

Conclusions of the SAGE Working Group on Measles and Rubella

21-22 June 2017, Geneva

WHO Policy Recommendation on administration of MCV to infants <6 months of age.

FOR DECISION

In light of the following considerations, SAGE is asked to provide recommendations on the vaccination of infants <6 months of age with measles-containing vaccine (MCV).

Background

Countries are experiencing measles outbreaks with high incidence in children younger than 9 months of age, an age group in which measles can be severe. Thanks to the success of the immunization programme in reducing measles incidence, many mothers now have measles antibodies induced by vaccination rather than natural disease. Antibody levels after vaccination are generally significantly lower than those after natural disease, leading to lower measles antibodies in infants born to women with vaccine-derived immunity.

In 2015, the National Institute for Public Health and the Environment (RIVM) in the Netherlands conducted a systematic literature review of the immunogenicity, effectiveness and safety of measles vaccination below 9 months of age. Based on this, and other evidence, current recommendations are to give the first dose of measles or MR vaccine at 9m, moving to 12m when coverage is high and the risk of measles in infancy is low, that is when overall incidence is close to elimination. In addition, SAGE (October 2015) recommended that:

“In the following situations, a supplementary dose of MCV should be given to infants from 6 months of age :

- 1. during a measles outbreak as part of intensified service delivery;*
- 2. during campaigns in settings where the risk of measles among infants < 9 months of age remains high (e.g. in endemic countries experiencing regular outbreaks);*
- 3. for internally displaced populations and refugees, and populations in conflict zones;*
- 4. for individual infants at high risk of contracting measles (e.g. contacts of known measles cases or in settings with increased risk of exposure during outbreaks such as day-care facilities);*
- 5. for infants travelling to countries experiencing measles outbreaks;
for infants known to be HIV-infected or exposed (i.e. born to an HIV-infected woman)*

Measles vaccine immunogenicity and effectiveness are lower at 6 months than at later ages, and there are concerns about the long-term effectiveness of an early 2-dose schedule and its potential for later blunting of immunity. MCV administered before 9 months of age should therefore be considered a supplementary dose and recorded on the child's vaccination record as “MCV0” unless the country has data showing high seroconversion when vaccination is carried out before 9 months of age. Children who receive a MCV0 dose should also receive MCV1 and MCV2 at the recommended ages

according to the national schedule. Available evidence on safety and immunogenicity of rubella and mumps-containing vaccines support their use from 6 months of age. Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formula”

“In areas where there is a high incidence of both HIV infection and measles, an initial dose of MCV may be offered as early as age 6 months (recorded as MCV0). The 2 routine doses of MCV (MCV1 and MCV2) should then be administered to these children according to the national immunization schedule.” (see 2017 measles vaccine position paper)

Because immunogenicity and effectiveness are lower than for doses administered at a later age and concern about the long-term effectiveness of an early 2-dose schedule, MCV administered at 6 months of age should be considered a supplementary dose and recorded on the child’s vaccination record as “MCV0”. Children who receive a MCV0 dose should then receive at least two doses of 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 from 6 months of age. Countries using measles rubella (MR) or measles, mumps and rubella (MMR) in their national schedule should use the combined vaccine rather than measles-only formulations in children aged <1 year. SAGE recognizes that this is an off-label use and recommends that national programmes do not restrict the use of either vaccine in the <1 year age group”.

However, recent outbreaks show that many cases occur in children less than 6 months of age. The key question is how can these children be better protected while maintaining robust population immunity? Should vaccination of infants below 6 months of age be recommended, and if so, in what settings?

The MR SAGE WG addressed the above questions in two ways:

1. A review of the epidemiology of measles in infants <6 months of age through the analysis of case-based surveillance data between 2011 and 2016;
2. An updated systematic review on the immunogenicity (humoral and cellular), duration of immunity, vaccine effectiveness, blunting of response to MCV2 after early MCV1, and safety of vaccination of infants <6 months of age.

Summary of the findings of epidemiological analyses and the systematic review are in the two reports below. More detailed reports of these two studies are available in the web as background documents for the session.

1. Epidemiology of measles in infants younger than 6 months: analysis of surveillance data 2011-2016

An analysis of the epidemiology of measles in infants younger than 6 months was conducted by the U.S. CDC and WHO using case-based measles surveillance data from 2011 to 2016.

The specific research questions for this analysis were:

1. What is the burden of disease due to measles among infants less than 6 months old?
2. What epidemiological circumstances and country situations are associated with a significant proportion of measles cases in children <6 months old?

The analyses were conducted using case-based measles surveillance data that were available at WHO-HQ for years of onset 2011-2016, except for the South-East Asia Region (SEAR) for which surveillance data were available only for 2014-2016. Confirmed measles cases were defined as either laboratory confirmed or epidemiologically linked to a confirmed case. Data from several countries were excluded from analysis due to small numbers of confirmed cases (n=32 countries excluded) or case ages that were only reported in full years (n=36 countries excluded; 30 in the European Region [EUR], 6 in the South-East Asian Region [SEAR]).

