HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2023 July 05.

Published in final edited form as:

Vaccine. 2012 July 06; 30(32): 4709–4716. doi:10.1016/j.vaccine.2012.04.058.

Research priorities for global measles and rubella control and eradication☆

James L. Goodson[*],
Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, United States

Susan Y. Chu,
Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, United States

Paul A. Rota,
Measles, Mumps, Rubella and Herpes Viruses Laboratory Branch, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States

William J. Moss,
Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States

David A. Featherstone,
Department of Immunization, Vaccines, and Biologicals, World Health Organization, Geneva, Switzerland

Maya Vijayaraghavan,
Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, United States

Kimberly M. Thompson,
Kid Risk, Inc., Newton, MA, United States

Rebecca Martin,
Vaccine Preventable Diseases and Immunization Programme, World Health Organization Regional, Office for Europe, Copenhagen, Denmark

Susan Reef,
Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, United States

☆*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.

[*] Corresponding author at: Global Immunization Division, Centers for Disease Control and Prevention, 1600 Clifton Road, NE; MS-E05, Atlanta, GA 30333, United States. Tel.: +1 404 639, 8170; fax: +1 404 639 8676. JGoodson@cdc.gov (J.L. Goodson).

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.

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.

Peter M. Strebel
Department of Immunization, Vaccines, and Biologicals, World Health Organization, Geneva, Switzerland

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.

Keywords

Measles; Rubella; Eradication; Research; Immunization; Vaccines

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).

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 ≥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 ≥90% administrative coverage [10]. During 2010, measles outbreaks occurred in several European countries with ≥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 ≥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).

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).

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 (≥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).

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 under-estimation 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).

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 subpopulations 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).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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.

References

[1]. Christie A, Gay A. The Measles Initiative: moving toward measles eradication. Journal of Infectious Diseases 2011;204(Suppl. 1):S14–7. [PubMed: 21666155]

[2]. Strebel PM, Cochi SL, Hoekstra E, Rota PA, Featherstone D, Bellini WJ, et al. A world without measles. Journal of Infectious Diseases 2011;204(Suppl. 1):S1–3.

[3]. World Health Organization. Proceedings of the global technical consultation to assess the feasibility of measles eradication, 28–30 July 2010. Journal of Infectious Diseases 2011;204(Suppl. 1):S4–13. [PubMed: 21666191]

[4]. Centers for Disease Control and Prevention. Progress in global measles control, 2000–2010. MMWR Morbidity and Mortality Weekly Report 2012;61:73–8. [PubMed: 22298303]

[5]. World Health Organization. Monitoring progress towards measles elimination. Weekly Epidemiological Record 2010;85(49):490–4. [PubMed: 21140596]

[6]. Centers for Disease Control and Prevention. Global measles mortality, 2000–2008. MMWR Morbidity and Mortality Weekly Report 2009;58(47):1321–6. [PubMed: 19959985]

[7]. World Health Organization. Progress in implementing measles mortality reduction strategies, India 2010–2011. Weekly Epidemiological Record 2011;86(40):439–44. [PubMed: 21984984]

[8]. Murhekar MV, Hutin YJ, Ramakrishnan R, Ramachandran V, Biswas AK, Das PK, et al. The heterogeneity of measles epidemiology in India: implications for improving control measures. Journal of Infectious Diseases 2011;204(Suppl. 1):S421–6. [PubMed: 21666194]

[9]. Murhekar M, Roy D, Das P, Bose A, Ramakrishnan R, Biswas A, et al. Measles in rural West Bengal, India, 2005–6: low recourse to the public sector limits the use of vitamin A and the sensitivity of surveillance. Journal of Infectious Diseases 2011;204(Suppl. 1):S427–32. [PubMed: 21666195]

[10]. Centers for Disease Control and Prevention. Measles outbreaks and progress toward measles preelimination—African region, 2009–2010. MMWR Morbidity and Mortality Weekly Report 2011;60(12):374–8. [PubMed: 21451448]

[11]. EUVAC.net. Measles surveillance annual report 2010. Copenhagen, Denmark: Statens Serum Institute; 2010, http://www.euvac.net/graphics/euvac/pdf/annual2010.pdf [accessed 10.02.12].

