

## Guidance to Increasing Population Immunity against Measles and Rubella

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## Opening Remarks

This document provides guidance to identify and address measles and rubella immunity gaps in order to raise population immunity. Countries' epidemiologic profiles are used to help prioritize interventions to increase population immunity. In addition, strategies to address specific immunity gaps (e.g. lower immunity in school-age children) are provided.

All guidance in this document should be considered in conjunction with any existing regional guidance as regional guidance may provide strategies better tailored to specific countries or sub-national areas. This guidance is intended mainly to support measles/rubella endemic countries although much of the guidance is applicable to countries that have achieved elimination, as they still need to maintain high population immunity. This framework may also be useful to countries as they prepare evidence for their national verification committees (NVCs) as demonstration of high population immunity is a key component to verification of measles and rubella elimination.

Note: This document focuses on strategies for increasing population immunity; it does not cover disease surveillance/surveillance systems nor provide detailed activities to improve the performance of routine immunization (RI) programs and campaigns. While these are all important areas to strengthen in order to increase population immunity, they are addressed in other documents.<sup>1,2,3</sup> and should be used in tandem with this document.

This guidance was developed with the following principles:

- Increasing population immunity should take a Continuous Quality Improvement (CQI) approach (explained below)
- Critical review of all available data sources is needed to identify immunity gaps
- Strengthening RI is the primary strategy for increasing population immunity
- Campaigns are needed (as rescue measures) where RI for two doses of measles and rubella-containing vaccines is sub-optimal and to address specific immunity gaps.
- During the time period following campaigns, activities must be quickly prioritized to strengthening RI systems.

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<sup>1</sup> Sniadack DH, Crowcroft, N, Durrheim, DN, Rota PA. Roadmap to elimination standard measles and rubella surveillance. *Weekly Epidemiological Record* 2017; 92: Nos 9/10: 97-105.

<sup>2</sup> Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.

<sup>3</sup> Planning and Implementing High-Quality Supplementary Immunization Activities for Injectable Vaccines using an example of measles and rubella vaccines: field guide. Geneva, WHO Press, 2016.

## Background

Despite the existence of an effective vaccine, measles is still a leading driver of child mortality.<sup>4</sup> In 2016, nearly 90,000 children died from measles despite an 84% reduction in annual deaths since 2000. From 2000-2016, measles vaccination prevented roughly 20 million deaths, showing the importance of vaccination. For rubella, considerable burden remains as many countries have not yet introduced rubella-containing vaccine (RCV).<sup>5</sup> However, considerable progress towards rubella control and elimination has been achieved in the nations that have introduced RCVs. All six World Health Organization (WHO) regions have established a measles elimination goal for 2020 at the latest<sup>6</sup> and three WHO regions have a rubella elimination goal<sup>7</sup>. A standardized method to classify countries has been proposed for Regional Verification Commissions (RVCs) use to document countries' progress toward measles and rubella elimination<sup>8</sup>.

Elimination will not be achieved and sustained without high population immunity in all administrative health areas and age groups. Table 1 shows core activities that all countries should implement as the foundation for achieving and sustaining high population immunity.

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<sup>4</sup> <http://www.who.int/news-room/fact-sheets/detail/measles>, Accessed September 13, 2018.

<sup>5</sup> <http://www.who.int/news-room/fact-sheets/detail/rubella>, Accessed September 13, 2018.

<sup>6</sup> Dabbagh A, Patel MK, Dumolard L, Gacic-Dobo M, Mulders MN, Okwo-Bele JM, Kretsinger K, Papania MJ, Rota PA, Goodson JL. Progress Toward Regional Measles Elimination - Worldwide, 2000-2016. *MMWR Morb Mortal Wkly Rep.* 2017 Oct 27;66(42):1148-1153.

<sup>7</sup> Grant GB, Reef SE, Patel M, Knapp JK, Dabbagh A. Progress in Rubella and Congenital Rubella Syndrome Control and Elimination - Worldwide, 2000-2016. *MMWR Morb Mortal Wkly Rep.* 2017 Nov 17;66(45):1256-1260.

<sup>8</sup> Meeting of the Strategic Advisory Group of Experts on Immunization, October 2017 – conclusions and recommendations. *Wkly Epidemiol Rec.* 2017 Dec 1;92(48):729-747.

Table 1: Core Strategies for Achieving Elimination-Standard Immunity against Measles and Rubella

Program	Target (as applicable)
Provide 2 doses of MRCV through routine immunization services <sup>9 10 11 12 13 14 15</sup>	95% nationally and within each sub-national unit
Conduct high quality national follow-up campaigns at intervals determined by the country's epidemiology and vaccination coverage (typically every 2-4 years) and sub-national campaigns where appropriate <sup>16</sup>	Continue with nationwide campaigns* until routine coverage with both MCRV1 and MCRV2 is at least 90-95% for 3 consecutive years
Implement missed opportunities for vaccination (MOV) strategy e.g. use every contact with a health provider to check vaccination history and provide any missed vaccinations <sup>17 18 19</sup>	
Implement school entry checks with or without school-based vaccination program as appropriate in local context <sup>20</sup>	
Establish programs to vaccinate health workers <sup>21</sup>	
Establish programs to vaccinate immigrants/refugees/travelers and other high-risk groups	
Conduct high quality outbreak response immunization when outbreaks occur	
*Guidance on appropriate use of sub-national campaigns is under development	

It is recognized that countries have varying levels of financial and other resources to implement the above strategies in a consistent, high quality manner. Hence immunity gaps occur. This guidance provides a broad step-wise framework for Ministries of Health and WHO country/regional offices to think about a country's epidemiologic profile and identify specific

<sup>9</sup> Global Measles and Rubella Strategic Plan 2012-2020. Geneva, WHO Press, 2012.

<sup>10</sup> Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.

<sup>11</sup> Rubella vaccines: WHO position paper. Wkly Epidemiol Rec. 2011 Jul 15;86(29):301-16.

<sup>12</sup> Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.

<sup>13</sup> [http://www.who.int/immunization/programmes\\_systems/service\\_delivery/red/en/](http://www.who.int/immunization/programmes_systems/service_delivery/red/en/), Accessed September 20, 2018.

<sup>14</sup> A Guide to Introducing a Second Dose of Measles Vaccine into Routine Immunization Schedules. Geneva, WHO Press, 2013.

<sup>15</sup> Introducing Rubella Vaccine into National Immunization Programmes. A step by step guide. Geneva, WHO Press, 2015.

<sup>16</sup> Planning and Implementing High-Quality Supplementary Immunization Activities for Injectable Vaccines using an example of measles and rubella vaccines: field guide. Geneva, WHO Press, 2016.

<sup>17</sup> Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.

<sup>18</sup> Global Routine Immunization Strategies and Practices (GRISP): a companion document to the Global Vaccine Action Plan (GVAP). Geneva, WHO Press, 2016.

<sup>19</sup> [http://www.who.int/immunization/programmes\\_systems/policies\\_strategies/MOV/en/](http://www.who.int/immunization/programmes_systems/policies_strategies/MOV/en/), Accessed 20 September 2018.

<sup>20</sup> Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.

<sup>21</sup> Measles vaccines: WHO position paper – April 2017. Wkly Epidemiol Rec. 2017 Apr 28;92(17):205-27.

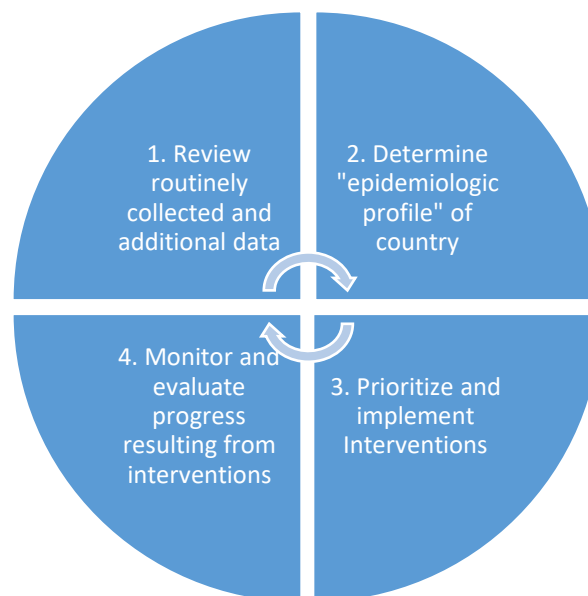
immunity gaps and then prioritize interventions to fill these gaps. As mentioned, all guidance should be used in conjunction with any regional guidance that may provide strategies specifically tailored to individual regions. In addition, measles and rubella interventions should be integrated together in approach, but their population immunity should be evaluated separately.

