Exploration of future immunization policies for measles and rubella: The need for continued investment and the potential benefits of eradication

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Executive Summary

Measles and rubella viruses continue to pose health and economic costs despite widespread use of highly-effective, safe, and relatively inexpensive vaccines that provide lifelong protection from the serious adverse health effects caused by both viruses. Decades of national and regional measles and rubella control activities led to significant progress toward achieving regional elimination targets, but a recent review found that despite tremendous gains, the progress toward regional elimination goals and the Global Vaccine Action Plan targets remains off track. Significant delays in the achievement of global polio eradication and post-polio eradication transition planning raise questions about global investments and targets to manage vaccine-preventable diseases, and increase demands for the justification of expenditures on a wide range of competing health priorities. This analysis explores the case for global investment in measles and rubella immunization by estimating the incremental potential health and economic benefits associated with a scenario that seeks to eradicate both diseases as quickly as possible within the constraints of historical programmatic performance (as an upper bound of the potential benefits of future investments) relative to maintaining the 2016 *status quo*.

The first section provides context about measles and rubella viruses and vaccines, and the current landscape for measles and rubella control and elimination targets. Readers familiar with measles and/or rubella may wish to skip or skim this section. The second section provides high level context about the integrated model used for this analysis and an annex provides more details. The third section presents preliminary results, and the fourth section briefly discusses insights. The fifth section discusses next steps for this work and the final section provides references.

1. Introduction

Measles virus infections remain a leading preventable cause of estimated child deaths worldwide,[1] and congenital rubella syndrome (CRS) caused by rubella virus infection in early pregnancy represents one of the leading infectious disease causes of congenital birth defects globally.[2] These continued global burdens of disease occur despite the availability over many decades of highly-effective, safe, and relatively inexpensive vaccines that provide lifelong protection from serious adverse health effects caused by both viruses.[3, 4] By 1980, all World Health Organization (WHO) Member States introduced measles vaccine (first-licensed in the US in 1963) into their national immunization programs.[4] In contrast, rubella vaccine (first licensed in the US in 1969) experienced more gradual global introduction, with some national immunization programs still yet to introduce it.[4] The licensure of combination vaccines containing measles and rubella (e.g., MR, MMR) created an opportunity for sharing the costs of vaccine administration, and all countries that include rubella vaccine in their national immunization schedules use a combination vaccine.[4] A large body of literature demonstrates the excellent cost-effectiveness and high net health and economic benefits of measles and rubella

immunization.[5, 6] Notably, a recent analysis for 94 relatively low-income countries estimated a net return on investment for 10 vaccines of about 16 times greater than costs, and found the highest returns came from averting measles, at 58 times the cost (uncertainty range: 28-105).[7]

Despite the significant health and economic benefits, recognizing the full potential of using measles and rubella vaccines remains uneven geographically. The US launched the first national measles elimination goal in 1967.[8] Indicative of the challenges of national elimination, after establishing three different national measles elimination initiatives over several decades, the US successfully stopped indigenous measles[9] and rubella[10] virus by 2004. Since the introduction of the vaccines, national goals to eliminate measles and/or rubella emerged at various times. The WHO Region of the Americas, under the leadership of the Pan American Health Organization (PAHO), established the first WHO regional elimination goals for measles and rubella: in 1994, to eliminate indigenous measles virus transmission by the year 2000,[11] and in 2003, to eliminate indigenous rubella virus transmission by the year 2010.[12] The WHO Region of the Americas declared indigenous rubella eliminated in 2015[12] and indigenous measles eliminated in 2016,[11] following successful regional elimination activities. The other 5 WHO regions also established target years for regional measles elimination, all by 2020 or earlier.[13]

Over the last several decades, the World Health Assembly (WHA) established several goals for related to measles and rubella, including:

- In 1974, recommending "that Member States develop or maintain immunization and surveillance programmes against measles" (resolution 27.57)[14]
- In 1978, resolving to "by 1990 make measles vaccine available to every child in the world as part of the Expanded Programme on Immunization" (resolution 31.53)[15]
- In 1989, resolving to "by 1995 reduce measles cases by 90% and measles deaths by 95% compared to pre-immunization levels" (resolution 42.32)[16]
- In 2003, resolving to "by 2005 reduce measles deaths by 50% compared to 1999 levels" (resolution 56.20)[17]
- In 2005, resolving "as part of the Global Immunization Vision and Strategy, 2006-2015 (GIVS),[18] by 2010 reduce measles deaths by 90% compared to 2000 levels" (resolution 58.15)[19]
- In 2010, discussing milestones for global eradication of measles and endorsing by 2015 "to reduce measles mortality by 95% or more in comparison with 2000 estimates" (provisional agenda A63.18).[20]
- In 2012, resolving "as part of the Global Vaccine Action Plan (GVAP),[21] by 2015 to "eliminate measles in four WHO regions and rubella/congenital rubella syndrome in at least two WHO regions and by 2020 eliminate measles and rubella in at least five WHO regions" (resolution 65.17)[22]