Epidemiology of measles among infants <6 months

Out of a total of 390,522 confirmed* measles cases of all ages during 2011-2016 in the countries included in this analysis, 16,953 (4.3%) were among infants <6 months (Figure 1). The largest numbers of measles cases <6 months were in countries in the African Region (AFR; 6,312 cases, 37.2%) and the Western Pacific Region (WPR; 5,354, 31.6%). This figure is an under-representation of the actual number of infant cases in the South-East Asian Region (SEAR) and the European Region (EUR) because most countries in those regions were excluded due to case ages only reported in full years.

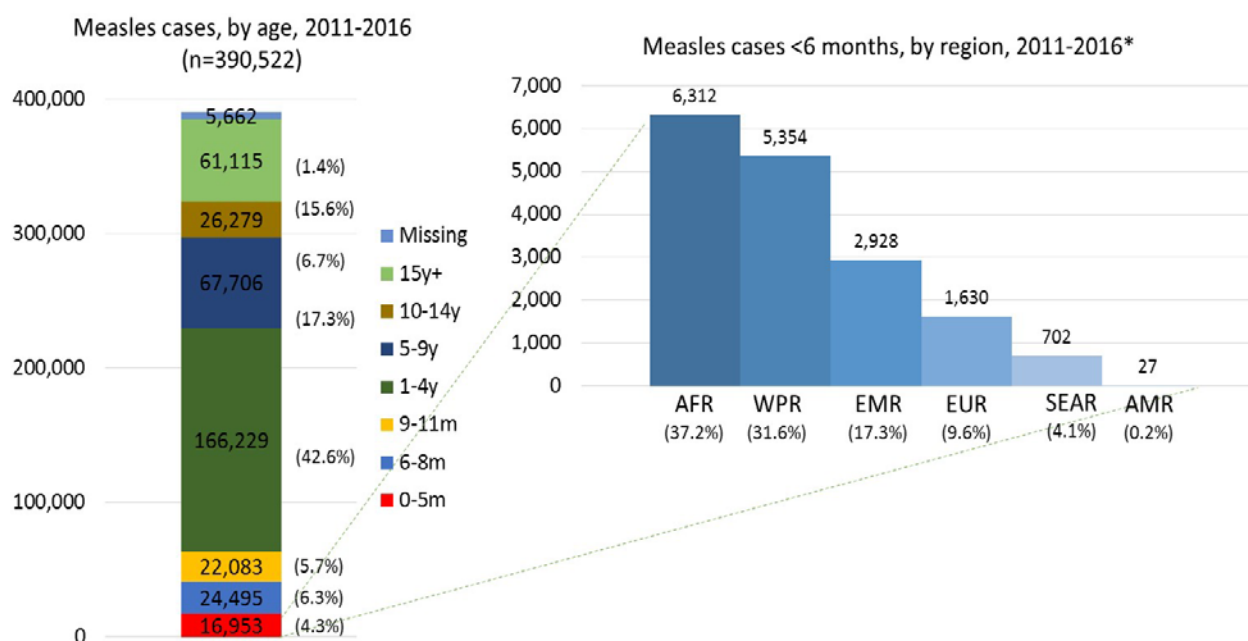


Figure 1. Ages of confirmed measles cases, and cases age <6 months by region, 2011-2016.

Compared to other age groups, infants <6-months were disproportionate among measles cases. Although infants <6 months comprise 1.2% of the total population of the countries included in the analysis, they comprised 4.3% of all measles cases in these countries.

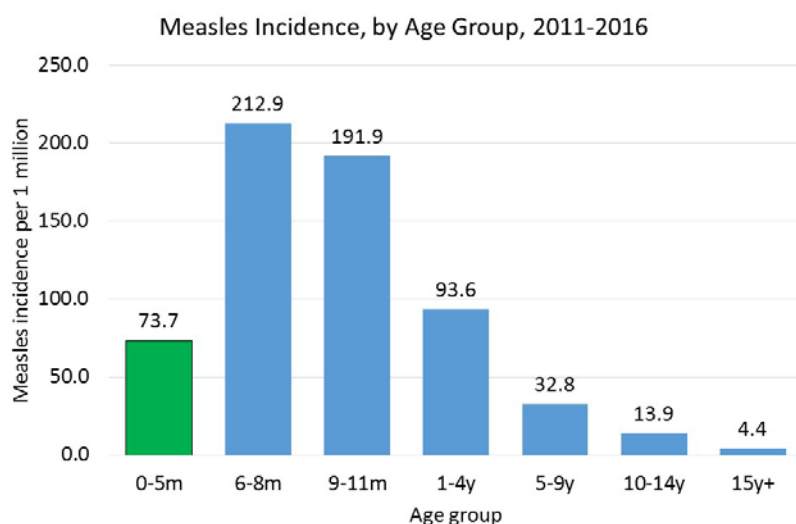


Figure 2. Age-specific average annual measles incidence per 1 million population, 2011-2016.

Average annual measles incidence among infants <6 months during 2011-2016 was 73.7 confirmed cases per 1 million population (Figure 2). Age-specific incidence was highest among 6-8-month-olds (212.9 per 1 million), followed by 9-11-month-olds (191.9 per 1 million). The age-specific incidence for infants <6 months was higher than that of older age groups including 5-9 years, 10-14 years, and ≥ 15 years.

