



## Meeting report

Research priorities for global measles and rubella control and eradication<sup>☆</sup>

## ARTICLE INFO

## Keywords:

Measles  
 Rubella  
 Eradication  
 Research  
 Immunization  
 Vaccines

## ABSTRACT

In 2010, an expert advisory panel convened by the World Health Organization to assess the feasibility of measles eradication concluded that (1) measles can and should be eradicated, (2) eradication by 2020 is feasible if measurable progress is made toward existing 2015 measles mortality reduction targets, (3) measles eradication activities should occur in the context of strengthening routine immunization services, and (4) measles eradication activities should be used to accelerate control and elimination of rubella and congenital rubella syndrome (CRS). The expert advisory panel also emphasized the critical role of research and innovation in any disease control or eradication program. In May 2011, a meeting was held to identify and prioritize research priorities to support measles and rubella/CRS control and potential eradication activities. This summary presents the questions identified by the meeting participants and their relative priority within the following categories: (1) measles epidemiology, (2) vaccine development and alternative vaccine delivery, (3) surveillance and laboratory methods, (4) immunization strategies, (5) mathematical modeling and economic analyses, and (6) rubella/CRS control and elimination.

## Introduction

At the World Health Assembly (WHA) in May 2008, following remarkable progress reducing measles deaths worldwide since the Measles Initiative was established in 2001 [1], World Health Organization (WHO) member states requested that an evaluation of the feasibility of global measles eradication. In July 2010, an expert advisory panel convened by WHO concluded that (1) measles can and should be eradicated, (2) eradication by 2020 is feasible if measurable progress is made toward the existing 2015 measles mortality reduction targets, (3) measles eradication activities should occur in the context of strengthening routine immunization services, and (4) measles eradication activities should be used to accelerate control and elimination of rubella and congenital rubella syndrome (CRS) [2,3]. In November 2010, the WHO Strategic Advisory Group of Experts (SAGE) endorsed the expert advisory panel conclusions and recommended that demonstration of sufficient progress toward 2015 regional measles elimination targets should serve as a basis for considering a target date for eradication. The WHA Executive Board endorsed the SAGE recommendations in January 2011 [2].

The WHO expert advisory panel also emphasized the critical role of research and innovation in any disease control or eradication program [3]. To begin the process of prioritizing research questions for measles eradication and accelerated rubella/CRS control and elimination, the U. S. Centers for Disease Control and Prevention hosted a meeting in May 2011 to identify and prioritize key research questions within the following categories: (1) measles

epidemiology, (2) vaccine development and effectiveness, and alternative delivery methods, (3) surveillance and laboratory methods, (4) immunization strategies, (5) mathematical modeling and economic analyses, and (6) rubella/CRS control and elimination. The list of questions generated by invited meeting experts reflects the views that emerged following group discussion. Key contextual issues for the research agenda include changing epidemiology that leads to shifts in age groups and subpopulations that primarily sustain measles and rubella virus transmission, technological advances that provide new opportunities to improve vaccination and laboratory techniques, and health systems development that enhance surveillance and vaccination activities. This manuscript highlights insights and research priorities for measles and rubella control and eradication identified by meeting participants; the comprehensive list of all identified questions is in the full meeting report (Appendix A).

## 1. Measles epidemiology

Progress toward measles elimination has varied among the regions of the world [4]. The WHO Region of the Americas declared interruption of endemic measles virus transmission in 2002. The WHO regions of Africa, Europe, Eastern Mediterranean, and Western Pacific adopted regional measles elimination goals with target dates by or before 2020 [4,5]. However; endemic measles virus circulation and large outbreaks continue to occur in these regions. The WHO South-East Asia region does not yet have a measles elimination goal and continues to have a substantial measles burden, accounting for more than two-thirds of the estimated global measles deaths in 2008, primarily from India [6,7]. Review of evidence from surveillance data and previous outbreaks led to the identification of the following key research questions (Panel 1).

<sup>☆</sup> *Disclaimer:* The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the World Health Organization or the U.S. Centers for Disease Control and Prevention.

