Measles and Rubella Research Meeting

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Meeting Report

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Background

In 2000, the United Nations General Assembly adopted a resolution to reduce extreme poverty by half by 2015 through achieving a series of Millennium Development Goals (MDG). MDG4 calls for reduction of mortality among children <5 years of age by two-thirds from 1990 to 2015. Due to the high measles mortality among children in low-income countries, measles vaccination coverage at one year of age is one of three indicators used to measure progress toward MDG 4. In 2010, the World Health Assembly (WHA) endorsed several accelerated measles control targets for 2015 that align with MDG4: ≥90% coverage with the first dose of measles-containing vaccine (MCV) nationally and >80% vaccination coverage in every district; reduction and maintenance annual measles incidence to <5 cases per million population; and reduce of measles mortality by 95%, compared with 2000 estimates.

While there has been progress towards MDG 4 as evidenced by a 28% decrease in child mortality during 1990-2008, achieving a 66% reduction by 2015 is increasingly challenging. Global mortality attributed to measles decreased by 78% between 2000 and 2008, from an estimated 733,000 annual deaths to 164,000 annual deaths. The decrease in measles mortality accounted for 23% of the overall decrease in childhood mortality since 1990 and for 24% since 2000.

In May 2008, encouraged by the progress made in reducing measles deaths worldwide, Member States requested that the World Health Organization (WHO) evaluate the feasibility of global measles eradication. In July 2010, at a Global Consultation on the Feasibility of Measles Eradication, an expert advisory panel concluded that measles can and should be eradicated and that eradication by 2020 is feasible given evidence of measurable progress towards the 2015 targets. The expert advisory panel emphasized that measles eradication activities should occur in the context of strengthening routine immunization services and should accelerate rubella control and the prevention of congenital rubella syndrome (CRS). In November 2010, the WHO Strategic Advisory Group of Experts (SAGE) agreed with the expert advisory panel that measles can and should be eradicated. As a basis for establishing a target date for measles eradication, the SAGE recommended the demonstration of sufficient progress toward the 2015 targets and regional measles elimination goals. The

Executive Board of the WHA supported the SAGE approach at its January 2011 meeting.

These recommendations also impact rubella vaccine policies given the ease of delivery of vaccine using combined vaccines (MR, MMR) and integrated rubella-measles surveillance. Globally, two-thirds of WHO members use rubella-containing vaccine (RCV) in their childhood immunization program and three WHO regions (Americas, Europe, Western Pacific Regions) have rubella control/elimination policies. The Region of the Americas (PAHO) established a goal in 2003 for regional rubella and CRS elimination by 2010; the goal was achieved on time and PAHO is in the process of documenting elimination. However, rubella and CRS are still major public health problems with an estimated 112,000 cases of CRS occurring globally in 2008, making CRS the most significant, vaccine-preventable birth defect in the world. In 2011, the WHO rubella vaccine position paper was updated with the recommendations that countries without RCV in the national routine childhood immunization program should take the opportunity of their two-dose measles vaccination schedules (either through routine services or mass campaigns) to accelerate rubella control and CRS prevention through use of combined measles-rubella (MR) vaccine. The preferred strategy for rubella vaccine introduction is to conduct a wide age-range campaign with MR vaccine followed immediately with use of MR vaccine in the routine program.

Moving toward measles eradication and accelerated rubella control will require evidence-based strategies. In addition to the challenges of an eradication goal, other key determinants that drive the research agenda include changing epidemiology, technological advances that provide new opportunities, and health systems development. Starting in the 1990s, the WHO Steering Committee on research related to measles and rubella vaccines and vaccinations provided a forum for presenting research findings and formulating an overarching research agenda. Funding support for the committee ended; however, at its final meeting in 2005, the committee provided research guidelines to support future measles and rubella control strategies that included evaluation of population immunity, outbreak investigation, design of vaccination strategies, and validation of new diagnostic tools for surveillance. At the Global Technical Consultation to Assess the Feasibility of Measles Eradication held during July 2010, the expert panel raised questions about research priorities required to provide the scientific underpinnings for activities toward a measles eradication goal. To begin the process of prioritizing research questions for measles and rubella control and elimination, the Centers for Disease Control and Prevention (CDC) hosted a Global Measles and Rubella Research Meeting Atlanta, Georgia in May 2011 to identify and prioritize the key research questions in the following categories: 1) Measles epidemiology, 2) Vaccine development and effectiveness, 3) Alternative delivery methods and laboratory methods, immunization strategies, 4) Mathematical modeling and Economic analyses, 5) Rubella control and elimination. The specific objectives were to: 1) identify research needed to achieve global and regional measles and rubella control goals; 2) prioritize research topics as high, medium, and low; and 3) outline strategies for raising resources needed to address the highest ranking research questions. This report summarizes the outcomes of the meeting.

1.0 Measles Epidemiology

Evidence from previously conducted epidemiologic investigations raised key questions about evidence-based policies and strategies to achieve measles eradication.

1.1 Disease burden and surveillance

Rationale: Laboratory-supported surveillance of measles and rubella supplemented by detailed outbreak investigations are the gold standard for monitoring the impact of vaccination and directing program activities. Improving the timeliness, completeness, accuracy, and efficiency of surveillance information and making it widely available to managers and decision-makers is a requirement for success. In addition, mathematical models are being used to estimate the number of measles cases and deaths but these estimates have become increasingly inaccurate with declining disease burden. The models require multiple inputs, including high quality surveillance data and case fatality ratios (CFRs). Measles CFRs, morbidity, and surveillance performance may change over time and with improved health systems. Under-reporting of measles cases to disease surveillance systems occurs in many settings and reporting efficiency might also vary by disease severity, age, and disease incidence. Notably, better reporting in younger age groups with higher rates of complications and deaths may imply a differential in reporting efficiency among age groups and under-representation of older cases. More field-based research is needed to accurately describe measles disease and epidemiology to guide strategies for vaccination and interrupt endemic measles virus transmission.

1.1.1 Epidemiology of measles in India

Rationale: In India, measles case-based surveillance has not been fully implemented and the epidemiology of measles in India is not well characterized.

- What are the basic epidemiological characteristics of measles throughout India (e.g. incidence rates, age distribution of cases)? (High priority)
- What are the age-specific measles CFR and the frequency of measles complications in India? (High priority)

1.1.2 Measles CFR and complications

Rationale: Measles morbidity and mortality may vary over time in developing countries.

