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National and Global Options for Managing the Risks of Measles and Rubella

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Abstract

Countries currently choose from several different measles and rubella containing vaccine options and use a wide range of vaccination schedules as they control the transmission of measles only or measles and rubella viruses within their borders and cooperate and coordinate to achieve regional and/or global goals. This paper discusses the current national options that countries use or could use for national measles and/or rubella control or elimination and existing associated regional goals to characterize the expected current global path and identify alternative paths. With highly effective, relatively inexpensive, and safe vaccines available we can potentially end indigenous measles and rubella virus transmission. The Pan American Health Organization eliminated endemic transmission of both measles and rubella, which demonstrated the possibility of global eradication, and four other regions of the World Health Organization are now pursuing targets for regional elimination. We discuss the choice of a global strategy of control compared to eradication to highlight the choices, opportunities, issues, and challenges that will ultimately determine the magnitude of human and financial costs of measles and rubella globally over the next several decades and beyond.

Keywords: Rubella; Risks of measles

Introduction

The introduction and widespread use of measles- and rubella-containing vaccines (MCVs and RCVs, respectively) significantly reduces the burden of these diseases nationally, regionally, and globally. National use of measles and rubella vaccines began with developed countries rapidly adopting the vaccines to control and ultimately eliminate indigenous transmission of measles and rubella. The United States licensed the first measles vaccine (M) in 1963 and the first combined measles, mumps, and rubella vaccine (MMR) in 1971 [1]. A major outbreak of rubella in the early 1960s led to an estimated approximately 20,000 infants born in the US with Congenital Rubella Syndrome (CRS). This outbreak motivated broad adoption of rubella vaccination in combination with measles immunization, which led to apparent interruption of transmission in 1996 [2] with confirmed interruption of endemic rubella by 2001 [3]. Using MMR, the US pursued a measles control strategy for decades but experienced periodic outbreaks due in part to importations [4,5] as it pursued three initiatives to eliminate indigenous transmission [1]. The final initiative, in response to the measles resurgence of 1989-1991, led to intensified efforts to strengthen routine immunization with two doses of MMR [6,7]. As a result of these efforts the US successfully documented the elimination of indigenous measles transmission in 2000 [8]. Similarly, Canada and many developed European countries rapidly and significantly reduced their burdens of measles and rubella following the introduction of vaccines [1]. The addition of measles vaccine to the Expanded Programme on Immunization (EPI) schedules in 1974 with support from UNICEF and other immunization partners significantly extended the number of countries using measles vaccines [9]. Middle- and low-income countries gradually started to increase their population immunity levels for measles by adding a second routine dose of measles vaccine (MCV2), conducting preventive supplemental immunization activities (SIAs), and/or more recently by responding to outbreaks with vaccination campaigns.

World Health Organization (WHO) regions began adopting regional measles and rubella goals following the successes of some of their member states. In 1994, the Pan American Health Organization (PAHO) set a goal of measles elimination for the region of the Americas by 2000 and in 2003 it set a goal for elimination of rubella by 2010 [10-12]. PAHO successfully stopped indigenous transmission of measles viruses in the Americas in 2002 and rubella in 2009 [13], but PAHO countries remain vulnerable to importations from other regions, which can cause extensive and expensive outbreaks [14-16]. Currently, four other WHO regions are pursuing goals to stop indigenous measles transmission (Eastern Mediterranean by 2015, European by 2015, Western Pacific by 2012, and African by 2020) and the South-East Asia Region set a goal to reduce measles mortality by 95% compared with 2000 levels by 2015 [13]. Regional goals for rubella currently lag those for measles, with the European Region targeting the cessation of indigenous transmission of rubella by 2015, the Western Pacific Region pursuing an accelerated rubella and CRS prevention goal for 2015, and other regions discussing the options [13]. While all 194 WHO member states include at least one dose of a MCV in their routine schedules, approximately 30% (n=63) have yet to introduce RCV.

