

Report for the SAGE Working Group on Measles and Rubella

17–19 April 2018, Geneva

The Roadmap to Immunity

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BACKGROUND

All six World Health Organization (WHO) regions have established a measles elimination goal for 2020 at the latest¹ and three WHO regions have a rubella elimination goal². A standardized method to classify countries has been proposed for global and regional use to document countries' progress toward measles and rubella elimination.³ Categorizations are based on assessment against the five lines of evidence for documentation of the elimination of measles and rubella. The four proposed categories are: (1) endemic; (2) eliminated/interrupted but not verified; (3) eliminated and verified; and (4) re-established endemic transmission post-verification.⁴ Formal verification is provided by Regional Verification Commissions (RVCs). The country categorization should be used to develop tailored immunization and surveillance strategies to assist countries to attain and sustain measles and rubella elimination.⁵

In October 2017, SAGE reviewed and endorsed the four proposed categories for classifying countries as appropriate, providing a standardized approach to country classification, and encouraged their use by RVCs.⁶ SAGE noted that countries in the endemic category included countries at different levels of control and that further sub-categories should be explored to facilitate development and implementation of strategies to improve vaccine coverage and increase population immunity.

SAGE also reviewed data on the level of immunity necessary for achieving and sustaining measles elimination.⁷ SAGE reiterated that achieving “at least 95% immunity across all age groups, geographical regions, and population subgroups.... should remain the primary strategy of measles elimination” and that “countries should attempt to identify specific age groups and subpopulations with immunity gaps, i.e. those with below 95% immunity, and offer vaccination accordingly.” However, they also acknowledged that “there is no perfect measure of immunity” and asked the SAGE Measles and Rubella Working Group to develop guidance on estimating age-specific immunity gaps.

It was suggested that a “Roadmap to Immunity” be developed, similar to the roadmap for elimination standard surveillance published in 2017.⁸ Two integral parts of progressing along the spectrum from control to elimination which entails (1) understanding the general epidemiologic profile of a country in regards to MR elimination and (2) identifying and estimating the scale of immunity gaps within a country. Furthermore, countries need to understand the strengths and weaknesses of possible data sources and methodologies used to understand their epidemiologic profiles and assess immunity gaps. With an understanding of a country’s epidemiology and immunity gaps, countries can best target their interventions to raise population immunity and close gaps.

METHODS

Roadmap to Immunity

To develop the roadmap to immunity, we reviewed existing recommendations and received expert opinions on the most pertinent activities for assessing a country’s immunity profile and determining priority activities for control/elimination. The activities identified were:

- 1- Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity
- 2- Using data sources and methodologies to estimate immunity gaps
- 3- Applying specific interventions to address specific immunity gaps

All of these activities should be conducted with a commitment to Continuous Quality Improvement (CQI). CQI is a philosophy that states that health care implementers should continue to assess how they are doing and how they could be performing better. It emphasizes a cyclical process, with repeated assessments of clinical and programmatic activities. Based on this philosophy, we recommend that all three activities are conducted through a CQI framework for ongoing identification of immunity gaps, taking measures to address them, reviewing progress and re-assessment of immunity gaps (Figure).

Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity

To assist countries to determine the most appropriate activities to increase population immunity, we proposed sub-categories for endemic countries based on their overall epidemiologic profiles for measles and rubella. For countries that have not introduced RCV, there is another specific sub-category. Each of these epidemiologic profiles is reflective of underlying population immunity, and consideration of the epidemiologic profile together with the characteristics of outbreaks provides direction as to the immunity gaps that require filling. In approaching these immunity gaps it is essential to consider program capacity. Based on these characteristics, we outlined each sub-category's priorities for control and elimination through routine immunization system strengthening and supplementary immunization activities (SIAs). Finally, we discussed the data sources and analytic methodologies that are likely to be most useful for further assessing the immunity gaps for each category. It should be emphasized that this is not a rigid grid but rather a spectrum both across and within categories. As such, few quantitative cut-offs (e.g. >XX%) were used to recognize that each country's situation is unique.

Methods for estimating immunity gaps for countries at different levels of measles and rubella control/elimination

To help countries to describe immunity gaps using data and methodologies that are likely to be most useful to them given their position on the elimination spectrum, we assessed several methods of estimating immunity gaps based on evidence in the literature. We reviewed peer-reviewed and grey literature for reports that discussed and utilized the following data sources and analytic methods/tools for estimating immunity gaps: 1) case-based surveillance data, 2) outbreak investigations, 3) historical coverage data (administrative and WUENIC), 4) population coverage surveys (including post-campaign, Multiple Indicator Cluster Surveys [MICS], Demographic and Health Surveys [DHS], etc.), 5) serosurveys, 6) WHO Measles Strategic Planning (MSP) tool and other excel-based tools, 7) data triangulation, and 8) mathematical modeling.