In November 2010, the WHO Strategic Advisory Group of Experts (SAGE) concluded: "measles can and should be eradicated. A goal for measles eradication should be established with a proposed target date based on measurable progress made towards existing goals and targets."[23] The International Task Force for Disease Eradication in 2009 identified measles as a good candidate for global eradication[24] and reached the same conclusions for measles and rubella in 2016.[25]

For a variety of reasons, including the very high coverage needed to achieve and maintain measles elimination and insufficient political commitment and resources, global progress toward reducing measles incidence and mortality slowed during the past several years, which makes on-time achievement of the GVAP targets unlikely.[13] A recent review[26, 27] of the status of the Global Measles and Rubella Strategic Plan 2012-2020[28] reached a similar conclusion that progress remains off track, while noting the tremendous gains made toward both measles and rubella elimination since 2001.[26, 27] The recent review conclusions included that "measles eradication is the ultimate goal but it is premature to set a date for its accomplishment[, existing] regional elimination goals should be vigorously pursued to enable setting a global target by 2020[, and the] basic strategic approaches articulated in the Global Measles and Rubella Strategic Plan 2012-2020 are valid to achieve the goals but have not been fully implemented (or not appropriately adapted to local situations)."[26, 27]

Recognizing the variability that exists in national immunization programs, the WHO SAGE continues to update its immunization recommendations for measles- and rubella-containing vaccines. Providing all children with 2 doses of measles vaccine became the standard for all national immunization programs in 2009, with the second dose delivered either through supplemental immunization activities (SIAs) or through routine health services.[29] In 2011, the WHO SAGE updated its guidance on the preferred strategy for the introduction of rubella vaccine into national routine immunization (RI) schedules, including an initial vaccination campaign usually targeting children aged 9 months-15 years.[30] As of December 2014, 140 countries included rubella vaccine in their national immunization schedules, which reflected an increase up from 99 countries in 2000.[2] As of the end of 2016, 152 WHO member states included rubella vaccine in RI.[31] Part of this increase reflected support of over $500 million from Gavi, the Vaccine Alliance, to facilitate rubella vaccine introduction into the Gavi countries without rubella vaccine in their RI schedules as of 2012.[32] In December 2015, the Gavi Board strengthened its commitment to measles and rubella immunization.[33] In 2016, the WHO SAGE recommended the inclusion of a second dose of measles vaccine in all national immunization schedules as part of routine health services.[34]

Disease eradication represents the ultimate opportunity to achieve global equity with respect to eradicable diseases, and in this context measles and rubella eradication would help to advance the achievement of the United Nations 2030 Sustainable Development Goal 3 "to end preventable deaths of newborns and children under 5 years of age"[35] by increasing vaccination coverage to levels needed to end vaccine-preventable disease (VPD) deaths in children. Although population immunity and immunization coverage at the local level determine transmission (or lack thereof), aggregation to national, regional, and global levels provide an important perspective for VPDs that transmit easily across borders. At the global level, slow progress of measles elimination implies high on-going health and financial burdens associated with indefinitely sustaining relatively high immunization coverage in countries that eliminated indigenous transmission.[36] Consistent with the series of WHA targets to reduce measles and rubella burdens, despite the variability that exists between countries and regions, measles and rubella appear relatively highly controlled at a global level.[36]

In countries that successfully eliminate measles and/or rubella, importations from endemic areas pose a threat of local transmission and expensive outbreak response activities.[36] Given the

available combination vaccines and the much lower transmissibility of rubella virus (compared to measles), rubella eradication could easily occur in the context of a measles eradication effort, which would prevent additional health and financials costs.[37] Moreover, in some countries with good disease control, children neither vaccinated nor exposed to these viruses remain susceptible as they reach older ages and even adulthood, which makes the task of stopping measles and rubella virus transmission epidemiologically more complex, expensive, and programmatically difficult to achieve.