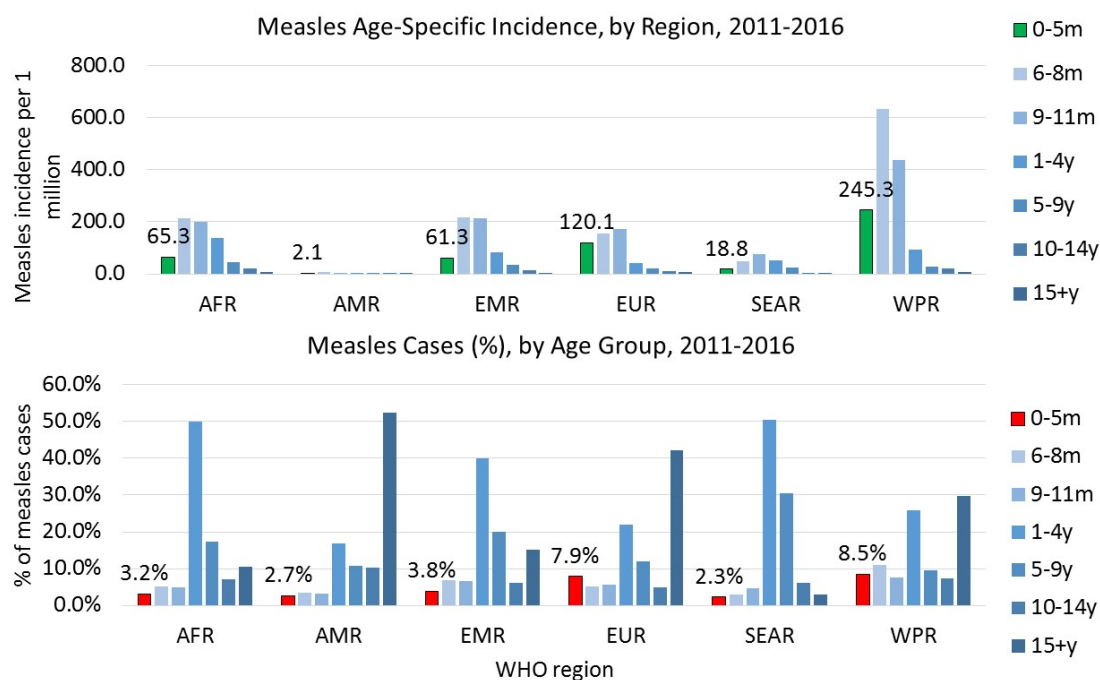


Figure 3. Age-specific incidence and percent of cases by age group, stratified by region, 2011-2016.

Compared to the <6-month incidence across all regions (73.7 cases per 1 million), the two regions with the highest <6-month incidences were EUR (120.1 per 1 million, figure based on 9 out of 39 EUR countries) and WPR (245.3 per 1 million) (Figure 3). The lowest <6-month incidence occurred in the Region of the Americas (AMR; 2.1 per 1 million).

Across all WHO regions, the highest age-specific incidence was among the 6-8 month age group and the 9-11 month age group (Figure 3). In EUR and WPR regions, the incidence among infants <6 months was higher than the incidence among older children aged 1-4 years. The percentage of all measles cases that were <6 months was highest in EUR (7.9%) and WPR (8.5%), notably the same two regions with the highest <6 month incidences. In the other regions, the percentage of measles cases that were <6 months ranged from 2.3% to 3.8%.

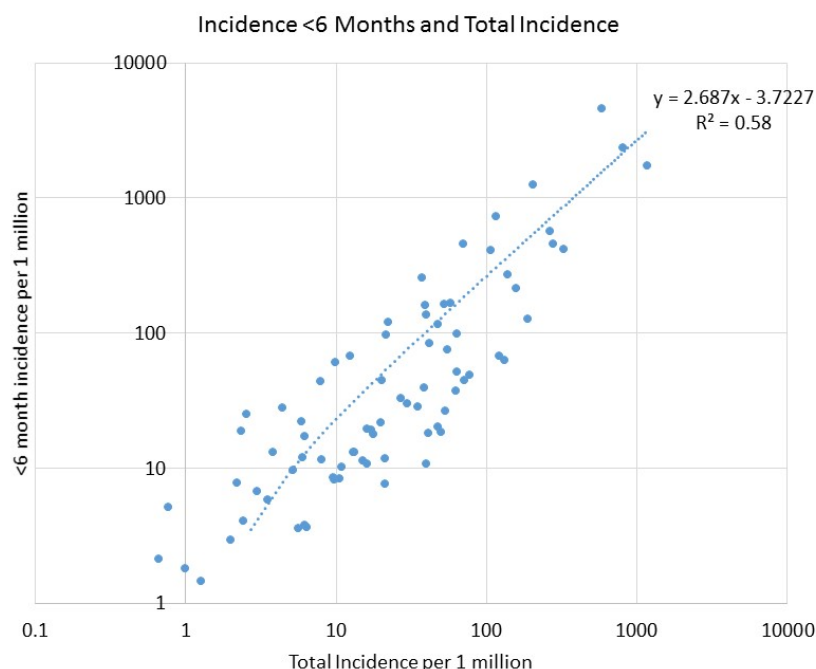


Figure 4. Correlation between incidence <6 months and total incidence (all ages), 2011-2016.