**Panel 1. Measles Epidemiology – Key Research Questions**

- What are the epidemiologic characteristics of measles (e.g., incidence, age distribution, case fatality ratios) in various settings in India?
- What are the causes of measles outbreaks in settings with high reported measles vaccination coverage?
- What is the prevalence of measles virus susceptibility among adults in settings with persistent suboptimal measles vaccination coverage?
- Can adults sustain measles virus transmission in the presence of high child immunity levels thereby making adult vaccination required to reach and maintain elimination?
- At what age do infants lose protection from maternal measles-specific antibodies in different epidemiological settings? What are the potential implications of receiving MCV1 at an early age (e.g., prior to 9 months)?
- What is the prevalence of measles virus susceptibility among human immunodeficiency virus (HIV)-infected adults in high HIV-prevalence settings?

**What are the epidemiologic characteristics of measles (e.g., incidence, age distribution, case fatality ratios) in various settings in India?**

India is the only country that has not fully implemented a two-dose measles vaccination strategy. In addition, measles case-based surveillance has not been established nationwide, measles cases and deaths are grossly underreported, and the epidemiology of measles in India is not well characterized [7–9]. Investigations are needed to document the burden of disease, determine likely causes of measles outbreaks, and assess reasons for non-vaccination to provide information for designing strategies that increase measles vaccination coverage and interrupt endemic measles virus transmission in India.

**What are the causes of measles outbreaks in settings with high reported measles vaccination coverage?**

In Africa, among the 28 countries that reported measles outbreaks during 2009–2010, 10 reported  $\geq 90\%$  coverage with the first dose of measles-containing vaccine (MCV1) in 2009 and 15 had conducted a supplemental immunization activity (SIA) within 24 months before the outbreak, with  $\geq 90\%$  administrative coverage [10]. During 2010, measles outbreaks occurred in several European countries with  $\geq 90\%$  reported MCV1 coverage [11,12]. Continued outbreaks might be related to low coverage in certain subpopulations, which might be obscured by high national vaccination coverage. Dynamics in epidemiology, particularly the shift in age of infection with increasing measles vaccination coverage, point to the need for investigations to identify evolving risk factors for measles and subpopulations at risk for sustained measles virus transmission.

**What is the prevalence of measles virus susceptibility among adults in settings with persistent suboptimal measles vaccination coverage?**

Prior to the widespread use of measles vaccine starting in 1963, epidemic cycles occurred every 2–3 years, virtually everyone experienced measles illness during childhood, and  $>90\%$  of individuals became infected by 10 years of age [13,14]. Before endemic measles virus transmission ended in the Americas in 2002, outbreaks among young adults occurred in Argentina, Bolivia, Brazil, Canada, Venezuela, and the Dominican Republic [15]. Increasing vaccination coverage among children tends to shift the age of infection toward older ages; in recent years, measles outbreaks in other regions have been characterized by cases among older children and young adults [4,16–18]. The observed cases in older age groups raise questions regarding the level of susceptibility among adults.

**Can adults sustain measles virus transmission in the presence of high child immunity levels thereby making adult vaccination required to reach and maintain elimination?**

Serologic and epidemiologic studies indicate approximately 85–90% efficacy for a single measles vaccine dose given at 9 months of age and  $>99\%$  efficacy following a second dose given at  $\geq 12$  months of age [14]. Primary and secondary vaccine failure and modified measles disease can occur among vaccinated individuals [19,20], and vaccine-induced immunity could wane in the absence of the boosting effect provided by circulating wild-type viruses. As regions move toward elimination, monitoring of immunity among adults might be needed to determine the potential need for measles vaccine booster doses.

**At what age do infants lose protection from maternal measles-specific antibodies in different epidemiological settings? What are the potential implications of receiving MCV1 at an early age (e.g., prior to 9 months)?**

Infants born to immune mothers receive maternal antibodies transferred during the prenatal period and remain protected until approximately 4–6 months of age [21]. However, in low-income settings, infants lose protection from maternal antibodies at a younger age [22]. In addition, transferred maternal antibodies from vaccine-induced protection rather than naturally acquired measles virus infection generally result in lower geometric mean titers that wane faster, leaving the infant unprotected in early infancy [23,24]. Few published reports exist documenting increased risk of measles in younger infants due to the loss of protection in infants in low income settings and among mothers with vaccine-induced immunity [25,26], and implications of receiving MCV1 at an early age [27,28]. Information is needed to understand the role of infants in sustaining measles virus transmission in these settings, and for development of vaccination strategies to achieve elimination, particularly as exposure to wild measles virus becomes rarer.