[12]. Centers for Disease Control and Prevention. Global routine vaccination coverage, 2010. MMWR Morbidity and Mortality Weekly Report 2011;60:1520–2. [PubMed: 22071590]

[13]. Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H, Network EPESe, et al. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. Epidemiology and Infection 2000;125(3):635–50. [PubMed: 11218214]

[14]. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record 2009;84(35):349–60. [PubMed: 19714924]

[15]. de Quadros CA, Izurieta H, Venczel L, Carrasco P, de Quadros CA, Izurieta H, et al. Measles eradication in the Americas: progress to date. Journal of Infectious Diseases 2004;189(Suppl. 1):S227–35. [PubMed: 15106116]

[16]. Centers for Disease Control and Prevention. Progress in measles control—Kenya 2002–2007. MMWR Morbidity and Mortality Weekly Report 2007;56(37):969–72. [PubMed: 17882128]

[17]. Goodson J, Wiesen E, Perry R, Mach O, Kitambi M, Kibona M, et al. Impact of measles outbreak response vaccination campaign in Dar es Salaam, Tanzania. Vaccine 2009;27(42):5870–4. [PubMed: 19656496]

[18]. Yameogo KR, Perry RT, Yameogo A, Kambire C, Konde MK, Nshimirimana D, et al. Migration as a risk factor for measles after a mass vaccination campaign, Burkina Faso, 2002. International Journal of Epidemiology 2005;34(3): 556–64. [PubMed: 15659463]

[19]. Hickman C, Hyde T, Sowers S, Mercader S, McGrew M, Williams N, et al. Laboratory characterization of measles virus infection in previously vaccinated and unvaccinated individuals. Journal of Infectious Diseases 2011;204(Suppl. 1):S549–58. [PubMed: 21666212]

[20]. Rota J, Hickman C, Sowers S, Rota P, Mercader S, Bellini W. Two case studies of modified measles in vaccinated physicians exposed to primary measles cases: high risk of infection but low risk of transmission. Journal of Infectious Diseases 2011;204(Suppl. 1):S559–63. [PubMed: 21666213]

[21]. Ferrari M, Grais R, Bharti N, Conlan AJK, Bjrnstad O, Wolfson L, et al. The dynamics of measles in sub-Saharan Africa. Nature 2008;451(7179):679–84. [PubMed: 18256664]

[22]. Black FL, Berman LL, Borgoo JM, Capper RA, Carvalho AA, Collins C, et al. Geographic variation in infant loss of maternal measles antibody and in prevalence of rubella antibody. American Journal of Epidemiology 1986;124(3):442–52. [PubMed: 3740044]

[23]. Cutts FT, Markowitz LE, Cutts FT, Markowitz LE. Successes and failures in measles control. Journal of Infectious Diseases 1994;170(Suppl. 1):S32–41. [PubMed: 7930752]

[24]. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. British Medical Journal 2010:2010.

[25]. Zhao H, Lu P-S, Hu Y, Wu Q, Yao W, Zhou Y-H. Low titers of measles antibody in mothers whose infants suffered from measles before eligible age for measles vaccination. Virology Journal 2010;7(1):87. [PubMed: 20444295]

[26]. Goodson JL, Masresha BG, Wannemuehler K, Uzicanin A, Cochi S. Changing epidemiology of measles in Africa. Journal of Infectious Diseases 2011;204(Suppl. 1):S205–14. [PubMed: 21666163]

[27]. Aaby P, Martins C, Garly M-L, Bal C, Andersen A, Rodrigues A, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. British Medical Journal 2010;341:c6495–500. [PubMed: 21118875]

[28]. Martins C, Garly M-L, Bal C, Rodrigues A, Ravn H, Whittle H, et al. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. British Medical Journal 2008;337:a661–70. [PubMed: 18653640]

[29]. Scott S, Moss WJ, Cousens S, Beeler JA, Audet UA, Mugala N, et al. The influence of HIV-1 exposure and infection on levels of passively acquired antibodies to measles virus in Zambian infants. Clinical Infectious Diseases 2007;45(11):1417–24. [PubMed: 17990222]

[30]. Choudhury S, Hatcher F, Berthaud V, Ladson G, Hills E, Humphrey A. Immunity to measles in pregnant mothers and in cord blood of their infants: impact of HIV status and mother's place of birth. Journal of the National Medical Association 2008;100(12):1445–9. [PubMed: 19110913]

[31]. Moss WJ, Scott S, Mugala N, Ndhlovu Z, Beeler JA, Audet SA, et al. Immunogenicity of standard-titer measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. Journal of Infectious Diseases 2007;196(3):347–55. [PubMed: 17597448]

[32]. Stermole B, Grandits G, Roediger M, Clark B, Ganesan A, Weintrob A, et al. Long-term safety and serologic response to measles: mumps, and rubella vaccination in HIV-1 infected adults. Vaccine 2011;29(16):2874–80. [PubMed: 21352938]

[33]. Ferrari M, Djibo A, Grais R, Bharti N, Grenfell B, Bjornstad O. Rural–urban gradient in seasonal forcing of measles transmission in Niger. Proceedings of the Royal Society B: Biological Sciences 2010;277(1695):2775–82.

