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Modeling and Managing the Risks of Measles and Rubella: A Global Perspective, Part I

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Abstract

Over the past 50 years, the use of vaccines led to significant decreases in the global burdens of measles and rubella, motivated at least in part by the successive development of global control and elimination targets. The Global Vaccine Action Plan (GVAP) includes specific targets for regional elimination of measles and rubella in five of six regions of the World Health Organization by 2020. Achieving the GVAP measles and rubella goals will require significant immunization efforts and associated financial investments and political commitments. Planning and budgeting for these efforts can benefit from learning some important lessons from the Global Polio Eradication Initiative (GPEI). Following an overview of the global context of measles and rubella risks and discussion of lessons learned from the GPEI, we introduce the contents of the special issue on modeling and managing the risks of measles and rubella. This introduction describes the synthesis of the literature available to support evidence-based model inputs to support the development of an integrated economic and dynamic disease transmission model to support global efforts to optimally manage these diseases globally using vaccines.

Keywords

Infectious disease; measles; modeling; rubella

1. CONTEXT

Following the development of measles vaccine in 1963 and rubella vaccine in 1969, developed countries rapidly adopted their use, and the devastating disease burdens caused by measles and rubella declined. Over time, global agreements established the measles targets summarized in Table I, which led to incremental progress toward increased measles control and elimination. As part of the Global Vaccine Action Plan (GVAP),[(1)] countries and regions continue to pursue goals to eliminate and control measles and rubella virus transmission within their borders.

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Developed countries finance their measles and rubella control efforts as part of their health system budgets and national immunization programs. In contrast, developing countries use national funds and may also receive support from donors and/or from the Measles and Rubella Initiative.[2] All countries currently include measles vaccine in their national routine immunization (RI) programs, and most countries include rubella vaccine.[3] The adoption of rubella immunization historically lagged measles vaccine adoption because some countries do/did not perceive rubella as a significant concern (i.e., the large burden of measles masks rubella incidence) and early mathematical modeling of rubella vaccine introduction raised concerns about use of the vaccine in a population with low coverage potentially increasing the risks of Congenital Rubella Syndrome (CRS) in infants of unvaccinated pregnant women.[4] In order to achieve high coverage and population immunity, some countries conduct periodic supplemental immunization activities (SIAs) for measles and rubella. The immunization strategies used and current level of control vary considerably by country, with most countries using two-dose routine schedules and combination vaccines that include both measles and rubella antigens, but some using only one dose of measles vaccine.[3]

National variability in measles and rubella immunization strategies and targets also reflects regional differences. For example, the WHO Region of the Americas (i.e., Pan American Health Organization, PAHO) set regional elimination goals for measles and rubella in 1994 and 2003, respectively. The Americas successfully interrupted indigenous transmission of measles in 2002 and rubella in 2009.[2] Countries in the Americas now need to maintain elimination and remain vigilant in their national measles and rubella immunization programs because they remain vulnerable to importations that lead to costly outbreaks. While most of the importations into the Americas have led to limited transmission stopped within six months due to aggressive outbreak response, an importation into Brazil in 2013 led to transmission that continued through January 2015, which has delayed the regional verification of the Americas as measles-free, while regional verification of rubella elimination occurred in April 2015. In the Americas and some other developed countries, the very low incidence of measles during the past several decades led to a shift in perception of the dangers of measles, with some parents and caregivers perceiving no need for measles immunization. In addition, fraudulent claims about measles–mumps–rubella (MMR) vaccine as a cause of autism led to increased, although unfounded, fears about MMR, and this reduced MMR vaccine coverage in some developed countries. In contrast, the African and Southeast Asia Regions include countries that only established measles elimination targets relatively recently, and many countries in these regions do not achieve or sustain sufficiently high RI coverage to disrupt measles transmission. These countries currently perform large-scale SIAs for outbreak prevention or response.

In this special issue, we consider measles and rubella together for several reasons. First, combination vaccines for measles include a rubella component, and most countries that include rubella in their RI programs use a combination vaccine.[3] Second, the Measles and Rubella Initiative now includes a focus on rubella.[2] Third, both viruses produce similar disease etiologies (i.e., fever, rash, cough, runny eyes), which leads to confusion of their clinical presentations but supports the development and maintenance of a shared disease surveillance system.