**What is the prevalence of measles virus susceptibility among human immunodeficiency virus (HIV)-infected adults in high HIV-prevalence settings?**

The effect of HIV infection on measles antibody titers and cell-mediated immunity among adults is not fully understood, but because measles antibody titers decline more rapidly after vaccination among HIV-infected compared with non-HIV infected persons [29–31], HIV infection could result in suboptimal protective immunity to measles [32]. In high HIV-prevalence settings, the prevalence of measles susceptibility among HIV-infected adults is unknown and might play a role in sustaining measles virus transmission.

**2. Vaccine development and effectiveness, and alternative vaccine delivery methods**

Widespread availability and use of safe, effective, and inexpensive measles and rubella vaccines has resulted in dramatic reductions in morbidity and mortality worldwide. Advances in vaccine effectiveness, and alternative delivery methods could improve coverage and efficiency of administration (Panel 2).

**Panel 2. Vaccine Development and Effectiveness, and Alternative Vaccine Delivery Methods – Key Research Questions**

- What is the effectiveness of measles vaccine in densely populated settings in developing countries?
- Can vaccine safety, effectiveness, and coverage be improved by development of more thermo-stable vaccines, advanced vaccine vial temperature monitors, self-reconstituting vials, or by alternative delivery methods (e.g., needle-free injection devices, aerosol, dry powder inhalation, microneedles)?

**What is the effectiveness of measles vaccine in densely populated settings in developing countries?**

Urban populations with high contact rates require higher population immunity to achieve herd immunity compared with sparsely

populated, rural settings [33]. Many areas with continuing measles transmission have extremely high population densities with other risks that could affect measles vaccine effectiveness, such as higher prevalence of other infectious diseases. Evaluation of potential reasons for lower measles vaccine effectiveness is needed in these high risk settings.

**Can vaccine safety, effectiveness, and coverage be improved by development of more thermo-stable vaccines, advanced vaccine vial temperature monitors, self-reconstituting vials, or by alternative delivery methods (e.g., needle-free injection devices, aerosol, dry powder inhalation, microneedles)?**

Current formulations of measles and rubella vaccines require cold chain storage at 4–8 °C until use, followed by reconstitution with diluent via needle and syringe by trained medical staff [14]. Once reconstituted, the vaccine must be discarded after 6 h due to risk of bacterial contamination and loss of potency with exposure to light and increased temperature. More thermo-stable vaccines with simplified storage and handling might help eradication efforts, particularly if wastage concerns impact decisions made about vaccinating individual children when only multi-dose vials are available. In addition, injectable vaccines might deter acceptance and require skilled medical staff to administer. The safe disposal of syringes and needles requires logistics that complicate mass vaccination campaigns and rapid outbreak response immunization activities. Needle-free jet injectors using single dose disposable cartridges offer an opportunity to avoid needles [34]. In addition, studies of devices for aerosol administration of measles vaccine continue, with licensure of these devices expected in the near future [35]. Inhalation of dry powder measles vaccine removes the need for reconstitution with diluents, microneedle administration offers the potential for development of a skin patch vaccine that house-to-house volunteers could easily administer. Research should continue to develop and test alternative delivery methods for the administration of combined measles and rubella vaccines.

### 3. Surveillance and laboratory methods

Acceleration of measles and rubella control efforts will require further enhancement of laboratory methods and surveillance systems, with more complete integration of epidemiological and laboratory information. The WHO Global Measles and Rubella Laboratory Network, established in 2000, includes 690 laboratories serving 183 countries [36]. Virologic surveillance that documents the interruption of transmission of measles and rubella viruses represents an essential element of control and elimination efforts and verification of their success [37]. To further improve global laboratory-based surveillance, research will need to identify and validate new methods and approaches in various settings (Panel 3).

