Feasibility Assessment of Measles and Rubella Eradication

October 8, 2019

Introduction

1. At the Seventieth World Health Assembly (WHA) held on May 31, 2017, the Director-General was requested to report through the Executive Board to the Seventy-third WHA in 2020 "on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication, taking into account the assessment of the Strategic Advisory Group of Experts on immunization (SAGE)."[1] This request arose from a proposal from Colombia on behalf of 18 Pan American Health Organization (PAHO) Member States to request a resolution on global eradication at the WHA. A compromise was reached to instead request an update on the feasibility and cost of eradication in 2020 as part of the resolution on the Global Vaccine Action Plan (GVAP). Historically, an Ad Hoc Global Measles Advisory Group was convened by the World Health Organization (WHO) in 2009, leading to a Global Technical Consultation to Assess the Feasibility of Measles Eradication held in July 2010.[2] On the basis of this review, SAGE concluded in November 2010 that measles can and should be eradicated, and that a goal for measles eradication should be established with a proposed target date based on measurable progress made towards existing goals and targets.[3] The *Measles and Rubella Global Strategic Plan: 2012-2020 Midterm Review* also recommended that a decision should be made by 2020 as to whether or not a target be set for measles eradication: "A determination should be made, not later than 2020, whether a formal global goal for measles eradication should be set with timeframes for achievement. In the meantime, all regions should work toward achieving the regional elimination goals."[4]

2. Eradication is defined as reduction of the global incidence of a disease to zero as a result of deliberate efforts, with no more risk of reintroduction obviating the necessity for further control measures. The benefits of disease eradication are permanent, whereas the costs of control programmes continue indefinitely. According to the 1993 International Task Force for Disease Eradication (ITFDE), "Eradication is the ultimate "sustainable" improvement in public health."[5] For measles and rubella, elimination refers to the absence of endemic virus transmission in a defined geographical area, such as a country or region, for more than 12 months in the presence of a well performing surveillance system. While measles elimination is a worthwhile goal in itself because of the health and economic benefits, measles elimination is a fragile state that must be continuously maintained due to the likelihood of importations. Regional elimination is thus a stage on the path toward global eradication. There is, however, urgency for all Regions to accelerate elimination efforts, as it is challenging for countries and regions that achieved elimination to sustain this indefinitely if other countries export measles virus.

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[1] World Health Organization. Resolution WHA 70.14: Strengthening immunization to achieve the goals of the global vaccine action plan. Geneva, World Health Assembly 70, 2017 (http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R14-en.pdf).

[2] World Health Organization. Proceedings of the Global Technical Consultation to assess the feasibility of measles eradication, 28-30 July 2010. *Journal of Infectious Diseases* 2011;204:S4-S13.

[3] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2010. Summary, conclusions and recommendations. *Weekly Epidemiological Record* 2011,86:1–16.

[4] Orenstein WA, Hinman A, Nkowane B, Olive JM, Reingold A. Measles and Rubella Global Strategic Plan 2012-2020 midterm review. *Vaccine* 2018;36 Suppl 1:A1-A34.

[5] Recommendations of the International Task Force for Disease Eradication. *Morbidity and Mortality Weekly Report* 1993;42(RR-16):1-38. (available at https://www.cdc.gov/mmwr/preview/mmwrhtml/00025967.htm).

3. This report addresses the epidemiological aspects and feasibility of measles and rubella eradication and the potential resource requirements in response to the request of the Director-General. A guiding principle is that the path toward measles and rubella eradication should serve to strengthen primary health care, promote universal health coverage, and be a pathfinder for new vision and strategy for immunization over the next decade as laid out in the Immunization Agenda 2030 (IA2030). Specifically, this report: 1) highlights the importance of measles and rubella as global health priorities; 2) reviews the current global measles and rubella situation; 3) summarizes prior assessments of the feasibility of measles and rubella eradication; 4) assesses the progress and challenges in achieving regional measles and rubella elimination; 5) assesses additional considerations for measles and rubella eradication, including the results of modelling and economic analyses; 6) assesses the implications of establishing a measles and rubella eradication goal and the process for setting an eradication target date; 7) proposes a framework for determining preconditions for setting a target date for measles and rubella eradication and how these preconditions should be understood and used; and 8) concludes with recommendations endorsed by SAGE.

Definitions

Control: The reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. Example: diarrheal diseases.

Elimination of disease: Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required. Example: neonatal tetanus.

Elimination of infections: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required. Example: measles, poliomyelitis.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed. Example: smallpox.

Extinction: The specific infectious agent no longer exists in nature or in the laboratory. Example: none.

Dowdle WR. The principles of disease elimination and eradication. *Morbidity and Mortality Weekly Report* 1999;48 (Suppl):23-27.

Measles and Rubella as Global Health Priorities

4. Measles was a leading global cause of child morbidity and mortality prior to the introduction of measles vaccines in the 1960's and was responsible for more than an estimated two million deaths annually before the increase in global measles vaccine coverage in the 1980's as a consequence of the Expanded Programme on Immunization (EPI). Measles incidence and mortality declined substantially due to the increasingly widespread use of attenuated measles-containing vaccines administered through immunization programmes and, subsequently, through supplementary mass preventive vaccination campaigns. Measles vaccination is estimated to have prevented 21.1 million

deaths globally, and 19.3 million deaths among Gavi-eligible countries, from 2000 to 2017.[6] Despite this enormous progress, measles remains an important vaccine-preventable cause of morbidity and mortality, responsible for more than 100,000 deaths each year, and is a key indicator of the quality of immunization programmes. Due to its high infectiousness, measles serves as the "canary in the coal mine": Outbreaks show where people have not been vaccinated and the age distribution of cases identifies age-specific immunity gaps reflecting past programme performance. Importantly, measles anywhere is a risk for measles everywhere, as witnessed by the frequency of measles outbreaks around the world, often a result of importation of cases from other countries. The current measles burden would rapidly increase if current efforts are not maintained or increased.

Rubella too remains a global health priority and vaccine-preventable cause of morbidity and mortality. As a result of maternal infection with rubella during pregnancy, approximately 105,000 children are born each year with congenital rubella syndrome (CRS), a fully preventable, yet potentially fatal condition that can result in heart disease, hearing impairment and deafness, cataracts, and developmental delay.[7] An estimated 131,000 deaths and 12.5 million disability adjusted life years (DALYs) due to CRS may be prevented from 2001 to 2030 with increased rubella vaccine coverage.[8]

5. **The Sustainable Development Goals, Global Health Security Agenda, Global Vaccine Action Plan, Universal Health Coverage, and the Immunization Agenda 2030.** Measles and rubella vaccination already play an integral and leading role in achieving the architecture that currently guides global health activities, including the Sustainable Development Goals (SDGs),[9] the Global Health Security Agenda (GHSA),[10] and GVAP.[11] In addition, measles and rubella vaccination is central to the IA2030 as a core indicator of the effectiveness of the overall childhood immunization programme and key to strengthening PHC. Immunization in general, and measles and rubella vaccination specifically, plays a central role in the SDG3 to "ensure healthy lives and promote well-being for all at all ages" by contributing to the achievement of two SDG targets: 1) ending preventable deaths in children younger than five years by 2030; and 2) achieving universal access to vaccines. Coverage with the second dose of measles-containing vaccine is a specific SDG3 indicator, selected in part because it encompasses the two doses of MCV and reflects the strength of the second year of life platform. In fact, immunization, and measles and rubella vaccination in particular, contributes in some way to most SDGs. By reducing the economic burden of infectious diseases, vaccination helps eliminate poverty (SDG1) and promotes sustainable economic growth and productive employment (SDG8). Measles vaccination was shown to have the greatest return on investment, with US$ 58 dollars saved in future costs for every US$ 1 dollar spent, among 10 diseases in 73 Gavi-supported low- and middle-income countries from 2001-2020.[12] By protecting urban public

[6] Dabbagh A, Laws RL, Steulet C, Dumolard L, Mulders MN, Kretsinger K, Alexander JP, Rota PA, Goodson JL. Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. *Morbidity and Mortality Weekly Report* 2018;67:1323-1329.

[7] Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar AM, Simons E, Yoshida L-M, Brown DWJ, Jackson C, Strebel PM, et al. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996-2010: a systematic review. *PLoS One* 2016;11:e0149160.

[8] Vynnycky E, Papadopoulos T, Angelis K. The impact of measles-rubella vaccination on the morbidity and mortality from congenital rubella syndrome in 92 countries. *Hum Vaccin Immunother* 2019;15:309-316.

[9] https://sustainabledevelopment.un.org

[10] https://www.ghsagenda.org

[11] https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

[12] Ozawa S, Clark S, Portnoy A, Grewal S, Stack ML, Sinha A, Mirelman A, Franklin H, Friberg IK, Tam Y, Walker N, Clark A, Ferrari M, Suraratdecha C, Sweet S, Goldie SJ, Garske T, Li M, Hansen PM, Johnson HL, Walker D.

health, measles and rubella vaccination also contribute to sustainable cities (SDG11). In addition, vaccination acts synergistically with other development objectives, enhancing the benefits achieved by other SDGs. For example, the impact of enhanced food security and reduced hunger (SDG2) on child development and maternal health will be greater if vaccine-preventable diseases are controlled or eliminated as these diseases impair physical and cognitive development. Similarly, quality education (SDG4) will deliver greater benefits if children are protected against these illnesses. One example is a recent study that found measles vaccination was associated with improved cognitive functioning and school-grade attainment.[13]

Measles vaccination coverage is an important indicator of the immunization action package for the prevention arm of the GHSA, which emphasizes protection against epidemic-prone vaccine-preventable diseases (VPDs). The goal is at least 90% coverage of the country's fifteen-month-old population with at least one dose of measles-containing vaccine (MCV). Measles vaccination coverage is emphasized because it is recognized as a proxy indicator for overall immunization against VPDs.

GVAP was endorsed in 2012 by the WHA to create a framework for immunization activities through 2020 and set target dates for regional measles and rubella elimination. By 2015, four WHO Regions were to have eliminated measles and two to have eliminated rubella. By 2020, five WHO Regions were to have eliminated measles and rubella. Given the high priority to deliver measles and rubella vaccines through essential immunization services, achieving measles and rubella elimination goals will require higher coverage with measles-containing vaccine first (MCV1) and second (MCV2) doses than currently achieved (86% and 69% in 2018).[14] A focus on measles and rubella elimination can promote both universal health care and primary health care by strengthening essential immunization services, addressing inequities in vaccine coverage, and reducing the number of unvaccinated children (including children and young infants for whom vaccination is not indicated or contraindicated such as immunocompromised children) who are not exposed to the virus when there are high levels of immunity in the population. In addition, a focus on measles and rubella elimination can help in enhancing subnational disease surveillance systems, identifying new approaches to reduce critical immunization gaps, and building national ownership of immunization programmes.

The IA2030 lays out core principles and strategic priorities that are aligned with the need to accelerate progress toward the measles and rubella elimination goals. In fact, progress toward achieving these elimination goals could be a pathfinder for the success of the IA2030. The core principles of the IA2030 are that immunization be people-focused, country-owned, based on partnerships, and data driven, all necessary to achieve the measles and rubella elimination goals. The seven strategic priorities are also key components of effective and successful measles and rubella elimination efforts: 1) immunization programmes for primary health care and universal health care; 2) coverage and equity; 3) commitment and demand; 4) outbreaks and emergencies; 5) lifecourse & integration; 6) research and innovations; and 7) supply and financing. The path towards measles and rubella elimination, and eventually eradication, could not be achieved without achieving these IA2030 strategic priorities and thus put measles and rubella elimination as a key indicator of IA2030 progress and success.

Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001-2020. *Bulletin of the World Health Organization* 2017;95:629-638.

[13] Nandi A, Shet A, Behrman JR, Black MM, Bloom DE, Laxminarayan R. Anthropometric, cognitive, and schooling benefits of measles vaccination: Longitudinal cohort analysis in Ethiopia, India, and Vietnam. *Vaccine* 2019.

[14] Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SV, Wallace AS. Global Routine Vaccination Coverage, 2018. *Morbidity and Mortality Weekly Report* 2019;68:937-942.

