Annex for presentation by Kimberly M. Thompson, Kid Risk, Inc. on the measles and rubella investment case

Context

Development of the integrated model used to support this analysis occurred over a period of several years and led to the publication of many manuscripts that collectively provide details about the various model components described in Figure 1 of the yellow book report. For those interested in understanding some of the technical highlights of the model, without reviewing all of the papers referenced in Figure 1, most of the details about the model development and cost inputs derive from the two publications included at the end of this annex. If you would like to review any of the other published manuscripts in Figure 1 of the yellow book report that describe part of the model and its development, you can request a copy of those papers from Dr. Thompson at kimt@kidrisk.org. This annex provides an overview of some of the key assumptions that support the results presented in the yellow book report with the goal of providing SAGE members with some insights about how the model works and the key assumptions.

The purpose of the presentation and the investment case analysis is to provide a high level (i.e., global) perspective on the decision to commit to the eradication of measles and/or rubella, not to explore national or regional elimination decisions or national or regional costs and benefits of control. While those types of analysis could be performed with the integrated model, they do not fall into the scope of the currently-funded work, except for an analysis of the US experience. Thus, while the model makes assumptions at the national level that could change for any individual country, the prospective nature of the modeling activity implies inherent uncertainty (i.e., no one can predict the future, we can use models to help us see possibilities and consider options for creating the future that we desire). In this regard, all models are wrong, and this modeling exercise strives to be useful for the purpose of stimulating discussion about insights relevant to global policy related to measles and rubella eradication.

Key assumptions used for this prospective application of the integrated model for the cost inputs appear in the first manuscript attached, which develops the cost and valuation inputs. The model computes costs at the level of World Bank Income Level (WBIL) as of 2016 (i.e., the model assumes that countries will stay in the same WBIL over the entire time horizon considered and assumes that average costs for the WBIL will in aggregate account for the overall costs for countries in the WBIL and some of the variability that exists between countries of very different WBILs (i.e., high income countries really differ from low income countries with respect to costs and risks) although they may not accurately represent the actual costs for any specific country within the WBIL. For specific estimates, see the tables (particularly Tables V, IX, and X). Note that for this prospective analysis, the estimates from the first attachment that use 2013 US dollars have been inflated using the US consumer price index to 2016 US dollars and the prospective analysis reports all costs in 2016 US dollars (US$2016), with summary costs discounted using a 3% rate to obtain 2016 net present values. The second attached manuscript describes the development of transmission model inputs and some examples of the transmission model fits. The integrated model includes a transmission model specific to each of 180 WHO member states. The inputs for each member state include assumptions about population using the

medium variant projections from the UN Population Division and estimates of historical immunization schedules and coverage using available data.

Prospective modeling for the two scenarios requires making numerous assumptions about future national immunization decisions. The following sections describe the development of some of the key assumptions for these 2 scenarios.

Assumptions for the 2016 Status Quo scenario

This scenario assumes that countries maintain their routine immunization schedule (i.e., vaccine choice and age(s)) and achieve the same coverage as the 2016 WHO-UNICEF estimates for the entire time horizon. For countries that introduced rubella immunization by the end of 2017, the model assumes that coverage for rubella matches measles coverage for scheduled doses that include both measles and rubella vaccines as of the year after introduction (allowing for mid-year introduction for those countries that introduce before the end of 2017). The model assumes that the following countries (identified by their ISO Codes) do not include rubella vaccine into their national schedules at all during the time horizon of 2017-2055: AFG, BEN, CAF, CIV, COD, COG, COM, DJI, ERI, ETH, GAB, GIN, GNB, GNQ, IDN, LBR, MDG, MLI, MOZ, NER, NGA, PAK, PRK, SDN, SLE, SOM, SSD, TCD, TGO, UGA, and ZAF.

The model continues the prior pattern (i.e., age range, coverage, timing) of SIAs for all countries that conducted SIAs during 2000-2016. If rubella vaccine introduction occurred within the years 2015-2017, then the model includes a catch-up MR SIAs during those years, and the model uses MR vaccine for any campaigns done in countries that include rubella immunization in their national schedules. The model includes outbreak response campaigns when triggered by importations of measles into countries that eliminated indigenous measles (i.e., when incidence in the model goes from 0 to something positive, the model assumes that countries that have eliminated measles will respond to the outbreak using outbreak response campaigns to preserve their elimination status. Currently, some countries that perform preventive SIAs to maintain high population immunity may accelerate the timing of the SIAs if or when an outbreak (i.e., a large spike in incidence) occurs. In contrast, currently some countries delay planned preventive SIAs for reasons not related to observed incidence. This scenario assumes a pattern of SIAs consistent on the global level with current behaviors and experience (i.e., non-optimal timing of inadequate SIAs in countries performing them such that transmission continues). For this scenario, the model allows for viruses to travel freely across borders throughout the time horizon such that importations can occur at any time and restart transmission in any countries in which population immunity has dropped to a point that the population (or an under-vaccinated subpopulation) can support transmission on some scale (local or larger).

Assumptions for Eradicate ASAP scenario

For this scenario, the model uses much more aggressive immunization assumptions. Given the objective of the scenario to model measles and rubella eradication ASAP, the model assumes that the countries yet to introduce rubella vaccine will all do so by 2023. The actual timing of the introduction and specifically the timing of the last adopters completely determine the timing of rubella eradication. In this scenario, the model assumes for exploratory purposes that rubella

vaccine introduction occurs in 2018 in 11 countries (BEN, CIV, COG, ERI, IDN, MLI, MOZ, NER, PRK, TGO, and UGA); in 2019 in 4 countries (COD, COM, MDG, and SLE); in 2020 in 8 countries (AFG, DJI, ETH, GIN, LBR, PAK, TCD, and ZAF); in 2021 in 2 countries (GAB and GNB); in 2022 in 5 countries (CAF, GNQ, NGA, SDN, and SOM); and in 2023 in one country (SSD). The model also introduces a second routine dose of measles (and rubella) containing vaccine in 2018 in 3 countries (ETH, TGO, and UGA), in 2019 in 9 countries (CIV, COD, COM, GNB, MDG, MLI, MRT, NGA, and TCD), in 2020 in 6 countries (BEN, CAF, GAB, GNQ, LBR, and VUT), and in 2025 in 2 countries (SOM and SSD). Changing these assumptions alters the behavior of the estimated incidence of measles, rubella, and CRS. More aggressive adoption of rubella vaccine in all countries done well would allow for rubella eradication more quickly, while less aggressive adoption or managing the introduction poorly will delay rubella eradication. The scenario thus includes analytical judgment about what might represent a realistic most aggressive path.

Consistent with the rubella vaccine introduction and historical practice, this scenario forecasts and bounds routine immunization coverage growth prospectively according to a computed global average compound growth rate. The model allows routine immunization coverage to increase annually, but not go above the growth implied by the rate or beyond 99%. Thus, countries with relatively poor programs cannot instantly achieve and maintain very high coverage, and the improvement in coverage require paying a cost premium (developed in a manuscript now under review). For this scenario, SIAs occurred on the same frequency or more frequently than those conducted for the status quo scenario, and the model generally assumes similar timing, target age groups (except requiring the inclusion of an SIA up to age 15 years for countries in the year that they introduce rubella vaccine), and other characteristics of the SIAs as the status quo scenario, but allows for better coverage and/or more frequent SIAs. Generally, the model allowed flexibility to conduct SIAs (preventive or in response to outbreaks) on an as needed basis in the model. For this scenario, the model allows viruses to export freely until the year before eradication occurs (i.e., consistent with decreasing global incidence and an assumption that as the world approaches eradication of one or both diseases, international health regulations will be established to limit exportations). This scenario ignores the potential for reintroduction of either virus due to (un)intentional release. However, the scenario maintains vaccination for the entire time horizon such that population immunity would continue to stay relatively high and vaccine supplies would continue to be available that could be used for outbreak response to respond to any emergency.

Cost estimation

The preliminary results in the yellow book focus on characterizing the incremental costs and benefits associated with changes in immunization inputs implied by the scenario (i.e., increased and more intensive immunization until eradication and reduced costs associated with outbreak response for the eradication ASAP scenario relative to the 2016 status quo scenario) and associated outcomes implied by the scenario (i.e., the economic value of avoided treatment costs and the productivity benefits of DALYs saved). The model assumes the same cost inputs for both scenarios, but applies a cost premium associated with the need to invest resources to increase coverage. The preliminary cost estimates do not account for changes in costs associated with global coordination, surveillance improvement, or other factors.

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The Costs and Valuation of Health Impacts of Measles and Rubella Risk Management Policies

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National and global health policymakers require good information about the costs and benefits of their investments in measles and rubella immunization programs. Building on our review of the existing measles and rubella health economics literature, we develop inputs for use in regional and global models of the expected future benefits and costs of vaccination, treatment, surveillance, and other global coordination activities. Given diversity in the world and limited data, we characterize the costs for countries according to the 2013 World Bank income levels using 2013 U.S. dollars (2013$US). We estimate that routine immunization and supplemental immunization activities will cost governments and donors over 2013$US 2.3 billion per year for the foreseeable future, with high-income countries accounting for 55% of the costs, to vaccinate global birth cohorts of approximately 134 million surviving infants and to protect the global population of over 7 billion people. We find significantly higher costs and health consequences of measles or rubella disease than with vaccine use, with the expected disability-adjusted life year (DALY) loss for case of disease generally at least 100 times the loss per vaccine dose. To support estimates of the economic benefits of investments in measles and/or rubella elimination or control, we characterize the probabilities of various *sequelae* of measles and rubella infections and vaccine adverse events, the DALY inputs for health outcomes, and the associated treatment costs. Managing measles and rubella to achieve the existing and future regional measles and rubella goals and the objectives of the Global Vaccine Action Plan will require an ongoing commitment of financial resources that will prevent adverse health outcomes and save the associated treatment costs.

KEY WORDS: Cost; economic analysis; immunization; measles; rubella

1. INTRODUCTION

Global management of infectious disease risks continues to improve as stakeholders commit to ambitious objectives, including existing disease eradication and elimination goals.[1] Similar to other major projects, health initiatives require significant financial commitments.[2] National and international efforts to manage vaccine-preventable diseases face significant risks related to financial shortfalls, in part due to the challenges associated with developing good estimates of future costs and providing continued justification for maintaining sufficient resources to support prevention activities. The World Health Organization (WHO) and the GAVI Alliance created tools to encourage and support national efforts to develop comprehensive multiyear plans for vaccine financing, particularly to support the Global Immunization Vision and Strategy 2006–2015.[3] Detailed analysis of routine immunization costs for six countries provides more recent information.[4] The WHO-CHOICE (CHOosing Interventions that are Cost-Effective) Project provided estimates of the nonmedical costs associated with hospitalization (i.e.,

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the "hotel" costs) and for outpatient services and other data to support generalized cost-effectiveness analysis.[5,6] A recent review of the costs of supplemental immunization activities (SIAs) provides updated estimates of the nonvaccine costs for SIAs.[7] These and other efforts provide generic data that may support global cost estimates, but the application to specific diseases requires further effort.

National governments, Gavi, and the Measles and Rubella Initiative (M&RI) currently support national, regional, and global efforts to reduce disease burden and prevent cases of measles and rubella, particularly in the context of achieving and maintaining goals for measles elimination in all six WHO regions and more extensive rubella control, consistent with the Global Vaccine Action Plan (GVAP).[1] However, countries historically used and currently use a wide range of national immunization strategies.[8] In the context of developing investment cases to support the consideration of options for measles and rubella management (i.e., control or elimination),[9] we recognize the importance of characterizing cost and valuation inputs and the assumptions that underlie overall benefit and cost estimates.[10] We separately reviewed and extracted cost and valuation data from the existing benefit-cost and cost-effectiveness analyses,[11] which included the identification of some cost-only studies for measles and rubella immunization interventions.[11] These and other cost studies[12–15] provide useful data to support characterization of cost and valuation inputs. In our reviews, we found one cost-only study for a developed country that characterized adverse health outcomes and costs associated with measles infections by age,[12] and noted that most economic analyses for measles that reported DALYs only considered mortality.[11] We found limited economic analyses for rubella and congenital rubella syndrome (CRS) for developed countries, with only one cost-only study that characterized costs of CRS[16] and one health utility analysis that reported quality-adjusted life years (QALYs) for CRS.[17] We identified many gaps in the available information, including uncertainties about the probabilities of various *sequelae* and associated treatment costs for developing countries.[11] Based on the approach used for global management of polioviruses,[18] we sought to develop appropriate age-specific (and for rubella sex-specific) estimates of the inputs needed to value the benefits and characterize the costs associated with a range of different options for managing measles and rubella to support economic analyses of different prospective policies and to identify key uncertainties.

2. METHODS

We used the data we collected as part of our comprehensive review and synthesis of the existing health economics literature,[11] data from the M&RI, and additional data extracted from the literature to characterize the inputs for previously developed cost and valuation equations,[10] including: probabilities and costs of health outcomes caused by measles or rubella disease or vaccination, costs of treatment, vaccination costs (including routine immunization (RI), supplemental immunization activities (SIAs), and outbreak response), surveillance, and global programmatic costs (e.g., vaccine stockpile, coordination, technical assistance). Although we focus on global policy, we seek to account for some of the significant variability in the world by stratifying the inputs into the four different World Bank income levels (WBIL): high-income (HIGH), upper-middle-income (UMI), lower-middle-income (LMI), and low-income (LOW),[19] similar to the approach used for polioviruses.[18] Specifically, based on the approach we applied to characterize probabilities of *sequelae* and disability-adjusted life years (DALYs) for CRS,[20] we characterize DALYs for all measles and rubella infection and vaccine-related adverse health outcomes assuming optimal treatment in high-income countries, minimal treatment in low-income countries, and different ratios for optimal:minimal treatment in UMI and LMI, respectively.

2.1. Probabilities of Adverse Health Outcomes

Characterizing the effects of measles and rubella interventions requires estimating the probabilities of the numerous potential adverse health outcomes per measles infection, rubella infection, and vaccine dose. We identified the ranges of prior estimates and then used these as a basis for developing best estimates, which included consideration of potential combinations of outcomes that might occur as appropriate for the estimation of DALYs and treatment costs. For measles and rubella disease, we faced the same significant challenges encountered by other researchers related to uncertainty about reporting and the large spectrum of complications associated with measles and rubella. Historically, reporting systems only captured a small fraction of the estimated

measles infections (i.e., 10%[21] to 18–33%[22]), while analysis of reporting of hospitalized cases suggests higher estimates of reporting captured for these more severe cases (i.e., 40–60%[23–25]), and one analysis suggested capture of 8–22% of CRS cases.[26] While these studies provide data on the United States and the United Kingdom, many national reporting systems (including in high-income European countries) did not include required reporting of measles and/or rubella infections until relatively recently, and reporting in relatively lower-income countries remains poorly quantified. Uncertainty about the reporting leads to unknown true denominators (i.e., infections) as well as unknown numerators (i.e., health outcomes). Dealing with this challenge leads to assumptions about the fraction of undetected infections that led to adverse health outcomes and fraction of infections that occur asymptomatically or without complications reported to the health system.

Age at the time of infection adds some complexity because the ability to become infected and presentation of complications may vary by age. For infants, maternal antibodies provide some protection from infection and disease, which may lead to relatively higher rates of asymptomatic infection or mild disease not recognized as infection in infants (e.g., 15–30%[27,28] for measles) and might suggest underestimation of the number of infections (denominator). At the same time, immaturity of infant immune systems and other vulnerabilities may put them at greater risk of complications if infected (i.e., relatively increased numerators). For older ages (e.g., adolescents and adults), utilization of the health-care system may occur relatively less frequently unless the infections lead to more severe complications, and this may also lead to underestimation of infections. The interactions between these possibilities remain poorly understood and understudied. Despite these challenges, for economic modeling we need to develop best estimates of the probabilities of the health outcomes per infection by age for those outcomes that appear to occur differentially per infection as a function of age.

We identified three studies that provided national data of age-related rates of reported measles *sequelae*: a 1963 U.K. study[29] and two U.S. studies from 1994[30] and 2004[31] (excluding another 2004 U.S. study[32] that relied primarily on the 1994 study[30]). We assume that these historical national data provide a good indication of the rates of the *sequelae* for measles reported cases in high-income countries, without significant biases associated with data from outbreaks or hospitalized or more severe cases.[33–35] However, these national studies[29–31] report data for different times, sets of health outcomes, and age ranges, and they give very different estimates of various *sequelae* (e.g., for children <5 years old the estimates range for otitis media (2–14%), pneumonia/respiratory (3–8.6%), and encephalitis (0.03–0.2%), with one study not reporting diarrhea at all[29] such that we list no comparison for this common health outcome). Instead of attempting to pool the data from these studies, we assume *sequelae* for high-income countries as a function of age based on the most recent U.S. study,[31] although this study did not provide the combinations of reported complications or probability of hospitalization as a function of the types of complications (i.e., it reported hospitalization overall). The most complete economic analysis we identified with respect to characterizing the combinations of complications, their severity, and probabilities of hospitalization associated with all outcomes used relatively older U.S. data.[30] We used this study[30] as a basis for assigning fractions of the overall probabilities of cases with diarrhea or otitis media to a combined category (i.e., diarrhea and otitis media) and the probabilities of cases with pneumonia or encephalitis to a combined category (i.e., pneumonia and encephalitis) and for characterizing probabilities of hospitalization by complication. We assume that 25% of encephalitis cases may lead to long-term disability.[30] We also considered the results of a thorough 2002 review that characterized complications and costs of measles infection and vaccination *sequelae* without consideration of age.[13]

In addition to the outcomes reported by the 2004 U.S. study,[31] we included other outcomes. We assume thrombocytopenia (including thrombocytopenic purpura) occurs for approximately 1% of reported measles cases in all ages based on limited data.[13,33,36] Prior economic analyses[13,30,37–39] generally assumed no age-related differences in the probabilities of subacute sclerosing panencephalitis (SSPE), which involves progressive deterioration of cerebral function and ends in death.[40,41] Older studies estimated overall probabilities of 0.85[42] to 2[43] SSPE cases per 100,000 measles infections, but more recent studies reported estimates reflecting increased risk at young ages,[44–46] which led us to assume approximately 2 and 1 SSPE cases per 10,000 measles reported cases, respectively, for individuals <5 years and 5 or more years of age. We added the total

Table I. Assumed Inputs for Percentages (%) of Vaccine Adverse Events per Dose for Immunization and Percentages of Adverse Health Outcomes per Measles or Rubella Case Reported by Age and Treatment (Excluding Infections in Pregnancy)

	Optimal				Minimal			
Health Outcomes (per unit)[refs]	<5 yr	5–14 yr	15–44 yr	45+ yr	<5 yr	5–14 yr	15–44 yr	45+ yr
Vaccine adverse events for measles vaccine								
Anaphylaxis (per dose)[30]	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Febrile seizures/convulsions (per dose)[30]	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Minor reactions (per dose)[30]	10	10	10	10	10	10	10	10
Thrombocytopenia (per dose)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Thrombocytopenia mortality (per thrombocytopenia case)[30]	3	3	3	3	3	3	3	3
Vaccine adverse events for rubella vaccine								
Transient arthropathy (per dose), all children and adult women	0.01	0.01	0.1	0.1	0.01	0.01	0.1	0.1
Chronic arthropathy (per transient arthritis case	0	0	10	10	0	0	10	10
Measles cases								
Blindness (per case)	0	0	0	0	0.1	0	0	0
Diarrhea (per case)	8.5	4	6	8.5	41	41	58	58
Encephalitis, acute (per case)	0.1	0.05	0.1	0.2	0.1	0.05	0.1	0.2
Otitis media, acute (per case)	11	2	0.7	0.7	0	0	0	0
Otitis media + diarrhea (per case)[b]	3	1	1	1	5	5	5	5
Pneumonia (per case)	8.5	2.45	5.9	9.2	21.9	27.95	32.9	32.9
Pneumonia + encephalitis (per case)[b]	0.1	0.05	0.1	0.1	0.1	0.05	0.1	0.1
SSPE (per case)[46]	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.01
Thrombocytopenia (per case)[13]	1	1	1	1	1	1	1	1
Wasting, acute (per case)	0	0	0	0	3.5	0	0	0
Uncomplicated illness (per case)[31))a]	58.6	86	73	68.6	5	20	2	2
Other clinical illness (per case)[c]	9.18	3.44	12.19	10.69	22.28	4.94	0.89	0.79
Encephalitis, residual damage (per encephalitis case)[30]	25	25	25	25	25	25	25	25
Encephalitis mortality (per encephalitis case)[30]	5	5	5	5	10	10	10	10
Other clinical illness mortality (per other clinical illness case)[30]	1	1	2	2	5	5	10	10
Pneumonia mortality (per pneumonia case)	2	2	2	2	10	10	10	10
SSPE mortality (onset 7 years after infection, death 2 years later) (per SSPE case)	100	100	100	100	100	100	100	100
Thrombocytopenia mortality (per thrombocytopenia case)[30]	3	3	3	3	3	3	3	3
Rubella cases								
Encephalitis, acute (per case)[30]	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.013
Thrombocytopenia (per case)[30]	0.033	0.033	0.033	0.033	0.033	0.033	0.033	0.033
Transient arthropathy, female (per case, female)[61]	1	1	52	52	1	1	52	52
Transient arthropahy, male (per case, male)[61]	1	1	8	8	1	1	8	8
Uncomplicated illness, female (per case)[a]	98.954	98.954	48	48	98.954	98.954	48	48
Uncomplicated illness, male (per case)[a]	98.954	98.954	92	92	98.954	98.954	92	92
Chronic arthropathy (per transient arthritis case)[61]	0	0	20	20	0	0	20	20
Encephalitis mortality (per encephalitis case)[30]	5	5	5	5	10	10	10	10
Thrombocytopenia mortality (per thrombocytopenia case)	3	3	3	3	3	3	3	3

[a]Uncomplicated cases may include symptoms of rash, fever, cough, runny nose, sore throat, and/or watery or inflamed eyes (conjunctivitis) not severe enough to lead to hospitalization.

[b]Combinations characterized[30] such that the total probabilities for diarrhea, encephalitis, otitis media, and pneumonia remain consistent with prior data.[31]

[c]Other clinical illness cases may include symptoms that lead to clinical care, including potential hospitalization (e.g., croup, febrile seizures, co-morbidites for immunocompromised individuals).

probabilities of diarrhea, otitis media, pneumonia, encephalitis, thrombocytopenia, and SSPE, and compared these to the reported proportion of cases with any complications.[31] We assume that the difference between the total and the reported cases with any complications represents cases with clinical illness with other symptoms that lead to clinical treatment (e.g., febrile convulsions, croup, complications due to co-morbidities), such that the probability of uncomplicated cases matched the reported percentages.[31] We assume uncomplicated cases included symptoms of rash, fever, cough, coryza, runny eyes, sore throat, nausea, and that some fraction of these cases seek clinical care with a physician and lead to purchases of medications to treat symptoms, but none require hospitalization. We assume hospitalization for 100% of thrombocytopenia, encephalitis, and SSPE cases, 100% for pneumonia cases in individuals 45+ years old, 75% of pneumonia cases <45 years old and all other clinical illness cases of all ages, and 50% of cases with diarrhea and/or otitis media, which allows us to approximate the estimated reported hospitalization by age.[31] Table I summarizes our assumed inputs for percentages (%) of adverse health outcomes per measles case reported by age and treatment.

Several measles *sequelae* lead to mortality (e.g., thrombocytopenia, encephalitis, SSPE, pneumonia, other clinical illnesses). U.S. studies with a historical perspective showed a significant decline and leveling off of overall case-fatality ratios (CFRs) over time as treatment and baseline health improved.[31,47,48] However, comparison of the age-based CFRs show similar values from 1973–1975[47] and 1987–2000,[31] but different overall rates (i.e., 0.09%[47] and 0.3%[31]), which occurs due to the relatively higher proportions of infections that occurred in younger and older individuals (i.e., 28%[47] and 53%[31] total of infections under 5 years old and over 20 years old). One comprehensive review of measles CFRs for countries of different income levels recommended CFRs for children <5 years old ranging from 0.05% to 6% (i.e., different values for specific countries within this large range) based on expert judgment due to overall limitations in the evidence.[49] Given the nature of some of the relatively rare serious outcomes that appear to reflect physiological responses to measles disease independent of treatment (e.g., SSPE), as long as measles virus circulates, some fatalities will occur. We estimate the health outcomes per infection by adjusting the proportions of health outcomes based on reported cases to account for asymptomatic infections and underreporting. We assume that 1% of measles infections occur without noted symptoms (i.e., essentially asymptomatic). We assume 0%, 25%, 50%, and 90% reporting of individuals with asymptomatic infections, uncomplicated infections, infections requiring clinical care but not hospitalization, and infections requiring hospitalization, respectively. These assumptions imply increased probabilities of reporting as severity of the health outcome increases, consistent with the available 1987–2000 data used for the 2004 study.[31] We use these assumptions as the baseline for all high-income countries and assume the rates of health outcomes per infection remained constant since 2000. We recognize that improvements in reporting most likely occurred in the United States and the Americas as they focused on national and regional measles elimination goals by 2000. We assume that after successful elimination, reporting of infections remains high due to aggressive outbreak control efforts that involve contact tracing.

For mortality, we assume an excess fetal loss of 3% for measles infections that occur in the first 20 weeks of pregnancy.[50] We assumed 2%, 3%, 5%, and 100% mortality for reported cases of pneumonia, thrombocytopenia, encephalitis, and SSPE, respectively. Recognizing the progressive nature and delayed mortality for SSPE, we assumed onset of SSPE symptoms occurs seven years after measles infection followed by two years of treatment and then death. For the category of reported other clinical illnesses, we assume 1% mortality for individuals <15 years old and 2% mortality for cases 15+ years old. The combined assumptions imply a CFR for children <5 years old of approximately 0.3%, which matches the value reported by prior U.S. studies.[31,47] We assume these mortality estimates reflect the experience in the United States in 2000, noting that this estimate exceeds the value for developed economies of 0.05% suggested by the 2009 expert review[49] by a factor of approximately 6.