[34]. Kis EE, Winter G, Myschik J. Devices for intradermal vaccination. Vaccine 2012;30(3):523–38. [PubMed: 22100637]

[35]. Low N, Kraemer S, Schneider M, Henao Restrepo AM. Immunogenicity and safety of aerosolized measles vaccine: Systematic review and meta-analysis. Vaccine 2008;26:383–98; [PubMed: 18082295] Henao-Restrepo AM, Greco M, Laurie X, John O, Aguado T; the WHO Product Development Group for Measles Aerosol Project. Measles Aerosol Vaccine Project. Procedia in Vaccinology 2010;2:147–50.

[36]. Featherstone DA, Rota PA, Icenogle J, Mulders MN, Jee Y, Ahmed H, et al. Expansion of the Global Measles and Rubella Laboratory Network 2005–09. Journal of Infectious Diseases 2011;204(Suppl. 1):S491–8. [PubMed: 21666205]

[37]. Castillo-Solrzano C, Reef S, Morice A, Andrus J, Ruiz-Matus C, Tambini G, et al. Guidelines for the documentation and verification of measles, rubella, and congenital rubella syndrome elimination in the region of the Americas. Journal of Infectious Diseases 2011;204(Suppl. 2):S683–9. [PubMed: 21954267]

[38]. Rota PA, Brown K, Mankertz A, Santibanez S, Shulga S, Muller CP, et al. Global distribution of measles genotypes and measles molecular epidemiology. Journal of Infectious Diseases 2011;204(Suppl. 1):S514–23. [PubMed: 21666208]

[39]. Cohen BJ, Parry RP, Doblas D, Samuel D, Warrener L, Andrews N, et al. Measles immunity testing: comparison of two measles IgG ELISAs with plaque reduction neutralisation assay. Journal of Virological Methods 2006;131(2):209–12. [PubMed: 16188328]

[40]. Ratnam S, Tipples G, Head C, Fauvel M, Fearon M, Ward BJ, et al. Performance of indirect immunoglobulin M (IgM) serology tests and IgM capture assays for laboratory diagnosis of measles. Journal of Clinical Microbiology 2000;38(1):99–104. [PubMed: 10618071]

[41]. Haralambieva I, Ovsyannikova I, O'Byrne M, Pankratz VS, Jacobson R, Poland G. A large observational study to concurrently assess persistence of measles specific B-cell and T-cell immunity in individuals following two doses of MMR vaccine. Vaccine 2011;29(27):4485–91. [PubMed: 21539880]

[42]. Chen M-H, Zhu Z, Zhang Y, Favors S, Xu W-B, Featherstone D, et al. An indirect immunocolorimetric assay to detect rubella virus infected cells. Journal of Virological Methods 2007;146(1–2):414–8. [PubMed: 17919742]

[43]. Rota PA, Brown KE, Hübschen JM, Muller CP, Icenogle J, Chen M-H, et al. Improving global virologic surveillance for measles and rubella. Journal of Infectious Diseases 2011;204(Suppl. 1):S506–13. [PubMed: 21666207]

[44]. Anderson RM, May RM. Vaccination and herd immunity to infectious diseases. Nature 1985;318(6044):323–9. [PubMed: 3906406]

[45]. Keegan R, Dabbagh A, Strebel PM, Cochi SL. Comparing measles with previous eradication programs: enabling and constraining factors. Journal of Infectious Diseases 2011;204(Suppl. 1):S54–61. [PubMed: 21666211]

[46]. Martin R, Wassilak S, Emiroglu N, Uzicanin A, Deshesvoi S, Jankovic D, et al. What will it take to achieve measles elimination in the World Health Organization European region: progress from 2003–2009 and essential accelerated actions. Journal of Infectious Diseases 2011;204(Suppl. 1):S325–34. [PubMed: 21666181]

[47]. Vijayaraghavan M, Wallace A, Mirza IR, Kamadjeu R, Nandy R, Durry E, et al. Economic evaluation of a child health days strategy to deliver multiple maternal and child health interventions in Somalia. Journal of Infectious Diseases 2012;205(Suppl. 1):S134–40. [PubMed: 22315381]

[48]. Biellik R, Madema S, Taole A, Kutsulukuta A, Allies E, Eggers R, et al. First 5 years of measles elimination in southern Africa: 1996–2000. The Lancet 2002;359(9317):1564–8.