Within the complex global context, exploring the case for continued and further investment in measles and rubella control and elimination goals may provide useful insights for national, regional, and global policy makers. Launched in 2001, the Measles & Rubella Initiative[38] remains committed to efforts to ensure "that no child dies from measles or is born with congenital rubella syndrome" and to "help countries to plan, fund and measure efforts to stop measles and rubella for good,"[38] although its funding and global support from key eradication donors pales in comparison to funds spent on the Global Polio Eradication Initiative (GPEI) and malaria eradication.[39] As the GPEI continues with the process of transitioning its responsibilities and any residual assets to countries, the significant support provided by the GPEI that benefits other VPDs, including measles and rubella, emerges as a concern. Notably, an April 2017 WHO report highlighted that: (i) 16 countries (i.e., Afghanistan, Angola, Bangladesh, Cameroon, Chad, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Myanmar, Nepal, Nigeria, Pakistan, Somalia, South Sudan, and Sudan) account for "90% of all the GPEI supported polio infrastructure;" (ii) budget decreases for 2017-2019 (compared to 2016) already led to a "substantial number of staff receiving termination notices, particularly in the African region;" (iii) "all of AFRO's 47 WHO country offices receive GPEI seed surveillance funding on a quarterly basis to allow countries to conduct active surveillance activities for, not only Acute Flaccid Paralysis (AFP) but other VPD surveillance activities" (including measles and rubella); and (iv) for 2016, "WHO globally spent US$587 million on polio eradication, which is 27% of its total expenditure in 2016."[40] The report also notes that the "loss of approximately 20% of WHO's biennium budget would have grave consequences for WHO's capacity at the country level in member states that have weak health systems or in fragile states, especially at the provincial and district levels."[40]

Given the current changes in national, regional, and global investments in VPD management and the demands from the GVAP for the development of investment cases to support difficult decisions related to expenditures on competing health priorities,[41] this analysis seeks to explore the bounds of the global incremental health and financial benefits that may arise from increased investment in measles and rubella immunization by comparing a scenario of eradication of both diseases as soon as possible to maintaining the 2016 *status quo*.

