely used and is unlikely to be a major source of uncertainty on the large global scale of the analysis. Greater sources of uncertainty are the future introduction dates and expected coverage level of new vaccines.

It would be useful to determine whether there is a standard set of information and variables that is useful for forecasting demand of all vaccines, or whether the factors to be considered in predicting introduction dates is vaccine-specific.

Validating forecasts (including forecasts made previously for new vaccine introductions, e.g. rotavirus, PCV) is important and potentially useful for determining accuracy of demand forecasts and identifying which factors are most important in predicting new introduction dates. The wastage rate may also be influential; a meta-analysis may be useful for informing this.

Intro dates/coverage for non-Gavi vaccines come from a variety of sources e.g. country plans, regional offices, expert review, and historical data. It is unclear how the data are synthesised and it might be useful to apply a hierarchy of evidence if there are multiple sources.

It might be useful to collaborate with countries to obtain private market demand. In China for example, privately purchased vaccines are delivered via government clinics run by the Chinese Center for Disease Control and Prevention so they may have data. A literature review (in local languages) may also help, although resources may be needed for this.

Supply model

While potentially reliant on confidential data, it is important to understand the timeframe on which manufacturers can react and increase supply for particular vaccines to meet unexpected demand.

To improve estimates of the overall mean supply for future scenarios as well as the uncertainty, it was suggested to obtain estimates of supply range for particular vaccines (rather than point estimates), and then sample from these ranges for multiple manufacturers.

The method proposed for anticipating the supply of pipeline products seems overly simplistic; since this is likely to vary depending on the target pathogen (certain vaccines have proven harder to develop than others, e.g. dengue, RSV).

For countries with domestic production, the introduction date assumed to coincide with forecasted date of product licensure. However, licensure of a domestic vaccine does not necessarily coincide with high coverage nationwide. For example, Rotavac in India and EV-71 vaccines in China. Close communication with national policy makers e.g. in the Ministry of Health in large countries would be useful.

Relation between demand and supply

The key question to be addressed by these data is the ability to project future demand and supply, in addition to current demand and supply. Hence there may be use (especially in the longer term as more data are compiled) for econometric forecasting models based on macroeconomic indicators and supply/demand feedback loops, and not purely survey responses (which may be less reliable about future). This will require further data beyond what is available in the summary sheets. It was questioned to what extent more details (suitably anonymised and/or aggregated where necessary) can be provided in a convenient form for analysts.

Pricing information / database

It may be useful to collect both retail and tender prices, as some countries may achieve greater cost efficiencies through bulk public tenders. Some retail price info may be in the public domain.

Advisory group

The advisory group has an excellent selection of key people, but may also benefit from methodological expert(s) e.g. in statistics, economics, market analyses etc. to develop new methods.

Discussion

The demand and supply balance is based on the assumption of a perfect market. However, this may not be the case, because vaccines might not be provided in certain markets, there might be Intellectual Property (IP) issues, or certain producing countries might first supply themselves and as a result a proportion of the vaccine is locked for these countries. This is partly addressed by the database of registration for different products which matches to a certain degree suppliers to countries, although it is difficult to obtain this information from manufacturers. Match to certain degree suppliers to countries, but not detailed.

The relevance of this work to policy was highlighted; if it becomes apparent that there are supply issues, then high risk groups can be prioritized for vaccination.

Questions to be answered

1. What is IVIR-AC's feedback on MI4A methodology, data and assumptions and use and interpretation of data on vaccine market information?
   a. Are you aware of data sources we have not used? E.g. for the private market estimate?
   b. In the medium to long term, do you have any specific recommendation to improve our forecasts? Are you aware of innovations in data or methodologies that we may be able to leverage in the future?
   c. Do you believe the methods are sound to derive policy implications?

Summary and Recommendations

The MI4A was launched by WHO to contribute to the achievement of Sustainable Development Goal 3.8 (Universal Health Coverage target) by enhancing access to safe, effective, quality, and affordable vaccines for all. MI4A focuses on vaccines that have availability constraints, affordability issues, or that are subject to important policy or vaccine pipeline changes. The purpose of MI4A is to address affordability and availability issues through enhanced market information.

IVIR-AC was requested to comment on the methodology, data and assumptions underlying the estimates of global demand and supply.

Recommendations

- This is a vital piece of work that no other group appears to be doing. It is producing a valuable public good with a potential to shape markets and ultimately save lives if greater transparency and less information asymmetry generally lead to more efficient markets. The initiative deserves IVIR-AC's support.