This guidance is organized in a step-wise approach:

- **Step 1:** Review all available data to understand measles and rubella/CRS epidemiology and potential immunity gaps
- **Step 2:** Assess general epidemiologic profile of country
- **Step 3:** Identify, prioritize and implement interventions
- **Step 4:** Assess outcomes resulting from interventions

The four steps above are meant to be implemented within a CQI framework (Figure 1). CQI is a cyclical framework in which problems are assessed, interventions are implemented, and then the impact of the interventions are evaluated.

Figure 1: Continuous Quality Improvement (CQI) Framework



## Stepwise Framework

### Step 1: Review available data sources to understand measles and rubella/CRS epidemiology and possible immunity gaps (including at sub-national levels)

In implementing Step 1, countries should gather ALL available data that may provide insight into levels of population immunity and gaps that may exist. Different sources of data (e.g. administrative coverage, campaign coverage, surveillance data) should be compared through a process called “triangulation.” Triangulation is described more fully in Annex A, but the basic principle is to look at different sources of existing data to see where complementary and contradictory information exists. As all data sources have their limitations, this can provide a more complete understanding of a country’s epidemiologic profile. Where data contradict each other, critical thinking is required to try to understand what is underlying the discrepancy. When interpreting data, the quality of the data must always be considered as well as the strengths, weaknesses and best usages for each type of data. Finally, if financial and human resources are available, a root cause analysis should be considered to better understand the underlying causes of the identified gaps.

Annex A provides more detailed information on various data sources and available tools/methodologies for assessing population immunity. Brief summaries of each data source and tool are provided here:

#### *Routinely available data:*

##### Surveillance

**Case-Based Surveillance** is the WHO-recommended surveillance standard for measles and rubella and is used to detect and investigate suspected measles and rubella cases. It involves the ongoing and rapid identification of suspected cases for the purpose of case investigation. Data from a case-based system may or may not be complete or representative, however it is critical for understanding which suspected cases are laboratory-confirmed, epidemiologically-linked or discarded.

Furthermore, as countries approach elimination, their case-based surveillance should become a more accurate source of data from the true number of cases in a country. Finally, vaccination history should be collected in all of the suspected cases; this can be used as another source of information on vaccination coverage. With good data on vaccination history, *vaccine effectiveness analyses* can be conducted which can be very helpful in populations where effectiveness may vary from the global norms which can result in inaccurate immunity estimates. If *genotyping* of samples is conducted, this data can help to define the spatial and temporal transmission dynamics of measles, which can highlight underlying immunity gaps. Countries may choose to analyze the 5 previous years of surveillance data stratified by age, sex, birth cohort, sub-national level (2<sup>nd</sup> or 3<sup>rd</sup> administrative level depending on population size) and vaccination status

**Aggregate surveillance data: The Integrated Disease Surveillance and Response (IDSR)** and other aggregate surveillance data systems typically collect aggregate case counts for selected priority

diseases or conditions. Aggregate systems require fewer resources than case-based systems, however they typically do not distinguish between suspected and confirmed cases; hence it is difficult to understand the true burden of disease.

## Historical Coverage Data

**Routine (administrative) vaccination coverage** data is a key measure of immunization system performance and can be used to assess population immunity when adjusted for vaccine effectiveness. Unfortunately, in many countries, administrative coverage estimates are inaccurate due to errors in the denominator (total target population), errors in recording vaccinations at health facilities, and errors in compiling the data to report to higher levels.<sup>22</sup> To address these challenges, WHO and UNICEF release WUENIC estimates each year which are estimates derived through triangulation of all data sources reflecting coverage in a country. These are typically considered to be more accurate than reported administrative data. National and sub-national coverage by birth cohort, and since the introduction of MRCVs should be reviewed.

**Campaign administrative coverage data:** Administrative coverage from campaigns is one source of information for assessing coverage. However, it must be interpreted cautiously because imprecision of both numerators and denominators can provide false reassurance that coverage objectives have been met.<sup>23</sup>

*In addition to the routinely available data sources above, the following critical sources should be reviewed if a country has them:*

## Population Coverage Surveys:

**Post-campaign coverage surveys** should be nationally representative surveys using probability sampling to assess the coverage. They provide an independent, and more accurate, estimation of campaign coverage. However they may not provide estimates at lower sub-national levels<sup>24</sup>.

**Other Coverage Surveys** (MICS, DHS, etc.): Household surveys include the Multiple Indicator Cluster Survey (MICS) from UNICEF and Demographic & Health Survey (DHS) from USAID. MICS and DHS are large-scale, nationally representative household surveys that typically include a component of vaccination coverage in young children (e.g. 12-23 months).<sup>25</sup> Coverage estimates from surveys are often trusted more than administrative estimates but, like administrative estimates, their accuracy depends in part on the quality of primary recording of vaccinations. In addition, surveys are subject to other types of information bias, selection bias and sampling error.<sup>26</sup> Finally, these surveys only provide data on one birth cohort of children and may only be administered every 3-10 years.

## Outbreak Investigation Reports:

In general, the primary reason for an outbreak investigation and response is to control the outbreak and help prevent future outbreaks. High quality outbreak reports will describe the

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<sup>22</sup> Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Med.* 2013;10(5):e1001404.

<sup>23</sup> Zuber PL, Yaméogo KR, Yaméogo A, Otten MW Jr. Use of Administrative Data to Estimate Mass Vaccination Campaign Coverage, Burkina Faso, 1999. *J Infect Dis.* 2003 May 15;187 Suppl 1:S86-90.

<sup>24</sup> World Health Organization Vaccination Coverage Cluster Surveys: Reference Manual. [http://www.who.int/immunization/documents/who\\_ivb\\_18.09/en/](http://www.who.int/immunization/documents/who_ivb_18.09/en/)

<sup>25</sup> <http://www.publishwhatyoufund.org/wp-content/uploads/2016/11/Household-surveys-do-competing-standards-serve-country-needs.pdf>, Accessed September 13, 2018.

<sup>26</sup> Cutts FT, Claquin P, Danovaro-Holliday MC, Rhoda DA. Monitoring vaccination coverage: Defining the role of surveys. *Vaccine.* 2016 Jul 29;34(35):4103-4109.

epidemiology of the outbreak, the causes contributing to the outbreak, and the outbreak response conducted. This information can be very helpful to see where immunity gaps developed in the past and how they resulted in an outbreak.<sup>27</sup> Reports from the last 5 years are the most relevant to current immunity gaps.

#### Serosurveys:

**Data/reports from past serosurveys** provide data on actual immunity to measles and rubella in a population. Serosurveys may be conducted through DHS/MICS surveys or other survey designs, including rubella serosurveys among women of childbearing age. While these provide high-quality data on immunity, they may be conducted in specific sub-populations or birth cohorts and this needs to be taken into consideration when interpreting the data. Furthermore, they may be based on convenience rather than representative sample populations.<sup>28</sup>

#### Modeling Studies (see Annex B)

**Reports/publications from previously-conducted modeling studies:** Modeling studies can be used to create estimates of immunity based on multiple sources of data. They can also be used to measure the impact of many scenarios on the progress and speed towards measles elimination and outbreak control. Scenarios may include demographic transitions, subclinical measles, investing resources for measles elimination, differing coverage rates, etc.

There are several tools/methodologies that can be used to analyze existing data. These are described briefly below and more thoroughly in Annex B. The quality of the source data used with these tools will strongly impact the accuracy of any estimates/results that they generate.