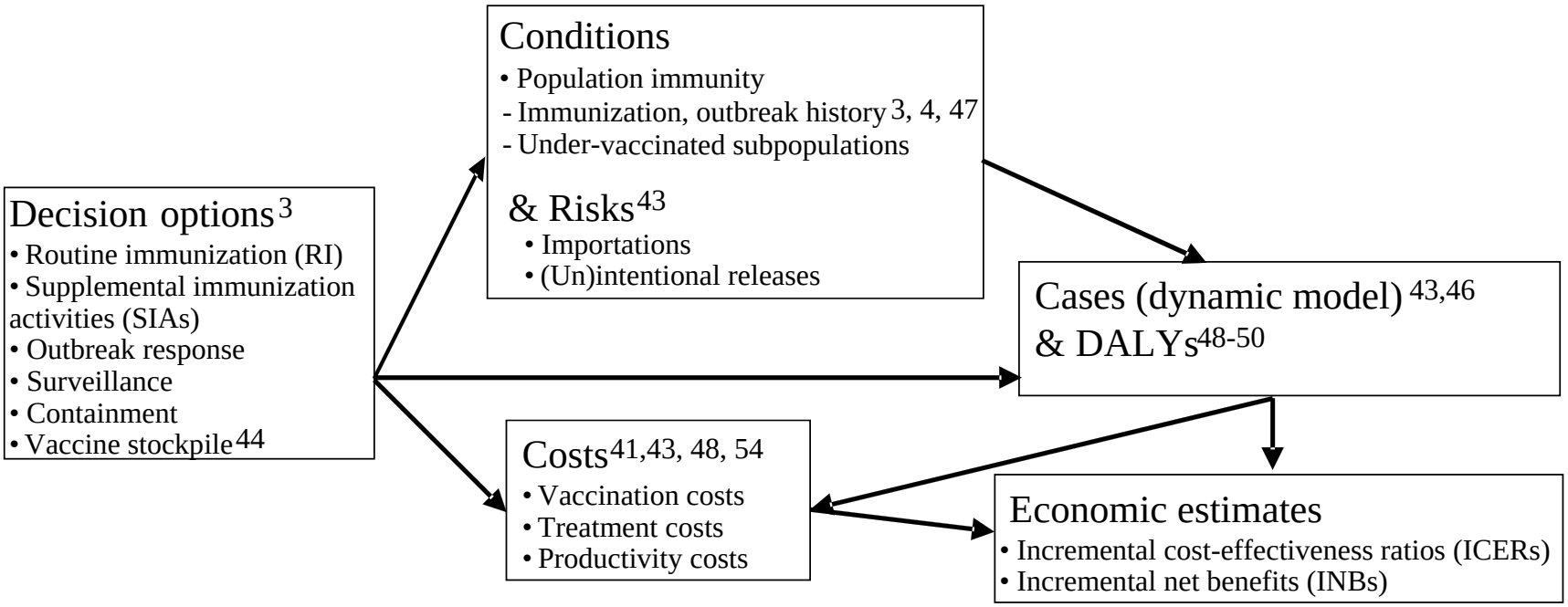
2. Methods

Similar to a model developed and used over a decade to support deliberations by the GPEI partners for polio eradication,[42] this analysis uses an integrated dynamic risk and economic model developed for measles and rubella.[43] The measles and rubella model includes multiple components, described at a high level in Figure 1, which includes references to the publications that provide details about the inputs and assumptions. Briefly, the model considers different

decision options that national, regional, and global policy makers consider, with a focus on RI and SIAs[3] and including some consideration of the importance of ensuring sufficient availability of vaccine.[44] The model characterizes national conditions that impact measles and rubella transmission (i.e., population immunity as a function of experience with historical immunization and reported incidence,[4] population structures,[45] and virus transmission conditions[46]). The model simulates transmission for each area separately for 180 WHO Member States and three other areas (i.e., Puerto Rico, Hong Kong, Macao)[43] with sufficient demographic and immunization data.[4] (For context, the population in the model represented >99.5% of the estimated global population of 7.16 billion people in 2013.[45]) The model[43] includes consideration of maternal immunity and tracks pregnancies to capture the dynamics of rubella virus infections in pregnancy[43] (see review[46] for the different types of assumptions used in published measles and rubella virus transmission models). The model[43] uses assumptions about historical RI and SIAs based on a review of the evidence,[4] and we characterize country-specific basic reproduction numbers (R_0s) for measles and rubella, and mixing and seasonal amplitude assumptions based on fitting the dynamic transmission model to the historical time series of incidence available for all countries for measles since 1980 and for rubella and since 2004[4] and data from serological studies available from many countries.[47] The estimates of incidence from the transmission model provide the basis for estimating the adverse health outcomes over time for each country, including estimated rates of complications from infections and vaccine-associated adverse events. The estimates of health outcomes support estimates of the associated disability-adjusted life years (DALYs) and the costs associated with treatment.[48-50] The DALY and economic estimates use available cost and valuation inputs by World Bank Income Level (WBIL).[48] For health and economic outcomes, the model includes discounting at a 3% rate.[51]

For this global investment case analysis, this work focuses on prospective modeling at the global level, with some consideration of variability that exists in the world accounted for by modeling costs as a function of WBIL. The annex in the web materials provides more technical details about the analysis. For purposes of projection, and recognizing the long time horizon of the potential benefits of investments in measles and rubella immunization, this analysis compares the health benefits and costs of immunization that extends over a time horizon from 2016-2055 (i.e., 40 years), with benefits extending for the entire lifetime of individuals vaccinated during the intervention time horizon. The analysis considers two scenarios developed to provide insights if the future looked like the path of the scenario (i.e., the analysis describes possible futures but does not predict the future). Briefly, the first scenario represents a *status quo* (SQ) immunization strategy as of 2016, which uses the 2016 WHO-UNICEF reported vaccine schedules and coverage,[52] except that it allows for rubella vaccine introduction to occur through the end of 2017, based on actual historical introductions and assuming rubella coverage match measles coverage in RI for 2018 on. The second scenario represents an aggressive trajectory of model assumptions that lead to eradication of measles and rubella virus transmission as soon as possible (ASAP) (within some bounds associated with historical program performance), which includes rubella vaccine introduction in all countries by 2023 (see annex). Consistent with the time horizon, the model uses updated input data for immunization and population inputs, and updated estimates for immunization-related costs (increased to US$2016) using adjustment based on the US Consumer Price Index.[53] The analysis for the ASAP scenario includes a cost premium for associated with achieving increased coverage to achieve high levels of population immunity.[54]

Figure 1: Components of the integrated measles and rubella model



3. Preliminary Results

This section presents preliminary results from the analysis. Figures 2 and 3 show the results of the time series of modeled measles and rubella incidence for the 2 scenarios, respectively. Figure 4 shows the modeled measles mortality, and Figure 5 shows the modeled burden of CRS (including fetal and infant mortality attributed to rubella infection in susceptible mothers in early pregnancy). Some of the CRS burden appears in infant mortality statistics and probably does not get attributed to rubella infection in pregnancy or CRS.