Current Global Measles and Rubella Situation

6. **Progress toward achieving regional and global measles and rubella milestones**. The WHA in 2010 established three milestones for measles control by 2015 that reflect the immunization strategies: 1) increase routine vaccination coverage with MCV1 to at least 90% nationally and at least 80% in every district; 2) reduce global annual measles incidence to less than 5 cases per million population; and 3) reduce global measles mortality by 95% from the 2000 estimate.[15] Although these targets were not achieved, progress is still assessed against these milestones as well as the GVAP regional elimination targets. Substantial gains were made from 2000 to 2010 but progress has slowed, and these milestones and goals remain unmet with variable progress among and within regions.

   Measles and rubella vaccination coverage: Global coverage with MCV1 was estimated at 86% in 2018 according to WHO and UNICEF (WUENIC) estimates. Regional MCV1 coverage by WHO region was 74% for African (AFR), 90% for the Americas (AMR), 82% for Eastern Mediterranean (EMR), 95% for European (EUR), 89% for South-East Asia (SEAR), and 95% for Western Pacific (WPR). In 2018, 118 (61%) Member States achieved at least 90% MCV1 coverage and 55 (28%) Member States achieved at least 80% MCV1 coverage in all districts. In addition, as of July 2019, 173 (89%) Member States had introduced MCV2, reaching 69% coverage globally, and 168 (87%) Member States had introduced rubella vaccine into their national programmes. Global coverage for rubella vaccine was 69%, with 32% coverage in AFR, 90% in AMR, 45% in EMR, 95% in EUR, 83% in SEAR, and 94% WPR.[16]

   Measles incidence: Annual measles incidence for reported cases was 49 cases/million population in 2018, with 353,236 cases reported through annual reporting.[17] However, fewer than 5% of measles cases are reported globally, making a measles incidence milestone difficult to accurately measure. In 2017, 6.7 million cases of measles were estimated to have occurred globally;[18] 2018 estimates will be released in December 2019. Of 179 countries, 96 had a measles incidence less than 5 cases per million population in 2018, and 66 countries had fewer than 1 case per million population. Every region had an increase in reported cases in 2018 relative to 2017, and major outbreaks have occurred in all regions, garnering global attention. While the proximate causes of the ongoing outbreaks are multifactorial and include conflict, repeated importations, historical gaps in immunization coverage, weak immunization systems with equity gaps, and insufficient vaccination demand, all outbreaks are characterized by the predominance of cases among unvaccinated persons, reflecting programme failure to systematically administer MCV over multiple birth cohorts. Thus, the current measles epidemiological situation in many settings reflects a predictable consequence of inadequate implementation of current strategies, with the build-up of susceptible individuals, endemic transmission, and imported measles cases sparking outbreaks.

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[15] World Health Organization. Global eradication of measles: report by the Secretariat. Geneva, Switzerland: World Health Organization; 2010.

[16] Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SV, Wallace AS. Global Routine Vaccination Coverage, 2018. *Morbidity and Mortality Weekly Report* 2019;68:937-942.

[17] Reported case data: measles cases (2018) from World Health Organization, as of July 15, 2019 (http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencemeasles.html).

[18] Dabbagh A, Laws RL, Steulet C, Dumolard L, Mulders MN, Kretsinger K, Alexander JP, Rota PA, Goodson JL. Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. *Morbidity and Mortality Weekly Report* 2018;67:1323-1329.

Measles mortality: The 2017 estimate of measles-related mortality was approximately 110,000 deaths globally, with wide confidence intervals.[19] This reflects an 80% decline in estimated measles mortality since 2000 and over 21 million lives saved due to measles vaccination during that time. While impressive, this number falls short of the 95% mortality reduction goal. 2018 global mortality estimates will be released in November 2019.

Molecular surveillance: Monitoring progress toward measles and rubella elimination requires high-quality case-based surveillance with laboratory confirmation, supported by genetic characterization of measles and rubella viruses to identify sources of transmission and monitor progress toward elimination through changes in genetic diversity. In 2000, WHO established the Global Measles and Rubella Laboratory Network (GMRLN) to provide high-quality laboratory support for surveillance for measles, rubella, and congenital rubella syndrome. GMRLN is the largest globally coordinated laboratory network, with 704 laboratories supporting surveillance in 191 countries. These laboratories support the confirmation of measles and rubella cases, and molecular surveillance provides a means of tracking progress toward elimination and potential sources of imported cases. However, sequence data and geographic representativeness of reported measles and rubella sequences is not complete, with the African Region particularly underrepresented.[20]

During 2016–2018, only six of the 24 recognized measles virus genotypes were detected, and only four in 2018. Two genotypes (B3 and D8) accounted for 95% of reported sequences. During 2016–2018, the diversity index of each measles virus genotype reported to the Measles Nucleotide Surveillance (MeaNS) system, defined as the number of distinct measles sequences divided by the total number of records in the database, decreased overall. Of the 13 known rubella virus genotypes, reported genotypes declined from five to two. Overall, the genetic diversity of detected measles and rubella strains has decreased globally, consistent with progress toward elimination.

7. **Regional measles and rubella elimination goals.** Member States in all WHO Regions adopted measles elimination goals to be reached by or before 2020. The original regional elimination dates were AMRO (2000), WPRO (2012), EURO (2015), EMRO (2015), AFRO (2020) and SEARO (2020, which has recently been updated to 2023). In addition, four of the Regions (AMRO, EURO, SEARO and WPRO) have rubella elimination goals. Regional goals were incorporated into the targets of the Regional Vaccine Action Plans (RVAPs) and GVAP.

   While progress has been made in several metrics, including the number of Member States achieving verified elimination status and the number of Regional Verification Commissions (RVCs) and National Verification Committees (NVCs) established, the Regional elimination goals have not been achieved. All Regions have established RVCs, and 148 of 194 (76%) countries have established NVCs. RVCs review all NVC reports and determine measles and rubella elimination status, following the WHO framework for verifying elimination.[21] As of September 2019, 82 of 194 (42%) Member States were verified as having eliminated measles and 81 as having eliminated rubella. The overall status of elimination verification progress by Region is summarized in Table 1.

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[19] Dabbagh A, Laws RL, Steulet C, Dumolard L, Mulders MN, Kretsinger K, Alexander JP, Rota PA, Goodson JL. Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. *Morbidity and Mortality Weekly Report* 2018;67:1323-1329.

[20] Brown KE, Rota PA, Goodson JL, Williams D, Abernathy E, Takeda M, Mulders MN. Genetic characterization of measles and rubella viruses detected through global measles and rubella elimination surveillance, 2016-2018. *Morbidity and Mortality Weekly Report* 2019;68:587-591.

[21] World Health Organization. Guidance for evaluating progress towards elimination of measles and rubella. *Weekly Epidemiological Record* 2018; 93:544–552.

The Region of the Americas was verified as having eliminated measles in 2016,[22] although most countries were verified by their NVCs many years earlier. Unfortunately, this regional elimination status was lost in 2018 due to circulation of measles virus in Venezuela following a decrease in vaccination coverage. Neighboring countries re-established transmission of measles virus (Brazil) or have experienced multiple prolonged outbreaks (Columbia).[23] The Region of the Americas is the only region to have eliminated measles, and thus demonstrates the feasibility of measles elimination. Many Member States have eliminated measles for decades and the last endemic case of measles in the Americas was in 2002. However, the reversal of this situation in 2018 also demonstrates the fragility of elimination status. Elimination status in a country or region should not be viewed as a fixed, stable state but a status that can be lost, requiring intensive efforts to regain. Rubella elimination was verified in the Region of the Americas in 2015 and has been sustained. No other region has yet achieved measles or rubella elimination.

Seven countries have re-established measles virus transmission after having been declared eliminated, and similar loss of elimination status threatens other countries. In the Americas, Venezuela and Brazil lost their measles elimination status as did Mongolia in the Western Pacific Region. In the European Region, Albania, the United Kingdom, the Czech Republic, and Greece lost their elimination status. No country has lost rubella elimination status. The recent reversals in measles elimination status are fundamentally linked to the challenges of achieving and sustaining the high level of population immunity (approximately 92% to 94%) required to interrupt transmission, associated in many countries with insufficient political will, conflict, migration, humanitarian emergencies, national financial investment and vaccine hesitancy. The precariousness of elimination status is also due to the extreme infectiousness of measles virus, more importations in an increasingly interconnected world, and ability to adequately respond to each importation.

Table 1. Measles and Rubella Elimination Verification by Region (as of September 2019)

WHO Region (number of countries)	Regional Verification Commission Established	Elimination Achieved, Number (%) of Member States (n=194)	
		Measles	**Rubella**
Americas (35)	**Yes**	33 (94)	35 (100)
Europe (53)*	**Yes**	35 (66)	39 (74)
Western Pacific (27)	**Yes**	7+2 non-Member States (26)	4+1 non-Member States (15)
Eastern Mediterranean (21)**	**Yes**	2 (10)	3 (14)
South-East Asia (11)	**Yes**	5 (45)	0
Africa (47)	**Yes**	0	0
TOTAL		**82 (42%)**	**81 (42%)**

[22] Pan American Health Organization. Plan of Action for Maintaining Measles, Rubella, and Congenital Rubella Syndrome Elimination in the Region of the Americas: Final Report. 55th Direction Council; 66th session of the WHO Regional Committee for the Americas; 26-30 September 2016; Washington, DC. Washington, DC: PAHO; 2012 (Resolution CD55/INF/10).

[23] Paniz-Mondolfi AE, Tami A, Grillet ME, Márquez M, Hernández-Villena J, Escalona-Rodríguez MA, Blohm GM, Mejías I, Urbina-Medina H, Rísquez A, Castro J, Carvajal A, Walter C, López MG, Schwabl P, Hernández-Castro L, Miles MA, Hotez PJ, Lednicky J, Morris JG Jr, Crainey J, Luz S, Ramírez JD, Sordillo E, Llewellyn M, Canache M, Araque M, Oletta J. Resurgence of Vaccine-Preventable Diseases in Venezuela as a Regional Public Health Threat in the Americas. *Emerging Infectious Diseases* 2019;25:625-632.

* In addition, a number of countries in EUR have been verified as having interrupted transmission of measles for 12 (n=1) or 24 (n=1) months and rubella for 24 (n=3) months; these are not reflected in the totals as 36 months is required for the RVC to declare elimination achieved.

**The EMR RVC verified three countries as having eliminated rubella, despite the absence of a regional rubella elimination goal.

8. **Strategies to achieve measles and rubella elimination**. Measles virus is one of the most highly contagious directly transmitted human pathogens. In a completely susceptible population, a single case of measles can result in 12 to 18 secondary cases, on average,[24] although this number varies across a wide range in different demographic settings.[25] Based on these estimates of the reproductive number, and the simplifying assumption of random mixing in a population, current strategies for measles elimination aim to achieve population immunity of 92% to 94%. This level of population immunity is the theoretical threshold needed to prevent sustained transmission of measles virus (i.e., reproductive number is less than one). However, measles cases and short chains of transmission can occur in settings that have achieved this level of population immunity, particularly if there are spatial clusters of susceptible persons. This level of population immunity requires at least 95% coverage with two doses of measles-containing vaccine (MCV), one in the first year of life and the second dose preferably in the second year of life,[26] at national and district levels. This high coverage should be achieved in every birth cohort, every community, and every district to ensure sufficiently high and homogeneous population immunity to interrupt virus transmission.[27] High coverage with the first dose of MCV is critical, with the goal of MCV2 to immunize those children who fail to respond to the first dose (approximately 15% vaccinated at nine months of age). Administration of measles vaccine in the second year of life also offers an additional opportunity for those children who did not receive a dose in the first year of life. For rubella, the herd immunity threshold is considerably lower, at approximately 83-85% because of the lower reproductive number (R_0 = 5-8) than measles.[28]

   Supplementary immunization activities (SIAs) targeted to specific age groups regardless of prior vaccination status are widely used to fill immunity gaps and address deficits in prior programme performance. Low MCV coverage through essential services results in a substantial fraction of susceptible older cohorts because they have neither been vaccinated, nor exposed to wild-type virus due to reductions in virus circulation. SIAs are implemented to prevent the accumulation of susceptible persons to a size that can sustain transmission and, thereby, prevent measles outbreaks. SIAs must be well planned to ensure very high coverage and to reach children who did not receive a dose of MCV ("zero-dose children") and immunize those who failed to respond to MCV1 but who did not receive MCV2 (under-immunized), rather than simply revaccinating already immunized populations. Subnational vaccination campaigns, targeting spatial immunity gaps, may be

[24] Gay NJ. The theory of measles elimination: implications for the design of elimination strategies. *Journal of Infectious Diseases* 2004;189:Suppl 1:S27-S35.