- The methods are transparent, reasonable and replicable. Each piece (pricing, supply and demand) is important - the most useful analyses will require all three pieces.

- It would be important to engage representatives of Ministries of Health (MoH) to assure the tool is helpful to them as well as methodologists (e.g. in statistics, economics, market analyses) to

help to ensure that the tool is accurate and the results are used for the most robust and useful analyses possible.

- The model uses coverage estimates of existing vaccines to project use of new vaccines. Efforts should be made to validate demand forecasts by looking at past introduction of new vaccines and their relationship to use of vaccines already in use at the time of the new introductions.

- At the moment ranges and scenarios are used for the demand and supply projections. However, for key input variables, point estimates are used. Uncertainty ranges should be placed on those point estimates.

- Currently, the estimation of the proportion of vaccines in various trial levels (e.g. Phase 1, 2 and 3) which become licensed and used is based on one single study. More data should be obtained to validate these assumptions.

- For private market demand, it may be best to work with countries. In some countries privately purchased vaccines are actually delivered via government clinics so they may have data. A literature review that includes papers in local languages may also help.

- To project longer term future demand and supply, use of econometric forecasting models based on macroeconomic indicators and supply, demand and pricing feedback loops, in addition to the current expert input and survey responses (which may be less reliable for the long-term forecasting) may be useful.

- Pricing information - it may be useful to collect both retail and tender prices, as some countries may achieve greater cost efficiencies through bulk public tenders. Some retail price information may be in the public domain already.

Session 5: Ebola Epidemiological modelling

Introduction

The model is used to simulate the evaluation of the outbreak in the Butembo/Katwa health zones and has simulated the impact of contact tracing and ring vaccination with the rVSV vaccine. The model is a microsimulation model of Ebola transmission which has previously been used to model outbreaks in Sierra Leone (Pujehun), Liberia and Guinea.[9,10,11] The model simulates each individual in the population and explicitly considers transmission in households, extended families, community and health care facilities, and accounts for individual variability in infectiousness and age-specific risk of infection. The model is calibrated for each health zone with historic data on confirmed and probable cases. To make predictions, estimates for vaccine operation and case detection activities (e.g. average time from symptom onset to admission to an Ebola treatment centre) are updated every two to three weeks using actual epidemiological data.

The purpose of the model is to assess vaccine impact and the performance projections of different strategies. The model provides estimates of the following epidemiological indicators: forward projections for the number of cases in health zones with sustained disease transmission, estimates of number of averted cases by the current implementation of ring vaccination protocol compared to scenarios with no vaccination, and forward projections for the demand of vaccine supplies. As such the model can be used to evaluate the probability of disease elimination in each health zone by looking at the number of stochastic microsimulations that have zero infectious individuals at any given future time.

Review

Usefulness of model

Together with empirical data, the model aims to inform the actions of the outbreak response. Overall, the methodology and analysis are sound. The investigators have published this modelling framework for Ebola ring vaccination in West Africa earlier in PLOS NTD in 2016. As noted by the investigators, there are many plausible epidemic scenarios that can be considered in disease modelling. The investigators have accounted for a majority of these plausible scenarios in their analysis.

The type of microsimulation approach under consideration has the potential to be much more important in fostering understanding of determinants of outbreaks and in guiding effective responses.

The modelers should make sure that they explicitly describe all important details of the model, including purpose, data and assumptions. These include for example: the purpose of this modelling exercise in the terms of its intended contribution to Ebola containment and mitigation in the field, and the start time of ring vaccination.

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[9] Merler S, Ajelli M, Fumanelli L *et al*. Spatiotemporal spread of the 2014 outbreak of Ebola virus disease in Liberia and the effectiveness of non-pharmaceutical interventions: a computational modelling analysis. Lancet infect Dis 2015, 15: 204-211

[10] Ajelli M, Merler S, Fumanelli L, *et al*. Spatiotermporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modelling analysis. BMC Medicine 2016,14:130.

[11] Merler S, Ajelli M, Fumanelli L, *et al*. Containing Ebola at the source with ring vaccination. PLoS Neglected Tropical Diseases 2016,10(11):e005093

Heterogeneity in transmission

The investigators should explicitly indicate whether the inference and forecasts are sensitive to heterogeneity in infectiousness such as for example between those who were hospitalized and those who were not.

Natural history of infection

When multiple contacts are identified for the same case, the average time between the contact and onset of symptoms was used, weighting all contacts the same. This likely underestimates the incubation period.