There was a strong and generally linear correlation between incidence in the <6 month age group and total incidence among all ages ($R^2 = 0.58$, $p < 0.0001$) (Figure 4). In countries where overall incidence was high, <6-month incidence also tended to be high.

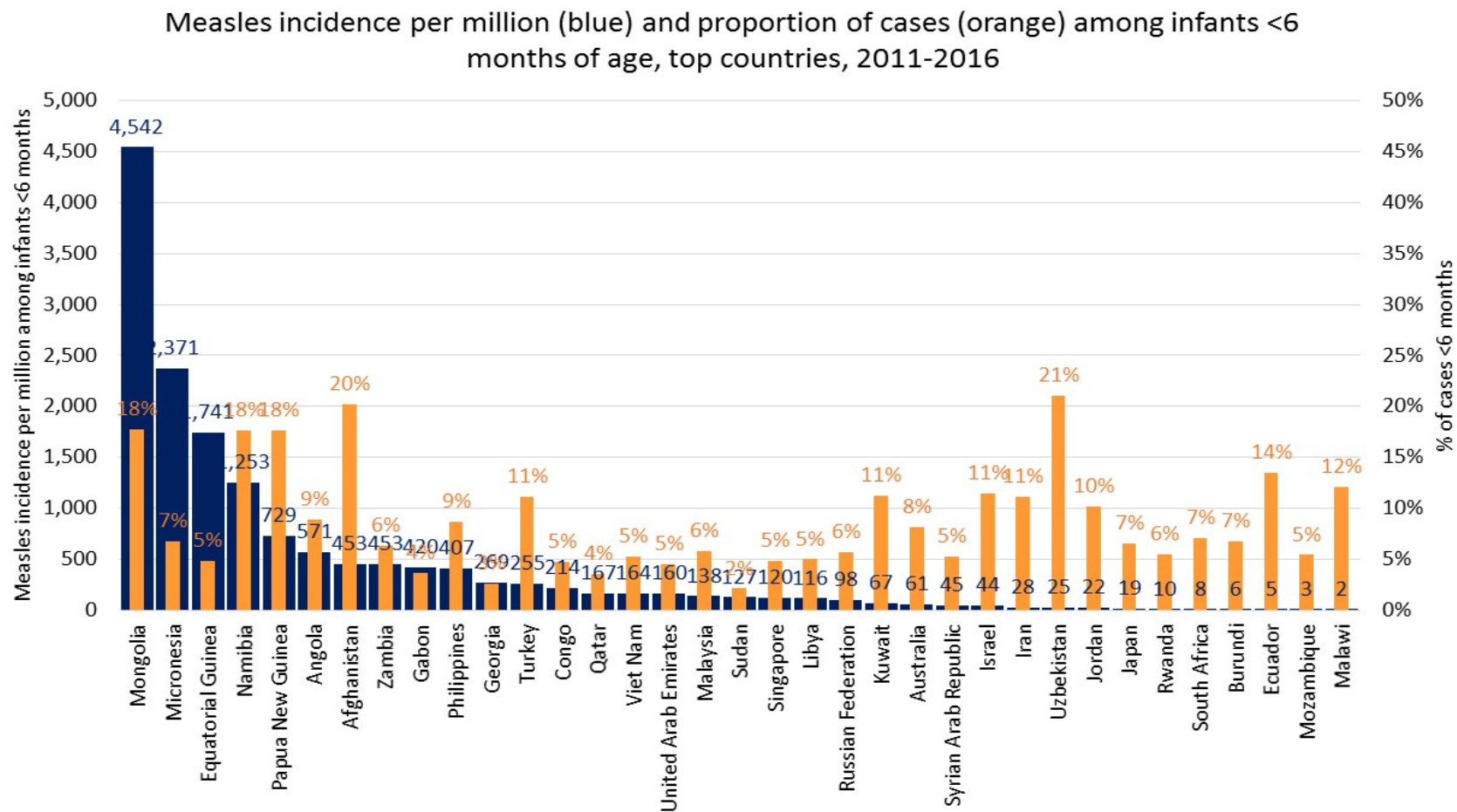


Figure 5. Measles incidence per 1 million and proportion of cases among infants <6 months of age, top countries, 2011-2016.

The countries with the highest <6-month average annual incidence during 2011-2016 were Mongolia, Micronesia, Equatorial Guinea, Namibia, and Papua New Guinea (Figure 5; shown in blue bars). All of these countries had large outbreaks at some point during 2011-2016. The percentage of all confirmed cases that were <6 months ranged from 0% (Djibouti, not shown in Figure) to 21% (Uzbekistan). The average proportion of cases that were <6 months old in a country was 5.2%, and the median was 3.5% (Q1 - Q3: 2.3% - 6.1%).

Bivariate (unadjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months

In order to estimate associations between country/programmatic characteristics and measles among infants <6 months, we used three types of regression models to estimate associations with: 1) incidence per million among infants <6 months (a continuous variable), 2) proportion of cases among infants <6 months (a continuous variable), and 3) a pre-determined cut-off for a “high” proportion of cases among infants <6 months ($\geq 5\%$ versus $<5\%$).

