Accelerating Measles-Rubella Elimination through Research and Innovation

Findings from the Measles and Rubella Initiative Research Prioritization Process, 2016

MEASLES & RUBELLA INITIATIVE

American Red Cross · CDC · unicef · UNITED NATIONS FOUNDATION · World Health Organization

Table of Contents

Acronyms

BMGF	Bill & Melinda Gates Foundation
CDC	United States Centers for Disease Control and Prevention
CRS	Congenital rubella syndrome
DTP3	Third routine dose of diphtheria, tetanus and pertussis vaccine
Gavi	Gavi, the Vaccine Alliance
GMP	Good manufacturing practice
GMRLN	Global Measles and Rubella Laboratory Network
GPLN	Global Polio Laboratory Network
GVAP	Global Vaccine Action Plan
M&RI	Measles & Rubella Initiative
MCV	Measles-containing vaccine
MCV1	First routine dose of measles-containing vaccine
MCV2	Second routine dose of measles-containing vaccine
ORI	Outbreak response immunization
PAHO	Pan-American Health Organization
POCT	Point-of-care test
PRC	Polio Research Committee
RCV	Rubella-containing vaccine
RIWG	M&RI Research & Innovation Working Group
SIA	Supplemental immunization activity
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Executive Summary

The Measles & Rubella Initiative[1] (M&RI), founded in 2001,[2] established a vision to achieve a world free of measles and rubella (1). Since the M&RI partnership was established, significant progress toward achieving this vision has been achieved through focused efforts by partners and countries. From 2000 to 2015, annual reported measles incidence decreased 75%, from 146 to 36 cases per million population, and the annual estimated number of measles deaths decreased 79%, from 651,600 to 134,200 (2). These decreases in measles morbidity and mortality were due to increasing levels of measles vaccination and surveillance activities. The M&RI partners identified five key strategies to achieve measles and rubella elimination, 1) High population immunity through vaccination with two doses of measles and rubella containing vaccine; 2) Effective surveillance, monitoring and evaluation; 3) Outbreak preparedness and response & case management; 4) Communication to build public confidence and demand for immunization; and 5) Research and development to support cost-effective operations and improve vaccination and diagnostic tools. To focus efforts on implementation of the fifth strategy, the M&RI Research and Innovation Work Group (RIWG) completed a research prioritization process in 2016 to identify key research questions.

The RIWG process objective was to prioritize the research questions to further progress toward achieving regional measles and rubella elimination targets and, eventually, eradication. The process including steps to identify potential research questions by reviewing previous research prioritization activities, strategic planning documents and gathering inputs from the operational level through a web survey, updates on identified challenges to elimination activities. The RIWG then organized and convened an expert meeting in November 2016 to prioritize the identified research questions through four workgroups, one for each of four strategic areas, 1) Epidemiology and economics, 2) Surveillance and laboratory, 3) Immunization strategy, and 4) Demand creation/communications.

Following this research prioritization process in 2016, further actions will be taken by the M&RI to ensure the identified key research questions are addressed, including advocacy to raise interest and mobilize resources to implement research activities that will support policy-making and strategy implementation.

[1] The Measles & Rubella Initiative was named the Measles Initiative from 2001 to 2012.

[2] The five founding partners of the M&RI are the World Health Organization, United Nations Children's Fund, the American Red Cross, the United Nations Foundation and the United States Centers for Disease Control and Prevention

The Research Questions Identified and Prioritized in 2016 by the Measles & Rubella Initiative Research and Innovation Work Group

Research strategic area	Research question
Epidemiology and Economics	1. How can programmatic data be used to better identify susceptible populations to target interventions? 2. What are common reasons for under diagnosing and reporting of measles, rubella and CRS cases and what strategies should be adopted to improve case ascertainment and reporting in different transmission settings? 3. What are the incremental costs and benefits of prevention, surveillance, and outbreak response for measles, rubella and CRS, and the financial resources required to achieve measles and rubella elimination? 4. What is the estimated public health impact at the national level of measles and rubella vaccination? 5. How best can data on population characteristics, susceptibility profiles and virus genotypes be used to identify transmission pathways and predict areas and populations at risk for measles and rubella outbreaks?
Immunization Strategies	1. What is the cost-effectiveness of interventions to increase coverage with MCV1 and MCV2 from 80% to 95%? 2. What are best strategies to reach geographically and socio-cultural hard-to-reach populations with two doses of measles-containing vaccine? 3. What factors determine the appropriate target age range, geographic parameters (national versus subnational) and frequency of SIAs to achieve rubella/CRS and measles elimination? 4. What indicators are needed to guide extent and timeliness of outbreak response immunization? 5. What is the potential programmatic impact of micro-array patches to increase measles vaccination coverage?
Surveillance and Laboratory	1. Can vaccine safety, effectiveness, and/or coverage be improved by developing more thermo-stable vaccines and by alternative delivery methods (e.g., microneedles)? 2. How can point-of-care tests be optimized to have the maximum impact to improve surveillance? 3. What innovations are needed to strengthen molecular epidemiology for measles and rubella to demonstrate the success of vaccination programs? 4. What are innovative/new methods and corresponding costs for CRS surveillance in areas with limited human and/or financial resources?
Demand Creation and Communications	1. How can service delivery be altered to create and increase vaccine acceptance and demand? 2. What is the effectiveness of social mobilization as a tool for vaccine demand creation for SIA, and adapting it for routine immunizations? 3. Are news and social media effective tools for demand generation? (Whatsapp, Facebook, etc.) 4. How to design laws and regulations to increase vaccine acceptance? 5. What is an appropriate MR vaccine behavioral demand and acceptance surveillance framework?

Background

The Measles & Rubella Initiative[3] (M&RI), founded in 2001,[4] has a vision of a world free of measles and rubella (1). The M&RI partners have seen significant progress toward achieving this vision through focused efforts by partners and countries. From 2000 to 2015, annual reported measles incidence decreased 75%, from 146 to 36 cases per million population, and the annual estimated number of measles deaths decreased 79%, from 651,600 to 134,200 (2). These decreases in measles morbidity and mortality are due to increasing levels of measles vaccination and surveillance activities.

Measles is a viral infection associated with significant childhood morbidity and mortality, with a case fatality ratio of 0.1%–10%, often due to respiratory and intestinal complications following measles virus infection (3). Measles virus transmission can be interrupted with two doses of measles containing vaccine (MCV) given to 90%–95% of children (4). Measles elimination efforts are focused on achieving and maintaining high levels of population immunity.

Rubella virus infection causes a mild fever and rash illness in children and adults. However, rubella during pregnancy, especially during the first trimester, can result in miscarriage, fetal death, stillbirth, or a constellation of congenital malformations known as congenital rubella syndrome (CRS). Ongoing measles elimination activities are an opportunity to achieve rubella elimination, as measles and rubella share vaccination and surveillance platforms (5). However, rubella control efforts at this time focus on introduction of rubella vaccine globally, with subsequent focus on achieving high population immunity in collaboration with measles elimination activities.

From 2000 to 2015, estimated coverage with the first dose of MCV (MCV1) increased globally from 72% to 85%, and the number of countries with ≥90% MCV1 coverage increased from 84 (44%) to 119 (61%) (2). In addition, the number of countries providing a second dose of MCV (MCV2) nationally through routine services increased from 97 (51%) to 160 (82%), increasing global MCV2 coverage from 15% in 2000 to 61% in 2015. Further acceleration of introduction is expected after the 2016 World Health Organization (WHO) policy change, which recommends less stringent criteria for MCV2 introduction (6). Routine immunization activities are bolstered by supplementary immunization activities (SIAs), also referred to as mass vaccination campaigns. For example, in 2015, approximately 184 million persons received measles-containing vaccine during SIAs implemented in 41 countries, with 32 (78%) providing one or more additional child health interventions during the measles SIA (2).