[25] Guerra FM, Bolotin S, Lim G, Heffernan J, Deeks SL, Li Y, Crowcroft NS. The basic reproduction number (R0) of measles: a systematic review. *Lancet Infectious Diseases* 2017;17:e420-e428.

[26] World Health Organization. Measles vaccines: WHO position paper – April 2017. *Weekly Epidemiological Record* 2017;92:205-28.

[27] Field studies of the effectiveness of the measles vaccine have found high effectiveness after one dose administered at the age of 12 months or later (median effectiveness, 93%; range, 39 to 100) and even higher effectiveness after two doses (median, 97%; range, 67 to 100). McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 2013;62(RR-4):1-34.

[28] Fine PEM, Mulholland K, Scott JA, Edmunds WJ. Community Protection in Ploktin's Vaccines 7th edition. Plotkin SA, Orenstein WA, Offit PA, Edwards KM eds. Elsevier 2018:1512-153.

more efficient in some settings and additional strategies are needed to identify and target those who are unvaccinated and non-immune.

Periodic intensification of routine immunization (PIRI) is an intermediate strategy marked by periodic or intermittent and intensified improvements to routine immunization services that often include information, education, communication (IEC) and social mobilization activities. Achieving high vaccination coverage, through these approaches, is a tactic to achieve the goal of high population immunity. The objectives of SIAs and PIRISs are to vaccinate susceptible (zero-dose and under-immunized) children and better methods of identifying these children would make these activities more efficient.

9. **Linking measles and rubella elimination**. Rubella elimination should be achieved in concert with measles elimination. Because rubella virus is less contagious than measles virus, rubella elimination will be easier than measles elimination where the vaccines are co-administered. To date, rubella virus transmission has not been re-established in any country following verification of elimination. The WHO recommends that countries take the opportunity offered by measles elimination activities to introduce rubella vaccine.[29] Measles vaccine delivery strategies provide an opportunity for synergy and a platform for advancing elimination of rubella, particularly congenital rubella syndrome. Sustained high coverage of rubella vaccine is needed to prevent the potential risk of increased incidence of rubella in women of child-bearing age and thus of CRS. Without sustained high coverage, girls may reach puberty neither vaccinated nor immune from infection with wild-type virus, potentially leading to susceptibility of pregnant women, rubella outbreaks, and increased cases of CRS. Thus, introduction of rubella vaccine into the childhood immunization programme requires long-term commitment to achieving and maintaining sufficient vaccine coverage to ensure a sustained reduction in the incidence of CRS and ultimately the interruption of rubella virus transmission. Strong political commitment to the elimination of rubella and CRS, and sustainable financing for vaccination and surveillance activities, should be in place before introducing rubella vaccination into the childhood immunization programme.

Measles and Rubella Eradication

10. Feasibility of measles and rubella eradication

The feasibility of measles eradication encompasses a combination of biological, technical and operational factors, as well as political, social and financial factors. Biologic feasibility refers to characteristics of the measles virus, including the fact that humans are the only natural reservoir of measles virus (although non-human primates can be infected) and the absence of persistently-infected humans who remain contagious, sustained subclinical virus transmission, or viral evolution away from vaccine-induced immunity.[30] Technical feasibility refers to the availability of tools needed to achieve measles eradication, including a low-cost, safe, and effective vaccine and accurate diagnostic tests. Operational feasibility refers to the ways these tools are deployed, including delivery of two doses of MCV through a strong routine immunization system supplemented by mass vaccination campaigns as needed to fill immunity gaps that accumulate over time, a sensitive surveillance system with timely and accurate reporting at the subnational level, and efficient and effective outbreak response. The elimination of measles and rubella in the Americas provides demonstration in a large geographical area that elimination can be achieved under rigid programmatic, political, financial and social conditions.

[29] World Health Organization. Rubella vaccines: WHO position paper. *Weekly Epidemiological Record* 2011;86:301-16.

[30] Moss WJ, Strebel P. Biological feasibility of measles eradication. *Journal of Infectious Diseases* 2011; 204 Suppl 1:S47-53.

While biologic, technical and operational feasibility are necessary to achieve measles and rubella eradication, they are not sufficient. The feasibility of measles and rubella eradication requires broad public support and political will as well as sufficient financial resources to stop virus transmission everywhere. Eradication requires access to children in humanitarian and conflict settings and in areas controlled by anti-government elements. In addition, an eradication programme requires strong governance, oversight and accountability as well as long-term commitment from all stakeholders. The International Task Force for Disease Eradication (ITFDE), established at The Carter Center in 1988 and currently supported by The Bill & Melinda Gates Foundation (BMGF), listed the following criteria for assessing whether a disease can be eradicated, highlighting the importance of both scientific feasibility and the need for political will and public support:[31]

Scientific Feasibility

- Epidemiologic characteristics, including the potential existence of nonhuman reservoirs; ease of spread; induction of natural immunity; and ease of diagnosis
- Availability of an intervention, such as a vaccine, that ideally should be effective, safe, inexpensive, long-lasting, and easily deployed
- Demonstrated feasibility of elimination, such as documented elimination from a defined country or region

Political Will/Popular Support

- Perceived burden of disease
- Expected cost of eradication
- Synergy of eradication efforts with other interventions
- Necessity for eradication rather than control

Measles and rubella meet the criteria for scientific feasibility of eradication. However, the ITFDE report did not fully address the programmatic feasibility of eradication. Significant challenges concern garnering the political will, public support, financial resources, and commitment to an eradication goal, and the programmatic feasibility of achieving and sustaining sensitive surveillance systems, vaccine delivery mechanisms to achieve the necessary coverage, and strategies to define and identify susceptible individuals and groups who require innovative tactics to vaccinate.

11. **Global Technical Consultation to Assess the Feasibility of Measles Eradication**. Since the introduction of measles vaccine in the early 1960's, there have been several rigorous assessments of the feasibility of measles eradication.[32] More recently, the Executive Board of the WHO requested in May 2008 that an ad hoc group of experts assess the feasibility of measles eradication. The Global Technical Consultation to Assess the Feasibility of Measles Eradication concluded in 2010 that "measles can and should be eradicated" and "recommended that the World Health Assembly consider establishing a target date for measles eradication once the South East Asian Region established an elimination target", which was then set in September 2013.[33] The assessment considered the feasibility of measles elimination in each WHO Region as well as the biological, technical, programmatic, and economic feasibility of measles eradication. Also considered were the impact of measles eradication on health systems and the implications for vaccine

[31] Recommendations of the International Task Force for Disease Eradication. *MMWR* 1993;42(RR-16):1-38. (available at https://www.cdc.gov/mmwr/preview/mmwrhtml/00025967.htm).

[32] Sencer DJ, Dull HB, Langmuir AD. Epidemiologic basis for eradication of measles in 1967. *Public Health Rep* 1967;82:253-6.

[33] World Health Organization. Proceedings of the Global Technical Consultation to assess the feasibility of measles eradication, 28-30 July 2010. *Journal of Infectious Diseases* 2011;204:S4-S13.

supply. The Advisory Group recognized that building the required political, social, and economic platforms for measles eradication would be both a disease control opportunity and an important developmental opportunity, requiring a broad multidisciplinary partnership, and stressed that the success of measles eradication would depend on strong management, accountability, communication, advocacy, and resource mobilization at all levels. Thus, the Advisory Group acknowledged the biological and technical feasibility of measles eradication but recognized the challenges in garnering the public support, political will, and financial resources that will be required to eradicate measles. A similar global technical consultation to assess the feasibility of rubella eradication has not been conducted.

12. **International Task Force for Disease Eradication**. A decade ago, in 2009, the ITFDE concluded that "measles eradication is biologically possible, using tools that are currently available…. [but that] the delay in eradication of polio is a special obstacle to global measles eradication".[34] The ITFDE reassessed measles eradication in 2015. The ITFDE restated the belief that measles and rubella eradication are technically feasible and recognized that efforts to control and eliminate measles and rubella accelerated since 2000. However, measles eradication "will require a much more demanding enterprise than the current effort, which has suffered from insufficient resources and wavering political commitment."[35] The ITFDE will again discuss measles and rubella eradication in October 2019 and the findings should be available prior to the Seventy-third WHA in 2020.

13. **The Measles and Rubella Midterm Review**. A comprehensive review of the *Global Measles and Rubella Strategic Plan, 2012-2020*[36] was conducted in 2016, assessing the global strategy for measles and rubella elimination. The *Measles and Rubella Midterm Review*[37] acknowledged that tremendous progress had been made towards measles and rubella elimination since 2001 and identified ten key points regarding the global strategy for measles and rubella elimination: 1) measles eradication is the ultimate goal but regional elimination goals should be pursued to enable a decision by 2020 as to whether or not a target be set for measles eradication; 2) 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; 3) reliance on SIAs should be changed to primary reliance on well-performing essential immunization services to assure administration of two doses of MCV; 4) reliance on vaccine coverage to measure progress should be changed to measurement of measles and rubella incidence as the metric to track progress toward elimination; 5) measles and rubella vaccination programmes should be considered an indicator of the quality of the overall immunization programme, and incidence and vaccination coverage should be considered primary indicators of immunization programme performance; 6) polio transition presents risks and opportunities for measles and rubella eradication, and the opportunities should be maximized; 7) school entry immunization checks could contribute to strengthening overall immunization services; 8) programme decisions should increasingly be based on high quality data and appropriate analysis; 9) incorporation of rubella vaccination into the immunization programme should be accelerated; and 10) outbreak investigation and response are critical but most important is the prevention of measles and rubella outbreaks. The *Measles and Rubella Midterm Review* emphasized the need to achieve and sustain

[34] Summary of the 14th Meeting of the International Task Force for Disease Eradication, 2009 (available at http://www.cartercenter.org/resources/pdfs/news/health_publications/itfde/ITFDEsum0609.pdf).

[35] World Health Organization. Meeting of the International Task Force for Disease Eradication, November 2015. *Weekly Epidemiological Record* 2016;91:61-72.

[36] World Health Organization. Global Measles and Rubella Strategic Plan: 2012-2020 (http://apps.who.int/iris/bitstream/10665/44855/1/9789241503396_eng.pdf).

[37] Orenstein WA, Hinman A, Nkowane B, Olive JM, Reingold A. Measles and Rubella Global Strategic Plan 2012-2020 midterm review. *Vaccine* 2018;36 Suppl 1:A1-A34.

elimination by strengthening health systems. Specifically, the report recommended "focusing on improving ongoing immunization systems – although this may delay reaching measles and rubella elimination goals – in order to ensure that gains in measles and rubella control can be sustained. Reorienting the measles and rubella elimination program to increase emphasis on surveillance so that programmatic and strategic decisions can be guided by data is critical."

Progress and Challenges in Achieving Measles and Rubella Elimination Goals

14. Operational challenges to measles and rubella eradication. Several operational challenges will need to be addressed to achieve measles and rubella eradication, including the: 1) high vaccine coverage required to achieve and sustain 92-94% homogeneous population immunity to measles virus and delivered through strong essential immunization programmes; 2) need for high quality data on vaccine coverage and measles and rubella incidence at the subnational level (e.g. district or health center catchment area); 3) need for logistically and financially feasible methods to identify immunity gaps, including zero-dose and under-immunized children; 4) risk of rapid, global spread of measles virus through unimmunized travelers; 5) potential for increased susceptibility among young infants from decreased levels of maternal antibody as a result of maternal vaccination and limited boosting; 6) possibility of significant waning immunity in vaccinated persons no longer boosted by exposure to wild-type virus; 7) and risk of measles and rubella virus re-introduction from laboratories after eradication.

Most importantly, region and country-specific challenges will continue to hinder progress: 1) weak health infrastructure and immunization programmes, including an inadequately trained workforce; 2) restricted access to children in regions of conflict, insecurity, and humanitarian emergency; and 3) vaccine hesitancy based on mistrust and misinformation about vaccines. These issues are likely to be major challenges to measles and rubella eradication and were identified among the ten threats to global health in 2019 (i.e., weak primary health care, fragile and vulnerable settings, and vaccine hesitancy).[38]

15. Progress and challenges in implementing the recommendations of the *Measles and Rubella Midterm Review*. The *Measles and Rubella Midterm Review* provided detailed recommendations on programme performance that have been used to guide immunization and surveillance programmes. The five strategic areas described in the *Measles and Rubella Midterm Review* are summarized and progress and challenges assessed.