We did not identify any studies with national data quantifying measles *sequelae* for children in low-income countries by age, in which children generally experience lower levels of baseline health such that vitamin A deficiency may lead to a higher risk of blindness following eye complications[51] and malnourished children may suffer from wasting (i.e., kwashiorkor/marasmus) following measles infection.[52,53] We considered the limited age-based data from 1996–1998 from a district-level study from Malawi[54] and estimates of overall risks related to

wasting and blindness for children <5 years old from a recent cost-effectiveness study performed while India still met the economic criteria for a low-income country.[53] For low-income countries, we assume relatively worse surveillance, leading to 0%, 10%, 25%, and 50% reporting of individuals with asymptomatic infections, uncomplicated infections, infections requiring clinical care but not hospitalization, and infections requiring hospitalization, respectively. Given less access to treatment, we assume lower rates of hospitalization (i.e., 75% for thrombocytopenia, encephalitis, and SSPE, 50% for pneumonia, wasting, blindness, and other clinical illnesses, and 25% for diarrhea and/or otitis media). We assumed the lower baseline health and treatment lead to 10%, 6%, 10%, and 100% mortality for pneumonia, thrombocytopenia, encephalitis, and SSPE, respectively, and used the same delays for onset and death for SSPE. For the category of other clinical illnesses, we assume 5% mortality for individuals <15 years old and 10% mortality for cases 15 or more years old. The combined assumptions imply a CFR for children <5 years old of approximately 3.4%, which matches the study from Malawi for around 1997[54] and falls close to the range (2–3%) suggested for Malawi by the 2009 expert review.[49] We use these assumptions as the baseline for all low-income countries.

Table I also summarizes our assumed inputs for percentages of adverse health outcomes per rubella case reported by age and treatment, excluding infections in pregnancy for which we use the results of prior separate analyses to account for the impacts of rubella infections in pregnancy on pregnancy outcomes[50] and birth outcomes.[20] We account for the few additional complications associated with rubella infections, assuming rubella cases present rarely with thrombocytopenia[30,37,38,55–59] (1 in 3,000) or with encephalitis[30,37,38,55,56,58–60] (1 in 8,000). We also assume that rubella cases in individuals may lead to arthropathy (i.e., arthralgia or arthritis) that requires treatment (i.e., approximately 30% of all cases,[30] with 52% of cases in women and 8% of cases in men[61]), which we assume leads to hospitalization in 4% of cases and persistent disability lasting approximately two years for 20% of the arthropathy cases.[30,55–61] For children under 15 years old, we assume arthropathy occurs in 1% of rubella cases, with no chronic arthropathy.[61] We assume uncomplicated rubella cases include symptoms of rash, fever, cough, and that some fraction of these cases seek clinical care with a physician and some infections lead to the purchase of medications to treat symptoms, but none require hospitalization. We assume uncomplicated illness for 99%, 48%, and 92% of cases <15 years old, ≥15 year old women, and ≥15 year old men, respectively, and we assume 50% of cases occur asymptomatically. We assume the same rates of underreporting for rubella infections as a function of severity of the health outcome and the same rates for hospitalization and mortality for encephalitis and thrombocytopenia as we used for measles.

Table I provides our assumed inputs for percentages of vaccine adverse events per vaccine dose. Adverse events from immunization include some rare serious complications that may lead to disability and treatment. Although many economic analyses considered vaccine adverse events based on evidence and expert judgments available at the time,[13,30,32,37,39,53,57,62–67] most included health outcomes not supported by the current weight of the evidence,[68] specifically for SSPE,[46] aseptic meningitis,[69] and encephalitis.[69] The most recent expert review of the evidence did not discuss thrombocytopenia[68] for measles containing vaccines (MCVs), presumably due to the prior finding of a correlation[70] and its widespread recognition as a rare event associated with viral infections. We assume minor reactions (e.g., pain, fever, nausea) for 10%, febrile seizures for 0.1%, and anaphylaxis for 0.001% (i.e., 1 in 10,0000) of immunizations.[30] For thrombocytopenia, other economic analyses[13,30] relied on a relatively old estimate from Finland of 23 thrombocytopenia cases contemporaneously occurring with 700,000 MCV immunization doses[71] (i.e., 0.003%). However, the study did not include a comparison group that would provide a baseline probability of this rare event to allow characterization of the excess risk attributable to MCV (i.e., the incidence may not exceed the background rate) and no controlled studies exist.[70] Nonetheless, a study that applied this rate to the U.S. experience of MCV-related thrombocytopenia reported to the U.S. Vaccine Adverse Event Reporting System (VAERS) during 1990–1995 led to a much lower estimate, which motivated a suggestion of a 4% reporting rate to VAERS.[72] A separate study of the same VAERS data suggested risk associated with any MCV dose (not just the first dose) and identified prior thrombocytopenia as a precaution for MCV immunization.[73] Given many more years of experience, we analyzed the data from VAERS for immunizations delivered during 1990–2014, which included 313 records, with 216 hospitalizations and

6 deaths, reporting thrombocytopenia contemporaneously occurring following receipt of measles-mumps-rubella vaccine (MMR).[74] During that time period, the United States delivered approximately 200 million doses (assuming delivery of a minimum of 8 million doses per year). Taking all of the hospitalized records as potentially related to the MCV, despite many records reporting contemporaneous receipt of other vaccines, preexisting conditions (e.g., thrombocytopenia prior to immunization) that may have accounted for the hospitalization and/or death, and other factors that led to questions about the attribution of the thrombocytopenia to the MCV, we conservatively assume thrombocytopenia temporally associated with MCV occurs with a probability of 1 in a million MCV immunizations (0.0001%). For vaccine adverse events, we assumed hospitalization for 10% of febrile seizures and 100% of thrombocytopenia and anaphylaxis cases, and mortality of 3% of thrombocytopenia cases.[30] This estimate remains consistent with a study that reported a mortality rate of 4.6%[75] and the VAERS data discussed above, which implied a rate of approximately 2–3%. We assume the same estimates of adverse outcomes for all ages and all income levels.

For vaccines that contain rubella, we include transient arthropathy[68] for 0.1% of immunizations for women (≥15 years of age) and 0.01% for children <15 years of age. These estimates exceed reported field experience, with 0.006% of immunization doses leading to reports of transient arthropathy adverse events following rubella immunization in Costa Rica[76] and lower reports to VAERS (i.e., <2,000 events per 200 million doses), but they fall below the 1% assumed by a prior economic analysis.[32] In the absence of sufficient evidence[68] and noting that the U.S. National Vaccine Injury Compensation Program paid a relatively small number of claims for chronic arthropathy for adult cases,[77] we assume 10% of transient arthropathy cases lead to chronic arthropathy due to rubella containing vaccines in women ≥15 years. These estimates probably significantly overestimate arthropathy risks associated with rubella containing vaccines. Based on the available evidence,[78–83] we did not include any adverse pregnancy outcomes associated with rubella vaccination during pregnancy.

For the probabilities of outcomes related to measles and rubella infections, we characterize the estimates assuming optimal and minimal treatment, which we assume applies to high-income and low-income countries, respectively. We interpolate between these for middle-income countries using the same approach we used to characterize DALYs for CRS,[20] which assumes optimal treatment in high-income countries, minimal treatment in low-income countries, and optimal:minimal treatment ratios for UMI and LMI countries, respectively. These assumptions attempt to provide some adjustment for income level to account for the impact of differences in baseline health and potential treatment.

We recognize that reporting rates and the probabilities of adverse health outcomes most likely changed over time. Specifically, increased public health attention and notification requirements increased reporting rates, and this effectively increases the denominator for CFRs by including more infections that led to less-severe health outcomes. Similarly, changes in standards of care and guidelines for treatment of measles cases[84] significantly improved overall outcomes, particularly due to the inclusion of delivery of vitamin A[85,86] and antibiotics,[87,88] although the introduction of immunization accounts for the most significant reduction in measles mortality. Consequently, economic analyses should consider the likely higher probabilities that occurred retrospectively and the possibility of lower probabilities prospectively. We focus on characterization of probabilities per infection for use in modeling to avoid biases associated with changes in reporting, and we assume that the actual occurrence of the adverse health outcomes per infection remains independent of reporting. Thus, for mortality we focus on infection-fatality ratios (IFRs). Given the importance of fatalities as an outcome for measles, some recent measles models[89,90] considered the decreasing trends in overall under-five-year-old mortality per 1,000 live births[91] (Fig. 1), which linear regression suggests declined from 2000 levels by approximately 5%, 3%, 1.5%, and 0.3% per year for low-, lower-middle-, upper-middle-, and high-income countries, respectively. For our analysis, we assume that the decline in under-five-year-old mortality provides a proxy for gradual improvement in treatment and baseline health for all ages as they impact mortality, and we assume a decline in mortality rates for measles-related encephalitis, pneumonia, thrombocytopenia, and other clinical illnesses between 2000–2052 at slightly lower rates of approximately 3%, 2%, 1%, and 0.2% per year for low-, lower-middle-, upper-middle-, and high-income countries, respectively. We assume that mortality from relatively rare SSPE cases remains constant, which implies asymptotic behavior of measles-associated IFRs due to SSPE.

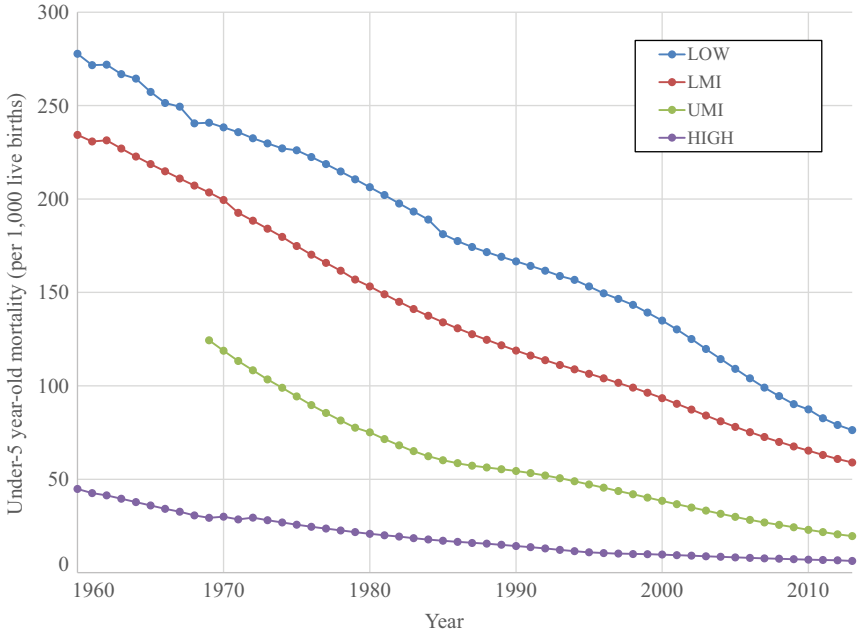

Fig. 1. Trends in under-five-year-old mortality per 1,000 live births.

We use all of the inputs to characterize the adverse health outcomes per dose of vaccine, per measles and rubella infection as a function of income level, age of immunization or infection, and sex, as appropriate, per CRS case, and per measles infection in pregnancy (MIP) or rubella infection in pregnancy (RIP). We use these estimates as the basis for estimation of DALYs and costs.

2.2. Disability-Weight and Health Outcome Duration Inputs for DALY Estimation

We characterize inputs for DALYs associated with the adverse health outcomes to estimate the years of life lost (YLL) and years lived with disability (YLD) using the same approach used for birth outcomes associated with CRS.[20] Table II provides the disability weight and health outcome duration assumptions for both the more recent Global Burden of Diseases (GBD), Injuries, and Risk Factors Study 2010 (GBD 2010)[92] and the GBD 1990 study.[93] The two sets of disability weights lead to very different DALY estimates for CRS,[20] and consequently we include both sets of disability weights for this analysis. We use the probabilities for the health outcomes chronic disability and mortality developed in the prior section. We assume average life expectancies (LEs) of 62, 66, 74, and 79 years for low-, lower-middle-, upper-middle-, and high-income countries, respectively, for 2013, and an expected increase in life expectancy of 0.33, 0.29, 0.27, and 0.20 per year for low-, lower-middle-, upper-middle-, and high-income countries, respectively, for 2013–2052. We assume disability weights of 1 for mortality and durations of LE minus the infection age for encephalitis, other clinical illness, pneumonia, and thrombocytopenia. We assume durations of LE, LE-1, LE-5, and LE-infection age nine years for fetal loss, congenital heart disease (CHD) mortality at one year of age,[20] CHD mortality at five years of age,[20] and SSPE, respectively. For measles and rubella infections, we assumed that all infected symptomatic individuals experience the short-term effects associated with uncomplicated infections (e.g., rash, fever, cough, sore throat, nausea, vomiting, coryza, runny eyes).

We use these inputs along with the probabilities of *sequelae* and the associated hospitalization to characterize the inputs required to estimate the YLL and YLD per vaccine dose, measles or rubella infection, CRS case, and per MIP or RIP as a function of age, sex, treatment, and year in the time horizon (i.e., used to account for declining IFRs for encephalitis, pneumonia, thrombocytopenia, and other non-SSPE causes).

2.3. Clinical Treatment Inputs and Treatment Cost Estimation

We characterized all costs in 2013 U.S. dollars (US$2013), taking a societal perspective and

Table II. Disability Weights and Duration Input Assumptions for DALY Calculations

Condition for Which Disability Weight Useda[a]	Duration	GBD2010[92] Disability Weight			GBD1990[93] Disability Weight by Age (yrs)				
		Description	Mid	(Min–Max)	Description	0–4	5–14	15–44	45+
Anaphylaxis (treated) (V)	2 days	Poisoning, short term, with or without treatment	0.171	(0.116–0.239)	Poisoning—episodes, treated or untreated	0.611	0.611	0.607	0.607
Arthropathy, acute (treated) (VR)	1 month	Musculoskeletal problems: arms, mild	0.024	(0.014–0.041)	Rheumatoid arthritis—cases, treated	0.174	0.174	0.174	0.174
Arthropathy, chronic (treated) (VR)	LE-age	Musculoskeletal problems: arms, mild	0.024	(0.014–0.041)	Rheumatoid arthritis—cases, treated	0.174	0.174	0.174	0.174
Arthropathy, acute (untreated) (VR)	1 month	Musculoskeletal problems: arms, moderate	0.114	(0.077–0.159)	Rheumatoid arthritis—cases, untreated	0.233	0.233	0.233	0.233
Arthropathy, chronic (untreated) (VR)	LE-age	Musculoskeletal problems: arms, moderate	0.114	(0.077–0.159)	Rheumatoid arthritis—cases, untreated	0.233	0.233	0.233	0.233
Blindness (M)	LE-age	Distance vision blindness	0.195	(0.132–0.272)	Glaucoma: blindness, treated or untreated	0.6	0.6	0.6	0.6
Clinical illness other (treated) (M)	4 days	Infectious disease: acute episode, moderate	0.053	(0.033–0.081)	Measles—episodes, treated or untreated, all ages	0.152	0.152	0.152	0.152
Clinical illness other (untreated) (M)	4 days	Infectious disease: acute episode, severe	0.21	(0.139–0.298)	Measles—episodes, treated or untreated, all ages	0.152	0.152	0.152	0.152
Diarrhea (treated) (M)	8 days	Diarrhea: moderate	0.202	(0.133–0.299)	Diarrhea—episodes, treated or untreated	0.119	0.094	0.086	0.087
Diarrhea (untreated) (M)	8 days	Diarrhea: severe	0.281	(0.184–0.399)	Diarrhea—episodes, treated or untreated	0.119	0.094	0.086	0.087
Encephalitis, acute (MR)	16 days	Severe traumatic brain injury: short term, with or without treatment	0.235	(0.156–0.331)	Japanese encephalitis—episodes, treated or untreated	0.616	0.616	0.613	0.613
Encephalitis, prolonged (M)	LE-age	Traumatic brain injury: long-term consequences, severe with or without treatment	0.625	(0.444–0.789)	Japanese encephalitis—neurological *sequelae*	0.616	0.616	0.616	0.616
Febrile seizures/ convulsions (V)	3 days	Epilepsy: treated, with recent seizures	0.319	(0.221–0.445)	Epilepsy—cases	0.099	0.15	0.15	0.15
Minor reactions (V)	1 day	Generic uncomplicated disease: worry and daily medication	0.031	(0.017–0.05)	Panic disorder, treated	0.091	0.091	0.091	0.091
Otitis media (M)	8 days	Ear pain	0.018	(0.009–0.031)	Otitis media—episodes, treated or untreated	0.023	0.023	0.023	0.023
Pneumonia (M)	8 days	Infectious disease: acute episode, severe	0.21	(0.139–0.298)	Lower respiratory infection, episode	0.28	0.276	0.276	0.28
Pregnancy termination (treated) (R)	2 days	Abdominopelvic problem: moderate	0.123	(0.083–0.176)	Abortion—episodes	0	0	0	0

(*Continued*)

Table II. (Continued)

Condition for Which Disability Weight Useda[a]	Duration	GBD2010[92] Disability Weight			GBD1990[93] Disability Weight by Age (yrs)				
		Description	Mid	(Min–Max)	Description	0–4	5–14	15–44	45+
Pregnancy termination (untreated) (R)	3 days	Abdominopelvic problem: severe	0.326	(0.219–0.451)	Abortion—episodes	0	0	0	0
SSPE, 2 years between onset and death (M)	2 years	Traumatic brain injury: long-term consequences, severe with or without treatment	0.625	(0.444–0.789)	Japanese encephalitis—neurological *sequelae*	0.616	0.616	0.616	0.616
Thrombocytopenia (treated) (VMR)	8 days	Anemia: moderate	0.058	(0.038–0.086)	Iron-deficiency anemia, moderate	0.011	0.011	0.011	0.012
Thrombocytopenia (untreated) (VMR)	8 days	Anemia: severe	0.164	(0.112–0.228)	Iron-deficiency anemia, severe	0.087	0.087	0.093	0.089
Uncomplicated illness (MR)	4 days	Generic uncomplicated disease: worry and daily medication	0.031	(0.017–0.05)	Measles—episodes, treated or untreated, all ages	0.152	0.152	0.152	0.152
Wasting (treated) (M)	8 days	Kwashiorkor	0.055	(0.033–0.085)	Wasting, treated or untreated	0.053	0	0	0
Wasting (untreated) (M)	1 month	Severe wasting	0.127	(0.081–0.183)	Wasting, treated or untreated	0.053	0	0	0

Abbreviations: GBD, global burden of disease; LE, life expectancy.
[a]Health outcomes listed for V = vaccine adverse event, M = measles, and R = rubella.

using a 3% discount rate (range 0–7%). The cost inputs include both national costs for providing treatment (and immunization, discussed in the next section) and the productivity losses associated with serious complications from measles, rubella, and/or receipt of vaccine.[94] We also include some costs associated with home care (including time to receive treatment or vaccination for patients, parents, and/or caregivers). We consider the cost inputs in the context of their application for modeling a time horizon of 2013–2052. When extrapolating from historical data, we estimate the U.S. dollar value of the costs using appropriate inflation and exchange rates from the year of any non-U.S. currency data to express these in US$ for that year. We rely on current population estimates and projections from the U.N. Population Division, World Population Prospects.[95]

Similar to numerous prior economic analyses,[30,37,38,55,56] we characterized treatment costs considering health-care system utilization based on estimated hospital days, physician visits, and home care days. Table III shows our input assumptions for acute care costs (i.e., hospital days, physician visits, and home care days) assumed for different *sequelae*. We inflated prior estimates of hospital and outpatient costs for the United States consistent with the assumptions in Table III[56] to US$2013 as the basis for estimating acute care treatment costs for *sequelae* in high-income countries (shown in Table III). For low-income countries, we assumed minimal treatment of cases associated with the cost of utilization of the health-care system facility (i.e., the outpatient clinic or hospital bed). We use the appropriate probabilities of *sequelae* and hospitalization per vaccine dose or per infection to characterize the costs using the same units.

Table IV summarizes some additional treatment cost inputs by World Bank income level.[19] To characterize the optimal:minimal treatment ratios, home care costs, and productivity losses associated with early mortality, we estimated the annual average gross national income (GNI) (Atlas method, US$2013) by income level.[96] We consider productivity losses by assuming the value of each DALY saved equals the GNI for the income level.[94,97] The GNI values suggest optimal:minimal treatment ratios of 0.23:0.77 for UMI and 0.08:0.92 for LMI countries, which we use consistently for cost and DALY estimates. We estimated the cost per hospital bed day and outpatient clinic visit for

Table III. Assumed Numbers of Home Care Days, Physician Visits, and Hospital Days for Acute Care for *Sequelae* Associated with Vaccine Adverse Events (V), Measles Infections (M), Rubella Infections (R), CRS Cases (CRS), Measles Infections During Pregnancy (MIP), Rubella Infections During Pregnancy (RIP), and Estimated Costs of Cases for Hospitalization and Outpatient Care in High-Income Countries (US$2013)[56]

Sequelae Requiring Acute Care	Hospital Days	Physician Visit[a]	Posthospital Physician Visit[b]	Home Care Days[c]	Posthospital Home Care Days[d]	Hospital Cost (High-Income)	Outpatient Cost (High-Income)
Anaphylaxis (V)	2.89	0	2.06	0	1	$21,171	$202
Febrile seizures/convulsions (V)	2	1	1	0	2	$7,165	$552
Minor reactions (V)	0	0.02	0	0	0	$0	$85
Thrombocytopenia (VMR)	4.8	0	5.91	3.5	3	$29,965	$550
Arthropathy, acute (VR)	2	0.5	0.5	0	3	$12,374	$184
Blindness (M)	1	3	3	21	21	NA[e]	NA[e]
Diarrhea (M)	1.33	0.5	0	3.5	1	$3,404	$93
Encephalitis, acute (MR)	8.7	0	3.52	5	7	$38,885	$445
Clinical illness other (M)	1.33	0.5	0	3.5	1	$3,404	$93
Otitis media, acute (M)	1.9	1	1	4	1.5	$5,690	$75
Otitis media + diarrhea (M)	1.9	1	1	4	1.5	$5,690	$93
Pneumonia (M)	5.5	1.75	1.75	4.5	3.5	$18,240	$146
Pneumonia + encephalitis (M)	8.7	1.75	3.52	5	7	$38,885	$445
SSPE (M)	10.9	0	10	0	30	$11,572	$263
Wasting, acute (M)	4	4	3	30	42	NA[e]	NA[e]
Uncomplicated illness (MR)	0	0.5	0	3.5	0	$0	$93
Encephalitis, residual damage (M)	9.1	0	0	0	0	$34,692	$0
Initial investigation (CRS)[f]	13.6	0	1.53	0	5	$50,569	$90
Spontaneous abortion (RIP or MIP)	0	1	0	0	3	$646	$0

[a]Physician visit for nonhospitalized cases.
[b]Physician visit following hospitalization.
[c]Home care days for nonhospitalized cases.
[d]Home care days following hospitalization.
[e]Not applicable given no probability of these outcomes assumed for high-income countries.
[f]Comprehensive medical evaluation for all CRS cases except the 28% with hearing defects only.

each World Bank income level[19] based on the WHO-CHOICE country-specific unit costs data from 2008 (i.e., the hotel or facility use costs).[5] We estimated these costs for each 2008 income level and then inflated the estimates to US$2013 assuming that these values apply to the countries in the 2013 World Bank income levels. We use the estimated hospital day and outpatient visit costs for low-income countries, the hospital days and outpatient visits per *sequelae* in Table III, and age- and sex-appropriate estimates of the probabilities of the *sequelae* and associated hospitalization to estimate the costs per vaccine dose or infection for low-income countries. As with the DALY estimates, we interpolated between the low- and high-income country acute care cost estimates based on the assumed ratios of optimal:minimal treatment. Based on review of the literature,[11] Table IV also characterizes estimated medication costs paid by individuals and additional costs associated with disability, including chronic care costs, not considered elsewhere.

For measles, Table IV includes estimates of medication costs for uncomplicated cases, for which we assume costs (in US$2013) of approximately $2 for low-income countries[98] and $16 for high-income countries.[99] We assume that the small fraction of encephalitis infections that result in residual damage lead to severe retardation requiring institutional care for 50 years for which we inflate a prior estimate[56] to US$2013 for high-income countries. We assume that in low-income countries, no additional costs apply and that the higher estimated risk of encephalitis mortality for encephalitis in low-income countries accounts for the encephalitis cases with residual damage.

For rubella, Table IV includes our assumed cost for chronic arthropathy for high-income countries, based on the average claim paid for chronic arthropathy by the U.S. National Vaccine Injury Compensation Program.[77] We assume individuals with chronic arthropathy in low-income countries receive minimal treatment for which we assume a lifetime cost of care of $1,000. Prior economic analyses for CRS provided

Table IV. Best Estimates (Range When Available) in US$2013 for Additional Treatment Cost Inputs for Disabilities for *Sequelae* Associated with Measles Infections, Rubella Infections, and CRS Cases by World Bank Income Levels[19]

Cost Input	LOW	LMI	UMI	HIGH	Notes[refs]
Population-weighted average GNI per capita	$770	$3,800	$11,200	$47,800	a[19,96]
Hospital day (hotel costs)	$4.5 ($4–5)	$25 ($21–29)	$108 ($87–118)	$674 ($574–774)	b[5]
Physician visit (facility costs)	$1.0 ($1–1.5)	$4.2 ($3.7–5.5)	$13 ($11–16)	$64 ($52–76)	b[5]
Time cost per day of home care	$3	$15	$45	$190	c[19]
Measles-specific costs					
Medications for uncomplicated cases	$2	$2.98	$5.22	$16	[98,99]
Encephalitis, residual care * (LE-age)	$0	$7,557	$24,831	$107,959	[56]
Rubella-specific costs					
Chronic arthropathy care	$1,000	$7,313	$21,741	$91,180	[77]
CRS-specific costs					
CHD surgery	$1,805	$3,733	$8,140	$29,350	[56,101]
Eye surgery (cataracts/glaucoma)	$55	$522	$1,590	$6,726	[56,102,103]
Cochlear implant/chronic hearing assistance	$193	$7058	$22752	$98,277	[113]
Retardation care per year for 50 years	$385	$3,406	$10,312	$43,547	[56]
Vision correction, per year for life	$8	$40	$113	$463	[114,115]

[a]Computed using gross national income (GNI), per capita, Atlas method for US$2012, and World Bank income level classification criteria for 2012, then inflated to US$2013.
[b]Computed using WHO-CHOICE unit cost estimates for 2008 in US$2008 and 2008 population estimates for 169 countries with complete data, and World Bank income level classification criteria for 2008, then inflated to US$2013.
[c]Computed as GNI divided by 250 days per year.

many estimates for chronic care for high-income countries, which we updated. We used existing cost estimates for CHD surgery, eye surgery, and special education associated with CRS for high-income countries[56] inflated to US$2013. We assumed approximately half of the 49% of CRS cases with CHD required surgery (i.e., 25% of all CRS cases), 40% of the 50% of CRS cases with eye defects required surgery (i.e., 20% of all CRS cases), and all of the 35% of CRS cases with intellectual disability required special education and institutional care for retardation. Although the treatment of patent ductus arteriosus (PDA) changed dramatically over time, with corresponding improvements in outcomes, these changes did not apparently reduce costs,[100] which led us to use the inflated estimate for CHD surgery costs with no additional modification. For low-income countries, we estimate the cost of CHD surgery based on a study from India while it qualified as a low-income country[101] and for eye surgery based on studies of cataract surgery in Nepal[102] and India.[103] For the 91% of CRS cases with hearing loss, we recognized the need to update cost estimates to include cochlear implants[11] given their well-established cost effectiveness in pediatric populations in high-income countries.[104–108] To date, limited penetration of cochlear implant technology exists in countries of relatively lower income,[109,110] although some children with CRS in these countries receive cochlear implants.[111] Cost-effectiveness analyses show cost savings associated with cochlear implants due to the reduction or elimination of the need to pay for special education and increased productivity.[112,113] Table IV includes the direct costs associated with cochlear implants[113] as our estimate of the treatment costs for hearing loss for CRS for high-income countries. This implicitly assumes that CRS cases with hearing loss that do not receive cochlear implants require the equivalent costs for hearing assistance and special education (i.e., costs for special education for deafness account for approximately 82% of this amount[113] and hearing aids account for the balance). We assume costs of cochlear implants will remain prohibitive in low-income countries for the time horizon. For low-income countries, we assume care for deaf children at a cost of 25% of the GNI per year (i.e., $193) for 20 years, and that retarded children will require care at a cost of 50% of the GNI per year (i.e., $385) for 50 years. Finally, we include costs associated with vision correction for all CRS children with eye defects assuming annual costs for vision correction in high-[114] and low-income countries[115] apply for the entire life expectancy. We do not consider costs associated with travel for vaccination or for treatment.