**Data triangulation** (concept presented above): There are many types and methods of data triangulation. It often includes a process of reviewing existing data from multiple data sources to understand an issue and assist with public health decision making.

**Risk assessment tool:** The World Health Organization (WHO) measles programmatic risk assessment tool was developed to help national programs to identify areas not meeting measles programmatic targets, and based on the findings, guide and strengthen measles elimination program activities and reduce the risk of outbreaks. It takes into consideration several areas of data that contribute to risk of measles outbreaks in sub-national geographic areas<sup>29</sup>

**WHO MSP Tool** (and other Excel based tools for birth cohort analyses): The WHO Measles Strategic Planning (MSP) Tool was developed in the mid-2000s to facilitate a combined analysis of national immunization and surveillance data and generate immunity estimates by birth cohort. It can also estimate the effectiveness and cost effectiveness of different vaccination strategies.

**Mathematical Modeling:** Mathematical modeling uses population-based disease transmission and susceptibility models to estimate gaps in immunity and susceptibility.

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<sup>27</sup> Guidelines for measles and rubella outbreak investigation and response in the WHO European Region. Copenhagen, WHO Regional Office for Europe, 2013.

<sup>28</sup> Guidance on conducting serosurveys in support of measles and rubella elimination in the WHO European Region. Copenhagen, WHO Regional Office for Europe, 2013.

<sup>29</sup> [http://www.who.int/immunization/monitoring\\_surveillance/routine/measles\\_assessment/en/](http://www.who.int/immunization/monitoring_surveillance/routine/measles_assessment/en/). Accessed September 13, 2018.



Key questions to consider when analyzing the data are: where is immunity high (>95%)? Where are immunity gaps? To identify gaps, both low vaccination coverage and the occurrence of cases/outbreaks should be considered. Sub-national levels, age group/birth cohort analyses, and high risk populations should be evaluated.

## Step 2: Determine the “epidemiologic profile” of the country

After reviewing and analyzing available data, countries should identify which row in Table 2 best describes their epidemiologic profile for measles and rubella which takes into account their disease burden, population immunity, immunization program capacity, and capacity to conduct outbreak investigations. When using Table 2, the first column is meant to summarize the overall epidemiologic profile of a country which takes into account the areas described in the following 4 columns. The last column presents overarching recommendations for countries who fit in that row. Countries may identify with characteristics in multiple rows, and if this is the case, they should determine which classification best fits their overall standing. *Table 2 is not meant to be a rigid classification system, but rather general guidance to help countries think about where they fit along a spectrum from high endemicity to elimination and then prioritize strategies to raise population immunity.*

Countries should also consider how their population size, density, and size of birth cohort nationwide and in sub-national areas may influence their capacity to interrupt transmission. For example, in small island countries or rural populations, sparsely populated areas’ transmission may appear to be interrupted at lower levels of population immunity while large, populous countries or cities may continue to have endemic transmission despite relatively high 2 dose coverage.

Table 2: Country-level epidemiologic profiles

Overall Epidemiologic Profile (summary of general characteristics in the next four columns)	General Characteristics of Countries with this Epidemiologic Profile (measles and rubella should be evaluated separately; countries may fall into different rows for different characteristics)				Recommendations for Immunization System Priorities
	Disease Burden	Population Immunity	Immunization Programme Capacity	Capacity to Conduct Outbreak Investigations	
<p>Low disease incidence with infrequent outbreaks, high population immunity, strong program capacity and outbreak investigations.</p> <p>Can include countries that have eliminated measles/rubella as well as endemic countries.</p> <p>Note that incidence may be very low in the honeymoon period<sup>30</sup>.</p>	<p>Low incidence of disease</p> <p>Infrequent outbreaks, temporally (&lt;12 months duration) and geographically-limited</p> <p>Cases predominantly in children too young to be immunized and/or adolescents/adults</p>	<p>High population immunity, particularly among children; however, may have age, sub-population or geographic immunity gaps.</p> <p>During the honeymoon period, susceptible individuals will accumulate rapidly unless routine immunization is strengthened</p>	<p>Consistent high coverage (e.g. ≥90%) <sup>31</sup>with both doses of MRCV<sup>†</sup>.</p> <p>Highly sensitive case-based surveillance system.</p> <p>Demonstrated capacity to conduct high-quality campaigns and timely ORI.</p>	<p>Each outbreak investigation is well conducted including looking for the source and documenting the end of transmission.</p> <p>Investigations provide valuable information on immunity gaps in the population and actions are taken to close gaps.</p>	<p>Increase or sustain coverage with two routine doses of MRCV to at least 95%.</p> <p>Actively look for age-specific, sub-population and/or geographic immunity gaps and address them so that outbreaks are averted.</p> <p>Conduct targeted interventions as needed to fill identified immunity gaps; may be sub-national or population-specific</p> <p>Rapidly investigate and contain outbreaks that occur.</p> <p>Immediately after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks.</p>

<sup>30</sup> When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)

<sup>31</sup> The 90% suggestion is not a prescriptive cut-off. It is rather an estimation signaling a strong coverage, although there may be fluctuation with this figure. As explained, countries may have various inconsistencies and may not fit directly into one of the categories.

<p>Medium disease incidence with periodic outbreaks, inadequate immunity in some populations, and moderate program/outbreak investigation capacity.</p> <p>Note that incidence may be very low in the honeymoon period<sup>32</sup>.</p>	<p>Medium incidence of disease</p> <p>Periodic outbreaks that are responded to and contained.</p> <p>Majority of cases in children &lt;15 years</p>	<p>Inadequate population immunity in children &lt;5 years old; may have gaps in older age groups.</p> <p>Most older children have had opportunities for 2 MRCV doses through routine immunization and/or campaigns; most adults were either vaccinated or had prior infection.</p>	<p>Suboptimal MRCV1 coverage (e.g. 85 - 90%); MRCV2 may or may not be introduced. if introduced, coverage is likely suboptimal or lower.</p> <p>Sensitivity of case-based surveillance system may be sub-optimal and may vary across sub-national divisions.</p> <p>Campaigns may have sub-optimal quality, and/or may not have been conducted recently.</p>	<p>Outbreak investigations are conducted for the majority of outbreaks.</p> <p>Investigations provide additional information on immunity gaps which may or may not be addressed.</p>	<p>Increase quality of routine immunization services with aim to decrease reliance on campaigns.</p> <p>Conduct high quality campaigns with a focus on reaching those unreached through the RI system. Determine inter-campaign intervals and targeted age group by epidemiologic analysis and population susceptibility analyses.</p> <p>If high quality data are available to allow accurate subnational analysis, campaigns may be targeted based on the epidemiological profile of the sub-national areas concerned<sup>33</sup></p> <p>Implement specific strategies to fill known immunity gaps (e.g. HCWs, migrants, subpopulations).</p> <p>Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.</p> <p>Immediately after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks.</p>
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<sup>32</sup> When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)

<sup>33</sup> This requires epidemiologically distinct and heterogeneous geographical areas, and the subnational approach must be programmatically feasible. The MR SAGE WG is working on more precise guidance for countries when carrying out targeted sub-national approach which will be presented to the SAGE in 2019.