Measles and Rubella Midterm Review Strategy 1. Monitor disease using effective surveillance and evaluate programmatic efforts to ensure progress.

- *All countries must implement case-based, laboratory-supported surveillance for measles and rubella, and report case information to the WHO Regional Office on a weekly basis.*
- *A working group on surveillance and outbreak investigation and response should be developed at the global level.*
- *Protocols should be updated or, when necessary, developed, to guide surveillance and outbreak investigation and response.*
- *Countries must dedicate resources for surveillance and partners need to supplement resources, including resources for staffing, laboratory support, training, and other operational costs.*
- *Sentinel surveillance for congenital rubella syndrome (CRS) should be implemented.*

[38] https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

- *Cases should be classified to determine the proportion of cases attributable to program failure, i.e. cases who should have been vaccinated according to the national schedule but were not, to allow for the underlying reasons to be identified and addressed. For cases that are not program failures, analysis should be undertaken to determine whether changes in strategy are needed such as changing the age for recommended vaccination.*

Progress and challenges: Most of the *Measles and Rubella Midterm Review* surveillance recommendations have been adopted or are in the process of being adopted. Global surveillance standards were updated for measles,[39] rubella,[40] and CRS,[41] and a roadmap to elimination quality surveillance was published.[42] All 194 Member States except one (Mauritius) report having measles case-based surveillance, although implementation and quality are variable. Member states report data weekly or monthly to the WHO Regional office. India is replacing previous outbreak-based surveillance with national case-based surveillance as it rolls out measles-rubella catch-up campaigns by state. In 2016, 126 countries reported conducting CRS surveillance, of which 95 (49%) have either population-based or sentinel surveillance. Monthly global surveillance bulletins are published and disseminated broadly and a working group on comprehensive disease surveillance was formed. Updated global guidance on outbreak investigation and response is under development but has not yet been completed. A global analysis of the proportion of cases that are attributable to programme failure was published,[43] with 63% of the 434,956 cases with available vaccination data categorised as programmatically preventable, but this approach has yet to be systematically implemented at the programme level in many countries.

While country investment in surveillance is generally considered inadequate, the extent of the gap is unknown. Substantial investment in surveillance will be needed for countries and regions to achieve and sustain regional elimination goals. A surveillance costing tool is under development and the completed version should help countries budget appropriately for surveillance needs. Several challenges remain in optimizing laboratory confirmation of measles and rubella cases. Elimination quality surveillance requires an investment to test and discard suspected cases. In outbreak settings, use of epidemiologic confirmation can prove problematic in countries without a clear protocol to select cases for laboratory confirmation, which requires close collaboration at the national level between the laboratory and surveillance epidemiologists. Specific threats to optimal implementation of elimination quality surveillance include reliance on polio staff and funding to conduct field surveillance, and dependence of the GMRLN on a single funding agency, the U.S. Centers for Disease Control and Prevention.

[39] World Health Organization. Measles - Vaccine Preventable Diseases Surveillance Standards, 2018. (available at https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_11_Measles_R2.pdf?ua=1)

[40] World Health Organization. Rubella - Vaccine Preventable Diseases Surveillance Standards, 2018. (available at https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_20_Rubella_R2.pdf?ua=1)

[41] https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_03_CRS_R2.pdf?ua=1

[42] Sniadack DH, Crowcroft NS, Durrheim DN, Rota PA, Roadmap to elimination standard measles and rubella surveillance. *Weekly Epidemiological Record* 2017;92:97-105.

[43] Patel MK, Orenstein WA. Classification of global measles cases in 2013-17 as due to policy or vaccination failure: a retrospective review of global surveillance data. *Lancet Glob Health* 2019;7:e313-e320.

Measles and Rubella Midterm Review Strategy 2. Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles and rubella-containing vaccines

- *Two doses of measles and rubella-containing vaccine delivered through routine immunization services should be the standard for all national immunization programs, with the goal of 95% coverage with both doses.*
- *Preventive supplementary immunization activities (SIAs) should be conducted as a rescue effort when countries have not yet implemented a routine second dose or when two dose coverage is insufficient to achieve and maintain high population immunity, with a focus on immunizing unvaccinated children.*
- *Immunization strategies and surveillance strategies should be tailored to the country categorization and immunity gaps should be addressed by a set of interventions based on whether disease incidence is low, medium or high.* [44]
- *All countries should institute a school entry check for immunization to provide missed doses of vaccines, particularly vaccination against measles and rubella as well as against other vaccine-preventable diseases.*
- *Immunity gaps among adolescents and adults need to be addressed by promoting effective strategies for vaccinating susceptible older children, adolescents, and adults.*

Progress and challenges: Implementation of the *Measles and Rubella Midterm Review* population immunity recommendations has proven challenging. Globally, MCV1 is part of the national immunization schedule in all countries and MCV2 has been introduced into 173 Member States, with another 3 countries planning to introduce MCV2 in 2019. WUENIC estimates of global coverage for MCV1 and MCV2 in 2018 was 86% and 69%, respectively, far below the 95% coverage with both doses that is generally required to achieve measles elimination. In fact, MCV1 coverage has remained at approximately 85% for a decade despite substantial investments. Thus, the continued need for preventive SIAs are forecast for many years based on projections of the accumulation of susceptible children. However, delays in conducting SIAs are common and are often linked to postponing the funding request submission or delays in approval for countries needing support. School entry vaccination checks are not universally implemented. WHO is currently documenting country case studies on the implementation of school entry vaccination checks to develop guidance on best practices. Although the benefits of catching-up children on missed doses is obvious, implementation of the strategy is complex, requiring legislative and policy frameworks, reliable monitoring systems, and collaboration with Ministries of Education. In addition, policies for school entry vaccination checks often focus on first entry (at 5-6 years of age), and not on older children. Where measles and rubella surveillance show disease occurring in older school-aged children, school vaccination checks for all age groups should be implemented to close susceptibility gaps for children already in school when a school entry check policy is introduced, or for those who entered the system later on. Unless effective campaigns are conducted and catch-up opportunities used, birth cohorts with immunity gaps will continue to age, resulting in older cohorts with residual immunity gaps. Closing immunity gaps in susceptible, older individuals out of school is much more challenging to implement and obtain high coverage. Although guidance on supplementary doses exists, there continues to be a gap in effective guidance on how to administer, record and report these doses.

[44] Susan Reef, Jennifer Harris, Alan Ou, Ty Kraniak. Guidance to Increasing Population Immunity against Measles and Rubella.
https://www.who.int/immunization/sage/meetings/2018/october/3_Country_classification_Guidance_measles_session_yellow_book_doc.pdf?ua=1

Measles and Rubella Midterm Review Strategy 3. Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases.

- *The primary goal must be to prevent outbreaks through monitoring risk status and increased attention to vaccination of underserved communities and in high risk settings.*
- *All measles outbreaks should be promptly investigated, and a susceptibility profile developed to inform measles control and elimination strategies.*
- *Training materials should be developed for use at global, regional and country levels on performing outbreak investigations as well as to understanding the underlying reasons for the outbreaks.*
- *Adequate financial, human and laboratory resources to conduct rigorous outbreak investigations should be ensured.*
- *Countries should take steps to mitigate measles and rubella outbreaks through vaccination, with the magnitude of the response based on the characteristics of the outbreak, the stage of measles control, and the country categorization.*

Progress and challenges: Global outbreak preparedness and response is quite variable. Although many initiatives to tailor preventive immunization approaches have been promoted, subnational risk stratification has not been conducted systematically across all countries. In some countries, outbreak response is rapid and rigorous, particularly those with sufficient domestic technical and financial resources. However, in many countries with weaker surveillance and competing priorities, outbreaks can go undetected for long periods, followed by inadequate response. The Measles & Rubella Initiative (M&RI) has administered Gavi-supported outbreak response funding (up to US$ 10 million per year) to enable rapid outbreak response in Gavi-eligible countries and is in the process of revising the standard operating procedures to enhance speed and effectiveness. Likewise, WHO is updating the measles and rubella outbreak response guidance documents and developing training materials in parallel.

Despite these efforts, measles outbreaks continue to occur with increasing frequency and magnitude, in low-, middle- and high-income countries, illustrating the challenges of controlling a virus with high contagiousness. Repeated importations in an increasingly interconnected world present an ongoing challenge to countries that have already eliminated endemic measles virus transmission, even those with very high levels of population immunity. In countries with endemic transmission, immunity gaps from substandard programme implementation result in repeated outbreaks and the potential to export virus to other countries.

Measles and Rubella Midterm Review Strategy 4. Communicate and engage to build public confidence and demand for immunization.

- *Resources for effective communication must be available to raise the visibility of vaccine-preventable diseases, with a focus on measles and rubella.*
- *Demand for immunization should be created and promoted through long term investment and as an integral part of the routine immunization strategy.*
- *Communication strategies should be planned and specific messages for different audiences developed (e.g., politicians, public health leaders and workers, health care providers, and caregivers).*
- *A range of audiences should be educated on measles incidence, complications, and deaths, as well as on the costs associated with outbreaks, supplemented with stories of actual cases to illustrate the statistical data.*
- *Case studies should be identified and promoted of how measles and rubella elimination efforts enhanced the overall immunization and health systems.*

Progress and challenges: Implementation of the *Measles and Rubella Midterm Review* recommendations are in progress; however, in most places these efforts have not achieved their potential impact due to a lack of locally-targeted interventions and measurement. Increasingly, there is awareness of the need to move away from one-size-fits-all and traditional communications-based approaches to generate community vaccination demand. There is also growing recognition of the full range of determinants of acceptance and demand, considering both attitudinal and supply-side factors, e.g. access, and related practical and logistical factors. However, programmes are yet to systematically gather and use local data to inform planning that covers the full range of social and behavioral drivers of uptake. Further, a range of new approaches and interventions are yet to be fully exploited by programmes to drive sustained uptake. Three main areas may be considered: 1) effective integration across services and communities and within PHC, leveraging new thinking and tools within systems science;[45] 2) innovation, such as the use of digital technologies for prompts and reminders, and engagement of non-traditional stakeholders to build local ownership and support; and, 3) specific strategies for high risk populations, including efforts to anticipate, assess, and address the emergence of pockets of vaccine hesitancy and refusal. The application of these more advanced strategies may be limited by capacity, resources, or limited user-centered planning to meet the needs of all caregivers. However, the opportunities should be seized to enable programmes to increase and sustain equitable coverage of both MCV1 and MCV2, and to benefit essential immunization services more broadly.

Measles and Rubella Midterm Review Strategy 5. Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

- *Programmatically-oriented operations research, in addition to technologically-oriented research, should be used to determine how to best interrupt measles virus transmission and should include achieving optimal uptake of vaccination in populations, which populations should be targeted for special immunization efforts, how to optimize surveillance systems, and the economic impact of disease.*
- *Sustained commitment to adequately funding measles and rubella research is required and an advocacy plan to secure funding for research should be developed.*
- *A measles and rubella research committee should be formed and supported, focusing on advocating for, promoting, and prioritizing measles and rubella research, similar to the Polio Research Committee.*

Progress and challenges: Priority research questions were identified by the M&RI Research Prioritization Process in 2016 across four strategic areas: 1) epidemiology and economics; 2) surveillance and laboratory; 3) immunization strategies; and 4) demand creation and communications.[46] The most transformative technologies would augment the technical feasibility of measles and rubella eradication, such as microarray patches for vaccine administration, rapid diagnostic tests, field-deployable molecular tests for measles and rubella virus detection and genotyping, and novel methods for rapid assessment of population immunity. See Section 23 below on the potential impact of innovations on the feasibility of measles and rubella eradication.

[45] Dowell AC, Menning L, MacDonald N, Turner N. An evolution in thinking to support the post 2020 global vaccine strategy: The application of complexity and implementation science. *Vaccine* 2019;37:4236-4240.
[46] Grant GB, Masresha BG, Moss WJ, Mulders MN, Rota PA, Omer SB, Shefer A, Kriss JL, Hanson MP, Durrheim DN, Linkins R, Goodson JL. Accelerating Measles and Rubella Elimination through Research and Innovation --- Findings from the Measles & Rubella Initiative Research Prioritization Process, 2016. *Vaccine* 2019.