To identify evidence for the application of these methods for estimating immunity gaps, we used the following:

1. Internet search of relevant guidelines and other documents on the websites of the WHO headquarters and regional offices
2. Requesting relevant materials from the measles and rubella focal persons at each of the WHO regional offices
3. Review of manuscripts generated from a PubMed search using the search terms (*measles OR rubella*) AND (*"immunity profile" OR "susceptibility" OR "herd immunity" OR "immunity gaps"*)
4. Targeted PubMed searches for additional manuscripts describing methods for estimating immunity gaps that were underrepresented in the first PubMed search results (e.g., *"rubella outbreak"*)

In two summary tables, we provided a brief description and described the strengths and limitations of each of the data sources (Table 2a) and analytic methods and tools (Table 2b). We considered data quality, guidance that can be obtained, and implementation issues such as cost and feasibility. We also considered the best use for each data source and method. In Appendix 1, we provide examples of prior use of each data source and analytic method to estimate immunity gaps, and where available, policy and practice outcomes that resulted from estimation of immunity gaps.

Interventions to assess specific immunity gaps

Using existing guidelines and expert opinion, we created a list of immediate actions and long-term activities to address immunity gaps in specific age groups and populations.

RESULTS

Utilizing country-level epidemiologic profiles to identify and prioritize activities to increase population immunity

In discussions of appropriate interventions to raise coverage in countries where measles and rubella is endemic, it was acknowledged that endemic countries have widely varying epidemiologic profiles, with different short-term control and elimination goals. Country-level epidemiologic profiles for endemic countries are stratified in Table 1. In order to assign a country to the correct stratum, a complete picture of the measles and rubella epidemiology is needed and should be based on all available sources of surveillance and coverage data. The table columns entitled “Population Immunity”, “Program Capacity” and “Outbreak Investigations” are meant to help identify characteristics that are typical of countries with the epidemiological profile described in the first column. Because each sub-category is a simplification, a spectrum between sub-categories and within sub-categories is to be expected, and a country may have characteristics that fall into more than one sub-category. The “Control/Elimination Priorities,” “Routine/System Interventions” and “SIAs” columns are provided to help countries prioritize activities. The “Tools to Assess Immunity Gaps” column will guide countries towards the most helpful tools to assess immunity gaps. It should be recognized that as a country approaches elimination, identification of remaining immunity gaps will likely require review of a wider range of data sources and a more intense level of scrutiny. Furthermore, immunity gaps will occur in increasingly focal population groups (e.g., smaller geographic areas, fewer birth cohorts, and/or smaller underserved populations).

Defining immunity gaps for countries at different levels of measles and rubella control/elimination

Tables 2a and 2b present an overview of the data sources and analytic methods for estimating measles and rubella immunity gaps. The Appendix complements the overview by highlighting several examples from the literature of the use of these tools and their

outcomes. We briefly describe each data source/method and provide one example below. Prior to using any of these methods, countries need to critically evaluate the quality of their collected data. This will greatly impact the accuracy of the data sources and analytic tools discussed below. In addition, while each data source is described separately, they should all be analyzed and considered in relation to each other, in order to provide the most complete epidemiologic profile of a country.

Data Sources

1. Case-based surveillance data: All confirmed cases (and a proportion of suspected cases) indicate people who were susceptible to disease, and highlight the susceptibility that exists even with high reported vaccination coverage. The ability to accurately estimate immunity gaps using case-based data depends on the quality and sensitivity of the surveillance system as well as the extent of virus circulation in the population. If surveillance sensitivity varies across the population, estimated immunity gap detection and description may be biased. Case-based surveillance is most useful to estimate immunity gaps in settings where there is virus circulation. Sensitive surveillance, even without any confirmed cases, will provide some information on immunity gaps if vaccination status is consistently collected for suspected cases. Case-based surveillance is recommended to be ongoing in all countries and its utility increases as the system achieves and maintains elimination-standard surveillance.

Example: Guris et al. analyzed case-based surveillance data from 1989-2001 to calculate measles incidence by age group in Turkey (Appendix 1).⁹ The majority (90%-95%) of measles cases were among children <15 years old in most years. Overall, the highest incidence was in children aged <1 year and 5-9 years. Turkey's Ministry of Health launched a comprehensive program for 2002-2010 targeting measles elimination, and called for a high-coverage ($\geq 95\%$) national mass vaccination campaign among all children aged 9 months to 14 years.

2. Outbreak investigations: Outbreak data can identify immunity gaps when characteristics of cases such as age and place of residence are systematically documented. Outbreak investigation data can be used in all settings, and can be helpful when high reported vaccination coverage suggests low population susceptibility. The accuracy of data provided depends on the sensitivity and quality of the outbreak investigation data, and if sensitivity varies by case characteristics (e.g. age group, geographic location, timing during the outbreak), estimates of the immunity profile may be biased. In countries that have eliminated or nearly-eliminated measles or rubella, outbreak investigations are very important to understand underlying issues that led to accumulation of susceptible persons in the population.

Example: Goodson et al. conducted an investigation of an outbreak in Dar es Salaam, Tanzania during 2006-2007 (Appendix 1).¹⁰ Cases peaked among individuals aged <2 years, 5-7 years, and 18-30 years. In response to the outbreak and based in part on the outbreak investigation, a sub-national campaign was conducted in 2006 in Dar es Salaam targeting children 6 months to 14 years, and a nationwide follow-up immunization campaign was conducted in 2008 targeting children 6 months to 10 years of age.