<p>High disease incidence with frequent outbreaks, inadequate population immunity, and limited program/outbreak investigation capacity.</p> <p>Note that incidence may be very low in the honeymoon period<sup>34</sup>.</p>	<p>High incidence of disease</p> <p>On-going, endemic transmission and regular large-scale, long duration outbreaks even shortly after campaigns.</p> <p>Majority of cases in children &lt;5 years (as adults were either vaccinated or had prior infection).</p>	<p>Inadequate immunity in multiple age groups, most significant gaps in children &lt;5 years old.</p>	<p>Long standing low MRCV1* coverage (e.g. &lt; 85%)</p> <p>MRCV2# not introduced or very low coverage.</p> <p>Case-based surveillance not implemented or inadequately sensitive.</p> <p>Quality of campaigns is inadequate and/or they have not been conducted in a timely manner.</p>	<p>Due to large-scale and frequent outbreaks, outbreak investigations are typically inadequate.</p> <p>The beginning and end of outbreaks may not be determined consistently.</p> <p>ORI may not be implemented in a timely manner (or at all)</p>	<p>Assess existing routine immunization system; develop and implement comprehensive plan to address shortcomings.</p> <p>Identify and address issues with quality of campaigns to ensure zero dose and under vaccinated children are reached.</p> <p>Conduct high quality campaigns with inter-campaign intervals and targeted age group determined by epidemiologic analysis.</p> <p>Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.</p> <p>Immediately after a campaign, rapid strengthening of RI with high coverage needs to be implemented and maintained to avoid later outbreaks</p>
<p><b>Applicable only for rubella in countries that have not yet introduced RCV<sup>35</sup>.</b></p> <p>Pre-vaccine epidemiology: high incidence with outbreaks typically among children</p>	<p>Endemic rubella virus transmission.</p> <p>Highest burden typically among children aged 5-9 years.</p>	<p>All immunity due to natural infection.</p>	<p>RCV not yet introduced.</p> <p>Case-based rubella surveillance may or may not exist as part of a joint measles-rubella surveillance system.</p> <p>CRS surveillance may or may not be implemented.</p>	<p>Rubella outbreaks may or may not be detected and investigated.</p>	<p>Set up basic structure for rubella elimination through wide-age range introductory campaign and introduction of two doses of RCV into routine immunization services.</p>

<sup>34</sup> When there are low amounts of cases following a campaign due to a spike in increased population immunity (especially following a wide-age range SIA)

<sup>35</sup> Some countries may provide RCV through the private sector. This category concerns countries that have not introduced RCV nationally.

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**Abbreviations:** CRS = congenital rubella syndrome; HCW = health care worker; MOV Strategy = missed opportunity for vaccination strategy ; MR = measles and rubella; MRCV = measles- and rubella-containing vaccine<sup>†</sup> (or MCV) ; MRCV1\* = first dose of measles- and rubella-containing vaccine (or MCV1); MRCV2# = second dose of measles- and rubella-containing vaccine(or MCV2); PIRI = periodic intensification of routine immunization; RCV = rubella-containing vaccine; campaign = supplementary immunization activity; WUENIC = WHO-United Nations Children's Fund (UNICEF) coverage estimate

### Step 3: Identify, prioritize, and Implement Interventions:

Using the last column of Table 2, countries can identify the overarching strategies that are most helpful to countries with their epidemiologic profile. This guidance provides several additional tools to plan more specific activities that are organized in three ways:

- Core activities that all countries should implement are shown in Table 1
- Activities most useful for countries within a specific epidemiologic profile (as described in Table 2). Some examples of activities prioritized in this way are discussed below.
- Activities to fill specific immunity gaps are shown in Table 3

When prioritizing interventions, the following need to be considered:

- Country context
- The effectiveness of interventions in addressing the identified issue/gaps
- The feasibility of conducting a high quality intervention, which includes the programmatic capacity in country as well as the availability of needed resources (human and financial)
- Size of the population, population movements, and migration

In addition, one good resource is the WHO'S GRISP guidance<sup>36</sup> which provides a more comprehensive overview of strategies to strengthen immunization programs. However, working within the context of epidemiologic profiles as presented in Table 2, the following are a few examples of interventions that should be prioritized for countries depending on their epidemiologic profile as described in Table 2:

For countries whose epidemiologic profile fits best in the **first** row of Table 2:

<u>Long Term Strategies To Raise Population Immunity</u>	<u>Short term and Immediate Approaches to Address Immunity Gaps</u>
Increase/sustain MRCV1* and MRCV2# coverage to ≥95% in all districts/areas and maintain this level of coverage.	Targeted activities may be needed if immunity gaps /susceptible populations are identified.
Set up country policy and establish vaccination of HCWs if not in place.	If national coverage is very high but a gap is identified, interventions should be targeted to the identified gaps
Extend school entry checks to other entry points into education where feasible, e.g., high school, university, or college.	
Promote vaccination (and develop innovative strategies) for migrants/travelers.	
Gain political support and strengthen MR surveillance	

For countries whose epidemiologic profile fits best in the **second** row of Table 2:

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<sup>36</sup> World Health Organization. Global Routine Immunization Strategies and Practices. 2016.

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
<p>Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Focus on strategies to increase coverage with both MRCV1* and MRCV2# to &gt;95% so that regular campaigns will not be necessary. Consider PIRIs and more outreach sessions.</p> <p>Ensure opportunistic screening and vaccination during health care visits (the MOV Strategy). Implement school entry checks if feasible and would not risk reducing school enrollment.</p> <p>Gain political support and strengthen MR surveillance</p>	<p>Conduct follow-up campaigns, focusing strategies on reaching those not reached through routine immunization services.</p> <p>Where epidemiologic data indicate immunity gaps in children &gt;5 years old, national or subnational wide age range campaigns may be considered if effective strategies to reach the under- or un-vaccinated are in place.</p>

For countries whose epidemiologic profile fits best in the **third** row of Table 2:

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
<p>Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Consider PIRIs, more outreach sessions. Introduce MRCV2# if not introduced.</p> <p>Ensure opportunistic screening and vaccination during health care visits (the MOV Strategy). Implement school entry checks if feasible and would not risk reducing school enrollment.</p> <p>Gain political support and strengthen MR surveillance</p>	<p>Address quality of campaigns. Determine why children are being missed and address the problems.</p> <p>Conduct follow-up campaigns at regular intervals. Focus strategies on reaching those not reached through routine immunization.</p> <p>Where epidemiologic data indicate immunity gaps in children &gt;5 years old, national or subnational wide age range campaigns may be considered if effective strategies to reach the under- or un-vaccinated are in place.</p>

For countries whose epidemiologic profile fits best in the **last** row of Table 2:

Primary Long Term Strategies To Raise Population Immunity	Short term and Immediate Approaches to Address Immunity Gaps
<p>Strengthen routine immunization services to ensure high coverage with RCV.</p> <p>Strengthen MR case-based surveillance; consider establishment of CRS surveillance.</p>	<p>Conduct RCV introductory catch-up campaigns.</p> <p>Introduce two doses of RCV into the routine program as MR/MMR vaccine.</p>

When immunity gaps are identified within specific sub-populations, interventions can be targeted to those specific sub-populations (Table 3). Again, this table is not an exhaustive list; activities should to be assessed and prioritized according to the country context and other issues listed above. Finally, root cause analyses are highly recommended to understand what is causing the gaps so that interventions can be tailored to address the true cause of the gap.

Table 3: Activities<sup>1</sup> to address specific immunity gaps.

Immunity Gap	Long Term Strategies to Avoid Accumulation of Susceptible Persons	Immediate Approaches to Address the Gap
<b>Under 1</b>	<ul style="list-style-type: none"> <li>- Implement strategies to improve the coverage and <u>timeliness</u> of MRCV1* in countries where vaccine is administered at 9-11 months of age.</li> </ul>	<ul style="list-style-type: none"> <li>- Include infants from 6 months of age in preventive vaccination campaigns and in outbreak response campaigns.</li> <li>- Consider source of exposure and consider targeting that group (e.g., parents/adults, older siblings, HCW).</li> </ul>
<b>Age 1 to 5</b>	<ul style="list-style-type: none"> <li>- Identify and address the underlying reasons for the immunity gap.</li> <li>- Strengthen routine MRCV1 and MRCV2 programs and improve coverage.</li> <li>- Remove maximum age limits for MRCV1 and MRCV2 to ensure that they receive both doses, even if they present for vaccination after the recommended ages for vaccination.</li> <li>- Implement entry checks for daycares, kindergartens and similar institutions.</li> <li>- Implement strategies to avoid missed opportunities for vaccination, e.g., vaccination record checks every time a child visits a health center</li> <li>- Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services.</li> <li>- Ensure that MRCV2 is included in Fully Immunized Child (FIC) estimates</li> <li>- Monitor the gap in coverage between MRCV1 and MRCV2; identify and address reasons for gap (ref GRISP).</li> </ul>	<ul style="list-style-type: none"> <li>- Conduct high quality campaigns (nationally or sub-nationally, depending on the extent of the identified gap; consider school-/daycare-based campaigns/strategies).</li> </ul>
<b>Children ≥5 and adolescents</b>	<ul style="list-style-type: none"> <li>- Identify and address the underlying reasons for the immunity gap.</li> <li>- Improve MRCV2 coverage and timeliness.</li> <li>- Implement school entry checks for elementary, high schools and universities.</li> <li>- Implement strategies to avoid missed opportunities for vaccination, e.g., vaccination record checks every time a child visits a health center and linkages to adolescent care.</li> <li>- Eliminate any policies that discourage use of MRCV vaccines in this age group</li> </ul>	<ul style="list-style-type: none"> <li>- Conduct a high quality, wide-age range campaign (nationally or sub-nationally, depending on the extent of the identified gap; consider school-based campaigns/strategies).</li> </ul>