Additional Considerations for Measles and Rubella Eradication

16. **Vaccine access.** Ensuring access to vaccines will be critical to measles and rubella elimination, eradication and achieving equity. Limited or poor access to measles and rubella vaccines could also be a major impediment to measles and rubella eradication, particularly in regions affected by prolonged conflict, mass population movement, and humanitarian emergencies. Marginalized populations, who lack recognition and government support, and those people in regions of internal conflict, face particular challenges in accessing vaccines. Efforts to achieve measles and rubella eradication would require strategies to maintain vaccine access in the most challenging countries and settings, with lessons learned from the GPEI.[47]

17. **Vaccine hesitancy and demand**. Critical to achieving progress toward measles and rubella elimination and eradication is ensuring demand for and access to measles and rubella vaccines. Vaccine hesitancy, particularly for measles vaccines, is an increasingly prevalent and complex challenge to measles and rubella elimination, in part enhanced because of misinformation spread through social media platforms and in distinct communities, and could be a major impediment to measles and rubella eradication. WHO identified vaccine hesitancy as one of the ten threats to global health in 2019.[48] Much has been written about vaccine hesitancy and demand, and the reasons underlying these views are complex. A vaccines advisory group to the WHO identified complacency, inconvenience in accessing vaccines, and lack of confidence as some of the key reasons underlying hesitancy.[49] Efforts to achieve measles and rubella elimination and eventually eradication would need on-going, multi-disciplinary approaches to address vaccine hesitancy and increase vaccine demand, within a broader framework of building trust and confidence in effective and engaged health services, to be successful.

18. **Vaccine and diagnostic test supply for measles and rubella eradication**. Measles and rubella eradication efforts require careful planning to ensure the necessary vaccine supply. The shortage of inactivated poliovirus vaccine at the time of widespread vaccine introduction provides a cautious reminder of the potential risks to an eradication initiative. Vaccine manufacturers should be fully engaged in the planning processes and the possible use of measles and rubella vaccines after eradication should be considered. An assessment of the feasibility of measles eradication by WHO in 2008 concluded that the number of MCV doses estimated at that time to be needed for eradication were within existing and planned MCV-manufacturing capacity, but supply-chain disruptions could reduce supply or increase prices.[50] Proposed mitigation strategies included stockpiling, long-term contracts, and further coordination with manufacturers. The WHO (MI4A) initiative is currently updating a global forecast for measles-containing vaccines supply and demand through 2030 and the analysis is expected by the end of 2019. A risk with the current vaccine supply is the heavy reliance on a single supplier. According to data reported through the WHO MI4A/V3P vaccine purchase database for 2017,[51] the Serum Institute of India supplies as much as 87% and 97% of the global measles and measles-rubella vaccine market, respectively. Having additional manufacturers supplying pre-qualified measles and measles-rubella vaccines would reduce the supply risks associated

[47] Nnadi C, Etsano A, Uba B, Ohuabunwo C, Melton M, Wa Nganda G, Esapa L, Bolu O, Mahoney F, Vertefeuille J, Wiesen E, Durry E. Approaches to Vaccination Among Populations in Areas of Conflict. Journal of Infectious Diseases 2017;216(suppl_1):S368-S372.

[48] https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

[49] https://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

[50] Smith G, Michelson J, Singh R, Dabbagh A, Hoekstra E, van den 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:S62-70.

[51] https://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module1/en/

with a dominant manufacturer in these markets and help to secure adequate supplies. There are currently three manufacturers that internationally supply measles-mumps-rubella and measles-mumps-rubella-varicella vaccines, which are principally used in non-Gavi eligible, middle- and upper-income countries. However, they are not expected to significantly change their supply strategy and should not be relied upon for additional supplies of measles or measles-rubella vaccine even if there is significantly more demand.

Also critical to achieving measles and rubella eradication is having an adequate supply of diagnostic test kits to support case-based surveillance with laboratory confirmation. Elimination standard surveillance, in which all suspected cases are laboratory confirmed or discarded, requires a robust and diverse supply of pre-qualified and quality-assured test kits.

19. **Data needs for measles and rubella eradication.** Measles and rubella eradication will require high quality and highly sensitive data on measles incidence and vaccination coverage (MCV1, MCV2 and supplementary doses). Importantly, an integrated and open data platform, rather than disparate data streams currently in use, will be needed for programme management.

    The *Measles and Rubella Midterm Review* highlighted that measles incidence and case trends could serve as an important indicator for progress toward elimination and eradication, and recommended case-based surveillance with weekly reporting and laboratory confirmation. The *Measles and Rubella Mid-Term Review* also identified the need to classify cases to determine the proportion attributable to programme failure, i.e., cases in persons who should have been vaccinated according to the national schedule but were not, to allow for the underlying reasons to be identified and addressed. For cases that are not programme failures, analysis should be undertaken to determine whether changes in strategy are needed such as changing the age for recommended vaccination. Surveillance systems for measles and rubella eradication will differ from those used for the GPEI, as the diseases and viruses are different (e.g., no environmental surveillance will be needed for measles and rubella; few or no asymptomatic infections). Surveillance for CRS will be particularly challenging as the condition is likely to be rare after the introduction of rubella vaccine, and identification and confirmation can be challenging in countries without access to specialized medical care.

    Surveillance systems for measles, rubella, and congenital rubella syndrome in many countries are inadequately sensitive. The 2017 *Roadmap to Elimination Standard Measles and Rubella Surveillance* [52] report identified eight key attributes of a measles and rubella surveillance system: 1) detection of cases and outbreaks; 2) notification; 3) investigation and confirmation; 4) data collection on cases, potential risk factors for infection, spread, complications and death; 5) data analysis; 6) feed-forward to higher levels; 7) feedback to peripheral levels; and 8) interpretation and use of data. Effective use and interpretation of data applies to case classification, risk factors, spread, complications and death, vaccine effectiveness, outbreak source, extent and characteristics of the outbreak, monitoring surveillance performance, monitoring immunization programme performance, calculation of the effective reproduction number, actions to prevent further transmission, and evaluation of interventions. At a minimum, these eight elements need to be in place throughout every country for surveillance to be adequate to verify elimination. For elimination standard surveillance, all suspected cases, defined as fever with rash, need to be reported following rapid investigation within 24 hours, with laboratory testing of all suspected cases and comprehensive contact tracing to target chains of transmission for interruption. Cases should also be classified according to the source of infection as

[52] World Health Organization. Roadmap to elimination standard measles and rubella surveillance. *Weekly Epidemiological Record* 2017;92:97-105.

imported, importation-related, endemic or unknown, and reporting should be weekly rather than monthly.

The global measles and rubella surveillance system necessary to achieve, sustain and verify eradication will need to improve upon current practices. Currently, fewer than 5% of global measles cases, and many fewer rubella or CRS cases, are reported to the WHO. However, a strengthened measles and rubella surveillance should not constitute a vertical disease surveillance programme but could be a key component of a broader comprehensive effort to strengthen surveillance for all VPDs. Notwithstanding, for measles and rubella eradication, countries would need to better implement current recommendations everywhere and work to achieve surveillance targets. Epidemiologic and laboratory data need to be better linked so that all cases are accounted for. More granular data, such as data on risk factors, might be requested at regional and global levels, and those levels will need to be staffed properly to handle the increased data demands. Innovation in laboratory methods will be needed to help refine virus tracking, and rapid diagnostic tests that are under development will need to be integrated into disease surveillance. CRS surveillance will need to be expanded. WHO is currently undertaking an exercise to estimate the cost of comprehensive surveillance, which includes measles, rubella, and CRS surveillance, and preliminary data will be available in the second quarter of 2020.

20. **Impact of measles and rubella eradication on health systems**. Measles and rubella eradication efforts could be leveraged to strengthen health systems, specifically the essential immunization and primary health care systems.[53,54] For example, delivery of MCV2 in the second year of life could be further deployed as a platform to deliver other child health interventions, and enumeration of high-risk communities in planning SIAs could be used to design strategies to deliver essential immunization and other health services to these communities. Measles and rubella SIAs have been used to deliver several child health interventions, including administration of vitamin A supplementation, deworming medications, and insecticide treated bed nets. As measles and rubella elimination efforts are accelerated, the potential positive and negative effects on immunization and health systems should be measured, and the positive impact maximized. Three approaches to achieve this goal are: 1) focus on strengthening immunization services to generate positive effects on other primary health care services; 2) increase integration with multifunctional health services; and 3) change partner and donor behavior that prioritizes vaccination campaigns and use uncoordinated staff incentives.[55] A survey of 23 countries working toward measles and rubella elimination identified ways to strengthen essential immunization services through measles and rubella SIAs and other elimination activities,[56] including: 1) advocacy for immunization and educational activities; 2) skills training for health professionals; 3) expansion of cold chain capacity to reach more communities, introduce new vaccines, and reduce the risk of vaccine stock-outs; 4) identification of zero-dose and under-vaccinated children; 5) generation of data through SIA microplanning exercises that permit revision of catchment populations for fixed site and outreach immunization services; 6) strengthen overall vaccine-preventable disease surveillance and outbreak preparedness; and 7) introduce school-entry vaccination checks covering other vaccines in addition to measles and

[53] Andrus JK, Cochi SL, Cooper LZ, Klein JD. Combining global elimination of measles and rubella with strengthening of health systems in developing countries. *Health Affairs* (Millwood) 2016;35:327-33.
[54] Orenstein WA, Seib K. Beyond vertical and horizontal programs: a diagonal approach to building national immunization programs through measles elimination. *Expert Review of Vaccines* 2016;15:791-3.
[55] Griffiths UK, Mounier-Jack S, Oliveira-Cruz V, Balabanova D, Hanvoravongchai P, Ongolo P. How can measles eradication strengthen health care systems? *Journal of Infectious Diseases* 2011;204 Suppl 1:S78-81.
[56] Biellik RJ, Orenstein WA. Strengthening routine immunization through measles-rubella elimination. *Vaccine* 2018;36:5645-5650.

rubella. The vision and strategy of the vaccine and immunization global enterprise for the decade spanning 2021 to 2030 is grounded in the concept that immunization is a foundation for and driver of primary health care.

21. **The polio transition and lessons from the GPEI**: The *Measles and Rubella Midterm Review* recognized the importance of learning from the GPEI and leveraging the know-how, tools, and human resources developed through the polio programme for measles and rubella regional elimination through the polio transition process. Importantly, the *Polio Endgame Strategy 2019-2023* specifically states integration as one of three goals, along with eradication and certification and containment.[57] Integration, as described in the strategy, consists of: 1) contributing to the strengthening of immunization and health systems; 2) ensuring sensitive poliovirus surveillance through integration with comprehensive vaccine-preventable disease surveillance systems; and 3) preparing for and responding to outbreaks and emergencies. However, there are great risks in relying on polio transition funding to support specific measles and rubella elimination activities, including surveillance. Country plans for the polio transition have prioritized mainstreaming polio functions and using polio assets to strengthen essential immunization services and strengthening surveillance for vaccine-preventable diseases, with little specific mention of measles.

    Several attempts have been made to derive lessons for consideration of measles and rubella eradication from the experiences of the GPEI, including the need to mobilize political and social support, policy development and strategic planning, programme operations and tactics, and partnership management and donor coordination.[58] Several key lessons were derived from polio eradication for measles and rubella eradication, including the need for: 1) high quality data and surveillance; 2) data-driven outbreak response; 3) building acceptance and demand for vaccines; 4) continued research and innovation; 5) strong programme management, governance, oversight, and accountability; 6) leveraging International Health Regulations and Global Health Security to establish and enforce travel requirements for vaccination; and 7) strengthening global partnerships and garnering political will.[59] An additional lesson from the GPEI is that the most challenging places for eradication (such as the Pakistan-Afghanistan border or north-eastern Nigeria) should be engaged early rather than left to the final efforts of the programme.

    The GPEI has been a 30-year effort with many missed target dates, costs of almost US$ 1 billion per year, a large global workforce and complex partnership management structures to ensure financial oversight and accountability, reliance on frequent SIAs leading to community fatigue and resistance, and in some cases creation of incentives that draw resources from other health priorities. A measles and rubella eradication initiative will have to be based on a different model and avoid a prolonged, expensive eradication effort.