The introduction of rubella vaccine into all countries by 2024 with associated appropriate catch-up campaigns can lead to rubella eradication by 2026. If the *status quo* continues, then rubella and CRS may increase slightly due to the demographic shifts in countries without rubella vaccine. In reality, countries that do not currently use rubella vaccine will likely continue to gradually introduce it such that the 2016 *status quo* scenario represents a worst-case scenario with respect to rubella vaccination policy. The analysis suggests, however, that in the context of widespread availability of MR combination vaccines that allow shared vaccine administration costs, ongoing efforts to increase measles vaccine coverage to reach measles mortality goals, and regional elimination targets, rubella eradication looks like “low hanging fruit.” Rubella eradication could occur prior to measles eradication once all countries introduce rubella immunization into their national programs.

Maintaining the 2016 *status quo* for measles vaccination leads to significant ongoing disease burden, predominantly in the lowest-income and most-disadvantaged countries, but with continued exportation of measles virus into countries and regions that successfully interrupted indigenous measles virus transmission leading to the threat of periodic outbreaks. Prevention of the outbreaks caused by reintroduction of imported viruses will continue to necessitate the expensive maintenance of high measles immunization coverage and reactive response efforts when outbreaks occur. Maintaining the status quo comes at a real cost for immunization on the order of $3 billion (in US$2016) globally per year (i.e., high control), or over $100 billion for the time horizon of 2017-2055. The eradication ASAP scenario considers the experience of the GPEI and the reality that some countries will likely fail to achieve and maintain sufficient measles immunization coverage to stop transmission until the world reaches the point of declaring any transmission of measles global emergencies (i.e., focusing on intensive activities in the last reservoirs). The model assumes that with a realistic global commitment to measles eradication, global measles transmission could stop by 2030. If the global commitment to measles and rubella eradication led to more significant commitments, then eradication could potentially occur sooner. The eradication of both diseases ASAP leads to relatively high short-term immunization costs, but lower treatment costs and productivity losses in the short term and lower all around health and financial costs for the long term. Following eradication, the treatment costs and productivity losses associated with measles and rubella infections disappear because the viruses die out and immunization continues. Similar to other eradicable diseases, after successful eradication, immunization policy changes could occur that would allow for a reduction of immunization costs (e.g., switching to schedules that deliver a single dose at a relatively higher age, stopping immunization complete at some point in time).

Figure 2: Modeled measles incidence for the 2 scenarios (curves overlap until 2016)