In 2011, WHO updated guidance on the preferred strategy for introduction of rubella-containing vaccine (RCV) into national routine immunization schedules, including an initial vaccination campaign with a targeted age group recommended to include children aged 9 months–15 years (7), an approach that can result in elimination. As of 2015, 46% of the world's infants were vaccinated against rubella through routine services; this was a result of the 149 of 194 countries that had introduced RCV (8). Of the countries that had not yet introduced, 37 of 45 were eligible for support from the Gavi Alliance (Gavi). Since 2000, approximately 70 low- and middle-income countries have received support from Gavi to increase equitable use of vaccines by strengthening health systems and accelerating the introduction and use of vaccines, including measles- and rubella-containing vaccines.

As of 2015, 189 (97%) countries were implementing measles case-based surveillance in at least part of the country, and 191 (98%) had access to standardized quality-controlled testing through the WHO Global Measles and Rubella Laboratory Network (GMRLN) (9). This surveillance network identified a decrease in the number of circulating measles virus genotypes. Of the 24 recognized measles virus genotypes, 11 were detected during 2005–2008, eight during 2009–2014, and six during 2015. Rubella

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surveillance is integrated into measles surveillance and CRS complements the integrated measles-rubella surveillance systems, with 161 countries reporting CRS cases in 2014 (10).

The progress toward measles and rubella elimination occurred following improvements of routine immunization programs. Commitments by country governments and the collaboration of global immunization partners led to a reduction in the number of infants who did not receive three doses of diphtheria-tetanus-pertussis vaccine (DTP3) and MCV1 to 19.4 million and 20.8 million infants, respectively, in 2015 (11). However, despite substantial progress, global DTP3 and MCV1 coverage has remained at 84%–86% during 2010 to 2015, with coverage improving in some countries and deteriorating in others. Although vaccines are being introduced into low-income countries more rapidly than ever before, equity in coverage has not yet been achieved and disparities exist, even for vaccines with long-standing recommendations such as DTP3 and MCV1. Improvements in equity of access are necessary to reach and sustain high coverage, increase protection from vaccine-preventable diseases, and achieve measles and rubella elimination goals in all regions of the world (11).

In 2012, the World Health Assembly endorsed the Global Vaccine Action Plan 2012–2020 (GVAP) (12). The GVAP set immunization coverage targets and established a goal to achieve elimination of measles and rubella in five of the six WHO regions by 2020. WHO member states have adopted elimination goals in all six regions for measles and in three for rubella. The elimination of measles (May 2016) and rubella (September 2015) in the Region of the Americas was verified; however, the remaining regions are not on track to meet elimination goals for measles or rubella by 2020 (13). Achieving elimination in all regions will require program improvements, as well as research and innovation. Research and innovation is critical to provide the underpinnings for policies and strategies designed to increase coverage, better identify and define disease epidemiology, and efficiently utilize limited resources to decrease virus transmission, in addition to assisting countries to achieve and maintain elimination status.

A strategic plan for elimination was developed by the M&RI with targets that are aligned with GVAP (14). The Global Measles and Rubella Strategic Plan, 2012–2020 (the Strategic Plan) has 5 key strategies, including "performing research and development needed to support cost-effective operations and improve vaccination and diagnostic tools." Research is critical for generating evidence and evaluating information to support evidence-based policies and strategies to achieve the elimination goals. In addition, research can lead to effective innovations and tools that enhance core elimination strategies, such as disease surveillance and immunization activities.

To ensure implementation of the Strategic Plan, the M&RI management team established 5 working groups for each of the five strategies, including a Research & Innovation Working Group (RIWG), chaired by the United States Centers for Disease Control and Prevention (CDC). The long-term aim of the RIWG is to develop a research program that will facilitate efforts to reach regional elimination goals and eventual measles and rubella eradication.

Research has provided critical evidence for establishing policy, strategies and key innovations for smallpox and polio eradication. For example, smallpox eradication was facilitated by development of the bifurcated needle and the jet injector (15, 16). For polio, research leading the availability of type-specific monovalent and bivalent oral polio vaccines was a "game-changer", resulting in the deployment of monovalent vaccines in 2005 and bivalent vaccine in 2009 (17). Polio surveillance has been strengthened by innovations and new tools, including refined protocols for laboratory testing, monitoring the quality of rapid outbreak response, as well as environmental sampling of sewage systems for enhanced surveillance for polioviruses. An ongoing focus on developing new technologies and data to achieve measles and rubella elimination is necessary to ensure progress continues (18).

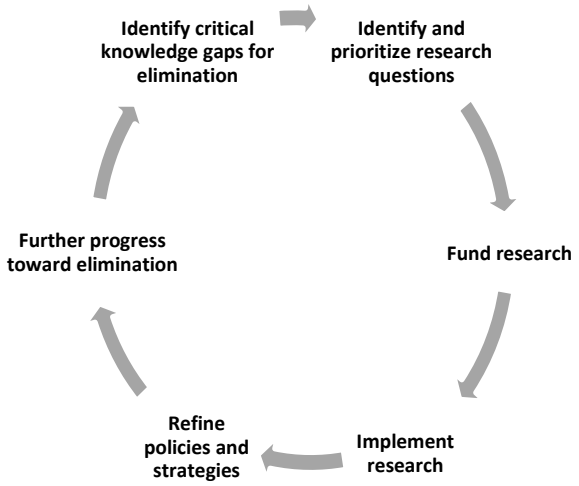
M&RI RIWG Prioritization Conceptual Framework

The M&RI RIWG initiated a prioritization process in 2016, building on previous efforts to identify and prioritize research and innovations. The research and innovations expand the evidence base for strategies and policies to achieve global and regional immunization goals to address emerging issues related to:

- Improvements to better detect and address the changing epidemiology of measles and rubella in a population or sub-population
- Further the development of routine immunization services, including a platform to deliver MCV during the second year of life
- Better utilize the introduction of measles- and rubella- containing vaccines to address and prevent immunity gaps
- Advances in development of new vaccine delivery devices and laboratory techniques
- Recognition of the critical role of communication to stimulate vaccine demand

A theoretical research cycle was constructed by the RIWG to visualize a process that starts with the identification and prioritization of knowledge gaps. Specific research projects are developed and funded for implementation leading to evidence to support refined policies and strategies. Until elimination is achieved, critical review and analysis identifies new or existing knowledge gaps that need reprioritization and the cycle is repeated. (Figure 1)

Figure 1 Theoretical research cycle for driving program improvements.



The Prioritization Process

To prioritize research needed to achieve elimination, the RIWG agreed on a prioritization process that included a large group of participants with input from all six WHO regions, and focused on operational research questions directly related to strategy implementation. The primary outcome of the prioritization process was to identify four to five priority research questions in each of four topic areas. These research questions should address the critical knowledge and evidence gaps needed to reach, maintain and verify measles and rubella elimination. In addition, the research priorities must be feasible (a question that is answerable with a proposed study design or approach) and have impact by addressing a significant bottleneck to achieve elimination. The workgroup agreed to have a four-part process to identify and prioritize research questions (Figure 2). The process generated potential research questions for consideration from a variety of sources, previous research prioritization processes, which was integrated into a web survey (which also generated additional questions), as well as expert opinions from work groups. The workgroups met and considered the various questions to prioritization research questions.