Table V. Immunization and Wastage Cost Inputs

Cost Input	LOW	LMI	UMI	HIGH	Notes[refs]
Surviving infants in modeled population (millions)	26	56	37	15	(116)
Fraction of modeled population	20%	42%	28%	11%	
Cost of domestically produced M only vaccine	NA	$0.24	$0.34	NA	(118)
Cost of domestically produced MR vaccine components	NA	$0.524	$0.91	$20	(118,122)
Cost of nondomestic M only vaccine	$0.24	$0.24	$0.34	NA	(118)
Cost of nondomestic MR vaccine components	$0.524	$0.524	$0.91	$20	(118,122)
Proportion of vaccine produced domestically	0%	58%	64%	NA	(116,117)
Average price M only vaccine	$0.24	$0.24	$0.34	NA	
Average price MR vaccine components	$0.524	$0.524	$0.91	$20	
Percent covered by RI with 1 dose M only	66%	60%	7%	0%	(116,136,137)
Percent covered by RI with 1 dose MR components	13%	16%	88%	94%	(116,136,137)
Percent covered by RI with second dose M only	7%	34%	4%	0%	(116,136,137)
Percent covered by RI with second dose MR components	11%	11%	82%	91%	(116,136,137)
Nonvaccine cost per child per RI injection	$0.35	$0.70	$5.76	$23.88	(123,124)
Wastage for RI	3.42	3.25	2.87	1.05	(123,124)
Number of children covered by SIA with 1 dose M only (millions)	37	113	5	0	(116,130)
Number of children covered by SIA with 1 dose MR components (millions)	9	29	3	0	(116,130)
Factor for increased cost for SIA compared to RI	2.3	2	1.75	1.5	
Nonvaccine cost per child per SIA injection	$0.81	$1.41	$10.09	$35.82	(7)
Costs for outbreak investigation (per measles case)	$45	$57	$84	$216	(98,128,129)
Wastage for SIA immunization	1.1	1.1	1.1	1.1	(124)

2.4. Immunization Cost and Wastage Inputs

Table V provides estimates of the numbers of the approximately 134 million surviving infants in the modeled global population for 2013[116] by income level and summarizes vaccine cost inputs. We assume that routine immunization (RI) in high-income countries will continue to use measles and rubella containing vaccines (MRCVs) (i.e., MMR or MR), while UMI, LMI, and low-income countries may use measles (with or without rubella) containing vaccines (M(R)CVs)[8] (i.e., M, MR, or MMR), with countries not currently using rubella containing vaccine formulations planning to introduce it in future years. We use the reported vaccine coverage for each modeled country[116] to characterize the percent of surviving infants in each income level covered with one dose of an MCV or MRCV and the percent covered with two doses.

Many of the prior health economic analyses we previously reviewed[11] provided estimates of vaccine costs and some nonvaccine costs, which vary over time and by country. Producers of measles and rubella containing vaccines use different strains and production processes, but we use a single cost for each income level and we consider the fraction of doses produced by middle-income countries that self-produce (e.g., China, India, Indonesia, Brazil[117]) and the associated potentially lower domestic production costs. We use and extrapolate the UNICEF prices and projections for M and MR for LOW and LMI.[118] No low-income countries self-produce vaccine. For LMI, we could not identify different prices for domestic production in India, and most of the UNICEF vaccine supply comes from a single producer from India, so we use the UNICEF prices for domestic production in LMI countries. For domestically produced vaccines in UMI, we use the M and MR vaccine prices for China, which comprises approximately 50% of the UMI (Wei, X, personal communication, 2014). For middle-income countries that purchase vaccine, we assume the same prices, although some middle-income countries purchase vaccine at the UNICEF prices and others purchase vaccine at higher prices.[119] For high-income countries, prior economic analyses showed a wide range of vaccine prices (e.g., $6–50 in US$2013).[14,120,121] We assume no use of M vaccine for high-income countries and we round up the U.S. price of $19.76 for MMR vaccine given by public providers[122] to use $20 as the assumed average cost for the MR components of MRCV used by high-income countries. We note that in the United States, if we appropriately assume 80% of U.S. children receive vaccine from private providers[123] at the associated higher

cost,[122] this implies an average price per MMR dose in the United States of approximately $48.

All current measles and rubella vaccines require injection, and we characterize the nonvaccine costs associated with injection equipment use and disposal, cold chain, personnel, training, and other miscellaneous costs to estimate the costs per dose for low- and high-income countries based on prior studies.[123,124] We assume twice the low-income country RI costs for LMI and we proportion the UMI costs using the same approach we used to apportion treatment costs. Although the shared nonvaccine costs for MRCVs could divide equally for the antigens contained in the vaccine and thus reduce the costs for measles or rubella alone, we generally attribute all of the nonvaccine costs to the measles component of combined vaccines. We also consider RI vaccine wastage,[123,124] which depends in large part on the vial size for MRCVs.[125–127]

In addition to RI, some countries conduct preventative SIAs (pSIAS) to improve coverage and/or they reactively respond to outbreaks with outbreak SIAs (oSIAs). For all SIAs, we assume the same vaccine cost per vaccine dose as used for RI. However, we use different nonvaccine costs per dose delivered for pSIAs and oSIAs. We assume that nonvaccine costs of pSIAs include the costs of RI plus social mobilization, supervision, planning/training, administrative costs, and transportation costs,[66] and we use an updated estimate for low-income countries.[7] Costs per SIA dose appear to decrease as a function of increased RI coverage.[7] Consequently, we assume fractions of 2, 1.75, and 1.5 times the RI costs to estimate the pSIA costs for LMI, UMI, and HIGH, respectively. We assume the same nonvaccine costs for oSIAs as for pSIAs, except that we also include costs associated with epidemiological investigation and management for oSIAs. For low-income countries, we assume outbreak response costs of approximately $45 per case[98] and for high-income countries we assume costs of $216 per case.[128] The outbreak response cost estimate for high-income countries may significantly underestimate the costs, with U.S. aggressive outbreak response to maintain national measles elimination implying costs of approximately $5,000[15] to $50,000 per case.[129] For LMI and UMI we estimate the costs using the same approach we used to apportion treatment costs. While SIAs vary year to year, we estimate the number of millions of children in the modeled countries covered by an SIA dose by income level and vaccine type using data from 2013 as an example,[116,130] and we use the same estimated wastage rates for all SIAs.[66]

Finally, Table VI captures some additional global programmatic costs, which represent our effort to capture other real costs based on limited available evidence. We consider the costs associated with creating a rotating vaccine stockpile[11] that would help to ensure stability of the MR vaccine supply during the time that countries increasingly transition from M to MR vaccine. We assume that WHO could create a rotating MR vaccine stockpile containing 50 million doses of prequalified vaccine at a one-time cost of approximately $50 million. Surveillance represents an important ongoing activity, with national laboratories and the measles and rubella Lab Net providing ongoing disease surveillance that assists with confirmation and tracking of viral transmission, regional elimination, and global eradication efforts. Many countries pay all or most of their national surveillance costs without requesting external support. The M&RI estimates the need for external support of approximately $15 million for surveillance and laboratory costs.[131] We estimate that global surveillance for measles and rubella, including all national costs, probably approaches twice the amount of anticipated global external needs. Efforts to more aggressively manage measles and rubella may require some expansion of the Lab Net, particularly for surveillance of CRS. We assume that expansion of the Lab Net to include increased surveillance for rubella and tracking of a larger fraction of measles cases would again double the estimated costs. This implies surveillance costs of approximately $60 million per year prior to measles and rubella eradication. We also estimate global programmatic costs for technical support, operational research, stockpile management, communication, and coordination costs. Ongoing analysis of research needs,[132] including opportunities to develop improved delivery strategies, will require the investment of resources. Although the M&RI currently budgets approximately $20–25 million,[131] we assume annual costs of approximately $35 million for global programmatic costs until eradication of measles and rubella. In the event of measles and rubella eradication (i.e., post-eradication), we assume annual costs of $10 million for global programmatic costs to maintain surveillance and coordination activities and manage an emergency response vaccine stockpile.

Table VI. Inputs for the Estimation of Future Global-Level Costs

Input	Estimate
Cost to create a global rotating MR vaccine stockpile	$50 million
Annual surveillance costs, including expanded rubella and CRS surveillance, pre-eradication	$60 million
Annual technical support, operational research, stockpile management, communication, and coordination costs, pre-eradication	$35 million
Annual costs for surveillance and technical support, operational research, stockpile management, communication, and coordination costs, post-eradication	$10 million
Cost of increasing RI coverage by 1% in an undervaccinated subpopulation of 10 million people	$10,000
Cost of global certification and increased containment following eradication	$5 million

In the context of achieving regional elimination goals, reaching undervaccinated subpopulations represents a critical element of measles and rubella elimination as occurred during the endgame of polio eradication. In Nigeria, efforts to increase coverage involved extensive mapping of the population and tracking individual vaccinators.[133] Heterogeneity also exists in high-income countries.[134,135] In general, increasing coverage requires extensive public engagement and communication campaigns. In the absence of data, we assume costs of $10,000 per 1% increase in RI coverage in a population of 10 million people. With respect to containment, we assume that even in the context of successful global eradication of one or both diseases, some vaccination for both would continue over the time horizon, and consequently we assume no change in laboratory or manufacturing facility containment requirements. However, we assume that at the time of global eradication of measles or rubella, we would incur a global cost of $5 million for certification of eradication, potentially including increased containment of measles or rubella viruses stored in laboratories.

3. RESULTS

Measles and rubella infections lead to a large range of complications that may cause permanent disability or death, while immunization for measles and/or rubella leads to relatively rare adverse events by comparison. Table VII provides the estimated percent of different health outcomes per vaccine dose and per measles or rubella infection. We use these values as the basis for estimation of costs and inputs for DALY estimates and DALYs for use in economic analyses. The probabilities of the *sequelae* depend on baseline healthcare and treatment, age, and sex. Fig. 2 shows the decline in the IFRs for the modeled time horizon for optimal treatment (used for high-income countries) and minimal treatment (used for low-income countries).

Table VIII provides the inputs for YLLs and YLDs required to characterize DALYs. Since YLLs and some YLDs depend on the age at the time of fatality, vaccination, or infection, Table VIII indicates the values that require multiplication by (LE-age) and adjustment for the reduction in the IFRs as a function of time using an IFR reduction factor (IFRRF). Table IX uses these inputs to estimate expected DALYs lost per dose by age of vaccination and expected DALYs lost per infection by age of infection for 2013. At the individual level, the expected DALY loss associated with measles infection significantly exceeds (by over a factor of 100) the expected DALY loss associated with vaccination, with the loss of approximately 1 DALY on average expected per measles infection in young children in relatively lower income countries.

Table X provides the expected costs from adverse health outcomes per vaccine dose, per measles or rubella infection, per CRS case, and per pregnancy loss for MIP or RIP by World Bank income level with and without home care costs. The expected costs of measles or rubella infection significantly exceed the expected costs of vaccine adverse events. Our estimated costs per measles infection for high-income countries fall within the range reported by prior studies,[13] although our results show higher costs for very young children and older individuals, similar to the other study that characterized costs by age.[12] The cost estimates per rubella case generally fall below the costs per measles case, except for women ≥15 years old, for which the costs associated with arthropathy increase the costs. The very high costs per CRS case for high-income countries stem largely from the relatively high fraction (35%) of CRS cases assumed to require expensive institutional care for mental retardation. For low-income

Table VII. Best Estimates for the Percent of Different Health Outcomes per Vaccine Dose or per Measles or Rubella Infection by Age and Optimal or Minimal Treatment

	Optimal Treatment				Minimal Treatment			
Health Outcomes per Vaccine Dose or per Infection	<5 yr	5–14 yr	15–44 yr	45+ yr	<5 yr	5–14 yr	15–44 yr	45+ yr
Vaccine adverse events								
Anaphylaxis (per dose)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Febrile seizures/convulsions (per dose)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Minor reactions (per dose)	10	10	10	10	10	10	10	10
Thrombocytopenia (per dose)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Thrombocytopenia mortality (per dose)[a]	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003
Arthropathy, transient, excluding adult men (per dose)[b]	0.01	0.01	0.1	0.1	0.01	0.01	0.1	0.1
Arthropathy, chronic, ≥15- year-old women (per dose)[b]	0	0	0.01	0.01	0	0	0.01	0.01
Measles infections								
Asymptomatic infection (per measles infection)	1	1	1	1	1	1	1	1
Blindness (per measles infection)	0	0	0	0	0.08	0	0	0
Diarrhea (per measles infection)	4	2	3	4	40	30	58	58
Encephalitis, acute (per measles infection)	0.04	0.02	0.03	0.07	0.07	0.03	0.07	0.14
Otitis media, acute (per measles infection)	5	0.8	0.3	0.3	0	0	0	0
Otitis media + diarrhea (per measles infection)	1	0	0	0	5	4	5	5
Pneumonia (per measles infection)	4	0.8	2	3	18	17	28	28
Pneumonia + encephalitis (per measles infection)	0.04	0.02	0.03	0.04	0.07	0.03	0.07	0.07
SSPE (per measles infection)	0.008	0.003	0.003	0.004	0.014	0.005	0.007	0.007
Thrombocytopenia (per measles infection)	0.4	0.3	0.3	0.4	0.7	0.5	0.7	0.7
Wasting, acute (per measles infection)	0	0	0	0	2.8	0	0	0
Uncomplicated illness (per measles infection)	80	94	88	87	15	45	6	6
Other clinical illness (per measles infection)	3.9	1.2	4.6	4.2	18	3	0.7	0.7
Encephalitis, residual damage (per measles infection)	0.019	0.008	0.017	0.026	0.035	0.013	0.036	0.054
Encephalitis mortality (per measles infection)	0.004	0.002	0.003	0.005	0.01	0.01	0.01	0.02
Other clinical illness mortality (per measles infection)	0.04	0.01	0.09	0.08	0.9	0.1	0.1	0.1
Pneumonia mortality (per measles infection)	0.07	0.02	0.04	0.06	1.8	1.7	2.8	2.8
SSPE mortality (per measles infection)	0.008	0.003	0.003	0.004	0.014	0.005	0.007	0.007
Thrombocytopenia mortality (per measles infection)	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02
Total mortality (per measles infection)[a]	0.13	0.04	0.15	0.16	2.7	1.9	2.9	2.9
Excess fetal loss (per measles infection in pregnancy (MIP) <20 weeks since last menstrual period (LMP) (per maternal MIP)[(50)]	3	0	0	0	3	0	0	0

(*Continued*)

Table VII. (Continued)

Health Outcomes per Vaccine Dose or per Infection	Optimal Treatment				Minimal Treatment			
	<5 yr	5–14 yr	15–44 yr	45+ yr	<5 yr	5–14 yr	15–44 yr	45+ yr
Rubella infection								
Asymptomatic infection, female (per rubella infection)	49.9	49.9	39.6	39.6	49.9	49.9	39.6	39.6
Asymptomatic infection, male (per rubella infection)	49.9	49.9	49.0	49.0	49.9	49.9	49.0	49.0
Encephalitis, acute (per rubella infection)	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Thrombocytopenia (per rubella infection)	0.005	0.005	0.006	0.006	0.005	0.005	0.006	0.006
Transient arthropathy, female (per rubella infection)	0.3	0.3	21	21	0.3	0.3	21	21
Transient arthropahy, male (per rubella infection)	0.3	0.3	2	2	0.3	0.3	2	2
Uncomplicated illness, female (per rubella infection)	49.9	49.9	39.6	39.6	49.9	49.9	39.6	39.6
Uncomplicated illness, male (per rubella infection)	49.9	49.9	49.0	49.0	49.9	49.9	49.0	49.0
Chronic arthropathy, female (per rubella infection)	0	0	4	4	0	0	4	4
Chronic arthropathy, male (per rubella infection)	0	0	0.4	0.4	0	0	0.4	0.4
Encephalitis mortality (per rubella infection)	0.00009	0.00009	0.00011	0.00011	0.00009	0.00009	0.00011	0.00011
Thrombocytopenia mortality (per rubella infection)	0.00014	0.00014	0.00018	0.00018	0.00014	0.00014	0.00018	0.00018
Total mortality (per rubella infection)[a]	0.00023	0.00023	0.00029	0.00029	0.0003	0.0003	0.0005	0.0005
Pregnancy termination (per maternal RIP)[50]	0	0	25	0	0	0	25	0
Excess fetal loss (per rubella infection in pregnancy (RIP) <20 weeks since last menstrual period (LMP) (per maternal RIP)[50]	28	0	0	0	28	0	0	0
CRS cases (per maternal RIP)[50]	0	0	43	0	0	0	43	0

[a]Infection-fatality ratio for 2000, adjusted to 2013 and later years by reduction factors that assume 3%, 2%, 1%, and 0.2% per year.
[b]For rubella containing vaccines.

countries, the costs of surgery for CHD account for most of the cost of CRS for low-income countries. The significant disability associated with the multiple congenital defects leads to high costs and DALYs per case.

The inputs in Table V lead to estimates of approximately $2.3 billion per year (55%, 28%, 14%, and 3% for HIGH, UMI, LMI, and LOW, respectively) to immunize the approximately 134,000,000 surviving infants annually (11%, 28%, 42%, 19% in HIGH, UMI, LMI, and LOW, respectively). The trends in coverage show the increasing shift toward the use of MRCV and increasing adoption of a second RI dose. This estimate includes costs paid by countries with or without the support of external donors, and we emphasize that the global benefits and costs of measles and rubella control will differ from estimates that consider a smaller scale.

Given the significantly higher costs per measles or rubella case than per dose of vaccine, our results suggest significant cost savings associated with investments in measles and rubella control and elimination, although future work will need to characterize the full benefits of prevention. The estimates in this

Table VIII. Inputs for Estimation of DALYs as a Function of Age, Sex, and Life Expectancy (LE) per Vaccine Dose and per Measles or Rubella Infection with Some Years of Productive Life Lost Due to Disability (YLD) Depending on (LE-Age) and Years of Life Lost Due to Premature Mortality (YLL) Depending on (LE-Age) and the Infection-Fatality Rate Reduction Factor (IFRRF)

	GBD 2010[92]				GBD 1990[93]			
Inputs for DALYs	LOW	LMI	UMI	HIGH	LOW	LMI	UMI	HIGH
Life Expectancy (2013)	62	66	74	79	62	66	74	79
Vaccine: per vaccine dose DALY = f(LE, age, sex)								
MCV, 0to4, YLD	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
MCV, 5to14, YLD	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
MCV, 15to44, YLD	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
MCV, 45plus, YLD	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
MCV, all ages, YLL * (LE-age) * IFRRF	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08
MRCV, 0to4, YLD	2E-05	2E-05	2E-05	1E-05	4E-05	4E-05	4E-05	4E-05
MRCV, 5to14, YLD	2E-05	2E-05	2E-05	1E-05	5E-05	4E-05	4E-05	4E-05
MRCV, 15to44 women, YLD	1E-04	1E-04	9E-05	3E-05	2E-04	2E-04	2E-04	2E-04
MRCV, 45plus women, YLD	1E-04	1E-04	9E-05	3E-05	2E-04	2E-04	2E-04	2E-04
MRCV, 15to44 women, YLD * (LE-age)	1E-04	1E-04	9E-05	3E-05	2E-04	2E-04	2E-04	2E-04
MRCV, 45plus women, YLD * (LE-age)	1E-04	1E-04	9E-05	3E-05	2E-04	2E-04	2E-04	2E-04
MRCV, all ages, YLL * (LE-age) * IFRRF	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08	3E-08
Measles: per infection DALY = f(LE, age)								
YLD, 0to4, constant	0.005	0.005	0.004	0.001	0.005	0.005	0.005	0.002
YLD, 5to14, constant	0.004	0.004	0.004	0.001	0.004	0.004	0.004	0.002
YLD, 15to44, constant	0.006	0.006	0.002	0.001	0.006	0.006	0.005	0.002
YLD, 45plus, constant	0.006	0.006	0.002	0.001	0.006	0.006	0.005	0.002
YLD, 0to4, * (LE-age)	4E-04	4E-04	0.005	0.007	7E-04	7E-04	6E-04	1E-04
YLD, 5to14, * (LE-age)	8E-05	8E-05	0.003	5E-05	8E-05	8E-05	7E-05	5E-05
YLD, 15to44, * (LE-age)	2E-04	2E-04	0.006	0.007	2E-04	2E-04	2E-04	1E-04
YLD, 45plus, * (LE-age)	3E-04	3E-04	0.006	0.007	3E-04	3E-04	3E-04	2E-04
YLL, 0to4, * (LE-age) * IFRRF	0.027	0.025	0.007	0.007	0.027	0.025	0.021	0.001
YLL, 5to14, * (LE-age) * IFRRF	0.019	0.017	0.005	4E-04	0.019	0.017	0.014	4E-04
YLL, 15to44, * (LE-age) * IFRRF	0.029	0.027	0.008	0.002	0.029	0.027	0.022	0.002
YLL, 45plus, * (LE-age) * IFRRF	0.029	0.027	0.008	0.002	0.029	0.027	0.022	0.002
YLL, 0to4, * (LE-age-9)	1E-04	1E-04	1E-04	8E-05	1E-04	1E-04	1E-04	8E-05
YLL, 5to14, * (LE-age-9)	5E-05	5E-05	5E-05	3E-05	5E-05	5E-05	5E-05	3E-05
YLL, 15to44, * (LE-age-9)	7E-05	7E-05	6E-05	3E-05	7E-05	7E-05	6E-05	3E-05
YLL, 45plus, * (LE-age-9)	7E-05	7E-05	6E-05	4E-05	7E-05	7E-05	6E-05	4E-05
Rubella: per infection DALY = f(LE, age, sex)								
YLD, Un15yrF	2E-04	2E-04	2E-04	2E-04	9E-04	9E-04	9E-04	9E-04
YLD, 15plusyrF	0.003	0.002	0.002	0.001	0.007	0.007	0.007	0.006
YLD, Un15yrM	2E-04	2E-04	2E-04	2E-04	9E-04	9E-04	9E-04	9E-04
YLD, 15plusyrM	4E-04	4E-04	4E-04	3E-04	0.001	0.001	0.001	0.001
YLD, Un15yrF * (LE-age)	0	0	0	0	0	0	0	0
YLD, 15plusyrF * (LE-age)	0.006	0.006	0.005	0.002	0.015	0.014	0.014	0.012
YLD, Un15yrM * (LE-age)	0	0	0	0	0	0	0	0
YLD, 15plusyrM * (LE-age)	6E-04	6E-04	5E-04	2E-04	0.001	0.001	0.001	0.001
YLL, Un15yrF * (LE-age)	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06
YLL, 15plusyrF * (LE-age)	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06
YLL, Un15yrM * (LE-age)	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06	2E-06
YLL, 15plusyrM * (LE-age)	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06	3E-06
CRS: per CRS case DALY = f(LE)								
YLL * LE	0.247	0.236	0.210	0.076	0.247	0.236	0.210	0.076
YLD * LE	0.225	0.223	0.218	0.168	0.382	0.385	0.391	0.404
Excess pregnancy loss: per MIP or RIP DALY = f(LE)								
YLL * LE	1	1	1	1	1	1	1	1
Pregnancy termination, 15 to 44F only DALY = YLD								
YLD, 15to44yrF	0.003	0.003	0.002	7E-04	0	0	0	0

Abbreviations: CRS, congenital rubella syndrome; DALY, disability-adjusted life year; GBD, global burden of disease; IFRRF, IFR reduction factor; LE, life expectancy; MIP, measles infection in pregnancy; RIP, rubella infection in pregnancy; VAE, vaccine adverse event; YLD, years of productive life lost due to disability; YLL, years of life lost due to premature mortality.