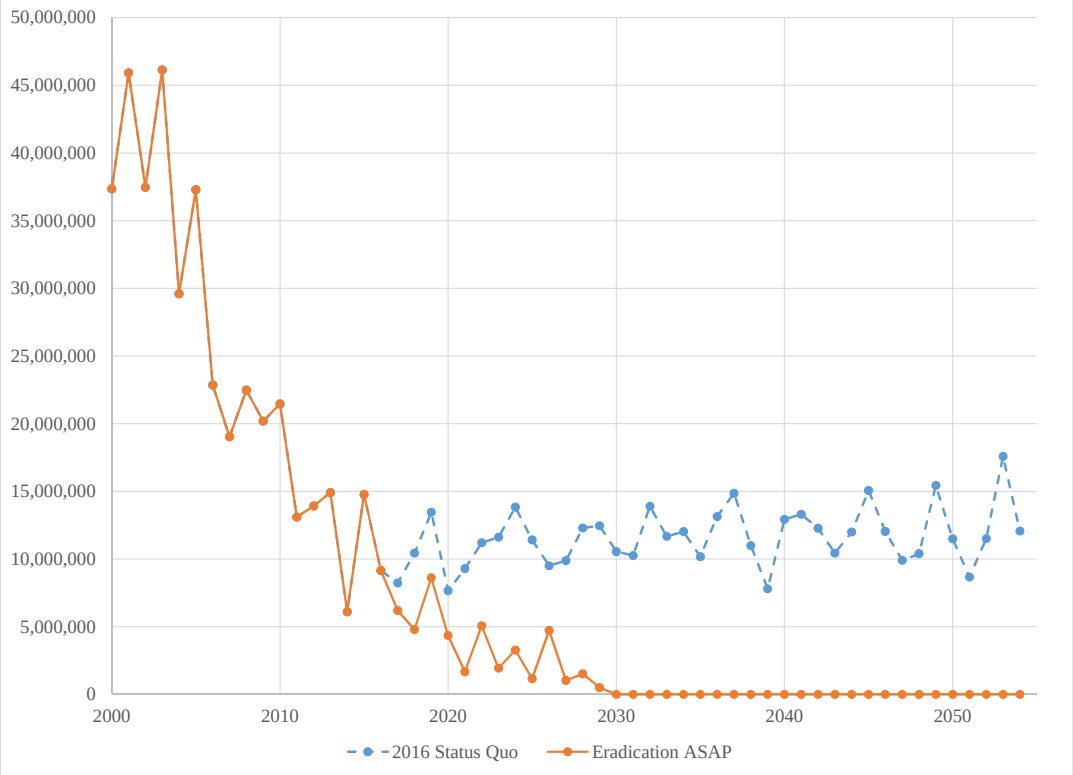


Figure 3: Modeled rubella incidence for the 2 scenarios (curves overlap until 2016)

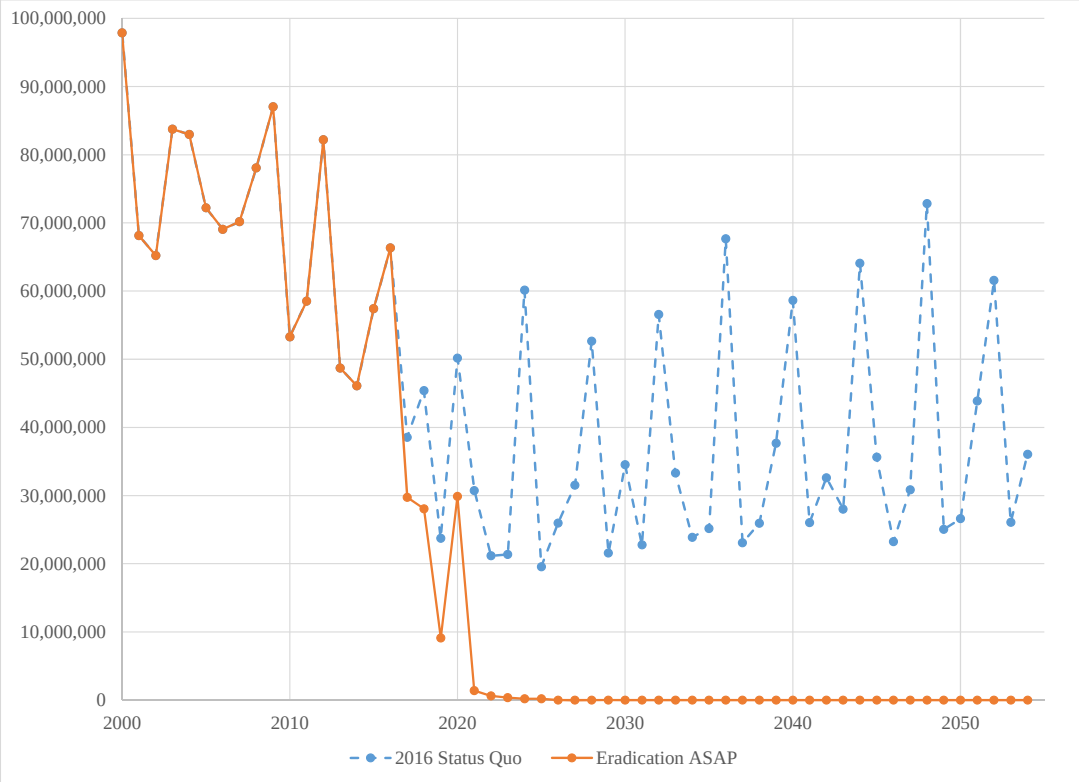


Figure 4: Modeled measles mortality for the 2 scenarios (curves overlap until 2016)