- What are measles CFR and the frequency of complications in developing countries? (High priority)

1.1.3 Changing age distribution of measles cases

Rationale: In recent years, measles epidemiology and outbreaks in post-SIA or high vaccination coverage settings have been characterized by cases occurring in older children and adults. In general, a shift in age distributions of cases follows increases in measles vaccination coverage that lead to variability of inter-epidemic periods. Despite a change in the epidemic intervals, catalytic models of measles dynamics indicate the relative force of infection for measles remains highest among children < 5 years of age and cases among older age groups occur during large outbreaks. Changing measles epidemiology raises a need for investigations to estimate disease burden and identify risk factors by age group. In addition, the occurrence of measles infection in older aged children and adults during outbreaks has implications for disease burden estimates and sustaining measles virus transmission.

- What are the causes of outbreaks in post-SIA and high vaccination coverage settings? (High priority)
- What are the measles epidemiology, disease burden, and risk factors by age group? (High priority)

1.1.4 Measles in adults

Rationale: The upward shift in the age of measles cases to older age groups with increasing MCV1 coverage is well documented. For example, in Africa, during 2002-2009, 40% of cases were >5 years of age and 14% were adults greater than 15 years of age. Towards the end of endemic virus transmission in the Americas, outbreaks in Argentina, Bolivia, Brazil, Canada, Venezuela, and the Dominican Republic included young adults. In 1997, the last large outbreak that occurred in Sao Paolo, Brazil included > 42,000 cases and was caused, in part, by a large accumulation of susceptible young adults who had escaped both natural measles infection and measles vaccination.

- What is the level of measles susceptibility among adults (i.e. persons born during period of low routine vaccination coverage or a one-dose measles vaccination schedule)? (High priority)
- Can adults sustain measles transmission even in the presence of high child immunity levels thereby making adult vaccination a requirement for reaching and maintaining elimination? (High priority)
- What is the role of waning immunity among adults in measles transmission? (Low priority)

1.1.5 Changing epidemiology of maternally-acquired immunity in infants

Rationale: Infants born to immune mothers receive maternal antibodies transferred during the perinatal period and remain protected, on average, until approximately 4-6 months of age. However, in low-income settings, protection from maternal antibodies is lost at a younger age in infants. In addition, transferred maternal antibodies that were vaccine-induced rather than naturally-acquired following measles infection generally result in lower geometric mean titers in the mother and infant that wane much earlier,

leaving the infant unprotected as early as in the first six months of life. Because of increases in measles vaccination and a decrease in exposure to measles infection, the mean age for loss of protection from maternal antibodies may be changing. This could result in increased morbidity and mortality among infants, who are especially susceptible to severe measles illness.

- What is the mean age for loss of protection and the persistence of maternal antibodies among infants in various settings? (Low priority)
- What is the immunogenicity of measles vaccination given before 9 months of age? (medium priority)

1.1.6 Surveillance indicators

Rationale: In May 2010, the World Health Assembly endorsed three targets to be used to measure progress towards measles eradication. WHO has identified 4 standardized indicators to determine measles surveillance system performance and 2 measures to monitor progress towards elimination.

- How valid are the recommended surveillance indicators and monitoring measures and their related targets? (high priority)
- How can these surveillance indicators be improved to monitor progress toward measles elimination? (high priority)

1.2 Measles Virus Transmission and Outbreaks

1.2.1 Measles outbreaks in India

Rationale: A two-dose measles vaccine strategy has not been fully implemented in India, where a large proportion of global measles deaths occur. Investigations to determine the cause of measles outbreaks and the reasons for non-vaccination would generate evidence to design strategies for preventing outbreaks and increase measles vaccination coverage in India.

- What are the causes of measles outbreaks and reasons for non-vaccination in India? (High priority)

1.2.2 Economic burden of measles importation in low and middle income countries

Rationale: Several studies have estimated the cost of containing and responding to measles importations and outbreaks in high income settings; however these estimates have not been made for other settings. Analyzing the economic burden of a measles outbreak and response activities in developing countries would provide evidence for advocacy and investment for measles elimination.

- What is the economic cost of measles outbreaks and response in low and middle income countries? (Medium priority)

1.2.3 Molecular epidemiology of measles virus

Rationale: Molecular techniques are available to provide high resolution genetic sequencing to differentiate measles viruses. These sequencing data will allow for molecular epidemiologic analyses to better understanding how measles viruses are related in place and time and to identify transmission pathways, circulating virus genotypes, and areas where measles case-based surveillance may be underperforming.

- What are measles virus transmission pathways in settings with unsuccessful measles control? (High priority)
- What measles virus genotypes have been eliminated? (High priority)
- What is the global distribution of circulating measles virus genotypes? (High priority)

1.2.4 Risk factors for measles virus transmission

Rationale: Different transmission patterns can increase the probability of sustained virus circulation, particularly in settings with a high force of infection where populations have poor access to vaccination services, e.g., migrant or nomadic populations or sparsely populated rural settings. Individual and population risk factors for measles transmission need to be better defined for progress towards measles elimination.

- What are the transmission patterns and the role in sustaining transmission among minorities, marginalized groups, nomads and migrants? (High priority)

1.2.5 Secondary vaccine failure and subclinical infection

Rationale: Prior to the widespread use of measles vaccine starting in 1960's, epidemic cycles occurred every two to three years and almost everyone experienced measles illness during childhood. Serologic and epidemiologic studies indicate that one-dose measles vaccine efficacy is approximately 85-90% when given at 9 months of age, and that two-dose efficacy is more than 99% when the second dose is given at ≥ 12 months of age. Primary and secondary vaccine failure and modified measles disease occurs among vaccinated individuals; however, in elimination settings, the contribution of subclinical infections and secondary vaccine failures to ongoing measles virus circulation is unknown. It is possible that vaccine induced immunity could wane in the absence of the boosting effect provided by circulating wild-type viruses. The potential effect of waning of vaccine-induced immunity to measles has been addressed in several studies, but research needs to continue as more regions move towards elimination.

- What is the role of subclinical infection and secondary vaccine failures in sustaining measles virus transmission? (Low priority)
- What is the impact of waning vaccine-induced immunity to measles virus in sustaining measles elimination? (Medium priority)

1.2.6 Nosocomial transmission of measles virus

Rationale: Nosocomial transmission during measles outbreaks has been described in countries from several regions; however, the role of nosocomial transmission in sustaining outbreaks is not known. In some countries where measles is uncommon, appropriate diagnosis and isolation procedures may be delayed leading to measles virus transmission within the health facility. In Africa, measles isolation wards that were commonplace a decade ago have since closed following reductions in measles incidence.