22. **Management and accountability framework**. A strong management and accountability framework will be critical to measles and rubella eradication, building on lessons learned from the GPEI,[60] and linked to the IA2030 management and accountability structure. The accountability framework for the GPEI is much more extensive than that described for measles and rubella in the *Global Vaccine Action Plan* and *Measles and Rubella Strategic Plan 2012-2020*. The *Measles and Rubella Midterm Review* emphasized that governments

[57] *Polio Endgame Strategy 2019-2023: Eradication, integration, certification and containment*. Geneva: World Health Organization; 2019 (WHO/Polio/19.04).

[58] Cochi SL, Freeman A, Guirguis S, Jafari H, Aylward B. Global polio eradication initiative: lessons learned and legacy. *Journal of Infectious Diseases* 2014;210 Suppl 1:S540-6.

[59] Goodson JL, Alexander JP, Linkins RW, Orenstein WA. Measles and rubella elimination: learning from polio eradication and moving forward with a diagonal approach. *Expert Review of Vaccines* 2017;16:1203-1216.

[60] http://polioeradication.org/who-we-are/governance-and-structure/

have primary responsibility for measles and rubella elimination and the need for local accountability. Given the central role of measles and rubella within the IA2030, the management and accountability framework for measles and rubella eradication should be consistent with this broader context.

23. Potential impact of innovations on the feasibility of measles and rubella eradication. Although measles and rubella were eliminated in the Americas with current vaccines and diagnostic tests, it is likely that novel tools will be needed to achieve similar impact in other settings. Innovative tools and strategies could facilitate progress toward measles and rubella eradication, particularly in the most challenging settings. Lessons from the GPEI highlight the importance of continuing to pursue a research agenda and the need to modify strategies and tools to meet unexpected programme needs. Examples include the adoption of monovalent and bivalent oral polio vaccines and recognition of the importance of environmental surveillance for polioviruses. The *Measles and Rubella Midterm Review* emphasized that sustained commitment to adequately funded measles and rubella research is required and that an advocacy plan to secure funding should be developed. The *Review* identified several priority research areas, including how best to: 1) achieve optimal uptake of vaccination in populations with low coverage; 2) accurately identify populations that should be targeted for focused immunization efforts; 3) optimize surveillance systems at the subnational level; and 4) measure the economic impact of measles and rubella. An eradication research agenda would need to be dynamic and responsive to and anticipatory of program needs.

Microarray patches consist of coated microneedles that deliver vaccine antigens into the dermis (i.e., skin patch), where many antigen-processing cells reside.[61] Delivery of measles and measles-rubella vaccines through microarray patches offers several potential advantages over the use of needles and syringes, including: 1) increased acceptability; 2) administration by persons who are not trained health care workers, or even self-administration, facilitating house-to-house vaccination and immunization in disordered settings; 3) reduced medical waste; and 4) increased thermostability, decreasing cold chain requirements.[62] The availability of microneedle patches for the delivery of measles and rubella vaccines is probably 7-9 years away given the time it will take to conduct clinical trials, gain regulatory approval, and build manufacturing capacity at commercial scale. However, experience with the Ebola vaccine showed that aspects of this process can be expedited and the timelines shortened. Rapid diagnostic tests for measles IgM antibodies (to assess acute infection) and IgG antibodies (to assess measles immunity) have been developed and pilot tested but are not yet widely available or pre-qualified.[63] A rapid diagnostic test for measles IgM antibodies could facilitate outbreak detection, obviating the need to send samples to a central laboratory, and a rapid diagnostic test for measles IgG antibodies could facilitate identification of susceptible individuals or subpopulations for targeted vaccination efforts. Work on rubella diagnostic tests is ongoing. More efficient strategies to identify and target susceptible individuals could be developed using a combination of serosurveillance and modeling,[64] and eradication strategies that do not rely on achieving 95% coverage could be explored based on

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[61] Peyraud N, Zehrung D, Jarrahian C, Frivold C, Orubu T, Giersing B. Potential use of microarray patches for vaccine delivery in low- and middle- income countries. *Vaccine* 2019.

[62] Arya, J, Prausnitz MR. Microneedle patches for vaccination in developing countries. *Journal of Controlled Release* 2016;240:135-41.

[63] Shonhai A, Warrener L, Mangwanya D, Slibinskas R, Brown K, Brown D, Featherstone D, Samuel D. Investigation of a measles outbreak in Zimbabwe, 2010: potential of a point of care test to replace laboratory confirmation of suspected cases. *Epidemiology and Infection* 2015;143:3442-50.

[64] Winter AK, Martinez ME, Cutts FT, Moss WJ, Ferrari M, McKee A, Lessler J, Hayford K, Wallinga J, Metcalf CJE. Serological surveys for measles and rubella elimination: benefits and challenges. *Journal of Infectious Diseases* 2018;218:355-364.

synchronized campaigns and targeted vaccination of exporters and importers of measles virus. However, a major challenge has been the availability of funding to support the measles and rubella applied research agenda.

24. **Modeling measles and rubella eradication strategies**. The investment case for measles and rubella eradication is a critical component to inform setting an eradication goal and timeline with a target date, including the expected cost and return on investment. To better understand the investment, consequences and value-for-money of efforts required to eliminate measles and rubella transmission globally, the relative impact, cost, and cost-effectiveness of different strategies for measles-rubella elimination (and potential eradication) have been modelled by a consortium of mathematical modelers. The consortium consists of a single-country measles model in Nigeria (the IDM model[65]), two multi-country measles models (the DynaMice[66] and PSU[67] models) and two multi-country rubella models (the PHE[68] and JHU[69,70] models). The IDM model tracks subnational measles epidemiology, potentially offering greater realism for the situations modeled. These transmission models projected long-term cases, deaths, and DALYs, along with the number and type of vaccinations administered, under four vaccination coverage scenarios (one based on assuming that routine coverage stays at 2017 levels, and three that project improved levels of coverage; see Annex). To evaluate the cost-effectiveness of different scenarios, outputs were used in an economic model which estimated the direct costs of vaccination and treatment associated with each scenario.

    The inherent limitations of the models qualify the interpretation and inferences that can be drawn from this exercise. An “elimination threshold” of 5 cases per million was used, representing the point at which incidence is likely low enough to produce transmission interruption at national levels. It is important to note that the models were not designed to actually represent elimination itself, because they do not explicitly model many factors that influence measles and rubella transmission, particularly when close to elimination (such as, localized outbreaks and the resulting outbreak response activities, decreases in coverage due to political and other crises, and enhanced surveillance). While case importation was accounted for in varying manners by the different models (thus allowing for the possibility for re-introduction), explicit cross-border transmission was not accounted for, although this is likely less of an issue for the rubella results. Countries were modeled independently, which fails to capture the impact of regional interactions (which both complicates elimination but also offers potential benefits of coordinated efforts). In addition, the scenarios themselves were coarsely specified and provided information on a national scale only, neglecting subnational heterogeneity (the single-country Nigeria analysis provides some sensitivity to this).

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[65] Zimmermann M, Frey K, Hagedorn B, Oteri AJ, Yahya A, Hamisu M, Mogekwu F, Shuaib F, McCarthy KA, Chabot-Couture G. Optimization of frequency and targeting of measles supplemental immunization activities in Nigeria: A cost-effectiveness analysis. *Vaccine* 2019;37:6039-6047

[66] Verguet S, Johri M, Morris SK, Gauvreau CL, Jha P, Jit M. Controlling measles using supplemental immunization activities: a mathematical model to inform optimal policy. *Vaccine* 2019;33:1291-6.

[67] Eilertson KE, Fricks J, Ferrari MJ. Estimation and prediction for a mechanistic model of measles transmission using particle filtering and maximum likelihood estimation. *Statistics in Medicine* 2019;38:4146-58.

[68] Vynnycky E, Papadopoulos T, Angelis K. The impact of measles-rubella vaccination on the morbidity and mortality from Congenital Rubella Syndrome in 92 countries. *Human Vaccines & Immunotherapeutics* 2019;15:309-16.

[69]Metcalf CJ, Lessler J, Klepac P, Cutts F, Grenfell BT. Impact of birth rate, seasonality and transmission rate on minimum levels of coverage needed for rubella vaccination. *Epidemiology & Infection* 2012;140:2290-301.

[70] Metcalf CJ, Lessler J, Klepac P, Morice A, Grenfell BT, Bjørnstad ON. Structured models of infectious disease: inference with discrete data. *Theoretical Population Biology* 2012;82:275-82.

Results from the models indicated that it is *possible* for all countries to achieve the elimination threshold for rubella and measles under most scenarios, including some in the base case scenario. However, the *probability* of reaching and sustaining the elimination threshold, and the time required to do so, varied by pathogen and across countries. The measles models suggest that a few countries may not reach the elimination threshold because the cessation of SIAs after high coverage with two doses of MCV would lead to measles resurgences. As expected, achieving and maintaining the elimination threshold for rubella is more probable and happens more quickly than for measles. Reaching the rubella elimination threshold is likely for most countries by 2060 under the three improved vaccination coverage scenarios. However, there remains a small risk of transient rubella outbreaks in a handful of countries that demonstrate variability in elimination probability and stability, producing a residual risk for elevated CRS cases.

All three improved coverage scenarios lead to dramatic (orders of magnitude) reductions in measles incidence and achieve the elimination threshold in most countries. Reaching conditions needed for elimination in <u>all</u> countries is unlikely under the modeled coverage scenarios as some countries have a low probability of reaching the conditions for elimination under any scenario. Targeted strategies, including enhanced surveillance, outbreak response, and prioritized subnational interventions, may increase the feasibility of elimination in these countries. The subnational model for Nigeria demonstrated that equity of coverage (i.e. ensuring that coverage improvements benefit the worst-performing districts and zero-dose children first) would greatly improve the probability of reaching low measles incidence.

The three improved coverage scenarios were more cost-effective for both measles and rubella (discounting costs but not DALYs) than the base case during the period from 2018 to 2047. The intensified investment scenario was the most cost-effective of these three for both diseases, and the continuing trends was more cost-effective than the constant improvement scenario for rubella only. However, the economic analyses had to make several assumptions on costs of surveillance, vaccination and treatment due to limited availability of these data. In addition, limited data were available on the cost of increasing immunization coverage in low- and middle-income countries. Outbreak response activities were also omitted due to lack of information on costs and frequency, and because the benefits of these activities were also not captured by the transmission models.

Overall, this analysis shows that each of the three improved coverage scenarios are predicted to realize substantial and cost-effective reductions in measles, rubella and CRS morbidity and mortality over the next three decades. Many countries would be likely to achieve the conditions for elimination under these three scenarios. While successful global rubella eradication is highly probable, global measles eradication would remain unlikely, leaving a risk of reimportation into post-elimination countries (as the Region of the Americas is currently experiencing) and highlighting the need for improvements in both routine and SIA coverage to be coupled with new tools, efforts, and strategies to tip the balance in the most challenging contexts. The large variance in the time to achieve eradication indicates that countries that achieve elimination early will need to maintain vigilance (with investments in surveillance and outbreak response) to prevent outbreaks or re-establishment due to imported cases. This will require accelerated efforts as even maintaining the already achieved reductions in measles and rubella morbidity and mortality over the past two decades will need continued effort and investment.

Global eradication necessarily requires the interruption of virus transmission even in the most poorly performing contexts, and its success thus relies critically on strategies to address and relieve persistent inequities (spatial, accessibility, etc.) in vaccination coverage. These analyses highlight that achieving levels of low incidence at which elimination is feasible, perhaps through coordinated “end game” strategies, is indeed

possible. A full assessment of the feasibility of measles and rubella eradication requires consideration of political, financial, supply, and distribution challenges as well as other contextual factors.

To generate a more complete picture of the path to eradication, further research is required. Additional modeling to evaluate strategies for implementing outbreak response, enhanced surveillance, and the appropriate conditions for ending SIAs would provide heightened detail around the degree of effort needed to make the final push to eradication as low incidence levels make stochastic extinction a possibility. Such work may benefit from modeling conditions seen in settings that have achieved elimination in the past, such as the Region of the Americas. Further sub-national modeling that allows for differential ramp-up of routine coverage in lower- and higher-performing districts would shed light on the importance of access and equity within countries. And finally, additional economic analyses are needed to determine variability in costs within and between countries, and to clarify the investment required in the end game to maintain rapid outbreak response and high-quality surveillance efforts until measles and rubella virus transmission is interrupted.