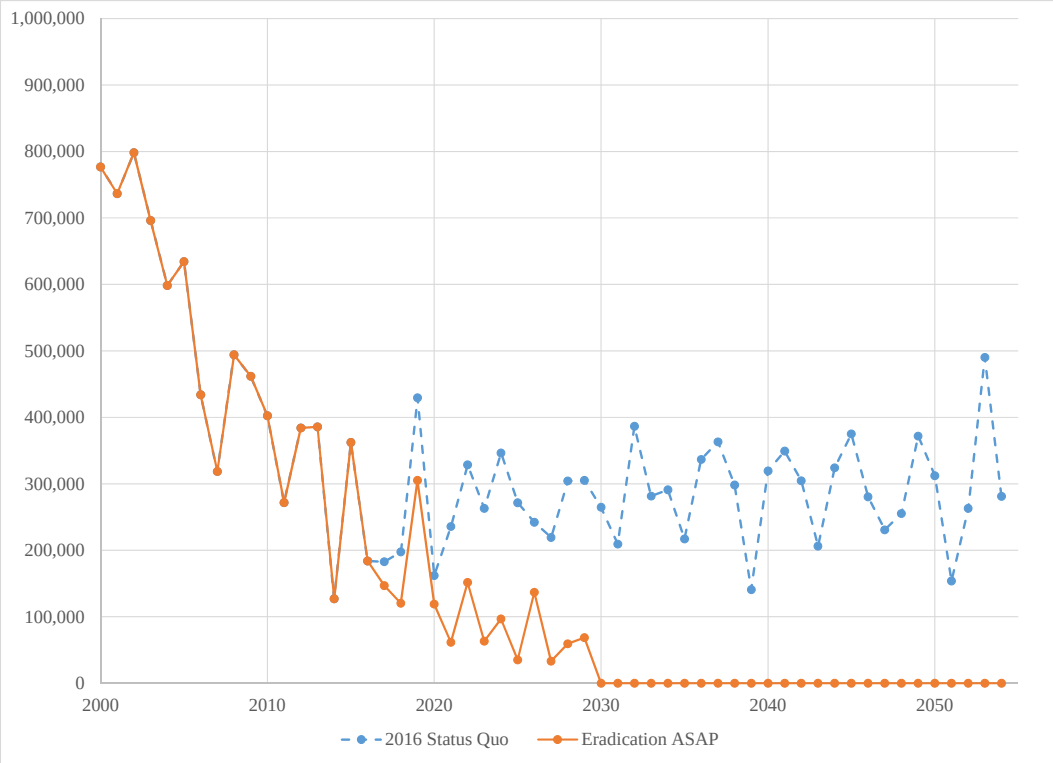
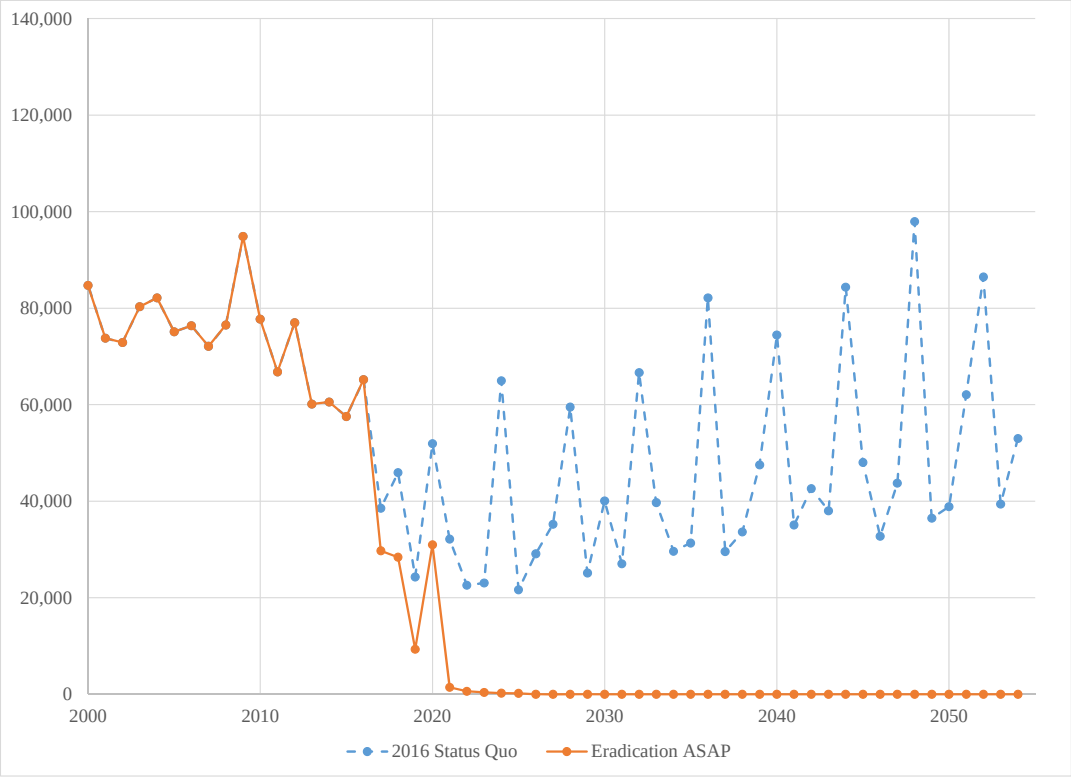