[49]. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, et al. Public-health impact of accelerated measles control in the WHO African region 2000–03. The Lancet 2005;366(9488):832–9.

[50]. Uzicanin A, Zhou F, Eggers R, Webb E, Strebel P. Economic analysis of the 1996–1997 mass measles immunization campaigns in South Africa. Vaccine 2004;22(25–26):3419–26. [PubMed: 15308367]

[51]. Wolkon A, Vanden Eng JL, Morgah K, Eliades MJ, Thwing J, Terlouw D, et al. Rapid scale-up of long-lasting insecticide-treated bed nets through integration into the national immunization program during child health week in Togo: 2004. American Journal of Tropical Medicine and Hygiene 2010;83(5): 1014–9. [PubMed: 21036829]

[52]. Vijayaraghavan M, Martin RM, Sangrujee N, Kimani GN, Oyombe S, Kalu A, et al. Measles supplemental immunization activities improve measles vaccine coverage and equity: evidence from Kenya, 2002. Health Policy 2007;83(1):27–36. [PubMed: 17174435]

[53]. Goodson JL, Kulkarni MA, Vanden Eng JL, Wannemuehler KA, Cotte AH, Desrochers RE, et al. Improved equity in measles vaccination from integrating insecticide-treated bednets in a vaccination campaign, Madagascar. Tropical Medicine & International Health 2012, 10.1111/j.1365-3156.2011.02953.x.

[54]. World Health Organisation. Description and comparison of the methods of cluster sampling and lot quality assurance sampling to assess immunization coverage. Department of Vaccines and Biologicals, World Health Organization; 2001.

[55]. Larson H, Cooper L, Eskola J, Katz S, Ratzan S. Addressing the vaccine confidence gap. The Lancet 2011;378(9790):526–35.

[56]. Grais RF, Conlan AJ, Ferrari MJ, Djibo A, Le Menach A, Bjornstad ON, et al. Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger. Journal of the Royal Society Interface 2008;5:67–74. [PubMed: 17504737]

[57]. Goodson JL, Sosler S, Pasi O, Johnson T, Kobella M, Monono ME, et al. Impact of a measles outbreak response immunization campaign: Maroua, Cameroon, 2009. Journal of Infectious Diseases 2011;204(Suppl. 1):S252–9. [PubMed: 21666170]

[58]. Cairns KL, Perry R, Ryman T, Nandy R, Grais R. Should outbreak response immunization be recommended for measles outbreaks in middle- and low-income countries? An update. Journal of Infectious Diseases 2011;204(Suppl. 1):S35–46. [PubMed: 21666184]

[59]. World Health Organization. Response to measles outbreaks in measles mortality reduction strategies; 2009.

[60]. Wolfson LJ, Strebel PM, Gacic-Dobo M, Hoekstra EJ, McFarland JW, Hersh BS, et al. Has the 2005 measles mortality reduction goal been achieved? A natural history modelling study. The Lancet 2007;369(9557):191–200.

[61]. Stein CE, Birmingham M, Kurian M, Duclos P, Strebel P, Stein CE, et al. The global burden of measles in the year 2000—a model that uses country-specific indicators. Journal of Infectious Diseases 2003;187(Suppl. 1):S8–14. [PubMed: 12721886]

[62]. Papania MJ, Strebel PM. Measles surveillance: the importance of finding the tip of the iceberg. The Lancet 2005;365(9454):100–1.