Despite the similarities in presentation, the viruses lead to some differences in *sequelae*. Measles, a human scourge recognized for centuries (also confusingly known as rubeola), is one of the most highly transmissible infectious diseases in humans, and it presents with noticeable symptoms and signs for most infections, with outcomes of complicated cases including pneumonia, blindness, encephalitis, thrombocytopenia, and death.[5] In contrast, rubella (also confusingly known as German measles) generally presents as a much milder disease that can go unnoticed (i.e., asymptomatic), with the most significant clinical symptoms of complicated rubella infections including arthritis, encephalitis, and thrombocytopenia. The clinical significance of rubella garnered recognition as a disease with serious adverse effects in 1941, when Australian ophthalmologist Dr. Norman McAlister Gregg made the connection between rubella infections in early pregnancy and serious congenital malformations observed in the infants.[6] Although preventable, rubella infection in early pregnancy remains the most common infectious cause of congenital birth defects, with CRS typically including one or more of the following clinical manifestations: congenital heart defects, eye defects, hearing loss, and mental disability.[7]

Although most developed countries use a MMR combination vaccine,[3] we do not include the consideration of mumps vaccine in the special issue, despite the potential health and economic benefits associated with its use. Variability in the strain of mumps vaccine used historically by different countries and vaccine formulations led to differences in associated adverse events (e.g., aseptic meningitis) that led some countries to consider it an unfavorable vaccine (e.g., Japan[8]). In addition, the relatively lower protection and faster waning of immunity associated with mumps vaccines[9,10] combined with some perception of mumps as not a serious disease, particularly in developing countries, currently limit regional and global efforts to coordinate its control.

Regionally and globally coordinated disease control efforts require the cooperation of multiple stakeholders and significant investments. However, cooperation and coordination often prove challenging, even with a global commitment to a goal. Similar to the analytical theme of prior special issues of *Risk Analysis* related to global poliovirus risk management,[11,12] the contents of this issue suggest that integrated risk, economic, decision, and dynamic models may play an important role in achieving disease elimination goals. Moreover, lessons learned from polio risk management efforts provide important insights relevant to measles and rubella modeling and management.

2. LESSONS FROM THE GPEI RELEVANT TO REGIONAL AND GLOBAL ELIMINATION GOALS FOR MEASLES AND RUBELLA

Twenty-five years into the GPEI and more than a decade late delivering on the initial 1988 goal of ending all poliomyelitis by 2000, many important lessons emerge from the polio effort relevant to coordinated regional and global measles and rubella elimination and/or control goals. The lessons include recognizing the importance of ensuring sufficient political and financial commitments, achieving and maintaining high population immunity including through the contribution of RI, addressing heterogeneity in immunization status within a population, and using integrated models to support resource management.

Managing vaccine-preventable diseases typically requires ongoing purchases of vaccine and support of RI and any SIAs, and this implies ongoing national financial and political commitments. Some exceptions exist when nonvaccine strategies can manage the disease; for example, most countries manage the risks of cholera by focusing on provision of clean water and effective sanitation and hygiene instead of vaccine. However, for polio, measles, and rubella, vaccination represents the primary intervention for disease control and elimination. In the case of polio, in spite of a global commitment to eradication dating back to 1988, many countries did not invest sufficient resources to interrupt transmission of the virus on their own, and many national RI programs remain inadequate. Thus, despite efforts and investments made to date to strengthen health systems, some health systems currently fail to perform sufficiently well to achieve or maintain national disease elimination goals. Underinvestment in health systems remains a significant concern for all vaccine-preventable diseases, with insufficient infrastructure (e.g., weak cold chains, poor surveillance) and chronic underservice of high-risk populations (e.g., migrants, displaced populations, the poor, individuals in insecure areas) presenting particular challenges.