Table IX. DALY Estimates by Age (yr) of Vaccination or Infection for Both Global Burden of Disease Disability Weights and by Sex as Appropriate

		GBD 2010				GBD 1990			
Vaccine or Virus	Unit	LOW	LMI	UMI	HIGH	LOW	LMI	UMI	HIGH
MCV-DALY by age (yr)									
0	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
4	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
5	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
14	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
15	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
44	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
45	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
60	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
MRCV-DALY by sex, age (yr)—female									
0	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
4	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
5	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
14	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
15	per dose	0.005	0.006	0.006	0.002	0.011	0.012	0.013	0.011
44	per dose	0.002	0.002	0.003	9E-04	0.004	0.005	0.007	0.006
45	per dose	0.002	0.002	0.003	8E-04	0.004	0.005	0.006	0.006
60	per dose	3E-04	7E-04	0.001	5E-04	7E-04	0.002	0.003	0.003
MRCV-DALY by sex, age (yr)—male									
0	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
4	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
5	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
14	per dose	2E-05	2E-05	2E-05	1E-05	5E-05	5E-05	5E-05	4E-05
15	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
44	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
45	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
60	per dose	1E-05	1E-05	1E-05	1E-05	3E-05	3E-05	3E-05	3E-05
Measles-DALY by age (yr)									
0	per infection	1.15	1.31	1.40	0.11	1.17	1.33	1.42	0.11
4	per infection	1.08	1.23	1.33	0.11	1.09	1.25	1.34	0.11
5	per infection	0.72	0.82	0.88	0.03	0.72	0.82	0.88	0.04
14	per infection	0.61	0.70	0.77	0.03	0.61	0.70	0.77	0.03
15	per infection	0.92	1.07	1.18	0.10	0.92	1.07	1.18	0.10
44	per infection	0.36	0.46	0.60	0.06	0.36	0.46	0.60	0.06
45	per infection	0.34	0.44	0.59	0.06	0.34	0.44	0.59	0.06
60	per infection	0.04	0.13	0.29	0.03	0.04	0.13	0.29	0.04
Rubella-DALY by sex, age (yr)—female									
0	per infection	3E-04	3E-04	3E-04	4E-04	0.001	0.001	0.001	0.001
4	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	0.001	0.001	0.001
5	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	0.001	0.001	0.001
14	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	1E-03	0.001	0.001
15	per infection	0.28	0.29	0.31	0.15	0.69	0.74	0.84	0.80
44	per infection	0.11	0.13	0.16	0.08	0.27	0.32	0.43	0.44
45	per infection	0.10	0.12	0.15	0.08	0.25	0.31	0.41	0.43
60	per infection	0.01	0.04	0.08	0.04	0.04	0.09	0.20	0.24
Rubella-DALY by sex, age (yr)—male									
0	per infection	3E-04	3E-04	3E-04	4E-04	0.001	0.001	0.001	0.001
4	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	0.001	0.001	0.001
5	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	0.001	0.001	0.001
14	per infection	3E-04	3E-04	3E-04	3E-04	1E-03	1E-03	0.001	0.001
15	per infection	0.028	0.029	0.031	0.015	0.069	0.074	0.084	0.081
44	per infection	0.011	0.013	0.016	0.008	0.027	0.033	0.043	0.045
45	per infection	0.01	0.012	0.016	0.008	0.026	0.031	0.042	0.043
60	per infection	0.002	0.004	0.008	0.005	0.004	0.01	0.021	0.025
CRS-DALY	per CRS case	29	30	32	19	39	41	44	38
RIP or MIP-DALY	per RIP loss	62	66	74	79	62	66	74	79
Pregnancy termination, 15- to 44-yr female	per termination	0.003	0.003	0.002	7E-04	0	0	0	0

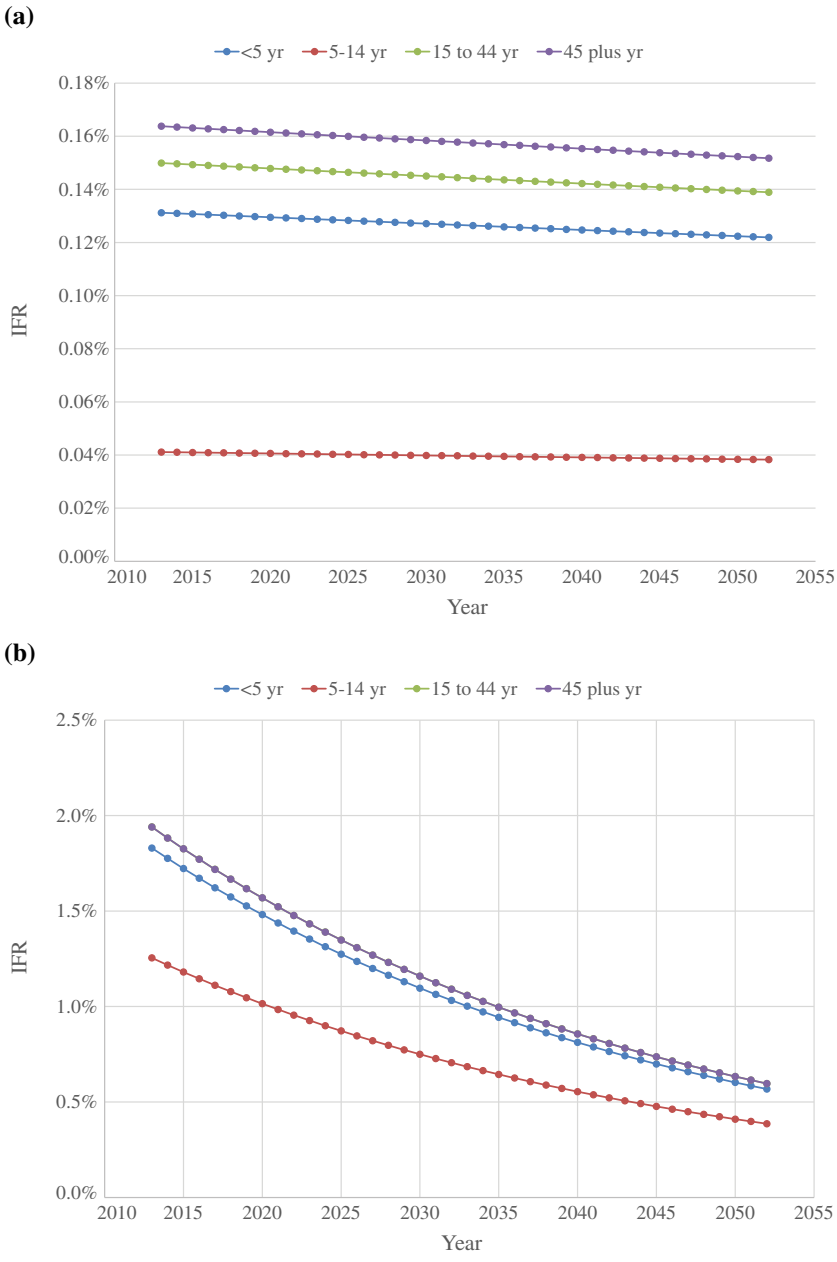

Fig. 2. Trends in under-five-year-old infection-fatality ratios for (a) optimal and (b) minimal treatment.

analysis should provide inputs for future economic analyses for measles and rubella interventions.

4. DISCUSSION

Managing measles and rubella requires ongoing financial commitments to cover the costs associated with prevention (i.e., primarily immunization) and treatment of any cases that occur. As all countries increasingly adopt the use of rubella immunization in their national programs, some additional cost reductions may occur due to the increased economy of scale for the fewer vaccine formulations used. Our estimates account for a much more complete clinical picture of both measles and rubella than prior models. This should help to better ensure full cost accounting of the costs and benefits of measles and rubella control, elimination, and eradication. Characterization of the costs, particularly for rubella, may also motivate national efforts to assess the

Table X. Expected Costs from Adverse Health Outcomes per Vaccine Dose or per Measles or Rubella Infection by World Bank Income Level With and Without Home Care Costs

		Without Home Care Costs				With Home Care Costs			
Total Cost	Unit	LOW	LMI	UMI	HIGH	LOW	LMI	UMI	HIGH
Vaccine adverse events									
MCV	per dose	$0.002	$0.11	$0.35	$1.51	$0.003	$0.11	$0.36	$1.55
MRCV, 0 to 14 yr	per dose	$0.002	$0.11	$0.36	$1.54	$0.003	$0.11	$0.37	$1.58
MRCV, females ≥15 yr	per dose	$0.103	$0.86	$2.60	$10.94	$0.10	$0.87	$2.61	$10.99
MRCV, males ≥15 yr	per dose	$0.002	$0.11	$0.35	$1.51	$0.003	$0.11	$0.36	$1.55
Measles infections									
0 to 4 yr	per infection	$4.91	$101	$329	$1,435	$17	$156	$483	$2,062
5 to 14 yr	per infection	$4.41	$40	$124	$534	$14	$95	$281	$1,183
15 to 44 yr	per infection	$5.54	$66	$210	$912	$15	$119	$364	$1,548
≥45 yr	per infection	$5.57	$81	$263	$1,155	$15	$134	$417	$1,789
Rubella infections									
Females, 0 to 14 yr	per infection	$0.25	$7	$22	$96	$5	$35	$103	$428
Females ≥15 yr	per infection	$42	$318	$948	$3,982	$46	$340	$1,013	$4,250
Males, 0 to 14 yr	per infection	$0.25	$7	$22	$96	$5.49	$35	$103	$428
Males ≥15 yr	per infection	$4.39	$38	$113	$479	$9.54	$65	$192	$805
CRS	per case	$11,255	$75,409	$222,874	$933,324	$11,266	$75,467	$223,040	$934,000
Pregnancy loss	per MIP or RIP	$1	$61	$199	$863	$10	$110	$337	$1,433

hidden costs of rubella in areas yet to introduce MRCVs into their immunization schedules.

Historically, most individuals became infected with endemic measles and rubella viruses at young ages and consequently the relatively high costs and high DALY losses associated with infections in adults remained relatively rare. However, rubella outbreaks occur in epidemic cycles, with relatively long interepidemic periods (e.g., 5–7 years), such that some individuals became infected as adults, leading to some burden associated with CRS. As long as measles and rubella viruses circulate, any individuals lacking immunological protection remain at risk for infection, and getting infected at a relatively older age leads to worse health and financial outcomes. Vaccination represents the best option with the lowest expected costs and DALY losses.

Our estimates reflect our review of the limited available evidence. Remarkably, while the literature includes a very large number of studies, the data remain very limited for low- and middle-income countries, and the extent to which these countries may further increase or decrease their levels of prevention and treatment remains uncertain. Our efforts to characterize DALYs and costs by income level and to stratify these by age and sex, as appropriate, represent the first attempt to develop these inputs for a global economic analysis for measles and rubella. We hope that this analysis provides a starting point for further improvements in synthesizing the available evidence and motivating the collection of additional evidence that will lead to improved estimates. We found large differences in the DALY estimates based on the two available sets of disability weights, and note that uncertainties remain with respect to appropriate valuation of adverse health outcomes.

Economic analyses can play a critical role with respect to informing individual and societal decisions about immunization. Our results clearly show the much higher expected costs and worse health outcomes associated with measles or rubella disease compared to getting the vaccine.

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REFERENCES

1. Decade of Vaccines. Global Vaccine Action Plan. Available at: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/, Accessed April 12, 2015.
2. Thompson KM, Tebbens RJD. Using system dynamics to develop policies that matter: Global management of poliomyelitis and beyond. System Dynamics Review, 2008; 24(4):433–449.
3. Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, Johns B, Hutubessy R, Salama P, Okwo-Bele JM. Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006–2015. Bulletin of the World Health Organization, 2008; 86(1):27–39.
4. Brenzel L, Young D, Walker DG. Costs and financing of routine immunization: Approach and selected findings of a multi-country study (EPIC). Vaccine, 2015; 33:A13–A20.
5. World Health Organization. Cost Effectiveness and Strategic Planning (WHO-CHOICE). Available at: http://www.who.int/choice/cost-effectiveness/en/, Accessed May 17, 2014.
6. Johns B, Baltussen R, Hutubessy R. Programme costs in the economic evaluation of health interventions. Cost Effectiveness and Resource Allocation, 2003; 1(1):1.
7. Gandhi G, Lydon P. Updating the evidence base on the operational costs of supplementary immunization activities for current and future accelerated disease control, elimination and eradication efforts. BMC Public Health, 2014; 14:16.
8. Thompson KM, Dabbagh A, Strebel PM, Perry R, Gacic-Dobo M, Cochi SL, Cairns L, Reef S. National and global options for managing the risks of measles and rubella. Journal of Vaccines and Vaccination, 2012; 3:165. doi: 10.4172/2157-7560.1000165.
9. Thompson KM, Duintjer Tebbens RJ. Development of investment cases for globally-coordinated management of infectious diseases. Journal of Vaccines and Vaccination, 2012; 3:164. doi: 10.4172/2157-7560.1000164.
10. Thompson KM, Strebel PM, Dabbagh A, Cherian T, Cochi SL. Enabling implementation of the global vaccine action plan: Developing investment cases to achieve targets for measles and rubella prevention. Vaccine, 2013; 31: Suppl 2:B149–B156.
11. Thompson KM, Odahowski CL. Systematic review of health economic analyses of measles and rubella immunization interventions. Risk Analysis, 2014; 36(7):1297–1314.
12. Beutels P, VanDamme P, VanCasteren V, Gay NJ, DeSchrijver K, Meheus A. The difficult quest for data on "vanishing" vaccine-preventable infections in Europe: The case of measles in Flanders (Belgium). Vaccine, 2002; 20(29-30):3551–3559.
13. Carabin H, Edmunds WJ, Kou U, vanden Hof S, Nguyen VH. The average cost of measles cases and adverse events following vaccination in industrialised countries. BMC Public Health, 2002; 2:22.
14. Carabin H, Edmunds WJ, Gyldmark M, Beutels P, Levy-Bruhl D, Salo H, Griffiths UK. The cost of measles in industrialised countries. Vaccine, 2003; 21(27-30):4167–4177.
15. Wendorf KA, Kay M, Ortega-Sanchez IR, Ismael R, Munn M, Duchin JL. Cost of measles containment in an ambulatory pediatric clinic. Pediatric Infectious Disease Journal, 2015;34(6):589–593.
16. Al-Awaidy S, Griffiths UK, Nwar HM, Bawikar S, Al-Aisiri MS, Khandekar R, Mohammad AJ, Robertson SE. Costs of congenital rubella syndrome (CRS) in Oman: Evidence based on long-term follow-up of 43 children. Vaccine, 2006; 24(40-41):6437–6445.
17. Lugner AK, Mollema L, Ruijs WL, Hahne SJ. A cost-utility analysis of antenatal screening to prevent congenital rubella syndrome. Epidemiology & Infection, 2010; 138(8):1172–1184.
18. Duintjer Tebbens RJ, Sangrujee N, Thompson KM. The costs of polio risk management policies after eradication. Risk Analysis, 2006; 26(6):1507–1531.
19. World Bank. New Country Classifications, World Bank Income Levels. Available at: http://data.worldbank.org/news/new-country-classifications, Accessed March 3, 2014.
20. Simons EA, Reef SE, Cooper LZ, Zimmerman L, Thompson KM. Systematic review of the manifestations of congenital rubella syndrome in infants and characterization of disability-adjusted life years (DALYs). Risk Analysis, 2014; 36(7):1332–1356.
21. Centers for Disease Control and Prevention. Measles Surveillance, Report 10 1973–1976. Atlanta, GA: US Centers for Disease Control, 1977.
22. Ewert DP, Westman S, Frederick PD, Waterman SH. Measles reporting completeness during a community-wide epidemic in inner-city Los Angeles. Public Health Reports, 1995; 110(2):161–165.
23. Clarkson JA, Fine PE. The efficiency of measles and pertussis notification in England and Wales. International Journal of Epidemiology, 1985; 14(1):153–168.
24. Davis SF, Strebel PM, Atkinson WL, Markowitz LE, Sutter RW, Scanlon KS, Friedman S, Hadler SC. Reporting efficiency during a measles outbreak in New York City, 1991. American Journal of Public Health, 1993; 83(7):1011–1015.
25. Ewert DP, Frederick PD, Run GH, Mascola L. The reporting efficiency of measles by hospitals in Los Angeles County, 1986 and 1989. American Journal of Public Health, 1994; 84(5):868–869.
26. Cochi SL, Edmonds LE, Dyer K, Greaves WL, Marks JS, Rovira EZ, Preblud SR, Orenstein WA. Congenital rubella syndrome in the United States, 1970–1985. On the verge of elimination. American Journal of Epidemiology, 1989; 129(2):349–361.
27. Krugman S, Giles JP, Jacobs AM, Friedman H. Studies with live attenuated measles-virus vaccine. Comparative clinical, antigenic, and prophylactic effects after inoculation with and without gamma-globulin. American Journal of Diseases of Children, 1962; 103:353–363.
28. Krugman S, Giles JP, Friedman H, Stone S. Studies on immunity to measles. Journal of Pediatrics, 1965; 66(3):471–488.
29. Miller DL. Frequency of complications of measles, 1963. Report on a national inquiry by the Public Health Laboratory Service in collaboration with the Society of Medical Officers of Health. British Medical Journal, 1964; 2(5401): 75–78.
30. Hatziandreu EJ, Brown RE, Halpern MT. A cost-benefit analysis of the measles-mumps-rubella (MMR) vaccine. In Report Prepared for the National Immunization Program, Centers for Disease Control and Prevention. Arlington, VA: Batelle, 1994.
31. Perry RT, Halsey NA. The clinical significance of measles: A review. Journal of Infectious Diseases, 2004; 189:S4–S16.
32. Zhou F, Reef S, Massoudi M, Papania MJ, Yusuf HR, Bardenheier B, Zimmerman L, McCauley MM. An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. Journal of Infectious Diseases, 2004; 189 Suppl 1:S131–S145.
33. Filia A, Brenna A, Pana A, Cavallaro GM, Massari M, Ciofi degli Atti ML. Health burden and economic impact of measles-related hospitalizations in Italy in 2002–2003. BMC Public Health, 2007; 7:169.
34. Yasunaga H, Shi Y, Takeuchi M, Horiguchi H, Hashimoto H, Matsuda S, Ohe K. Measles-related hospitalizations and complications in Japan, 2007–2008. Internal Medicine, 2010; 49(18):1965–1970.

35. Antona D, Levy-Bruhl D, Baudon C, Freymuth F, Lamy M, Maine C, Floret D, Parent du Chatelet I. Measles elimination efforts and 2008–2011 outbreak, France. Emerging Infectious Diseases, 2013; 19(3):357–364.
36. Godoy P, Dominguez A, Alvarez J, Camps N, Jansa JM, Minguell S, Salleras L. Measles epidemiology in Catalonia (Spain): Implications for a regional vaccination programme. International Journal of Epidemiology, 1999; 28(3):558–562.
37. White CC, Koplan JP, Orenstein WA. Benefits, risks and costs of immunization for measles, mumps and rubella. American Journal of Public Health, 1985; 75(7):739–744.
38. Koplan JP, White CC. An update on the benefits and costs of measles and rubella immunization. Pp. 117–127 in Gruenberg EM, Lewis C, Goldston S (eds). Immunizing Against Mental Disorders: Progress in the Conquest of Measles and Rubella. Oxford, UK: Oxford University Press, 1986.
39. Pelletier L, Chung P, Duclos P, Manga P, Scott J. A benefit-cost analysis of two-dose measles immunization in Canada. Vaccine, 1998; 16(9-10):989–996.
40. Horta-Barbosa L, Fuccillo DA, London WT, Jabbour JT, Zeman W, Sever JL. Isolation of measles virus from brain cell cultures of two patients with subacute sclerosing panencephalitis. Proceedings of the Society for Experimental Biology and Medicine, 1969; 132(1):272–277.
41. Modlin JF, Halsey NA, Eddins DL, Conrad JL, Jabbour JT, Chien L, Robinson H. Epidemiology of subacute sclerosing panencephalitis. Journal of Pediatrics, 1979; 94(2):231–236.
42. Modlin JF, Jabbour JT, Witte JJ, Halsey NA. Epidemiologic studies of measles, measles vaccine, and subacute sclerosing panencephalitis. Pediatrics, 1977; 59(4):505–512.
43. Farrington CP. Subacute sclerosing panencephalitis in England and Wales: Transient effects and risk estimates. Statistics in Medicine, 1991; 10(11):1733–1744.
44. Miller C, Farrington CP, Harbert K. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970–1989. International Journal of Epidemiology, 1992; 21(5):998–1006.
45. Miller C, Andrews NR M., Munro H, Jin L, Miller E. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990–2002. Archives of Disease in Childhood, 2004; 89(12):1145–1148.
46. Bellini WJ, Rota JS, Lowe LE, Katz RS, Dyken PR, Zaki SR, Shieh WJ, Rota PA. Subacute sclerosing panencephalitis: More cases of this fatal disease are prevented by measles immunization than was previously recognized. Journal of Infectious Diseases, 2005; 192(10):1686–1693.
47. Engelhardt SJ, Halsey NA, Eddins DL, Hinman AR. Measles mortality in the United States 1971–1975. American Journal of Public Health, 1980; 70(11):1166–1169.
48. Gindler J, Tinker S, Markowitz L, Atkinson W, Dales L, Papania MJ. Acute measles mortality in the United States, 1987–2002. Journal of Infectious Diseases, 2004;189:S69–S77.
49. Wolfson LJ, Garis RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: A comprehensive review of community-based studies. International Journal of Epidemiology, 2009; 38(1):192–205.
50. Thompson KM, Simons EA, Badizadegan K, Reef SE, Cooper LZ. Characterization of the risks of adverse outcomes following rubella infection in pregnancy. Risk Analysis, 2014; 36(7):1315–1331.
51. Semba RD, Bloem MW. Measles blindness. Survey of Ophthalmology, 2004; 49(2):243–255.
52. Qaisar I, Ahmad A, Ahmad F, ullah Mazhar A. Comparison of measles complications in well-nourished and malnourished children. Journal of Ayub Medical College, 2009; 21(2):30–32.
53. Dabral M. Cost-effectiveness of supplementary immunization for measles in India. Indian Pediatrics, 2009; 46(11):957–962.
54. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in Blantyre, Malawi: Analyses of passive surveillance data from 1996 to 1998. Epidemiology and Infection, 2002; 129(2):361–369.
55. Schoenbaum SC, Hyde JN, Bartoshesky L, Crampton K. Benefit-cost analysis of rubella vaccination policy. New England Journal of Medicine, 1976; 294(6):306–310.
56. Zhou F, Reef S, Massoudi M, Papania MJ, Yusuf HR, Bardenheier B, Zimmerman L, McCauley MM. An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. Journal of Infectious Diseases, 2004; 189:S131–S145.
57. Riviere M, Tretiak R, Levinton C, Fitzsimon C, Leclerc C. Economic benefits of a routine second dose of combined measles, mumps and rubella vaccine in Canada. Canadian Journal of Infectious Diseases, 1997; 8(5):257–264.
58. Pelletier L, Chung P, Duclos P, Manga P, Scott J. A benefit-cost analysis of two-dose measles immunization in Canada. Vaccine, 1998; 16(9-10):989–996.
59. Bae GR, Choe YJ, Go UY, Kim YI, Lee JK. Economic analysis of measles elimination program in the Republic of Korea, 2001: A cost benefit analysis study. Vaccine, 2013; 31(24):2661–2666.
60. Sencer DJ, Axnick NW. Utilization of cost/benefit analysis in planning prevention programs. Acta Medica Scandinavica, 1975; 197(S576):123–128.
61. Tingle AJ, Allen M, Petty RE, Kettyls GD, Chantler JK. Rubella-associated arthritis. I. Comparative study of joint manifestations associated with natural rubella infection and RA 27/3 rubella immunisation. Annals of the Rheumatic Diseases, 1986; 45(2):110–114.
62. Bloch AB, Orenstein WA, Stetler HC, Wassilak SG, Amler RW, Bart KJ, Kirby CD, Hinman AR. Health impact of measles vaccination in the United States. Pediatrics, 1985; 76(4):524–532.
63. Koplan JP. Benefits, risks and costs of immunization programmes. Ciba Found Symposium, 1985; 110:55–68.
64. Berger SAG, GM; Slater PE Cost-benefit analysis of routine mumps and rubella vaccination for Israeli infants. Israel Journal of Medical Sciences, 1990; 26(2):74–80.
65. Acharya A, Diaz-Ortega JL, Tambini G, Quadros C, Arita I. Cost-effectiveness of measles elimination in Latin America and the Caribbean: A prospective analysis. Vaccine, 2002; 20(27-28):3332–3341.
66. Dayan GH, Cairns L, Sangrujee N, Mtonga A, Nguyen V, Strebel P. Cost-effectiveness of three different vaccination strategies against measles in Zambian children. Vaccine, 2004; 22(3-4):475–484.
67. Uzicanin A, Zhou FJ, Eggers R, Webb E, Strebel P. Economic analysis of the 1996–1997 mass measles immunization campaigns in South Africa. Vaccine, 2004; 22(25-26):3419–3426.
68. Institute of Medicine Immunization Safety Review C. Adverse Effects of Vaccines: Evidence and Causality. Washington, DC: National Academy Press, 2012.
69. Makela A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics, 2002; 110(5):957–963.
70. Institute of Medicine Vaccine Safety Committee. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Washington, DC: National Academy Press, 1994.
71. Nieminen U, Peltola H, Syrjala MT, Makipernaa A, Kekomaki R. Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23 patients. Acta Paediatrica, 1993; 82(3):267–270.
72. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. American Journal of Public Health, 1995; 85(12):1706–1709.