In bivariate unadjusted regression analyses, some characteristics were found to be associated with at least one of the measures indicating disproportionately more measles among infants <6 months compared to other ages. Specifically, countries with the following characteristics had either increased proportions of cases among infants <6 months or higher incidence among infants <6 months: WPR, upper-middle income, $\geq 95\%$ MCV1 coverage, 80-89% or 90-94% MCV2 coverage, and MCV2 introduced. Several of the country/programmatic characteristics that we analyzed had no statistically significant associations with any of the three measures of measles among infants <6 months of age, including age at MCV1 or MCV2 administration, year of MCV1 or MCV2 introduction, number of years since last SIA, birth rate, and population density.

Multivariate (adjusted) analysis of associations between country/programmatic characteristics and measles among infants <6 months

In multivariate regression, variables were included in a fully adjusted model if they were significantly associated in at least one of the regression models. The only variable that was significant when adjusting for all other variables was $\geq 95\%$ MCV1 coverage, which was associated with a higher proportion of cases among infants <6 months.

Limitations

This epidemiologic analysis of measles case-based surveillance data has several limitations. First, data from several countries were excluded from these analyses because they contained incomplete age data. This included a majority of EUR countries, and almost all SEAR countries. Consequently, some countries with recent large outbreaks (e.g., Romania) were not included in this analysis. It would be beneficial to be able to include such countries in the analysis. Second, the quality of some of the data used in this analysis may be sub-optimal. The sensitivity of the case-based surveillance data is unknown. Sensitivity of surveillance data may vary by age groups even within the same country, but we were not able to measure or estimate that. There may be reporting bias in which younger cases are more likely to be reported (younger infants may be more likely to have severe disease and require medical care). Vaccination coverage data estimates are based on countries' administrative data and WHO/UNICEF estimates, and the quality probably varies in different regions and/or countries. Third, surveillance data from India do not represent a truly case-

based surveillance system, so those data were included in the epidemiologic analysis, but were not included in the regression analysis. Fourth, this was an ecologic analysis at the country level rather than an analysis of individual-level data. This limits our ability to investigate how individual level characteristics such as family composition or maternal immunization affect infants. Our results can only be generalized at the country level. Fifth, due to its observational nature, results from this study can imply only association, and not causation.

Conclusions

During 2011-2016, there were almost 17,000 confirmed measles cases among infants <6 months in the countries included in our analysis. There was a significant linear correlation between incidence in the <6 month age group and total incidence among all ages. Multivariate adjusted analysis showed the only variable significant associated with a higher proportion of cases among infants <6 months of age was high MCV1 coverage.

Future research should attempt to determine the source of measles transmission to infants <6 months. Family structures and transmission patterns should be studied to determine whether these infant cases are primary or secondary cases in families, whether nosocomial transmission to infants is a problem, and the role of maternal immunity sourced from vaccination or infection. Answering these questions will help to determine whether infants <6 months must be protected directly through vaccination, or whether they can be protected indirectly by reducing or eliminating transmission in older children and adults. Outbreak investigations in which these data can be collected should be supported in representative communities.

2. Systematic literature review and meta-analyses of the benefits and risks of measles vaccination below 6 months of age

Laura Nic Lochlainn, Susan Hahné, RIVM, 8th September 2017

A comprehensive systematic review and meta-analysis of measles containing vaccines (MCV) administered to infants <9 months of age was conducted in 2015 by the National Institute for Public Health and the Environment (RIVM) in the Netherlands.¹ The authors concluded that humoral immunogenicity was dependent on age of MCV, as well as on the vaccine strain and presence of maternal antibodies. Based on this systematic review and meta-analysis, and other evidence, SAGE made recommendations that infants from 6 months of age receive a supplementary dose of MCV under certain conditions².

However, recent outbreaks have found many cases of measles are occurring in children less than 6 months of age. As a result, countries have requested information on the benefits and risks of providing MCV <6 months of age. Therefore, RIVM conducted an updated systematic review and meta-analysis with the following primary questions:

- What is the immunogenicity, duration of immunity, efficacy and effectiveness of MCV (M, MR and MMR) when given to infants younger than 6 months of age (as compared infants aged 6-8 months).
- Does a dose of MCV administered <6 months of age blunt the immune response to a subsequent dose of measles vaccine?
- Is the safety profile for infants vaccinated with MCV <6 months of age comparable with infants vaccinated with MCV at 6-8 months of age?

An initial literature search was carried out on 01 June 2015 for any articles published in relevant databases reporting MCV <9 months.¹ An updated search was carried out on 13 April 2017 for articles published after 01 January 2015 reporting MCV <6 months.

Data on the following outcomes were extracted from included studies: immunogenicity (humoral and cellular), vaccine efficacy or effectiveness (VE), duration of immunity, blunting and safety. Where appropriate, results were stratified by age at administration of MCV in months. Where sufficient data was available, results were pooled by meta-analyses. Heterogeneity between results of different studies were examined with forest plots and quantitatively using the I^2 statistic. Where possible, random effects meta-regression was employed. The quality of all included studies was assessed using the GRADE methodology.

From the initial literature search carried out in June 2015, 867 references were identified and 18 met criteria for inclusion in the updated review. Following the updated literature search in April 2017, an additional 186 references were identified and one met criteria for inclusion. Therefore, a total of 19 studies from both searches were included. The majority of included studies (n=16) were from Africa, while two were from Asia and one from Europe.