<b>Adults</b>	<ul style="list-style-type: none"> <li>- Introduce immunization of adults as part of occupational health services for health care workers, employees in educational and day-care institutions, and all occupations that are in daily contact with many individuals.</li> <li>- Offer vaccination at medical appointments, post-partum care for women, and other interactions with health care services.</li> <li>- Offer vaccination before international travel.</li> </ul>	<ul style="list-style-type: none"> <li>- Consider conducting campaign targeting the affected groups.</li> <li>- Make MRCV available free of charge to affected age groups, with priority given to persons who are unvaccinated or vaccinated with only one dose, but available to all regardless of vaccination status.</li> </ul>
<b>Migrants</b>	<ul style="list-style-type: none"> <li>- Identify and address the underlying reasons for the immunity gap among migrants.</li> <li>- Implement at work permit/visa-based vaccination program.</li> <li>- Establish long-term programs with immigration services and migrant organizations/associations/community.</li> <li>- Create capacities in health systems (through partners, NGOs, or government) that will provide immunization as a part of basic, free of charge service to migrants.</li> <li>- Tailor social mobilization, advocacy and communication activities to increase demand and uptake of immunization services among migrants.</li> </ul>	<ul style="list-style-type: none"> <li>- Conduct a high quality campaign targeting migrants as a priority, but with extension to local susceptible populations, under the same rights and rules (strategies used to vaccinate migrants should not be discriminatory).</li> <li>- Offer vaccination through immigration services and migrants organizations/associations/communities.</li> <li>- Offer vaccinations services through the health system, regardless of the patients' residency status and legal/administrative regulations.</li> </ul>
<b>Refugees</b>	<ul style="list-style-type: none"> <li>- Establish systematic immunization activities in refugee camps.</li> <li>- Establish long-term programs with immigration services and migrant organizations/associations/community.</li> <li>- Create capacities in health systems (through partners, NGOs, or government) that will provide immunization as a part of basic, free of charge service to refugees.</li> </ul>	<ul style="list-style-type: none"> <li>- Provide vaccination services in line with national regulations and with equal rights to refugees at entry and in camps.</li> <li>- Conduct campaigns in refugee camps starting from 6 months of age.</li> <li>- Offer vaccination services through the health system, regardless of the patients' residency status and legal/administrative regulations.</li> </ul>
<b>Populations not vaccinated due to lack of vaccination services (e.g., rural, indigenous populations)</b>	<ul style="list-style-type: none"> <li>- Increase frequency of outreach services and social mobilization/demand-generating activities associated with the outreach.</li> <li>- Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services to ensure that people come for vaccination.</li> <li>- Consider activities such as Periodic Intensification of Routine Immunization as a periodic systematic intervention</li> </ul>	<ul style="list-style-type: none"> <li>- Conduct periodic intensification of routine immunizations (PIRIs) (or mop-up activities for populations missed during a campaign).</li> </ul>
<b>Populations not vaccinated</b>	<ul style="list-style-type: none"> <li>- Register new inhabitants with health services and include in target population for routine immunization.</li> </ul>	<ul style="list-style-type: none"> <li>- Conduct campaigns in low coverage areas; consider different strategies e.g. many vaccination sites/mobile</li> </ul>

<b>due to "invisibility" to vaccination services (e.g., urban, border populations)</b>	<ul style="list-style-type: none"> <li>- Increase social mobilization, advocacy and communication about vaccination services.</li> </ul>	<p>teams, vaccination at markets, transportation centers, work places, schools and universities, extended vaccination hours,</p> <ul style="list-style-type: none"> <li>- Increase social mobilization, advocacy and communication (targeting diverse age groups).</li> </ul>
<b>Populations not vaccinated due to vaccine hesitancy</b>	<ul style="list-style-type: none"> <li>- Identify and address the underlying reasons for vaccine hesitancy</li> <li>- Tailor social mobilization, advocacy and communication activities to increase uptake of immunization services, considering the unique local context</li> </ul>	<ul style="list-style-type: none"> <li>- Identify and address the underlying reasons for vaccine hesitancy</li> <li>- Tailor social mobilization, advocacy and communication activities to increase uptake of immunization services, considering the unique local context</li> <li>- Campaigns/ORI in surrounding communities to ensure high herd immunity in surrounding populations.</li> </ul>
<b>Populations not vaccinated due to stock-outs</b>	<ul style="list-style-type: none"> <li>- Address root cause that resulted in stock-out and prevent further episodes.</li> </ul>	<ul style="list-style-type: none"> <li>- Campaigns/PIRIs in areas where gaps occurred.</li> <li>- Strengthen follow-up services to ensure that the children that missed vaccination come back when the vaccine is in stock.</li> <li>- Ensure sustained confidence in health services/immunization.</li> </ul>
<b>Any population identified due to an outbreak or serosurvey</b>	<ul style="list-style-type: none"> <li>- Identify and address root cause of immunity gap.</li> <li>- Consider periodic campaigns targeted at this population if they are being missed by other vaccination activities.</li> <li>- Review all available information and sources to identify similar populations and address immunity gaps systematically.</li> </ul>	<ul style="list-style-type: none"> <li>- Adjust ORI to population affected (including all ages affected), e.g., geographic area, work place, university, ethnicity, religion, etc.</li> </ul>
<sup>1</sup> Activities presented are not a comprehensive list		

Note: When conducting interventions, campaigns should be used as a temporary measure to address immunity gaps and strengthening RI must be the primary focus. Countries should continually look for opportunities to incrementally improve routine immunization coverage. In addition, it is worth noting (as mentioned in Table 2) that countries often experience no/few cases shortly following a campaign, which is known as the "honeymoon period" by some experts. However, susceptible persons are still accumulating during this time period if routine immunization programs are not reaching full birth cohorts. This reiterates the need to strengthen RI so that countries can eventually stop depending on campaigns.

## Step 4: Assess outcomes resulting from interventions

Re-enforced by the CQI Framework, this process is cyclical in nature. All interventions should be evaluated with the attempt to improve upon past successes as figure out how to improve things. As part of this process, countries should:

- Conduct on-going monitoring and evaluation of interventions implemented
- Evaluate progress of interventions several months after implementation
- Consider: Does sufficient data exist to evaluate the implementation effectively? Or is additional data needed? If so, what kind of data, and what is the best way to collect it?
- Review roadblocks to the success of the intervention and figure out how to overcome them

## Conclusion

In conclusion, this guidance attempts to guide countries to assess their epidemiologic profile and then implement targeted and data driven interventions at the national and sub-national levels. A four-step process was introduced with in-depth tables for many of the elements. However, in order to provide effective and appropriate interventions, multiple sources of data must be analyzed both pre- and post-intervention with a continuous focus on monitoring and evaluation to improve interventions. Finally, this guidance should be used in conjunction with any existing regional advice, as well as other resources that provide more in-depth guidance for specific areas.

## Draft Recommendations from the SAGE WG:

### Guiding Principles:

These recommendations are to serve as guiding principles for the immunization program for all countries.

- 1) Increasing population immunity should take a Continuous Quality Improvement (CQI) approach
- 2) Critical review of all available data sources is needed to identify immunity gaps
- 3) Strengthening RI is the primary strategy for increasing population immunity
- 4) Campaigns are needed (as rescue measures) where RI for two doses of measles and rubella-containing vaccines is sub-optimal and to address specific immunity gaps.
- 5) During the time period following campaigns, activities must be quickly prioritized to strengthening RI systems.