Cases infected via contacts with relatives, non-relative contacts, in general community, and in healthcare facilities are unlikely to be mutually independent. A multivariate distribution with a correlation hyperparameter could be used instead.

Nosocomial transmission

The model indicates that the absence of nosocomial infections appears to make a big difference to the elimination probability, as well as the time to isolation / hospitalization. This is recognized and in there is a dedicated team working on infection prevention and control. Vaccinated contacts and contacts of contacts are regularly followed-up and monitored.

Discussion

The Committee agreed with the use of conservative estimates for vaccine efficacy. Uncertainty about vaccine efficacy is dealt with by assuming different rates of vaccine efficacy, i.e. 100%, 90% and 85%. Furthermore, it is assumed that the vaccine is not effective if given after exposure.

Questions to be answered

1. Are the models valid to determine the optimal Ebola vaccine strategies in an outbreak setting in terms of the model design, parameters, attributes and the assumptions given the sparsity of data available?

Summary and Recommendations

The model is used to simulate the evaluation of the outbreak in the Butembo/Katwa health zone and has simulated the impact of contact tracing and ring vaccination with the rVSV vaccine, providing estimates of the following epidemiological indicators: forward projections for the number of cases in health zones with sustained disease transmission, estimates of number of averted cases by the current implementation of ring vaccination protocol compared to scenarios with no vaccination, and forward projections for the demand of vaccine supplies. IVIR-AC was asked to comment on whether the model is valid to determine the optimal Ebola vaccine strategies in an outbreak setting in terms of the model design, parameters, attributes and the assumptions given the sparsity of data available.

Recommendations

- IVIR-AC believes that the model is useful for the forward projection of the number of cases, estimates of number of cases averted, and demand for vaccine supplies for various control strategies (e.g. ring vaccination, contact tracing and isolation, etc). The Committee sees the value of the combination of model outputs and empirical data to inform response activities.

- IVIR-AC agrees that the investigators have accounted for the majority of the plausible epidemic scenarios in their model.

- The investigators should explicitly indicate the purpose of this modelling exercise in terms of its intended contribution to Ebola containment and mitigation in the field.

- Infectiousness (secondary case/offspring distribution) of those who were hospitalized and those who were not might be fundamentally different. The investigators should explicitly make clear that the inference and forecast are sensitive to this heterogeneity.

- There are numerous strengths of the model parameters (e.g. vaccine efficacy based on trial data as well as continuing assessments of vaccine effectiveness) and attributes (e.g. temporal changes in transmission dynamics (e.g. time to admission to health care facilities) and vaccine operations depend on regular revision of data)

Session 6: WHO guide on vaccine delivery costs

Introduction

WHO, in collaboration with Levin and Morgan Global Health Consultants, has developed several costing tools including the WHO Cervical Cancer Prevention and Control Costing Tool (C4P), the Seasonal Influenza Vaccine Costing Tool, and the Malaria Vaccination Introduction and Costing Tool. Other tools are currently under development or piloted, including the Typhoid delivery costing tool, and the Cholera vaccine costing tool. Other actors are also developing costing tools; the Bill and Melinda Gates Foundation (BMGF) has published a working paper on a common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs. Because these tools use different definitions and apply different methodological approaches, there is a need for standardization. In March 2018 IVIR-AC concluded that standardization of costing tools is required to compare delivery costs within and across countries and to compare delivery costs by product or by delivery strategy.

An overview of existing methods and guidance costing tools, with an explanation of the different purposes they serve, were presented to IVIR-AC. Furthermore, the Immunization Costing Action Network (ICAN) and EPIC3 (immunization costing) programme of work in the area of standardization of vaccine delivery costs was presented.

Review

A systematic review has highlight the strong need for standardization of definitions and data collected for vaccine delivery costing studies. Moreover, it is clear that there is also a need to standardize the way cost of delivery data is reported in publications. The reporting should be done in such a way that individual cost components can be broken down so that both financial and economics costs, and (ideally) costs from societal versus healthcare provider prospective can be determined for future studies. The Immunization Delivery Cost Catalogue (IDCC) might provide a useful template for this. Systematic and standardized data collection and reporting would make extraction and comparison of data across different studies more manageable.

It is important to ensure that the cost of delivery for campaign doses is collected in a way that these can be directly compared to costs for routine doses.

WHO should consider whether it is possible to develop a cost of delivery tool that can be easily adapted to new vaccines, e.g. by offering different options for oral vs injectable vaccines, delivery strategies, etc. rather than developing new tool for each vaccine.