**Panel 3. Surveillance and Laboratory Methods – Key Research Questions**

- What is the global distribution of circulating measles virus genotypes and which genotypes have been eliminated?
- Can diagnostic tests be developed to rapidly and accurately detect measles and rubella cases in field conditions?
- Can tests be developed to accurately measure neutralizing antibodies to measles and rubella viruses, and provide results faster than the plaque reduction neutralization assay (PRNT) with high throughput?
- What molecular sequencing methods can be used to distinguish between closely related measles and rubella viruses?
- What are the technical requirements and epidemiologic utility of developing serologic assays to differentiate immunity acquired from exposure to wild-type viruses and immunity acquired from exposure to vaccine strains?

**What is the global distribution of circulating measles virus genotypes and which genotypes have been eliminated?**

Molecular techniques provide measles virus genotype and genetic sequencing that allow the differentiation and tracking of measles viruses [38]. Genomic data combined with findings from epidemiologic investigations will result in a better understanding of how circulating measles viruses relate in space and time, and will help identify transmission pathways and areas where measles surveillance might be failing to detect cases and chains of virus transmission.

**Can diagnostic tests be developed to rapidly and accurately detect measles and rubella cases in field conditions?**

A rapid response to outbreaks critically depends on laboratory confirmation of suspected measles or rubella cases. The turnaround times for reporting serologic test results in most national laboratories meet or exceed the minimum standard established by the WHO LabNet [36]. However, results from specimens collected in remote areas can be delayed due to poor infrastructure for collection, storage and transportation of specimens. For this reason, research efforts are needed to develop diagnostic assays that can be performed in remote locations that do not have efficient access to laboratories.

**Can tests be developed to accurately measure neutralizing antibodies to measles and rubella viruses, and provide results faster than the plaque reduction neutralization assay (PRNT) with high throughput?**

PRNT is the gold standard for measuring immunity to measles virus [39,40]. However, PRNT is difficult and time-consuming to perform, limiting the number of samples that can be tested [41]; moreover, few laboratories are proficient using PRNT. Efforts are underway to standardize a neutralization assay to measure rubella immunity [42]. Research is needed to develop new techniques for rapid and accurate measurement of protective immunity to measles and rubella viruses, with high throughput to meet the needs of measles and rubella control and elimination efforts.

**What molecular sequencing methods can be used to distinguish between closely related measles and rubella viruses?**

The value of molecular epidemiologic surveillance for measles and rubella viruses is well established, but existing sequencing methods have limited ability to distinguish between closely related viruses [43]. Research is needed to develop additional sequencing methods to distinguish between closely related strains of measles and rubella viruses, which will provide a better understanding of viral transmission pathways, the distribution of circulating virus genotypes, and help to identify areas with underperforming surveillance.

**What are the technical requirements and epidemiologic utility of developing serologic assays to differentiate immunity acquired from exposure to wild-type viruses and immunity acquired from exposure to vaccine strains?**

Existing assays do not have the capacity to distinguish between measles virus-specific antibodies induced by vaccination and antibodies acquired from natural infection. Serologic assessments of population immunity to measure the effectiveness of vaccination campaigns would be improved by the ability to distinguish individuals with measles antibodies due to prior infection from those with antibodies induced by vaccination. To develop such a test, the technical requirements, feasibility, and cost should be determined, and descriptions of vaccine and wild-type specific epitopes, information currently not available in the published literature, would be needed.

### 4. Immunization strategies

Vaccine-preventable disease elimination and eradication efforts require evidence-based immunization strategies implemented



with effective vaccination program services. To interrupt endemic measles virus transmission and achieve measles elimination, country experience and mathematical models both demonstrate the need for high ( $\geq 95\%$ ) levels of homogeneous population immunity [14,44]. To reach this level of immunity, WHO recommends two MCV doses for all children given through routine services and/or supplemental immunization activities (SIAs) (i.e., mass campaigns) [14]. Achieving high vaccination coverage requires high community demand for vaccination services; effective advocacy and communication activities with relevant stakeholders (e.g., public and private providers), a secure vaccine supply and logistics, and strong political and financial commitments at every level of government [45,46]. Efficient program management, skilled medical staff, and accurate vaccination coverage monitoring are also needed. In addition, special vaccination strategies are needed for communities with difficult to access to immunization services (e.g., civil unrest, migratory patterns, poor infrastructure, etc.) [47] (Panel 4).