Figure 2- The four steps of the research prioritization process agreed upon by the workgroup.

Prioritization Process Implementation

Prior to the meeting, efforts were made to collect information that would help guide the process. To develop a foundation for prioritization of current research questions, a review of the previous research priority questions was completed as well as inclusion of perspectives from the Measles and Rubella Elimination Strategy 2012–2020 Midterm Review Report (19), released in October 2016 as well as through a web survey.

Review of previous research priority activities

Previous research activities started with a WHO steering committee that discussed measles and rubella vaccines in India in 2007 (20), followed by a Global Measles and Rubella Research External Peer Review meeting in Atlanta in December 2008 to update priorities for measles and rubella research. In July 2010 in Washington D.C., the WHO convened the Global Technical Consultation to Assess the Feasibility of Measles Eradication. The group of experts concluded that measles can and should be eradicated and emphasized the need to continue to prioritize and conduct research (21).

In 2011, CDC hosted a WHO Global Measles and Rubella Research Meeting in Atlanta to establish research priorities for global measles and rubella control and eradication (18). In addition, in 2013, the Strategic Advisory Group of Experts for Measles and Rubella conducted a survey to obtain expert opinion to prioritize specific research areas. These topic areas were presented at the WHO Global Vaccine and Immunization Research Forum meeting in Maryland in 2014 (22). The research group's findings were compiled and reviewed, with the many research questions integrated into the web survey for the current process.

Several lessons were learned from the previous processes. First, participant characteristics influence the outcome of the research prioritization process; therefore, participation should include a broad group of individuals from laboratorians, field epidemiologists, academics and program implementers. In addition, perspectives vary by program level; therefore, representation from global, regional and country levels was considered necessary to have a valid process. Web surveys help identify broad research areas but do not provide the opportunity to explore detailed, answerable research questions because the survey becomes too burdensome.

All but one previous research prioritization efforts used expert panels to identify and prioritize research projects; the exception used only a web survey to list priorities from a broad group of experts. Recognizing the benefits of both approaches, the current process used both a web survey to collect

information from a broad group of experts as well as an expert panel that allowed a frank and efficient consultation to synthesize the gathered information.

Lastly, the greatest challenge of the research prioritization process is securing the funding necessary to conduct the research needed to influence policy and implementation, and tracking progress in addressing priority research questions. The lessons learned included the challenge of monitor progress in addressing research questions. Progress was difficult to monitor because the research questions were often vague, making it difficult to clearly specify the required research activities.

The previous research prioritization processes identified several areas where research and innovations could be categorized. The RIWG identified areas of work used during previous meetings and consolidated them into four areas of work. Workgroups were established for each area of work. The four workgroups were: 1) epidemiology and economic analysis; 2) immunization strategies; 3) surveillance and laboratory; and 4) demand creation and communication.

Web Survey Implementation

To gather information from a broad group of participants, direct invitations to participate in a seminar and complete a web survey were sent to over 750 individuals, and many more individuals received indirect invitations through forwards of the initial invitation. A total of 163 individuals responded to the web survey during October 17–November 4, 2016, including 145 who answered all questions in the survey and 18 who partially completed the survey, whose responses were included in the analysis for questions they answered. Respondents had immunization experience from all WHO regions, with the largest numbers from the African region (n=59), the Global level (n=20), and the European region (n=33). Respondents worked for a variety of organizations, with the largest numbers employed by government or Ministry of Health (n=43), the WHO (n=41), CDC (n=22), universities (n=13), and the United Nations Fund for Children (UNICEF) (n=12). Almost half of respondents worked on measles and/or rubella for 10 years or longer (48%), and another 28% for 5–9 years. Respondents' primary work areas of work (respondents could mark more than one area) were broad including epidemiology (51%), routine immunization service delivery (50%), field surveillance (44%), outbreak response (43%), campaigns (41%), vaccine delivery (28%), and research (28%). Smaller numbers worked in communications (15%), health behavior (5%), economics (5%), and mathematical modeling (2%).

The results of the web survey were presented for each of the areas of work defined for each workgroup. The survey asked respondents to select top priority research questions in each topic area from a pre-determined list developed by technical experts, rate the significance and urgency of listed research questions, and write-in their region's top implementation challenges to achieving elimination as well as new research questions. Top research priorities were similar across most regions, with minimal differentiation of significance and urgency of research questions across regions.

Workgroup Preparation

These workgroups were led by one or two global experts on the subject area to identify the priority research questions. Data from the web survey were summarized for review by the workgroups, as well as the results of the previous research prioritization activities. Individual workgroups reviewed the open-ended responses to identify questions on implementation challenges to achieving elimination goals and new research questions. For each workgroup, the number of participants was 6–8 individuals to balance broad inputs with a size that facilitated discussion and consensus. Global experts were selected so that each group would have a mix of participants who came from academics, country-level and global experts (See list of participants in the Annex). Following the preparations, a consultation meeting was held November 29–30, 2016.

Prioritization Meeting of Experts

The meeting was held at the Pan-American Health Organization (PAHO) in Washington, D.C., USA with the support of the M&RI, Sabin Institute and PAHO. The meeting agenda included a plenary session to orient the participants to the research prioritization process, define the role of the meeting workgroups, and provide an update on the key inputs for the process. The session also included a discussion on steps toward an implementation plan for measles and rubella research.

The meeting was opened with a welcome by Assistant Director Francisco Becerra from PAHO who emphasized the importance of research to achieve elimination of measles and rubella. To orient the participants to the meeting, an overview was provided of the M&RI RIWG, which is responsible for research within the M&RI, and the meeting objectives. The three objectives of the meeting were:

- To convene subject matter experts to identify the critical knowledge and evidence gaps for achieving, maintaining and verifying measles and rubella elimination
- To develop a list of the highest priority research questions within the scope of four meeting workgroup topic areas for achieving, maintaining and verifying measles and rubella elimination
- To discuss the vision and plan for global coordination and implementation of the prioritized measles and rubella research

To supplement the information gathered prior to the meeting, and to provide background to the working groups, a review of the status and current challenges identified to eliminate measles and rubella were presented by the WHO. In addition, given the timeliness of the report, the findings of the Measles and Rubella Elimination Strategy 2012–2020 Midterm Review Report were also shared with the participants.

Review of Current Challenges to Elimination

The global status of measles-rubella elimination was presented in three parts: 1) lessons learned from outbreak investigations, 2) epidemiologic aspects of surveillance and 3) laboratory aspects of surveillance. Three country-examples were presented to highlight challenges to elimination. The M&RI partners, SAGE MR Work Group, and academic institutions have identified a number of challenges to elimination. For example, methods are needed to accurately identify population immunity gaps within countries, especially those near- or post-elimination with sub-optimal data quality or where there is minimal epidemiologic data. This information is necessary for decision-making process to address the immunity gap. Population immunity gaps include individuals aged <9 months, adolescents and adults, and are complicated by heterogeneity, particularly within large countries. In some countries, concerns exist regarding the impact of secondary measles vaccine failure. In addition, assessing the risk of rubella outbreaks is difficult, and methods to assess rubella susceptibility are needed, especially given the poor sensitivity of detecting rubella cases through current disease surveillance systems.

Where supplemental immunization activities (SIAs) play a significant role in measles and rubella elimination strategies, evaluations of strategies that can optimize limited resources are needed. SIA challenges include the need for better methods to define an adequate target population in terms of age and geographic area. The optimal timing between campaigns needs to be rigorously assessed. For countries introducing rubella-containing vaccine (RCV), the optimal time to introduce RCV and how introductory measles and rubella SIAs can achieve optimal coverage need to be identified. Outbreak response immunization campaigns also need evidence-based strategies for defining optimal timing and scope.