The GPEI raised financial support to help countries with inadequate health system performance to increase their immunization coverage through SIAs. Unfortunately, many national RI programs for measles similarly remain inadequate. Like the GPEI, the Measles and Rubella Initiative provides some funding to support SIAs, with the amount of funding available determining the extent of annual SIAs. Programmatically, in addition to supporting immunization activities, the GPEI also provides financial and technical support for surveillance, research, outbreak response, coordination, communications, and development of a vaccine stockpile. The Measles and Rubella Initiative acts similarly, albeit currently with much lower levels of financial resources and without a global resolution for measles or rubella eradication. Insufficient political and financial support represented a chronic challenge for the GPEI, with funding gaps each year limiting progress (e.g., using resources for firefighting and reactive activities without sufficient investment in preventive activities required to achieve milestones and objectives),[13] at least until recently. Similar situations of insufficient financial support currently exist for measles and rubella, with funding for the Measles and Rubella Initiative remaining level (i.e., $60–80 million) since 2009, during a time that regional and global commitments to measles and rubella control and elimination increased.[14] The Measles and Rubella Initiative spent just over $1 billion cumulatively for the 2001–2013 (i.e., less than $100 million annually),[14] while in contrast the GPEI expects to spends nearly $6 billion for 2013–2018 (i.e., nearly $1 billion annually).[15] In the absence of both a strong commitment by stakeholders and the financial resources to support required activities to meet performance goals, large-scale coordinated disease management efforts will not meet their targets, although they may still make progress and improve health by providing immunizations to individuals who otherwise would not be protected. However, the lack of funding leads to failure to meet expectations, and this undermines further efforts to get the resources required. Underfunding can lead to delays, which will most likely ultimately lead to higher cumulative costs associated with reaching the objectives.[13,16]

Eradication and regional elimination require sustained, permanent prevention of transmission, which implies achieving and maintaining high levels of population immunity

in all places contemporaneously. If the immune fraction of the population exceeds the virus transmission threshold for that population, then imported viruses will not encounter sufficient numbers of susceptible individuals to continue transmission and the virus will die out.[17] However, instead of focusing on just reaching immunization coverage levels expected to achieve the threshold immunity, countries need to aim for higher coverage and achieve high coverage as rapidly as possible.[16] In addition, in the absence of circulating wild virus and particularly if immunization intensity declines and population immunity drops, imported viruses can circulate and cause outbreaks.[17] Thus, stopping transmission represents a necessary but not sufficient condition for eradication or regional elimination goals. Permanent prevention of transmission requires maintenance of high levels of immunity, even in the absence of cases, until all viruses stop transmitting everywhere. Repeated reintroductions of imported viruses into previously wild-virus-free areas represent an ongoing issue for polio,[17] measles, and rubella. Ironically, successfully managing population immunity (and therefore preventing cases) can threaten support for continued prevention efforts. Specifically, as countries approach and reach the goal of no cases, perceptions about the importance of continued investments in and needs for immunization may change. Instead of recognizing the role of the vaccine in preventing bad outcomes, individuals may mistakenly believe that bad outcomes can no longer occur and thus assume immunization is no longer necessary or not a priority. This can unfortunately lead to a wavering commitment, which can make the achievement of targets take longer and cost more overall.[16]

One of the challenges to achieving and maintaining high population immunity relates to managing heterogeneity in immunization coverage and conditions conducive to viral transmission. All populations include some individuals missed by immunization, either because they fall outside of the health system (e.g., underserved, immigrants), the vaccine is not indicated due to a comorbidity or their age (e.g., interference with maternal antibodies for young infants for measles), or vaccine refusal. If undervaccinated individuals cluster in the population and mix preferentially, then this can lead to pockets of susceptible individuals who can sustain transmission[18–20] In the polio endgame, the GPEI increasingly emphasized the need to reach every child because low immunization coverage in some underserved populations (e.g., nomads, migrant groups, the poor, individuals living in insecure areas) and the resulting heterogeneity in population immunity to transmission threatens the goal of eradication. The same populations that posed difficulties for polio eradication also present challenges for measles and rubella elimination goals; however, recent efforts to identify and immunize these populations for polio should make it easier to identify and immunize them for measles and rubella and ideally to bring them into the national health system.

Similar to the situation for polio, surveillance for measles and rubella represents an essential activity. The relatively high frequency of poliovirus infections that do not lead to paralytic cases detected by the global surveillance system can lead to delays in the detection of an outbreak, which presented challenges for the GPEI, particularly as detection and management of the last reservoirs with circulating polioviruses represent the primary barrier to achieving polio eradication. In contrast, most measles cases appear to lead to detectable cases, although underreporting remains an issue. Rubella leads to some asymptomatic

infections and symptoms confused with measles infections, which limits the extent to which national health programs see its transmission as a problem. In addition, surveillance for rubella and CRS remains insufficient to support some existing and potential future rubella control and elimination targets.

