Proceedings and Draft Recommendations from the Fifth Meeting of the SAGE Working Group on Measles and Rubella
3-4 September 2015, Geneva

Executive Summary

The 2014 Annual Report on the Global Vaccine Action Plan (GVAP) noted that while substantial progress has been made in reducing the burden of measles and rubella, the 2015 global measles control targets would not be achieved on time, and, except for the Americas, the regional measles and rubella elimination goals were off-track.

Reports on the status of measles elimination and rubella elimination were presented to the SAGE Decade of Vaccines Working Group at their meeting on 31 August 2015. Their assessment was similar to the 2014 GVAP report that concluded vaccination coverage was "*a very long way from the 95% in every district that will be required to eliminate measles". A huge amount of work and political commitment lies ahead if elimination goals are to be achieved…"*

With this background, the SAGE Measles Rubella Working Group met on 3-4 September to review progress and discuss refinements to existing immunization policies that would protect more individuals and increase population immunity. The specific objectives of their September 2015 meeting were:

1. to review most recent progress and challenges in worldwide efforts to control and eliminate measles and rubella and discuss the need for a mid-term review of the Global Measles and Rubella Strategic Plan, 2012-2020
2. to review the evidence to determine the epidemiological circumstances under which it should be recommended to provide a zero dose of MCV to infants <9 months of age
3. to review the evidence for recommendations to guide countries on how to use coverage, surveillance, seroprevalence and other sources of data to determine the target age range for a measles or measles-rubella supplementary immunization activities (SIAs) in order to interrupt endemic transmission of measles and rubella
4. to review the evidence to determine if HIV-infected children receiving HAART should be revaccinated against measles.

This report has 4 sections, one for each of the meeting objectives. Each section provides a summary of the information presented and puts forward conclusions and draft recommendations (only for objectives 2 and 4) for consideration by SAGE at their October 2015 meeting. The draft recommendations for administration of a zero dose of MCV to infants <9 months of age are presented on page 13. Draft recommendations for revaccination of HIV-infected children on HAART can be found on page 28. Work is ongoing to develop more operational guidance on determining the target age range for measles or measles-rubella SIAs.

1. Measles and Rubella Status Report

In 2010, the sixty-third World Health Assembly endorsed three global measles targets for 2015 as milestones towards global eradication of measles,[1] and in 2012, the World Health Assembly (WHA) endorsed the Global Vaccine Action Plan (GVAP) and its objective to eliminate measles in 4 WHO Regions and rubella in 2 WHO Regions by 2015 and eliminate measles and rubella in 5 WHO regions by 2020. Below is an update of the progress and challenges towards these milestones.

Between 2010 and 2014, global routine measles vaccine coverage remained at 85%[2] – well below the 2015 target of ≥90%. By region, three of the six WHO regions have sustained MCV1 coverage above 90% (Region of the Americas, European Region and Western Pacific Region), one region achieved coverage between 80 and 90% (South-East Asia Region) and two regions achieved coverage below 80% (African Region and Eastern Mediterranean Region). The number of Member States achieving the global MCV1 coverage target at the national level remained the same in 2014 when compared to 2010; 122 Member States achieved the ≥90% MCV1 national coverage target[3].

Since 2010, global reported measles incidence has decreased by 21% from 50.1 cases per million population in 2010 to 39.8 in 2014 with only one region (Region of the Americas) meeting the global 2015 milestone target of fewer than five cases per million population. During the same period, there was a decrease in the number of Member States (98 Member States in 2014 compared to 114 Member States in 2010) meeting the global 2015 incidence target.

Between 2000 and 2013, estimated measles deaths decreased by 75% (from 544 200 to 145 700) and all regions reported substantial reductions in estimated measles mortality. However, progress since 2010 has been too slow (from 69% mortality reduction in 2010 to 75% in 2013) making it highly unlikely that the target of a 95% mortality reduction can be achieved by the end of 2015.

In 2014, 154 (79%) Member States had introduced a second dose of MCV (compared to 136 (70%) in 2010) and MCV2 global coverage was 56% (compared to 40% in 2010). Among those 154 countries, 53 provide MCV2 to infants less than 2 years of age *and* have reported coverage

[1] The global milestones endorsed are to: 1) exceed 90% coverage with the first dose of MCV nationally and exceed 80% vaccination coverage in every district or equivalent administrative unit; 2) reduce annual measles incidence to fewer than five cases per million and maintain that level; 3) reduce measles mortality by 95% or more in comparison with 2000 estimates.

[2] data source: Joint Reporting Forms (JRFs) for disease incidence and WHO-UNICEF estimates of national immunization coverage (WUENIC) data for coverage rates

[3] It should be noted that the 90% MVC1 coverage target for 2015 is a milestone towards elimination. In order to achieve the regional elimination targets, vaccination coverage needs to be >95% for two doses of MCV administered through routine immunization or routine immunization and SIAs. To prevent measles outbreaks, this high level of coverage needs to be achieved uniformly across all districts and across people in all age groups born since the introduction of measles vaccine.

both for MCV1 and MCV2. In these 53 countries,[4] the difference between MCV1 and MCV2 reached 16% in 2014 (87% MCV1 compared to 71% MCV2). This highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and the inability to interrupt measles virus transmission.

In decreasing order, the following six large Member States had the highest number of susceptible infants in 2014 and accounted for more than two-thirds of the measles mortality burden in 2013: India, Nigeria, Pakistan, Indonesia, Ethiopia and Democratic Republic of the Congo. Measles disease is an indicator of weaknesses and gaps in the immunization and health systems. Indeed, these six countries are characterised by weak health systems (low MCV1 coverage, low density of nursing and midwifery personnel per 10 000 population, poor data quality, etc.) and this highlights the importance of strengthening health systems in order to achieve higher immunization coverage and optimise child health programmes.

As of December 2014, 140 (72%) Member States had introduced Rubella containing vaccines (RCV), a 49% (46 countries) increase from 2000. Of the 54 Member States that had not introduced RCV into their routine immunization programme, 42 (78%) are eligible for GAVI Alliance support. Average coverage globally has gradually increased from 41% in 2010 to 46% in 2014. However, it varies from 12% in the South-East Asia Region to 94% in the European Region. In 2014, an additional three Member States introduced rubella vaccine in their routine programme and introduction of rubella vaccine is ongoing in six Member States in 2015.

The global incidence of rubella has decreased from 14 per million population in 2012 (reported by 176 (91%) of member states) to 4.8 per million population in 2014 (reported by 161 (84%) of Member States). While this suggests progress, it is hard to interpret because the proportion of Member States reporting rubella cases has also declined. The same trend can be seen with Congenital rubella syndrome (CRS) reporting. In total 111 (57%) Member States reported CRS incidence in 2014 (4.32 per 100,000 live births) compared with 130 (67%) in 2012 (2.01 per 100,000 live births). The very low reported incidence is probably a reflection of very limited or non-existent CRS surveillance systems outside the Americas and a few other Member States.

Many countries regularly supplement routine immunization efforts through the use of supplementary immunization activities (SIAs). Approximately 197 million children in 33 Member States were vaccinated during SIAs with measles-containing vaccines in 2013 and an additional 215 million children in 28 Member States in 2014. Among 34 countries that conducted SIAs between 2012 and 2014 and that conducted a coverage evaluation survey of the SIA, less than half (16 Member States) were able to reach the target of 95% national coverage.

The Region of the Americas achieved measles elimination in 2002 and sustained the elimination for more than 10 years. The reestablishment of endemic measles transmission in Brazil in 2014 highlights the constant risk of spread from importations, especially in communities with low vaccination coverage. In 2014, more than 80% of measles cases in Brazil, Canada and the

[4] Countries that had introduced MCV2 in 2014 were excluded from this comparison,

United States were not vaccinated and, as a whole, the region has witnessed a decline in routine MCV1 coverage since 2012 with heterogeneous coverage at the subnational level where many municipalities have less than 80% coverage. Experience in the Americas indicates that maintaining measles elimination may be more challenging than achieving it because of the problems of complacency, hesitancy, declining routine coverage, decreasing quality of surveillance and competing public health priorities[5]. The Region achieved its 2010 rubella elimination goal in 2009 and very few cases of rubella and CRS have been reported in the region since then. The Region has the longest standing regional Verification Commission (RVC) called the International Expert Committee (IEC). As of December 2014, 98% of its Member States were verified as having achieved measles elimination. The IEC awaits interruption of measles transmission in Brazil and fulfilment of verification criteria by an external team, to declare the elimination of measles in the Americas. In 2015, the region was verified by the IEC as having eliminated rubella and CRS (table 1).

In the African Region many countries continued to experience measles outbreaks in 2014, with large outbreaks occurring in Angola, Ethiopia, Democratic Republic of the Congo, Nigeria and South Sudan. Outbreaks are mainly the result of stagnating coverage levels, with MCV2 coverage lagging behind MCV1 coverage, and poor quality of SIAs in many countries. Funding gaps also led to countries limiting the age ranges covered by SIAs despite a wider age range being indicated, and delaying MCV2 and RCV introduction owing to uncertainty about future financial commitments. The African Region does not have a rubella control or elimination target and, in 2014, reported the highest incidence of rubella of all WHO regions. This is not surprising given the low uptake of RCV in the region. By the end of 2014, seven (15%) countries had introduced RCV. Of these, four countries are GAVI eligible. The Region has not yet established a RVC.