The challenges that face surveillance systems are varied, but were classified into several areas. The first area was the need to improve consistency between the various, often inconsistent, data sources (case-based, aggregate and laboratory reporting). Data quality also needs to be improved, for example, data from case-based surveillance systems do not have consistent results compared to aggregate or other parallel surveillance systems. Also, differing rubella case definitions are used within and between

countries, and there is a lack of CRS surveillance data to assess progress and disease burden. Triangulation of surveillance data is often not done, which hinders adequate analysis and improvement of data quality. It was noted that technology can solve some but not all of these surveillance challenges.

Surveillance systems are additionally challenged by lack of ownership and political will and antiquated data management systems resulting in to poor linking of epidemiological data with laboratory results and feedback to the immunization program. Laboratory-supported measles and rubella case-based surveillance is heavily reliant on polio surveillance activities, and evaluations of the cost and planning for transitioning polio resources to a broader vaccine-preventable disease surveillance platform are needed.

Measles and Rubella Elimination Strategic Plan Midterm Review

A summary of the research suggestions from the Measles and Rubella Elimination Strategy 2012–2020 Midterm Review Report was provided (19). The four research-specific recommendations were noted:

- Programmatically-oriented operations research, in addition to technologically-oriented research such as the development of new vaccine delivery or antibody testing methods, should be used to determine how to best interrupt measles virus transmission. Such operations research should include achieving optimal uptake of vaccination in populations, which populations should be targeted for special immunization efforts, how to optimize surveillance systems, and the economic impact of disease.
- Research should be conducted to determine the impact at the country level of measles and rubella control and elimination efforts on the overall immunization system.
- Sustained commitment to adequately funding measles and rubella research is required. An advocacy plan to secure funding for research should be developed.
- A measles and rubella research committee focusing in a sustained fashion on advocating for, promoting, and prioritizing measles and rubella research, similar to the Polio Research Committee, is critical. The natural home for this working group is WHO.

The first two recommendations are specific research ideas considered by the workgroups, the third and fourth recommendation was the basis for a discussion on how to develop a reliable platform to implement measles and rubella programmatic research in the future. Several challenges to developing a research agenda that is easily implemented were identified. First, it was noted that countries are at various stages of elimination, and that post-elimination countries have specific research needs to maintain elimination that might not be relevant for highly endemic countries. In addition, innovation must come from needs based on the challenges faced at the community, district and provincial levels, and vigorous involvement of country-level implementation is necessary to properly establish research priorities.

Workgroup Summaries

Epidemiology and Economics Workgroup

1. *How can programmatic data be used to better identify susceptible populations to target interventions?*
2. *What are common reasons for under diagnosing and reporting of measles, rubella and CRS cases and what strategies should be adopted to improve case ascertainment and reporting in different transmission settings?*
3. *What are the incremental costs and benefits of prevention, surveillance, and outbreak response for measles, rubella and CRS, and the financial resources required to achieve measles and rubella elimination?*
4. *What is the estimated public health impact at the national level of measles and rubella vaccination?*
5. *How best can data on population characteristics, susceptibility profiles and virus genotypes be used to identify transmission pathways and predict areas and populations at risk for measles and rubella outbreaks?*

Background

The workgroup considered the broad topics of the epidemiology and economics of measles, rubella and CRS, topics of critical importance for the design and implementation of elimination strategies. Research on the epidemiology and economics of measles, rubella and CRS is critical to support cost-effective operations and improve vaccination and diagnostic tools. Of importance, epidemiology and economics are critical to each of the other four core strategies of the Measles and Rubella Elimination Strategic Plan 2012–2020 (5).

Research and Innovation Priorities

The workgroup discussed research priorities related to the epidemiology and economics of measles, rubella and CRS and identified five priority research areas as described below. The workgroup identified the following key gaps in knowledge to achieve measles and rubella elimination:

- Identification of susceptible populations and immunity gaps
- Accurate measures of measles, rubella and CRS cases at the subnational level
- Magnitude of the costs and benefits of prevention of and surveillance for measles, rubella and CRS
- Public health impact of immunization programs, particularly in low burden settings
- Detailed knowledge of transmission pathways and the outbreak risk and prediction

The workgroup drafted priority research questions with multiple sub-questions nested within them. One important example is the question on population-specific measles and rubella susceptibility profiles that has embedded within it questions about susceptibility of young infants and adults, and subpopulations such as migrants and internally displaced persons. Consequently, most of the potential research questions discussed were finally integrated within the five priority research areas.

Research areas that were discussed but not prioritized included: 1) whether individuals re-infected with measles virus (identified using antibody avidity assays) can transmit virus to others; and 2) how much does secondary vaccine failure contribute to measles outbreaks.

The workgroup recognized overlap in potential research questions, particularly with the immunization strategies and surveillance and laboratory workgroups. Example research questions included: 1) what is most effective way to document every dose of measles and rubella containing received and to what degree are previously unvaccinated children vaccinated during SIAs? (Immunization Strategies); 2) how best can vaccination be targeted at the subnational level? (Immunization Strategies); 3) development of rapid immunoassays to distinguish between natural and vaccine-induced immunity for measles and rubella viruses (Surveillance and Laboratory); and 4) development of rapid point-of-care test (POCT) to detect measles and rubella IgM and IgG antibodies (Surveillance and Laboratory).

The workgroup also recognized that several of the priority research questions address issues that extend beyond measles and rubella and involve health systems, particularly data management systems for disease surveillance and vaccine coverage estimates. The workgroup also noted the importance of considering how to operationalize the research findings in countries after the research is conducted.

Priority Research Questions

Question #1:

How can programmatic data be used to better identify susceptible populations to target interventions? Specifically, under what conditions do existing programmatic data accurately predict population-specific measles and rubella susceptibility profiles at the subnational level compared with serosurvey or outbreak data? Based on this understanding, what improvements in existing programmatic data are critical to improve their accuracy in predicting susceptibility profiles and when are targeted serosurveys needed to identify susceptible populations?

Existing programmatic data include: 1) administrative and survey vaccine coverage data; 2) age-specific case data; 3) programmatic gaps, stock outs, drop outs and interruptions in health services; 4) characteristics of hard to reach populations including migrants, refugees and internally displaced persons (IDPs); 5) and estimated shifts in vaccine-induced immunity from immunity conferred by natural infection.

Population-specific susceptibility refers to subpopulations, including: 1) specific age groups (infants, adolescents, adults); 2) individuals who received different numbers of vaccine doses (to assess importance of waning immunity); 3) subnational regions, including settings with high vaccine coverage; and 4) special populations such as refugees, IDPs, and labor migrants.

A potential research outcome is a software tool to assist program managers in integrating, analyzing and interpreting the multiple data sources and susceptibility profiles.

Rationale

The fundamental challenge to measles and rubella elimination is the need to increase population immunity and reduce the proportion of susceptible individuals. These susceptible individuals are invisible to the program until an outbreak occurs; thus, strategies to identify susceptible populations prior to an outbreak are critical to achieving elimination (23, 24). Ideally, existing programmatic data could be used to identify susceptible subpopulations (25-28); however, data quality often impede accurate prediction. Knowing when these data are sufficient, which data are critical, and when serosurveys are justified is fundamental to achieving and sustaining measles, rubella and CRS elimination by identifying and targeting susceptible populations.

Question #2:

What are common reasons for under diagnosing and reporting of measles, rubella and CRS cases and what strategies should be adopted to improve case ascertainment and reporting in different transmission settings (pre-introduction, endemic post-introduction, pre-elimination, and post-elimination settings)?