¹ Nic Lochlainn, L. et al., 2015 Measles vaccination below 9 months of age: Systematic literature review and meta-analyses of effects and safety. Available at:

http://www.who.int/immunization/sage/meetings/2015/october/2_MCV_below_9_months_Effect_safety_28092015.pdf

² World Health Organization. "Measles vaccines: WHO position paper, April 2017–Recommendations." Vaccine (2017).

The pooled estimates for seroconversion following MCV <6 months were derived from five studies and found that MCV at 4 months of age increased from 50% (95% CI 29-71) to 67% (51-81%) following MCV at 5 months of age.^{3,4,5,6,7,8} As a reference, the proportion seroconverted following MCV1 at 6 months of age (of 76%)¹, at 9 months of age (92%)⁹ and at 11 months of age (98%)⁹ were included in Figure 1 where it can be seen that seroconversion rates following MCV1 <6 months of age are lower than the reference values.

The proportion of infants seroconverting was found to be further dependent on the vaccine strain used, with a seroconversion rate of 83% achieved at 5 months with the Edmonston-Zagreb strain (Figure 1).

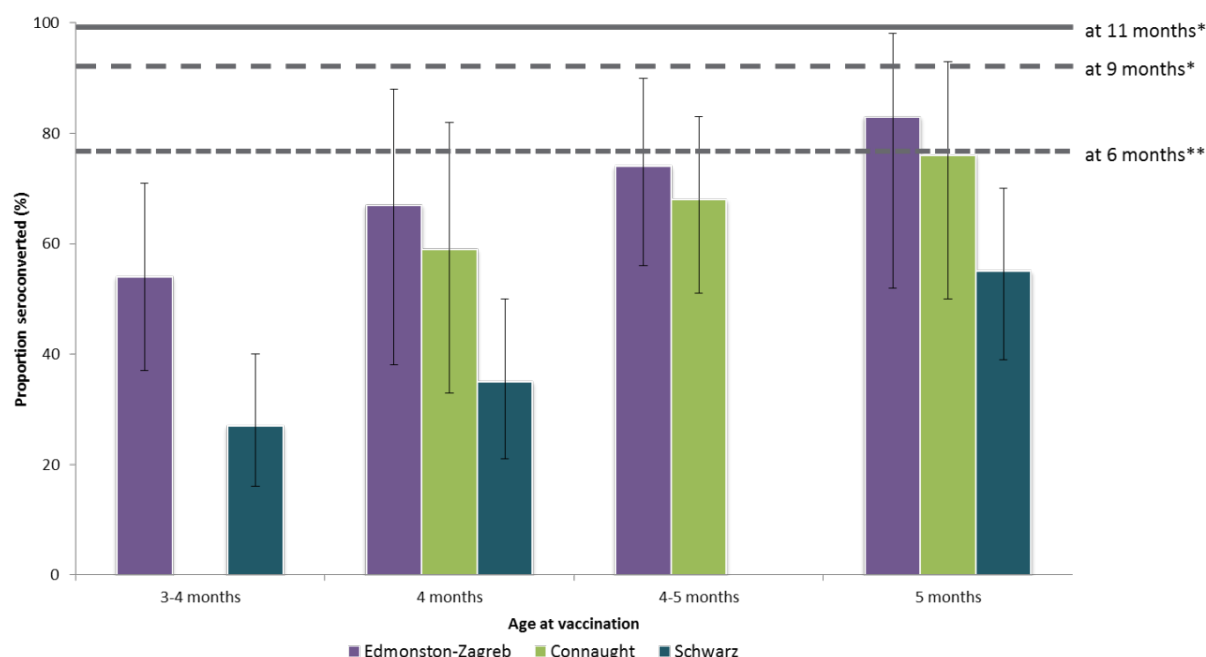


Figure 1: Pooled estimates of the proportion seroconverted by age of MCV (4-5 months), derived from five studies. Error bars present 95% confidence intervals. *This horizontal line represents the proportion of infants seroconverted following MCV at 6 months (small dashed line) Nic Lochlainn et al., 2015¹. ******The horizontal lines represent the median proportion of infants seroconverted following MCV at 9 months (wide dashed line) and 11 months (filled line) Moss and Scott, 2009⁹.

³ Anonymous. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. Collaborative study by the Ministry of Health of Kenya and the World Health Organization. Bull World Health Organ. 1977;55(1):21-31.

⁴ Khanum S, et al., Comparison of Edmonston-Zagreb and Schwarz strains of measles vaccine given by aerosol or subcutaneous injection. Lancet. 1987;1(8525):150-3.

⁵ Ndumbe PM, et al., Comparison of Edmonston-Zagreb, Connaught and Schwarz measles vaccines in Cameroonian infants aged 3-8 months. Vaccine. 1995;13(3):276-80.

⁶ Rogers S, et al., Immunogenicity of standard dose Edmonston-Zagreb measles vaccine in highland Papua New Guinean children from four months of age. J Trop Med Hyg. 1991;94(2):88-91.

⁷ Jensen TG, et al. Trials of Edmonston-Zagreb measles vaccine in Guinea-Bissau: serological responses following vaccination with Edmonston-Zagreb strain at 4-8 months versus vaccination with Schwarz strain at 9-12 months of age. Vaccine. 1994;12(11):1026-31.