For countries with the following epidemiological profiles:

- 1) Countries with Low disease incidence with infrequent outbreaks, high population immunity, strong program capacity (with consistently high coverage with both doses of MRCV) and outbreak

investigations. This also can include countries that have eliminated measles/rubella as well as endemic countries.

- a. Recommendations for Immunization System Priorities include:
  - i. Increase or sustain coverage with two routine doses of MRCV to at least 95%.
  - ii. Actively look for age-specific, sub-population and/or geographic immunity gaps and address them so that outbreaks are averted.
  - iii. Conduct targeted interventions as needed to fill identified immunity gaps; may be sub-national or population-specific
  - iv. Rapidly investigate and contain outbreaks that occur.
  - v. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.
- 2) Medium disease incidence with periodic outbreaks, inadequate immunity in some populations, and moderate program (with suboptimal coverage of MRCV) and outbreak investigation capacity.
  - a. Recommendations for Immunization System Priorities include
    - i. Increase quality of routine immunization services with aim to decrease reliance on campaigns.
    - ii. Conduct high quality campaigns with a focus on reaching those unreached through the RI system. Determine inter-campaign intervals and targeted age group by epidemiologic analysis and population susceptibility analyses.
    - iii. If high quality data are available to allow accurate subnational analysis, campaigns may be targeted based on the epidemiological profile of the sub-national areas concerned<sup>37</sup>.
    - iv. Implement specific strategies to fill known immunity gaps (e.g. HCWs, migrants, subpopulations)
    - v. Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.
    - vi. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.
- 3) High disease incidence with frequent outbreaks, inadequate population immunity, and limited program (with low coverage of MRCV) and outbreak investigation capacity.
  - a. Recommendations for Immunization System Priorities include
    - i. Assess existing routine immunization system; develop and implement comprehensive plan to address shortcomings.
    - ii. Identify and address issues with quality of campaigns to ensure zero dose and under vaccinated children are reached.
    - iii. Conduct high quality campaigns with inter-campaign intervals and targeted age group determined by epidemiologic analysis.
    - iv. Increase outbreak response preparedness so that outbreaks can be rapidly detected, investigated and contained.
    - v. During the time period immediately following campaigns, activities must be quickly prioritized to strengthening RI systems.

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<sup>37</sup> This requires epidemiologically distinct and heterogeneous geographical areas, and the subnational approach must be programmatically feasible. The MR SAGE WG is working on more precise guidance for countries when carrying out targeted sub-national approach which will be presented to the SAGE in 2019.

- 4) **Applicable only for rubella in countries that have not yet introduced RCV<sup>38</sup>.** Pre-vaccine epidemiology: high incidence with outbreaks typically among children
- a. Recommendations for Immunization System Priorities include
    - i. Set up basic structure for rubella elimination through wide-age range introductory campaign and introduction of two doses of RCV into routine immunization services.

## Annexes

Annex A: Data sources for estimating immunity gaps

Annex B: Analytic tools for estimated immunity gaps

Annex C: Classification based on Epidemiologic Profile and Priority Interventions in Algorithm format

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<sup>38</sup> Some countries may provide RCV through the private sector. This category concerns countries that have not introduced RCV nationally.

## Annex A: Data sources for estimating immunity gaps

	Surveillance Data	Historical Coverage Data (Administrative and WUENIC)	Population Coverage Surveys (Including Post-Campaign, MICS, DHS, etc.)	Outbreak Investigations	Serosurveys
<b>Description</b>	<p>Case-based surveillance is the WHO-recommended surveillance standard for measles and rubella. Case-based surveillance is used to detect and investigate suspected measles and rubella cases. A standardized case definition is used to classify suspected cases as lab-confirmed, epi-linked, clinically compatible, or discarded. Case data typically include for each case demographics, date of onset, medical care, vaccination status and history, epidemiological linkage to a known case, and serum specimen testing. In addition, exposure status (imported, endemic) can be determined. WHO recommends routine reporting of measles and rubella cases by each country where measles is endemic, with reports by district (third administrative level), age group, and immunization status. In low-incidence or elimination settings, case-based surveillance can be used to quickly identify measles/rubella outbreaks early in the outbreak, and every suspected measles/rubella case should be reported and investigated immediately in order to quickly halt an outbreak. With good data on vaccination history, <i>vaccine effectiveness analyses</i> can be conducted which can be very helpful in populations where effectiveness may vary from the global norms which can result in inaccurate immunity estimates. If genotyping is done, this data can help to define the spatial and</p>	<p>Use administrative or WUENIC coverage data, adjusted for vaccine effectiveness, to estimate the proportion of each birth cohort that is immune based on vaccination with 1 or 2 doses of measles- and rubella-containing vaccines in the cohorts born since vaccine introduction. As this is coverage, rather than immunity data, it needs to be adjusted for vaccine effectiveness. Alternatively, a simplified standard of 95% coverage with 2 doses is often used to classify a specified population as having sufficient immunity.</p> <p>Administrative coverage from campaigns is another source of information for assessing coverage.</p>	<p>Population-based surveys are typically cluster surveys such as WHO Vaccination Coverage Cluster Surveys, Demographic and Health Surveys (DHS), and Multiple Indicator Cluster Surveys (MICS). Surveys typically target a specified age range, i.e. 12-23 or 24-35 months. When coverage surveys are conducted following SIAs, they typically include all ages targeted during the SIA. History of vaccination prior to the SIA can be included in post-SIA surveys, but data reliability is low for older children and adults that do not have written records of their vaccination history. If using coverage surveys to estimate immunity and gaps in immunity, coverage needs to be adjusted to account for vaccine effectiveness.</p>	<p>Outbreak investigation data can be used to estimate measures such as distribution of case characteristics, outbreak size and duration, size and number of chains of transmission, and proportion of imported and import-related cases. The investigation should also investigate the causes for the outbreak and identify issues related to immunization service delivery and community access to immunizations that are contributing to the immunity gaps. Outbreak data can be useful in identifying susceptibility gaps because characteristics (age, place of residence) can be identified for cases that occur during an outbreak period.</p>	<p>Serologic measurements can provide a direct measurement of population immunity. A population-based (representative) sample of the population of interest is recommended, hence cluster survey procedures (as described in the section on population coverage surveys) are typically followed. Specimens may be collected specifically for the serosurvey, or specimens previously collected may be used. If specimens from a previous survey/study are used, these results need to be interpreted carefully, with recognition of sampling procedures, as they may not be a representative sample of the population.</p> <p>Reports/publications from modeling studies: Modeling studies can be used to create estimates of immunity based on multiple sources of data</p>