Strategies to be evaluated include the use of mHealth tools, training health care workers on clinical diagnosis and reporting, and strategies to improve surveillance for measles and rubella in the community.

Rationale: Accurate measurement of the burden of disease due to measles and rubella at the subnational level is critical to designing effective elimination strategies and tracking progress toward achieving and sustaining elimination (29).

Question #3:

What are the incremental costs and benefits of prevention, surveillance and outbreak response for measles, rubella and CRS at the national, regional, and global levels, and the financial resources required to achieve measles and rubella elimination?

Several incremental costs are important and include the following:

- What are the incremental costs and benefits of prevention, surveillance and outbreak response for measles, rubella and CRS at the national, regional, and global levels, and what are the financial resources required to achieve and sustain elimination of measles and rubella in different country settings (including Gavi status/income level)?
- Operational, country-specific research in selected country settings based on country-level demand to characterize the costs and benefits of:
    - Outbreak response vs. preventing outbreaks through vaccination
    - Different vaccination strategies (e.g., SIAs, 2nd dose introduction/2nd year of life platform, strategy innovations, strategies to reach hard-to-reach)
    - Different vaccination coverage levels
    - Different degrees of measles and rubella-specific interventions integration with broader health system
    - New vs. traditional technologies (delivery and diagnostic)
    - Different health care access and incentive policies (e.g., free vaccination, per diem top ups, conditional cash transfers) to increase vaccination coverage
    - Additional data on economic burden of disease
- What strategies are needed to maintain a sufficient supply of vaccine to support measles and rubella elimination at national and global levels?

Rationale: Estimates of the costs and monetary value of the benefits achieved from prevention, outbreak response and surveillance for measles, rubella, and CRS are critical for advocacy and resource mobilization at country, regional, and global levels (30, 31). Country programs need demonstration of the value measles and rubella vaccination to secure the funds necessary to support and expand their activities.

Question #4:

What is the estimated public health impact (cases, hospitalizations and deaths) at the national level of measles and rubella vaccination in the past, present and future?

Rationale: Ensuring government ownership and public support for immunization programs requires accurate estimates of the public health benefits (32). This is of particular importance in low burden settings where diseases such as measles and rubella are no longer common and misunderstandings of the need to sustain high vaccination coverage arise. Accurate estimates of the number of cases, hospitalizations and deaths averted by vaccination are critical to advocacy efforts to ensure sustained commitment to measles and rubella elimination.

Question #5:

How best can data on population characteristics (including population movements, population settlements, contact patterns), susceptibility profiles and virus genotypes be integrated and used to

identify transmission pathways (including sustained transmission among adults) and predict areas and populations at risk for measles and rubella outbreaks?

Population movement data include satellite imagery, transportation routes, cell data records and geo-location logger data.

Rationale: To anticipate measles and rubella outbreaks and intervene pre-emptively, knowledge of both susceptibility patterns and transmission pathways is critical to assessing risk (33). Increasingly, detailed data on population movements and settlements, contact patterns, susceptibility profiles and virus genotypes are available but need to be integrated and used by programs to target interventions to prevent measles and rubella outbreaks (23, 24).

Populations are fluid in space and time and the classic static view of populations masks both regional and sub-national heterogeneity in at-risk populations. The extent and causes of this spatial variation in target populations, susceptibility, and outbreak risk is a critical knowledge gap that prevents efficient targeting of efforts to achieve and maintain elimination.

In the endemic setting, uncertainty about the spatial distribution of target populations is a critical gap to evaluation of vaccination coverage and disease (measles, rubella, CRS); i.e. uncertainty in the denominator. In the elimination setting, uncertainty about population movements and contact patterns is a critical gap to the evaluation of the risk of outbreaks.

Immunization Strategies Workgroup

1. *What is the cost-effectiveness of interventions to increase coverage with MCV1 and MCV2 from 80% to 95%?*
2. *What are best strategies to reach geographically and socio-cultural hard-to-reach populations with two doses of measles-containing vaccine?*
3. *What factors determine the appropriate target age range, geographic parameters (national versus subnational) and frequency of SIAs to achieve rubella/CRS and measles elimination?*
4. *What indicators are needed to guide the extent and timeliness of outbreak response immunization?*
5. *What is the potential programmatic impact of micro-array patches to increase measles vaccination coverage?*

Background

The workgroup was responsible for identifying priority research questions in the areas of routine delivery of measles and rubella vaccinations and outbreak response immunization activities, such as outbreak response MCV vaccination campaigns. There are a variety of approaches to improving routine delivery of vaccines, and the types of strategies are sometimes categorized as focusing on enhancing access to vaccination services, increasing community demand for vaccinations, and provider- or system-based interventions. For outbreak response activities, many of the strategies depend on the timing and scope of response immunization.

Research and Innovation Priorities

The workgroup discussed research priorities for ensuring high coverage of measles and rubella-containing vaccines through both routine immunization and outbreak response immunization delivery mechanisms. Using the results of the web survey as a guide for discussion, the workgroup discussed the

main implementation challenges related to immunization strategies and measles/rubella outbreak response in achieving measles and rubella elimination goals across all WHO regions. The workgroup also reviewed the significance and urgency of research priorities related to immunization strategies and outbreak response, using the web survey results as a guide.

The working group broke into two sub-groups, one focused on immunization strategies and the other on outbreak response immunization. As an outcome of the discussions in both sub-groups, some of the knowledge gaps identified included:

- Addressing missed opportunities for vaccination
- Evaluating the cost-effectiveness of various vaccination strategies
- Utilizing technology to support efforts to improve coverage
- Understanding the optimal timing and scope of outbreak response immunization
- Identifying and utilizing lessons from the Global Polio Eradication Initiative and from the PAHO region (which has attained measles and rubella elimination),
- Assessing methods to increase political commitment to increase routine immunization coverage

After these sub-group discussions, the working group re-convened for a discussion of priority research questions across both topic areas. The working group identified five research questions, with associated research sub-areas, to address the main implementation challenges to ensuring high routine measles and rubella vaccination coverage and well performing outbreak response immunization activities.

Priority Research Questions

Question #1:

What is the cost-effectiveness of strategies to increase coverage with MCV1 and MCV2 from 80% to 95%?

These include evaluation of the following topics in a variety of country settings:

- Magnitude, determinants, and costs of missed opportunities for measles vaccination and development of interventions to reduce these missed opportunities
- Cost and effectiveness of implementing best practices in defaulter tracing to reach 95% coverage
- Cost and effectiveness of using 5-dose or 1-dose measles vaccine vials to improve coverage to 95%
- Impact of school entry checks to improve measles vaccination coverage

Rationale: Routine immunization is a key strategy for measles and rubella elimination. Achieving two dose vaccination coverage of 95% is the target to achieve herd immunity thresholds. However, many countries have stagnated at 80% coverage. Multiple strategies to improve coverage have been identified (11), but identification of appropriate strategies that are cost-effective is necessary for countries to achieve their goals. With the need to understand the most cost-effective strategies to achieve high coverage, evaluation of multiple approaches to increase coverage for both MCV1 and MCV2 are necessary.

Question #2:

What are best strategies to reach geographically and socio-culturally hard-to-reach populations with two doses of measles vaccine?