- What is the role of nosocomial transmission in sustaining outbreaks? (Low priority)
- Which strategies are most effective in preventing nosocomial transmission (Low priority)

1.3 Refining control strategies to achieve eradication

Rationale: To interrupt endemic transmission of measles virus and achieve measles elimination, mathematical models suggested that ≥ 95% population immunity is needed. In the region of the Americas, measles was declared eliminated in 2002 after the successful implementation of a strategy that included achieving and sustaining a very high measles vaccination coverage (≥ 95%) of children aged 1 year through routine services and periodic high quality mass measles vaccination campaigns. Similar results were achieved in seven southern African countries after this measles control strategy from the Americas was adapted and implemented. These efforts led to historic low measles incidence and near elimination of measles-related deaths in these seven countries, and prompted regional accelerated measles control efforts throughout Africa. However, because of the unique challenges in Africa, the strategies used in the Americas need further refinement over a longer period of time to achieve regional elimination.

1.3.1 Measles elimination in densely-populated urban settings

Rationale: In the pre-vaccine era, measles epidemiology was different in urban settings compared with rural settings. Urban settings with large populations have higher contact rates and may require a higher population immunity to achieve herd immunity compared with sparsely populated, rural settings. Some of the highest population densities in the world are in SEAR countries, including parts of Bangladesh and India. In northern India, population densities appear to have presented some challenges to the polio eradication efforts to interrupt poliovirus transmission in these areas.

- What is the population immunity threshold to interrupt transmission of measles virus in densely-populated urban settings? (Medium priority)

1.4 Impact of the HIV pandemic

Rationale: There is evidence that HIV infection may be associated with waning immunity following measles vaccination, and protective immunity to measles is lower among infants born to HIV-infected mothers. Studies in HIV infected adults have shown suboptimal seroprevalence response to measles vaccine, ranging from 0-80%. The prevalence of measles susceptibility among HIV infected adults is unknown and may play a role in sustaining measles virus transmission.

1.4.1 Measles in HIV-infected adults

Rationale: Among HIV-infected adults, severity of measles illness and the effect of HIV infection on measles antibody titers have not been well characterized.

- What are measles CFR and the frequency and severity of measles-related complications among HIV infected adults? (Medium priority)
- What is the prevalence of measles susceptibility among HIV infected adults? (Medium priority)

1.4.2 Revaccination of HIV-infected children

Rationale: The recent scale-up of early infant diagnosis and the use of highly active antiretroviral therapy (HAART) among HIV-infected children in Africa have increased survival rates among children on HAART. Following initiation of HAART, a process of immune reconstitution occurs; however, vaccine-induced immunity against measles may not be restored and revaccination may be necessary to ensure protection. The optimal timing of measles vaccination in relation to HAART initiation is unknown.

- What is the optimal schedule for measles vaccination and revaccination following initiation of HAART and immune reconstitution? (Medium priority)

2.0 Vaccine Development and Effectiveness, Alternative Delivery Methods and Laboratory Methods

The widespread use of live attenuated measles and rubella vaccines has been one of the most effective disease intervention strategies ever employed. Vaccination programs have produced dramatic reductions in disease incidence and in the morbidity and mortality associated with measles and rubella. Still, vaccination coverage is less than optimal in many countries. Research is needed to monitor the effectiveness of vaccination campaigns and to assess the role of waning immunity or suboptimal immune responses to vaccination. These studies will help to identify populations that are at risk for measles outbreaks. Rapid and effective identification of these at risk populations is necessary to avoid large, sustained outbreaks and possible reintroduction of endemic virus after successful elimination.

Enhancing measles surveillance with integration of epidemiological and laboratory information is one of the key strategies for accelerated measles control and elimination. The WHO Global Measles and Rubella Laboratory Network (LabNet) was developed in 2000 and currently includes 690 laboratories serving 183 countries. The LabNet testing strategy follows well validated, standardized procedures for confirming suspected cases and for monitoring measles and rubella virus transmission patterns. The strength of the LabNet is a strong quality assurance program which monitors the performance of all laboratories through annual proficiency testing programs and a continuous assessment program. An important aspect of laboratory surveillance for measles and rubella is the genetic characterization of circulating wild-type viruses to support molecular epidemiologic studies and to track transmission pathways. Virologic surveillance that is sufficient to document the interruption of transmission of measles and rubella viruses will be an essential criterion for verification of elimination. As the LabNet continues to expand virologic surveillance, there is a need to conduct research on new methods and approaches to further improve global laboratory-based surveillance.

2.1 Vaccine efficacy and immunogenicity

2.1.1 Serosurveys

Rationale: Serosurveys to monitor immunity are a useful tool to guide program activities. Oral fluid (OF) and dried blood samples (DBS) have been used for case confirmation (IgM, PCR) during surveillance and for outbreaks but the sensitivity of OF for IgG detection is lower in well-vaccinated populations in comparison to serum. Continued comparisons of OF and DBS to serum might be necessary to monitor the sensitivity and specificity in a given population.

- Can periodic cross-sectional surveys (using OF, serum, DBS samples) identify populations susceptible to measles or be useful for planning SIAs or other targeted vaccination activities? (High priority)
- Can OF/DBS measles and rubella antibody be monitored on a national level in concert with other disease programs (e.g., HIV, malaria)? (High priority)
- Can lateral flow devices (LFDs) be used with finger prick samples to provide rapid immunity evaluations under field conditions? (Medium priority)

2.1.2 Vaccine immunogenicity and efficacy in India

Rationale: Some areas or districts in India have reported decreases in the efficacy of live attenuated polio vaccine. Although co-morbidities have been suggested, the reasons for this lower vaccine efficacy are not well understood and the subject of intensive research. Taking a lesson from the polio experience, it would be important to determine if there is a similar decrease in measles and rubella vaccine efficacy in these populations or areas.

- What is the immunogenicity and efficacy of measles vaccine in Uttar Pradesh and Bihar, India? (High priority)
- What is the effect of co-morbidities on vaccine immunogenicity? (Low priority)

2.2 New vaccines and novel routes of immunization

Rationale: Measles and rubella vaccines are among the safest, most efficacious and most inexpensive vaccines in use globally. Use of these vaccines has resulted in dramatic reductions in disease and the morbidity and mortality associated with measles and rubella. While new measles and rubella vaccines may not be required to reach the planned elimination targets, the incorporation of novel methods into the current vaccination programs could improve the efficiency and safety of the program.