The Eastern Mediterranean Region has seen a decline in reported measles cases since 2012. However in 2013- 2014, measles outbreaks occurred in Afghanistan, Pakistan, Somalia, Sudan, Yemen and in the Syrian Arab Republic and neighbouring countries hosting Syrian refugees. The majority of the reported measles outbreaks in the Region affect children under 10 years of age, indicating poor implementation of routine vaccination and poor quality of SIAs. In addition, the deteriorating security situation, and/or inadequate funds hamper adequate implementation of elimination strategies. Although the Region has not yet set a rubella elimination goal, 13 countries (60%) have set a national target for rubella/CRS elimination and 12 countries are now implementing CRS surveillance. In 2014, 2945 confirmed cases of rubella were reported by the countries of the Region, the majority of these (95%) were reported from four countries[6] which had not yet introduced RCV. So far, only one of the six GAVI-eligible countries (i.e. Yemen) has benefited from GAVI support to conduct SIAs with RCV. Although no RVC has yet been established, National verification Commissions (NVC) were established in 9 of 21 Member States. Three countries in the region (Bahrain, Oman and Palestine) are ready for verification of

[5] Ad-hoc Meeting of the International Expert Committee: Paving the road for the regional verification process April 22-23, 2015. PAHO, Washington DC

[6] Afghanistan, Pakistan, Sudan and Yemen

measles elimination, as they have reported zero cases for the past three years in the presence of a nationwide measles case-based surveillance and high coverage with both MCV1 and MCV2.

Following the establishment in 2013 of a measles elimination and rubella/CRS control target of 2020 in the South-East Asia Region, all countries have developed national plans of action to achieve these goals. By the end of 2014, regional coverage with MCV1 had increased to 84% and MCV2 to 59%. However, measles continued to circulate widely in most countries of the Region primarily due to underutilization of measles vaccine. Of the 40 625 measles cases reported in the region in 2014, India continued to report the most cases, followed by Indonesia, Sri Lanka and Nepal. Six of the 11 countries in Region had introduced RCV by the end of 2014, 2 countries introduced RCV in 2015, and the remaining 3 (accounting for 87% of children under 1 year of age in the region) have committed to introducing the vaccine in the next few years. The majority of rubella cases reported from the region in 2014 were reported from India followed by Indonesia and Nepal. CRS surveillance is routinely conducted in three countries in the region, Bangladesh, Nepal and Sri Lanka. The remaining countries in the region have agreed in principle to establish sentinel surveillance for CRS. There is no measles RVC in the Region yet however, it is likely to be established in 2015.

The European Region reported the lowest level of measles incidence since 2010 with 50% fewer measles cases reported in 2014 (14 020) than in 2013 (26 385). However, in 2014 outbreaks occurred in Bosnia and Herzegovina, Georgia, Italy, Russian Federation and Ukraine with the majority of the reported cases (78%) being either unvaccinated or of unknown vaccination status and more than half of those affected were 15 years of age or older. All 53 Member States in the Region use the combined measles, mumps and rubella (MMR) vaccine (except for Tajikistan that uses combined measles-rubella (MR) vaccine) in a two-dose schedule. Based on JRF data, the number of rubella cases reported in the region dropped by 98% between 2013 (39614) and 2014 (640). However, only 19 countries in the Region reported rubella cases in the 2015 JRF. Most of the cases occurred in Poland even though no cases were reported in their JRF. In the Region, 50 of 53 Member States have established NVCs and at the RVC meeting in November 2014, 22 (41%) and 23 (43%) of the Member States were verified to have interrupted endemic measles and rubella transmission, respectively (table 1).

Measles incidence (per 1 million population) in the Western Pacific Region increased from 5.9 in 2012 to 17.2 in 2013 and 70.6 in 2014. This is largely the result of a resurgence of transmission in endemic countries (China and the Philippines) and outbreaks following importation in countries with a period of low or no documented transmission (e.g. Papua New Guinea and Viet Nam). The region is witnessing increased incidence of measles among people outside the target group of current immunization strategies for measles elimination (i.e. infants aged <8 months, adolescents and adults). In 2014, the Regional Committee endorsed a regional rubella elimination goal and a 2020 target date will be discussed by Member States at the 2015 Regional Committee meeting. The number of reported rubella cases has been declining in the Region since 2011 (from 76 022 in 2011 to 12 814 in 2014) with the majority of cases being reported from China and Japan. Reported CRS cases have also declined in the region (44 in

2013 and 12 in 2014) with most cases being reported from China. CRS surveillance remains weak in some countries in the region. At the 2014 Regional RVC meeting in 2014, Australia, Macao (China), Mongolia and Republic of Korea were verified as having achieved measles elimination based on a verification-standard epidemiological surveillance system supported by accredited laboratories. Three additional countries were included in 2015: Brunei Darussalam, Cambodia and Japan.

Conclusions

1. Measles remain an important cause of mortality among children. For example, from 2000 to 2008, the decrease in measles mortality has accounted for 24% of the overall decrease in childhood mortality[7]. Continued efforts to reach the measles mortality reduction targets will be an important contributing factor towards achieving Sustainable Development Goal 3.2[8]
2. Although in 2014 some improvement was seen in MCV2 immunization coverage and a small reduction was reported in measles incidence (compared to 2010), based on current trends and programme performance, the 2015 global milestone targets will not be achieved.
3. To achieve the 2015 global measles incidence and mortality reduction milestone targets, it is essential to strengthen immunization systems as a whole in the six Member States with the highest measles disease burden. A strategic cross-cutting approach by all immunization stakeholders is needed in these countries to address the combined challenges of lack of health infrastructure and human resources as well as civil conflict in some areas.
4. Measles is a highly infectious disease, and its elimination requires very high and homogeneous population immunity and a high-quality surveillance system. Without a robust routine programme, elimination is very difficult to achieve and cannot be sustained. For Member States that are now at <90% coverage nationally, reaching ≥95% coverage will require substantial additional investment over a sustained period. The gap between MCV1 and MCV2 coverage highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and ongoing measles transmission.
5. Rubella and CRS surveillance systems are weak and cases remain underreported, particularly in Member States that have not yet introduced RCV and/or do not have rubella control or elimination goals. Hence, global rubella and CRS surveillance data do not reflect the true burden of these diseases. Failure to fully integrate prevention of rubella and CRS with measles elimination activities represents a major missed opportunity for immunization.
6. Except for the Americas, the WHO regions are not on track to achieve measles and rubella elimination. Substantially greater commitment and investment by Member States and the global immunization community will be required to achieve the GVAP goal of measles and rubella elimination in five WHO regions by 2020.
7. Financial support from the GAVI Alliance together with the leadership, coordination and technical expertise from the Measles & Rubella Initiative (M&RI), provide an opportunity for Member States and regions to accelerate progress in rubella control and CRS prevention.

[7] Van den Ent et al. Measles Mortality Reduction Substantially Contributes to Lower Under-Five Mortality d JID 2011:204 (Suppl 1) 18-23.

[8] The SDG 3.2: By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births

Table 1: Progress towards measles and rubella elimination, by WHO region (as of 31 December 2014)

WHO region	Target year for measles/ rubella elimination in region	RVC established	Regional measles elimination verification report provided in 2015 by RVC for 2013/ 2014 data	Member States that have established an NVC n (% of total)	Established NVCs that submitted annual status reports[a] n (% of total)	Member States that were verified free of endemic measles based on 2013 reporting n (% of total)[b]	Member States that were verified free of endemic rubella based on 2013 reporting n (% of total)
African Region	2020	No	No	Unknown	Not applicable	Not applicable	Not applicable
Region of the Americas	2000	Yes	Verification reports sent in 2013. No need to send updates in 2014	24 (100%)	Reports not submitted on annual basis	43/44 (98%)	44/44 (100%)
Eastern Mediterranean Region	2015	Yes	No	9	Not applicable	Not applicable	Not applicable
European Region	2015	Yes	Yes (for2013)	50 (94%)	46 (87%)	22 (41%)[c]	23 (43%)
South-East Asia Region	2020	No	No	Unknown	Not applicable	Not applicable	Not applicable
Western Pacific Region	2012	Yes	Yes (for 2014)	17[d] (100%)	17 (100%)[d]	3 (11%)	Not applicable

a Percentage is out of the total number of established NVCs, not the total number of Member States. Note that a total of 46 reports were submitted to the European RVC. Percentage is based on Member States submitting reports in time for RVC review in October 2013.

b Percentage is out of the total number of Member States, and not the total number of established NVCs.

c These 22 countries were not verified as having been free of endemic measles for 36 months or longer, but were documented to have interrupted endemic measles transmission in 2013 (see Table 5).

d 13 Pacific island countries formed one Joint Subregional Verification Committee (they are: Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Samoa, Solomon Islands, Tonga, Tuvalu and Vanuatu). China, Hong Kong SAR and China, Macao SAR established their own Committees in addition to the Chinese NVC. So there are a total of 17 NVCs for 27 Member States in the Western Pacific Region

2. Under what epidemiological circumstances is it recommended to provide a zero dose of MCV to infants <9 months of age?

Background

Recent measles outbreaks have manifest a bi-modal age distribution with an increased proportion of cases either too young to receive their scheduled first dose of MCV or in adolescents and young adults who are not usually targeted for vaccination. Recent examples of outbreaks with a high proportion of measles cases among infants include China, Mongolia, Sri Lanka, and Papua New Guinea.

In response to these outbreaks countries have recommended, or wanted to recommend, that infants at risk receive a dose of measles containing vaccine starting at 6 months of age. However, neither the current measles (2009) nor the current mumps (2007) vaccines position papers recommend vaccine use at a younger age during outbreaks. In contrast, the 2011 rubella vaccines position paper does recommend use of rubella containing vaccine (RCV) starting at 6 months of age during measles outbreaks. In addition, most manufacturer package inserts provide indications for measles (M) and MMR vaccine starting at age 9 months, however the indication for use of MMR vaccine manufactured by Serum Institute of India is from 12 months to 10 years. Hence, there is need for standardized global recommendations on use of MCVs (M, MR, MMR) under the age of 9 months that will enable countries to provide earlier protection to infants at risk of measles during outbreaks and for other specific indications.