25. **Public, political and donor support and responsibility**. The global landscape has changed significantly since polio eradication was first declared in 1988, and bold global health goals consisting of top-down, vertical, disease-specific eradication programmes no longer have the public, political and donor support they once had. Early discussions of polio eradication took place in the context of the successful smallpox eradication programme (eradication was declared in 1980), whereas discussions of measles and rubella eradication have the prolonged polio eradication efforts and stagnant global vaccine coverage, despite large investments over the past decade, as their backdrop. Public, political and donor support will be essential to measles and rubella eradication, particularly country commitment. Engagement with key stakeholders, including governments, political leaders, donors, and policy makers, is needed. Heads of state, Ministries of Health and Ministries of Finance must support measles and rubella eradication, in addition to major donors. Planning should begin with an analysis of current political and donor support for measles and rubella eradication and development of a plan to engage such support.

    Measles and rubella eradication cannot be achieved without public support, community ownership, and committed accountability. Comprehensive communication and stakeholder engagement strategies should be implemented, with monitoring and review of successes and learning. The *Measles and Rubella Midterm Review* identified multiple strategies to garner and sustain public support for measles and rubella eradication, including: 1) increase resources for communication to raise the visibility and perceived risks of vaccine-preventable diseases, with a focus on measles and rubella; 2) create and promote sustained demand for immunization through tailored and targeted strategies that are informed by local evidence; 3) develop targeted communication and engagement plans for different audiences, including politicians, public health leaders and workers, healthcare providers, caregivers, and non-traditional stakeholders; 4) use data on measles incidence, including complications and deaths, as well as information on the costs associated with outbreaks, to communicate the importance of eradicating measles and rubella and the related investment case; 5) supplement these data with stories of actual cases and deaths, including cases of congenital rubella syndrome; 6) identify the most effective means of communication, including methods to counter misinformation; 7) use the opportunity of measles and rubella outbreaks to promote the importance of vaccination; 8) collect stories on how a focus on measles and rubella elimination enhanced overall immunization and health systems; and 9) ensure community engagement in planning, implementation and oversight of immunization. Carefully crafted communication and advocacy strategies are particularly important as the disease burden decreases, when

there is less public memory of the disease burden and an increased concern for potential risks associated with vaccines.

26. Can measles vaccination be stopped after eradication? Measles and rubella eradication will face many of the same challenges faced by the GPEI to contain infectious laboratory materials after eradication.[71] A risk analysis concluded that measles will become a credible agent for bioterrorism through intentional release should population immunity decrease.[72] Genetic engineering of a measles virus strain that was not neutralized by antibodies induced by the current measles vaccines would likely have reduced infectivity, although virulence could potentially be augmented. Whether the threat from bioterrorism precludes stopping measles vaccination after eradication is unclear but a single-dose rather than a 2-dose measles vaccination strategy could be adopted, and the high levels of population immunity required for eradication would not need to be sustained.[73] Countries that decide to add mumps and varicella vaccines to their immunization schedule could include measles and rubella as part of a combined vaccine at relatively low cost.

Costs of Delaying Measles and Rubella Elimination and Eradication

27. Costs to countries and regions that have eliminated measles. The costs of delaying measles and rubella elimination and eradication are considerable and include both human and financial costs.[74] Human costs are counted in preventable deaths (currently estimated to be more than 100,000 per year), morbidity (e.g. hospitalizations, clinic visits, neurologic impairment, blindness), poverty, and poor school performance, among the numerous effects of measles and rubella, which have negative impact on long-term productivity and economic growth. These benefits are seen by countries and regions that have achieved elimination. However, elimination status is fragile, expensive to maintain and may not be sustainable in the long-term while the risk of virus importation persists. Several studies reported the cost of containing measles outbreaks in high-income settings where elimination was achieved. For example, the estimated cost of containing an outbreak of 34 measles cases in Indiana, United States in 2005 was US$ 167,686 following exposure to an unvaccinated 17-year-old adolescent who contracted measles in Romania.[75] A measles outbreak in 2008 in California, United States was sparked by an intentionally unvaccinated child who acquired measles in Switzerland and led to an additional eleven cases, with the outbreak response costing US$ 10,376 per case.[76] Another outbreak in 2008 in Arizona, United States, resulting from an infected traveler from Switzerland who visited a hospital, led to 14 cases and a cost to two hospitals of US$ 799,136 to respond to and contain

[71] Bandyopadhyay AS, Singh H, Fournier-Caruana J, Modlin JF, Wenger J, Partridge J, Sutter RW, Zaffran MJ. Facility-associated release of polioviruses into communities - Risks for the posteradication era. *Emerging Infectious Diseases* 2019;25:1363-1369.

[72] Sanders R, Dabbagh A, Featherstone D. Risk analysis for measles reintroduction after global certification of eradication. *Journal of Infectious Diseases* 2011;204 Suppl 1:S71-7.

[73] Meissner HC, Strebel PM, Orenstein WA. Measles vaccines and the potential for worldwide eradication of measles. *Pediatrics* 2004; 114:1065–9.

[74] Durrheim DN, Crowcroft NS. The price of delaying measles eradication. *Lancet Public Health* 2017; 2: e130–e131.

[75] Parker AA, Staggs W, Dayan GH, Ortega-Sánchez IR, Rota PA, Lowe L, Boardman P, Teclaw R, Graves C, LeBaron CW. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. *New England Journal of Medicine* 2006;355:447-55.

[76] 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;125:747-55.

seven cases.[77] An outbreak of 58 measles cases in New York City in 2013, following importation from London, England, was estimated to cost the local health department US$ 394,448.[78] A total of 10,054 hours were spent responding to and controlling the outbreak. Although these examples are from the United States, they highlight the enormous financial costs of sustaining elimination when measles virus is circulating in other countries and the potential to lose the political and public will to maintain elimination. Costing of current measles outbreak responses in several countries is underway.

28. **Equity and ethical considerations for measles and rubella elimination and eradication.** Measles and rubella elimination and eradication raise issues related to equity and ethics. The 1989 Convention on the Rights of the Child states that children have the right to the best health care possible and that rich countries should help poorer countries achieve this right.[79] Governments should ensure that children enjoy the protection offered by measles and rubella vaccines, which are both affordable and effective in preventing severe disease and death. Because children who are at high-risk for missing out on vaccination, including migrants, nomadic communities, those residing in urban slums, and the rural poor, are often at greatest risk of severe disease because of poor nutrition, co-infections, and limited access to health care, reaching them with vaccines can have a substantial impact on health inequities. Furthermore, because of the herd immunity conferred in communities with high levels of measles vaccine coverage, measles vaccination can protect those too young to be vaccinated or those with immunodeficiencies who cannot be immunized. Measles and rubella viruses could be called the equity viruses: without vaccination, everyone gets them, and without equitable health-care systems to deliver vaccination, measles and rubella will continue to present a threat to the most vulnerable.

29. **Risks in delaying measles and rubella elimination and eradication.** The changing epidemiology of measles could make elimination and eradication even more challenging in the future, thus creating urgency in accelerating progress toward regional elimination goals. First, as more women of child bearing age have vaccine-induced immunity and are not exposed to wild-type measles virus, lower levels of maternal antibodies are transferred to their infants, who then become susceptible to measles at a younger age.[80] This has led to discussions as to whether the age of administration of MCV should be reduced from nine to six months of age and a change to the EPI schedule. The WHO currently recommends an early dose of measles-containing vaccine at six months of age, in addition to the routine doses at nine months and in the second year of life, in some circumstances, including during outbreaks, for refugees or internally displaced persons, and to HIV infected or exposed infants.[81] However, measles vaccination at six months of age results in reduced immunogenicity and effectiveness compared to nine months of age.[82] Second, there remains the possibility that vaccine-derived measles immunity may wane in older

[77] 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;203:1517-25.

[78] Rosen JB, Arciuolo RJ, Khawja AM, Fu J, Giancotti FR, Zucker JR. Public health consequences of a 2013 measles outbreak in New York City. *JAMA Pediatrics* 2018;172:811-817.

[79] https://www.ohchr.org/en/professionalinterest/pages/crc.aspx

[80] Guerra FM, Crowcroft NS, Friedman L, Deeks SL, Halperin SA, Severini A, Hatchette TF, Bolotin S, and the Immunity of Canadians and Risk of Epidemics (iCARE) Network. Waning of measles maternal antibody in infants in measles elimination settings - A systematic literature review. *Vaccine* 2018;36:1248-1255.

[81] World Health Organization. Measles vaccines: WHO position paper – April 2017. *Weekly Epidemiological Record* 2017;92:205-27.

[82] Lochlainn LN, de Gier B, van der Maas N, Strebel PM, Goodman T, van Binnendijk RS, de Melker HE, Hahné SJM. Immunogenicity, effectiveness, and safety of measles vaccination in children younger than 9 months: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2019 (in press).

individuals, particularly those receiving their first vaccination below 12 months of age who were not subsequently exposed to wild-type virus, expanding the age range of susceptibility and need for vaccination.[83] The experience thus far in the United States suggest this has not contributed to sustained measles virus transmission but more data from other settings are needed, particularly from countries where MCV1 was administered at nine months of age. Third, increasing urbanization,[84] resulting in increased contact rates and thus measles virus transmission, could lead to higher levels of population immunity needed to interrupt measles virus transmission, hindering eradication efforts. Finally, increasing globalization, travel, and population movement greatly amplify the risk of re-importations into countries that have eliminated measles. The constant threat of measles outbreaks creates an unsustainable burden even on the countries with strong programmes and sustainability for an indefinite time period may not be feasible.

Measles and Rubella Elimination Goals and Benchmarks toward an Eradication Goal

30. **Reaffirming country and Regional elimination goals and the vision of a world without measles and rubella**. Enormous progress has been made in reducing global measles and rubella incidence, morbidity, and mortality through vaccination. However, global MCV1 coverage has stalled at about 85% for the past decade and global milestones for vaccine coverage and reductions in measles incidence and mortality have not been met. Countries and regions are at different stages along the path to measles and rubella elimination.[85] Global, regional, country, and donor support for pathogen-specific eradication initiatives has shifted and become more diverse, influenced by the challenges faced by the GPEI and changing global health and development priorities. Eradication is complex because it is multi-dimensional, encompassing not only biological, technical, operational and programmatic issues, but also multifaceted political, economic, social and cultural factors. Eradication is a fundamentally different public health activity, one that requires trade-offs and sacrifices not usually made in public health. Eradication is controversial because there are legitimate differences in opinion on the need for and value of setting a global measles and rubella eradication goal and target date, and how such a declaration would require changes to programme strategies, political will, public support, and available resources.

    We can all agree on the aspirational goal of a world without measles and rubella. At issue is the optimal timing of an eradication goal and target date.

    A time-bound measles and rubella eradication goal should be set only when accelerated progress has been made, benchmarks that establish the conditions for a successful endgame to achieve eradication have been achieved, and there is evidence of a clear trajectory toward the goal. Setting an eradication goal when the endgame is in sight could catalyze a surge in commitment, effort, and resources to complete the task, thus heeding the call to go “big and fast” with measles and rubella eradication, and avoid a premature and drawn-out eradication effort with the potential for unmet goals, delayed milestones, and prolonged input of financial and human resources.[86] Setting a target date for measles and rubella eradication prematurely could create the expectation of an initiative modeled after the GPEI: a large vertical programme with a substantial management structure, and

[83] Hughes SL, Bolotin S, Khan S, Li Y, Johnson C, Friedman L, Tricco AC, Hahné S, Heffernan JM, Dabbagh A, Durrheim DN, Orenstein WA, Moss WJ, Jit M, Crowcroft NS. Is there evidence for waning measles vaccine effectiveness? A systematic review. 2019 (in press).

[84] https://ourworldindata.org/urbanization

[85] Graham M, Winter AK, Ferrari M, Grenfell B, Moss WJ, Azman AS, C. Jessica E. Metcalf CJE, Lessler J. Measles and the canonical path to elimination. *Science* 2019;364:584-587.