73. Beeler J, Varricchio F, Wise R. Thrombocytopenia after immunization with measles vaccines: Review of the vaccine adverse events reporting system (1990 to 1994). Pediatric Infectious Disease Journal, 1996; 15(1):88–90.
74. Centers for Disease Control and Prevention (CDC). Department of Health and Human Services (DHHS), Public Health Service (PHS), Food and Drug Administration (FDA)/CDC, Vaccine Adverse Event Reporting System (VAERS), 2015. Available at: http://wonder.cdc.gov/wonder/help/vaers.html, Accessed March 5, 2015.
75. Chu Y-W, Korb J, Sakamoto KM. Idiopathic thrombocytopenic purpura. Pediatrics in Review, 2000; 21(3):95–104.
76. Nationwide campaign for vaccination of adults against rubella and measles—Costa Rica, 2001. Morbidity and Mortality Weekly Report, 2001; 50(44):976–979.
77. Weibel RE, Benor DE. Chronic arthropathy and musculoskeletal symptoms associated with rubella vaccines—A review of 124 claims submitted to the National Vaccine Injury Compensation Program. Arthritis and Rheumatology, 1996; 39(9):1529–1534.
78. Enders G. Rubella antibody titers in vaccinated and nonvaccinated women and results of vaccination during pregnancy. Reviews of Infectious Diseases, 1985; 7 Suppl 1:S103–S107.
79. Rubella vaccination during pregnancy—United States, 1971–1988. Morbidity and Mortality Weekly Report (MMWR), 1989; 38(17):289–293.
80. Burgess MA. Rubella vaccination just before or during pregnancy. Medical Journal of Australia, 1990; 152(10):507–508.
81. Bar-Oz B, Levichek Z, Moretti ME, Mah C, Andreou S, Koren G. Pregnancy outcome following rubella vaccination: A prospective controlled study. American Journal of Medical Genetics Part A, 2004; 130A(1):52–54.
82. Badilla X, Morice A, Avila-Aguero ML, Saenz E, Cerda I, Reef S, Castillo-Solorzano C. Fetal risk associated with rubella vaccination during pregnancy. Pediatric Infectious Disease Journal, 2007; 26(9):830–835.
83. Castillo-Solorzano C, Reef SE, Morice A, Vascones N, Chevez AE, Castalia-Soares R, Torres C, Vizzotti C, Ruiz Matus C. Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001–2008. Journal of Infectious Diseases, 2011; 204 Suppl 2:S713–S717.
84. World Health Organization. WHO guidelines for epidemic preparedness and response to measles outbreaks. Report WHO/CDS/CSR/ISR/99.1. Geneva, Switzerland, May, 1999.
85. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. New England Journal of Medicine, 1990; 323(3):160–164.
86. Huiming YM, Chaomin WM, Meng M. Vitamin A for treating measles in children. Cochrane Database of Systematic Reviews, 2005(4):23.
87. Kabra SK, Lodha R, Hilton DJ. Antibiotics for preventing complications in children with measles. Cochrane Database of Systematic Reviews, 2008(3):38 doi: 10.1002/14651858.CD001477.pub3.
88. Garly ML, Bale C, Martins CL, Whittle HC, Nielsen J, Lisse IM, Aaby P. Prophylactic antibiotics to prevent pneumonia and other complications after measles: Community based randomised double blind placebo controlled trial in Guinea-Bissau. British Medical Journal, 2006; 333(7581):1245–1247.
89. Bishai D, Johns B, Lefevre A, Nair D, Simons E, Dabbagh A. Measles eradication versus measles control: An economic analysis. Journal of Vaccines and Vaccination, 2012. Available at: http://dx.doi.org/10.4172/2157-7560.S3-002.
90. Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, Strebel P. Assessment of the 2010 global measles mortality reduction goal: Results from a model of surveillance data. Lancet, 2012; 379(9832):2173–2178.
91. World Bank. Mortality Rate, Under-5 per 1000 Live Births. Available at: http://data.worldbank.org/indicator/SH.DYN.MORT, Accessed February 19, 2015.
92. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Bin Abdulhak A, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Diaz-Torne C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, Richardson K, Room R, Saha S, Sampson U, Sanchez-Riera L, Segui-Gomez M, Shahraz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, vander Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng ZJ, Murray CJ, Jonas JB. Common values in assessing health outcomes from disease and injury: Disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859):2129–2143, S1–S26.
93. Murray CJL, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, MA: Harvard University Press, 1996.
94. World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. Report No.: WHO/IVB/0814. Geneva: Initiative for Vaccine Research, Department of Immunization, Vaccine, and Biologicals, December 2008.
95. United Nations Population Division. World Population Prospects: The 2012 Revision. Available at: http://esa.un.org/unpd/wpp/index.htm, Accessed September 11, 2013.
96. World Bank. World Databank, World Development Indicators, GNI per Capita, Atlas Method (Current US$). Available at: http://data.worldbank.org/indicator/NY.GNP.PCAP.CD, Accessed December 23, 2014.
97. Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassilak SG, Linkins J, Sutter RW, Aylward RB, Thompson KM. Economic analysis of the global polio eradication initiative. Vaccine, 2010; 29(2):334–343.
98. Wallace AS, Masresha BG, Grant G, Goodson JL, Birhane H, Abraham M, Endailalu TB, Letamo Y, Petu A, Vijayraghavan M. Evaluation of economic costs of a measles outbreak and outbreak response activities in Keffa zone, Ethiopia. Vaccine, 2014; 32(35)4505–4514.
99. Ginsberg GM, Tulchinsky TH. Costs and benefits of a second measles inoculation of children in Israel, the West Bank, and Gaza. Journal of Epidemiology and Community Health, 1990; 44(4):274–280.
100. Yarrabolu TR, Rao PS. Transcatheter closure of patent ductus arteriosus. Pediatrics and Therapeutics, 2012. Available at: http://dx.doi.org/10.4172/2161-0665.S5-005:S5.

101. Saxena A. Congenital heart disease in India: A status report. Indian Journal of Pediatrics, 2005; 72(7):595–598.
102. Marseille E. Cost-effectiveness of cataract surgery in a public health eye care programme in Nepal. Bulletin of the World Health Organization, 1996; 74(3):319–324.
103. Singh AJ, Garner P, Floyd K. Cost-effectiveness of public-funded options for cataract surgery in Mysore, India. Lancet, 2000; 355(9199):180–184.
104. Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, Hoyle M, Liu Z, Price A, Stein K. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: A systematic review and economic model. Health Technology Assessment, 2009; 13(44):1–330.
105. Bond M, Elston J, Mealing S, Anderson R, Weiner G, Taylor RS, Liu Z, Stein K. Effectiveness of multi-channel unilateral cochlear implants for profoundly deaf children: A systematic review. Clinical Otolaryngology, 2009; 34(3):199–211.
106. Summerfield AQ, Lovett RE, Bellenger H, Batten G. Estimates of the cost-effectiveness of pediatric bilateral cochlear implantation. Ear and Hearing, 2010; 31(5):611–624.
107. Turchetti G, Bellelli S, Palla I, Forli F. Systematic review of the scientific literature on the economic evaluation of cochlear implants in paediatric patients. Acta Otorhinolaryngologica Italica, 2011; 31(5):311–318.
108. Forli F, Arslan E, Bellelli S, Burdo S, Mancini P, Martini A, Miccoli M, Quaranta N, Berrettini S. Systematic review of the literature on the clinical effectiveness of the cochlear implant procedure in paediatric patients. Acta Otorhinolaryngologica Italica, 2011; 31(5):281–298.
109. Garg S, Singh R, Chadha S, Agarwal AK. Cochlear implantation in India: A public health perspective. Indian Journal of Medical Sciences, 2011; 65(3):116–120.
110. Saunders J, Barrs D. Cochlear implantation in developing countries as humanitarian service: Physician attitudes and recommendations for best practice. Otolaryngology Head and Neck Surgery, 2011; 145(1):74–79.
111. Kanchanalarp C, Cheewaruangroj W, Thawin C, Lertsukprasert K. Indication and surgical consideration of cochlear implantation at Ramathibodi hospital. Journal of the Medical Association of Thailand, 2006; 89(8):1171–1177.
112. Francis HW, Koch ME, Wyatt J, Niparko JK. Trends in educational placement and cost-benefit considerations in children with cochlear implants. Archives of Otolaryngology–Head & Neck Surgery, 1999; 125(5):499–505.
113. Cheng AK, Rubin HR, Powe NR, Mellon NK, Francis HW, Niparko JK. Cost-utility analysis of the cochlear implant in children. Journal of the American Medical Association, 2000; 284(7):850–856.
114. Zheng Y-F, Pan C-W, Chay J, Wong TY, Finkelstein E, Saw S-M. The economic cost of myopia in adults aged over 40 years in Singapore. Investigative Ophthalmology & Visual Science, 2013; 54(12):7532–7537.
115. Baltussen R, Naus J, Limburg H. Cost-effectiveness of screening and correcting refractive errors in school children in Africa, Asia, America and Europe. Health Policy, 2008; 89(2):201–215.
116. Thompson KM, Odahowski CL, Goodson JL, Reef SE, Perry RT. Synthesis of evidence to characterize national historical measles and rubella exposure and immunization histories. Risk Analysis, 2015; 36(7):1427–1458.
117. Smith G, Michelson J, Singh R, Dabbagh A, Hoekstra E, vanden Ent M, Mallya A. Is there enough vaccine to eradicate measles? An integrated analysis of measles-containing vaccine supply and demand. Journal of Infectious Diseases, 2011; 204 Suppl 1:S62–S70.
118. UNICEF. Supplies and Logistics: Vaccine Price Data 2015. Available at: http://www.unicef.org/supply/index_57476.html, Accessed April 10, 2015.
119. Pan American Health Organization. PAHO Revolving Fund. Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=1864&Itemid=4135&lang=en, Accessed April 10, 2015.
120. Chen SY, Anderson S, Kutty PK, Lugo F, McDonald M, Rota PA, Ortega-Sanchez IR, Komatsu K, Armstrong GL, Sunenshine R, Seward JF. Health care-associated measles outbreak in the United States after an importation: Challenges and economic impact. Journal of Infectious Diseases, 2011; 203(11):1517–1525.
121. Takahashi K, Ohkusa Y, Kim JY. The economic disease burden of measles in Japan and a benefit cost analysis of vaccination, a retrospective study. BMC Health Services Research, 2011; 11:254.
122. Centers for Disease Control and Prevention. Vaccines for Children Program, Vaccine Price List, 2015. Available at: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/, Accessed April 10, 2015.
123. Zhou F, Shefer A, Wenger J, Messonnier M, Wang LY, Lopez A, Moore M, Murphy TV, Cortese M, Rodewald L. Economic evaluation of the routine childhood immunization program in the United States, 2009. Pediatrics, 2014; 133(4):577–585.
124. Dayan GH, Cairns L, Sangrujee N, Mtonga A, Nguyen V, Strebel P. Cost-effectiveness of three different vaccination strategies against measles in Zambian children. Vaccine, 2004; 22(3-4):475–484.
125. Drain PK, Nelson CM, Lloyd JS. Single-dose versus multidose vaccine vials for immunization programmes in developing countries. Bulletin of the World Health Organization, 2003; 81(10):726–731.
126. Lee BY, Norman BA, Assi TM, Chen SI, Bailey RR, Rajgopal J, Brown ST, Wiringa AE, Burke DS. Single versus multi-dose vaccine vials: An economic computational model. Vaccine, 2010; 28(32):5292–5300.
127. Lee BY, Assi TM, Rookkapan K, Connor DL, Rajgopal J, Sornsrivichai V, Brown ST, Welling JS, Norman BA, Chen SI, Bailey RR, Wiringa AE, Wateska AR, Jana A, VanPanhuis WG, Burke DS. Replacing the measles ten-dose vaccine presentation with the single-dose presentation in Thailand. Vaccine, 2011; 29(21):3811–3817.
128. Wichmann O, Siedler A, Sagebiel D, Hellenbrand W, Santibanez S, Mankertz A, Vogt G, Treeck U, Krause G. Further efforts needed to achieve measles elimination in Germany: Results of an outbreak investigation. Bulletin of the World Health Organization, 2009; 87(2):108–115.
129. Ortega-Sanchez IR, Vijayaraghavan M, Barskey AE, Wallace GS. The economic burden of sixteen measles outbreaks on United States public health departments in 2011. Vaccine, 2014; 32:1311–1317.
130. World Health Organization. Retrospective Measles Data on Supplementary Immunization Activities 2000–2014. Available at: http://www.who.int/entity/immunization/monitoring_surveillance/data/Summary_Measles_SIAs_2000_2014_Nov2014.xls?ua=1, Accessed April 21, 2015.
131. Measles & Rubella Initiative. Financial Resource Requirements for Measles and Rubella Elimination, 2014. Available at: http://www.measlesrubellainitiative.org/wp-content/uploads/2014/08/MRI-Financial-Resources-Requirement-Report.pdf, Accessed April 4, 2015.
132. Goodson JL, Chu SY, Rota PA, Moss WJ, Featherstone DA, Vijayaraghavan M, Thompson KM, Martin R, Reef S, Strebel PM. Research priorities for global measles and rubella control and eradication. Vaccine, 2012; 30(32):4709–4716.

133. Barau I, Zubairu M, Mwanza MN, Seaman VY. Improving polio vaccination coverage in Nigeria through the use of geographic information system technology. Journal of Infectious Diseases, 2014; 210 Suppl 1:S102–S110.
134. Thompson KM, Logan GE, Research Team from Florida SHOTS™. Characterization of heterogeneity in childhood immunization coverage in central Florida using immunization registry data. Risk Analysis, 2015; 36(7):1418–1426.
135. Lieu TA, Ray GT, Klein NP, Chung C, Kulldorff M. Geographic clusters in underimmunization and vaccine refusal. Pediatrics, 2015; 135(2):280–289.
136. World Health Organization. WHO Vaccine-Preventable Diseases: Monitoring System. 2014 Global summary Time Series of Coverage. Available at: http://www.who.int/entity/immunization/monitoring_surveillance/data/coverage_estimates_series.xls?ua=1, Accessed July 15, 2014.
137. World Health Organization. WHO Vaccine-Preventable Diseases: Monitoring System. 2014 Global Summary Schedules. Available at: http://www.who.int/entity/immunization/monitoring_surveillance/data/schedule_data.xls?ua=1, Accessed July 15, 2014.

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Modeling the Transmission of Measles and Rubella to Support Global Management Policy Analyses and Eradication Investment Cases

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Policy makers responsible for managing measles and rubella immunization programs currently use a wide range of different vaccines formulations and immunization schedules. With endemic measles and rubella transmission interrupted in the region of the Americas, all five other regions of the World Health Organization (WHO) targeting the elimination of measles transmission by 2020, and increasing adoption of rubella vaccine globally, integrated dynamic disease, risk, decision, and economic models can help national, regional, and global health leaders manage measles and rubella population immunity. Despite hundreds of publications describing models for measles or rubella and decades of use of vaccines that contain both antigens (e.g., measles, mumps, and rubella vaccine or MMR), no transmission models for measles and rubella exist to support global policy analyses. We describe the development of a dynamic disease model for measles and rubella transmission, which we apply to 180 WHO member states and three other areas (Puerto Rico, Hong Kong, and Macao) representing >99.5% of the global population in 2013. The model accounts for seasonality, age-heterogeneous mixing, and the potential existence of preferentially mixing undervaccinated subpopulations, which create heterogeneity in immunization coverage that impacts transmission. Using our transmission model with the best available information about routine, supplemental, and outbreak response immunization, we characterize the complex transmission dynamics for measles and rubella historically to compare the results with available incidence and serological data. We show the results from several countries that represent diverse epidemiological situations to demonstrate the performance of the model. The model suggests relatively high measles and rubella control costs of approximately $3 billion annually for vaccination based on 2013 estimates, but still leads to approximately 17 million disability-adjusted life years lost with associated costs for treatment, home care, and productivity loss costs of approximately $4, $3, and $47 billion annually, respectively. Combined with vaccination and other financial cost estimates, our estimates imply that the eradication of measles and rubella could save at least $10 billion per year, even without considering the benefits of preventing lost productivity and potential savings from reductions in vaccination. The model should provide a useful tool for exploring the health and economic outcomes of prospective opportunities to manage measles and rubella. Improving the quality of data available to support decision making and modeling should represent a priority as countries work toward measles and rubella goals.

KEY WORDS: Control; disease outbreaks; dynamic modeling; eradication; measles; rubella

1. INTRODUCTION

Policy makers responsible for managing measles and rubella immunization programs currently use a wide range of different vaccine formulations and immunization schedules for routine immunization (RI)

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and some countries increase their population immunity using periodic supplemental immunization activities (SIAs), including preventive SIAs (pSIAs).[1] When outbreaks occur, some countries conduct outbreak response immunization (ORI) (i.e., outbreak SIAs [oSIAs]) and/or other public health interventions (e.g., contact tracing and isolation). Existing models for measles and rubella consider a wide range of different assumptions about the nature of immunity, transmission, population mixing, seasonality, heterogeneity, and other factors applied to real and hypothetical populations on different geographic scales.[2] Within the last 15 years, analysts demonstrated the importance of using dynamic disease models to appropriately characterize the economic and policy impacts of interventions on population immunity for transmissible infectious diseases.[3–5] The World Health Organization (WHO) recognized the use of integrated dynamic disease and economic models as the preferred approach for policy modeling of vaccine-preventable diseases.[6]

Despite the large number of prior dynamic disease transmission models for measles and/or rubella,[2] only two dynamic models included global-scale analyses for measles[7,8] and neither of these demonstrated the ability to replicate historical epidemiology. A statistical model used to characterize the historical global burden of measles to assess the achievement of mortality reduction goals does not dynamically model transmission or support prospective analysis.[9] For context, the 2015 update of this model estimated that nearly 115,000 deaths due to measles occurred in 2014.[10] A 2016 study provided a best estimate of the global burden of congenital rubella syndrome (CRS) annual cases of approximately 105,000 (95% confidence interval of 54,000–158,000).[11] No existing models simultaneously track the dynamic transmission of measles and rubella to support analyses of regional or global control or elimination and prospective risk management options.[2] To support efforts to prepare investment cases[12] for measles and rubella to explore a range of future global management options,[1] we developed a dynamic disease transmission model that tracks measles and rubella virus transmission within a modeled area, and we model WHO member states separately then aggregate the results to the global level.

We use a similar methodological approach to the one developed to model poliovirus transmission and global management policies to capture the dynamics of preferential age-heterogeneous mixing, preferential mixing between subpopulations (i.e., the general population and an undervaccinated subgroup), and viral die out and importations.[13–15] Application of the polio model to some countries demonstrated the importance of sufficient numbers of undervaccinated individuals that mix preferentially to sustain transmission despite high national immunization coverage.[13–17] Some prior models of measles or rubella similarly demonstrate the importance of explicitly considering population heterogeneity in immunization coverage.[18–20] Preferentially mixing undervaccinated subpopulations become epidemiologically noticeable and of concern in the context of otherwise high national immunization coverage (i.e., in the context of low overall national coverage, heterogeneity in coverage matters less). Programmatically, in the context of otherwise high immunization coverage the existence of such subpopulations and heterogeneity can lead to the need for specific interventions targeted at these groups.[13–17]

We explore the behavior of the model in the context of available epidemiological data[21] and the results of serological surveys[22] that provide a snapshot of the dynamic population immunity at the time of data collection. For measles, we could potentially observe most of the cases (i.e., relatively few asymptomatic infections), while for rubella relatively more asymptomatic infections occur.[23] For both measles and rubella, not all symptomatic infections get detected and/or reported, with almost no systematic reporting systems existing for CRS. Prior models of measles and rubella for individual countries demonstrate significantly higher estimated cases from modeling than cases reported,[2,24,25] and significant underreporting of cases represents a well-recognized issue for modelers and program managers.[26] For those countries that eliminated endemic transmission, the underreporting of cases decreases significantly as surveillance improves over time to support elimination effort. Models should estimate timing for the disruption of transmission (i.e., die out of endemic transmission) and consequences of importations consistent with reported data.

The next section describes the assumptions, structure, and development of the overall measles and rubella transmission model and input assumptions, which we further combine with economic and other inputs to develop an integrated model to support global risk management efforts for measles and rubella. We then present the results of application of the transmission model to multiple diverse situations to demonstrate its performance and we use the integrated model to estimate the global health costs

of 2013 investments in control to provide context about the potential health and economic benefits of eradication of measles and rubella compared to current control. The discussion explores important insights, limitations, and sources of uncertainty, and the need for continued improvement of the model to make it a living tool that will support future global risk management efforts.

2. METHODS

2.1. Model Structure

Recognizing the variability in current national measles and rubella immunization programs,[1] experience with historical immunization,[21] population structures,[27] and viral transmission conditions,[2] we model each area separately and then aggregate the results to regional and global levels. The model includes 180 WHO member states and three other areas (i.e., Puerto Rico, Hong Kong, and Macao) for which we found sufficient demographic and immunization data.[21] The 2013 population in the model represents >99.5% of the estimated global population of 7.16 billion people.[27] Table I summarizes the model inputs that we use for all areas (i.e., virus-specific and other inputs used to characterize model inputs for measles and/or rubella that do not change by area). We summarize area-specific inputs in the context of describing individual modeled areas, with assumptions about historical RI and SIAs and seasonality based on a review of the evidence,[21] and we characterize R_0, mixing, and seasonal amplitude assumptions based on fitting the model to the historical time series of incidence[21] and data from serological studies.[22]

2.2. Demographics and Pregnancies

We obtained available global population historical data and projections by year or five-year interval between 1950 and 2100, including the estimated numbers of individuals of each sex, live births by sex, infant mortality rate, fertility rates, and life expectancy at birth.[27] We used these data in the model to stratify the population for each area by sex and into 35 age groups: 0 to <6, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 to <18, 18 to <21, 21 to <24 months, and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, and 50+ years. The model tracks females and males separately because the immunity of pregnant women impacts the maternal antibodies that infants passively receive for both measles and rubella, and some countries historically used selective immunization of adolescent and/or adult women for rubella.[21] The model adds infants into the first age group using a daily rate estimated from the number of surviving infants for each calendar year (i.e., the number of live births minus the number of infants who do not survive the first year of life). We do not allow any deaths to occur during the first year in the model because we account for all infant deaths by including only surviving infants, so all infants who enter the model at birth survive to one year of age. We estimate infant mortality outcomes attributable to measles and rubella infections in pregnancy[28] in the context of modeling the pregnancies. Similar to models developed for polio,[13] for all age groups over one year of age, we compute the numbers of individuals in the group implied by the estimated population for the age group (i.e., six-year olds represent approximately one-fifth of the five- to nine-year olds), and we estimate the annual death rates (μ) required to achieve the estimated population numbers at the end of each year accounting for the current size of the age group and the numbers of individuals entering and leaving the age group due to aging during the year.[13] We assume that measles and rubella mortality represents a small fraction of overall mortality and use the age-group and sex-specific annual death rates for all immunity groups.

We model maternal immunity and the risks associated with infections in pregnancy to properly attribute levels of immunity in newborns. We apportion the distribution of pregnancies using area-specific time series of age-based fertility rate estimates[27] for women in each five-year age group between 15 and 49 years to capture differences in fertility and immunity. Rubella infections in pregnancy can lead to induced terminations, spontaneous abortions, fetal death/stillborn births, infant mortality (including infants born with CRS who die prior to reaching one year of age), and the birth of surviving infants with CRS (i.e., adverse *sequelae* that resulted from the fetal infection), with some infants born with congenital rubella infections (CRIs) (i.e., excreting transmissible virus).[28] To account for these outcomes, we modeled pregnancies as a coflow.[29] We made the simplifying assumption that all births follow pregnancies that last for 280 days from the time of the mother's last menstrual period (LMP), and consequently we associate the births that occur in the model with pregnancies that started 280 days

Table I. Model Inputs for an Expanded Poliovirus Transmission Model for Measles (M) and Rubella (R)

Model Input (Symbol)	Best Estimate	Source(s)	Notes
Demographics for 180 WHO member states + Puerto Rico, Hong Kong, and Macao	Country-specific time series 1950–2100	27	Population data by gender (medium variant), birth rates, infant deaths, fertility, and life expectancy data, death rates after first year fitted to match estimates of population by age group using effective birth rates based on surviving infants
Number of stages per latent and infectious periods		2, 30	Choice, used to more realistically simulate infection process (Fig. 2, which shows the stages as E1 and E2 for latent and I1 and I2 for infectious)
Latent period intervals	2		
Infectious period intervals	2		
Duration of latent and infectious periods (days)		2	Used along with the number of stages per period to estimate δ and γ (see Fig. 2), such that $\delta = 1/$(one-half the duration of the exposed (latent) period), $\gamma = 1/$(one-half the duration of the infectious period)
M: Latent	10		
M: Infectious	8		
R: Latent	12		
R: Infectious	8		
Duration of gestation time since LMP (days)		28	Used to estimate ζ (see Fig. 1), infants born 280 days after the LMP
0 to <20 weeks	140		
20 to <39 weeks	133		
Last week	7		
Vaccine take rate for fully susceptible individuals (*tr*)		36	Take rate for fully susceptible individuals, the proportion of individuals with maternal antibodies implies lower population vaccine effectiveness when vaccine given routinely below one year of age
M	0.95		
R	0.95		
Vaccine take rate for susceptible individuals with a prior unsuccessful dose (*trsd*)			
M	0.99		
R	0.99		
Exponential decay rate for maternal immunes born to mothers with infection-induced immunity to wane to fully susceptible (k_{MIR}, in 1/yr)		22, 25	All individuals with residual maternal immunity become fully susceptible on first birthday, assumed rates combined with assumed vaccine take rates imply vaccine effectiveness for measles vaccine given in RI at 6, 9, and 12 months of approximately 50%, 85%, and 95%
M: 0 to <6, 6, 7, 8, 9, 10, 11 mo	1,3.5,5,8,11,14,17		
R: 0 to <6, 6, 7, 8, 9, 10, 11 mo	8,10,13,17,21,25,29		
Exponential decay rate for maternal immunes born to mothers with vaccine-induced immunity to wane to fully susceptible (k_{MIV}, in 1/yr)		25, 34	
M: 0 to <6, 6, 7, 8, 9, 10, 11 mo	2,5,9,12,15,18,21		
R: 0 to <6, 6, 7, 8, 9, 10, 11 mo	9,11,14,18,22,26,30		

(*Continued*)

Table I (Continued)

Model Input (Symbol)	Best Estimate	Source(s)	Notes
Excess pregnancy loss due to viral infection 0-<20 weeks since LMP		28	Assume the same rates for measles and rubella for spontaneous terminations and fetal death/stillborn births for developed countries, with no increase in induced termination or neonatal/infant mortality due to measles infections in pregnancy
M all, R developed: Spontaneous termination($f_{sponttem}$)	0.02		
M all, R developed: Fetal death/stillborn($f_{fetdeath}$)	0.01		
M all, R developed: Neonatal/infant mortality($f_{infmort}$)	0.02		
R undeveloped: Spontaneous termination($f_{sponttem}$)	0.04		
R undeveloped: Fetal death/stillborn($f_{fetdeath}$)	0.02		
R undeveloped: Neonatal/infant mortality($f_{infmort}$)	0.04		
Rate of maternal rubella infections 0 to <20 weeks since LMP terminated due to rubella infection($f_{indterm}$)		28	Assumed (actual rates vary by country, but not available, developed countries include all high- and upper middle-income countries except those in Africa, undeveloped includes all other countries)
R, developed	0.3		
R, undeveloped	0		
Probability of fetal infection leading to development of infant born with IgM immunity (f_{FI})		28	
M: Maternal infection 0 to <20 weeks since LMP(f_{FI1})	0		
M: Maternal infection 20–39 weeks since LMP(f_{FI2})	0		
M: Maternal infection last week(f_{FI3})	0.82		
R: Maternal infection 0 to <20 weeks since LMP(f_{FI1})	0.65		
R: Maternal infection 20–39 weeks since LMP(f_{FI2})	0.42		
R: Maternal infection last week(f_{FI3})	0.82		
Probability of fetal infection leading to birth of infected infant (f_{inf})		28	Infants infected in utero born infected (i.e., fetal infections from which the infants did not yet recover, one minus these fractions gives the rate of infants born with induced immunity)
R: Maternal infection 0 to <20 weeks since LMP (f_{infl})	0.5		
R: Maternal infection 21+ weeks since LMP(f_{inf2})	0.1		
Probability of CRS in fetal infections carried to term		28	
R: Maternal infection 0 to <20 weeks since LMP(f_{CRS})	0.43		

(*Continued*)

Table I (Continued)

Model Input (Symbol)	Best Estimate	Source(s)	Notes
Fraction of previously missed individuals receiving a first dose at scheduled second dose (f_{new})		[a]	
Second routine dose scheduled for <4-year olds	0.05		
Second routine dose scheduled for 4+ year olds	0.25		
Effective infectious proportion below which we assume 0 force of infection (EIP[a])	5/1,000,000	[a]	Used to produce approximately correct timing of die out in the model (see text); assumed equal for all mixing age groups and subpopulations
Average basic reproductive number ($R_{0v}{}^{ave}$) range by World Bank income level[39]	Range[b]	2	
M: High	9–13		
M: Upper middle	10–14		
M: Lower middle	11–18		
M: Low	12–18		
R: High	2–5		
R: Upper middle	2–7		
R: Lower middle	3–9		
R: Low	3–9		
Number of annual seasonal cycles (s_C)		[a]	Default values, actual value could be any integer representing any of 365 days in the year with day 0 indicating January 1 and day 364 indicating December 31 (model ignores leap days)
Temperate:	75 and 280		
Nontemperate	75 or 280		
Seasonality amplitude (s_v)	Range[b]		
M	0–0.8		
R	0–0.9		
Proportion of potentially infectious contacts of individuals reserved for individuals within the same mixing age group, κ	Range[b] 0.3–0.45	13, 38	
Relative number of contacts for individuals in mixing age group *i* (RCi)			
0 to <5 yrs	1.0		
5 to <15 yrs	1.5		
≥15 yrs	1.0		

Notes: LMP, last menstrual period; M, measles-associated; R, rubella-associated.
[a]Indicates based on judgment.
[b]Best estimates vary by modeled area so values given reflect the range of estimates used.