Current recommendations on use of MCVs <9 months of age

The 2009 measles position paper[9] recommends that all national immunization programmes should provide children with 2 doses of MCV delivered through routine services and/or periodically through supplemental immunization activities. Where risk of measles mortality among infants remains high, the first dose of MCV (MCV1) should be administered at 9 months of age. In countries with low risk of measles infection among infants (i.e., near elimination), MCV1 can be administered at or after 12 months, because higher sero-conversion rates are achieved at 12 months. Increasing the age of administration of MCV1 from 9 months to 12 months represents a rational and desirable policy change. Before increasing age of MCV1, policy-makers should review local measles epidemiology and programmatic data on vaccination.

The 2011 Rubella Position Paper[10] recommends that RCVs: be administered at age 12–15 months, but may be administered to children aged ≥9–11 months and to older children, adolescents and adults. In most countries, rubella vaccine is given as MR or MMR, and the age of administration follows the schedule for measles. Thus, the first dose is usually given 9 months or 12–15 months and a second dose at 15–18 months or 4–6 years. During outbreaks of measles, RCVs may be administered to infants as young as 6 months. Because of the possibility of lower seroconversion, the dose administered at 6 months should not be counted as a valid dose, and the child should be vaccinated with subsequent dose(s) of RCVs according to the usual national immunization schedule.

[9] WHO. Measles vaccines: WHO position paper. Weekly epidemiological record, 2009. 35:84, 349-360.
[10] WHO. Rubella vaccines: WHO position paper. Weekly epidemiological record, 2011. 29:86, 301-316.

The 2007 Mumps Position Paper[11] recommends that the first dose of the mumps vaccine (monovalent or MMR) be given at the age of 12–18 months. For this reason, countries planning to add mumps vaccine should first reduce measles transmission to low levels to enable them to increase the age of administration of the first dose of measles vaccine to 12 months before considering adding mumps vaccine to their schedule.

At their November 2013[12] meeting, SAGE recommended that in countries using a two-dose schedule of MCV, both doses should be the same formulation of M, MR or MMR; that is, the same vaccine should be used for both doses irrespective of the age of administration of the first dose.

The 2009 WHO guidelines on Response to Measles Outbreaks in Measles Mortality Reduction Settings[13], recommend that as soon as a measles outbreak is suspected, all children six to 59 months of age (or other target age group determined by the local disease epidemiology) presenting to a health facility or an outreach vaccination site without a history of measles vaccination (either written or verbal), should be vaccinated. Children receiving measles vaccine before the age of nine months must be revaccinated after the age of nine months (with at least a one-month interval between the doses).

The 2012 WHO International Travel and Health[14] recommends that for infants travelling to countries experiencing extensive measles transmission, a dose of vaccine may be given as early as 6 months of age. However, children who receive the first dose between 6 and 8 months of age should subsequently receive the two conventional doses according to the national schedule.

WHO Regional recommendations for MCV administration under 9 months emphasize use in outbreak settings, humanitarian emergencies and for travellers to endemic areas. They are summarized below:

WHO Regional recommendations for use of MCV at <9 months
Africa: Outbreaks: M ≥6 months; Preventive M SIAs: 6-59 months
Americas: Outbreaks: MCV0 at 6-11 months
Eastern Mediterranean: Outbreaks: MCV0 at 6 months
Europe: Outbreaks: MCV0 at 6 months
SE Asia: Emergencies or outbreaks: Supplementary M dose at 6 months
Western Pacific: Outbreaks or travellers to endemic areas: MCV0 at 6 months

[11] WHO. Mumps vaccines. WHO position paper. 2007. Weekly epidemiological record, 2009. 7:82, 49-60.
[12] WHO. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013– Conclusions and recommendations. Weekly epidemiological record, 2014. 1:89, 1-20.
[13] WHO. Response to Measles Outbreaks in Measles Mortality Reduction Settings. WHO/IVB/09.03
[14] WHO. International Travel and Health. Vaccine Preventable Diseases Update, 2014 ; Ch 6, pg 25.

Systematic review & meta-analysis of the safety, immunogenicity and effectiveness of measles vaccine administered to children <9 months of age

A comprehensive systematic review and meta-analysis of measles containing vaccines administered to children <9 months of age was conducted by the National Institute for Public Health and the Environment (RIVM) in the Netherlands[15]. The authors concluded that humoral immunogenicity depends on age of MCV1, as well as on the vaccine strain and presence of maternal antibodies. In meta-analyses of 20 studies meeting inclusion criteria, the age-specific seroconversion proportions were: 4 months - 50%; 5 months - 67%; 6 months – 76%; 7 months – 72%; 8 months – 85% (see figure below).

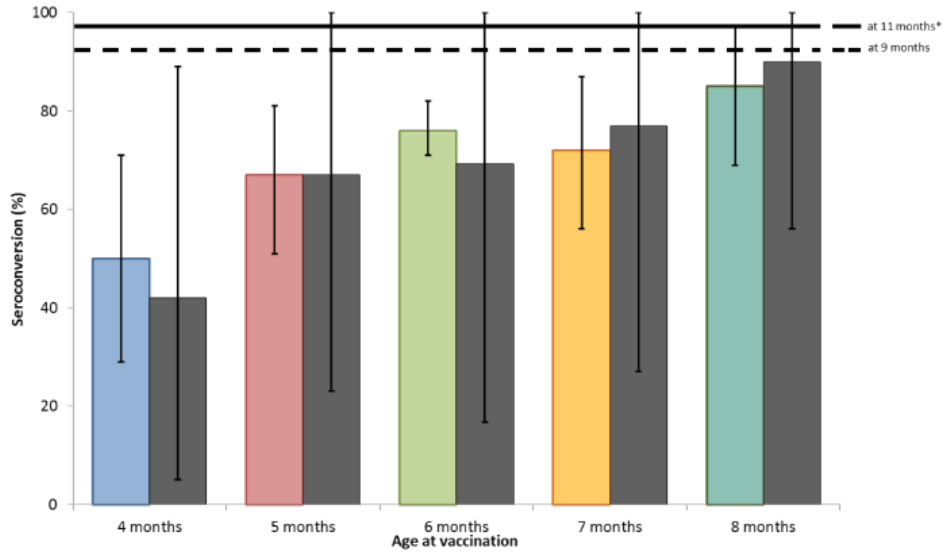


Figure 1. Proportion seroconverted by age MCV1 (4-8 months), pooled estimates derived from 20 studies (coloured blocks) and the proportion seroconverted by age of MCV1 (4-8 months) from a previous review (grey blocks).[16] Error bars present 95% confidence intervals. * The horizontal lines represent the median proportion of infants responding to MCV1 at 9 months (dashed line) and 11 months (filled line).[15]

Seroconversion rates <9 months of age are lower than the reference values of 92% and 98% for MCV1 at 9 months and 11 months, respectively. Seroconversion rates depended on measles strain used in the vaccine formulation, with Edmonston-Zagreb Mexico having the highest sero-conversion rate (95% at 6 months; (95% CI 92-97%)). Limited data on head-to-head comparisons found significantly higher seroconversion rates after vaccination with Edmonston-Zagreb compared to Schwarz (difference: 18%, (95% CI 3-34%)). Substantially lower geometric mean titres (GMT) of anti-measles IgG measured by the plaque reduction neutralization test (PRNT) were found comparing infants <9 months (283 mIU/ml) to infants ≥9 months (615 mIU/ml). The pooled estimate of vaccine effectiveness (VE) against clinical measles after MCV1 <9 months was 72%, compared to a VE of 77% between 9-11 months and 92% ≥12 months estimated in a previous review.[17] The current review found a larger

[15] L. Nic Lochlainn, N. van der Maas, B. de Gier, N. Rots, R. van Binnendijk, H. de Melker, S. Hahné. Measles vaccination below 9 months of age: Systematic literature review of effects and safety (available to SAGE members as a background document on the web)
[16] The immunological basis for immunization series. Module 13: Measles. 2008.
[17] Uzicanin and Zimmerman. Field effectiveness of live attenuated measles-containing vaccines: A review of published literature. JID 2011:204.

difference in VEs between MCV1 given at <9 months versus MCV1 given at ≥9 months of 18% (95% CI 15-20%) when considering within study comparisons only.

Limited evidence suggests avidity of measles specific antibodies to be significantly lower after MCV1 at 6 months compared to 9 and 12 months of age, whilst T cell proliferation was not dependent on age at MCV1. Regarding duration of immunity, one of three studies found significantly faster waning after MCV1 <9 months. Regarding blunting of the immune response to subsequent doses of MCV, early MCV1 was not found to affect seropositivity rates after MCV2. Limited evidence suggested avidity to be lower after MCV2 when MCV1 was given <9 months of age. Three studies reported GMTs after MCV2 with MCV1 administered <9 months versus MCV1 ⩾9 months. GMTs were lower after a two dose MCV schedule starting <9 months compared to MCV1 ⩾9 months of age. However, this difference was significant in only one of the three studies. No evidence of blunting was found considering VE. The pooled VE of two studies for a two dose schedule with MCV1 <9m was 93%, whilst the reference VE for two doses with MCV1 ≥9 months was 94%[16].

Regarding adverse events, fever after MCV1 occurred more often in infants <9 months of age than in infants aged 9 months or older, but in the absence of studies with control groups, it is impossible to know whether this is attributable to vaccination or to higher age-specific background rates. No reports of serious adverse events were found for infants given MCV1 <9 months, although this observation is limited by a small sample size.

Overall, the strength of the evidence from the review was limited by the nature of the study designs, which were mostly observational, as well as the limited comparability of the various laboratory assays used. However, the available information suggests that an early (<9 months) dose of MCV is effective and safe, although not as effective as a first dose at an older age (≥9 months).