3. Historical coverage data (administrative and WUENIC): Administrative vaccination coverage data or WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) data can be used to estimate the proportion of each birth cohort that is immune based on vaccination with 1 or 2 doses of vaccine, adjusted for age-specific vaccine effectiveness. Alternatively, a simplified standard of 95% coverage with 2 doses can be used to classify a population as having sufficient immunity. However, these data do not account for immunity due to SIAs or natural infection and administrative coverage is often inaccurate. This is a particular problem for measles because the margins of error are so small. Coverage data can be used to estimate immunity gaps in countries in all categories on the elimination spectrum. It is most accurate, and thus most useful for estimating immunity gaps, in countries where disease incidence is low, and most people gain immunity through routine vaccination rather than through natural infection or SIAs. Every effort should be made to accurately record routine immunization doses administered.

Example: The WHO publishes annual reported coverage data and WUENIC estimates on their website each year. Looking at Ethiopia's MCV1 coverage from 2005-2016, administrative coverage has risen from ~60% to ~93% while WUENIC estimates have only reached ~70%. While the administrative coverage suggests they are approaching the target of 95%, the WUENIC estimates suggest that a large proportion of each birth cohort is still not receiving MCV1 vaccine and that high quality follow-up campaigns are needed along with strengthening of routine immunization.¹¹

4. Population coverage surveys (including post-campaign, MICS, DHS, etc.): Population-based coverage surveys are typically cluster surveys that target individuals in a specified age range. Data from population coverage surveys can be adjusted for vaccine effectiveness to estimate immunity among individuals of a specific age. Coverage surveys typically provide more accurate estimates than administrative data and can be used to validate SIA or routine immunization coverage. They can identify geographic gaps, if designed to provide estimates with sufficient precision at the district level or lower. Coverage surveys can collect detailed demographic data that may not be available from other sources, which can be useful to define sub-populations with immunity gaps. However, the accuracy of coverage survey data is contingent upon surveying a representative sample of the population. Coverage surveys are most useful to estimate vaccine coverage gaps in countries that have difficulty obtaining accurate administrative coverage data and/or lack immunization registries.

Example: Analysis of the 2013-2014 DHS in the Democratic Republic of Congo (DRC) shows vaccination coverage stratified by several demographic characteristics including sex, birth order, province, mother's education level, and socio-economic quintile (Appendix 1).¹² The DHS estimate for MCV1 for children aged 12-23 months was 71.6% (compared with official and WUENIC estimates for MCV1 in DRC in 2014 at 89% and 77%, respectively). The DHS results are probably a more accurate coverage estimate and show that a large proportion of the birth cohort evaluated is susceptible to measles. This suggests that a high quality follow-up campaign is needed along with strengthening of routine immunization.

5. Serosurveys: Serosurveys can provide a direct measurement of population immunity and can include individuals of all ages, as there is no need for records or recall of vaccination, although waning antibody levels may influence interpretation. The sampling frame should be designed to ensure that results are representative of the population in order to avoid biased estimates. Validated laboratory methods calibrated to WHO standards should be used. Because serosurveys are typically less granular than coverage surveys (due to intensive resource requirements), they may not identify immunity gaps in population sub-groups, especially marginalized sub-groups, unless the study is designed to over-sample such groups. Serosurveys are most useful when coverage data are unreliable. Although serosurveys can be conducted in countries of all classifications, careful consideration of the cost and availability of the technical expertise that can address sampling, laboratory, and data interpretations issues are needed before a decision to use a serosurvey.

Example: In a 2002 study from the region of Catalonia in Spain, representative samples of children and adults were used to estimate the seroprevalence of antibodies against measles, mumps, and rubella in children five years and older and adults of all ages (5-year age bands) (Appendix 1).¹³ Based on these data, the author recommended MMR vaccination for susceptible children aged 5-14 years and adolescents/young adults age 15-24, identified using pre-vaccination screening.

Analytic Tools and Methods

1. WHO MSP tool and other excel-based tools: The WHO MSP Tool facilitates analysis of national immunization and surveillance data and calculates a baseline immunity profile for a country's population age 0-20 years using routinely available data (MCV1 and MCV2 coverage data, SIA coverage, surveillance data, and age-specific population estimates). It is a simple Excel interface that is based on underlying statistical models that account for vaccine effectiveness, probability of infection, and case-fatality ratios. Other similar Excel-based tools have been developed that take into account protection from multiple sources: maternal antibodies, routine immunization, SIAs, etc. Accuracy of the results produced by the MSP and other tools depends on the quality of the data used; if coverage, population, or surveillance data are poor quality, the results will be inaccurate. The MSP and other similar tools are most useful for estimating immunity gaps in countries that have high quality coverage and surveillance data. This tool has been well accepted by countries in SEAR, though it requires some revision including the addition of dynamic calculation to reflect transmission patterns in countries that are close to elimination and expansion of the assessment beyond 20 birth cohorts.