	<p>temporal transmission dynamics of measles and rubella, which can highlight underlying immunity gaps.</p> <p>Aggregate surveillance data systems typically collect aggregate case counts for selected priority diseases or conditions, such as measles and rubella.</p>				
<b>Strengths</b>	<ul style="list-style-type: none"> <li>Confirmed cases indicate actual susceptibility, and show where there are susceptible groups in the population</li> <li>Can be used to determine exposure status: imported and import-related cases</li> <li>Highlights susceptibility that may not otherwise be evident due to high reported vaccination coverage</li> <li>If a case-based surveillance system is already in place and maintained in a country, ongoing nationwide surveillance data should be readily available</li> <li>Countries have ownership of the data</li> <li>Aggregate systems require fewer resources than case-based systems</li> </ul>	<ul style="list-style-type: none"> <li>Data readily available</li> <li>Data is typically available for many years, at multiple levels, often since vaccine introduction</li> <li>Countries have ownership of the data</li> </ul>	<ul style="list-style-type: none"> <li>Obtain more accurate coverage estimates than administrative data since survey data do not depend on poor quality data on doses administered and population estimates</li> <li>Can validate (or provide more accurate estimate) of SIA or routine immunization coverage</li> <li>Less expensive and easier to implement than a serosurvey</li> <li>Can collect data on communication channels and reasons for non-vaccination</li> <li>Can collect detailed demographic data, not available from other sources</li> </ul>	<ul style="list-style-type: none"> <li>Shows where actual cases are occurring during an outbreak period</li> <li>Can be used to estimate measures such as generations of transmission, imported and import-related cases, and reproduction numbers, which can enhance understanding of disease transmission in addition to population susceptibility patterns</li> <li>Can be used to estimate susceptibility in settings where there is high reported vaccination coverage which would indicate low susceptibility, but an outbreak still occurs</li> <li>Collection of outbreak data builds upon the existing case-based surveillance system, so if a high-quality surveillance system is already in place in a country, these data should be available with minimal additional effort</li> <li>Generates solid evidence for policy changes to improve vaccination service delivery and/or vaccine demand</li> </ul>	<ul style="list-style-type: none"> <li>Serologic testing provides direct measurement of immunity</li> <li>No need for vaccination records or population data</li> <li>All ages can participate, as there is no need for records/recall of vaccination that may have happened many years prior</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>Some data analyses (age, sex, residence of cases) is only feasible when there are confirmed cases; however vaccination history should be attained from all suspected cases and can be another measure of immunity gaps</li> </ul>	<ul style="list-style-type: none"> <li>Does not account for protection from SIAs, catch-up vaccination, natural infection</li> <li>Administrative coverage is often inaccurate due to inaccurate</li> </ul>	<ul style="list-style-type: none"> <li>Require technical/statistical expertise and detailed data on population settlements in order to select a representative sample</li> <li>May not get representative sample of population if surveyors cannot access all selected</li> </ul>	<ul style="list-style-type: none"> <li>Can only be used when there is an outbreak</li> <li>Depends on sensitivity and strength of the surveillance system; cases are likely to be missed if the surveillance system has low sensitivity or if the</li> </ul>	<ul style="list-style-type: none"> <li>The sensitivity and specificity of the test used to detect measles or rubella IgG need to be taken into consideration</li> <li>Waning antibodies may</li> </ul>

	<ul style="list-style-type: none"> <li>• Sensitivity of surveillance may vary by age group, geographic location, population sub-groups, etc., thus biasing estimates of the immunity profile</li> <li>• Relies on passive surveillance data, the quality of which (including sensitivity) may decline as the incidence of disease declines</li> <li>• It would be better to identify immunity gaps before there are cases, and prevent cases through vaccination, rather than wait until there are cases to be able to identify immunity gaps</li> <li>• Ability to accurately estimate immunity gaps using case-based data depends on the quality of the surveillance system</li> <li>• While it is recommended that all countries have a case-based surveillance system, they require substantial resources to maintain; hence some countries do not have high-quality case-based surveillance systems</li> <li>• Aggregate data typically do not distinguish between suspected and confirmed cases.</li> </ul>	<p>denominator data. Poorly documented numerator data can also affect estimates</p> <ul style="list-style-type: none"> <li>• WUENIC estimates are only available at a national level, hence sub-national gaps in immunity are not evident</li> <li>• WUENIC data are the best estimates of coverage, though their accuracy is unknown</li> <li>• Vaccine effectiveness may be lower than accepted estimates in areas with programmatic challenges</li> <li>• Quality of results depends on the quality of the data collection and reporting system</li> <li>• Campaign administrative coverage data must be interpreted cautiously because imprecision of both numerators and denominators can provide false reassurance that coverage objectives have been met.</li> </ul>	<p>settlements (especially applicable in countries with security concerns)</p> <ul style="list-style-type: none"> <li>• Household surveys are difficult to implement in some settings and some populations (e.g., dense cities, places where both parents work away from home, places with older subjects that are typically away from home at school or work)</li> <li>• Surveys are expensive and costs increase rapidly if sub-national estimates are desired</li> <li>• To understand the evolution of coverage levels and have up-to-date data, surveys are recommended to be conducted regularly in most countries (frequency may vary)</li> <li>• The accuracy of the assessment of children's vaccination status may depend on how many participants have written vaccination records available for review</li> <li>• The availability of written records and the accuracy of recall decrease as time passes between vaccination and the survey (e.g. to increase the accuracy of vaccination history on 10 year old children is more difficult than 1 year old children because parents are less likely to still have vaccination record and/or remember which vaccines their child received)</li> </ul>	<p>surveillance system is overwhelmed as in the case of a large outbreak</p> <ul style="list-style-type: none"> <li>• Sensitivity of surveillance during an outbreak may vary by age group, geographic location, population sub-groups, timing of the outbreak, etc., thus biasing estimates of the immunity profile</li> <li>• The age distribution of cases during an outbreak shows what the pre-outbreak susceptibility gaps were. However, individuals infected during the outbreak will convert to immune, and if the outbreak is large enough, susceptibility patterns may change post-outbreak</li> <li>• It would be better to identify immunity gaps before an outbreak begins, and prevent cases through vaccination, rather than wait until an outbreak occurs to be able to identify immunity gaps</li> <li>• There is a risk that surveillance data collected during an outbreak period has reduced specificity compared with routine case-based surveillance, particularly if relying on non-lab-confirmed cases</li> <li>• Quality of results depends on the quality of the investigation</li> </ul>	<p>affect results in persons sampled many years after vaccination</p> <ul style="list-style-type: none"> <li>• Measles and rubella IgG testing does not distinguish between antibodies induced by vaccination versus those induced by natural infection</li> <li>• High cost: serosurveys have the same costs and technical needs as a coverage survey, plus the costs of specimen collection, transport, storage and laboratory testing</li> <li>• Potential for bias if sample not representative of the population.</li> <li>• Due to resource requirements, serosurveys are typically less granular than coverage surveys (which are already a sample of the population). These may not efficiently identify immunity gaps in sub-groups, especially marginalized sub-groups</li> <li>• If using samples collected for a purpose other than an intended vaccination serosurvey, the ethical implications of testing the samples need to be considered</li> </ul>
<b>Best Use of Data Source to</b>	Case-based surveillance is recommended to be ongoing in all	Historical coverage should be monitored during all	Most useful in countries that have difficulties obtaining accurate	In endemic countries, outbreak investigations are used to identify	Serosurveys are most helpful when coverage



<b>Estimate Immunity Gaps</b>	countries. It can be useful to estimate immunity gaps for all countries; utility increases as the system achieves and maintains elimination standard surveillance standards.	phases of control/elimination. It is most accurate, and thus most useful for estimating immunity gaps, in countries where disease incidence is low, and most people are protected through routine vaccination rather than natural infection or SIAs.	administrative coverage data. Most helpful for providing: (1) estimates of SIA coverage, for all age groups targeted in an SIA; and (2) estimates of routine immunization coverage in single birth cohorts. They can identify geographic gaps, but only if designed to provide estimates at the district level or lower, which is very expensive.	target populations for response. As outbreak investigation quality increases, root causes for the outbreak are also identified that can identify gaps to be addressed to stop susceptible populations from accumulating. In countries that have eliminated or nearly-eliminated, outbreak investigations are very important to understand the underlying issues that led to susceptible persons in the population.	data are unreliable and there is little or no circulating disease. Another common use is to test for rubella susceptibility in women of child-bearing age as these age cohorts have not been vaccinated in many countries where rubella-containing vaccine has not yet been introduced or was only recently introduced
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## Annex B : Analytic methods for estimating immunity gaps