Is there blunting of the immune response following MCV given at <9 months?
A review of the literature[18] showed a high prevalence of seropositivity following an early two-dose schedule with the first dose given at <9 months and no evidence of "immunological tolerance" – that is the non-reactivity of the immune system to an antigen as a consequence of specific immunologic mechanisms by which auto-reactive B and/or T cells are either deleted or rendered anergic. However, some evidence did exist for lower antibody concentrations and avidity, but not T cell proliferation, in children who received MCV1 younger than 9 months of age, which persisted after receipt of MCV2. The likely biological mechanism for this phenomenon is the presence of pre-existing neutralizing antibodies that impede replication of vaccine virus. In one VE study conducted during an outbreak in Niger, VE among those vaccinated at 9 months (95%) was similar to VE for those vaccinated at 6 months and 9 months (93%)[19]. In another study in Florida, VE of an "early" two-dose schedule (99.5%) was found to be similar to the VE for a single dose administered at 6-11 months (97.6%) or 12-18 months (99.7%).

[18] Presentation by William Moss, Is immunological tolerance a real concern? (available to SAGE members on the website)
[19] Kaninda AV, Legros D, Jataou IM et al. Measles vaccine effectiveness in standard and early immunizaiotn strategies, Niger, 1995. Pediatr infect Dis J. 1998; 17:1034-9.

Safety and immunogenicity of mumps and rubella vaccines (MR, MMR) among children <9 months of age

A literature review on safety and immunogenicity of the mumps and rubella components of MR and MMR among children < 9 months of age was conducted by CDC/Atlanta. Both the mumps and rubella components had comparable immunogenicity when administered to infants <9 month of age compared with infants ≥12 months; efficacy and effectiveness data were lacking. No significant adverse events were associated with MR or MMR in children <12 months old.

Impact of maternal vaccination on decay of maternally-derived measles and rubella antibodies among infants < 9 months of age

A specific concern relates to the duration of protection from maternally-derived measles and rubella specific antibodies in women with vaccine-induced immunity (as opposed to naturally-derived immunity). A review of the literature on the decay of maternally-derived measles and rubella antibodies was conducted by CDC/Atlanta. In a study comparing the decay of maternal antibodies in infants born to vaccinated and unvaccinated mothers in Netherlands, the half-life of IgM antibodies was found to range from 35 to 64 days and the duration of protection ranged from 3.5 months in infants born to mothers with vaccine induced immunity to 5.5 months in infants born to mothers with natural induced immunity [20]. Cross-sectional studies also supported the hypothesis that infants born to women with measles vaccine-induced immunity receive fewer measles maternal antibodies and therefore have shorter protection than infants born to women with naturally acquired immunity. For rubella, no strong evidence was found that maternal antibody levels are different between vaccinated versus naturally immune mothers, and transplacental transfer of antibodies is higher in women with low antibody levels. The decay of maternal rubella antibodies is variable, ranging from 30 to 45 days.

Programmatic considerations

Implementing a change in the recommended schedule of routinely administered vaccines has substantial implications for health workers and parents. Specific considerations of a six month dose include integration into the current vaccination schedule and the impact on wastage and cold-chain logistic issues. Resources are required for introductions, such as communication, training and creating new recording materials. In most developing countries, giving MCV at 6 months of age would require an additional visit and, depending on the national schedule, the issue of multiple injections would need to be considered. In countries with high MCV wastage, wastage may decrease, and in countries with cold chain logistics issues, capacity to provide an additional dose would need to be considered. The country experience with a dose of MCV at 6 months and at 9 months (e.g., Papua New Guinea and Saudi Arabia) is limited with problems related to recording doses and confusion in providers and parents. In settings where timeliness of routine vaccination is an issue, the dose at 6 months may be administered closer to 9 months, creating questions about optimal spacing for the next MCV dose.

[20][9] Leuridan, E., et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ, 2010. 340: p. c1626.

Non-specific beneficial effects of MCV on mortality were considered, but the evidence related to measles control was the dominant consideration in formulating recommendations.

Conclusions

Available evidence on immunogenicity, effectiveness and safety supports the use of MCV among infants aged 6 to 8 months and suggests a significant proportion of these infants will be protected against measles. The scientific evidence on immunogenicity suggests that MCV doses given before 9 months may be adequate if a subsequent routine dose is administered on schedule. Limited data on a two dose schedule starting <9 months suggests it leads to high seropositivity but may result in lower avidity antibodies and lower GMTs; T cell proliferation seems unaffected. The clinical relevance of this is unclear. Lower GMTs after an early two dose schedule may indicate that the duration of protection could be affected over the longer term.

Draft Recommendations

SAGE recommends that infants from 6 months of age receive a dose of measles containing vaccine in the following epidemiological circumstances: 1) in the presence of a measles outbreak as part of intensified service delivery; 2) during supplementary immunization activities (i.e., mass vaccination campaigns) in settings where risk of measles among infants remains high; 3) for internally displaced populations and refugees, and populations in conflict zones; 4) for individual children at high risk of contracting measles (exposed or at high risk of exposure to measles); 5) for infants travelling to countries experiencing extensive measles transmission; and 6) for infants known to be HIV positive (see section 4 below).

Because immunogenicity and effectiveness is lower than for doses administered at a later age, and because of the concern about the long term effectiveness of an early two dose schedule, a dose administered more than a month prior to the recommended age of MCV1 should be considered a “zero dose” (MCV0) rather than the first dose. Children who receive an early dose of MCV (i.e., MCV0) should then receive subsequent measles containing vaccines at the recommended ages according to the national schedule.

Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use down to 6 months of age. Thus, in countries using measles vaccine in combination with rubella vaccine or rubella-mumps vaccines (i.e., MR or MMR) in their national routine schedule, the combined vaccine rather than measles-only formulations of MCV should also be administered to children under 1 year of age. SAGE recognizes that this is an off-label recommendation and recommends that governments do not restrict the use of the vaccine in this age group for this reason only, and that manufacturers consider obtaining licensure down to 6 months of age.

Research needs

While it is possible that an early 2 dose schedule of MCV at 6 and 9 months is as effective as 9 and 12 months, evidence is lacking to support a SAGE recommendation for administration of MCV1 at 6 months of age. A particular concern is that coverage with the second dose is often much lower (than with the first dose) and, hence, many young children would be left unprotected after a single dose administered at 6 months of age. A clearer understanding of the biological basis for the observed immunological blunting after MCV given at 6 months would be helpful. Further research, including vaccine effectiveness and

immunogenicity studies, is needed to better understand whether a dose of MCV given <9 months should be counted as MCV1 or MCV0. Further modelling would be helpful to identify the optimal 1 dose and 2 dose schedule as a function of birth rate, coverage, age-specific vaccine effectiveness and incidence, and impact on overall population immunity. In addition, it would be helpful to perform more head-to-head comparisons of different vaccine strains.

Epidemiologically, it would be useful to document whether there is clear evidence of an increasing incidence of measles in infants below 9 months of age.

Further studies of the non-specific effects of measles-containing vaccines on overall mortality, and severity of measles vaccine failures compared to non-vaccinated cases should be conducted.

In addition, operational research on the programmatic impact of implementing and operating different schedules would be helpful. The impact of changing the age of a routine dose or adding a dose may be significantly disruptive for programs. Whether an earlier dose would increase uptake of measles vaccine (or other vaccines) and overall coverage is unknown.

3. How can data on vaccination coverage, surveillance, seroprevalence and other sources be used to determine the target age range for measles or MR SIAs in order to stop measles and rubella transmission?

Introduction

As pioneered in the Region of the Americas (AMR), the classic SIA strategy for measles control and elimination is for programmes with low to moderate MCV1 coverage (<90%) to conduct a wide age-range "catch-up" supplementary immunization activity (SIA) targeting children <15 years of age, followed by regular "follow-up" SIAs targeting children <5 years of age. Some countries with high coverage with two doses of MCV (i.e., >90%) have done only a "catch-up" targeting older children and adolescents, based on low coverage in earlier years, surveillance or seroprevalence data. When these SIAs are successful countries report low numbers of cases. After several years of low measles incidence, countries in AFR reaching high coverage of routine MCV1 and reported high coverage during follow-up SIAs experienced large outbreaks with an increase in the proportion of cases in older age groups. In response these countries conducted a second SIA targeting children <15 years of age and have not had large outbreaks since but also have not yet achieved elimination. Other countries in AFR and EMR experienced initial decreases in measles incidence after initial catch-up SIAs, but after 3-4 follow-up SIAs began to have large outbreaks with a high proportion of cases >5 years of age. Some of these countries have targeted wider target age ranges in subsequent follow-up SIAs. Gavi, the Vaccine Alliance, has focussed their support on SIAs targeting children <5 years of age, because this age group experiences the highest mortality risk from measles.

Rubella vaccine currently has not yet been introduced into the immunization programmes of 54 countries. Some of these countries have increasing susceptibility to rubella among women of childbearing age (WCBA) due to demographic factors (e.g., declining birth rates). Identifying these countries will be important in order to avoid outbreaks in adults which may lead to cases in pregnant women resulting in children born with congenital rubella syndrome (CRS). An algorithm has been developed to guide countries and partners in determining if the SIA to introduce MR vaccine should target adolescents 15 years of age and older. If validated the results of this algorithm could be used for resource mobilization, given that currently most donor funding is restricted to SIAs targeting children <15 years of age.

Current Global and Regional Recommendations

The 2009 measles position paper [21] recommends that follow-up SIAs be conducted nationwide every 2–4 years and target children aged 9–59 months. Data on vaccination coverage should be used to monitor the accumulation of susceptible people and follow-up SIAs conducted before the number of susceptible children of pre-school age reaches the size of the birth cohort.

The 2009 WHO guidelines on Response to Measles Outbreaks in Measles Mortality Reduction Settings [22], recommend that the target age range for a non-selective SIA be chosen depending upon the susceptibility profile of the population. Key elements to consider are 1) routine vaccination coverage and coverage during SIAs in each birth cohort; 2) age-

[21] WHO. Measles vaccines: WHO position paper. Weekly epidemiological record, 2009. 35:84, 349-360.
[22] WHO. Response to Measles Outbreaks in Measles Mortality Reduction Settings. WHO/IVB/09.03

specific attack rates; and 3) absolute number of cases. All age groups contributing to cases should be considered for vaccination. Even if the attack rate is low in some age groups, especially in older age groups, they may represent a large proportion of cases and large potential groups at risk of contracting measles and of transmitting the infection to younger persons.