Example: Simons et al. developed a baseline immunity profile for children aged 0-14 years in Kenya in 2008 generated by the MSP tool (Appendix 1).¹⁴ This takes into account their historical coverage, SIAs, population and surveillance data that was entered into the tool. It estimates that ~30% of children 3 years and younger were susceptible to measles, as these birth cohorts had not yet been exposed to an SIA. The estimated immunity in older cohorts

was close to 100%, with 60-70% of the children immune due to routine immunization and 30-40% protected by SIAs.

2. Data triangulation: Data triangulation is a process of reviewing existing data from multiple data sources, assessing the quality and external validity of the different sources, and comparing for concordance across data types that measure similar issues. For assessing gaps in immunity, all available sources of surveillance and coverage data should be reviewed. The methodology for triangulating data for purposes including estimation of immunity gaps has not been standardized. Countries in all classifications should use data triangulation to assess immunity gaps. Critically examining and comparing available data provides a more complete picture and understanding of the population immunity situation. As demonstrated in countries in the Americas, very few countries have perfect data for all indicators, but can still achieve and sustain elimination. Data gaps can be compensated for through good analysis of the data that are available as well as triangulation of different sources. In countries that have eliminated measles, their surveillance data may not contain confirmed cases, but surveillance indicators should still be evaluated while considering coverage estimates to identify potential gaps.

Example: Bhatnagar et al. triangulated all available administrative and coverage data in India, taking into account the reliability of each estimate and using methodology based on WUENIC methodology (Appendix 1).¹⁵ This included consideration of things that may have affected coverage like stock outs and a comparison of data across different vaccines to look for inconsistencies. Estimates of coverage for routine child immunization were generated for 17 states and then combined into a national estimate to provide both national and state-level estimates.

3. Mathematical modeling: Mathematical modeling can estimate age and geographic gaps in immunity using population-based disease transmission and susceptibility models. Mathematical models can be used in settings where there are not currently any cases, using historical data to estimate future patterns of disease, and 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. However, the quality of the estimated outputs from a model are only as good as the data that go into it and the assumptions that the model is based upon. It may be difficult for countries to conduct mathematical modeling in-country, since modeling requires statistical expertise and specialized mathematical modeling skills. Mathematical modeling is most useful when assessing the impact of theoretical interventions on immunity gaps, particularly when there are known limitations to the data (e.g. coverage estimates are inaccurate) or in order to account for multiple factors and build assumptions into the estimates.

Example: Takahashi et al. used generalized additive models and Demographic and Health Survey data to quantify spatial patterns of measles vaccination in ten contiguous countries in the African Great Lakes region during 2009-2014 (Appendix 1 posted on the SAGE website).¹⁶

The model shows that over 14 million children <5 years of age live in ‘cold spots’ where vaccine coverage is below the WHO target of 80%, and a total of 8–12 million children are unvaccinated. This clustering of low vaccination areas allows for pockets of susceptibility that could sustain circulation despite high overall coverage.

Interventions to assess specific immunity gaps identified

To achieve the regional and national goals, countries should identify specific immunity gaps and conduct corrective actions. After a country identifies its immunity gaps, it should review potential vaccination and surveillance options, taking into account the program capacity. Interventions to assess specific immunity gaps are shown in Table 3. For each population group we present immediate approaches to address the gap for a 2–5 year period as well as long term strategies to avoid the accumulation of susceptible persons in the population.

CONCLUSIONS

To achieve the GVAP and regional measles and rubella elimination goals, all countries should continue to repeatedly monitor and review case-based surveillance and immunity gaps using a CQI approach. A roadmap for elimination standard surveillance has been published¹⁷ and all countries should commit to achieving this quality of surveillance. Of equal importance is that all countries prevent the accumulation of further immunity gaps. The most effective way of achieving this is to ensure 95% or higher coverage with two doses of measles and rubella containing vaccine (MRCV) in each birth cohort.

In order to increase immunity levels to those needed for elimination, countries must first identify where immunity gaps exist in their populations. We presented here several methods that can be used to help identify immunity gaps, each of which is most useful in certain settings and has certain strengths and limitations. Countries should determine which method or set of methods to use in order to estimate immunity gaps based on the availability and quality of data, and based on their current status with regards to control/elimination of measles and rubella. All countries, regardless of their categorization, should continue to strengthen their health systems, improve their surveillance, and improve vaccination coverage systems to ensure high data quality.

Figure 1. Continuous Quality Improvement (CQI) framework for countries to assess immunity gaps.