Using integrated models to support resource management can provide useful information to support decisions, and economic analyses can play a critical role in providing support for eradication or elimination efforts, particularly by characterizing the health and economic benefits associated with financial investments. For example, the GPEI benefited from studies that demonstrated the significant health and economic benefits associated with eradication compared to control[16] and the GPEI investment.[21] Two studies suggested significant benefits associated with measles eradication,[22,23] but no studies characterize the benefits of improved control or elimination of rubella. Current measles and rubella efforts would benefit from the development of investment cases that will help stakeholders appreciate the risks, costs, and benefits of options,[24] which requires the development of an integrated economic and dynamic disease model for measles and rubella. The model may also help to support efforts to identify priority areas for further research.[25]

3. SPECIAL ISSUE MOTIVATION AND CONTENTS OF PART I

The articles in this special issue use numerous abbreviations, which we summarize for readers in Table II of this first introductory article. The second article[26] systematically reviews the literature of health economic analyses (i.e., cost-effectiveness and benefit-cost analyses) of measles and rubella vaccine interventions. The review identifies a wealth of prior literature, but suggests the need for an integrated model that would support the consideration of the risks, costs, and benefits of interventions for both measles and rubella using a dynamic disease transmission model. The review also reveals the absence of prior characterization of disability-adjusted life year (DALY) estimates for health outcomes associated with rubella. The third article[27] systematically reviews the literature to characterize the pregnancy outcomes (i.e., spontaneous termination [miscarriage], fetal death [stillbirth], birth defects, and reduced survival for live-born infants) associated with rubella infections in pregnancy. The fourth article[7] systematically reviews the literature on birth outcomes associated with rubella infections in early pregnancy and characterizes DALYs as a function of 2013 World Bank Income Levels.[28] The fifth article[29] uses the model inputs from prior economic analyses, a prior discussion of measles and rubella cost and benefit characterization for the GVAP,[30] and other cost studies to characterize the cost and valuation inputs for integrated measles and rubella models and DALY estimates for measles as a function of 2013 World Bank Income Levels.[28]

The sixth article provides a review of prior models developed as dynamic transmission models for measles and rubella risk and policy analysis.[4] This article includes discussion of the evolution of policies related to rubella, and highlights the opportunity of eliminating rubella simultaneously with measles and the missed opportunity of failing to do so. Recognizing the importance of heterogeneity and building on an individual-based model used to characterize poliovirus transmission in the North American Amish,[31] the seventh article[32] characterizes measles transmission in the Amish with a focus on the large 2014

outbreak in Ohio. The eighth article[33] explores heterogeneity in the vaccination coverage in central Florida, which represents a relatively high-risk area for importations given its family-oriented tourist attractions. This analysis provides some contrast with the more significant clustering of undervaccinated individuals in California,[34] which supported a large measles outbreak during the winter of 2014–2015 associated with Disney theme parks in California.

To model measles and rubella transmission in each country, the ninth article[35] synthesizes and characterizes the immunization and exposure histories for over 180 WHO member states and three associated geographic areas based on available data. The tenth article[36] systematically reviews the available peer-reviewed measles and rubella serological studies published in English, which provide information about population immunity at the time of data collection for the individuals studied. The eleventh article[37] of the special issue provides a framework for developing a vaccine stockpile for currently used vaccines and discusses the direct application to measles and rubella vaccines with some contrast to cholera vaccines.

4. THE ROAD AHEAD

The contents of Part I of the special issue provide a foundation for using integrated models to support policy discussions related to achieving the GVAP goals for measles and rubella and for the development of the associated investment cases. Further efforts to develop integrated models and investment cases should help policymakers explore the tradeoffs associated with various options and value the health benefits associated with financial investments in economic terms.

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Table I.

Global Measles Control Targets

By 1990 make measles vaccine available to every child in the world as part of the Expanded Programme on Immunization (EPI)
By 1995, reduce measles cases by 90% and measles deaths by 95% compared to preimmunization levels
By 2005, reduce measles deaths by 50% compared to 1999 levels
By 2010, reduce measles deaths by 90% compared to 2000 levels
By 2015, reduce measles deaths by 95% compared to 2000 levels, eliminate measles in four World Health Organization (WHO) regions
By 2020, eliminate measles in five WHO regions

Table II.