2.2.1 Vaccination errors

Rationale: Programmatic errors in vaccination, although extremely rare, can sometimes have severe consequences for the vaccine recipient and can reduce public trust in vaccinations. Although these occurrences are rare, additional research could improve on the current outstanding safety record.

- What are novel mechanisms for improving vaccine delivery, including methods to improve the existing programmatic activities of vaccination and development of better auto-destructible syringes, self-reconstituting vials, vial labeling, more thermostable vaccines and more advanced vaccine vial temperature monitors? (High priority)

2.2.2 Alternative routes of measles vaccination

Rationale: Most vaccines, including measles vaccine, are given by hypodermic injection. This delivery method is sub-optimal because the pain of injection can be a deterrent to acceptance of immunization, safe delivery of vaccines by injection requires skilled health professionals, improper injection technique or reuse of needles can result in transmission of blood-borne pathogens and disease, and safe disposal of syringes and needles creates a substantial logistic and economic burden. These logistical concerns could possibly be resolved by novel routes of administration for measles and rubella vaccines. Some projects, such as the measles aerosol project, are well advanced and licensure is expected in the near future. Other promising delivery methods such as dry powder and intradermal vaccines are still in the pre-clinical stage. Research should focus on evaluating these new delivery methods in clinical studies. All of the studies on new delivery methods have used monovalent measles vaccine, so research into developing a combined measles and rubella vaccine that could be delivered by alternative routes is critical and should start immediately.

- What is the relative potential for novel routes of vaccination (e.g. aerosol, dry powder, microneedle, intradermal delivery) to increase population immunity

against measles and rubella vaccines among all age groups including infants younger than 6 months of age? (High priority)
- What is the utility of intradermal vaccination? (High priority)
- How can new delivery methods help achieve and maintain high vaccine coverage? (High priority)
- Can measles-rubella (MR) vaccine be administered via aerosol, dry powder, or via intradermal injection? (High priority)

2.3 Diagnostics, molecular epidemiology and serology

2.3.1 Point-of-care diagnostics for measles and rubella infection

Rationale: To respond quickly and appropriately to outbreaks of measles and rubella, laboratory confirmation of suspected cases must be conducted as quickly as possible. Though the turnaround times for serologic testing in LabNet are generally rapid, testing of samples from remote areas may be delayed because of the lack of infrastructure to properly collect, store and ship the clinical samples. For this reason, assays that can be performed in field conditions are desirable.

- What are better assay formats for point of care (POC) diagnostic tests for measles and rubella and what is their utility in outbreak investigations? (High priority)
- How well does the prototype POC test to detect measles IgM perform under field conditions? (High priority)
- How effectively can a POC test be integrated into the current surveillance strategy? (High priority)
- In what settings will a POC test will have clear programmatic utility? (High priority)
- Can any test to detect rubella IgM be developed and tested? (High priority)
- What new technologies for rapid detection of viral antigens or viral RNA in clinical samples can be developed, including combining the measles and rubella assays with rapid tests to detect other rash causing illnesses (e.g. dengue virus, parvovirus B19, HHV-6)? (High priority)

2.3.2 Serologic assays

Rationale: The plaque reduction neutralization assay (PRNT) is the gold standard for measuring immunity to measles virus. However, the test is very difficult to perform and time consuming. This limits the number of samples that can be tested in the few labs that are performing the test. As the measles and rubella control programs move forward, there will be an increasing demand for serologic testing to measure immunity.

- Can new tests be developed to measure protective immunity to measles and rubella viruses that are faster to perform, amenable to a high throughput format, and that give results comparable to those obtained by PRNT? (High priority)
- What are the protective levels of rubella neutralizing antibody? (High priority)

2.3.3 Molecular epidemiology

Rationale: Molecular virologic techniques are being developed to provide high resolution genetic sequencing to differentiate individual measles viruses. These sequence data will provide a better understanding of how measles viruses are related in place and time and will help to identify transmission pathways, circulating virus genotypes, and areas where measles case-based surveillance may be underperforming. While, the value of molecular epidemiologic studies for measles and rubella has been established, it is clear that the current methods cannot distinguish between closely related viruses from different sources. Studies have shown that obtaining additional sequence information from the viral isolate or clinical sample can help to distinguish between lineages.

- What are the best methods to improve the resolution of the molecular epidemiologic data for measles and rubella? (High priority)

2.3.4 Laboratory quality control for molecular epidemiology

Rationale: Outstanding quality control has been a hallmark of the WHO Measles and Rubella Laboratory Network. Many laboratories are now initiating molecular testing, so it is necessary to develop a quality control program to monitor molecular methods. Because these molecular methods are not commercially available, research is needed to develop a high quality but cost-effective program that can accurately assess the quality of the in-house tests currently in use. One of the goals of this research would be to also develop methods that minimize the need for shipment of infectious agents and the need for dry-ice shipments.

- How best to develop and assess quality control measures for molecular tests including sequencing? (High priority)
- How can PCR reagents, RNA controls, and RT-PCR Proficiency test panels be shipped at room temperature? (High priority)

2.3.5 Distinguish antibodies due to vaccine and wild-type viruses

Rationale: There is a need to be able to distinguish between antibodies induced by vaccination and antibodies that arise after natural infection with measles. This information could be used to help refine vaccination strategies. Since none of the currently used serologic assays has this capacity, it will be necessary to design a new diagnostic test. Because the development of this test will not be straightforward as there are no descriptions of vaccine and wild-type specific epitopes in the literature, an assessment of the requirements and potential best approaches for developing this likely costly and time-consuming project needs to done first.

- What are the technical requirements and epidemiologic utility of developing serologic assays to differentiate immunity due to wild type or vaccine virus? (Medium priority)

- What are the best technical approaches to developing such an assay? (Medium priority)

3.0 Immunization Strategies

Disease elimination and eradication programs require high quality immunization services to achieve and maintain coverage ≥95% in all sectors of the population. This requires strong political and financial commitment at every level of government, a secure vaccine supply and logistics, effective advocacy and communication activities with all relevant stakeholders (e.g., private providers), and high community demand for immunization. In addition, efficient program management, skilled staff, and accurate coverage monitoring are requirements for success. For communities that are difficult to access (e.g., civil unrest, migrants, remote location), special pulse immunization activities may be needed.