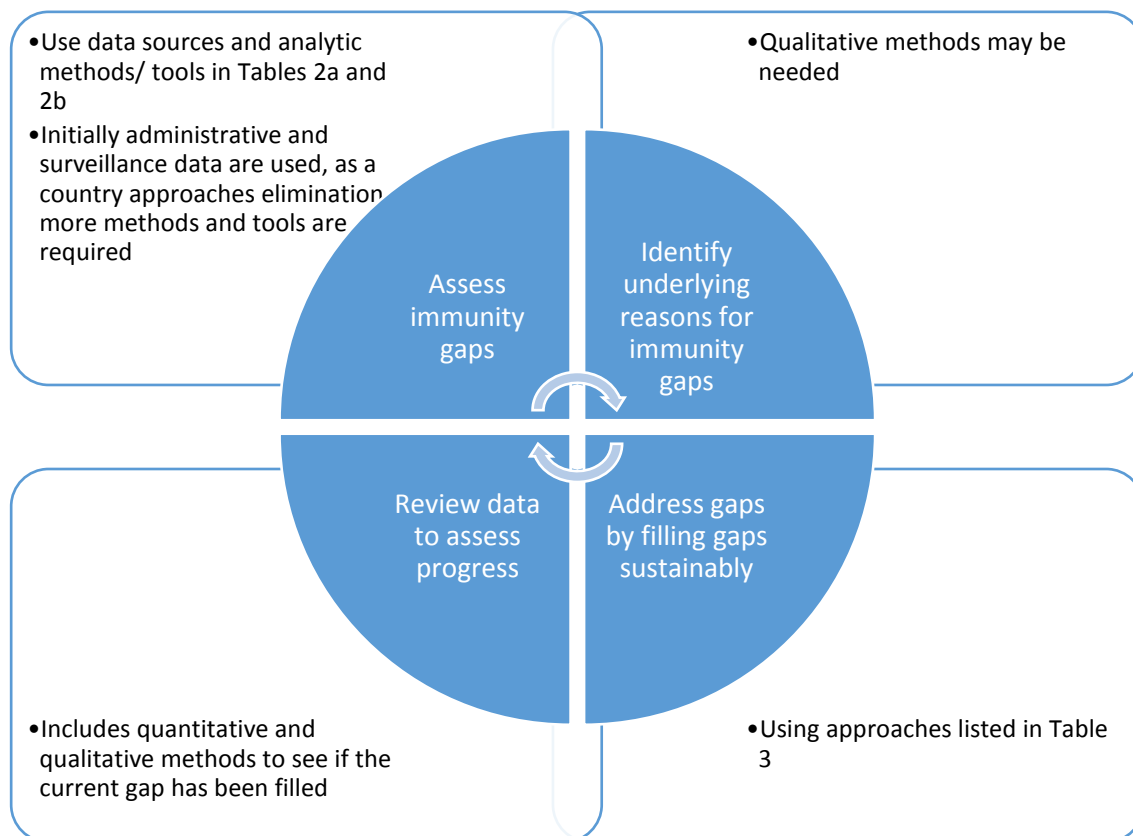


Table 1. Country-level epidemiologic profiles.

General Epidemiology of Country Based on Triangulation of Surveillance and Coverage Data (all sources of each)	General Characteristics of Countries in this Category (assume spectrum across and within each category)			Control/Elimination Priorities	Control Strategies (see Table 3)		Tools to Assess Immunity Gaps (see tables 2a and 2b)
	Population Immunity	Programme Capacity	Outbreak Investigations		Routine/System Interventions	SIAs	
Low incidence of measles/rubella. Irregular, infrequent outbreaks, temporally- (generally <12 months duration) or geographically-limited, predominantly adolescents/adults or children too young to be immunized.	High population immunity, particularly among children; however, may have age or geographic immunity gaps resulting in occasional outbreaks.	Consistent high coverage (e.g. ≥90%) with both doses of MRCV1. Good demonstrated capacity to conduct high-quality campaigns. Highly sensitive surveillance systems.	Outbreaks are infrequent and irregular. Each outbreak investigation is well conducted including looking for the source and documenting the end of transmission. Investigations provide valuable information on immunity gaps in the population.	Elimination: Increase routine coverage with both doses to at least 95%; actively look for age-specific, sub-population and geographic immunity gaps and address them so that outbreaks are quickly contained.	Increase MRCV1* and MRCV2# coverage to ≥95% in all districts/areas and maintain this level of coverage. Set up country policy and establish vaccination of HCWs if not in place. 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.	May not be needed if coverage with both MRCV1* and MRCV2# are greater than 90% unless an immunity gap is identified. In that situation, SIAs will likely be targeted to the identified gaps rather than nationwide follow-up campaigns.	Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments. Consider serosurveys or modeling to assess gaps that may be unidentified if there is very little circulating virus.
Regular outbreaks that are contained. Majority of cases in children <15 years.	Inadequate population immunity in children <5 years old; may have gaps in older age groups. Most older children have had opportunities for 2 doses	Suboptimal MRCV1* and MRCV2# coverage (e.g. 85 - 90%) ,either nationally or sub-nationally). MRCV2# may not be introduced. SIAs are of	Outbreak investigations provide additional information on immunity gaps.	Increase quality of routine services with aim to eventually decrease reliance on follow-up SIAs.	Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Consider PIRIs, more outreach sessions. Focus on strategies to increase coverage with both MRCV1* and MRCV2# to >95% so that regular SIAs will not be necessary.	Conduct follow-up SIAs, focusing strategies on reaching those not reached through routine immunization services. Generally the SIAs will be for children <5 years; consider wider age range SIAs where the epidemiologic data	Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments. Consider serosurveys if quality of available data is poor and