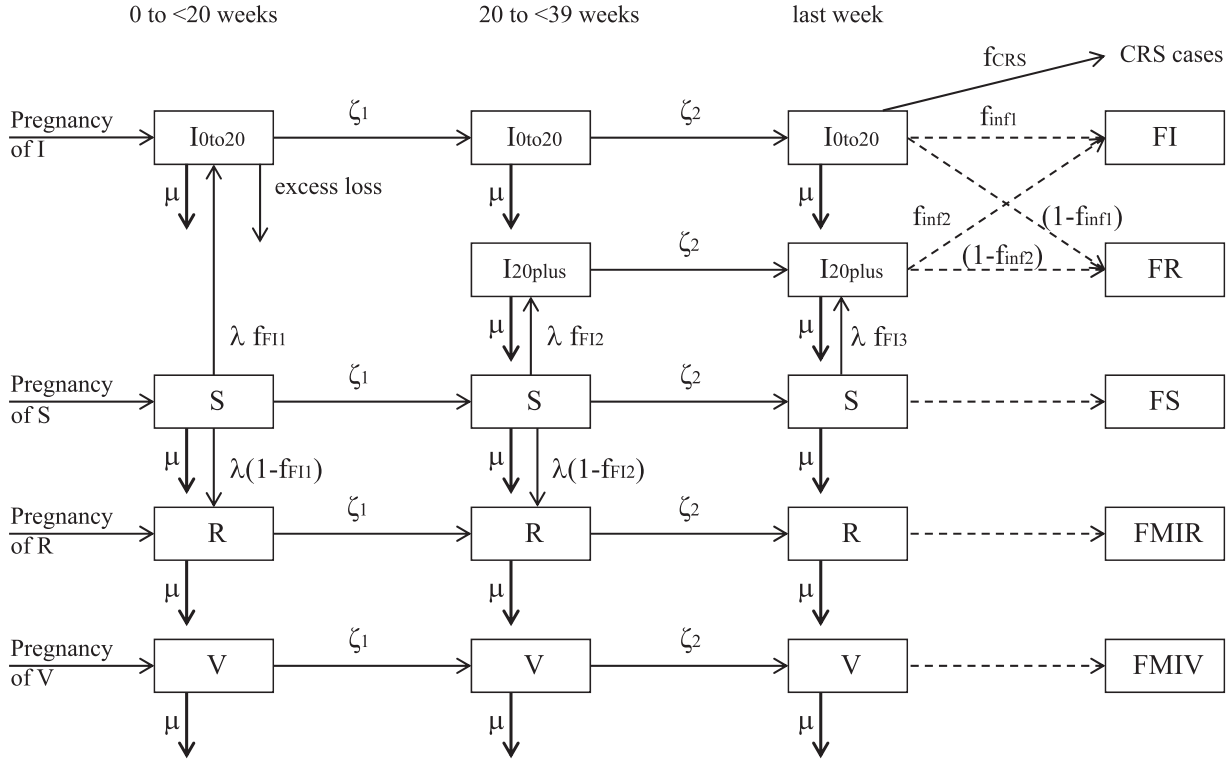

Fig. 1. Schematic for pregnancy flows in the model by gestation time.
Abbreviations: CRS = congenital rubella syndrome; f_{CRS} = probability of CRS in fetal infections carried to term for maternal infection 0 to <20 weeks since last menstrual period; f_{FIi} = probability of fetal infection for gestation period i; f_{inf1} = probability of fetal infection during gestation period 1 leading to birth of infected infant; f_{inf2} = probability of fetal infection during gestation period 2 or 3 leading to birth of infected infant; FI = fetus with infection at birth; FMIR = fetus born with maternal antibodies from mother who recovered from infection prior to pregnancy; FMIV = fetus born with maternal antibodies from mother effectively vaccinated prior to pregnancy; FR = fetus born following maternal infection during pregnancy; FS = fetus born to fully susceptible mother; I_{0to20} = maternal infection <20 weeks since last menstrual period; I_{20plus} = maternal infection 20 or more weeks since last menstrual period; R = recovered from infection with wild virus prior to pregnancy; S = fully susceptible at the time of pregnancy; V = effectively vaccinated prior to pregnancy; λ = force of infection; μ = mortality; ζi = 1/duration of time in gestation state i.

earlier. We estimate the fractions of pregnancies that do not result in surviving infants due to induced termination, spontaneous abortion (miscarriage), fetal death (stillborn birth), and infant mortality, including the CRS cases that lead to death in the first year of life. We estimate the number of total pregnancies by dividing the number of surviving infants by adjustments for infant mortality and pregnancy loss.

Fig. 1 provides the structure of the pregnancy model components, which tracks pregnancies through three time periods (0 to <20 weeks, 20 to <39 weeks, and the last week of pregnancy). We treat the last week separately because we allow some fetal infections during that week to lead to the birth of an infected and infectious newborn. The proportion of fetuses in the different groups in the last week of gestation determine the fractions of infants born as fully susceptible (FS), infected (FI), recovered (FR, for rubella only), or maternally immune from a mother with infection-induced immunity (FMIR) or vaccine-induced immunity (FMIV). Infants born infected with CRI (i.e., fetal infections, FI) may contribute to transmission after birth. We estimate the number of infants born with CRS as a fraction of the births to mothers with a maternal rubella infection <20 weeks since the LMP carried to term, and note that these births will include surviving infants born either as infected (FI) (i.e., infectious CRI) or recovered (FR) (i.e., not infectious). We assume the rates in Table I for induced and spontaneous terminations, fetal deaths, neonatal/infant deaths, and CRS based on our review of the literature of these outcomes following rubella infections in pregnancy for developed (i.e., high- and

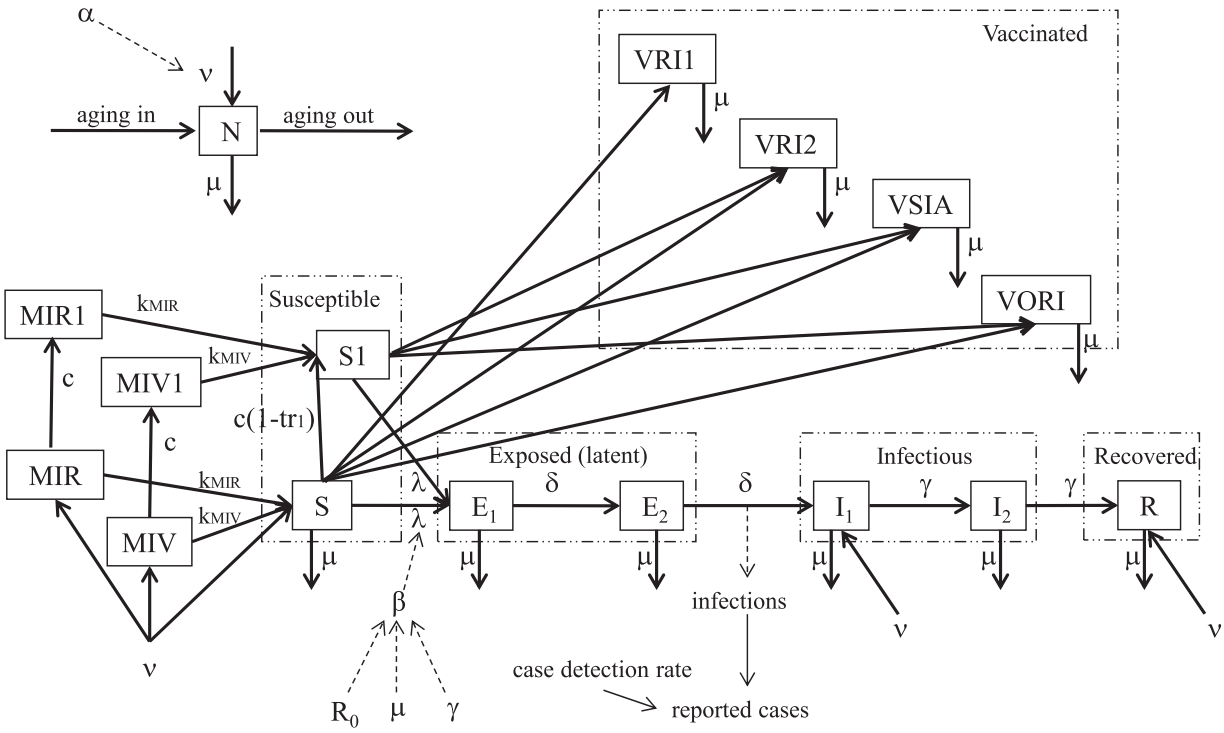

Fig. 2. Schematic of transmission model states (list of symbols).
Abbreviations: c = routine immunization coverage rate; E_i = Exposed state i ($i = 1,2$); I_i = Infectious state i ($i = 1,2$); k_{MIR} = decay rate of maternal protection for transmission from MIR(1) to S(1) immunity state; k_{MIV} = decay rate of maternal protection for transmission from MIV(1) to S(1) immunity state; MIR = maternally immune with antibodies from a mother who recovered from wild virus infection; MIR1 = maternally immune with antibodies from a mother who recovered from wild virus infection and received one or more doses of vaccine; MIV = maternally immune with antibodies from a mother with vaccine-induced immunity; MIV1 = maternally immune with antibodies from a mother with vaccine-induced immunity and received one or more doses of vaccine; R_0 = basic reproduction number; R = recovered from infection with wild virus; S = fully susceptible; $S1$ = fully susceptible but received one or more doses of vaccine; SIA = supplemental immunization activity; $tr1$ = take rate for first dose of vaccine; $tr2$ = take rate for second dose of vaccine; VORI = effectively vaccinated by a dose from an outbreak response SIA; VRI1 = effectively vaccinated with the first routine immunization dose; VRI2 = effectively vaccinated with the second or a later routine immunization dose; VSIA = effectively vaccinated by a dose from a preventive SIA; δ = 1/duration in exposed or latent period, λ = force of infection; μ = mortality.

upper middle-income) countries,[28] and the assumptions of no induced terminations attributable to rubella for lower-middle- and low-income countries and all countries in Africa. We track all of the adverse outcomes in the model for inclusion in economic analyses. Based on similar evidence of increased risks of spontaneous termination associated with maternal measles infection for infections between 0 weeks and 20 weeks since the maternal LMP for measles,[26] we accounted for increased additional terminations from maternal measles infections less than 20 weeks since the LMP. For all maternal measles infections prior to the last week of pregnancy and for the fraction of maternal rubella infections that do not impact the fetus, we assume that the maternal infection during pregnancy leads to the production of maternal antibodies that provide the infant with maternal immunity, but the infant does not acquire immunity (i.e., the infant becomes fully susceptible once maternal antibodies wane).

2.3. Transmission Model Structure

Considering insights from a review of measles and rubella models,[2] Fig. 2 provides the structure of the differential-equation-based model that we use to track immunity and viral transmission for both measles and rubella within a population. Most newborn infants benefit from maternal immunity (MI) provided by mothers who recovered from wild virus infection (MIR) or acquired immunity from vaccination (MIV). Until they wane, maternal antibodies

protect infants from infection, infectiousness, and disease, in addition to inhibiting their ability to seroconvert if given a dose of vaccine. Individuals with no (remaining) maternal immunity, no successful vaccine doses, and no successful prior infections with wild virus remain fully susceptible (S), and these individuals collectively put the population at risk with respect to sustaining viral transmission. We assume that fully susceptible individuals exposed to measles or rubella enter an exposed (i.e., latent infection but not yet infectious) phase (E) and then become infectious (I) to others after some time delay. Given some variability in the durations of latency and infectiousness, and clear evidence of nonexponential distributions,[2] we model the duration of the exposed (E) and infectious (I) periods using two stages for each (i.e., E1, E2 and I1, I2), which implies a gamma distribution overall for the duration of infection and infectiousness.[30] In addition to the virus-specific inputs, Table I summarizes the ranges we use for area-specific inputs, which vary due to differing conditions in different areas. Individuals who recover (R) remain permanently immune to disease and infection following infection with wild virus, and individuals who receive a dose of vaccine and "take" (i.e., acquire protective immunity) move into the appropriate immunity state for the vaccine dose (i.e., the first RI dose [VRI1], second RI dose [VRI2], an SIA dose [VSIA], or outbreak response dose [VOR]).

In contrast to a rare case of reinfection following a previous wild virus infection, first infections that follow receipt of one or more doses of vaccine may occur in some cases due to the failure of the vaccine to "take," which in some cases may occur due to the interference of maternal antibodies with the vaccine. Consequently, we account for individuals who received one or more doses of vaccine but failed to "take" and who remain fully susceptible to infection despite receipt of vaccine by tracking them in immunity states that indicate susceptibility or continued protection from maternal immunity following one or more vaccine doses (i.e., S1, MIR1, MIV1). Individuals who receive a dose of vaccine while maternally immune (i.e., MIR or MIV) go into the appropriate state of MIR1 or MIV1, and once maternal immunity wanes for these individuals, they move into the S1 state, which includes any fully susceptible individuals of the same age and sex who received at least one dose of vaccine but did not take. Tracking the immunity states shown in Fig. 2 allows us to better capture any benefits associated with revaccination of individuals for national immunization strategies that deliver more than one dose, which provide additional opportunities for "take" (i.e., a second dose in RI, SIAs, and/or ORI).

Although some prior models included the possibility of limited participation in transmission following reinfection because antibodies may wane over time,[2] reinfection of successfully immunized individuals appears to occur rarely for measles[31] and/or rubella[32] and only one recent study documented measles transmission from an infected previously vaccinated individual to other individuals.[33] Thus, in contrast to transmission models for polio that must include the dynamics of waning immunity, reinfection, and some participation in transmission of reinfected individuals to properly characterize transmission,[13] we assume that models for measles and rubella transmission can ignore the relatively negligible role of reinfection. The model structure assumes lifelong immunity to the severe outcomes associated with disease (i.e., we assume that any rare cases of reinfection that occur do not result in illness severe enough to lead to hospitalization or death, and they do not contribute significantly to transmission).

We characterize the immunity of infants entering the model as a mixture (i.e., S, MIR, and MIV), which reflects the reality that some women of child-bearing age (WCBA) remain fully susceptible at the time of their pregnancy, while others pass on maternal antibodies that result from their prior infection- or vaccine-induced immunity. After birth, infants lose their maternal immunity at slightly different exponential decay rates as they age (i.e., more slowly for the first 0 to <6 months then increasingly more rapidly after that time) and we assume that any infants with residual maternal immunity become fully susceptible and all maternal immunity wanes immediately prior to the first birthday. Evidence for measles increasingly suggests that infants born to mothers with vaccine-induced immunity may receive lower titers of maternal antibodies and their protection may wane relatively more rapidly compared to infants born to mothers with infection-induced immunity,[25,34] so we assume more rapid decay for infants born into MIV than for those born into MIR. In addition, as wild virus circulation declines globally, WCBA increasingly become pregnant without any (recent) exposure to wild measles or rubella virus in many countries.[35]

Table I provides the decay rates we assumed for the waning of maternal immunity for age groups less than 12 months (i.e., 0 to <6, 6, 7, 8, 9, 10, and 11 months) for both measles and rubella and both

types of maternal immunity. The proportion of infants with maternal immunity impacts the observed vaccine effectiveness because only infants modeled as fully susceptible can respond to vaccine (or become infected). Thus, vaccine effectiveness studies[36] report the results of observations from the mixture of maternally immune and fully susceptible infants, such that populations with a relatively larger proportion of infants born into the MIR immunity state yield lower estimates of vaccine effectiveness for vaccine doses given at ages under one year old. We assume 95% vaccine effectiveness for both measles and rubella vaccines for individuals ≥12 months, and we use maternal immunity decay rates that lead to approximately 50%, 85%, and 95% effectiveness at 6, 9, and 12 months, respectively, for measles for infants born to mothers with infection-induced immunity. The evidence suggests relatively more rapid waning of maternal antibodies for rubella than measles, such that the difference in maternal antibodies between infection-induced and vaccine-induced mothers represents less of a concern at the typical ages of rubella immunization, and this leads to vaccine effectiveness estimates of approximately 95% for rubella immunization of all individuals over six months of age.

2.4. Transmission Model Dynamics

Consistent with the real differences that exist in the transmissibility of measles and rubella in countries with different levels of crowding, contact rates, family sizes, and other factors that impact transmission, we use relatively higher R_0 values for countries with relatively lower gross national incomes, which we take as a proxy for the multitude of factors that impact R_0.[13] Consistent with prior models, we assume a higher R_0 for measles than for rubella in each modeled area.[2] Similar to global poliovirus models[37,38] and consistent with an approach of stratifying the economics of measles and rubella[23] by World Bank income level,[39] we use different ranges for R_0 values by the area income level (i.e., high, upper middle, lower middle, low) with ranges of area-specific values for each income level summarized in Table I.

We included three additional factors that add complexity to the transmission model dynamics: seasonality, age-heterogeneous preferential mixing, and the possibility of population heterogeneity in coverage (i.e., existence of an underimmunized subpopulation that preferentially mixes with itself). We use similar mathematical relationships to methods described in detail elsewhere[13,14,17] to characterize heterogeneity. Given the similarity of transmission of measles and rubella, we assume that seasonality timing and mixing-related inputs vary by area, but not by disease. Briefly, we model seasonal forcing by multiplying the R_0 for each disease using a sine wave with an annual peak occurring in the late winter or early spring for nontemperate climates and with peaks occurring in both spring and fall for temperate climates[13,40] and with the amplitude varied by area and virus.

For mixing between age groups, we assume preferential mixing between age groups using values that vary by area, which implies that individuals within the same mixing age group tend to mix relatively more with each other than with other age groups. Prior to immunization starting (and for countries for which we do not need to model a preferentially mixing undervaccinated subpopulation), we define $M(a, b)$ as the mixing matrix that describes the relative contact rate from individuals in age group a to individuals in age group b:[13,14,17,41,42]

$$M(a,b) = \kappa(a)\, 1_{\{a=b\}} + \frac{(1-\kappa(a))\,(1-\kappa(b))\,RC(b)N(b)}{\sum_{c=1}^{n} N(c)RC(c)\,(1-\kappa(c))},$$

where $\kappa(x)$ represents the proportion of contacts for individuals in mixing age group x reserved for other individuals in the same mixing age group, the function $1_{\{a=b\}}$ equals 1 if the condition holds or 0 otherwise, $N(y)$ equals the total number of people in mixing age group y, $RC(y)$ represents the relative number of contacts for individuals in mixing age group y, and n equals the number of mixing age groups. This approach allows the model to apply the same assumptions about age-heterogeneous mixing for both measles and rubella. For some areas and as appropriate, we consider the possibility of a relatively isolated and underimmunized subpopulation, which we model as a single subpopulation using assumptions related to the relative amount of mixing inside and outside of the subpopulation with the general population (i.e., the extent of isolation of the subpopulation) and relative rates of immunization. We calculate the mixing matrix at each time step (i.e., each day) because the population changes with time. Following exposure to a wild virus, fully susceptible individuals become infected according to the force of infection of age group a and virus strain j ($\lambda_{a,j}$) (and an undervaccinated subpopulation if used

for the modeled area; see the appendix of Ref. 43 for model equations and added complexity in the force of infection estimation process when modeling undervaccinated subpopulations). The force of infection for virus j and age group a (and subpopulation if used) depends on the assumed R_0 for the given virus, the product of the country-specific age-mixing matrix, and the number of infectious individuals in each age group with virus j. We assume that individuals mix the same way with respect to the spread of respiratory viruses (i.e., for measles and rubella) within an area (and subpopulation if used), but we allow mixing patterns and input assumptions to vary for different areas. Individuals only contribute to the force of infection while infectious, with equal infectiousness assumed for the two stages of infection (i.e., I1 and I2).

2.5. Immunization

According to the estimated national annual RI coverage, some individuals receive the scheduled vaccine dose at the time that they age into the age group with the scheduled dose. We ignore the reality that some individuals actually receive their scheduled dose at a younger or older age than implied by the RI schedule. We used reconstructed historical RI schedules for all of the 183 areas modeled using available data from the WHO and UNICEF and information obtained from the published literature.[21] The historical RI data should account for actual reductions in coverage that occurred due to disruptions in program performance and/or vaccine supply (e.g., due to insecurity, instability, humanitarian and natural disasters, and/or other challenges). For prospective modeling, we must make assumptions about future RI coverage, which may include multiple scenarios (e.g., continuation of the status quo, implementation of interventions that may affect coverage, and other assumptions, including the possibility for future changes in program performance). In the absence of any data, we accounted for the correlation between receiving the first and second RI doses for those schedules that include a second dose by assuming that 5% or 25% of fully susceptible and maternally immune children (i.e., children who missed the first dose) receive the second dose coverage as their first dose if the schedule recommends the second dose at <4 years old or ≥ 4 years old, respectively. We assume that the remaining 95% or 75% of the second dose coverage represents a true second dose for individuals in the S1, MIR1, or MIV1 states for schedules that deliver the second dose at <4 years old or ≥ 4 years old, respectively. Although the current vaccines use live attenuated virus formulations for measles and rubella vaccines, the vaccine viruses do not circulate or cause secondary infections, and consequently they only provide protection to the individual vaccine recipients with no further circulation. We assume no impacts of maternal receipt of vaccine during pregnancy on the pregnancy outcome or fetus based on the existing evidence.[44]

SIAs include both pSIAs performed to increase population immunity with the objective of preventing outbreaks, and ORI efforts (i.e., oSIAs) that respond to outbreaks. SIAs vary by target age group, geographic area, and other factors (e.g., sex, immunization history), and in general no systematic recording of oSIAs occurs. In contrast to RI, SIAs occur in the form of campaigns that generally last for durations of much less than a year, but can span beyond a year in some cases. The model accounts for campaigns by assuming that all individuals in the target age group, including those already immune (unless the SIA otherwise specifically targets only those without prior vaccination), receive a dose of vaccine assuming an equal number of doses per day distributed at a rate that reaches the overall estimated coverage. Similar to prior models, we characterize the effective SIA vaccination rate based on the proportion of the target population that should remain not vaccinated by the SIA after application of the rate.[13] For national SIAs, we assume the SIA targets the entire population within the target age range. For subnational SIAs, we adjust the SIA coverage to account for the fraction of the total population targeted. Thus, for all SIA rounds, we consider the geographic scale of the round and relative coverage in the subpopulation (if used) as we estimate the coverage input for the model. We do not assume any correlation between RI and SIA coverage, except for the correlation introduced by assuming reduced relative RI and SIA coverage compared to the general population for modeled areas that include an undervaccinated subpopulation. Limitations in data quality imply significant uncertainty about actual coverage levels for RI and SIAs, particularly for ORI (i.e., oSIAs), and consequently in the process of fitting the model to individual areas we adjusted the uncertain coverage for some SIAs to obtain results consistent with the historical conduct of oSIAs and/or epidemiology as appropriate, and vaccine procurement data if available. For example, we found inconsistency between

estimates of SIA coverage and the number of doses used divided by the target population size, which led us to explore different values of true coverage for individual rounds in many cases. We found very limited information about the nature of ORI, although we know that ORI occurred historically and continues to occur in some countries, in some cases at significant expense. For example, nongovernmental organizations like Médecins Sans Frontières (MSF) deliver immunization in addition to treatment during measles outbreaks, and public health departments in the United States aggressively used ORI to stop outbreaks during the last several decades,[45,46] but for which we could not find ORI coverage data.

2.6. Simulation

We coded the model in Java. We start a simulation for each area with its 1954 population as fully susceptible and we run the model without population growth for the equivalent of 99 years with the mixing assumptions to approach the endemic equilibrium. We then turn on seasonality and run the model for varying numbers of additional years that may differ for measles and rubella transmission to initialize the timing in the interepidemic period for the specific population and virus. After this initialization process, we start population growth and aging consistent with the population data and run the model from 1954 forward, introducing immunization in the simulated years that correspond to the timing in which vaccine introduction actually occurred. The model separately tracks measles and rubella transmission simultaneously as simulated time passes with a time step of one day.