[86] Omer SB, Orenstein WA, Koplan JP. Go big and go fast--vaccine refusal and disease eradication. *N Engl J Med* 2013;368:1374-6.

billions of dollars in funding. Such an initiative is unlikely to receive the needed support in light of the ongoing challenges to polio eradication and the changing strategic approaches to global health and development in the coming decade.

Nevertheless, reaffirming the importance of achieving and sustaining the country and Regional measles and rubella elimination goals, and restating the vision of a world without measles and rubella, would convey an aspirational vision and provide further support and motivation for accelerating the rate of progress. Such a reaffirmation would highlight the fact that the global public health community remains firmly committed to the country and Regional measles and rubella elimination goals. A goal and target date for measles and rubella eradication would then be set when the endgame is in sight and benchmarks for setting such a goal have been achieved. A reaffirmation of the measles and rubella elimination goals and a vision for a world without measles and rubella could be based on the following principles:

- The status quo is unacceptable and progress toward achieving and sustaining country and Regional measles and rubella elimination goals must be accelerated. Measles and rubella remain global public health priorities and require increased global, regional and national commitment.
- Current, uncoordinated approaches toward measles and rubella elimination in individual countries is inadequate to achieve our existing goals. Measles and rubella transmission in any country is a threat to elimination in all countries. Stronger support and more coordinated strategies within Regions and across transmission blocks must be developed to complement individual country efforts to achieve elimination.
- Accelerated progress should be based on strengthening immunization, primary healthcare, and surveillance systems, supplemented by targeted vaccination campaigns and other programme innovations to reach unvaccinated and under-vaccinated populations, rather than reliance on repeated emergency responses or non-selective and wide-age range supplementary immunization activities to make up for weak immunization services.
- Reaffirmation of country and Regional elimination goals, and the aspirational vision of a world without measles and rubella, could foster increased political and public will to facilitate country efforts to achieve their elimination goals, would be aligned with the strategic priorities of the IA2030, and could foster strategic programme development and innovation for the endgame, including contingency planning for expected and unexpected obstacles and promotion of new strategies and technologies to support eradication such as rapid diagnostic tests and microarray patches.
- A time-bound measles and rubella eradication goal should only be set when substantial and measurable progress has been made, and the strategies, resources and commitment are likely to be in place to interrupt the final transmission pathways. The endgame would comprise a time-limited (e.g. five years) intensification of efforts with a realistic chance of achieving eradication by the target date. Updated analyses and models would be needed to inform the decision to set an eradication goal and target date.

31. **Benchmarks toward measles and rubella eradication.** The path toward measles and rubella eradication should strengthen routine immunization, primary health care and universal health coverage to achieve equity and the strategic priorities of the IA2030. Benchmarks for setting a measles and rubella eradication goal should be developed through a consultative process with key stakeholders, including representatives from countries, regions, donors, industry, Civil Society Organizations, the M&RI partners, and the public, informed by rigorous analyses and modeling. The benchmarks should be used to gauge when it is appropriate to commit to an eradication goal and target date through a well-developed and sufficiently resourced endgame strategy. The benchmarks should not

be absolute and final but should be modified and updated based on changing epidemiological conditions, innovations, updated analyses and models, the public, political and financial landscape, and other contextual factors, such as conflict, political instability and large-scale population movements that impact the feasibility of eradication. Judgement will continually be needed to assess the prospects of measles and rubella eradication and the progress necessary to accomplish the goal. A measles and rubella eradication advisory group should be established to lead development of the benchmarks and metrics, monitor progress and trajectories toward achieving these benchmarks, and to ensure accountability. The benchmarks should include a range of categories essential to achieving measles and rubella eradication, based on evidence and analyses with measurable metrics and trajectories, and could include:

- Introduction of MCV2 and RCV into national immunization programs
- MCV1 and MCV2 coverage
- Vaccine coverage data quality
- SIA quality and efficiency
- School entry checks
- Surveillance quality
- Measles incidence
- Equity measures
- Verification of elimination
- Vaccine and diagnostic test supplies
- Communications and advocacy
- Technology and innovations

Thus, the path toward measles and rubella eradication should be through accelerated progress toward country and Regional measles and rubella elimination goals and integral to the strategic priorities of the IA2030, including strengthening primary health care, fostering universal health coverage, and achieving equity. Benchmarks on the path toward measles and rubella eradication should be specified and progress and trajectories toward achieving these benchmarks should be assessed.

32. Recommendations

1. Measles and rubella can be eradicated with sustained, uniformly high coverage with two doses of measles- and rubella-containing vaccine. A world without measles and rubella remains our collective vision. Given the current global context, achieving measles eradication is not realistic without significant further effort. There is an urgent need for all countries and regions to accelerate progress towards achieving and maintaining measles and rubella elimination goals. An eradication target date should only be considered when substantial and measurable progress has been made towards elimination. At the time of setting a target, a strategic plan for the eradication endgame should be in place, including cost estimates for implementation.

2. Measles and rubella virus transmission in any country is a threat to elimination in all countries. Stronger support and more coordinated strategies globally, within regions, and across transmission blocks must be developed to complement individual country efforts.

3. Efforts to achieve and maintain measles and rubella elimination must be deployed through substantial strengthening of primary health care systems that are effective in delivering routine immunization. Improving measles and rubella immunization coverage is viewed as an important marker for progress towards achieving equity in access to vaccination and primary health care, and a driver to advance the IA2030 strategic priorities.

4. A monitoring and accountability framework should be established as part of the future governance structures of IA2030, with new benchmarks to measure progress determined through a consultative process. The purpose of the benchmarks is to gauge when it is appropriate to set a measles and rubella eradication time-bound target, by providing metrics toward achieving the necessary conditions for a successful eradication endgame within a defined period. Progress towards achieving these benchmarks should be monitored and reported on periodically.

5. The development of innovative tools (e.g. microarray patches) should be prioritized to support the acceleration of progress toward eradication. Additional research and modelling should be carried out to identify the effort and quantify investments required to achieve eradication, particularly in the most challenging settings, as well as the costs of inaction.

Annex 1: Vaccination scenarios
Base year: 2017

Three vaccination scenarios were developed by US Centers for Disease Control and Prevention, and one was based upon assumptions provided by the Vaccine Impact Modeling Consortium (VIMC)[87]: (i) base case (routine coverage remains at 2017 levels), (ii) continuing trends (coverage increases based on current trends and existing introduction commitments), (iii) constant improvement (coverage improves at 1%/year with all countries introducing MCV2 and RCV by 2020, up to 95% for Gavi-eligible countries and up to 90% for all others), and (iv) intensified investments (coverage increases at 4.4%/year compounded, with all countries introducing MCV2 and RCV by 2024). All scenarios aside from base case include termination of SIAs when two-dose MCV coverage is sufficiently high. An "elimination threshold" of 5 cases per million was used as a proxy for elimination, providing a conservative threshold at which incidence is likely low enough to produce transmission interruption at national levels. These models do not explicitly account for enhanced surveillance or outbreak response; thus, this elimination threshold is a conservative indicator of the feasibility of elimination.

Scenario	**1** **CDC Scenario A – Base case**	**2** **CDC Scenario B – Continuing trends**	**3** **Constant improvement**	**4** **CDC Scenario C – Intensified investments**
Assumptions	- Constant, inflation-adjusted investments in national programmes - Policies, practices implemented by 2017 held constant throughout analytic period - Counterfactual, but establishes a baseline for programmatic inputs, health costs, and outcomes	- Current investments and conservative projection of future investments - Includes limited set of improvements that national programmes and global partners are expected to support even in the absence of a formal, unified commitment to eradication - Incorporation of RCV and MCV2 into routine immunization programs is expected to continue	- Current investments and conservative projection of future investments - Includes a limited set of improvements that national programmes and global partners are expected to support even in the absence of a formal, unified commitment to eradication	- Intensified investments and inputs in national programs - Models the minimum reasonable, if optimistic, time to achieve eradication - Serves as a lower bound for costs, upper bound for benefits - Increased coverage, more frequent preventive SIAs
MCV1 coverage	All countries remain at base year coverage.	Historical coverage used to fit natural log function up to 99%. Countries with high, constant or inconsistent recent coverage,	All Gavi supported countries with coverage <95% improve coverage from base year by 1%/year up to 95%.	Global median compound rate (**CGR**) (4.4%) used to estimate coverage up to 99% for countries that have not yet eliminated measles /

[87] https://www.vaccineimpact.org/

		prospective coverage held constant at average of recent coverage.	All other countries with coverage <90% improve coverage from base year by 1%/year up to 90%.	rubella, or reached 95%, by 2016.
MCV2 introductions	No new MCV2 introductions beyond 2017.	MCV2 introductions continue as projected by current country commitments and SME assessment. MCV2 age in countries introducing MCV2 in 2017 or later based on MCV1 age and coverage, and regional schedules	All countries introduce MCV2 in 2020 if they have not already done so. MCV2 coverage starts at 10% below MCV1 coverage at introduction.	MCV2 introduced in 2018-2024 if not already done so, timing as projected by SMEs. MCV2 age based on MCV1 age and coverage, and regional schedules
MCV2 coverage	All countries remain at base year coverage.	For countries w/ ≥ 4 yrs of MCV2 data, historical coverage used to fit natural log function up to 99%; countries with high, constant or inconsistent recent coverage, prospective coverage held constant at average of recent coverage. For countries w/ < 4 yrs of MCV2 data, coverage projections based on region- and income level-derived natural log functions: - Countries w/ 1-3 yrs of MCV2 data: 2017 MCV2 = I.V. for prospective coverage (2018-2055) - Countries w/o MCV2 intro by end of 2017: MCV2 coverage = % of MCV1 coverage based on WB income level-specific MCV1-MCV2 differences	All Gavi supported countries with MCV2 coverage <95% improve coverage from base year by 1%/year up to 95%. All other countries with coverage <90% improve coverage from base year by 1%/year up to 90%.	For countries that have not yet eliminated measles / rubella, or reached 95% MCV1 coverage by 2016: - Countries w/ MCV2 by end of 2017: 2017 MCV2 = I.V. for prospective coverage - Countries w/o MCV2 by 2018: MCV2 coverage = % of MCV1 coverage based on WB income level-specified MCV1-MCV2 differences - Forecasted MCV2 coverage subject to dynamic capping such that MCV2 ≤ MCV1 and relative values are realistic

RCV introductions	No new RCV introductions beyond 2017.	RCV introductions continue as projected by current country commitments and SME assessment. RCV1 coverage = MCV1 coverage; RCV2 coverage = MCV2 coverage.	All countries introduce MR in 2020 if they have not already. MR coverage assumption is the same as MCV1 coverage.	RCV2 introduced in 2018-2024 if not already done so, timing as projected by SMEs. RCV1 coverage = MCV1 coverage; RCV2 coverage = MCV2 coverage.
SIAs	SIAs up to 2017 based on historical events. SIAs beyond 2017 based on the current WHO rule of thumb.	SIAs up to 2017 based on historical events. Age categories and frequency for prospective SIAs based on historical SIAs. SIA coverage based on historical averages and increased by 10% of the incremental difference between the previous coverage estimate and 100% for 3 subsequent SIAs and then held constant through 2055. Cessation of SIAs in countries w/ both MCV1 and MCV2 ≥ 90.5% for 5 years; RCV introduction; accumulation of susceptibles < 1 birth cohort w/in 8 years after previous SIA	SIAs up to 2017 based on historical events. Any SIA scheduled up to 2020 continues. After 2020, countries with MCV2 coverage below 90% have SIAs every 3 years.	SIAs up to 2017 based on historical events. Age category <5 years old following MR introduction. Frequency based on accrual of susceptibles (as driven by MCV1 & MCV2 activities) = 75% of size of birth cohort. Cessation of SIAs in countries w/ MCV2 ≥ 5 yrs; RCV introduction; MCV1 & MCV2 coverage high enough to prevent 75% threshold accumulation w/in 8 years after previous SIA.
Within country variation	No change in variation between admin level 1 division within each country. No variation assumed below admin level 1 divisions.	No change in variation between admin level 1 division within each country. No variation assumed below admin level 1 divisions.	No change in variation between admin level 1 division within each country. No variation assumed below admin level 1 divisions.	Variation between admin level 1 division within each country halves every year. No variation assumed below admin level 1 divisions.