	through routine immunization and/or SIAs; most adults were either vaccinated or had prior infection.	adequate quality.			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. Gain political support.	indicate immunity gaps in children >5 years.	better information is needed on immunity gaps in order to target SIAs.
On-going, endemic transmission and regular large-scale, long duration outbreaks even shortly after SIAs. Majority of cases in children <5 years (as adults were either vaccinated or had prior infection).	Inadequate immunity in multiple age groups, most significant gaps in children <5 years old.	Long standing low MRCV1* coverage (e.g. < 85%). MRCV2# not introduced or very low coverage. Quality of SIAs may be inadequate.	Due to the large-scale outbreaks, outbreak investigations are inadequate.	Control: Address quality of SIAs to quickly raise overall population immunity while strengthening routine immunization services.	Strengthen routine immunization services (logistics, cold chain, demand, coverage, etc.). Consider PIRIs, more outreach sessions. Introduce MRCV2# if not introduced. 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. Gain political support.	Address quality of SIAs. Determine why children are being missed and address the problems. Conduct follow-up SIAs for children <5 years at regular intervals. Focus strategies on reaching those not reached through routine immunization. Where the epidemiologic data indicate immunity gaps in children >5 years old, national or subnational wide age range SIAs may be considered if effective strategies to reach the under- or un-vaccinated are in place.	Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments.

For RUBELLA: The rubella epidemiology is that of the pre-vaccine era with most cases occurring among children. Rubella outbreaks usually among children; CRS cases, particularly during rubella outbreaks.	Immunity due to natural infection; rubella vaccine not introduced into the national program.	Rubella outbreaks are frequent and may go undetected. Outbreaks may or may not be investigated.	Rubella outbreaks may or may not be investigated.	Set up basic structure for control.	Strengthen MR case-based surveillance; consider establishment of CRS surveillance and introduction of RCV. Strengthen routine immunization services.	Conduct RCV introductory catch-up SIA and then introduce RCV into the routine program as MR vaccine.	Triangulation of case-based surveillance data, vaccine coverage data (administrative, WUENIC, available coverage surveys), and outbreak assessments.
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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[†] (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; SIA = supplementary immunization activity; WUENIC = WHO-United Nations Children's Fund (UNICEF) coverage estimate.

Table 2a. Data sources for estimating immunity gaps.

	Case-Based Surveillance Data	Outbreak Investigations	Historical Coverage Data (Administrative and WUENIC)	Population Coverage Surveys (Including Post-Campaign, MICS, DHS, etc.)	Serosurveys
Description	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.	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.	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 <u>2</u> doses is often used to classify a specified population as having sufficient immunity.	Population-based surveys are typically cluster surveys such as WHO Vaccination Coverage Cluster Surveys, DHS, and 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.	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.
Strengths	<ul style="list-style-type: none"> Confirmed cases indicate actual susceptibility, and 	<ul style="list-style-type: none"> Shows where actual cases are occurring during an outbreak 	<ul style="list-style-type: none"> Data readily available Data is typically available for 	<ul style="list-style-type: none"> Obtain more accurate coverage estimates than administrative 	<ul style="list-style-type: none"> Serologic testing provides direct measurement of immunity

	<p>show where there are susceptible groups in the population</p> <ul style="list-style-type: none"> • Can be used to determine exposure status: imported and import-related cases • Highlights susceptibility that may not otherwise be evident due to high reported vaccination coverage • If a case-based surveillance system is already in place and maintained in a country, ongoing nationwide surveillance data should be readily available • Countries have ownership of the data 	<p>period</p> <ul style="list-style-type: none"> • 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 • 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 • 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 • Generates solid evidence for policy changes to improve vaccination service delivery and/or vaccine demand 	<p>many years, at multiple levels, often since vaccine introduction</p> <ul style="list-style-type: none"> • Countries have ownership of the data 	<p>data since survey data do not depend on poor quality data on doses administered and population estimates</p> <ul style="list-style-type: none"> • Can validate (or provide more accurate estimate) of SIA or routine immunization coverage • Less expensive and easier to implement than a serosurvey • Can collect data on communication channels and reasons for non-vaccination • Can collect detailed demographic data, not available from other sources 	<ul style="list-style-type: none"> • No need for vaccination records or population data • All ages can participate, as there is no need for records/recall of vaccination that may have happened many years prior
Limitations	<ul style="list-style-type: none"> • 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 • Sensitivity of surveillance may vary by age group, geographic location, population sub-groups, etc., thus biasing estimates of the immunity profile • Relies on passive surveillance 	<ul style="list-style-type: none"> • Can only be used when there is an outbreak • 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 surveillance system is overwhelmed as in the case of a large outbreak • Sensitivity of surveillance during an outbreak may vary by age group, geographic location, population sub-groups, timing of the outbreak, etc., thus 	<ul style="list-style-type: none"> • Does not account for protection from SIAs, catch-up vaccination, natural infection • Administrative coverage is often inaccurate due to inaccurate denominator data. Poorly documented numerator data can also affect estimates • WUENIC estimates are only available at a national level, hence sub-national gaps in immunity are not evident • WUENIC data are the best estimates of coverage, though their accuracy is unknown 	<ul style="list-style-type: none"> • Require technical/statistical expertise and detailed data on population settlements in order to select a representative sample • May not get representative sample of population if surveyors cannot access all selected settlements (especially applicable in countries with security concerns) • Household surveys are difficult to implement in some settings and some populations (e.g., dense cities, places where both 	<ul style="list-style-type: none"> • The sensitivity and specificity of the test used to detect measles or rubella IgG need to be taken into consideration • Waning antibodies may affect results in persons sampled many years after vaccination • Measles and rubella IgG testing does not distinguish between antibodies induced by vaccination versus those induced by natural infection • High cost: serosurveys have the same costs and technical needs as a coverage survey, plus the