We characterize population immunity (i.e., the effective immune proportion, EIP) and the number of effective secondary infections caused by each infection (R_n). Once the EIP drops below the threshold required to sustain transmission ($EIP^* = 1 - 1/R_0$) or equivalently R_E drops below 1, transmission will die out. We model die out by assigning the force of infection to 0 when the number of infections drops below five infections per million people in a mixing age group and subpopulation if used. Die out of all transmission occurs when the force of infection for all age groups equals 0. Given the reality of importations, we include the possibility of virus introductions into populations, and we allow these importations to lead to transmission only if EIP < 1, otherwise the importations die out. Thus, the impact of importations remains relatively limited in (sub)populations with relatively high levels of population immunity, although importations may result in some local cases and lead to significant costs associated with outbreak response.[47–50] In contrast, importations into countries with relatively lower population immunity or into undervaccinated subpopulations will lead to reestablished transmission, although this may be limited due to seasonality and the size of the population. The model also estimates the average age of infection (with infections only occurring in susceptible individuals) and the average age of immunity (which depends on the immunity in the entire population) as functions of time.

We found that simply using a single value to characterize underreporting of incidence (e.g., a factor of 10) did not capture the changing nature of surveillance, which generally improved over time (i.e., implying both country-specific and time-varying rates of underreporting). Consequently, we focused on matching the pattern of the historical epidemiological dynamics with consideration of any serological results available at any points in time. We developed an algorithm for searching the model input space that relied on comparing the pattern of peaks and troughs of the model estimates of incidence to the pattern of reported cases (see appendix.[43]) As initial estimates for R_0, we assumed values that provided consistent ranking with those used in global modeling for polio,[38] with relatively higher values used for measles and relatively lower values used for rubella compared with the polio estimates, and using R_0 estimates for African countries for rubella from a prior study.[51] We demonstrate the historical model behavior for different areas that represent highly variable transmission situations and historical immunization strategies to explore the model performance. We selected six countries to demonstrate the model: the United States (USA), which introduced both vaccines into its national schedules in the 1960s, relies on RI without SIAs to manage population immunity, and uses ORI to respond to outbreaks, the Netherlands and Oman, which both primarily use RI, Vietnam and Kenya, which as of 2013 used only measles vaccine in their RI schedules and performed periodic pSIAs, and Haiti, which introduced rubella immunization into its RI schedule despite low RI coverage and performed pSIAs and oSIAs.

We provide the area-specific model inputs that do not vary with time (i.e., $R_{0,V}$, seasonality peak day (S_C) and amplitude (S_V), κ, the fraction of the total population in the undervaccinated subpopulation,

and the extent of preferential mixing in the undervaccinated subpopulation (p_{within})) and the time-varying input assumptions related to RI and SIAs (i.e., pSIAs, oSIAs, and/or ORI) separately in area profiles. When possible, we obtained estimates of national vaccine procurements and used these data to inform our coverage estimates for SIAs. For countries for which RI second doses occur, but the country does not report coverage estimates to the WHO (e.g., the United States), we estimated first and second dose RI coverage based on the best available information. Given significant revisions in coverage estimates in the WHO–UNICEF estimates that occurred, we updated our coverage estimates from those previously reported.[21] We conceive of the model as a living tool such that the model inputs can reflect updates over time and include future projections, which will allow it to support prospective analyses.

2.7. Outcomes

We use the model to estimate all of the adverse health outcomes over time for each area using a daily time step and aggregating the results for each calendar year. For all of the adverse health outcomes, including estimated rates of complications from infections and vaccine-associated adverse events, we characterized the associated disability-adjusted life years (DALYs)[23] to estimate the number of adverse health outcomes from measles and rubella infections and the costs associated with treatment and vaccination for 2013 using available cost and valuation inputs.[23] We characterize the costs of control of measles and rubella in 2013 and the expected costs potentially saved by their eradication to provide context about the value of investments in eradication efforts. For health and economic outcomes, the model includes discounting at a 3% rate.[6]

3. RESULTS

For each modeled area, we encountered challenges associated with estimating the area-specific model inputs, in large part due to the relatively poor-quality historical surveillance data and resultant low reported case estimates. We also recognized that some of the historical peaks associated with reported measles incidence could potentially reflect fever and rash illnesses caused by rubella infections but captured as measles cases by surveillance systems.

Fig. 3 shows the results of the model fit for the United States for measles (Fig. 3a) and rubella (Fig 3b). Modeling the incidence and the die out of transmission required that we include an undervaccinated subpopulation, which in the United States includes some communities that do not obtain immunization for religious reasons (e.g., the Amish[52]) and some families who intentionally remain undervaccinated.[53] Given aggressive outbreak response in the United States, we included ORI starting in 1967 assuming that outbreaks led to the immunization of some previously unvaccinated individuals only. In 1989, at the time the United States introduced a second RI dose into its schedule, we allowed ORI to capture all individuals in the target age range, including those previously immunized. Although the United States stopped endemic transmission of measles by 2000,[54] frequent importations occur.[55] The model includes regular importations into the general population, which may lead to transmission in undervaccinated subpopulations. However, for importation events that involved known importations into an undervaccinated subpopulation[52] we modeled the importation directly into the undervaccinated subpopulation. The model yields estimates of rubella cases that correspond to approximately 24,000 pregnancy outcomes adversely affected (e.g., pregnancy terminations due to rubella, fetal deaths, infant mortality, and CRS cases) due to the maternal rubella infection associated with the large outbreak that peaked in 1964, similar to prior estimates.[56] Fig. 3 includes the model and reported data back to 1963 to show the historical fit given available historical data, and shown for 1980–2013. The outbreak of measles around 1990 most likely led to increased laboratory testing of rash and fever cases, which may also explain increased detection of rubella infections in 1990, but in 1991 an outbreak of rubella in North American Amish occurred and led to increased incidence[57] for which the model includes an importation into the undervaccinated subpopulation. As of 2013, measles and rubella incidence in the United States follows a pattern characterized by importations that take off as seasonality increases the force of infection followed by limited transmission in part due to ORI efforts that lead to die out.

Fig. 4 shows the results of the model fit for the Netherlands for measles (Fig. 4a) and rubella (Fig 4b). Like the United States, the model for the Netherlands includes an undervaccinated subpopulation, which played an important role in measles

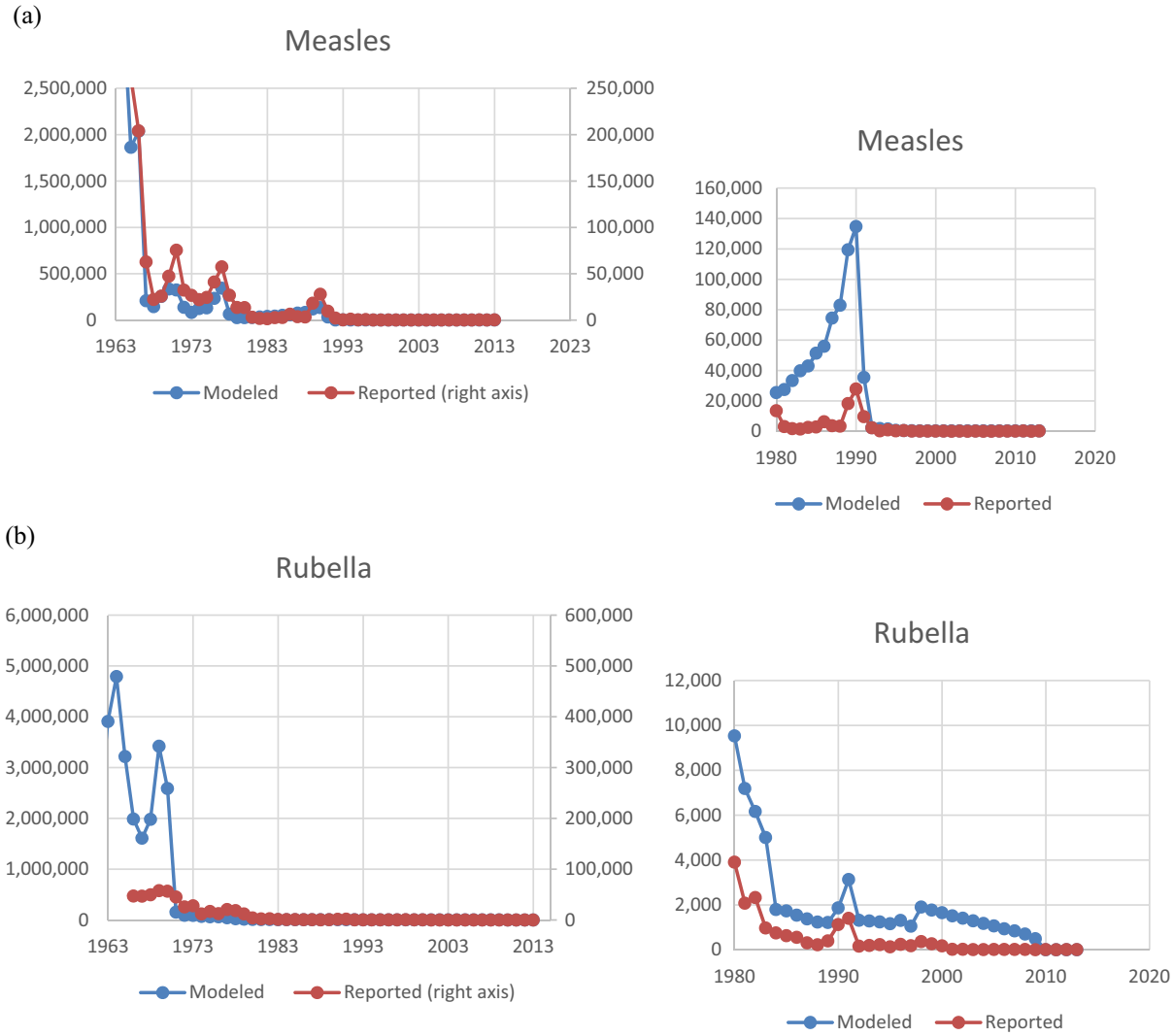

Fig. 3. Model fit for the United States for measles (Fig. 3a) and rubella (Fig 3b) (high-income country, undervaccinated subpopulation fraction 1/32, $p_{\text{within}} = 0.3$, $R_{0,M} = 10$, $R_{0,R} = 3$, $\kappa = 0.35$, $s_C = 75$, $s_M = 0.194$, $s_R = 0.74$, first year of outbreak response immunization = 1967).

outbreaks in 1999–2000[58] and 2013–2014,[50] and the rubella outbreak in 2004–2005[59] and led to ORI activities. Consistent with the adoption of a rubella immunization strategy that involved selective immunization of adolescent and adult females, transmission of rubella did not decline until after the mid 1980s. Similar to the United States, in 2013 measles and rubella incidence in the Netherlands follows a pattern of limited transmission after importations that largely impact the undervaccinated population.

Fig. 5 shows the results of the model fit for Oman for measles (Fig. 5a) and rubella (Fig 5b). We found that while matching the epidemic peaks for rubella that occurred around 1988 and 1993, the model also generated a peak around 1981. We noted a disproportionately high peak for measles reported in 1981 and we hypothesized that given the quality of surveillance at that time, the rubella outbreak that most likely occurred around that time might explain some of the rash and fever cases reported as measles. Unfortunately, we could not find any available data to test this hypothesis. After making rubella a reportable disease in 1991, Oman reported a rubella outbreak between November 1992 and May 1994 for which it conducted surveillance that identified 60 CRS cases.[60] During the same time

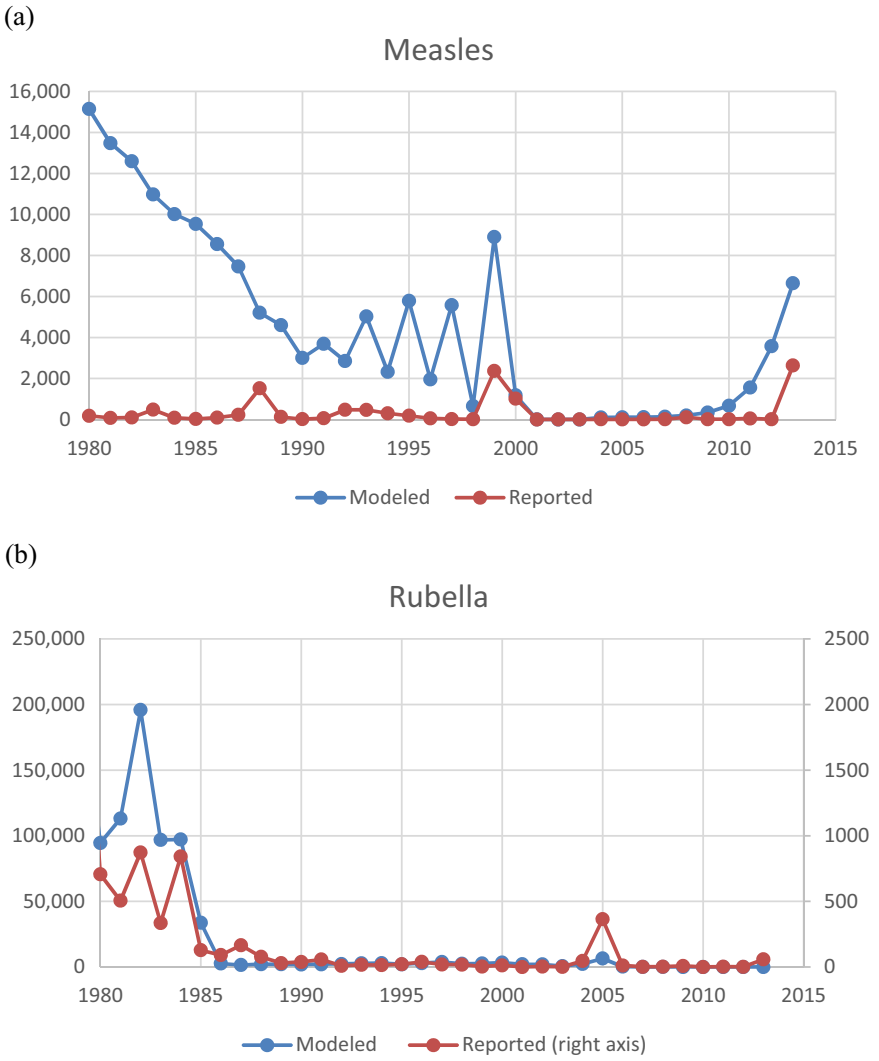

Fig. 4. Model fit for the Netherlands for measles (Fig. 4a) and rubella (Fig 4b) (high-income country, undervaccinated subpopulation fraction 1/50, $p_{\text{within}} = 0.99$, $R_{0,M} = 10$, $R_{0,R} = 3.9$, $\kappa = 0.4$, $s_C = 75$, $s_M = 0.21$, $s_R = 0.32$, first year of outbreak response immunization = 1988).

period, our model estimates approximately 90 CRS cases. As in the models for the United States and the Netherlands, we included an undervaccinated subpopulation, which we assume represents the expatriate population estimated as approximately 24% of the population;[61] however, unlike the United States and the Netherlands, the model for Oman does not include any ORI.

Fig. 6 shows the results of the model fit for Vietnam for measles (Fig. 6a) and rubella (Fig 6b). Vietnam conducts periodic pSIAs that help to keep its population immunity higher, but lead to more episodic outbreaks. Significant uncertainty exists about the actual coverage obtained in SIAs in many modeled countries, including Vietnam, which highlights the challenges with fitting model inputs in the context of data of poor or uncertain quality. Vietnam did not begin immunization for rubella until after 2013, and it conducted active surveillance for CRS beginning in 2011, following a rubella outbreak during 2010–2011 that led to an estimated 292 CRS cases.[62] For Vietnam, we do not assume induced terminations occurred associated with rubella infections in pregnancy. The model estimates approximately 600 CRS cases and approximately 300 total spontaneous terminations, fetal deaths, and infant deaths due to maternal rubella infections. The model does not include an undervaccinated subpopulation,

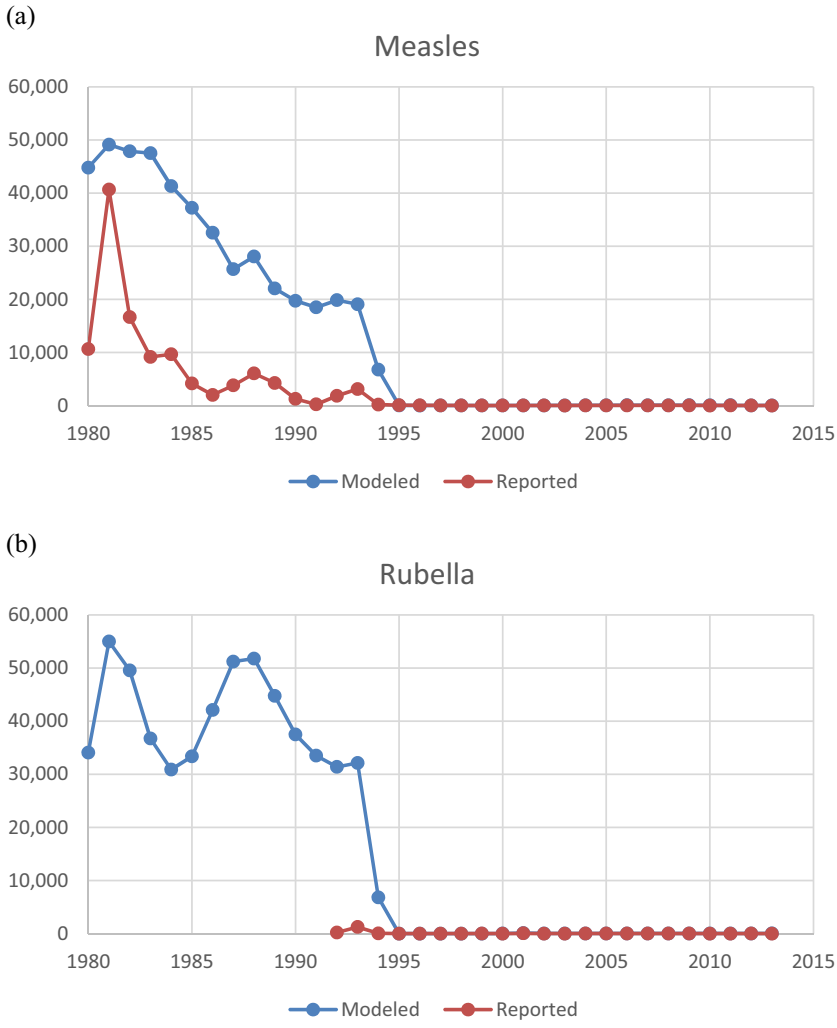

Fig. 5. Model fit for Oman for measles (Fig. 5a) and rubella (Fig 5b) (high-income country, undervaccinated subpopulation fraction 1/4, $p_{\text{within}} = 0.6$, $R_{0,M} = 10$, $R_{0,R} = 3$, $\kappa = 0.35$, $s_C = 75$, $s_M = 0.125$, $s_R = 0.76$).

but heterogeneity in coverage and increasing coverage rates will most likely motivate inclusion of a subpopulation in prospective modeling.

Fig. 7 shows the results of the model fit for Kenya for measles (Fig. 7a) and rubella (Fig 7b). Kenya continues to conduct pSIAs to increase its population immunity for measles, but the model does not require inclusion of a separate undervaccinated subpopulation given the continued relatively low coverage and ongoing transmission. Kenya did not include rubella immunization in its RI schedule until 2016, although we assume a small fraction of children who see private physicians receive MMR vaccine (i.e., 1% in 1990 increasing to 5% in 2013). Overall, the results show significant uncertainty about rubella infections given the very low number of reported cases.

Fig. 8 shows the results of the model fit for Haiti for measles (Fig. 8a) and rubella (Fig 8b). Consistent with the available epidemiological data, the model limits the importations of measles into Haiti assuming that the effort in the Americas to eliminate measles reduced importations into Hispaniola. Given the relatively late introduction of rubella immunization into Haiti, the model includes widespread rubella transmission until the time of rubella vaccine introduction, followed by rapid die out. Due to its relatively low RI coverage, Haiti remains susceptible to importations of measles and rubella, and the prevention of large outbreaks following any importations depends on continued pSIAs given its relatively low RI coverage. However, the introduction of rubella vaccine into Haiti overall significantly decreased the expected number of annual CRS cases.

Table II summarizes the estimated measles, rubella, and adverse outcomes associated with infections in early pregnancy aggregated by 2013 income

Table II. Aggregate Estimates by World Bank Income level[39] and Globally for Estimated Outcomes and Costs for 2013

Income Level	Low	Lower Middle	Upper Middle	High	Global
Incidence					
M: Infections					
<4 yrs	6,300,000	4,900,000	830,000	490,000	12,500,000
5–14 yrs	180,000	110,000	38,000	21,000	350,000
15–49 yrs	22,000	21,000	27,000	9,000	79,000
≥45 yrs	280	310	1,900	6,000	8,500
M: Infant mortality and pregnancy losses	97	100	46	11	254
R: Infections					
<4 yrs	8,300,000	16,000,000	1,800,000	30,000	26,100,000
5–14 yrs	8,600,000	18,000,000	1,800,000	31,000	28,400,000
15–49 yrs	400,000	370,000	80,000	19,000	870,000
≥45 yrs	400,000	380,000	81,000	26,000	890,000
R: Infant mortality (including CRS cases that do not survive to 1 year old) and pregnancy losses	13,000	7,000	1,300	110	21,000
R: CRS cases in surviving infants	30,000	17,000	2,900	83	50,000
DALY losses due to					
M: Infections	7,100,000	5,600,000	930,000	56,000	13,700,000
M: Infant mortality and pregnancy losses	6,000	6,100	3,000	850	16,000
M: Total	7,100,000	5,600,000	930,000	57,000	13,700,000
R: Infections	61,000	69,000	17,000	2,100	150,000
R: Infant mortality (including CRS cases that do not survive to 1 year old) and pregnancy losses	790,000	450,000	93,000	9,000	1,300,000
R: CRS cases in surviving infants	890,000	460,000	66,000	1,600	1,400,000
R: Total	1,700,000	980,000	180,000	13,000	2,900,000
M&R: Total	8,900,000	6,600,000	1,100,000	70,000	16,700,000
Treatment cost estimates[a] ($ millions) [additional home care costs]					
M: Infections	32 [78]	510 [270]	280 [140]	740 [360]	1,600 [850]
M: Infant mortality and pregnancy losses	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
M: Total	32 [78]	510 [270]	280 [140]	740 [360]	1,600 [850]
R: Infections	23 [290]	370 [930]	160 [300]	95 [15]	650 [1,500]
R: Infant mortality (including CRS cases that do not survive to 1 year old) and pregnancy losses	0.1[0]	0.7 [0]	0.4 [0]	0.2 [0]	1.4 [0]
R: CRS cases in surviving infants	340 [0]	1,300 [0]	640 [0]	77 [0]	2,400 [0]
R: Total	360 [290]	1,700 [1,000]	800 [300]	170 [15]	2,900 [1,600]
M&R: Total	400 [360]	2,100 [1,300]	1,100 [440]	910 [380]	4,500 [2,500]
Vaccination cost estimates ($ millions)					
Routine immunization	37	130	560	1,200	1,900
SIAs[b]	54	260	800	320	1,400
Adverse events	0.2	25	53	52	130
Total	91	420	1,400	1,600	3,400
Productivity ($/DALY for WBIL)	770	3,800	11,200	47,800	
Productivity losses ($ millions)	6,900	25,000	12,000	3,300	47,000
Total costs ($ millions)					
Vaccination + treatment + home care	850	3,800	2,900	2,900	10,000
Vaccination + treatment + productivity	7,800	29,000	15,000	6,200	58,000

Notes: CRS, congenital rubella syndrome; DALY, disability-adjusted life year; M, measles-associated; R, rubella-associated; SIAs = supplemental immunization activities; WBIL = World Bank income level.

[a]Does not include home care costs [reported separately].

[b]Includes vaccine costs associated with outbreak response SIAs (oSIAs).

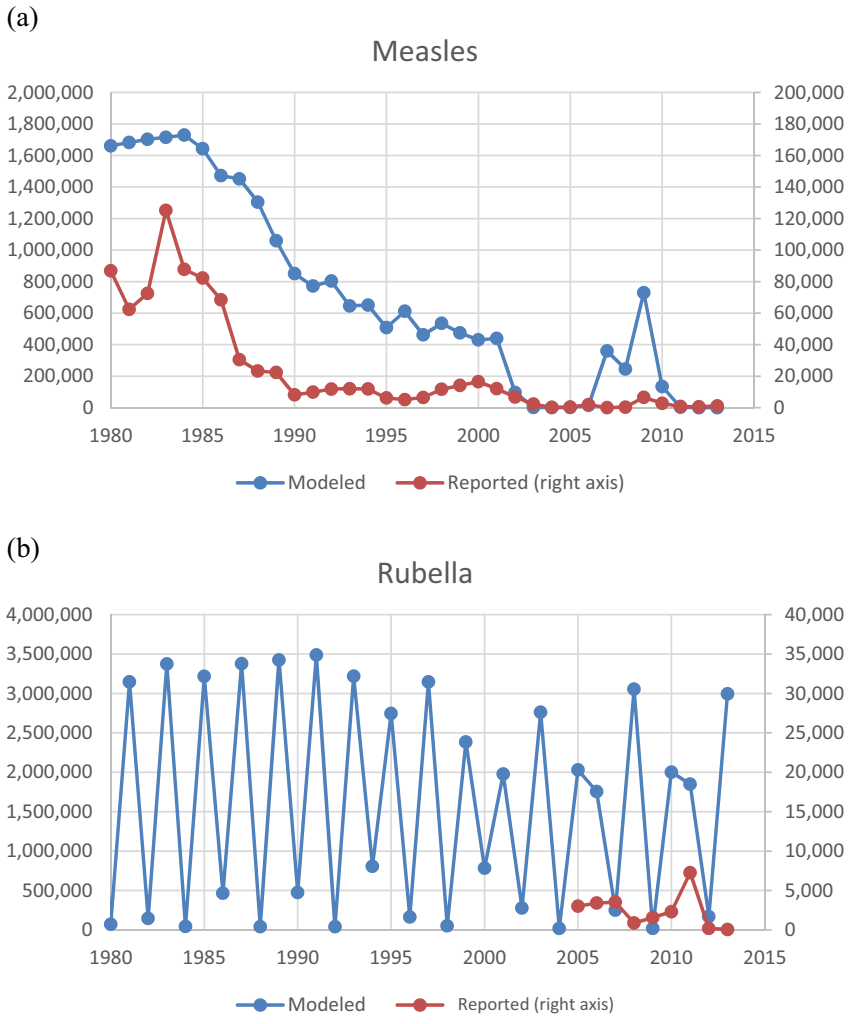

Fig. 6. Model fit for Vietnam for measles (Fig. 6a) and rubella (Fig 6b) (lower middle-income country, $R_{0,M} = 13.1$, $R_{0,R} = 6.8$, $\kappa = 0.4$, $s_C = 75$, $s_M = 0.13$, $s_R = 0.31$).

level and the associated estimated DALYs and costs for treatment and vaccination for 2013. Table II also shows estimated costs of $3 billion associated with measles and rubella immunization in 2013 using the estimated doses from the model, which leads to slightly higher estimated immunization costs than a prior $2.3 billion estimate[23] due to changes in coverage estimates and the inclusion of ORI in the model (e.g., for the United States and the Netherlands). When combined, these results suggest potential savings of over $7 billion or $10 billion (if including home costs) per year if the world were to eradicate measles and rubella instead of continuing to pursue control.