3.1 Advocacy and political commitment

Rationale: Disease elimination and eradication programs require commitment from all political levels to ensure the political profile and resources necessary to succeed. Advocacy for these programs must be ongoing, and target local, mid-level and national leaders. Measles-specific funding must be allocated and sustained. Political commitment and funding can then be translated into effective policies and programs. Historically, elimination programs have relied on the natural ability and intuition of program managers to develop political commitment and advocate for the necessary resources. A more scientific approach to advocacy and building political commitment is needed.

- What are the most effective communication strategies for advocacy on behalf of measles elimination to different political and administrative levels within a country? (High priority)
- What are the characteristics of durable financing, and what financing mechanisms are best suited for eradication efforts? (Low priority)
- In what settings, and how, can school attendance and immunization be most effectively linked? (Medium priority)
- How can those advocating measles elimination best engage the Ministry of Education? (Medium priority)
- What strategies will maximize the vaccination of health care professionals? (Medium priority)
- Which management models will result in the most efficient and effective vaccination programs? (Medium priority)

3.2 Measles vaccine demand

Rationale: Vaccine policy is developed at the national level. However, vaccine uptake depends critically on vaccine providers and recipients. Reaching very high coverage

with measles vaccine demands that providers promote vaccination and that clients accept it. Nonetheless, work remains to ensure that providers recommend vaccination, and that target populations seek it. While the area of creating demand for consumer goods and services is well advanced, there is a gap in understanding of how to create demand for preventive services like immunization.

- What attitudinal barriers to vaccination exist among communities and health care providers? (Medium priority)
- How can demand for vaccination in the community and, specifically, among parents be increased through the use of social media? (High priority)
- How can greater trust regarding immunizations be established between vaccine providers and clients? (High priority)

3.3 Delivery strategies

Rationale: Elimination and eradication of measles will require achieving and maintaining uniformly high vaccination coverage across all population groups and susceptible age cohorts. Vaccine delivery strategies need to be adapted to the social, cultural and geographical circumstances to optimize vaccination coverage.

3.3.1 Vaccine coverage

Rationale: Accurate vaccination coverage information (MCV1, routine MCV2 and SIAs) is required to assess population immunity and direct program activities. Recent large outbreaks (e.g. in Burkina Faso and Malawi) occurred in settings where coverage data erroneously suggested high population immunity.

- What are the most accurate and efficient methods to monitor vaccination coverage (vaccination registers/registries, surveys, LQAs)? (High priority)
- How can vaccination coverage monitoring be made more accurate, timely and user-friendly? (High priority)
- Which methods are best suited for monitoring coverage achieved through routine service delivery (MCV1 and MCV2) vs. SIAs? (High priority)

3.3.2 Local adaptation of vaccine delivery strategies

Rationale: Vaccine delivery strategies and tactics need to be adapted to local circumstances and leverage the resources required to achieve and maintain high coverage.

- What are the most effective delivery strategies to increase coverage and reach all populations (e.g., outreach services, PIRIs, SIAs) (Medium priority)
- What is the optimal combination of delivery strategies and what works best when? (Medium priority)
- What are the reasons for missed vaccination opportunities (e.g., lack of a “flexible schedule”, optimizing vial size, others)? (Medium priority)

- What strategies are effective for increasing uptake of a routine second dose in the second year of life? (Low priority)
- What is the optimal SIA schedule in countries with low routine coverage? (High priority)
- What tactics are effective for increasing coverage in SIAs (e.g., house to house canvassing)? (Medium priority)
- What strategies are useful for identifying and reaching nomadic populations, migrants, refugees and internally-displaced persons? (High priority)

3.3.3 Human resource needs

Rationale: Quality immunization and surveillance activities require highly trained, personally motivated, and adequately resourced program managers as well as immunization and surveillance field staff. Efficient program management is a critical component for success.

- What human resources are needed to run a successful measles elimination effort? (High priority)
- What is the optimal balance between using EPI staff vs. dedicated staff (pulse staffing) for implementing measles elimination activities? (Low priority)
- What training and management approaches result in strong program managers (e.g., who use evidence-based decision making) at national and sub-national levels? (Medium priority)

3.3.4 Integration with other public health programs

Rationale: Integrating measles vaccine delivery with other child health services and linking measles vaccination with other child survival or targeted programs has the potential to increase vaccination coverage.

- What are the feasible and effective linkages with other public health interventions (e.g., polio eradication, meningococcal vaccine, Global Action Plan for Pneumonia, bed nets for malaria prevention)? (High priority)

3.3.5 Role of private sector

Rationale: Private providers are playing an increasing role in delivery of immunization services even in low resource settings.

- What are the best methods for engaging private sector health care providers in measles eradication efforts, including improving their quality of service and accurately measuring coverage among their clientele? (High priority)

3.4 Vaccination strategies for outbreak control

Rationale: Measles outbreak response is one of the most challenging aspects of measles control. Outbreaks, particularly after a period of low incidence, are associated with increased societal and political pressure to intervene. The timing, target population, vaccine delivery strategies and cost-effectiveness of outbreak response activities remain controversial.

3.4.1 Effectiveness of outbreak response guidelines

Rationale: In 2009, WHO published new measles outbreak response guidelines. There has been little evaluation of the usefulness and effectiveness of the new guidelines. Outbreak response immunization (ORI) has been used to successfully control measles outbreaks and to limit the spread of the virus. Because many mothers now have vaccine induced immunity, maternal antibodies are often not present in infants older than 6 months of age. The effectiveness of ORI has been established, but not for children at 6-9 months of age. This will require using more sensitive serologic assays, e.g., PRNT, to measure immune levels among 6-9 month olds than the hemagglutination inhibition assays used in previous studies.

- Have the 2009 guidelines been useful, effective, and cost-effective in controlling outbreaks? (Medium priority)
- What are the optimal vaccine delivery strategies (timing, target age group, geographic extent) for effective measles outbreak response? (High priority)
- Is ORI efficacious when given to children 6-9 months of age? (Medium priority)

3.4.2 Public perceptions of measles outbreaks

Rationale: Outbreaks offer the opportunity to raise awareness of the importance of prevention and the value of the immunization program. A better understanding of the societal and political response to outbreaks and how the media can support or thwart control activities would benefit the design and implementation of these activities.