The Measles and Rubella Initiative (http://www.measlesrubellainitiative.org/) launched in 2001 to coordinate regional and global activi-

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ties on measles, which formally expanded to include rubella in 2012, provides ongoing support and strategic planning for the achievement of major milestones [13]. In 2003, the 52nd World Health Assembly (WHA) endorsed a resolution by the 2002 UN General Assembly Special Session on Children to reduce mortality from measles by 50% of the 1999 levels by the year 2005 [17]. Following achievement of this goal [18], in 2008 the 61st WHA resolved to reduce mortality from measles by 90% of the 2000 levels by the year 2010 [19]. Assuming near achievement of the goal set in 2008, in 2010 the 63rd WHA resolved to reduce measles mortality by 95% or more compared to 2000 estimates by 2015 [20]. A recent analysis found that resurgence of measles in Africa in the late 2000s and delayed implementation of accelerated measles immunization efforts in India led to missing the global goal of 90% reduced mortality by 2010 (i.e., the analysis found a 74% reduction achieved globally), compared to the 2000 levels [21]. Nonetheless, pursuit of the 2015 goals continues and reduced mortality for measles contributed significantly to efforts to achieve the United Nations (UN) Millennium Development Goal 4 (MDG4) of reducing overall deaths among children by two-thirds between 1990 and 2015 with routine measles vaccination coverage serving as one of 3 main indicators of progress toward MDG4 [22]. Estimates suggest that the acceleration of measles control efforts accounted for approximately 23% of the total reduction in averted deaths of children under 5 years old between 1990 and 2008 [23], although the estimated impact expressed in relative or absolute terms remains a subject of debate and depends on how analysts attribute deaths and the time period they use [21,23-25].

Coordinated efforts for rubella began later than efforts for measles, and countries continue to gradually adopt rubella vaccination into their routine immunization schedules. The WHO recommends that member states yet to introduce rubella vaccination take the opportunity offered by accelerated measles control and elimination activities to introduce RCVs [26]. Recently, the GAVI Alliance sought to stimulate increased adoption of RCVs and opened significant funding opportunities to support eligible countries to introduce rubella vaccination and/or deliver a second dose of MCV [27]. Eligible countries can apply for and receive GAVI Alliance support for the bundled measles and rubella vaccine (MR). The GAVI Alliance will also cover a share of the operational costs to introduce rubella vaccine through a MR catch-up campaign of males and females aged 9 months to 14 years (with the exact age range depending on national rubella epidemiology). In addition, eligible countries can apply for an MR vaccine introduction grant to facilitate activities in the first year of MR introduction into routine immunization [27]. The GAVI Alliance anticipates that 48 countries will introduce MR vaccine by 2018 with its support [28], and it requires countries to meet certain requirements to receive support, including a demonstrated ongoing financial commitment to maintain RCVs in routine immunization [27].

Discussions about potential eradication (i.e., elimination in all six WHO regions) of measles began shortly after introduction of the vaccine [29,30], with attention to rubella eradication appearing relatively later [2,31]. Steady and significant progress and existing regional elimination goals supported recent discussions of eradication [32], but no global eradication goal (i.e., no commitment or target date) currently exists for measles or rubella. Notably, the current global focus on completing the eradication of wild polioviruses as a public health emergency and experience with delays associated with that effort impacts perceptions about eradication as a global goal and the availability of financial and other resources for other disease eradication and control initiatives. The reality of resource constraints motivates demands for the development of an investment case to characterize the risks, costs, and benefits of globally-coordinated efforts for measles and rubella management in the context of polio eradication. Developing an investment case requires characterization of the current expected path (i.e., the *status quo* or baseline) and alternative options [33]. This paper seeks to characterize the current expected path and identify alternative options for measles and rubella management following the approach used for managing polioviruses to characterize the current national immunization strategies [34], global options [35], and post-eradication options [36]. We discuss key issues associated with the full set of options with the hope that this will encourage broader discussions with groups of stakeholders and facilitate efforts to manage expectations and support coordination efforts to establish and achieve global goals for measles and rubella.

Before discussing the methods, we note that despite the inclusion of mumps in some MCVs, we do not include consideration of mumps in this analysis. While the perceived and actual benefit of mumps control remains well-established in some developed countries [37,38], experience with adverse events (e.g., aseptic meningitis) from MMR immunization with the Urabe mumps vaccine strain led Japan to replace MMR with MR in its schedule [39]. In addition, many developing countries do not appear to perceive the benefits of routine mumps vaccination as exceeding the associated costs and/or risks. The relatively less effective protection provided by mumps vaccine compared to measles and rubella vaccines [38], waning of immunity, perception of mumps as not a serious disease, and lack of funding available to support the introduction of mumps vaccination also make it less attractive at this time for consideration in an investment case, although it may become relatively more attractive in the future.