List of Abbreviations

Ab = neutralizing antibody (generic term)
ASD = atral septal defect
BCA = benefit-cost analysis
CDC = U.S. Centers for Disease Control and Prevention
CEA = cost-effectiveness analysis
CFR = case-fatality ratio
CHD = congenital heart disease
CNS = central nervous system
CRI = congenital rubella infection
CRS = congenital rubella syndrome
DALY = disability-adjusted life year
DPT = diphtheria–pertussis–tetanus vaccine
E1 = exposed and latent infection immunity state 1
E2 = exposed and latent infection immunity state 2
EIP = effective immune proportion
EIP* = threshold level of EIP below which a population can sustain transmission
ESP = effective susceptible proportion
ESP* = threshold level of ESP above which a population can sustain transmission
FS = fully susceptible fetus
FI = infected fetus
FR = recovered fetus (for rubella only)
FMIR = fetus with maternal antibodies from a mother with infection-induced immunity
FMIV = fetus with maternal antibodies from a mother with vaccine-induced immunity
GBD = global burden of disease
GNI = gross national income
GPEI = Global Polio Eradication Initiative
GVAP = Global Vaccine Action Plan
HEPB = hepatitis B vaccine
HIB = *Haemophilus influenzae* type b
HIGH = high-income country

HIV = human immunodeficiency virus

I1 = infectious immunity state 1

I2 = infectious immunity state 2

ICER = incremental cost-effectiveness ratio

IFR = infection-fatality ratio

IFRRF = infection-fatality ratio reduction fraction

INB = incremental net benefits

IPV = inactivated poliovirus vaccine

$\kappa(x)$ = the proportion of contacts for individuals in mixing age group x

LE = life expectancy

LMI = lower-middle-income country

LMP = last menstrual period

LOW = low-income country

M = measles vaccine

M or MCV= measles vaccine or measles containing vaccine

MI = maternally immune

MIP = measles infection during pregnancy

MIR = maternally immune with antibodies provided by mothers who recovered from wild virus infection immunity state

MIR1 = maternally immune with antibodies provided by mothers who recovered from wild virus infection and received one or more doses of vaccine that did not “take”

MIV = maternally immune with antibodies provided by mothers who recovered from vaccination

MIV1 = maternally immune with antibodies provided by mothers who recovered from vaccination and received one or more doses of vaccine that did not “take”

MMR = measles–mumps–rubella vaccine

MNG = Meningococcal vaccine

MR = measles–rubella vaccine

MRCV = measles and rubella containing vaccine

M(R)CV = measles (with or without rubella) containing vaccine

M&RI = Measles & Rubella Initiative

MSEIR = transmission model with maternal immunity, susceptibility, infected but not infectious, infectious, and recovered immunity states

MSEIRV = transmission model with maternal immunity, susceptibility, infected but not infectious, infectious, recovered, and vaccinated immunity states

MSP = measles strategic planning

NA = not applicable

ND = not done

NID = national immunization day

NR = not reported

OPV = oral poliovirus vaccine

ORI = outbreak response immunization

ORS = oral rehydration salts

PDA = patent ductus arteriosus

PNE = pneumococcal conjugate vaccine

PS = pulmonic stenosis

QALY = quality-adjusted life year

R = recovered from wild virus infection immunity state

RCV = rubella containing vaccine

RI = routine immunization

RIP = rubella infections during pregnancy

R_0 = basic reproduction number

S = fully susceptible and never exposed to wild virus or vaccine immunity state

S1 = fully susceptible despite receipt of one or more doses of vaccine immunity state (i.e., vaccine failure immunity state)

SEIR = transmission model with susceptibility, infected but not infectious, infectious, and recovered immunity states

SIA = supplemental immunization activity

SIR = transmission model with susceptibility, infectious, and recovered immunity states

SNIDs = subnational immunization days

SSPE = subacute sclerosing panencephalitis

UK = United Kingdom

UMI = upper-middle-income country

UN = United Nations

UNPD = United Nations Population Division

US = United States

VAERS = Vaccine Adverse Event Reporting System

VAR = varicella vaccine

VORI = immune due to take of dose received during outbreak response SIA immunity state

VPD = vaccine-preventable disease

VRI1 = immune due to take of RI dose 1 immunity state

VRI2 = immune due to take of RI dose 2 immunity state

VSD = ventricular septal defect

VSIA = immune due to take of dose received during a preventive SIA immunity state

WBIL = World Bank income level

WCBA = women of child-bearing age

WHA = World Health Assembly

WHO = World Health Organization

YLD = years of productive life lost due to disability

YLL = years of life lost due to premature mortality