- How can messages (e.g., press releases) delivered during outbreaks optimally develop societal and political commitment and to increase overall vaccine uptake? (High priority)
- What communication guidelines can be given to countries to use during measles outbreaks at the national, district and community levels? (Medium priority)

3.4.3 Targeted outbreak prevention

Rationale: The ability to identify high risk areas for measles outbreaks may allow focused use of resources for outbreak prevention and reduce the disease burden and costs of outbreak response efforts.

- What factors are associated with increased risk of measles outbreaks and can these factors be incorporated in a risk analysis tool for outbreak prediction? (High priority)

- Are currently available outbreak prediction tools able to predict outbreaks? (High priority)
- Do these outbreak prediction tools result in targeted outbreak prevention activities in identified high risk areas? (Low priority)

3.5 Vaccination system strengthening

Rationale: Measles elimination has played a key role in developing national immunization programs. A recent study by investigators at the London School of Hygiene and Tropical Medicine found that the negative effects of measles elimination activities on the health system (e.g., personnel and resources) were most likely to occur in low income countries with weak health services.

3.5.1 Immunization system and health system strengthening

Rationale: Disease control programs are increasingly being challenged to document their contribution to developing the health system as a whole.

- What are the most important ways in which elimination activities can contribute to the overall development of immunization programs? (High priority)
- What are the critical components (i.e., best practices) of measles SIAs that create positive synergies with routine immunization services? High priority)
- What indicators can be used to monitor the impact of measles/rubella elimination activities on the immunization system? (Medium priority)
- How can elimination programs optimize the positive effects and minimize the negative effects on the health system as a whole? (Low priority)

Rationale: Although countries are often aware of the opportunity to strengthen routine immunization and surveillance systems when conducting measles SIAs, efforts to capitalize on this opportunity are not actively sought out by many countries.

- What are the obstacles (e.g., financial, managerial, etc) that prevent countries from fully benefiting from SIAs to strengthen routine immunization and surveillance systems? (High priority)
- How can these obstacles be effectively addressed at the local, national, and global level? (High priority)

4.0 Mathematical Modeling and Economic Analyses

Mathematical modeling and integrated risk, decision, and economic analyses represent critical components of a research agenda for any disease eradication initiative that may offer insights about behavior at the individual and population levels in addition to valuable information about risks, benefits, and costs of various policy options. Dynamic disease models that characterize the transmission of measles and rubella viruses aid in interpreting observed epidemiological trends and guide the collection of

data that improves the understanding of the complex interactions between policy options and outcomes. Economic, risk, and decision analyses provide estimates of the economic burdens associated with diseases and characterization of the impacts of different policies.

4.1 Global coordination of measles eradication and the eradication investment case

Rationale: Attendees at a meeting on "Disease Eradication in the Context of Global Health in the 21st Century," recommended that future eradication initiatives should develop an eradication investment case to support international deliberations on the need for cooperation to achieve the eradication goal. Recent cost-effectiveness analyses of measles eradication suggest that measles eradication is economically justified, but additional work is needed to further refine the investment case for measles, including the explicit consideration of rubella.

- What are the eradication investment cases for measles and rubella, separately and jointly? (High priority)
- Can models be used to determine the best and most robust metrics to measure program success toward an eradication goal? (High priority)
- In an environment of constrained financial resources, what is the optimal allocation of resources? (High priority)
- Can models be used to demonstrate the benefits of coordinated regional vaccination activities? (Medium priority)
- Can models be used to capture the adverse impact of misinformation and to identify key indicators and measures of quality to improve accountability? (Medium priority)
- What can models tell us about the value of: (1) national financial and budgetary planning for immunization activities, (2) a line item in national budget, and (3) accountability for availability of allocated funds? (Medium priority)
- How can we use economic models to quantify the positive and negative effects on health systems? (Medium priority)
- How can game theoretic models be used to help inform national incentives and choices (e.g., program adherence, reporting, commitment etc)? (Medium priority)
- What are the costs of failing to sustain a commitment to an eradication goal? (Low priority now, but expected to increase in priority after establishment of the goal)

4.2 Characterization and management of measles outbreaks

Rationale: Mathematical characterization of measles outbreaks and the costs and benefits of surveillance and outbreak response activities provide insights about the benefits of prevention, the risks of outbreaks, and the impacts of different strategies. Measles outbreaks often involve significant costs, and estimating the economic burden of measles outbreaks and response activities in countries of different income levels will provide important evidence to demonstrate the impact of measles control and eradication efforts.

- What outbreak response models are needed to support decisions (e.g., scale of vaccination response, age targets etc.) in the field and to evaluate the benefits of rapid response? (High priority)
- What are the costs of outbreaks, outbreak response activities and planned SIAs? (High priority)
- What are the costs of outbreak investigations and response each year at the global level? (High priority)
- How does the age distribution of susceptibility and within-population mixing affect the outbreak threshold population size (susceptible density) for an outbreak and effect estimates for critical community size to sustain transmission? (High priority)
- What levels of vaccine coverage and transmission dynamics create susceptibility among older children and adults and what do models suggest about the role of waning immunity in measles transmission? (High priority)
- What level of immunization among children and adults is required to interrupt measles transmission and sustain elimination? (High priority)

4.3 Characterization of national activities to prevent measles

Rationale: Existing tools to guide country-level program planning for measles vaccination strategies remain poorly evaluated and require improvement if national health leaders use these tools to manage population immunity levels and guide decisions on vaccine policies.

- What can be done to evaluate and improve existing tools (e.g., Measles Strategic Planning tool) currently used at the country level? (High priority)
- Can useful tools be developed to help countries track population immunity for measles and/or rubella as a function of time? (High priority)
- What is the relative cost-effectiveness of a 2-dose routine measles vaccine schedule compared to a single-dose routine schedule supplemented with regularly scheduled campaigns? (Medium priority)
- What is the relative cost-effectiveness of going from a measles vaccine to a measles-rubella vaccine? (Medium priority)
- What operational research is needed assess the impact of misreporting of national coverage and incidence on decisions and data collection activities? (Medium priority)

4.4 Characterization of individual risk and behavioral dynamics

Rationale: Variations in disease endemicity at the regional and country-level require different strategies to control and eliminate a disease, and experience shows that as countries successfully eliminate endemic measles transmission, public perception about the need for vaccination changes. Models that improve our understanding about the demand for vaccination will provide information needed to characterize and more effectively communicate the risk of outbreaks,

- What is the individual demand for vaccination (i.e., health seeking behavior) under different levels of endemicity? (High priority)
- How can we model perceptions of the disease and vaccine risks and how risk perception impacts vaccination coverage? (High priority)
- How can behavioral models be used to guide and inform communication? (High priority)

4.5 Prioritization of data collection

Rationale: Disease eradication initiatives require numerous types of information to ensure optimal use of scarce resources; selection of the most appropriate data sources is critical.