[63]. Harpaz R, Harpaz R. Completeness of measles case reporting: review of estimates for the United States. Journal of Infectious Diseases 2004;189(Suppl. 1):S185–90. [PubMed: 15106109]

[64]. Chen SY, Anderson S, Kutty PK, Lugo F, McDonald M, Rota PA, et al. Health care–associated measles outbreak in the United States after an importation: challenges and economic impact. Journal of Infectious Diseases 2011;203(11):1517–25. [PubMed: 21531693]

[65]. Parker AA, Staggs W, Dayan GH, Ortega-Sanchez IR, Rota PA, Lowe L, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. New England Journal of Medicine 2006;355(5):447–55. [PubMed: 16885548]

[66]. Dayan GH, Ortega-Sanchez IR, LeBaron CW, Quinlisk MP, Iowa Measles Response Team, Dayan GH, et al. The cost of containing one case of measles: the economic impact on the public health infrastructure—Iowa, 2004. Pediatrics 2005;116(1):e1–4. [PubMed: 15995008]

[67]. Sugerman DE, Barskey AE, Delea MG, Ortega-Sanchez IR, Bi D, Ralston KJ, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. Pediatrics 2010;125(4):747–55. [PubMed: 20308208]

[68]. World Health Organization. WHO position paper on rubella vaccines. Weekly Epidemiological Record 2000;75:161–72, http://www.who.int/wer/pdf/2000/wer7520.pdf [accessed 10.02.12].

[69]. Cutts FT, Robertson SE, Diaz-Ortega JL, Samuel R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: burden of disease from CRS. Bulletin of the World Health Organization 1997;75(1):55–68.

[70]. World Health Organisation. WHO supports GAVI Board decision to open a funding window for human papillomavirus and rubella vaccines. Department of Immunization, Vaccines and Biologicals, WHO, /[accessed 10.02.12].

[71]. Reef SE, Strebel P, Dabbagh A, Gacic-Dobo M, Cochi S. Progress toward control of rubella and prevention of congenital rubella syndrome—worldwide, 2009. Journal of Infectious Diseases 2011;204(Suppl. 1):S24–7. [PubMed: 21666168]

[72]. World Health Organizaiton. Rubella vaccines: WHO position paper—recommendations. Vaccine 2011;29(48):8767–8. [PubMed: 21930175]

[73]. Castillo Solorzano C, Marsigli C, Danovaro Holliday MC, Ruiz-Matus C, Tambini G, Andrus J. Measles and rubella elimination initiatives in the Americas: lessons learned and best practices. Journal of Infectious Diseases 2011;204(Suppl. 1):S279–83. [PubMed: 21666173]

[74]. Goodson JL, Masresha B, Dosseh A, Byabamazima C, Nshimirimana D, Cochi S, et al. Rubella epidemiology in Africa in the prevaccine era, 2002–2009. Journal of Infectious Diseases 2011;204(Suppl. 1):S215–25. [PubMed: 21666164]

[75]. Irons B, Morris Glasgow V, Andrus J, Castillo-Solrzano C, Dobbins J. Lessons learned from integrated surveillance of measles and rubella in the Caribbean. Journal of Infectious Diseases 2011;204(Suppl. 2):S622–6. [PubMed: 21954257]

[76]. Bloom S, Rguig A, Berraho A, Zniber L, Bouazzaoui N, Zaghloul Z, et al. Congenital rubella syndrome burden in Morocco: a rapid retrospective assessment. The Lancet 2005;365(9454):135–41.

[77]. Upreti SR, Thapa K, Pradhan YV, Shakya G, Sapkota YD, Anand A, et al. Developing rubella vaccination policy in Nepal—results from rubella surveillance and seroprevalence and congenital rubella syndrome studies. Journal of Infectious Diseases 2011;204(Suppl. 1):S433–8. [PubMed: 21666196]

[78]. Castillo-Solrzano C, Marsigli C, Bravo-Alcntara P, Flannery B, Ruiz-Matus C, Tambini G, et al. Elimination of rubella and congenital rubella syndrome in the Americas. Journal of Infectious Diseases 2011;204(Suppl. 2):S571–8. [PubMed: 21954249]

[79]. Abernathy ES, Hübschen JM, Muller CP, Jin L, Brown D, Komase K, et al. Status of global virologic surveillance for rubella viruses. Journal of Infectious Diseases 2011;204(Suppl. 1):S524–32. [PubMed: 21666209]

[80]. Levin A, Burgess C, Garrison LP, Bauch C, Babigumira J, Simons E, et al. Global eradication of measles: an epidemiologic and economic evaluation. Journal of Infectious Diseases 2011;204(Suppl. 1):S98–106. [PubMed: 21666220]

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 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?

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)?

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?

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?

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?

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?