Methods

We reviewed the existing national immunization schedules reported to the WHO to characterize current national measles and rubella containing vaccine choices and potential options for the 194 WHO member states [40]. This analysis represents a snapshot of current reported national choices, because countries periodically change their schedules as local disease epidemiology, vaccine options, and opportunities change (e.g., the new GAVI Alliance funding discussed above), and many countries also increase their population immunity by conducting SIAs.

In addition to reviewing the reported schedules, we developed decision trees that identify categories of current policies and list the possible decision options within those categories from the perspective of a national policy maker. We then highlighted the implied set of options of the globally-coordinated minimum strategy. We sought to make comprehensive decision trees that would represent all of the options, and we included the option of "Others" to recognize the possibilities that we inadvertently missed some options and/or new options may emerge in the future. We focus on the globally-coordinated minimum because countries and regions remain interdependent with respect to the control or eradication of highly-transmissible infectious diseases like measles and rubella. The viruses easily cross international borders in our highly interconnected world and they have the propensity to cause outbreaks or epidemics [33,35,41]. Any individual country can always pursue a strategy that exceeds the minimum, but the minimum will determine the least that countries can expect with respect to global collaboration and coordination towards goals. We define a goal as the combination of a specific target (e.g., reduced mortality by 95%, elimination) and a target date (e.g., by 2020, 2025).

Given uncertainty about the future, we characterized the current

expected global path and potential alternative paths using all available information from the literature. We also sought input from stakeholders, which we collected as part of a process to solicit their input on the development of investment cases (see details about stakeholder engagement process reported elsewhere [33]). With respect to the current expected path and future options, we specifically requested input from stakeholders related to the timing of potential alternatives and perspectives on the impact of other global initiatives (e.g., polio eradication).

Results

Figure 1 shows the options that the 194 WHO member states currently choose from as they determine their national immunization strategy for measles and/or rubella with the possibility of other potential options captured in the other category. All WHO members currently include at least one dose of MCV in their routine immunization schedules (MCV1) and most include a second dose (MCV2). The WHO recommends two doses of MCV [42], but a few countries include a third dose (MCV3) or revaccination contact after the MCV2 presumably to ensure the receipt of at least 2 doses, which in some cases target specific risk groups. The decision tree shows the different vaccines that WHO member states use: measles (M), measles and rubella (MR), measles, mumps, and rubella (MMR), and measles, mumps, rubella, and varicella (MMRV), with a hyphen used to separate each dose and the number of member states reporting use of the vaccine(s) shown in brackets if more than one member state reported use of the vaccine(s). Most countries that include MMRV in their schedules include the option of either MMR or MMRV, which we denote in the figure as MMR[V]. Although the tree shows a large number of vaccination options, most WHO member states use at least 2 doses of MMR (with or without varicella) (n=107, 55%). Approximately a quarter of member states (n=47, 24%) use M and another 16 (8%) member states use M-M. The figure also shows the recommended timing of the MCV1 in months and the MCV2 and MCV3 in years, with the number of member states reporting the recommended age shown in brackets if more than one member state reported the indicated age. Although the tree shows a wide range of ages for MCV1, most member states deliver MCV1 routinely at either 9 months (n=71, 37%), 12 months (n=82, 42%), or 15 months (n=14, 7%).

Currently countries that do not deliver MCV2 through routine immunization and some countries that do not achieve or maintain high coverage in routine immunization conduct SIAs. Figure 2 shows the choices related to implementing preventive SIAs. As suggested by Figure 2, countries may perform SIAs with different frequencies (e.g., depending on the MCV coverage they achieve through routine immunization and SIAs and local disease epidemiology) using a range of vaccine options. Most SIAs currently use M or increasingly MR, as countries adopt rubella vaccination. For SIAs, countries may target different ages, genders, and risk groups. In addition, while most countries perform national SIAs, the scope could focus on a specific sub-national area or risk group. We indicate that SIAs might also use a mixed strategy that may for example use one approach nationally