The 2011 Rubella Position Paper [23] recommends that countries undertaking the elimination of rubella and CRS begin with MR vaccine or MMR vaccine in a campaign targeting a wide age range, followed immediately by the introduction of MR or MMR vaccine into the routine programme. Depending on their targeted goal, burden of disease and available resources, countries may choose to accelerate their progress towards elimination by conducting campaigns targeting a wide range of ages of both adult males and females.

At their November 2013 [24] meeting, SAGE recommended that countries integrate their surveillance, demographic, survey and (if available) seroprevalence data together with vaccination coverage information, history of MCV and RCV use, and local knowledge to determine the age distribution of susceptibility and hence the target age range of measles and MR SIAs. Additional information to consider in relation to MR SIAs is rubella immunity among women of child-bearing age, the epidemiology of rubella and CRS, age-specific fertility rates, and the age of mothers of CRS-affected infants.

WHO Regional recommendations on the target age range for measles follow-up SIAs are summarized below:

Region (Document)	**Recommended interval between SIAs**	**Recommended target age range**
AFR (TAG, 2005)	MCV1 >80% - interval of 4 y MCV1 60-79% - interval of 3 y MCV1 <60% - interval of 2 y	9-59 m 9-47 m 9-35 m
AFR (SIA Guide, 2015)		Determined according to the epidemiology: the age breakdown of confirmed measles cases & deaths, age specific incidence rates
AMR (13th TAG, 1999)	When number of susceptibles approaches the size of a birth cohort	1-4 years
EMRO (N Teleb, personal communication)		Depends on epidemiology of the disease and previous vaccination activities
EURO (MR Strat Plan 2003)	Every 3-5 years	Children not targeted by previous mass campaign
SEARO (Strategic Plan	Every 3-5 years, depending on the quality of the initial national wide-	Monitor the age specific population immunity with

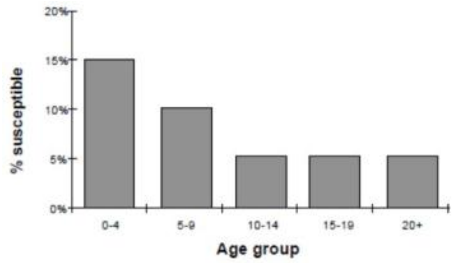
[23] WHO. Rubella vaccines: WHO position paper. Weekly epidemiological record, 2011. 29:86, 301-316.
[24] WHO. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013– Conclusions and recommendations. Weekly epidemiological record, 2014. 1:89, 1-20.

for measles elimination and rubella control, 2015)	age range MR SIA and coverage with MCV1 and MCV2	laboratory supported case-based surveillance, the use of the MSP tool, the use of the sub-national risk assessment tool and other data as available. Cover ages with population immunity <95%
WPRO (Measles Elimination Guide 2013)		<2y or <5y, depending on national SIA guidelines

The 16th Technical Advisory Group meeting for PAHO recommended that rubella-endemic countries conduct SIAs targeting men and women in rubella endemic countries from 15-29 or 15-39 years of age, depending on susceptibility in adults, with adult susceptibility determined by year of introduction of the MMR vaccine in the national schedule, the extent of follow-up MR or MMR vaccination campaigns to maintain measles elimination, and the rubella epidemiology in the country.

The only recommendation on how to use age-specific susceptibility data for measles is from the EUR 1999 Strategic Framework for the Elimination of Measles. This guidance was developed and validated by Nigel Gay based on data from England, Denmark and Canada. It recommends separate cut-offs by 5-year age groups: 15% for 0-4 years, 10% for 5 – 9 years, and 2% for every 5-year age group 10 years of age or older. Keeping susceptibility below these thresholds would maintain R < 1. However, these cut-offs were based on interpersonal contact patterns from studies done in Europe and assume a low birth rates, and therefore may not be appropriate for other settings.

Figure. Susceptibility targets for measles elimination, European Strategic Framework for the Elimination of Measles, 1999.



Global and regional recommendations for follow-up measles SIAs are to monitor accumulation of susceptible children and conduct an SIA targeting <5 years of age when that number equals the size of one birth cohort. Recommendations are not different for control or elimination settings. For CRS prevention and rubella elimination, global and regional recommendations are to start with an SIA targeting at minimum children <15 years of age, though elimination can be accelerated with an SIA targeting men and women. More recent recommendations are to assess gaps in immunity to measles or rubella by age group, using a susceptibility profile, age-specific attack rate, percentage or numbers of cases, serosurveys, and programme history. Outside of the European context, there are no fixed

cut-offs to decide when the immunity gap is large enough that an age group should be targeted by an SIA.

Review of impact of different SIA strategies on measles incidence – a multi-country analysis

A multi-country analysis of the impact of different SIA strategies on measles incidence is being done by CDC / Atlanta. Preliminary results reviewed the measles prevention strategies that have been used, their impact on measles incidence, and regional differences. Data on cases, coverage, vaccine introductions, and SIAs were accessed from WHO IVB and population data from the UN Population Division projections, 2012 revision. Countries were grouped as to their use of SIAs and / or MCV2 in routine (Table).

Table. Measles vaccination strategies

Abbreviation	Strategy defined according to intervention order
MCV_2	MCV1 + MCV_2 in routine schedule
SIA_{WA}	MCV1 + a wide-age SIA and regular follow-ups
SIA_{WA}/MCV2	MCV1 + a wide-age SIA and routine MCV2
MCV2+SIA_{WA}	MCV1 + MCV2 routine + wide-age SIA
SIA_{WA}+MCV2	MCV1 + wide-age SIA with regular follow-ups +MCV2 routine

Each added intervention, first adding a second dose (through routine or SIAs) and second adding both SIAs and MCV2 in routine, decreased median measles incidence 10-fold, as shown in the figure.

Figure. Median measles incidence per million by vaccination strategy, 1985 – 2014.

Between 2000 and 2014, most countries experienced years with excellent control (<5 cases / million), though countries in AFR, EMR and SEAR spent more time with poor (50-100 cases / million) or “no control” (>100 cases / million). Future work will look at characteristics of measles SIAs that are most effective in reducing disease incidence.

Comparison of age distribution of cases and seroprevalence studies

A literature review done at CDC / Atlanta of measles and rubella seroprevalence studies published between 2000-2014 identified 14 studies. Rubella testing only was done in four while 10 included testing for both measles and rubella. Eight were done only in WCBA and one (from Nepal) was done after a measles-rubella SIA targeting children <15 years of age. Annual numbers of measles and rubella cases reported through the JRF were used to calculate disease incidence and identify countries with high incidence (>20 cases per million population) in the year before, during or after the survey. Case-based measles data from countries with both high incidence and available serosurveys was then used to calculate age-specific incidence. Preliminary results from this work were difficult to interpret and further analysis of data from seroprevalence studies will include countries in elimination or

near-elimination settings to determine the age-specific seroprevalence associated with achieving elimination.

Modelling of age distribution of cases from outbreaks to determine vaccination strategies

Modelling is ongoing to assess the marginal benefit of wide age-range SIAs in four countries, with a deeper look at sub-national dynamics in Ethiopia[25]. Because mathematical modelling using achievement of elimination as the outcome is challenging, the approach being taken is to model the conditions needed to maintain elimination. When the effective reproduction number is below one (R < 1) persistent measles transmission is unlikely and measles has been eliminated. When the routine immunization programme cannot reach and immunize all children born, R increases with time until an effective SIA immunizes previously susceptible children and decreases R. When R<1, outbreaks are possible but will be small and self-limited whereas when R>1 they are more frequent, larger, and more likely to persist. This analysis looks at the outbreak risk over 15 years, normalized to be 1 for the least aggressive strategy. The strategies involve SIAs repeated every 4 years with different target age ranges, and different proportions of susceptible children immunized by the SIA. In the figures "coverage" or "immunization" is not the proportion of children in the target population reached, but rather the proportion of susceptible children immunized. The least aggressive strategy is targeting children <5 years of age and reaching 70% of susceptible children.

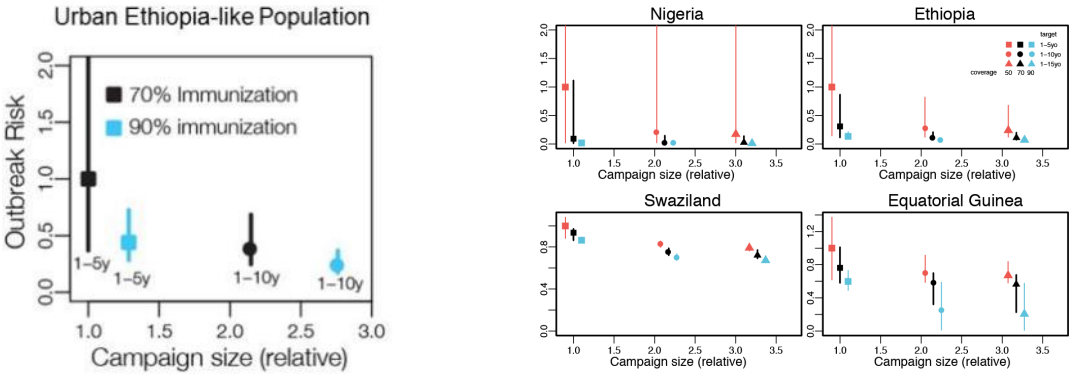


Figure. Comparison of relative outbreak risk and campaign size for different choices of target age range and proportion of susceptible children immunized by SIAs. Left panel is for a population like urban Ethiopia, right panel is for Nigeria, Ethiopia, Swaziland and Equatorial Guinea. SIA targeting <5 years represented by squares, <10 years by circles, and <15 years by triangles.