Several specific areas need special attention. These include:

- Use of geospatial mapping to improve micro-planning and identification of unreached populations
- Developing and evaluating strategies to reach populations not reached in urban and peri-urban settings

- Developing and evaluating strategies to reach transient communities

Rationale: While achieving high population immunity is necessary to interrupt transmission, additional efforts are necessary to ensure that susceptible sub-populations do not exist. Achieving homogenous high coverage across all districts and age groups is important for reducing immunity gaps and decreasing measles virus transmission (3, 23).

Question #3:

What factors determine the appropriate target age range, geographic parameters (national versus subnational) and frequency of SIAs to achieve measles and rubella elimination? The key areas that require assessment are:

- The relevance of herd immunity thresholds and other parameters used for determining frequency of SIAs and how this relevance may differ by country.
- The role of adults and adolescents in transmission of measles virus to infants.
- If and when it is appropriate to close immunity gaps among adults to help mitigate measles outbreaks.

Rationale: Given routine immunization coverage in some countries, SIAs need to be implemented to increase population immunity to herd-immunity thresholds. Currently, efforts to identify the timing, and scope of planned preventative campaigns is based on expert opinion, with limited data. To reach herd immunity thresholds, an understanding of how to use available epidemiological data to target appropriate populations to eliminate measles and rubella transmission is necessary.

Question #4:

What indicators are needed to guide the extent and timeliness of outbreak response immunization (by age, different settings, health system capacity and geographically)?

Key data that should be assessed include:

- Age distribution of cases
- Health system capacity to manage cases
- Current geographic spread of infection and potential transmission to other geographic areas
- The role of national support for ORI activities.

Rationale: Similar to preventative SIAs, development of an evidence-based rationale for conducting ORI activities is necessary to ensure progress toward elimination (34). In recent years, many outbreak response activities have failed to achieve their aim of interrupting transmission, or have been implemented after the outbreak has peaked. At the country level, determining which information to use to help guide when to conduct outbreak response immunization activities is a common question, with substantial financial and policy-related implications.

Question #5:

What is the potential programmatic impact of micro-array patches to increase measles vaccination coverage?

Rationale: The micro-array patch (described also in the surveillance and laboratory workgroup) has the potential to overcome key challenges including cold chain and medical waste associated with syringe-injectable vaccines that may hinder optimal measles coverage levels (35). However, little is known about whether the patch could contribute to high levels of measles vaccination coverage and whether the costs are acceptable for wide-scale use. As part of the development of the micro-array patch, development of an investment case, with estimates of cost-effectiveness of use are needed. Additionally, when suitable, field trials of the patch should incorporate evaluation of both costs and effects of the patch on measles vaccination coverage and timeliness.

Surveillance and Laboratory Workgroup

1. *Can vaccine safety, effectiveness, and/or coverage be improved by developing more thermo-stable vaccines and by alternative delivery methods (e.g., microneedles)?*
2. *How can point-of-care tests be optimized to have the maximum impact to improve surveillance?*
3. *What innovations are needed to strengthen molecular epidemiology for measles and rubella to demonstrate the success of vaccination programs?*
4. *What are innovative/new methods and corresponding costs for CRS surveillance in areas with limited human and/or financial resources?*

Background

The surveillance and laboratory workgroup discussed improving surveillance quality, data reporting and surveillance indicators. In addition, the workgroup also considered issues related to novel vaccine delivery technologies that are currently under development.

Research and Innovation Priorities

The surveillance and laboratory workgroup discussed research priorities related to several priority research areas as follows:

- Surveillance performance indicators
- Improving the ability to implement CRS surveillance in developing countries
- Impact of new vaccine delivery methods on the program
- Use and development of serologic assays for determining population immunity
- Strengthening molecular epidemiology to monitor progress toward elimination

Given the heavy reliance on polio surveillance laboratory infrastructure for the measles and rubella laboratory network, strategies to transition laboratory surveillance for viral vaccine preventable disease to an integrated laboratory platform must be considered when prioritizing existing and future research projects. Support from various partners, especially the Bill & Melinda Gates Foundation (BMGF) and CDC have led to improvements in surveillance and laboratory technologies which was appreciated by the work group.

Several research questions were considered important, but not prioritized as top-five research questions. First it was recognized that research need may be needed to evaluate the effects of the polio transition on the GMRLN. The workgroup did not consider this to be a high priority research area at this time; however, Global Polio Laboratory Network (GPLN) and GMRLN laboratories and laboratory coordinators should consider some research projects that may help guide transition efforts. The first step will be to catalogue the overlapping functions of GPLN and GMRLN and to map the sources of financial support for each network. In addition, assessment of what is the most appropriate method for determining the level of population immunity in developing countries was also considered important. Multiplex assays for simultaneous detection of antibodies to multiple antigens would reduce the cost and need to conduct individual tests for each antigen. Additionally, serosurveys can be used as a planning and management tool for some priority countries. The methodology can be specific cluster-based studies, based on convenience sampling, or jointly with other surveys. An accurate and faster method than the plaque reduction neutralization assay to measure neutralizing antibodies to measles and rubella viruses was considered important, but was not prioritized in the top-five research questions.

Lastly, the best methods to classify measles cases in outbreaks with a high proportion of vaccinated cases was also considered important, but not prioritized. The workgroup considered testing algorithms for classification of measles reinfection cases. These methods will be useful in countries that have achieved or are near elimination, but this topic was not considered to be a high priority research area at this time.

Priority Research Questions

Question #1:

Can vaccine safety, effectiveness, and coverage be improved by developing more thermo-stable vaccines and by alternative delivery methods (e.g., microneedles)?

Rationale: A significant way to increase coverage would be to use house-to-house delivery (35). Currently, microneedle patches are being developed as a platform for drug delivery in addition to vaccines (36, 37). There are three measles and rubella-microneedle patch projects focusing on pre-clinical development and testing of measles and rubella microneedle patches. Other vaccination projects with microneedles are being considered, and the following vaccines are in preclinical or early stage clinical development: influenza, inactivated polio, human papilloma virus, rabies, rotavirus, and hepatitis B vaccines. Some devices have completed a phase I safety and immunogenicity study with influenza and field acceptability studies are ongoing (36, 37). A proof of concept for a live attenuated vaccine for measles and rubella has been conducted in experimental animal models (38). Other new innovations, such as a microarray that delivers an invisible marker to the recipient for monitoring vaccination campaigns is also under-development.

Several critical knowledge gaps for microneedle vaccines were defined including immunogenicity, thermal stability, reactogenicity, minimal wear time, and possible dose sparing. Some of these questions are being addressed by ongoing projects. However, a demand forecast and implementation strategy will need to be developed to help define the value proposition for this technology and support the transition away from delivery of measles and rubella vaccine by subcutaneous injections, possibly as early as 2025–2030. A product development pathway including requirement for a good manufacturing practice (GMP) facility and scale up to a commercial GMP manufacturing process will need to be developed to work with existing vaccine suppliers. The regulatory pathway is likely to be complex since this is a unique project and a timeline needs to be developed for licensure of technology to vaccine manufacturers. Finally, vaccine specific clinical studies need to be conducted in the field to demonstrate safety and non-inferiority of microneedles patch delivery as compared to standard sub-cutaneous delivery by needle and syringe. Evidence should be provided to measure the increase in coverage that could be provided by microneedles patch delivery in house-to-house vaccination by modelling or operational research based on experience with inactivated and oral polio vaccine campaigns. Alternative vaccine delivery strategies used in the polio eradication program may inform the way the microneedle patches could be deployed to control measles and rubella.

Question #2:

How can a POCT be optimized to have the maximum impact to improve surveillance? Optimization should be assessed in three areas?