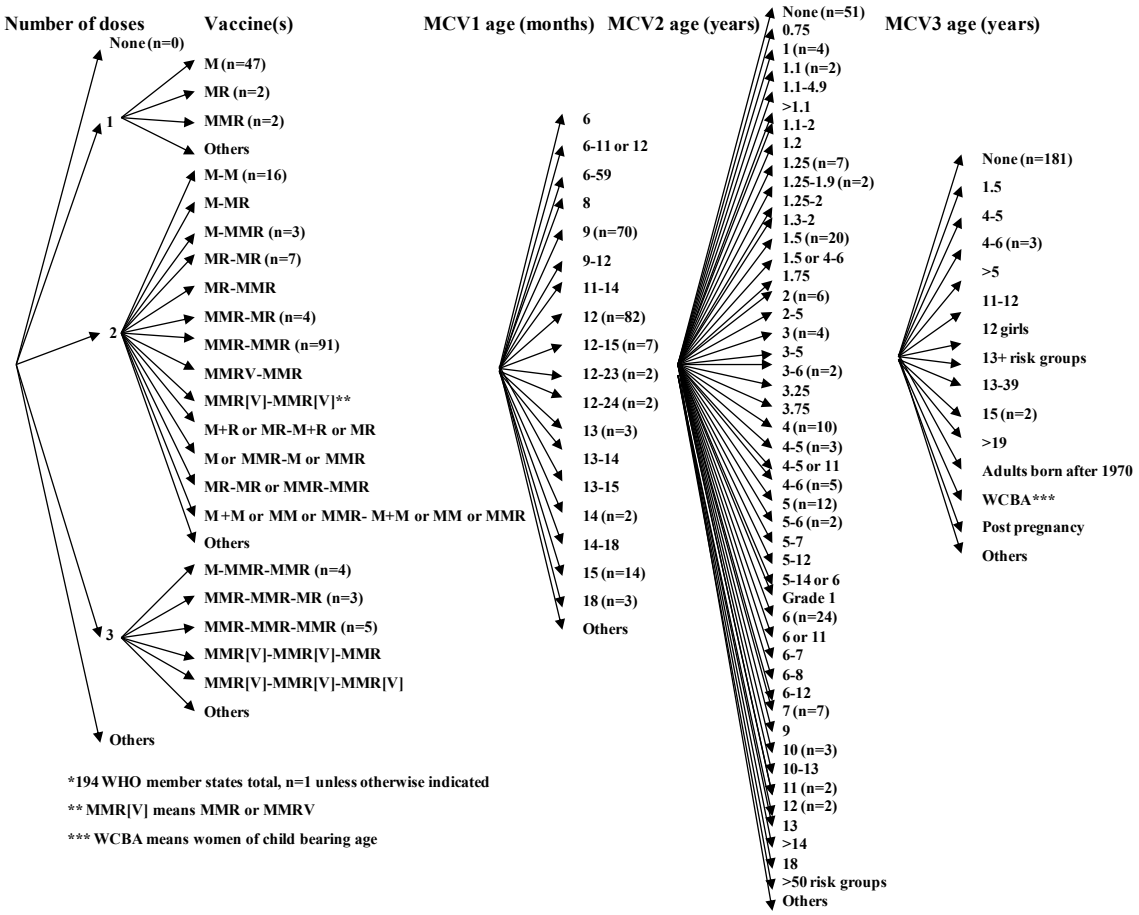

Figure 1: National measles and rubella routine immunization choices*.