EPIC's proposed meta-regression analysis of delivery costs across different countries is potentially very useful in understanding uncertainty in delivery costs both for existing studies and extrapolation to new countries.

It is important to understand how different the needs are for cost of delivery tools for retrospective vs prospective (new vaccine) analyses.

It might be useful to have a workshop to explore the existing guidelines (being developed by EPIC/ICAN) and tools in more detail, standardize definitions and cost categories collected/reported, provide an overview of modelling approach(s), and obtain input from country-level users (target audience).

Discussion

It was discussed whether there is a need for the WHO guide to be developed, or whether the existing tools and those that are already being developed are enough. It was proposed that this requires a critical review from WHO with participation from EPI programme managers (possibly through the International Organisation of Immunization Managers). If the current tools are promising, then perhaps a third effort is not needed.

The ICAN guidelines seem very developed but it was unclear whether they meet the need for retrospective and prospective data collection.

There seems to be some divergence between the ICAN (BMGF tools) and those developed by WHO because partly they have the different aims (prospective or retrospective). The possibility was discussed to have a workshop with all partners to come up with joint guidelines.

Questions to be answered

- Does IVIR-AC have any feedback on the plan of work for the development of the WHO guide?
- How should the WHO guide build on existing guidance documents and/or provide additional guidance where there are gaps?

Summary and Recommendations

WHO is considering the development of a Guide on Vaccine Delivery Costs. Costing tools for vaccine delivery have been developed for a variety of disease. ICAN is also in the process of developing costing guidance and tools. An overview of activities on vaccine delivery costing was presented, and IVIR-AC was asked to comment on how the WHO guide should build on existing guidance documents and/or provide additional guidance where there are gaps.

Recommendations

- A systematic review has highlighted the need for standardization of data collection and reporting, to allow extraction of costing data for example so that both financial and economic costs[12] can be calculated.

- It is important to identify the target group for the guide and tools. IVIR-AC recommends that members of the target group (e.g. National Immunization Programme Managers) are included in the development of the guide.

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[12] Financial costs are actual monetary costs that appear in budgets, whereas economics costs are opportunity costs that include the value of alternative uses of resources such as staff or cold chain capacity.

- IVIR-AC noted that there is a lot of activity going on with different tools being developed, but also that there seems to be some potential divergence between the ICAN (BMGF/funder focused tools) and those developed by WHO (EPI manager focus), partly because they have different aims (prospective costing for vaccine introduction versus retrospective costing of existing programmes). Some of this apparent divergence may be simply due to different terminology.

- IVIR-AC feels that the need for a WHO guide to be developed requires some careful consideration, given the availability of existing guides and tools. This requires a critical review from WHO, with participation from EPI programme managers.

- IVIR-AC recommends a workshop with all partners involved in vaccine costing methodology to have detailed discussions and potentially develop joint guidelines; WHO should develop a guide on its own only if this is not possible.

Session 7: Measles Rubella vaccines investment case

Introduction

Modelling has been used to assess global, national and regional measles elimination and eradication goals. After thorough review of the KidRisk model by IVIR-AC and its predecessor QUIVER on various occasions, both IVIR-AC and SAGE Measles and Rubella WG recommended the commissioning of a second modelling group to provide a second opinion or back up to the KidRisk model. A measles and rubella modelling consortium is now being established and the proposed structure and activities were presented to IVIR-AC.

A proposed simulation study was presented to IVIR-AC with the request to comment on the proposed plan of work. The study aims to evaluate the relative performance of four future vaccine programme improvement scenarios in terms of the expected future burden of measles and rubella (incidence cases, deaths, cases of congenital rubella syndrome and disability-adjusted life years), the proportion of simulations in which the burden of measles and rubella will fall below a certain threshold within a certain time horizon, and the first year in which the burden of measles and rubella falls below a certain threshold. Four groups with well documented existing models (two measles models and two rubella models) will be asked to model the standardized scenarios for 98 countries. In addition, one or two fine-scale models will be included to provide a comparison that illustrates subnational dynamics due to subnational heterogeneity in control and eradication programmes.

Review

Challenges remain with the incorporation of heterogeneity in vaccine coverage. Spatial variation of vaccination coverage may or may not correlate to sub-national administrative units. Pockets of low coverage can result in outbreaks. Although the included models can incorporate some spatial variations, it is challenging to do so for all the countries within the time frame. The solution to do modelling on country level and add one or two countries for which a regional model is compared with the country level model is acceptable for the current time frame, but the need to move towards models adapted to sub-national geography and sub-populations is there.