The overall results depend largely on a small set of countries with large populations and relatively low RI coverage (e.g., India, Nigeria, Indonesia, Bangladesh, Vietnam, Kenya, Democratic Republic of the Congo, Pakistan, Philippines, United Republic of Tanzania, and Uganda), and changes to the model fitting for these countries could notably change the overall estimates. Historically, prior to the introduction of immunization, developed large countries (e.g., China, the United States, and Russia) also contributed significantly to annual burden of disease estimates. In relatively higher income countries, the results of CRS cases depend on the timing of episodic outbreaks (e.g., an outbreak in Japan in 2013[63]). The opportunity to update the model with improved information makes it a useful living tool, but it also implies that as information improves, some estimates will change. However, the overall conclusion that eradication would save billions of dollars per year in treatment costs and could save over a billion dollars

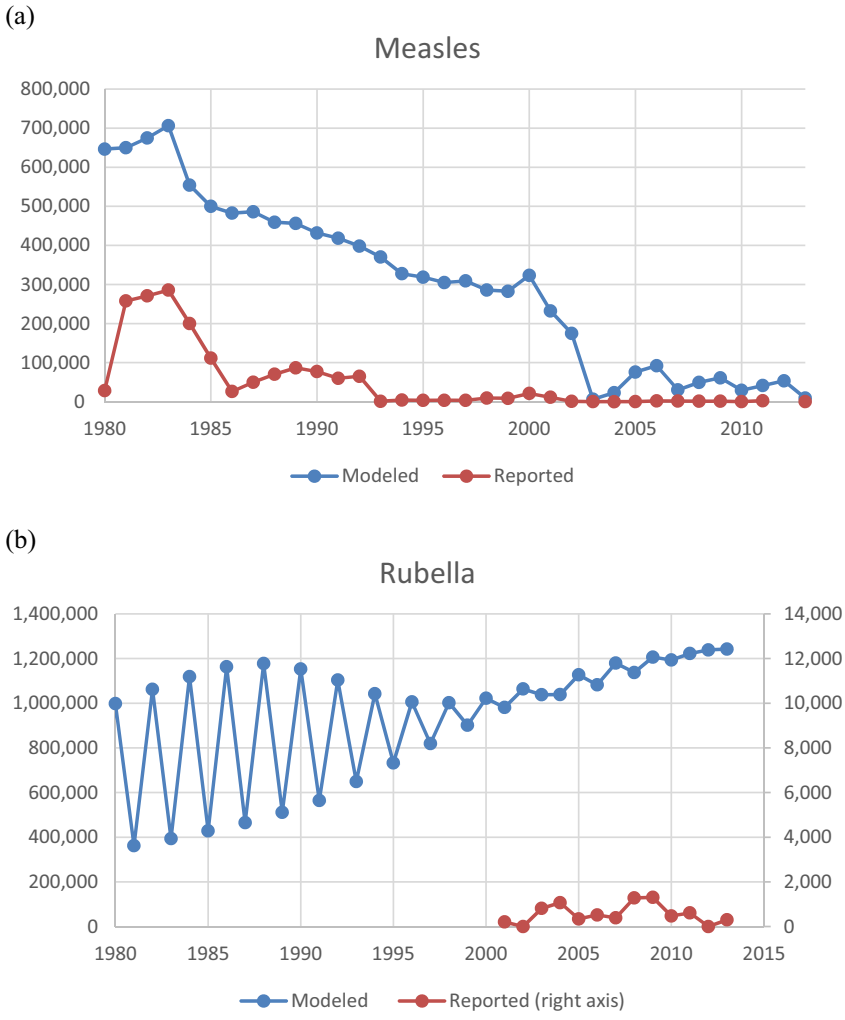

Fig. 7. Model fit for Kenya for measles (Fig. 7a) and rubella (Fig 7b) (low-income country, $R_{0,M} = 12.2$, $R_{0,R} = 5.2$, $\kappa = 0.35$, $s_C = 75$, $s_M = 0.012$, $s_R = 0.15$).

per year associated with vaccination costs remains robust, and it reflects the reality that the expected costs associated with treating measles and rubella infections far exceed the expected costs associated with immunization.[23]

4. DISCUSSION

Similar to other vaccine-preventable diseases, despite extensive experience with measles and rubella, many aspects of their transmission remain uncertain and variable, and data quality issues limit our understanding and ability to model their transmission with confidence. We created and applied a transmission model to support the comparison of national and global policies despite the uncertainties, and we use the best available historical evidence to create the initial estimates of population immunity in 2013. The level of measles and rubella control in 2013 represents relatively high control in most countries, although the level of control remains highly variable, with some countries performing relatively poorly and continuing to experience a significant burden of disease. When eradication represents an option, economic analyses suggest that eradication represents a better option than control,[64–66] and our results suggest this is the case for measles and rubella. Specifically, our results suggest that the world could save over $10 billion dollars every year by eradicating measles and rubella instead of continuing relatively high control. Achieving eradication will require a global commitment to coordinate efforts to achieve and maintain high population immunity in all places at the same time, which will require the investment of sufficient and sustained financial resources.

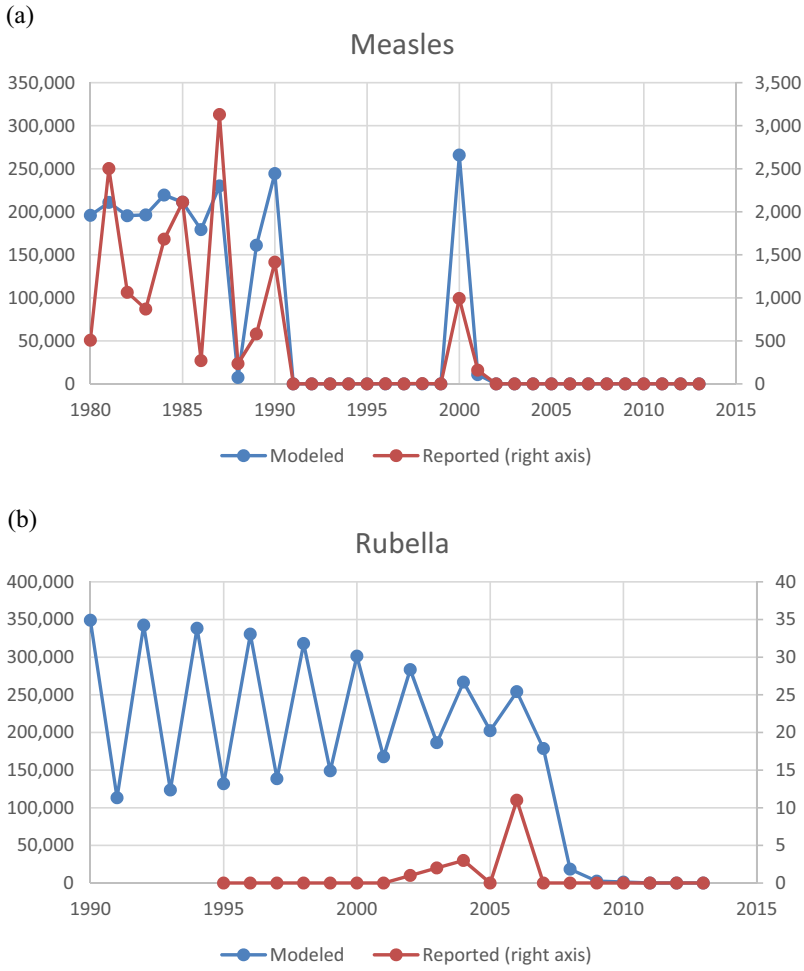

Fig. 8. Model fit for Haiti for measles (Fig. 8a) and rubella (Fig 8b) (low-income country, $R_{0,M} = 13.7$, $R_{0,R} = 6.5$, $\kappa = 0.3$, $s_C = 75$, $s_M = 0.3$, $s_R = 0.1$).

As in the case of modeling polio, retrospective fitting allows us to match the patterns of incidence including die out and importations. For example, restricting the timing of importations to approximate times and subpopulations with known importations yields a different pattern of incidence than allowing importations to occur at any time. In reality, importations occur stochastically, and for prospective modeling we cannot predict when or where future importations will occur. This suggests that for prospective modeling, modeling the importations stochastically may represent a necessary approach to explore all of the possible futures.[38]

As measles and rubella incidence decline, fear about the infectious diseases also decreases, and any concerns about vaccine-associated risks become more important. Evidence already suggests that some individuals perceive the risks of measles and rubella immunization as greater than the risks of measles (and rubella) infections, such that some individuals may seek to free ride on high levels of population immunity. Individuals who forgo measles and rubella immunization for themselves and/or their families put themselves and their communities at risk. When outbreaks occur, perceptions about the risks of the diseases change, leading to reactive increases in immunization that increase population immunity. This type of wavering can threaten efforts to sustain elimination of transmission in an area and support sustained global transmission that prohibits regional elimination and global eradication efforts. Elimination and eradication become more challenging over time because the population continues to increase and susceptible individuals of increasingly older ages may accumulate as transmission of the wild viruses decrease. Delayed commitments to elimination and eradication of measles and rubella continue to lead to significant health and financial

costs, most of which could be prevented and saved. Thus, with respect to the dynamics of achieving eradication, these dynamic factors combined with the significant potential annual net savings suggest that the world could recognize the greatest health and economic benefits by mobilizing resources and engaging in a committed intensive effort to rapidly eradicate measles and rubella. Engaging in this effort on the heels of polio eradication would most likely benefit significantly from its investments in efforts to identify and reach undervaccinated subpopulations (e.g., extensive microplanning, performance monitoring, accountability models, etc.). Similar to polio eradication, efforts to eradicate measles and rubella will need to deal with identifying and immunizing undervaccinated people, including those in insecure and socially disrupted areas and those who may not perceive that the benefits of vaccination exceed the risks and costs. In addition, global measles and rubella eradication will require global capacity to manage any unexpected events that occur that would otherwise lead to a delay in regional elimination and global eradication efforts.

Our model makes many simplifying assumptions, although it includes the capacity to capture sufficient heterogeneity in age mixing and with respect to the potential for underimmunized individuals to preferentially interact. Other assumptions about mixing would lead to input parameters that may suggest a different behavior in the model and that may offer an alternative and possibly improved fit. We assume that true and unknown values for R_0, seasonality characteristics, and preferential mixing (κ) exist for every area, and that some generic model inputs related to the measles or rubella virus remain constant across all countries. However, in reality, disease transmission occurs stochastically and any model represents a simplification.

We believe that the differential-equation-based model described here will support the characterization of population immunity and the exploration and comparison of potential options for prospective policy analyses, similar to models developed for polio. The model provides reasonable characterizations for endemic measles and rubella transmission before and after vaccination and for countries with continued and eliminated endemic transmission. The process of developing the model led us to identify and use input values that may not represent a unique solution, and other combinations of inputs may lead to similar or better model fits. We suggest that while this model may provide the best currently available estimates, further iteration could and should improve estimates. Thus, we anticipate that this model will prove most useful not by providing a current best estimate, but as a living model used to evaluate and use the best available evidence over time, explore key prospective policy questions, and identify key sources of uncertainty that may impact the costs and benefits of measles and rubella immunization over time.

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REFERENCES

1. Thompson KM, Dabbagh A, Strebel PM, Perry R, Gacic-Dobo M, Cochi SL, Cairns L, Reef S. National and global options for managing the risks of measles and rubella. Journal of Vaccines and Vaccination, 2012; 3:165. doi: 10.4172/2157-7560.1000165.
2. Thompson KM. Evolution and use of dynamic transmission models for measles and rubella. Risk Analysis, 2016; 36(7):1383–1403.
3. Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: A dynamic perspective. Statistics in Medicine, 1999; 18(23):3263–3282.
4. Brisson ME, Edmunds WJ. Economic evaluation of vaccination programs: The impact of herd-immunity. Medical Decision Making, 2003; 23(1):76–82.
5. Thompson KM, Tebbens RJ. Retrospective cost-effectiveness analyses for polio vaccination in the United States. Risk Analysis, 2006; 26(6):1423–1440.
6. World Health Organization. WHO Guide for Standardization of Economic Evaluations of Immunization Programmes. Geneva: Initiative for Vaccine Research, Department of Immunization, Vaccine, and Biologicals, Report No.: WHO/IVB/0814, December 2008.
7. Levin A, Burgess C, Garrison LP, Jr., Bauch C, Babigumira J, Simons E, Dabbagh A. Global eradication of measles: An epidemiologic and economic evaluation. Journal of Infectious Diseases, 2011; 204(Suppl 1):S98–S106.
8. Bishai D, Johns B, Lefevre A, Nair D, Simons E, Dabbagh A. Measles eradication versus measles control: An economic analysis. Journal of Vaccines and Vaccination, 2012; S:3. Available at: https://doi.org/10.4172/2157-7560.S3-002, Accessed March 1, 2017.
9. Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, Strebel P. Assessment of the 2010 global measles mortality reduction goal: Results from a model of surveillance data. Lancet, 2012; 379(9832):2173–2178.
10. Perry RT, Murray JS, Gacic-Dobo M, Dabbagh A, Mulders MN, Strebel PM, Okwo-Bele J-M, Rota PA, Goodson JL. Progress toward regional measles elimination—Worldwide, 2000–2014. Weekly Epidemiological Record, 2015; 90(46):623–631.

11. Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar-Boggan AM, Simons E, Yoshida LM, Brown DW, Jackson C, Strebel PM, Dabbagh AJ. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996–2010: A systematic review. Plos One, 2016; 11(3):e0149160.
12. Thompson KM, Duintjer Tebbens RJ. Development of investment cases for globally-coordinated management of infectious diseases. Journal of Vaccines and Vaccination, 2012; 3:164. doi: 10.4172/2157-7560.1000164.
13. Duintjer Tebbens RJ, Pallansch MA, Kalkowska DA, Wassilak SG, Cochi SL, Thompson KM. Characterizing poliovirus transmission and evolution: Insights from modeling experiences with wild and vaccine-related polioviruses. Risk Analysis, 2013; 33(4):703–749.
14. Duintjer Tebbens RJ, Kalkowska DA, Wassilak SG, Pallansch MA, Cochi SL, Thompson KM. The potential impact of expanding target age groups for polio immunization campaigns. BMC Infectious Diseases, 2014; 14:45.
15. Kalkowska DA, Duintjer Tebbens RJ, Grotto I, Shulman LM, Anis E, Wassilak SGF, Pallansch MA, Thompson KM. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. Journal of Infectious Diseases, 2015; 211(11):1800–1812.
16. Kalkowska DA, Duintjer Tebbens RJ, Thompson KM. Modeling strategies to increase population immunity and prevent poliovirus transmission in two high-risk areas in northern India. Journal of Infectious Diseases, 2014; 210(S1):398–411.
17. Kalkowska DA, Duintjer Tebbens RJ, Thompson KM. Modeling strategies to increase population immunity and prevent poliovirus transmission in the high-risk area of northwest Nigeria. Journal of Infectious Diseases, 2014; 210(S1):412–423.
18. de Boo TM, van Druten JA, Plantinga AD. Predicting the dynamic effects of rubella vaccination programmes. Statistics in Medicine, 1987; 6(7):843–851.
19. Agur Z, Danon YL, Anderson RM, Cojocaru L, May RM. Measles immunization strategies for an epidemiologically heterogeneous population: The Israeli case study. Proceedings. of the Royal Society, Series B: Biological Sciences, 1993; 252(1334):81–84.
20. Glass K, Kappey J, Grenfell BT. The effect of heterogeneity in measles vaccination on population immunity. Epidemiology and Infection, 2004; 132(4):675–683.
21. Thompson KM, Odahowski CL, Goodson JL, Reef SE, Perry RT. Synthesis of evidence to characterize national historical measles and rubella exposure and immunization histories. Risk Analysis, 2016; 36(7):1427–1458.
22. Thompson KM, Odahowski CL. Systematic review of measles and rubella serology studies. Risk Analysis, 2016; 36(7):1459–1486.
23. Thompson KM, Odahowski CL. The costs and valuation of health impacts of measles and rubella risk management policies Risk Analysis 2016; 36(7):1357–1382.
24. Edmunds WJ, van de Heijden OG, Eerola M, Gay NJ. Modelling rubella in Europe. Epidemiology and Infection, 2000; 125(3):617–634.
25. Bauch CT, Szusz E, Garrison LP. Scheduling of measles vaccination in low-income countries: Projections of a dynamic model. Vaccine, 2009; 27(31):4090–4098.
26. Strebel PM, Papania MJ, Fiebelkorn AP, Halsey NA. Measles vaccine. Pp. 352–387 in Plotkin SA, Orenstein WA, Offit PA (eds). Vaccines: Expert Consult, 6th ed. Philadelphia, PA: Elsevier Saunders, 2012.
27. United Nations Population Division. World Population Prospects: The 2012 Revision. Available at: http://esa.un.org/unpd/wpp/index.htm, Accessed September 11, 2013.
28. Thompson KM, Simons EA, Badizadegan K, Reef SE, Cooper LZ. Characterization of the risks of adverse outcomes following rubella infection in pregnancy. Risk Analysis, 2016; 36(7):1315–1331.
29. Sterman JD. Business Dynamics: Systems Thinking and Modeling for a Complex World. Boston, MA: McGraw-Hill, 2001.
30. Lloyd AL. Realistic distributions of infectious periods in epidemic models: Changing patterns of persistence and dynamics. Theoretical Population Biology, 2001; 60(1):59–71.
31. Rota JS, Hickman CJ, Sowers SB, Rota PA, Mercader S, Bellini WJ. 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–S563.
32. Fogel A, Handsher R, Barnea B. Subclinical rubella in pregnancy—Occurrence and outcome. Israel Journal of Medical Sciences, 1985; 21(2):133–138.
33. Rosen JB, Rota JS, Hickman CJ, Sowers S, Mercader S, Rota PA, Bellini WJ, Huang AJ, Doll MK, Zucker JR, Zimmerman CM. Outbreak of measles among persons with prior evidence of immunity, New York City, 2011. Clinical Infectious Diseases, 2014; 58(9):1205–1210.
34. Gans HA, Maldonado YA. Loss of passively acquired maternal antibodies in highly vaccinated populations: An emerging need to define the ontogeny of infant immune responses. Journal of Infectious Diseases, 2013; 208(1):1–3.
35. World Health Organization. Measles Vaccine: WHO Position Paper. Weekly Epidemiological Record, 2009; 84(35):349–360.
36. Uzicanin A, Zimmerman L. Field effectiveness of live attenuated measles-containing vaccines: A review of published literature. Journal of Infectious Diseases, 2011; 204 (Suppl 1):S133–S148.
37. Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassilak SG, Linkins J, Sutter RW, Aylward RB, Thompson KM. Economic analysis of the global polio eradication initiative. Vaccine, 2010; 29(2):334–343.
38. Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassilak SGF, Thompson KM. An economic analysis of poliovirus risk management policy options for 2013–2052. BMC Infectious Diseases, 2015; 15(1):1–21.
39. World Bank. New Country Classifications, World Bank Income Levels, 2013. Available at: http://data.worldbank.org/news/new-country-classifications, Accessed March 3, 2014.
40. Goodson JL, Masresha B, Dosseh A, Byabamazima C, Nshimirimana D, Cochi S, Reef S. Rubella epidemiology in Africa in the prevaccine era, 2002–2009. Journal of Infectious Diseases, 2011; 204(Suppl 1):S215–S225.
41. Jacquez JA, Simon CP, Koopman J, Sattenspiel L, Perry T. Modeling and analyzing HIV transmission: The effect of contact patterns. Mathematical Biosciences, 1988; 92:119–199.
42. Glasser J, Feng ZL, Moylan A, Del Valle S, Castillo-Chavez C. Mixing in age-structured population models of infectious diseases. Mathematical Biosciences, 2012; 235(1):1–7.
43. Measles and rubella model technical details and input profiles, 2016. Available at: http://www.kidrisk.org, Accessed April 5, 2017.
44. Badilla X, Morice A, Avila-Aguero ML, Saenz E, Cerda I, Reef S, Castillo-Solorzano C. Fetal risk associated with rubella vaccination during pregnancy. Pediatric Infectious Disease Journal, 2007; 26(9):830–835.
45. Bloch AB, Orenstein WA, Stetler HC, Wassilak SG, Amler RW, Bart KJ, Kirby CD, Hinman AR. Health impact of measles vaccination in the United States. Pediatrics, 1985; 76(4):524–532.
46. Orenstein WA. The role of measles elimination in development of a national immunization program. Pediatric Infectious Disease Journal, 2006; 25(12):1093–1101.

47. Wichmann O, Siedler A, Sagebiel D, Hellenbrand W, Santibanez S, Mankertz A, Vogt G, Treeck U, Krause G. Further efforts needed to achieve measles elimination in Germany: Results of an outbreak investigation. Bulletin of the World Health Organization, 2009; 87(2):108–115.
48. Ortega-Sanchez IR, Vijayaraghavan M, Barskey AE, Wallace GS. The economic burden of sixteen measles outbreaks on United States public health departments in 2011. Vaccine, 2014; 32:1311–1317.
49. Wallace AS, Masresha BG, Grant G, Goodson JL, Birhane H, Abraham M, Endailalu TB, Letamo Y, Petu A, Vijayraghavan M. Evaluation of economic costs of a measles outbreak and outbreak response activities in Keffa zone, Ethiopia. Vaccine, 2014; 32(35):4505–4514.
50. Suijkerbuijk AWM, Woudenberg T, Hahné SJM, Lochlainn LN, de Melker HE, Ruijs WLM, Lugnér AK. Economic costs of measles outbreak in the Netherlands, 2013–2014. Emerging Infectious Disease Journal, 2015; 21(11):2067–2069.
51. Lessler J, Metcalf CJ. Balancing evidence and uncertainty when considering rubella vaccine introduction. PLoS One, 2013; 8(7):e67639.
52. Thompson KM, Kisjes KH. Modeling measles transmission in the North America Amish and options for outbreak response. Risk Analysis, 2016; 36(7):1404–1417.
53. Sugerman DE, Barskey AE, Delea MG, Ortega-Sanchez IR, Bi D, Ralston KJ, Rota PA, Waters-Montijo K, Lebaron CW. Measles outbreak in a highly vaccinated population, San Diego, 2008: Role of the intentionally undervaccinated. Pediatrics, 2010; 125(4):747–755.
54. Katz SL, Hinman AR. Summary and conclusions: Measles elimination meeting, 16–17 March 2000. Journal of Infectious Diseases, 2004; 189:S43–S47.
55. Gastañaduy PA, Redd SB, Fiebelkorn AP, Rota JS, Rota PA, Bellini WJ, Seward JF, Wallace GS. Measles—United States, January 1–May 23, 2014. Morbidity and Mortality Weekly Report, 2014; 63(22):496–499.
56. Orenstein WAB, KJ, Hinman AR, Preblud, SR, Greaves WL, Doster SW, Stetler HC, Sirotkin B. The opportunity and obligation to eliminate rubella from the United States. JAMA, 1984; 251(15):1988–1994.
57. Briss PA, Fehrs LJ, Hutcheson RH, Schaffner W. Rubella among the Amish: Resurgent disease in a highly susceptible community. Pediatric Infectious Disease Journal, 1992; 11(11):955–959.
58. van den Hof S, Conyn-van Spaendonck MAE, van Steenbergen JE. Measles epidemic in the Netherlands, 1999–2000. Journal of Infectious Diseases, 2002; 186(10):1483–1486.
59. Hahne S, Macey J, van Binnendijk R, Kohl R, Dolman S, van der Veen Y, Tipples G, Ruijs H, Mazzulli T, Timen A, van Loon A, de Melker H. Rubella outbreak in the Netherlands, 2004–2005: High burden of congenital infection and spread to Canada. Pediatric Infectious Disease Journal, 2009; 28(9):795–800.
60. World Health Organization. Expanded programme on immunization. Rubella outbreak. Weekly Epidemiological Record, 1994; 69(45):333–337.
61. Patel PK, Al-Awaidy ST, Bawikar S, Al-Busaidy S, Al-Mahrooqi S. Measles epidemiology and its implications for a vaccination programme in Oman. Eastern Mediterranean Health Journal, 2008; 14(3):579–589.
62. Toda K, Reef S, Tsuruoka M, Iijima M, Dang TH, Duong TH, Nguyen VC, Nguyen TH. Congenital rubella syndrome (CRS) in Vietnam 2011–2012—CRS epidemic after rubella epidemic in 2010–2011. Vaccine, 2015; 33(31):3673–3677.
63. Centers for Disease Control and Prevention. Nationwide rubella epidemic—Japan, 2013. Morbidity Mortality Weekly Report, 2013; 14(62):457–462.
64. Geoffard P-Y, Philipson T. Disease eradication: Private versus public vaccination. American Economic Review, 1997; 87(1):222–230.
65. Barrett S. Eradication versus control: The economics of global infectious disease policies. Bulletin of the World Health Organization, 2004; 82(9):639–718.
66. Thompson KM, Tebbens RJ. Eradication versus control for poliomyelitis: An economic analysis. Lancet, 2007; 369(9570):1363–1371.