- Can inexpensive and sustainably produced point of care diagnostic tests be developed to rapidly and accurately confirm measles and rubella cases?
- Can these tests be performed using samples other than serum, e.g. capillary blood and oral fluid?
- Can both serologic and molecular diagnostics be performed using POCT technology?

Rationale: Improving laboratory diagnostics by developing POCT would enable case confirmation to occur at the location of the suspected case, minimize specimen handling, and obtain a specimen suitable for sending to a laboratory for molecular analysis (39). An inexpensive POCT has been developed to

detect IgM for measles, with excellent sensitivity and specificity, relative ease of use, can be used with different specimen types (serum, whole blood or oral fluid), and can facilitate virus detection and genotyping. Additional field testing is in progress. However, one of the challenges facing widespread use of this test is the need for a licensing and manufacturing agreement. This agreement will be unique because of the combination of parties involved. The availability of this POCT has the potential to impact surveillance throughout GRMLN.

A POCT could provide surveillance programs with the tools needed improve completeness and timeliness of laboratory confirmation when specimen transport to the national laboratory is logistically challenging. In low incidence settings, serologic testing becomes expensive because EIA kits expire relatively quickly. Other related questions will address how POCT performs in the field including evaluating sensitivity and specificity in a variety of settings and measuring the impact of POCT on reporting of negative cases, specimen collection for genotyping, and the ability to implement quality control and quality assurance protocols. These questions will have to be addressed before full-scale implementation of any POCT occurs. Once developed, additional research will have to be conducted on the role of POCT within the GMRLN. The need for a similar POCT test for rubella IgM was considered a high research priority.

Question #3:

What innovations are needed to strengthen molecular epidemiologic studies of measles and rubella to monitor the success of vaccination programs?

Rationale: The molecular epidemiology of measles and rubella is essential data required for verification of elimination of measles and rubella. In countries with endemic circulation, molecular studies are used to establish a baseline of genotypes. The global distribution of genotypes is relatively well established for measles virus with the exception of the African region. Of the 24 measles genotypes, only 6 are currently circulating (9). The sequence of the N450 region of the measles genome is often not sufficient to adequately define pathways of transmission and distinguish between discreet lineages. The decrease in genetic diversity in circulating measles viruses may limit the utility of molecular epidemiology and research into methods to increase the resolution of the sequence analysis is necessary. Whole genome sequences or sequences of the M-F non-coding region of the measles genome can provide better resolution, but more research is needed before these methods can be introduced into routine virologic surveillance (40). For rubella virus, knowledge about global distribution of circulating viruses is still very limited. There are currently only 3 rubella genotypes circulating; therefore, molecular epidemiological analyses are limited by current sequencing protocols. The WG was informed that a WHO guiding document for enhancing the sensitivity of molecular surveillance for measles and rubella based on the deliberations of the WHO Next Generation, Extended Window and Whole Genome Sequencing Working Group will be published by the end of 2017.

A major problem, especially for rubella, is the failure to collect samples for viral detection and genotyping from suspected cases (9). In addition to research on advanced sequencing methods, research to identify the obstacles for collecting appropriate samples for virus detection should be considered. In addition, the WG recognized that there is a need to develop standardized protocols for obtaining additional sequences from clinical samples and viral isolates and to develop more efficient methods for development and distribution of cell lines suitable for isolation of measles and rubella virus.

In addition to supporting molecular epidemiologic studies, the sequence information can be used to predict amino acid substitutions in the viral proteins that are targets of the immune response. This will make it possible to predict antigenic differences in neutralizing epitopes. Sequencing studies must be accompanied by biologic studies to assess the ability of serum from human vaccinees to neutralize wild-type measles and rubella viruses.

Question #4:

What are innovative/new methods and corresponding costs for CRS surveillance in areas with limited human and/or financial resources?

- Evaluating modification of the case definition to align with the human and financial resources in the country according to the elimination status.
- Development of alternative laboratory methods for confirming CRS and expanding the age of diagnosis.
- Modeling exercises to assess the costs of different methods for surveillance in different settings.

Rationale: CRS surveillance is suboptimal in most areas. Many countries and regions are not performing adequate CRS surveillance, which is essential to verify elimination. Furthermore, there is an increasing awareness of the burden of disease from CRS. The workgroup noted that it is easier to find CRS than rubella in elimination and post-elimination settings but that birth defect surveillance systems may be overwhelmed. The critical knowledge gap identified was to determine why CRS surveillance is so weak. The workgroup recognized that several research questions may need to be addressed to adequately address CRS surveillance.

Demand Creation and Communications Workgroup

1. *How can service delivery be altered to create and increase vaccine acceptance and demand?*
2. *What is the effectiveness of social mobilization as a tool for vaccine demand creation for SIA, and adapting it for routine immunizations?*
3. *Are news and social media an effective tools for demand generation? (e.g. Whatsapp, Facebook)*
4. *How to design laws and regulations to increase vaccine acceptance?*
5. *What is an appropriate MR vaccine behavioral demand and acceptance surveillance framework?*

Background

Despite overwhelming evidence on the safety of the measles-mumps-rubella vaccination, misinformation, rumors, and concerns exist among parents, politicians, policy makers, and even some health care providers (41). The 1998 paper that falsely linked measles, mumps and rubella vaccination to autism, which has since been discredited, has led to years of skepticism and alarm from parents regarding childhood vaccines (42). This has led to decreasing rates of vaccination in many developed and developing countries, which in turn has caused multiples measles outbreaks in the United States, United Kingdom, and other countries (43, 44).

The challenges and ultimate success of the smallpox eradication campaign taught many lessons about how to approach global eradication efforts and the role that vaccine hesitancy plays in this process. It was demonstrated in the United States that the incidence the smallpox was inversely related to emergence of vaccine hesitancy (45). Vaccine hesitancy campaigns thrive in environments where the immediate risk of a vaccine-preventable disease is minimal or absent. The narrative around vaccine hesitancy campaigns favors personal interest stories from close friends and families with a negative vaccine experience, rather than statistical data supporting widespread successes of a vaccine (46). Social mobilization, communication strategies and demand generation have been proposed as potential methods to curb and control vaccine refusal.

Social mobilization efforts involve active communications with community members to raise awareness about a particular health outcome (47). These strategies can improve overall awareness of vaccine-preventable diseases, such as measles and rubella, and increase overall vaccine knowledge and attitudes in hesitant populations. Eradication campaigns should commit to social mobilization strategies proactively rather than toward the end to reap the fullest benefits of this strategy. As part of the polio eradication efforts, dialogue with respected community leaders was crucial to overcome non-compliance and hesitancy, although this strategy was not fully embraced until the late-stages of eradication campaigns. Future eradication efforts must use the social support of respected community and religious leaders in targeted vaccine-hesitant areas early on in the process of eradication.

Having the buy-in and involvement from health professionals also promotes vaccine compliance and demand generation. The ability to observe patient-provider interaction is important to fully understanding the most common approaches used among health professionals to target vaccine hesitancy and refusal (48). By providing training and resources to health professionals in developed and developing regions of the world with appropriate strategies and methods of effective communication, it is ensured that evidence based strategies are being used to combat issues of non-compliance globally.

It is crucial to enlist demand generation and communication strategies for vaccination early on in eradication efforts to lessen the probability that vaccine hesitancy and refusal plague an eradication campaign.

Research and Innovation Priorities

The group first identified the challenges occurring in all settings, including endemic regions, near elimination regions and post-elimination regions. There were a number of research questions identified during the prioritization process. These include:

- How can communities be best engaged in planning, implementing and monitoring activities?
- What are communities' perceptions and attitudes?
- What misconceptions exist among health care providers?
- What are the best strategies to address information gaps or confidence gaps?
- What are effective strategies to enable health workers to obtain up to date information on populations?
- What aspects of service delivery affect demand?
- What are the primary reasons for low confidence/demand?
- What are the suggested methods for increasing coverage during the second year of life?