Some strengths of the proposal include the addition of heterogeneous mixing, the building in of case-fatality rate (CFR) meta-analysis, and the targeting of supplementary immunization activities to different children. The effort to have at least two models for each disease is appreciated.

It might be necessary to separate out different scenarios. For example, in order to evaluate what the introduction of measles containing vaccine second dose (MCV2) can bring in comparison with achieving 95% coverage of measles containing vaccine first dose (MCV1) instead of 90%, this needs to be *split out* in the scenarios. Similarly it was questioned whether it is necessary to separate out the effects of MCV2 and Supplementary immunization activities (SIAs). Furthermore, it was suggested that the worst case scenario was perhaps too bad and that this scenario should be elevated to a more realistic approach.

With regard to subnational modelling, it is now planned to look at specific data from a country from which you have data. However, a sensitivity analysis by varying levels of heterogeneity in vaccine coverage might be more useful, when time and resources allow.

This work is well organized and clearly a step in the right direction. While the timeline is tight it should be feasible. Although perhaps not possible within the current timeframe, further work is ultimately required on regional differences and subnational data, and also on costs.

Discussion

In order to inform SAGE and then the WHA, the possibility was raised to stratify countries in different categories according to where they are in the progress of measles elimination. It was noted that this is perhaps difficult to do within the timelines, but that it can perhaps be fairly easily done if it is requested.

It is important to consider the potential positive and negative impacts from an eradication effort; these could either distract from or enhance the routine immunization programme.

Questions to be answered

- Does IVIR-AC have any comments/ suggestions on the new proposed plan of work for the measles rubella investment case?

Summary and Recommendations

IVIR-AC and SAGE WGs previously recommended that a second modelling group be invited to assess global measles eradication. In response, a second measles and rubella modelling consortium is being proposed incorporating 2 measles models, 2 rubella models and 1 or 2 subnational models. The proposed work of the Vaccine Impact Modelling Consortium was presented to IVIR-AC with the request to comment on the proposed plan of work.

Recommendations

- IVIR-AC believes the proposed modelling will be a tremendous help in efforts to eliminate and potentially eradicate measles/rubella. The current ongoing approach has the potential to overcome some of the concerns with earlier models. The timelines are tight but feasible

- To the extent possible economic considerations of elimination should be included in the models

- Modelling groups need to lay out the assumptions behind each model (e.g. herd immunity thresholds, vaccine effectiveness of MCV1, MCV2 etc.)

- In the future there is a need to move towards models adapted to sub-national geography and sub-populations and if possible extend the efforts initially planned for one country using a variety of modelling approaches.

- Perhaps not within the current time frame, but ultimately further work is required on:

    - Heterogeneity of vaccine coverage

    - Cost and cost-effectiveness

    - *S*tratification of countries according to burden and other factors such as country income group.

Session 8: Enteric disease burden estimation

Introduction

The WHO convened a global stakeholder workshop on 29th and 30th November 2018 to discuss enteric Burden of Disease (BoD) estimates; specifically the reported mortality and aetiology in children under five years of age. This workshop resulted from a recommendation from WHO's Product Development for Vaccines Advisory Committee (PDVAC), and its effort to better evaluate and communicate the full public health value of vaccines (FPHVV). During the workshop, the two primary models for assessment of disease burden, the models of IHME and the Johns Hopkins University (JHU) Maternal and Child Epidemiology Estimate (MCEE), were compared to identify areas of commonality and divergence across methodologies and assumptions. The models report different mortality estimates in under 5 year olds, and different aetiology (pathogen underlying diarrhoeal disease and deaths.

There is a need to gain a better understanding of the relationship between presence of pathogen and diarrhoea, and to obtain more information on the case fatality rate of different pathogens. For this reason two systematic reviews are planned: 1) Systematic review on the number and type of enteric pathogens present in stools of healthy controls and patients with diarrhoea, and 2) Systematic review of case fatality ratios for enteric pathogens in hospitals and communities.

IVIR-AC was asked to comment on the proposed approach to compare and characterize the IHME and MCEE input data to identify key variables in the models, on the review of the forensic data analysis, and the validity, scope, methodology and scientific approach for the proposed systematic reviews.

Review

Importance

The Committee commended the activities of both modelling groups, and WHO and the wider community for their involvement and cooperation. This work is time consuming but vital to advance the field. The estimates of burden of disease obtained by modelling will directly drive investments and decisions with regard to the development of interventions. In addition, there is a general need to use multiple models and to carry out comparisons of BoD modelling. This is particularly relevant in light of the memorandum of understanding that was signed between WHO and the IHME, which might lead to convergence methodology. In this light it is important that adequate resources are available for model comparison activities.