**Panel 4. Immunization Strategies – Key Research Questions**

- What are effective strategies for increasing uptake of the routine first dose of measles vaccine administered at nine or 12 months and second dose given during the second year of life?
- What are effective strategies (e.g., house-to-house social mobilization) to maximize SIA coverage in different epidemiological settings?
- What are accurate and efficient methods for monitoring first- and second-dose measles vaccination coverage through routine immunization services and SIAs?
- What are effective strategies for identifying and vaccinating nomadic populations, migrants, refugees, and internally-displaced persons in various settings?
- What misconceptions and attitudinal barriers exist among communities and public and private sector health care providers regarding measles- and rubella-containing vaccines, and what communication messages and strategies can increase demand for vaccination in various settings?
- What are the most effective strategies for outbreak response immunization activities?

**What are effective strategies for increasing uptake of the routine first dose of measles vaccine administered at nine or 12 months and second dose given during the second year of life?**

In most low income countries, multiple visits are included in routine childhood immunization services during the first year of life concluding with MCV1 dose given at nine months of age. Many countries extended services to include MCV2 given during the second year of life. Research efforts will need to identify effective strategies to ensure high coverage of both MCV1 and MCV2 administered in routine immunization services.

**What are effective strategies (e.g., house-to-house social mobilization) to maximize SIA coverage in different epidemiological settings?**

In addition to routine immunization services, SIAs are a well-established service delivery method for reaching high vaccination coverage [48,49]. SIAs are cost-effective, can improve vaccination equity within populations, and deliver other health interventions, such as vitamin A, albendazole, and insecticide-treated bed nets [50–53]. Successful SIAs need to reach all eligible children, particularly those with poor access to immunization services. This requires detailed micro-planning at the community level for positioning of vaccination sites, vaccine storage and handling, and social mobilization including house-to-house mobilization. Operational research is needed to identify the most effective strategies.

**What are accurate and efficient methods for monitoring first- and second-dose measles vaccination coverage through routine immunization services and SIAs?**

Homogenous high population immunity is needed to achieve elimination of human virus transmission in a geographic area. Accurate estimates of vaccination coverage are required to assess population immunity, direct program activities, and prioritize

resources to prevent outbreaks and subsequently, achieve elimination. Recent large measles outbreaks (e.g., in Burkina Faso and Malawi) occurred in settings where inflated coverage estimates suggested high population immunity [10]. Inaccurate coverage estimates can occur for a variety of reasons, including underestimation of the target population, over-estimation of the number vaccinated, or sampling methods in coverage surveys that exclude mobile or underserved communities. A variety of methods (e.g., vaccination registries, school entry checks, population-based surveys, lot quality assurance sampling) may help to improve coverage estimates [54]; however, research is needed to determine the optimal methods for estimating routine and SIA vaccination coverage.

**What are effective strategies for identifying and vaccinating nomadic populations, migrants, refugees, and internally displaced persons in various settings?**

Measles eradication will require achieving and maintaining uniformly high vaccination coverage across all population groups. Thus, delivery strategies need to be adapted to various social, cultural and geographical circumstances to effectively reach all subpopulations. Populations with difficulty accessing vaccination services (e.g., migrant, nomadic, or displaced populations) will require additional or different strategies to achieve high coverage; research is needed to assess migration patterns, seasonal availability, security issues, and other factors to develop innovative strategies for improving vaccination coverage.

**What misconceptions and attitudinal barriers exist among communities and public and private sector health care providers regarding measles- and rubella-containing vaccines, and what communication messages and strategies can increase demand for vaccination in various settings?**

Achieving and maintaining high vaccination coverage requires that providers promote vaccination and clients accept vaccination [55]. In many Western European countries, misconceptions and concerns exist regarding vaccine and vaccine safety. For example, in the United Kingdom, a controversy over the relationship of measles vaccine and autism resulted in a decrease in coverage that led to a resurgence of measles [55]. Disease elimination and eradication programs require sustained advocacy and engagement of health care providers within the public and private sector. Private providers are playing an increasing role in delivery of immunization services, even in low income settings. Research is needed to identify the beliefs and attitudes causing barriers to acceptance of vaccination, and to identify evidence-based communication messages and strategies that effectively counter misconceptions.