Figure 5: Modeled CRS cases (including infant and fetal mortality from rubella infections in early pregnancy) for the 2 scenarios (curves overlap until 2016)



Considering the discounted costs of immunization, treatment, and productivity over the time horizon of 2017-2055, and accounting for a premium associated with increasing immunization coverage in the short term needed to stop transmission as soon as possible, the costs of vaccination for the eradication ASAP scenario exceed the costs for the *status quo* by approximately $12 billion (US$2016), with over half of that amount representing the costs paid to increase coverage up until the time of eradication of both diseases. However, the reduced burden of disease leads to significantly greater incremental savings in expected treatment costs, with the eradication ASAP scenario leading to on the order of $100 billion saved in treatment costs compared to the *status quo*. Accounting for productivity losses avoided by ending transmission of both measles and rubella the eradication ASAP leads to expected net savings of over $1.5 trillion. Combined, the expected incremental net benefits of eradicating measles and rubella as soon as possible exceeds $1.6 trillion. Notably, this analysis does not consider the long-term risks, costs, or benefits associated with any dramatic changes in immunization strategy following eradication. The analysis simply seeks to provide an indication of the space of potential global health and financial costs for measles and rubella control and eradication.

4.0 Discussion

The failure to maintain or intensify MR vaccination will lead to sustained or increased burdens of disease at high costs. Countries and regions that successfully eliminate(d) measles and/or rubella will continue to need to invest in immunization programs that maintain high coverage to prevent transmission of virus exported from endemic areas. In the context of widespread availability of MR combination vaccines that allow shared vaccine administration costs, introducing rubella vaccine as quickly as possible into all countries with appropriate catch-up campaigns could lead to global rubella eradication relatively quickly.

Numerous limitations of the model warrant mention. First, all models depend on the information and assumptions that go into them. While this model attempted to use the best available historical information, all future projections remain inherently uncertain. The model seeks to provide a perspective at the global level related to the incremental net benefits of eradicating both diseases as soon as possible. Second, the model uses simplistic assumptions about exportations that limit its ability to reflect the true range of stochastic possibilities. Third, the model does not account for potential long-term risks associated with the containment of measles and rubella viruses that may exist in laboratories. Fourth, the costs represent a first look that focuses on the increase in immunization costs required to achieve global eradication of both measles and rubella viruses as soon as possible (with some reality included based on some lessons learned from experiences with past and current measles and rubella goals and prior disease eradication efforts). Future efforts will need to consider any increased resource needs for surveillance, coordination, and any required regional and global support activities. Fifth, all of the limitations associated with the various components of the model aggregate into the global analysis.

This background document and the presentation at SAGE aim to provide a high-level perspective and global comparison of the health and economic costs for potential future measles and rubella eradication discussions. Eradication of rubella will not occur until all countries include rubella

vaccine in their immunization schedules, and thus the timing of rubella vaccine introduction directly influences the timing of potential rubella eradication. For both measles and rubella, achieving the programmatic performance required to stop transmission and then maintain high population immunity to prevent any importations from restarting transmission will imply on-going high costs for all countries that have eliminated until the last county stops transmission.

5.0 Next steps

Following review of the estimates used to support the cost premium and additional analyses, the preliminary estimates will be updated and finalized, and this work will be developed into a manuscript for peer review. The preliminary results provide some perspective on the direction and magnitude of the likely expected savings from eradicating measles and rubella as soon as possible, but the numbers presented here are not intended to represent final estimates and should not be cited or quoted. More importantly, the estimates depend on the assumptions used for the scenarios, and the actual costs and benefits that the world will realize will depend on the choices that national, regional, and global leaders make with respect to measles and rubella eradication. As an incremental analysis, the model accounts for the savings associated with reduced outbreaks due to importations for countries that have already eliminated measles and rubella, but it does not account for potential cost savings that could occur with respect to the potential reduction in required vaccination.

This preview of the analysis provides an opportunity for members of SAGE to see the scope and nature of the analysis. The analysis will undergo review by IVIR-AC in September 2018 and a peer review journal. Comments received during the review process will lead to further improvements in the analysis.

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