Uncertainty

It was questioned how precise mortality estimates need to be to inform downstream analysis (e.g. vaccine prioritization), and what the margin of error is that decision-makers are willing to accept. Several areas of uncertainty were highlighted, including the large uncertainty with regard to mortality which is difficult to estimate because there are few studies available. It was proposed that, instead of trying to obtain one estimate, the researchers should identify key assumptions, or compare assumptions that drive the results. It was furthermore noted that while there are differences in estimates between groups, there are also variations between years which are as large as or larger than differences between models. Another point for consideration was the fact that there are likely to be variations between different geographies, resulting in large uncertainties around global estimates.

For the model comparison, it is important to differentiate between uncertainty that derives from the model structure, and uncertainty that derives from the data. By using a standardized dataset for both

models, this differentiation can be done. There might be a role for WHO, in helping to standardize the dataset.

Systematic reviews

The plans and the approach for the systematic reviews look good. They will benefit both modelling groups as well as wider scientific and immunization community when they are complete.

It was suggested to take care in developing the definition for the CFR, considering that the purpose of the vaccine is to prevent infection. Furthermore, the CFR might be highly variable depending on whether it is measured in a community or in a clinical setting. Within clinical settings, the CFR might also differ.

It should be highlight that this systematic review is only part one of the process, which will be followed with quite complicated statistical analysis, possibly involving network meta-analysis, requiring further input and support from IVIR-AC.

Discussion

The CFR study will help to answer the accurateness of assumptions on the use of hospitalizations as a proxy for diarrheal mortality. This will help in future to better extrapolate from hospitalization to death.

The proposed search terms related to death / CFR might lead to bias towards studies in which deaths occurred. It was proposed to also include other search terms, for example related to hospitalization.

The model comparison will be a useful exercise, helping to derive at a dataset that is well characterized and that can be used for both models. It was mentioned that the models might require modification as a result of the review / model comparison.

Questions to be answered

- Assessment of the variation in aetiology estimates as a consequence of differences in IHME and MCEE model structures
  - Does the committee agree on the proposed methodology to compare model outputs
- Assessment of the variation in aetiology estimates as a consequence of model input data
  - Does the committee agree with the proposed analytical methodology for comparing pathogen aetiology estimates and the proposed approach for a sensitivity analysis
- Does the committee agree with the scope, methodology and scientific approach for the both systematic reviews?

Summary and Recommendations

Enteric BoD estimates; specifically, the reported mortality and aetiology in children under five years of age is challenging. The two most important models are those of IHME and MCEE. However, there is divergence across methodologies and assumptions, particularly related to diarrheal mortality proxy, and the use of qPCR data to define pathogenicity. Two systematic reviews are planned to gain a better understanding of the relationship between presence of pathogen and diarrhoea, and to obtain more information on the case fatality rate of different pathogens.

IVIR-AC was asked to comment on the proposed approach to compare and characterize the IHME and MCEE input data to identify key variables in the models, on the review of the forensic data analysis, and the validity, scope, methodology and scientific approach for the proposed systematic reviews.

Recommendations

- IVIR-AC agrees with the approach proposed to be taken and highlights the importance of having multiple models and model comparison exercises to better understand methodology involved in estimating disease burden.

- IVIR-AC recommends that we better understand the margin of error in mortality estimates that policy-makers are prepared to accept in prioritizing development of vaccine candidates.

- For the systematic review the inclusion of search terms related to death / CFR might lead to bias towards studies in which deaths occurred. Therefore, it is important to also include other search terms, e.g. related to hospitalization.

- It is critical given the importance of these estimates that adequate resources are available to conduct this comparison exercise.

Update on IVIR-AC logistics

In the face of a generally full meeting agenda which limits time for detailed review and discussion, several proposals were made to improve IVIR-AC logistics:

The IVIR-AC experts who report on each agenda item in future meetings should have a conversation with the presenters at least two weeks in advance of the IVIR-AC meeting to discuss the presentation, make comments and propose any changes that should be made to the presentation prior to the IVIR-AC meeting.

Specifically when reviewing work that is highly technical and which requires detailed discussion, it might be useful for the reviewers to have an initial exchange with the investigators prior to the meeting. This could be done by e-mailing them a list of queries/suggestions and receiving a written response from them. At the IVIR-AC meeting they can then summarize the exchange, explain whether they are satisfied with the response, and use the session mainly to outline any major outstanding issues or areas for further discussion.