	<p>data, the quality of which (including sensitivity) may decline as the incidence of disease declines</p> <ul style="list-style-type: none"> • 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 • Ability to accurately estimate immunity gaps using case-based data depends on the quality of the surveillance system • 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 	<p>biasing estimates of the immunity profile</p> <ul style="list-style-type: none"> • 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 • 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 • 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 • Quality of results depends on the quality of the investigation 	<ul style="list-style-type: none"> • Vaccine effectiveness may be lower than accepted estimates in areas with programmatic challenges • Quality of results depends on the quality of the data collection and reporting system 	<p>parents work away from home, places with older subjects that are typically away from home at school or work)</p> <ul style="list-style-type: none"> • Surveys are expensive and costs increase rapidly if sub-national estimates are desired • 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) • The accuracy of the assessment of children's vaccination status may depend on how many participants have written vaccination records available for review • 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) 	<p>costs of specimen collection, transport, storage and laboratory testing</p> <ul style="list-style-type: none"> • Potential for bias if sample not representative of the population. • 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 • If using samples collected for a purpose other than an intended vaccination serosurvey, the ethical implications of testing the samples need to be considered
Best Use of Data Source to Estimate Immunity Gaps	<p>Case-based surveillance is recommended to be ongoing in all countries. It can be useful to estimate immunity gaps for all countries; utility increases as the system achieves and maintains elimination standard surveillance standards.</p>	<p>In endemic countries, outbreak investigations are used to identify 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</p>	<p>Historical coverage should be monitored during all 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.</p>	<p>Most useful in countries that have difficulties obtaining accurate 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.</p>	<p>Serosurveys are most helpful when coverage 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.</p>

		issues that led to susceptible persons in the population.			
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Table 2b. Analytic methods and tools for estimating immunity gaps.

	WHO Measles Strategic Planning (MSP) Tool and Other Excel-Based Tools	Data Triangulation	Mathematical Modeling
Description	<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>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"> • 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? • 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? <p>Data should also be compared for concordance across different types of data, e.g.,</p> <ul style="list-style-type: none"> • Do outbreak data show that cases are arising in geographic areas with low or high coverage? Does the age distribution of cases align with the perceived levels of population immunity across age groups, based on historical coverage and coverage surveys? • Based on evaluating these and other aspects of the data, where do there appear to be immunity gaps in your population? • Comment: WUENIC estimates of vaccination coverage are developed by triangulating all available data sources on vaccination coverage in a country 	<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>
Strengths	<ul style="list-style-type: none"> • Uses underlying statistical models that take into account 	<ul style="list-style-type: none"> • Takes into account several data sources when evaluating a 	<ul style="list-style-type: none"> • Can combine several sources of data including vaccination

	<p>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</p> <ul style="list-style-type: none"> • Uses routinely available data • Pre-loaded with data for all countries through 2008 (only data since 2009 needs to be entered into tool) • Can be easily performed at the country level 	<p>public health issue</p> <ul style="list-style-type: none"> • Through comparison of data sources, the evaluator is encouraged to consider the strengths and limitations of each source • Uses readily available data; accepts and recognizes the limitations of each type of data 	<p>coverage, historical surveillance data, and others to model estimates of gaps in immunity and susceptibility</p> <ul style="list-style-type: none"> • Can use models for settings where there are not currently any cases, using historical data to estimate future patterns of disease • 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 • 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.
Limitations	<ul style="list-style-type: none"> • 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 • Difficult to account for phased and sub-national campaigns as well as outbreak response immunization • Assumes that vaccination through routine immunization and SIAs are independent of each other with regards to probability of a child being vaccinated • The underlying models are somewhat simplified compared to some other modeling strategies, and therefore may be less realistic • Developed for use at the national level. Separate profiles would need to be developed for subnational analysis 	<ul style="list-style-type: none"> • Dependent on the quality and generalizability of the data used (see limitations for data sources previously described) • No standard methodology has been developed to triangulate data from multiple data sources (surveillance, coverage, etc.) • Evaluation of different data sources can often only be done qualitatively, hence quantitative estimates are frequently based on 'expert opinion' and dependent on the skill and experience of the experts 	<ul style="list-style-type: none"> • 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 • The quality of the outputs from a model are only as good as the data • Models are based on assumptions that go into the model, which may or may not accurately reflect reality • 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
Best Use of Data Source to Estimate Immunity Gaps	<p>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.</p>	<p>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.</p>	<p>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.</p>

Table 3. Activities to address recognized/confirmed specific immunity gaps in general population or parts of the population.