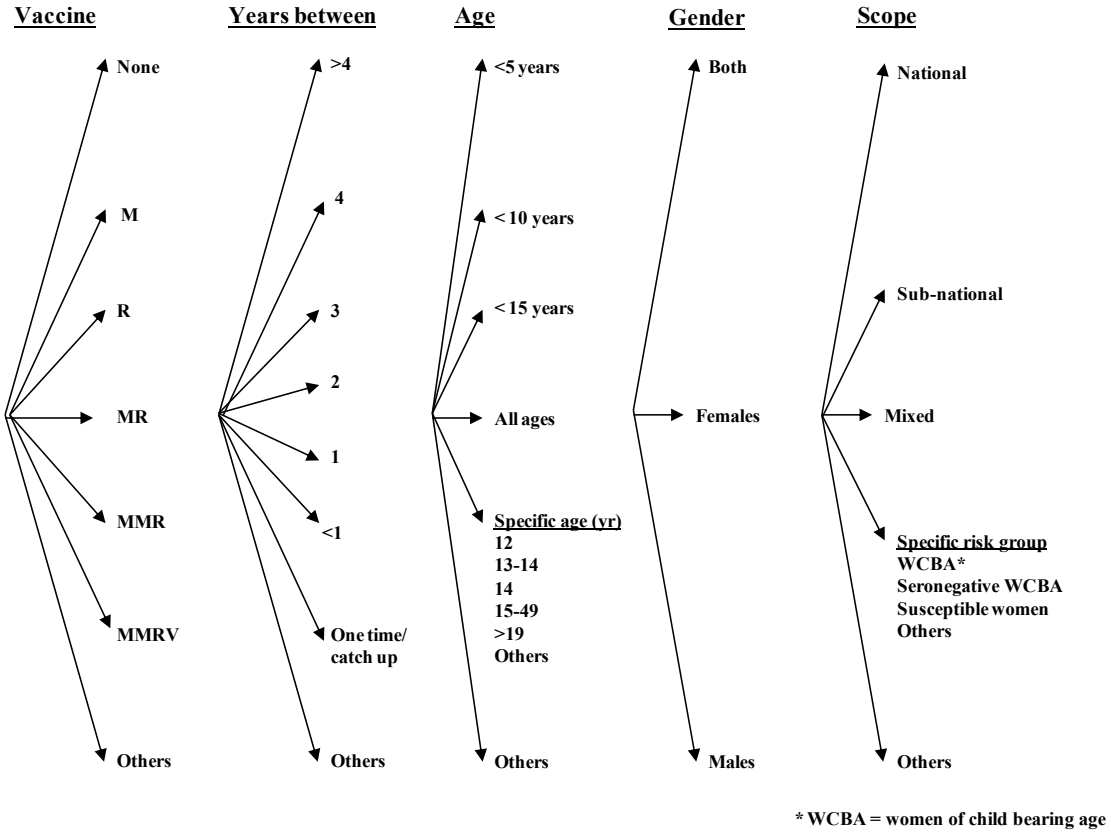

Figure 2: National measles and rubella supplemental immunization activity (SIA) choices.

with additional vaccination of a specific risk group or use of a different vaccine or age range in some sub-national areas.

Coverage represents an important factor for all immunization efforts. Achieving and maintaining levels of population or herd immunity sufficient to prevent transmission does not require 100% coverage, but national immunization efforts should target all susceptible individuals. Currently countries achieve very different levels of coverage with routine immunization [43] and SIAs, and the levels they achieve determine their national risks of transmission, outbreaks, and the need for more frequent and/or additional efforts.

Figure 3 shows the various global control and eradication options for measles and rubella. The choices range from uncoordinated control at the bottom to coordinated control of measles and/or rubella, to eradication (i.e., global elimination) of measles and/or rubella. We represent the option of uncoordinated control at the bottom of figure 3 for completeness, although we anticipate that WHO member states will continue to find coordinated control of measles at some level in their collective interest given prior global goals [17,19,20]. With many countries currently yet to introduce rubella-containing vaccine, we characterize the current situation as globally-coordinated control of measles (i.e., all countries include an MCV in their routine schedule) and uncoordinated control of rubella. As discussed above, the goal of 95% reduced mortality compared to year 2000 levels by 2015 represents the current global goal for measles, and Figure 3 depicts the options of other targets and/or target dates for measles and options for regional elimination goals. Figure 3 also includes potential options for rubella regional elimination goals and CRS reduction targets as example strategies, and we include the possibility of mixed control goals that include both regional elimination targets combined with mortality or CRS reduction targets.

With 5 of 6 WHO regions pursuing existing measles elimination goals and the remaining region making increasingly more aggressive efforts to control measles, inclusion of an eradication goal represents a logical progression, and consequently the top three branches of the tree include eradication of measles or rubella or both. For eradication of either measles or rubella, Figure 3 indicates some options for target dates expressed in years, but we emphasize the possibility of essentially any future date as an option. Finally, the top branch of the tree in Figure 3 indicates the goal of eradication of both measles and rubella, with potential synchronization options for the target date identified. With no synchronization, we assume a target of eradication of both measles and rubella with no target date for either. With a single target date, we assume pursuit of the goal toward one date for both diseases, although achievement of the goal may occur earlier for either. For different target dates, Figure 3 depicts the choice of which disease to target first, the target dates for the first in years, and the target for the second in terms of the number of years after the first target date. Notably, the member state(s) and regions that pursue(s) the least ambitious goals will ultimately determine the globally-coordinated minimum, although any individual country can strive to achieve beyond the minimum [35].