This could help focus the face to face time on the major issues that could benefit from discussion from the whole committee, while still giving the investigators the opportunity to receive detailed (and often highly useful) comments on their work from the most relevant members,

Considering the diversity of research topics and areas, there might be a rationale for dividing the methods addressed /evaluated according to the following categories:

A. Quantitative research subdivided into 3 major themes:
    a. "Simple" / direct calculations of indicators, metrics, or statistics (immunization coverage [session 1], HPV coverage [session 2], market information [session 3], vaccine delivery costs [session 6], disease burden [session 8].
    b. Mathematical models (Ebola vaccine impact [session 5], M&R eradication [session 7]
    c. Statistical models including methods used for construct validation/instrument development (not explored but perhaps could be as per needs of Global Vaccine Acceptance and Demand [session 3].

B. Qualitative research which includes theoretical models/frameworks for the development of tools and/or interventions (not extensively explored but could be as per needs of Global Vaccine Acceptance and Demand [session 3])

Annex 1: Agenda

Tuesday, 12 March 2019

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
09.00-09.15	Welcome	Charge of the Committee Introduction of new IVIR-AC members		K. O'Brien W. Orenstein
	THEME 1: Research to improve methods for monitoring of immunization programs			
09.15-10.45	*Session 1*: WUENIC vaccine coverage methods and estimates	- Introduction and context by M. Gacic-Dobo (10 min) - The use and challenges of WUENIC coverage estimates for immunization progress monitoring (20 min) (Presenter to be determined) - IVIR-AC reviewers' comments Discussion (50 min)	- Is the WUENIC method still relevant/valid for immunization programme monitoring?	IVIR-AC members: Y. Teerawattananon D. Lyimo WHO focal points: M. Gacic-Dobo
10.45-11.15	*Coffee/tea break*			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
11.15-12.45	*Session 2:* HPV vaccine coverage methods	- Introduction and context by P. Bloem (10 min) - HPV vaccine coverage methods by L. Bruni (10 min) - Expert review by J. Brotherton (10 min) - IVIR-AC reviewers' comments Discussion (50 min)	- Does IVIR-AC have any comments on the HPV vaccine coverage methods and its validity?	IVIR-AC members: A. Lopez M. Brisson WHO focal point: P. Bloem
12.45-13.45	*Lunch*			
13.45- 15.15	*Session 3:* HPV vaccine supply	- Introduction and context by T. Cernushi (10 min) - MI4A methods applied to HPV vaccines by XX (TBC) (20 min) - IVIR-AC reviewers' comments Discussion (50 min)		IVIR-AC members: W. Ndifon M. Jit WHO focal point: T. Cernushi

15.15-15.45	**Coffee/tea break**			

THEME 2: Research to minimize barriers and improve coverage of vaccines currently in use

15.45-17.15	**Session 4:** Global Vaccine Acceptance and Demand	- Introduction by L. Menning (10 min) - Research and methods update for proposed framework by J. Leask (20 min) - IVIR-AC reviewers' comments (each 5 mins) Discussion (50 min)	- Specific questions - xx	IVIR-AC members: M. Amuyunzu V. Nankabirwa WHO focal point: L. Menning
17.15-17.30	Summary Day 2	Summary of key conclusions and next steps		W. Orenstein
17.30	**Cocktail**	**WHO Cafeteria**		

Wednesday, 13 March 2019

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
		THEME 3: Research to conduct impact evaluation of vaccines in use		
09.00-10.15	*Session 5:* Ebola Epidemiological Modelling	- Introduction by AM. Henao (10 min) - Epidemiological model by A. Vespignani (20 min) - IVIR-AC reviewers' comments (each 5 mins) Discussion (50 min)	- Specific questions - xx	IVIR-AC members: J.Wu M. Brisson WHO focal point: AM. Henao
10.15-10.45	*Coffee/tea break*			

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
10.45-12.15	**Session 6:** WHO Guide on Vaccine Delivery Costs	- Introduction and context by R. Hutubessy (10 min) - Outline of the WHO Guide on Delivery Costs by A. Levin/V. Mogasale (10 mins) Immunization Costing Action Network (ICAN) methods and guidance Costing Tools. S. Resh/L.Brenzel (TBC) (10 mins) - IVIR-AC reviewers' comments - Discussion (40 min)	- Does IVIR-AC have any feedback on the plan of work for the development of the WHO Guide?	IVIR-AC members: A. Lopez V. Pitzer WHO focal point: R. Hutubessy
12.15-13.15	**Lunch**			
13.15-14.45	**Session 7:** Measles Rubella vaccines investment case	- Introduction and context by S. Shendale (10 mins) - To present the overall plan and scenarios for the investment case by M. Ferrari/M. Jit - IVIR-AC reviewers' comments - Discussion (50 min)	- Does IVIR-AC have any comments/suggestions on the new proposed plan of work for the measles investment case?	IVIR-AC members : Q. Bassat P. Cruz WHO focal point: S. Shendale