- What is the value of information of surveillance and other monitoring activities for measles and rubella elimination and eradication? (High priority)
- What is the value of information collected from field and laboratory studies and do the existing data collection efforts provide valuable information for policy makers? (High priority)
- What cost and valuation data need to be collected to support rigorous policy analyses? (High priority)

5.0 Rubella Control and Elimination

Rubella is still a major public health problem with an estimated 112,000 cases of congenital rubella syndrome (CRS) occurring in 2008 globally. In 2011, WHO updated the rubella vaccine position paper with the recommendations that countries that have not introduced rubella-containing vaccine (RCV) into their routine program should take the opportunity to combine introduction of RCV with accelerated measles control and elimination activities. The measles vaccine delivery strategies provide an opportunity for synergy of the strategies and a platform for advancing rubella and CRS elimination. By combining both measles and rubella/CRS elimination goals, several aspects of these strategies are integrated including use of combined vaccines (MR, MMR) and integrated rubella-measles surveillance. Currently 2/3 of WHO member states uses RCV in their childhood immunization program and 3 WHO regions have rubella control/elimination policies. However, there are remaining issues on determining rubella/CRS disease burden including the economic burden of disease, the most appropriate surveillance strategies, vaccination policies and laboratory diagnoses for persons with CRS.

5.1 Economic burden of disease and vaccination policies

Rationale: There are little data regarding the overall economic burden of disease of CRS including CRS morbidity and mortality and lifetime costs of resulting CRS

sequelae. Economic studies conducted in mainly middle and high income countries have shown introduction of rubella vaccine into routine childhood program as cost beneficial and effective. However, economic studies in low income countries are lacking including the cost of treating children with CRS. With the possibility of establishing a measles eradication goal, integrating rubella/CRS eradication to measles eradication is timely with the synergy between measles and rubella initiatives. However, the global economic burden of rubella and CRS needs to be determined, especially in the context of a measles eradication goal.

- What is the health and economic burden of rubella/CRS globally in context of measles/rubella eradication (including DALYS)? (High priority)
- What are the eradication investment cases for measles and rubella jointly? (High priority)
- What is the cost-effectiveness of implementing rubella vaccination program in various settings, particularly low income settings? (High priority)
- What is the cost of treating infants and children with CRS in low and middle income settings? (Medium priority)
- What is the economic and epidemiological impact of immunizing adult males against rubella? (Low priority)

5.2 Burden of Disease

Rationale: In many countries, the epidemiology of rubella is based on measles case-based surveillance, with rubella IgM testing of sera for of laboratory negative suspected measles cases. Until recently, most of the epidemiology of rubella and CRS in developing countries has been derived through mathematical models and seroprevalence studies. However, because of decreasing birth rates in many of the countries that have not introduced rubella containing vaccines, these estimates and models need to be updated to more accurately predict factors that will affect the epidemiology of rubella in these settings.

5.2.1 Basic epidemiology and disease burden

Rationale: Data on both rubella and CRS disease burden are needed in different epidemiological settings to assist in the development of appropriate vaccination strategies and monitor progress towards rubella control and CRS prevention goals.

- What is the epidemiology of rubella and CRS in developing countries with different birth rates or where no or minimal information is available, particularly in the WHO regions (Africa and Asia)? (High priority)

- How do the changes in birth rates over time impact incidence of CRS? (Medium priority)
- What are the predictors for rubella outbreaks in endemic countries? (Low priority)

5.2.2 Burden of disease due to CRS

Rationale: CRS burden is usually estimated through modeling of seroprevalence studies. However, countries in the regions with the highest CRS burden (AFR, SEAR) often do not have accurate estimates of CRS due to the lack of available data on rubella seroprevalence.

- What are estimates of CRS prevalence in various country settings (e.g., AFR, SEAR, and WPR) using seroprevalence studies. (High priority)

5.2.3. CRS surveillance

Rationale: Unlike rubella surveillance which can be integrated with measles surveillance, CRS is a standalone surveillance system for identifying infants with suspected CRS <12 month of age. Documenting the burden of CRS is challenging due to varied clinical presentation, and the need for coordination of clinical screening, referral, and diagnostic testing. To increase the feasibility of CRS surveillance, the most effective surveillance strategies need to be identified, especially in settings with weak health infrastructure. This may involve the use of new techniques, such as using biomarkers for CRS, to more accurately assess the burden of CRS in older children and adults.

- What are the optimal methods for identifying CRS cases, including using single birth defect and/or combination of defects, and what are the different sensitivities, specificities, and predictive values of these various clinical definitions for CRS? (High priority)
- What is the cost of CRS surveillance in different health infrastructures (e.g., very weak, moderate, developed)? (High priority)
- What is the utility of new techniques (e.g., biomarkers of CRS) in children, adults and pregnant women? (Medium priority)

5.3 Vaccine introduction and strategies

Rubella control and elimination efforts are expanding globally. According to the WHO, the number of countries that have incorporated RCV into their routine national immunization programs increased from 83 (43%) in 1996 to 131 (68%) in 2010. Of the remaining 62 countries, measles vaccine (MCV1) is administered at 9 months of age

which could be replaced with MR/MMR vaccine for countries introducing RCV into their childhood program. Almost all of the studies evaluating the seroconversion rate of RCV have been in children from developed countries. Developing countries have different challenges that will affect the effectiveness and feasibility of different vaccination schedules, vaccine delivery methods, and durability of vaccine-induced protection. For example, in many of the remaining countries that have not introduced RCV, HIV and AIDS are common. Several studies have documented the loss of antibodies titers in individuals with HIV infection and receiving antiretroviral therapy, but the impact of HIV on rubella immunity levels is unknown.