	Data Triangulation	Measles Risk Assessment Tool	WHO Measles Strategic Planning (MSP) Tool and Other Excel-Based Tools to evaluate immunity by birth cohort	Mathematical Modeling
<b>Description</b>	<p>There are many types and methods of data triangulation. It often includes a process of reviewing existing data from multiple data sources to understand an issue and assist with public health decision making. Data sources can be combined in a quantitative measure like risk assessment tools, however statistical modeling is not typically used with triangulation. Other times the interpretation of triangulated data is more qualitative. There should always be a focus on assessing the quality and external validity of the data sources used and considering this in the interpretation of the data. For assessing gaps in immunization, all available sources of surveillance and coverage data should be reviewed. Data sources should be compared for concordance across data types that measure similar issues, e.g.,</p> <ul style="list-style-type: none"> <li>• Do historical coverage data and coverage survey data show similar trends? If one shows an immunity gap but the other does not, what are the limitations of each source that might lead to the discrepancy? Which is likely to be the “best estimate”? Do you think the “best estimate” is accurate? Or is the true value likely to be higher or lower given the limitations of the data source?</li> <li>• Are the numbers of cases in the case-based and aggregate surveillance system the same? If not, what led to the discrepancies? How does this influence what the true number of confirmed measles cases actually is?</li> </ul> <p>Data should also be compared for concordance across different types of data, e.g.,</p> <ul style="list-style-type: none"> <li>• Do outbreak data show that cases are arising in geographic areas with low or high coverage? Does</li> </ul>	<ul style="list-style-type: none"> <li>• The Measles Risk Assessment Tool is meant to “help national programmes to identify areas not meeting measles programmatic targets, and based on the findings, guide and strengthen measles elimination programmatic activities and reduce risk of outbreaks.”<sup>39</sup> It is an Excel-based tool that uses programmatic data encompassing vaccination coverage, surveillance quality, program performance and indicators of outbreak threats such as population density and the presence of vulnerable groups. After inputting the required indicators, the tool classifies subnational areas into 4 categories of high and low risk. Data is meant to be input geographic areas representing the 2<sup>nd</sup> subnational administrative unit (e.g. districts) and then provides risk assessments at this administrative level.</li> </ul>	<p>The WHO Measles Strategic Planning Tool was developed in the mid-2000s to facilitate analysis of national immunization and surveillance data and estimate the effectiveness and cost effectiveness of different vaccination strategies. It uses formulas built-in to an Excel spreadsheet to create a baseline immunity profile for a country’s population age 0-20 years using historical coverage data from routine (MCV1 and MCV2) and SIA vaccination, surveillance data, and age-specific population estimates. Others have developed similar Excel-based tools that take into account protection from multiple sources: maternal antibodies, routine immunization, SIAs, etc.</p>	<p>Mathematical modeling uses population-based disease transmission and susceptibility models to estimate gaps in immunity and susceptibility. Models use one or several different sources of data including vaccination coverage, historical surveillance data and incidence patterns, transmission patterns, contact patterns, etc. Age-specific differences in data can be accounted for to produce estimates of susceptibility/immunity that are specific to small age strata. One commonly used type of model is the SIR (Susceptible, Infected, and Recovered) Model which models individuals moving between the three states. The equations used in the model estimate transmission of virus between individuals who are infected to those who are susceptible.</p>

<sup>39</sup> World Health Organization. Measles Programmatic Risk Assessment Tool.  
[http://www.who.int/immunization/monitoring\\_surveillance/routine/measles\\_assessment/en/](http://www.who.int/immunization/monitoring_surveillance/routine/measles_assessment/en/)

	<p>the age distribution of cases align with the perceived levels of population immunity across age groups, based on historical coverage and coverage surveys?</p> <ul style="list-style-type: none"> <li>Based on evaluating these and other aspects of the data, where do there appear to be immunity gaps in your population?</li> </ul> <p>Comment: WUENIC estimates of vaccination coverage are developed by triangulating all available data sources on vaccination coverage in a country</p>			
<b>Strengths</b>	<ul style="list-style-type: none"> <li>Takes into account several data sources when evaluating a public health issue</li> <li>Through comparison of data sources, the evaluator is encouraged to consider the strengths and limitations of each source</li> </ul> <p>Uses readily available data; accepts and recognizes the limitations of each type of data</p>	<ul style="list-style-type: none"> <li>Takes into account several data sources when evaluating a public health issue.</li> <li>Provides overall risk estimates by administrative/geographic unit (2<sup>nd</sup> subnational administrative unit, e.g. districts)</li> <li>Uses routinely available data</li> <li>It is an Excel based tool that is available on the WHO website.</li> <li>Several WHO regional offices have learned to support the tool</li> <li></li> </ul>	<ul style="list-style-type: none"> <li>Uses underlying statistical models that take into account vaccine efficacy, probability of infection, and case-fatality ratios but the interface is an Excel spreadsheet that does not require advanced technical skills to use</li> <li>Uses routinely available data</li> <li>Pre-loaded with data for all countries through 2008 (only data since 2009 needs to be entered into tool)</li> <li>Can be easily performed at the country level</li> <li></li> </ul>	<ul style="list-style-type: none"> <li>Can combine several sources of data including vaccination coverage, historical surveillance data, and others to model estimates of gaps in immunity and susceptibility</li> <li>Can use models for settings where there are not currently any cases, using historical data to estimate future patterns of disease</li> <li>Can include estimates of transmission and contact rates between specific age groups in the model to produce a better estimate of age-specific differences in infection and susceptibility</li> <li>Mathematical modeling results can be used to estimate what immunity profiles might be under different policy/programmatic decisions such as vaccination campaigns conducted at varying time intervals and targeting various age groups, routine immunization doses administered at varying ages, supplementing with a second dose, etc.</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>Dependent on the quality and generalizability of the data used (see limitations for data sources previously described)</li> <li>No standard methodology has been developed to triangulate data from multiple data sources (surveillance, coverage, etc.)</li> <li>Evaluation of different data sources can often only be done qualitatively, hence quantitative</li> </ul>	<ul style="list-style-type: none"> <li>Does not focus on areas identified solely by low population immunity; takes into account many factors (this is not a limitation for its general use; but needs to be noted when using the tool as a method to assess population immunity). May need to concentrate on the parameters used to assess</li> </ul>	<ul style="list-style-type: none"> <li>Accuracy of results depends on the quality of the data used; if coverage, population or surveillance data is poor quality, the results may be inaccurate</li> <li>Difficult to account for phased and sub-national campaigns as well as outbreak response immunization</li> </ul>	<ul style="list-style-type: none"> <li>Requires statistical expertise and specialized mathematical modeling skills; these skills may not be available in-country, thus an external expert is likely to be required to conduct any modeling</li> <li>The quality of the outputs from a model are only as good as the data</li> </ul>

	estimates are frequently based on 'expert opinion' and dependent on the skill and experience of the experts	<p>vaccination coverage/population immunity if that is the area of interest.</p> <ul style="list-style-type: none"> <li>Only uses data from the past 3 years. Hence vaccination coverage focuses on the youngest age cohorts.</li> </ul>	<ul style="list-style-type: none"> <li>Assumes that vaccination through routine immunization and SIAs are independent of each other with regards to probability of a child being vaccinated</li> <li>The underlying models are somewhat simplified compared to some other modeling strategies, and therefore may be less realistic</li> <li>Developed for use at the national level. Separate profiles would need to be developed for subnational analysis</li> </ul>	<ul style="list-style-type: none"> <li>Models are based on assumptions that go into the model, which may or may not accurately reflect reality</li> <li>Requires a priori assumptions that may or may not be based on evidence from the specific setting or context; may be based on historical data from settings with different characteristics</li> </ul>
<b>Best Use of Data Source to Estimate Immunity Gaps</b>	Endemic countries should always triangulate their available data. Critically examining and comparing available data provides a more complete picture and understanding of the situation. In countries that have eliminated measles, their surveillance data may not have confirmed cases, but surveillance indicators should still be evaluated while considering coverage estimates to identify potential gaps.	This is best used in countries that are closer to elimination and are trying to assess overall risk of outbreaks in subnational geographic areas. It does not directly estimate immunity gaps, but takes into consideration multiple risk factors to help countries tailor where they should concentrate interventions geographically. Examination of individual risk components by geographic subunits may provide additional insight into specific immunity gaps and what factors are contributing to the gaps and resultant outbreaks.	This tool is most useful when countries have fairly good coverage (including national and sub-national SIAs) and surveillance data to input into the tool.	Mathematical modeling is most useful when assessing the impact of theoretical interventions on immunity gaps. It can be particularly useful when there are known limitations to the data (e.g. coverage estimates are inaccurate) or in order to account for multiple factors and thus build some assumptions into the estimates.

## Annex C: Stepwise framework in algorithm format