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Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
14.45-15.15	*Coffee/tea break*			
15.15- 17.15	*Session 8* Enteric Disease Burden estimation	- Introduction by G. Giersing (10 min) - Overview of the IHME and MCEE burden of enteric disease models by L Lamberti (20 min) *(by WebEx) (10 mins)* - Presentation of recommendations and next steps (workplan) – H. Prudden – (10 min) - IVIR-AC/PD-VAC reviewers' comments (each 5 min) - Discussion (50 min)	- Does IVIRAC have any comments on the recommendations, and the proposed workplan?	IVIR-AC/PDVAC members: J. Wu M. Jit P. Smith WHO focal point: G. Giersing
17.15-17.30	Summary Day 2	Summary of key conclusions and next steps		W. Orenstein
17.15	*Adjourn*			

Thursday, 14 March 2019

CLOSED SESSION FOR IVIR-AC MEMBERS ONLY

Time	Session	What will be presented?	What are the questions?	AC reviewers and WHO focal points
9.00-10.30	Formulation of IVIR-AC recommendations			
10.30-11.00	*Coffee/tea break*			
11.00 -12.30	Formulation of IVIR-AC recommendations			
12.30	*Adjourn*			

Annex 2: List of Participants

Advisory Committee Members

Quique Bassat, Paediatrician and ICREA Research Professor, ISGlobal Barcelona Institute for Global Health, Hospital Clínic - Universitat de Barcelona, Barcelona, **Spain**

*Marc Brisson, Professor, Mathematical Modelling and Health Economics of Infectious, Diseases Department of social and preventive medicine, Faculty of Medicine, Laval University**, Canada (unable to attend)***

Mark Jit, Professor Vaccine Epidemiology, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, **United Kingdom of Great Britain & Northern Ireland**

Julie Leask, Proferssor, Susan Wakil School of Nursing and Midwifery, Sydney Nursing School, Faculty of Medicine and Health, Camperdown NSW 2050, Sydney, **Australia**

*Jean-Daniel Lelièvre, Department of Clinical Immunology INSERM, CHU Henri Mondor 51 avenue Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, **France (uable to attend)***

Anna Lena Lopez, Director, Institute of Child Health and Human Development, Research Associate Professor, University of the Philippines Manila-National Institutes of Health, Manila, **Philippines (***via webex***)**

Paula M. Luz, Professor, Evandro Chagas Clinical Research Institute (IPEC/ FIOCRUZ), Av. Brasil 4365, Manguinhos, 21040-360 Rio de Janeiro, **Brazil**

*Dafrossa C. Lyimo, Programme Manager, Immunization and Vaccines Development, Ministry of Health, Community Development, Gender, Elderly & Children, Dar es salaam, **United Republic of Tanzania (unable to attend)***

Victoria Nankabirwa, Professor, Department of Epidemiology and Biostatics, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**

Wilfred Ndifon, Chair, Career Development Research, African Institute for Mathematical, Sciences, 5 Melrose Rd, Muizenberg 7945, Cape Town, **South Africa**

Mary Nyamongo, Executive Director and co-founder, African Institute for Health and Development (AIHD), Nairobi, **Kenya**

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Yot Teerawattananon, Founding Leader of Health Intervention and Technology Assessment Program & Senior Researcher Scholar of Thailand's Research Fund, Health Intervention and Technology Assessment

Program, Department of Health, Ministry of Public Health, Nonthaburi, 11000 **Thailand (unable to attend)**

Stéphane Verguet, Assistant Professor, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115, **United States of America** *(by Webex)*

Joseph Wu, Professor, Division of Epidemiology and Biostatistics, School of Public Health, The University of Hong Kong, Pok Fu Lam, **Hong Kong SAR, China**

Participants

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Niel Hens, Associate Professor at the Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Diepenbeek, **Belgium** *(by Webex)*

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Craig Roberts, Associate Vice President, Product Line Vaccines, Merck Sharp & Dohme Corp, **United States of America**

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