⁸ World Health Organization. Expanded Programme on Immunisation: Seroconversion after measles immunisation - Tanzania. WER. 1981;30:3.

⁹ Moss, W.J. and Scott, S. 2009 "WHO Immunological Basis for Immunization Series Module xx: Measles." Geneva, Switzerland.

GMTs were found to be higher following MCV <6 months compared to ≥6 months of age, but results for MCV <6 months were derived from only two studies.^{10,11}

There was no evidence to assess measles avidity following MCV <6 months of age.

One study was found comparing cellular immunity among unvaccinated infants and infants vaccinated with MCV1 at 4 months and 9 months of age. They study found infants vaccinated at 4 months had higher IFN-γ memory T-cell responses at 9 months compared to the unimmunized group. They also found that the presence of maternal antibodies had no effect on memory T-cell responses nor did the number of MCVs the infants received.¹²

Estimates of the proportion seropositive by age of MCV ranging from 3 to 5 months, pooled across strain and titre were derived from eight studies.^{Error! Bookmark not defined.,7>Error! Bookmark not defined.,13,14,15,16,17}

Seropositivity was found to increase with age and to be strain dependent (Figure 2). The overall pooled estimate for seropositivity following MCV <6 months was 68% (95%CI 58-78).

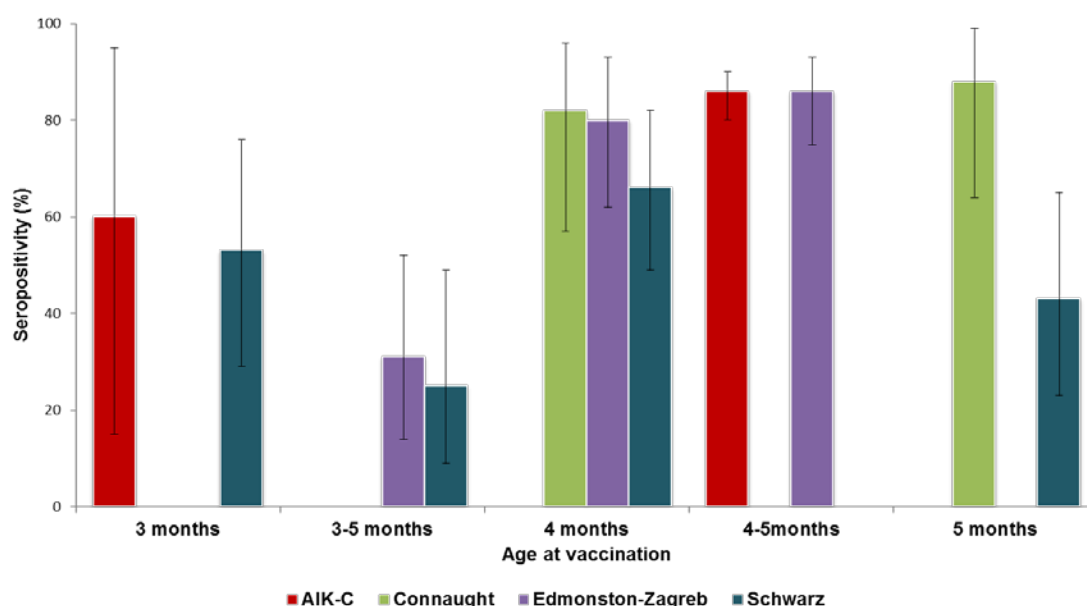


Figure 2: Pooled estimates of the proportion seropositive by age of MCV (3-5 months) and vaccine strain derived from seven studies. Error bars present 95% confidence intervals.

¹⁰ Ko B, et al., Neutralising antibody responses to two doses of measles vaccine at 5 and 13 months of age in the United Kingdom. *Commun Dis Public Health*. 1999;2(3):203-6.

¹¹ Whittle HC, et al. Effects of dose and strain of vaccine on success of measles vaccination of infants aged 4-5 months. *Lancet*. 1988;1(8592):963-6.

¹² Njie-Jobe J, et al. Immunological impact of an additional early measles vaccine in Gambian children: responses to a boost at 3 years. *Vaccine*. 2012;30(15):2543-50.

¹³ Martins C, et al. Measles virus antibody responses in children randomly assigned to receive standard-titer edmonston-zagreb measles vaccine at 4.5 and 9 months of age, 9 months of age, or 9 and 18 months of age. *J Infect Dis*. 2014;210(5):693-700.

¹⁴ Kiepiela P, Coovadia HM, Loening WE, Coward P, Botha G, Hugo J, et al. Lack of efficacy of the standard potency Edmonston-Zagreb live, attenuated measles vaccine in African infants. *Bulletin of the World Health Organization*. 1991;69(2):221-7.

¹⁵ Sakatoku H, Nakano T, Arai S, Afari EA. Antibody response to measles immunization in rural Ghanaian infants. *J Trop Pediatr*. 1994;40(5):291-3.

¹⁶ Tidjani O, Grunitsky B, Guerin N, Levy-Bruhl D, Lecam N, Xuereff C, et al. Serological effects of Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains given at ages 4-5 or 8-10 months. *Lancet*. 1989;2(8676):1357-60.

¹⁷ Martins CL, et al. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ*. 2008;337:a661.