**What are the most effective strategies for outbreak response immunization activities?**

Measles outbreaks, particularly following a period of low incidence, can increase societal and political pressure for outbreak response immunization activities (ORI). Successful ORI efforts control measles outbreaks and limit the spread of the virus [56,57,17]. The approach to ORI can vary depending on the level of health service infrastructure, susceptibility by age in the population, the risk for disease spread and severity of clinical complications; debate continues related to optimal timing, target populations, and vaccine delivery methods [58]. In 2009, WHO revised its measles outbreak response guidelines to include recommendations for ORI [59], but the usefulness and effectiveness of these guidelines require evaluation.

**5. Mathematical modeling and economic analyses**

Mathematical modeling and economic analyses represent critical research components for disease eradication initiatives and can offer valuable insights about group behavior, disease

dynamics within populations, and the risks, benefits, and costs of various policy options [60,61] (Panel 5).

**Panel 5. Mathematical Modeling and Economic Analyses – Key Research Questions**

- What are the most useful modeling approaches for measuring progress toward measles eradication?
- What are the most useful modeling approaches to estimate the threshold population size and susceptible density required to sustain measles virus transmission in various settings?
- What is the economic burden of measles outbreaks in low and middle income countries?

**What are the most useful modeling approaches for measuring progress toward measles eradication?**

The Measles Initiative monitors progress toward global measles control using mathematical models that estimate the number of measles cases and deaths. The accuracy of these estimates relies on the availability and accuracy of data that support model inputs; however, under-reporting of measles cases and deaths presents an ongoing challenge [62,63]. In addition, existing models have limited use for producing estimates in low incidence settings where virus importations and mixing patterns among susceptible sub-populations determine the potential for sustaining transmission. Research is needed to develop useful models that can guide vaccination strategies in the final stages of eradication.

**What are the most useful modeling approaches to estimate the threshold population size and susceptible density required to sustain measles virus transmission in various settings?**

The high transmissibility of measles virus causes different epidemiologic patterns depending on population dynamics and level of susceptibility. The critical community size required to sustain measles virus transmission and the level of population immunity required to interrupt transmission in certain scenarios remain unknown (e.g., settings with large birth cohorts, high population density, or intense within-population mixing). Research is needed to estimate the threshold population size and susceptibility density required to sustain measles virus transmission in order to better understand the levels of population immunity required for elimination in various settings.

**What is the economic burden of measles outbreaks in low and middle income countries?**

Several studies provided estimates of the cost of responding to measles virus importations and containing outbreaks in high income countries [64–67]; however, the economic burden of measles outbreaks in low and middle countries is uncertain. Cost estimates of measles outbreaks and response activities in low and middle income countries would provide evidence for shaping national immunization policies, advocating for political and financial commitment, and demonstrating the economic benefits of measles eradication.

**6. Rubella/CRS control and elimination**

Rubella virus infection, particularly during pregnancy, is an important public health problem that causes an estimated 112,000 CRS cases annually [68–70]. Approximately two-thirds of the WHO member states now include rubella-containing vaccine (RCV) in childhood immunization programs and 3 WHO regions have rubella/CRS control or elimination goals [71]. In 2011, WHO recommended that countries without RCV in routine childhood immunization programs introduce RCV with accelerated measles control and elimination activities [72]. In November, 2011, the GAVI Alliance approved funding for mass campaigns using combined measles and rubella vaccines to support countries introducing RCV [70]. Implementation of measles vaccination strategies provides an

opportunity for synergy and a platform for accelerating rubella and CRS control and elimination [73]. Research is needed to determine appropriate CRS surveillance strategies, vaccination policies, and laboratory diagnostic tests for CRS (Panel 6).