In a setting like urban Ethiopia, where most susceptibility is in children <5 years of age, increasing from 70% to 90% the proportion of susceptible children immunized and targeting <5 years in follow-up SIAs reduces the 15-year outbreak risk by 50%. The same results can be achieved when the follow-up SIAs target is increased to <10 years of age while still reaching only 70% of susceptible children. Using national data from Ethiopia, Equatorial Guinea, Nigeria and Swaziland and adding <15 year follow-up SIAs, in urban Ethiopia, Equatorial Guinea and Nigeria, where routine coverage is low and most susceptibility is in children <5 years, outbreak risk is most affected by SIA quality. Increasing the target age of follow-up SIAs to <10 years also reduces outbreak risk, but extending to <15 years provided

[25] Presentation by Dr Matthew Ferrari, Penn State University, given at the Measles Rubella Working Group Meeting, 3-4 September 2015

little additional benefit. In Swaziland, where routine coverage is high and susceptibility is low, the benefit of targeting wider age ranges is less marked. This analysis shows that follow-up SIAs targeting children < 5 years of age are sufficient to maintain herd immunity when they reach high coverage in unvaccinated children in SIAs. However, where high quality follow-up SIAs are difficult to achieve, targeting children <10 years can achieve similar effect. Repeated follow-up SIAs targeting children <15 years of age have little marginal impact on outbreak risk.

In larger countries subnational variations in susceptibility may require subnational variation in strategies. The age distribution of cases was compared for each region in Ethiopia. Ethiopia started accelerated disease control in 2002 with a multi-year, rolling SIA targeting children < 15 years of age and reaching 90% coverage. Since that SIA the country has done four SIAs targeting children <5 years of age (except for a target of <4 years in 2010) that reached 88 – 106% coverage. Routine MCV1 coverage has gone from 36% in 2002 to 70% in 2014. Reported cases initially decreased to low levels but have been increasing since 2006. Despite SIAs reaching 90% of children in recent SIAs (confirmed by survey), large outbreaks have been occurring since 2013 with increasing incidence and proportion of cases in children >5 years of age (see Annex 2).

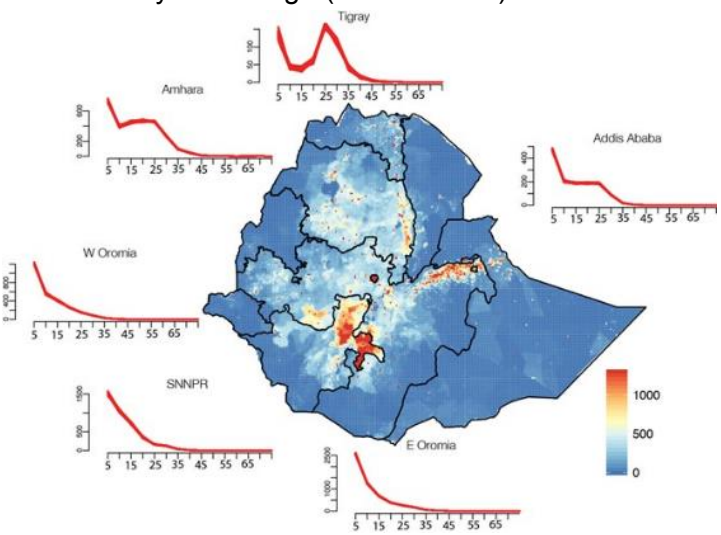


Figure. Map of Ethiopia showing density of children <5 years susceptible to measles and age distribution of confirmed measles cases by age (2004-2014).

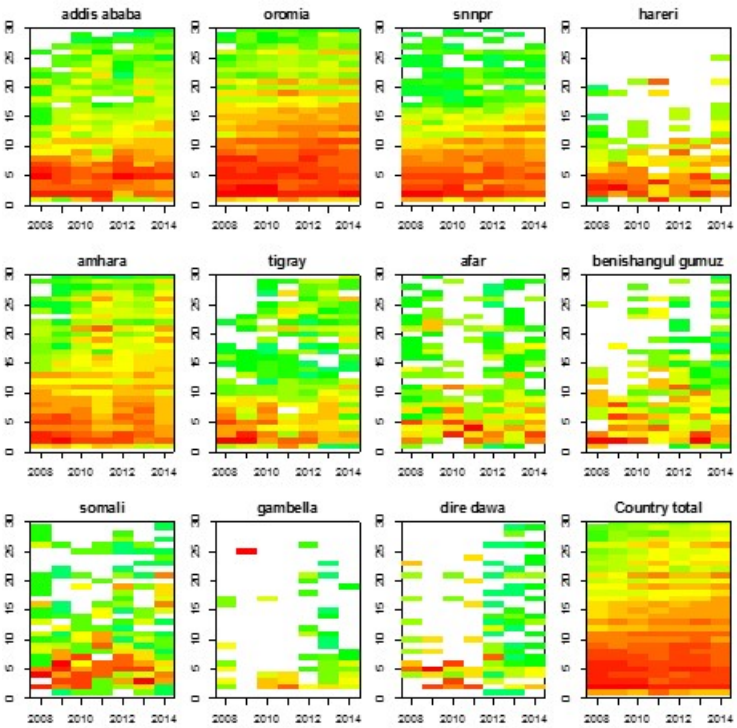


Figure. Time trends in the age distribution of measles cases by region in Ethiopia from 2008-2014. Cases increase as the colour changes from green to red.

In Northern Ethiopia a larger proportion of cases are in older age groups, reflecting the strength of the programme in this area and the lower risk of exposure to measles (see figures). Here, SIAs should target accumulated susceptibility by covering a wider age group (<35 years). In Southern Ethiopia a larger proportion of cases are in younger age groups, reflecting endemic transmission. SIAs in the South should target transmission in those age groups. However, in the most populated Southern regions of Oromia and SNNPR, large outbreaks have been occurring in 2013-2015 with high incidence in children 5-14 years of age (see Annex), so SIAs should continue to target children up to 10 – 15 years of age.

Taxonomy of measles control regimes and its relation to the age distribution of cases
A group at Johns Hopkins University has been developing a taxonomy approach using two indicators: adjusted measles incidence vs. coefficient of variation. A state-space model was used to adjust for under-reporting of measles cases. Lexis diagrams are used to estimate the susceptible proportion by age, given adjusted cases, along with routine and supplementary vaccination. As countries move to higher coefficient of variation, they are more likely to have susceptibility in older ages.

This work suggests that the current approach, based on a the current or past age distribution of cases, may not be as effective as basing SIA target age ranges on predicted age group likely to have immunity gaps in the future. Using the current approach, SIAs have targeted only younger ages as they experience the highest incidence but may be missing pockets of susceptibility in older age groups. Data from Africa from 2006-2014 show that the current approach did not predict the large multi-country outbreak in 2009-2011 affecting children >5 years of age.

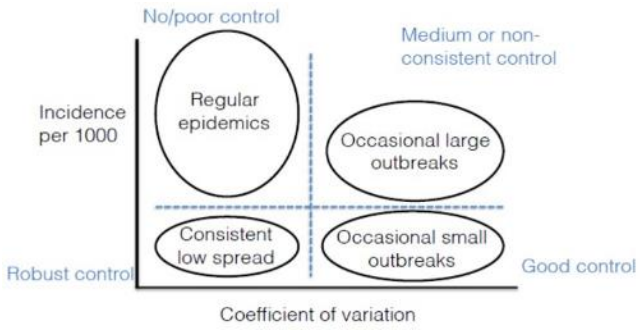


Figure. Taxonomy of measles control to help guide future SIA target age range.

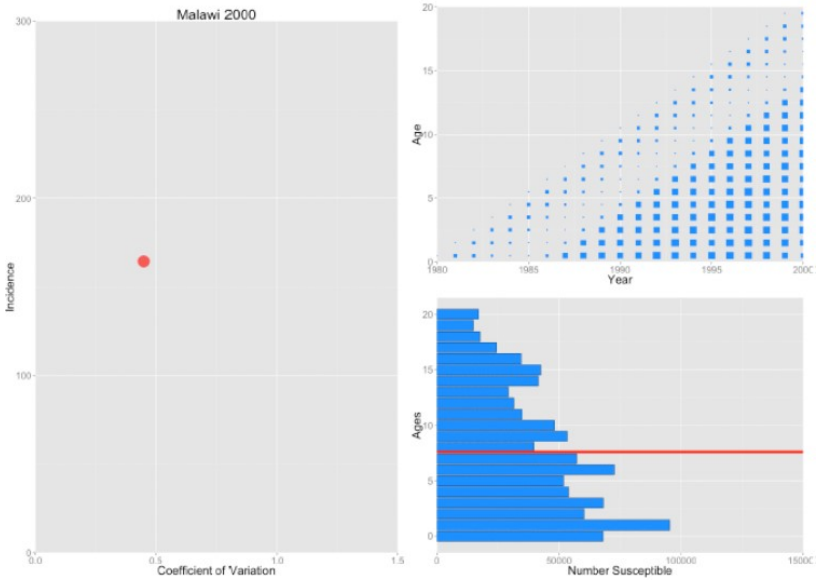


Figure. Taxonomy of measles control – example of Malawi. Red line is the mean age of adjusted cases.

The taxonomic approach suggests common dynamics as countries approach elimination, implying that there is a fundamental process underpinning this evolution. Though the results are not definitive, the approach after further refinement may help guide countries without the need for a detailed serological survey.

Algorithm for determining upper age limit for rubella introduction SIAs

Based on projections using disease transmission models, effective rubella control requires at least 80% of the population to be immune. When introducing RCV into an immunization schedule, programmes are often faced with the question of what criteria would require them to target older adolescents or young adults. An algorithm has been developed to guide programmes. In general, when >=80% of WCBA are immune to rubella, the initial MR catch-up campaign does not need to target age groups over 15 years of age. When immunity is below that level then the older age groups should be considered for inclusion into the target population for the catch-up SIA.