Table 1 uses the information from Figure 3 and input from stakeholders to identify a representative set of current expected and alternative paths for a time horizon of 2013 to 2053 with respect to the global management of measles and rubella. Forecasting the expected

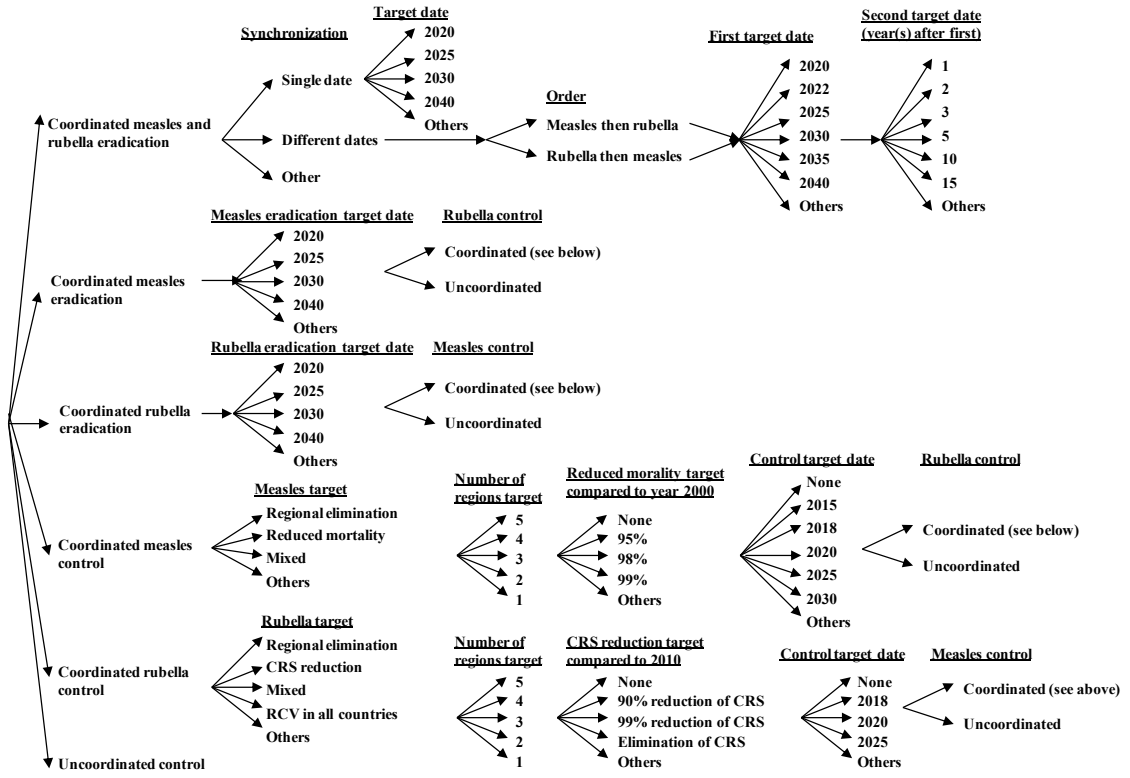

Figure 3: Global measles and rubella management options.

path into the future introduces uncertainty, and Table 1 spans a wide range of possible paths ranging from uncoordinated control to aggressive eradication, although the limited set shown in the table captures only a few of the infinitely many potential paths that exist. Prior economic analyses for measles explored the cost-effectiveness of going from the baseline option of 90% reduced mortality compared to year 2000 by 2010 to the options of: (1) 95% reduced mortality compared to year 2000 by 2015, (2) 98% reduced mortality compared to year 2000 by 2020, and (3) measles eradication by 2020 for the time horizon of 2010 to 2050 [44,45]. Consistent with the Global Vaccine Action Plan vision of extending the full benefits of vaccines to all populations by 2020, Table 1 includes an option that achieves aggressive goals by 2015 and results in elimination of measles and rubella in 5 WHO regions by 2020 [46]. As suggested by Table 1, adding simultaneous goals for rubella increases complexity. Immunization efforts for measles and rubella become even more complicated in the context of consideration of other ongoing disease eradication efforts, notably the Global Polio Eradication Initiative (GPEI), for which measles and rubella efforts may compete for and possibly share resources. Thus, while Table 1 presents the measles and rubella options in the context of a specific timeline,