Immunity Gap	Immediate Approach to Address Gap	Long-term Strategy to Avoid Accumulation of Susceptibles
Under 1	<ul style="list-style-type: none"> - Conduct intensive vaccination (or SIA) of children as young as 6 months (“zero” dose) as indicated in WHO published policy (e.g., outbreak). - Consider source of exposure and consider targeting that group (e.g., adults). 	<ul style="list-style-type: none"> - Implement strategies to improve the <u>timeliness</u> of MRCV1* vaccination in countries where vaccine is administered at 9-11 months of age.
Age 1 to 5	<ul style="list-style-type: none"> - Conduct high quality SIAs (nationally or sub-nationally, depending on the extent of the identified gap; consider school-/daycare-based campaigns/strategies). 	<ul style="list-style-type: none"> - Identify and address the underlying reasons for the immunity gap. - Strengthen routine MRCV1* and MRCV2# programs and improve coverage. - Ensure that MRCV1* will be given to children after 12 months of age, even if schedule calls for administration at 9 months. - Implement entry checks for daycares, kindergartens and similar institutions. - Implement strategies to avoid missed opportunities for vaccination, e.g., vaccination record checks every time a child visits a health center - Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services.
Children ≥5 and adolescents	<ul style="list-style-type: none"> - Conduct a high quality, wide-age range SIA (nationally or sub-nationally, depending on the extent of the identified gap; consider school-based campaigns/strategies). 	<ul style="list-style-type: none"> - Identify and address the underlying reasons for the immunity gap. - Improve MRCV2# coverage and timeliness. - Implement school entry checks for elementary, high schools and universities. - 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.
Adults	<ul style="list-style-type: none"> - Consider conducting SIA targeting the affected groups. - Make MRCV available free of charge to affected age groups, with priority given to persons that are unvaccinated or vaccinated with only one dose, but available to all regardless of vaccination status. 	<ul style="list-style-type: none"> - 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. - Offer vaccination at medical appointments, post-partum

		<p>care for women, etc.</p> <ul style="list-style-type: none"> - Offer vaccination before international travel.
Migrants	<ul style="list-style-type: none"> - Conduct a high quality SIA targeting migrants as a priority, but with extension to local susceptible populations, under the same condition and rules (strategies used to vaccinate migrants should not be discriminatory). - Offer vaccination through immigration services and migrants organizations/associations/communities. - Offer vaccinations services through the health system, regardless of the patients' residency status and legal/administrative regulations. 	<ul style="list-style-type: none"> - Identify and address the underlying reasons for the immunity gap among migrants. - Implement at work permit/visa-based vaccination program. - Establish long-term programs with immigration services and migrant organizations/associations/community. - 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. - Tailor social mobilization, advocacy and communication activities to increase demand and uptake of immunization services among migrants.
Refugees	<ul style="list-style-type: none"> - Provide vaccination at entry/in refugee camps. - Conduct SIA in refugee camps. - Offer vaccination services through the health system, regardless of the patients' residency status and legal/administrative regulations. 	<ul style="list-style-type: none"> - Establish systematic immunization activities in refugee camps. - Establish long-term programs with immigration services and migrant organizations/associations/community. - 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.
Populations not vaccinated due to lack of vaccination services (e.g., rural populations)	<ul style="list-style-type: none"> - Conduct periodic intensification of routine immunizations (PIRIs) (or mop-up activities for populations missed during a campaign). 	<ul style="list-style-type: none"> - Increase frequency of outreach services and social mobilization/demand-generating activities associated with the outreach. - Enhance social mobilization, advocacy and communication to increase demand and uptake of immunization services to ensure that people come for vaccination.
Populations not vaccinated due to "invisibility" to vaccination services (e.g., urban populations)	<ul style="list-style-type: none"> - Conduct SIAs in low coverage areas; consider many types of vaccination sites/mobile teams, e.g., markets, transportation centers, work places. - Increase social mobilization, advocacy and communication (targeting diverse age groups). 	<ul style="list-style-type: none"> - Register new inhabitants with health services and include in target population for routine immunization. - Increase social mobilization, advocacy and communication about vaccination services.
Populations not vaccinated due to vaccine hesitancy	<ul style="list-style-type: none"> - Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication 	<ul style="list-style-type: none"> - Identify and address the underlying reasons for vaccine hesitancy - Tailor social mobilization, advocacy and communication

	activities to increase uptake of immunization services, considering the unique local context - SIAs/ORI in surrounding communities to ensure high herd immunity in surrounding populations.	activities to increase uptake of immunization services, considering the unique local context
Populations not vaccinated due to stock-outs	- SIAs in areas where gaps occurred. - Strengthen follow-up services to ensure that the children that missed vaccination come back when the vaccine is in stock. - Ensure sustained confidence in health services/immunization.	- Address root cause that resulted in stock-out and prevent further episodes.
Any population identified due to an outbreak	- Adjust ORI to population affected (including all ages affected), e.g., geographic area, work place, university, ethnicity, religion, etc.	- Identify and address root cause of immunity gap. - Consider periodic SIAs targeted at this population if they are being missed by other vaccination activities. - Review all available information and sources to identify similar populations and address immunity gaps systematically.

*MRCV1 (or MCV1)

#MRCV2 (or MCV2)

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