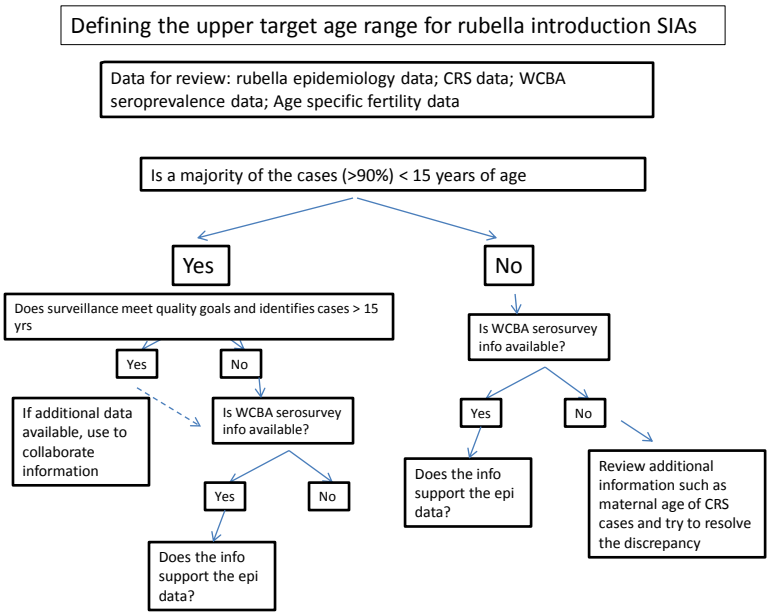


Figure. Proposed algorithm for determining if an introductory SIA for MR should target people >15 years of age.

The algorithm assesses the proportion of rubella cases <15 years of age, serosurvey data from WCBA, and additional data such as age of mothers of CRS cases and country fertility rates. This algorithm was applied to available data from Egypt, Ghana and Nepal and compared rubella incidence after the SIA. In Egypt rubella cases in 2007 were mostly aged 10-20 years and a serosurvey done in 2002 showed low immunity in children below 11 years of age. After an MR SIA in 2007-2008 targeting people 2 – 20 years of age, annual incidence of reported rubella sharply decreased and since 2010 has been <1 case per million population. In Ghana and Nepal the majority of reported rubella cases were <15 years of age and serosurveys in WCBA showed high immunity in women >15 years of age. MR SIAs were done targeting children <15 years of age and since then both countries have had an annual incidence of lab-confirmed rubella <1 per million population.

Based on these country examples the 80% cut-off for determining age range predicts successful prevention of rubella and CRS. The recommendations based on the algorithm may have been more robust for these countries as seroprevalence data were available. Monitoring rubella incidence in countries applying the algorithm and modelling results expected when following the algorithm should help to validate it and possibly refine the parameters used. A similar algorithm should be developed for measles to guide decisions on including older age groups in follow-up SIAs, providing an integrated process for determining the target age range for measles-rubella SIAs.

Conclusions

Current recommendations are for countries to monitor the accumulation of susceptible children and conduct an SIA when the number reaches the size of one birth cohort, targeting children from the age of routine MCV1 to at least 59 months. Recent experience suggests significant pockets of susceptibility to measles exist in older age groups, but outside of Europe no explicit criteria exist to determine when to include age groups >5 years of age. For rubella introduction, no clear WHO guidance exists on when to target age groups >15

years of age. Analyses of the impact of SIA strategies and the comparison of surveillance and susceptibility data are still at an early stage. Dynamic disease models for four countries shows that immunization of susceptible children through an SIA is a critical indicator of the impact of the SIA on reducing transmission. Countries can maintain R < 1, and lower the risk of outbreaks, more efficiently when the proportion of susceptibles immunized is high. When SIAs have difficulty reaching a high (90%) proportion of susceptibles, a wider target age range will be equally effective but less efficient. Data from Ethiopia show that throughout the country susceptibility is high in children <15 years of age, with pockets in young adults in regions with stronger immunization programmes. A taxonomy using adjusted incidence and the coefficient of variation of incidence looks promising to help predict when significant susceptibility exists in older age groups.

An algorithm to guide the inclusion of older age groups in introductory MR SIAs, when applied in selected countries, appears to result in very low rubella incidence. Additional examples and modelling is needed to confirm the applicability of the algorithm and adjust its parameters. A similar algorithm for inclusion of older (>5 years of age) age groups for measles SIAs is needed, allowing for an integrated measles-rubella approach.

4. Should an additional dose of measles-containing vaccine be recommended for HIV-infected children receiving highly active antiretroviral therapy?

Introduction

Human immunodeficiency virus (HIV)-infected children are at increased risk of measles morbidity and mortality and could play a role in sustaining measles virus transmission in regions of high HIV prevalence. Protective antibody concentrations wane following measles vaccination of HIV-infected children as a consequence of impaired immunity. Until the widespread introduction of antiretroviral therapy, the high mortality rate of HIV-infected children prevented the build-up of a sizeable pool of measles susceptible children. Highly active antiretroviral therapy (HAART) is effective in prolonging survival in HIV-infected children by suppressing viral replication and restoring immune function. However, immune reconstitution in children is primarily achieved through the generation of naïve T-cells rather than the expansion of memory T-cells and antiretroviral therapy does not restore measles vaccine-induced immunity established prior to therapy. As a consequence, HIV-infected children are at increased risk of measles morbidity and mortality despite measles vaccination. In countries with a high prevalence of HIV infection, susceptible children receiving HAART could become sufficiently numerous to sustain measles virus transmission despite high levels of measles vaccine coverage.

In 2012, the Advisory Committee on Immunization Practices recommended measles revaccination of persons with perinatal HIV infection who were vaccinated before establishment of effective antiretroviral therapy with two appropriately spaced doses of MMR vaccine once effective ART has been achieved. In low and middle-income countries, particularly those in sub-Saharan Africa that bear the greatest burden of pediatric HIV infection, antiretroviral treatment programs have scaled-up dramatically, increasing access to life-prolonging treatment for HIV-infected children. To protect these children against measles, and ensure high levels of population immunity, revaccination with MCV after immune reconstitution with HAART should be recommended.

Evidence in Support of the Recommendations

An increasingly large number of HIV-infected children will receive antiretroviral therapy

As of December 2013, an estimated 740,000 HIV-infected children in low and middle-income countries were receiving antiretroviral therapy, with 630,300 (85%) residing in Africa. These children represent only 23% (21-25%) of the estimated 3.2 million (2.9 to 3.5 million) children younger than 15 years of age living with HIV.

Measles case fatality ratio is higher in HIV-infected children

In the largest prospective study of measles mortality among hospitalized HIV-infected children, involving 1227 Zambian children with confirmed measles and HIV infection status, death during hospitalization occurred in 23 HIV-infected children (12.2%) and 45 HIV-1-uninfected children (4.3%, P <0.001). After adjusting for age, sex and measles vaccination status, HIV infection (OR 2.5, 95% CI: 1.4, 4.6) and the presence of a desquamating rash were significant predictors of measles mortality.

Measles seroprevalence is lower in HIV-infected than uninfected children after vaccination

The Global Advisory Committee on Vaccine Safety (GACVS) published a report on the immunogenicity and effectiveness of measles vaccination in HIV-infected children in 2009 based on a systematic review and meta-analysis. Serological assessments of measles antibody levels after vaccination showed that measles vaccination at the age of 6 months resulted in similar levels of antibody in HIV-positive children and children who had not been exposed to HIV. However, by the age of 9 months, fewer HIV-positive children responded to measles vaccine than did children who had not been exposed to HIV. At the time of the review there were scant data about the effects of HAART on responses to measles vaccination.

The systematic review was updated based on articles published after the availability of HAART in 1996 through February 2015. For the five studies reporting on children vaccinated at nine months of age, the seroprevalence ratio comparing HIV-infected to uninfected children ranged from 0.44 to 1.05, although the confidence intervals for individual studies were wide. Heterogeneity across studies precluded meta-analysis. The updated systematic review did not find evidence contradicting the earlier review.

Protective measles antibody levels wane in HIV-infected children not receiving HAART
Two prospective studies documented waning measles antibody levels in HIV-infected children not receiving antiretroviral therapy. In a prospective study of the immunogenicity of measles vaccine administered at 9 months of age to HIV-infected and uninfected children in Lusaka, Zambia, 88% of 50 HIV-infected children developed antibody levels of ≥120 mIU/mL, compared with 94% of 98 HIV-unexposed children and 94% of 211 HIV-exposed, uninfected children, suggesting a good primary response to measles vaccine. By 27 months after vaccination, however, only half of the 18 HIV-infected children who survived and returned for follow-up maintained measles antibody levels ≥120 mIU/mL, compared with 89% of 71 uninfected children

Low measles seroprevalence at the time of starting treatment provides supportive evidence that antibody levels wane in HIV-infected children not receiving antiretroviral therapy. In the largest study, involving HIV-infected children receiving antiretroviral therapy in the United States, only 52% of 193 children had protective antibody concentrations at the time of starting antiretroviral therapy. Among 61 HIV-infected Zambian children starting antiretroviral therapy, only 23% were measles seropositive.

Antiretroviral therapy does not restore measles immunity in the absence of revaccination
In a study of the impact of HAART on measles vaccine immunogenicity in Lusaka, Zambia, HAART was not associated with measles seroconversion in 46 children who were seronegative at enrolment nor was there a trend indicating that seroconversion was more likely with increased time on HAART after adjusting for baseline age and $CD4^+$ T lymphocyte percentage.