Path	Measles	Rubella
Current expected	Achieve 95% reduced mortality by 2020 and existing national and regional goals 5 years later than target date then maintain	Introduce at least one dose in 75% or more of countries yet to introduce RCV by 2020 and achieve existing national and regional goals 5 years later than target date
Achieve existing goals on time	Achieve 95% reduced mortality by 2015 and existing national and regional goals (eliminate in 4 regions by 2015, 5 regions by 2020)	Introduce at least one dose in 75% or more of countries yet to introduce RCV by 2018 and achieve existing national and regional goals (eliminate in 2 regions by 2015)
Achieve GVAP goals [46]	Achieve 95% reduced mortality and elimination in at least four WHO regions by 2015, and eliminate measles in at least 5 WHO regions by 2020 then maintain	Eliminate rubella in at least two WHO regions by 2015 and in at least 5 WHO regions by 2020 then maintain
Accelerated eradication	Achieve 95% reduced mortality by 2015 and eradication by 2020 then maintain	Eradicate rubella by 2020 then maintain
Delayed eradication	Achieve 95% reduced mortality by 2020 and eradication by 2030 then maintain	Eradicate rubella by 2035 then maintain
Eradicate through routine immunization	Achieve 95% reduced mortality by 2030 and eradication by 2040 then maintain	Eradicate rubella by 2040 then maintain
Control	Coordinated control associated with continued use of MCVs in all countries	Uncoordinated control associated with one or more countries not choosing to use a RCV
Uncoordinated	Uncoordinated control associated with continued use of MCVs in all countries	Uncoordinated control associated with one or more countries not choosing to use a RCV

Table 1: Range of minimum global immunization options for measles and rubella.

we could alternatively pick the starting year as the uncertain year of achieving polio eradication or achieving a specified milestone towards polio eradication and start the clock from that point in time.

For the current expected path, we reflect our assessment that currently we are not on track to achieve the existing national and regional elimination goals for 2015. However, we include the existing goals as one path with the recognition that with some work and investment, opportunities to get back on track exist. With respect to rubella, we consider the current GAVI Alliance funding opportunity and the addition of rubella to the vaccine schedules of 48 of the 63 countries yet to introduce rubella (75%) by 2018 (as an aspiration) or by 2020 (as the current expectation). Thus, as countries take advantage of the GAVI Alliance support for introducing RCVs and recommending a measles second dose (MCV2) over the next several years, the current minimum global vaccine of a single M dose will move toward a minimum of MR-MR or MR-M. We recognize the significant challenges that we face with respect to achieving the current goals and that no global commitment exists, so we consider both control and eradication options.

Similar to an analysis of global polio options [35], the global strategy depends on the WHO member states that commit to the least ambitious goal. Thus, although any country or region can always do more than the minimum, achieving a regional elimination or global eradication goal requires coordination and cooperation.

Discussion

Progress toward the reduced mortality goals demonstrates the ability to achieve global goals for measles, and PAHO demonstrated the technical feasibility of sustained regional elimination of measles and rubella. Despite these achievements that demonstrate successful collaboration toward ambitious goals, the future path remains a subject of discussion.

In the context of discussions with stakeholders about the content for inclusion in investment cases [33], we received diverse opinions about how to best characterize the current expected path and alternative paths for measles and rubella. Notably, several people raised concerns about the sustainability of reduced mortality gains, particularly given the resurgence that occurred in Africa, and they highlighted the need to continue to move forward. Without continued progress toward goals, measles and rubella control efforts may lose ground and go back toward widespread endemic transmission. For example, one stakeholder suggested that the "expected *status quo* would be persistent outbreaks in Western Europe, increasing susceptibility in North America due to vaccine refusal, and ongoing outbreaks in Africa and India", while alternative paths include "regression i.e., the Americas cannot maintain elimination in the face of persistent imports or very concerted efforts to reduce cases in Africa/Europe/India". Others stakeholders questioned the feasibility of eradication goals given the lack of optimal measles control now, the current lack of use of RCVs in many countries, and the fragmented and incomplete existing goals in different regions. These stakeholders emphasized that inappropriate pursuit of an eradication goal might undermine the credibility of disease control efforts, divert attention and resources from other priority areas, and distract from the strengthening of health systems and routine immunization services. In addition, issues related to inadequate surveillance and the current dependence of the measles and rubella lab network on the polio infrastructure and resources led some stakeholders to raise questions about long-term financing for valuable surveillance information.