**Panel 6. Rubella/CRS Control and Elimination – Key Research Questions**

- What is the epidemiology of rubella/CRS in developing countries with varying birth rates?
- What are the optimal methods and corresponding costs for identifying CRS cases (e.g., using a single or combination of birth defects), particularly in areas with weak health system infrastructure)?
- What is the global distribution of circulating rubella virus genotypes and which genotypes have been eliminated?
- What is the economic burden of rubella and CRS at global, regional and national levels? Does the economic burden differ for low and middle income countries?

**What is the epidemiology of rubella/CRS in developing countries with varying birth rates?**

Along with age-specific immunity levels, general population dynamics including age distribution and birth rate affect rubella/CRS epidemiology. Until recently, estimates of rubella epidemiology and CRS were derived using mathematical models extrapolated from seroprevalence survey results [74]. However, with declining birth rates and increasing RCV use in many countries, research is needed to predict how varying birth rates affect the epidemiology of rubella/CRS.

**What are the optimal methods and corresponding costs for identifying CRS cases (e.g., using a single or combination of birth defects), particularly in areas with weak health system infrastructure)?**

Unlike rubella surveillance, which can be integrated with measles surveillance [75], CRS surveillance requires a system that can identify suspected CRS cases among infants <12 months of age. Identifying and properly investigating suspected CRS cases is challenging due to a variety of potential clinical presentations (e.g., hearing deficits, cataracts, heart defects), and the need for coordinating screening and referral for diagnostic testing [76,77]. To ensure the feasibility of CRS surveillance, research will need to identify optimal methods, and corresponding costs for detecting suspected CRS cases, particularly in settings with weak health system infrastructures.

**What is the global distribution of circulating rubella virus genotypes and which genotypes have been eliminated?**

In the region of the Americas, the last confirmed endemic rubella case was reported in February 2009, indicating achievement of the regional goal of elimination by 2010 [78]. However, baseline information about endemic rubella virus genotypes does not exist for many countries. The global distribution of endemic rubella virus genotypes needs to be determined and monitored to better understand the molecular epidemiology of rubella virus and to verify the elimination of genotypes [37,79].

**What is the economic burden of rubella and CRS at global, regional and national levels? Does the economic burden differ for low and middle income countries?**

A recent cost-effectiveness analysis provided economic justification for measles eradication [80]. Integration of rubella and CRS elimination activities in the strategic plan for measles eradication requires efforts to establish the investment case for these combined efforts. Economic studies demonstrated the economic benefits of rubella vaccination in high income countries [64,66,67]; however, the burden of disease and life-long costs of individuals with CRS in low and middle income countries requires characterization to support estimates of the global economic burden of rubella and CRS.

## Acknowledgments

Other Working Group members at the Global Measles and Rubella Research Meeting, Atlanta, GA, May 2011: Abhijeet Anand, MD; Bettina Bankamp, PhD; William Bellini, PhD; Lisa Cairns, MD; Steve Cochi, MD; Louis Cooper, MD; Vance Dietz, MD; Walter Dowdle, MD; Matthew Ferrari, PhD; Manoj Gambhir, PhD; Christopher Gregory, MD; Ana-Maria Henao-Restrepo, MD; Alan Hinman, MD; Edward Hoekstra, MD; Joseph Icenogle, MD; Robert Keegan, MPH; Nino Khetsuriani, MD; Katrina Kretsinger, MD; Robert Linkins, PhD; Sara Lowther, PhD; Sara Mercader, MS; Claude Muller, MD; Linda Quick, MD; David Sniadack, MD; Maya van den Ent, MD; Emilia Vynnycky, PhD; Kathleen Wannemuehler, PhD; Margaret Watkins, PhD; and Leo Weakland, MPH. We also are grateful to Jim Barnes, MPH, Alya Dabbagh, MD for their valuable assistance, and to Eric Mast, MD, for his thoughtful review and helpful comments.

**Funding:** World Health Organization, U.S. Centers for Disease Control and Prevention. **Financial interest:** The authors do not have a financial or proprietary interest in a product, method, or material or lack thereof. **Conflict of interest statement:** None. **Previous presentation:** None

## Appendix A. Supplementary data

The full meeting report associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2012.04.058>.

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24 February 2012

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12 April 2012

17 April 2012

Available online 28 April 2012