Antiretroviral therapy improves responses to measles vaccine
In six published studies, measles seroprevalence following revaccination of HIV-infected children receiving antiretroviral therapy ranged from 64% to 95%, with a mean of 83%. The two largest studies also had longer follow-up. In a study of 51 HIV-infected children receiving highly active antiretroviral therapy in Thailand, measles seroprevalence was 90% one month after measles revaccination and 85% three years after revaccination. In a study of 193 HIV-

infected children receiving highly active antiretroviral therapy in the United States, measles seroprevalence was 89% eight weeks after measles revaccination and 80% 80 weeks after revaccination. These two studies provide the best evidence of the long-term immunogenicity of measles revaccination in children receiving HAART.

Measles vaccine is safe in HIV-infected children
GACVS published a report on the safety of measles vaccination in HIV-infected children in 2009 based on a systematic review. The Committee concluded that the evidence does not demonstrate a serious risk in using measles vaccine in HIV-positive children. Although millions of doses of measles vaccine have been administered to HIV-positive children, only one case report was identified that suggested possible severe adverse events following immunization. However, ascertainment of such events may be incomplete, particularly given the need for molecular detection and sequencing to distinguish wild-type from vaccine measles virus.

An updated systematic review through February 2015 found no additional evidence of severe adverse events attributable to measles vaccine in HIV-infected children. Deaths after vaccination were reported in six studies, with a case fatality of 19% in 309 HIV-infected children who received measles vaccine. However, no deaths were attributed to measles vaccine and there were no reported cases of pneumonitis, measles inclusion body encephalitis or thrombocytopenia. Any potential increased risk of adverse events following measles vaccination of HIV-infected children is likely to be substantially lower in children who achieve immune reconstitution following antiretroviral therapy.

Optimal timing of measles revaccination in relation to antiretroviral therapy
The optimal timing of vaccination after initiation of antiretroviral therapy is not known. Most cross-sectional and prospective studies found that higher $CD4^+$ T lymphocyte counts and lower HIV viral loads were crudely or independently associated with seropositivity after measles vaccination of HIV-infected children receiving antiretroviral therapy, suggesting standard markers of immune reconstitution are associated with improved responses to measles vaccine.

HIV-infected children who start antiretroviral therapy prior to or shortly after the first dose of MCV may not require revaccination
Age at initiation of antiretroviral therapy in relation to the timing of measles vaccination may be important in enhancing vaccine responses. In one study, children who initiated antiretroviral therapy younger than 12 months had higher levels of protective immunity than children who initiated antiretroviral therapy later in childhood, with levels of immunity comparable to uninfected children of the same age. Little data exist on the immunogenicity of measles vaccine in children who start HAART prior to 9 or12 months of age.

Revaccination of HIV-infected children should be programmatically feasible
HIV-infected children receiving antiretroviral therapy have intensive follow-up, most often at clinics devoted to the care of HIV-infected children and adults where they are typically evaluated every 3 months, particularly after the start of antiretroviral therapy. Frequent follow-up visits would facilitate revaccination against measles. However, a policy to revaccinate HIV-infected children against measles will require coordination between the clinics that provide HIV care and those that provide routine immunizations to children.

Evidence to recommendations

1. The quality of evidence is moderate for benefits and harms as it is based on prospective and cross-sectional observational studies and not randomized controlled trials.
2. There is strong evidence that the benefits of providing an additional dose of MCV to HIV-infected children receiving HAART outweigh the risks of measles vaccine.
3. There is confidence in the estimate of the relative importance of preventing measles in HIV-infected children and that this would be preferred by caregivers.
4. The costs associated with an additional dose of MCV are trivial compared to the cost of treating and caring for HIV-infected children.

Draft Recommendations

These draft recommendations emphasize current World Health Organization recommendations and expand them to include an additional dose of MCV for HIV-infected children receiving HAART.

1. Early diagnosis of HIV infection is critical to allow early initiation of HAART, immune reconstitution and better responses to vaccines.
2. In areas where there is a high incidence of both HIV infection and measles, the first dose of MCV may be offered as early as age 6 months to provide protection to HIV-exposed infants, as currently recommended by the World Health Organization, followed by two doses of MCV.
3. Age-appropriate MCV should be administered to HIV-infected children according to World Health Organization recommendations and country immunization schedules, including measles supplementary immunization activities. Current World Health Organization recommendations are that measles vaccination should be routinely administered to potentially susceptible, asymptomatic HIV positive children and adults. Vaccination may be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions.
4. An additional dose of MCV should be administered to HIV-infected children receiving HAART following immune reconstitution:
    a. Where $CD4^+$ T lymphocyte counts are monitored, an additional dose of MCV should be administered when immune reconstitution has been achieved, e.g. when $CD4^+$ T lymphocytes are ≥ 20 to 25%.
    b. Where $CD4^+$ T lymphocyte monitoring is not available, children should receive an additional dose of MCV 9-12 months after initiating HAART.
5. HIV-infected children who start HAART prior to the first dose of MCV may develop protective immunity to measles virus. Current evidence is insufficient to recommend revaccination of these children.
6. A supplementary dose of MCV should be considered shortly after diagnosis of HIV infection in children older than 6 months of age who are not receiving HAART, and for whom the risk of measles is high, to provide protection until they are revaccinated after immune reconstitution with HAART. This additional dose should be administered at least one month after a prior dose of MCV.
7. Long-term immune responses to measles vaccine should be monitored in HIV-infected children revaccinated after starting HAART and in HIV-infected children who start HAART prior to receiving their first dose of MCV.

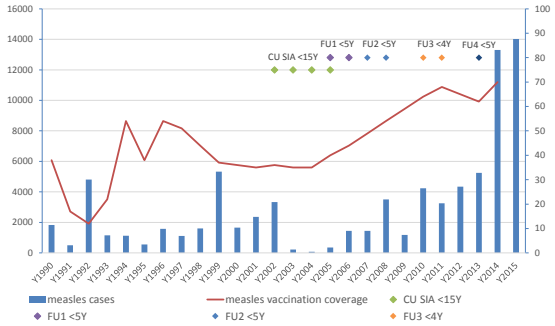
Annex 1: Acronyms

AFR	WHO African Region
AMR	WHO Region of the Americas
CRS	congenital rubella syndrome
EMR	WHO Eastern Mediterranean Region
EUR	WHO European Region
HAART	highly-active antiretroviral therapy
HIV	human immunodeficiency virus
JRF	joint reporting form
MCV	measles-containing vaccine
MCV0	early, supplemental dose of MCV
MCV1	first dose of MCV
MCV2	second dose of MCV, typically implying dose is part of routine immunization schedule
MMR	measles-mumps-rubella vaccine
MR	measles-rubella vaccine
PAHO	Pan-American Health Organization
R	effective reproduction number
RCV	rubella-containing vaccine
SEAR	WHO South-East Asian Region
SIA	supplementary immunization activity
WCBA	women of childbearing age
WPR	WHO Western Pacific Region

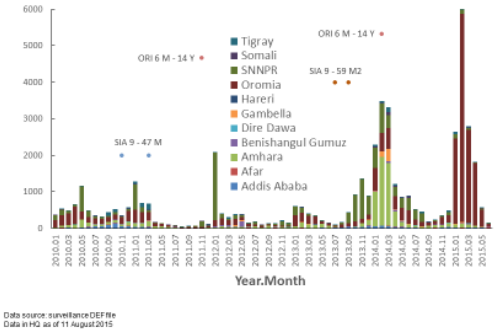
Annex 2: Measles Epidemiology in Ethiopia

SIA	Year	Admin	Survey
Catch-up	2002	98%	
	2003	92%	
	2004	89%	
	2005	82%	
Follow-up 1	2005	97%	
	2006	87%	
Follow-up 2	2007	98%	
	2008	92%	
Follow-up 3	2010	107%	88%
	2011	98%	93%
Follow-up 4	2013	98%	91%

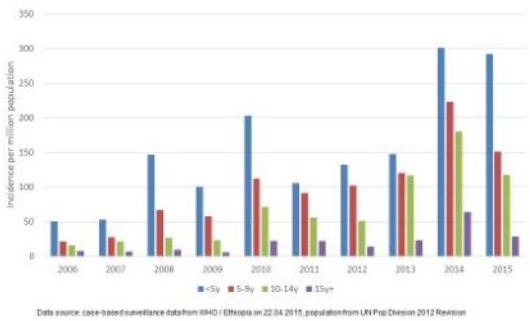
Reported measles cases, routine MCV1 coverage, and SIAs, 1990-2015, Ethiopia



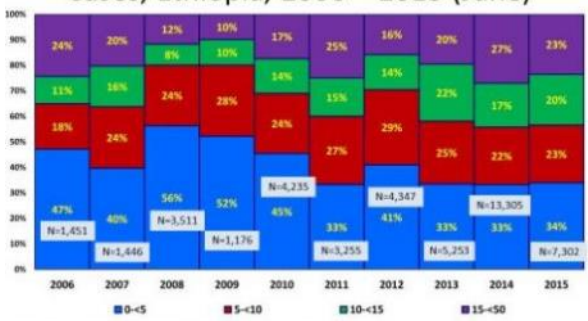
Ethiopia, confirmed measles cases by month and province and SIA dates, 2010-2015



Incidence of confirmed measles per million, by age group, Ethiopia, 2006-2015

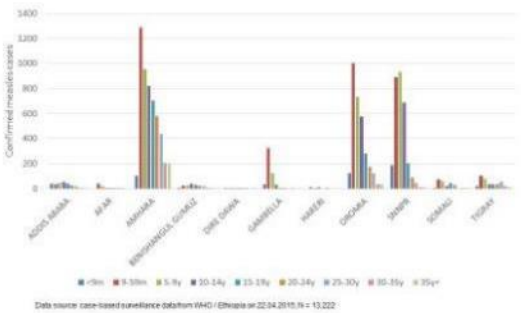


Age Distribution of Confirmed Measles Cases, Ethiopia, 2006 – 2015 (June)



Yearly totals from JRF (2006-2014), country updates (2015)

Confirmed measles, by age group and region, Ethiopia, 2014



Confirmed measles, by age group and region, Ethiopia, 2015