5.3.1 Rubella vaccination strategies

Rationale: In the new WHO rubella vaccine position paper, the recommendation is to use the measles vaccine platform to introduce rubella vaccine into the routine EPI program. As more countries will be introducing RCVs, exploring new delivery systems will be important. Trials are underway evaluating the feasibility of aerosolized measles vaccine. With the preference to use combined measles-rubella vaccine, assessing the feasibility of using a combined MR vaccine is warranted.

- What is the optimal vaccination schedule for MR/MMR vaccine in developing countries? (Low priority)
- What is the efficacy and safety of RCV aerosol vaccines? (High priority)
- How does immunodeficiency affect seroconversion and durability of protection with rubella vaccine? (Low priority)

5.3.2. Rubella vaccine coverage

Rationale: Even though RCV have not been introduced in 62 countries, there is some use in the private sector, although the level of use is unknown. Mathematical modeling has suggested that the sole use of RCV in the private sector could theoretically result in a potential increase in CRS cases compared to the prevaccine era. There is also the concern that if high vaccination coverage cannot be achieved and maintained, the resulting decrease in virus circulation would increase the average age of rubella infection for females from childhood to the childbearing years, thereby potentially increasing the risk of CRS. In 2010 and 2011, the SAGE and SAGE working group reviewed two different mathematical models and various countries examples with different vaccination strategies and coverage achieved. This review suggested that if ≥ 80%RCV coverage through routine services and/or SIAs can be achieved and maintained, then it would be safe and beneficial to introduce RCV. With additional

countries introducing RCV using the measles platform, this will provide an opportunity to validate the mathematical models.

- What is the rubella vaccine coverage in private sector in different epidemiological settings, how has it changed over time and how has it changed the epidemiology of rubella and CRS? (Medium priority)
- What criteria should be used to determine the minimum level of rubella vaccine coverage required to safely introduce rubella-containing vaccine (RCV) into routine childhood vaccination programs (i.e. RCV immunization coverage of 80% either through routine services or SIAs a reasonable threshold)? (Medium priority)

5.3.3 Rubella vaccination of boys and men

Rationale: As countries introduce RCVs, two strategic approaches are considered to achieve either CRS reduction or rubella and CRS elimination. In both strategies, women of childbearing age are targeted for vaccination. Alternatively, a strategy to include boys and men for vaccination may rapidly, and perhaps more efficiently, achieve rubella elimination. In PAHO, three countries conducted campaigns to vaccinate adult males after the initial mass campaigns targeting adult females failed to stop rubella virus transmission.

- What is the impact on the epidemiology on rubella and CRS and overall costs of the vaccination program to include vaccination of adult males against rubella? (Medium priority)
- Is vaccination of adult males required to achieve rubella elimination? (Medium priority)

5.3.4 Rubella vaccine strains

Rationale: The RA 27/3 rubella virus strain is the most commonly used rubella vaccine strain globally. However, two countries (China, Japan) do not use RA 27/3 rubella vaccine in their routine childhood program. In 2008, China introduced the BRD-II as part of their routine program, vaccinating approximately 16 million children. These two vaccines differ in strain types (BRD-II is a clade 2 rubella vaccine virus, RA 27/3 rubella virus vaccine strain, as with the other earlier rubella vaccines, is clade 1). However, almost all studies of immunological responses to rubella vaccines have been conducted using the RA 27/3 or earlier vaccines, and data on the response to BRD-II are quite limited. Because BRD-II rubella vaccine will be used in China's routine immunization

program, understanding the immunological response, including cell mediated immunity, will be critical for rubella elimination in China and globally.

- Does the human immune response vary by rubella virus vaccine type? (Medium priority)

5.4 Achieving and maintaining rubella and CRS elimination

Since 2003, two WHO regions, region of the Americas (AMR) and EURO, have established the following goals: rubella and CRS elimination by 2010 (PAHO), and rubella elimination and CRS prevention by 2015 (EURO). AMR has successfully eliminated rubella and CRS, and the documentation process has started. However, rubella continues to circulate in several EUR countries, impacting this region's progress toward elimination.

5.4.1 Public perceptions of rubella vaccine safety

Rationale: In many Western European countries, parents are concerned about vaccine safety issues. In the late 1990s, a controversy over the relationship of measles vaccine and autism resulted in a significant decrease in coverage in the UK resulting in the re-introduction of measles into that country.

- What are the reasons parents refuse vaccination with MMR vaccine and how can the public health community best communicate the reasons for MMR vaccination? (Medium priority)
- Are reasons for MMR vaccine refusal related to a specific antigen (measles versus rubella)? (Medium priority)

5.4.2 Rubella surveillance indicators

Rationale: Countries in the region of the Americas have used the measles surveillance indicators to monitor progress toward elimination of rubella. However, these indicators have not been validated for use for monitoring progress toward rubella elimination. As countries in other regions are making or have achieved rubella elimination, determining the appropriateness of the measles indicators for monitoring rubella elimination will be important. As part of achieving and maintaining elimination of rubella and CRS, identifying the most appropriate strategies for identification and confirmation of rubella and CRS cases in very low incidence settings is needed.

- Are the currently used measles surveillance indicators appropriate for monitoring progress toward rubella elimination? (High priority)
- What are the best methods for case identification and confirmation in low incidence/elimination settings? (Medium priority)

5.4.3 Molecular epidemiology of rubella virus

Rationale: Molecular epidemiology is one of the critical lines of evidence for documenting the elimination of rubella and CRS in the region of the Americas. However, molecular epidemiology information for rubella virus is limited compared to available information on measles virus. In the region of the Americas, the last confirmed endemic rubella (genotype 2B) case was reported in February 2009; suggesting that the countries of the Americas have achieved the elimination goal set for 2010. However, there are many countries that have no baseline information on molecular genotype. To enhance rubella surveillance and understand the molecular epidemiology of rubella virus, countries need to establish systems to study the molecular epidemiology of rubella virus.

- What is the molecular epidemiology of rubella virus globally? (High priority)
- What is the diversity and fluctuation of rubella virus strains in populations with low vaccine coverage? (High priority)
- What are the optimal methods for whole genome sequencing of rubella virus (High priority)

Appendix 1
Working Group Members

Measles Epidemiology

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Other members of working group: Abhijeet Anand, Nino Khetsuriani, William Moss, David Sniadack

Vaccine Development and Effectiveness, Alternative Delivery Methods and Laboratory Methods Research Agenda

Leads: Paul Rota, David Featherstone
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Immunization Strategies Research Agenda

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Mathematical Modeling and Economic Analyses Research Agenda

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Rubella Research Agenda

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