The current situation of delayed polio eradication complicates discussions about the eradication of other diseases, with some stakeholders indicating that consideration of measles or rubella eradication would need to wait until after the completion of polio eradication, although all stakeholders expressed general agreement that for vaccine-preventable diseases like measles and rubella global efforts should ultimately move toward complete prevention. The path of pursuing reduced mortality goals appears to benefit from broad support, with some stakeholders suggesting that such a path might ultimately result in eradication without the establishment of an eradication goal. Several stakeholders also raised concerns about use of the term eradication due to perceptions of negative effect associated with the delays and high costs of the GPEI. Stakeholders also suggested the need to consider the effect of the potential success or failure of the GPEI on global measles and rubella initiative efforts, because after 2013 the GPEI success or donor fatigue may diminish support for campaigns and surveillance supported by the GPEI, particularly in the most challenging areas, and donor support for EPI may also change.

Multiple stakeholders raised issues about the significant challenges that exist with respect to dealing with weak routine immunization services in many countries and the consequent need for reliance on SIAs. They noted that outbreaks indicate both poor routine immunization and sub-optimal quality of SIAs, and suggested the importance of learning lessons from polio elimination in India about surveillance, and engaging social mobilizers, laboratory and health workers and volunteers to achieve national goals. While the GAVI Alliance and other stakeholders continue to support efforts aimed at strengthening routine immunization in low- and middle-income countries, ultimately every WHO member state will need to accept and maintain responsibility for providing high immunization coverage to all people living within its borders, including migrants. Stakeholders also highlighted the challenges associated with maintaining success and negotiating additional commitments to achieve further goals (i.e., yet more ambitious reduced mortality or elimination goals) as measles disappears and other problems appear more threatening. The perceptions and social norms associated with vaccination clearly matter nationally and regionally, and the fact that these differ significantly for various regions impacts global efforts (e.g., social norms in PAHO differ considerably from those in the African Region). Some stakeholders also identified communication issues as an important concern for all paths. They noted significant refusal or vaccine hesitancy among some communities and suggested the need to develop strategies to sustain political will, social stability, and cooperation with civil society partners, particularly in the most difficult areas.

With respect to synchronization, stakeholders suggested that measles and rubella elimination should occur together, because the wide age range MR catch-up campaigns for rubella will benefit measles elimination. In addition, many countries may not worry much about rubella due to its low visibility, even though its elimination may occur more easily than measles given its relatively lower infectiousness than measles and the high effectiveness of rubella vaccine. Stakeholders also urged further evaluation of the feasibility of rubella eradication and the relative timing of concurrent *vs.* staggered goals for measles and rubella and suggested that the risk of failure for rubella eradication might exceed that for measles due to increased CRS burden.

Some stakeholders expressed frustration about the lack of clarity about long-term goals and commitments by other stakeholders and potential funders, which underscores the need for clearly defining roles and responsibilities. They also identified the need for realistic, long-term estimates of costs for all of the potential paths. The lack of sustained

political commitment and leadership also leads to mixed messages within and among stakeholder organizations and in communication with the media and the public, and several stakeholders indicated the need for ongoing education and engagement with a wide range of communities at all levels.

Financial risks pose a significant, on-going threat to all globally-coordinated disease control or eradication efforts [41,47]. Funding shortfalls and a focus on fire fighting instead of prevention lead to non-optimal decisions (e.g., delaying SIAs such that outbreaks occur that require even more costly outbreak response campaigns) [48]. Stakeholders emphasized the need to develop realistic expectations and cost estimates that account for uncertainties instead of overly optimistic simplistic estimates that ultimately get viewed as disappointing false promises.

For all of the paths, vaccine supply issues, including the need to ensure adequate amounts to meet all routine immunization and campaign needs, will continue to require coordination. The creation of a stockpile using rotating stocks may offer an important opportunity to improve the stability of supplies. Significant uncertainty exists about the future, but by identifying and analyzing the options we hope that stakeholders can negotiate the best possible path, develop the resources required to achieve it, and better manage expectations for all.

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