These questions are broad in nature, presenting a challenge to policy makers. Countries are different, and our approaches toward vaccine acceptance and demand generation need to differ as well. Demand for a vaccine in any given country may depend on several factors, including: the overall population's exposure to the vaccine, its collective experience with the disease and how much the media covers vaccine related stories. Identifying individuals and organizations who could be focal points for vaccine advocacy, such as policymakers, religious leaders, celebrities or community makers was also discussed as an important step to demand generation.

The vaccine needs in a country are often known, but the best way to implement the needed strategies is not always known. For this reason, the workgroup posed the question as to if it would be best to focus efforts on the "how" questions, as this will help generate next steps in research. Currently, governments can identify where there are gaps in immunization coverage and demand generation strategies, but problems arise if they do not have a plan to address these gaps. Following this point, the group discussed how to most effectively communicate research findings to decision makers.

While immunization practices are normalized overall, they are not being used to the fullest extent possible. Relating to this, the question of how to best leverage social norms to create and maintain vaccine demand was posed. The ability to evaluate and learn from social mobilization as a tool for

vaccine demand creation for routine immunization and SIAs was discussed. Finding ways to enhance and maximize community engagement could help in demand creation for measles and rubella vaccines. As a result of this discussion, the workgroup outlined and prioritized the following questions.

Prioritized Research Questions

Question #1:

How can service delivery be altered to create and increase vaccine acceptance and demand?

- How can patient provider interaction be improved to increase vaccine demand?
- How can the health center processes and information flow be modified to decrease missed opportunities for vaccination?

Rationale: The rationale for this research topic is four-fold. First, clinic experience is an important driver for demand. Second, healthcare providers are the most trusted sources of vaccine information. Third, a key issue relating to routine immunization is missed opportunities for vaccination. Fourth, missed opportunities to catch-up children on routine immunizations are missed, such as leveraging SIAs to catch-up children.

This research question is important to consider because it has not been evaluated rigorously in the developing world, and could be beneficial across multiple settings, including endemic regions, near elimination/re-introduction regions and in post-elimination regions.

Question #2:

What is the effectiveness (and cost effectiveness) of social mobilization as a tool for vaccine demand creation for SIAs and adapting it for routine immunization?

Rationale: During SIAs, social mobilization is the most widely used tool for increasing community level vaccine acceptance. However, social mobilization has not been rigorously evaluated, nor has it been systematically adapted for routine immunizations, making this an important research topic area. This research could also address the effectiveness and cost effectiveness of different versions of social mobilization tools, which has also not been assessed in previous research.

This research question is relevant to multiple core strategies in the overall strategic plan, including the goal to achieve and maintain high levels of population immunity through high vaccination coverage for two doses of measles- and rubella- containing vaccines.

Question #3:

Are news and social media effective tools for demand generation? (i.e. Whatsapp, Facebook, etc.) Linked to this question is which populations is social media most effective at reaching?

Rationale: Younger populations and new parents are increasingly engaged in social media tools such as Facebook and Twitter and hybrid platforms, such as Whatsapp. There is an emerging media landscape that is shifting from mass media sources into segmented new media sources, such as the platforms listed above. Examining and understanding the effectiveness of these media sources could help to better understand and reach the younger populations and new parents.

There is currently substantial evidence regarding the utility of SMS messaging as reminders; however, there is a current knowledge gap related to the operational aspects of these reminders (e.g. one way vs. two way messaging, location based messaging, etc.). There is also currently little evidence in the utility of social media and news media platforms, making this an important and relevant research question to consider.

Question #4:

How to design laws and regulations to increase vaccine acceptance without being coercive or risking backlash?

Rationale: In a few developed country settings, vaccine mandates have been effective. While a vaccine mandate presents as a promising tool, it is unclear what form of mandates are most effective (i.e. draconian measures vs. behavioral nudges). There is potential for the abuse of vaccine laws, particularly among vulnerable and marginalized populations, which is why research is this area is increasingly important. There is also the risk of diminishing of services if vaccines mandates are not effective, another reason supporting the importance of this question. Outside of the United States and a few developed countries, there is little evidence that vaccine mandates and legal and regulatory tools increase vaccine acceptance.

Question #5:

What are appropriate measles and rubella vaccine behavioral demand and acceptance surveillance frameworks for caregivers? Addressing this question will require four specific items to be addressed:

- Develop a validated scale that correlates with measles and rubella vaccine acceptance
- Pilot the scale in multiple contexts.
- Develop a typology to identify how people react to different types, and identify the receptivity to different forms of persuasive messages.
- Develop an evidence base for a sentinel surveillance platform.

Rationale: A validated tool to longitudinally track vaccine attitudes will help monitor and sustain demand of vaccines (49). There is currently no tool available to longitudinally track vaccine attitudes in a variety of communities, making this an important research topic. This toolkit could be used in future eradication and surveillance efforts, or be applied to other infectious diseases of interest. The workgroup believes the ability to understand the thoughts and attitudes of a community in context to vaccine acceptance and hesitancy is invaluable in planning eradication efforts.

Conclusions and Next Steps

Nineteen priority research questions were identified by the four workgroups. The research questions are broad but address key areas of work to move towards elimination. The workgroup's efforts identified five areas of research. These areas are: 1) Improve vaccine delivery, 2) Advance the tools available for countries to best implement immunization activities, 3) Improve surveillance tools to better monitor progress towards elimination, 4) Generate evidence to identify effective tools to vaccinate populations, and 5) Develop tools to better utilize and make available data at the country level for advocacy/high-level decision making. The research questions all have a unique character that they are ongoing questions that can be addressed in the short term, but will require ongoing work to reach their full potential in the long term.

The prioritization process results will be widely disseminated by the RIWG through partner meeting presentations and a planned publication in a scientific journal. The RIWG will help link research partners with the prioritized research questions and develop a network of research sites, research institutions, and funding sources to achieve measles and rubella elimination. To develop a source of research funding within the M&RI partnership, the R&I WG will develop a concept note for establishing a research funding mechanism and implementation platform. To develop this platform, the meeting plenary discussion focused on the following five steps: 1) developing a short list of the highest priority questions from those identified; 2) identifying potential funding agencies; 3) identifying research stakeholders and implementing partners; 4) ensuring implementation of research to answer the highest priority questions; and 5) communicating the results and next steps. Currently, limited funds are available for measles and rubella research from partners, foundations, and donor agencies (13). Future discussions with partners will be needed to develop a clearer picture of how research can be funded, conducted and interpreted, leading to programmatic changes. In addition, leveraging existing resources

including the Immunization and Vaccines Related Implementation Research Advisory Committee, Strategic Advisory Group of Experts Measles-Rubella Workgroup, and Immunization Practices Advisory Committee can also support measles and rubella elimination research activities. The short term vision is to ensure that key priority research is funded so that the data can be used to achieve regional and global measles and rubella milestones. The long term vision is to develop a sustainable research funding mechanism. In addition, having a 'small grants' fund for innovative ways to reach the unreached would be critical. The existing model is the Polio Research Committee (PRC) (50). The PRC sets priorities, funds some research while providing a forum for current and future research ideas are discussed, to avoid duplication and synergize efforts; however, prioritization is ad hoc. Because organizations prefer to fund activities rather than endowments, work will need to be done to establish a similar framework to support measles and rubella elimination efforts.

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Annex

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