For vaccine efficacy and effectiveness and safety, there were two eligible studies following MCV1 <6 months which had small sample sizes. One study reported vaccine effectiveness of 54% (95%CI 0-84%) among infants vaccinated with MCV1 below 5 months (n=5), and vaccine effectiveness of 37% (95%CI 0-74%) among infants vaccinated with MCV1 at 6-8 months (n=11).¹⁸ The second study reported vaccine efficacy among infants vaccinated with MCV1 at 4.5 months of 91% (95%CI 62-98) (n=43), vaccine efficacy against measles related hospitalisation was 100% (95%CI 46-100)] and against measles related death [100% (95%CI -42-100)]. However, the follow-time was very short.¹⁷ Only two studies were identified reporting duration of immunity following MCV <6 months and ≥ 6 six months of age. One study infants who responded to MCV1 had significantly higher responses four to six weeks following MCV2 at 13 months, compared to those who did not respond to MCV1.^{Error!}

^{Bookmark not defined.} Martins *et al.*, examined the GMTs of infants following vaccination with MCV1 at 4.5 months and MCV2 at 9 months using standard-titer Edmonston-Zagreb. Overall, they found that at 24 months, infants vaccinated early maintained high protective antibody levels.^{Error! Bookmark not defined.}

The effect of maternal antibodies following MCV <6 months was examined as a secondary question in this review. Results of the meta-analysis of the proportion seroconverted stratified by presence of maternal antibodies found that the proportion seroconverted is higher in infants without maternal antibodies compared to those with maternal antibodies (Figure 3).

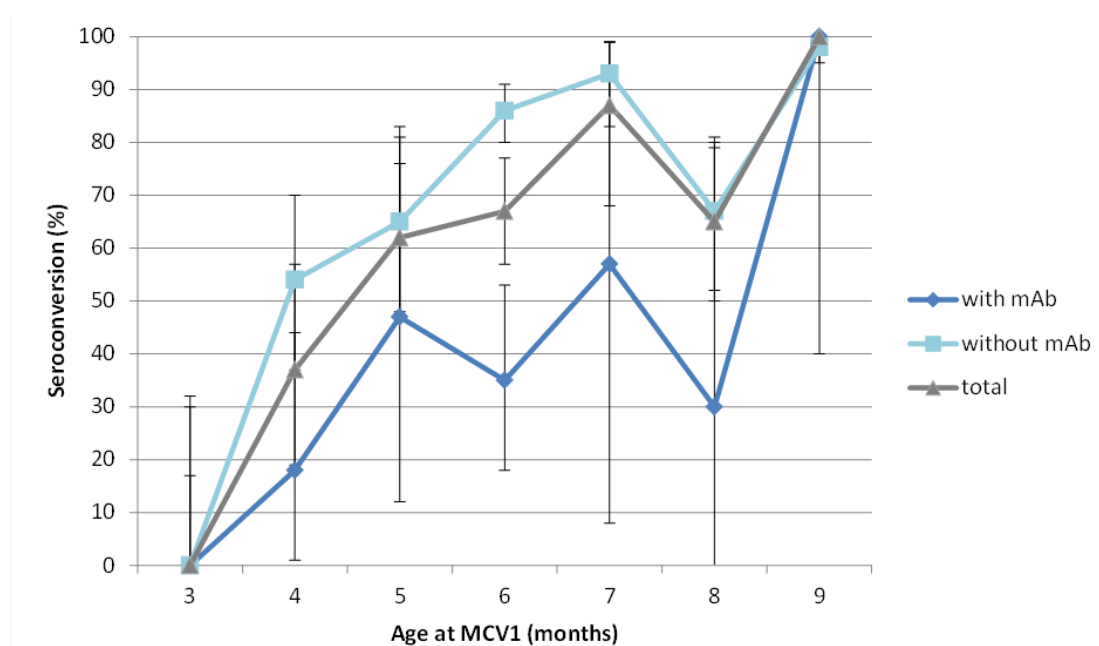


Figure 3: Proportion seroconverted by month of MCV, stratified by presence of maternal antibodies.

Seventeen of nineteen included studies were observational. Therefore, for all outcomes, the quality of evidence was found to be moderate, low or very low but of importance.

¹⁸ Hull HF, et al., Measles mortality and vaccine efficacy in rural West Africa. Lancet. 1983;1(8331):972-5.

Conclusions:

The authors concluded that humoral immunogenicity following MCV<6 months of age was dependent on age of MCV and levels of maternal antibodies. In addition, they concluded that there was limited evidence available for cellular immunity, vaccine effectiveness, duration of immunity, safety and blunting. This paucity of data, together with heterogeneity between studies, warrants caution when interpreting the results.

In order to obtain reliable evidence to inform decisions, the authors recommend conducting a trial, with a long follow-up after subsequent doses of MCV in an endemic area with MCV at 4-6-9 months, or observational case-control studies in high endemicity areas where MCV has been given at 6 months of age in the past e.g. South Africa or Papua New Guinea. Finally, seroepidemiological studies in low and middle income countries could provide a better understanding of population immunity towards measles and other vaccine preventable diseases.

SAGE WG Conclusions and Recommendations:

- The data from the systematic review are insufficient to recommend vaccination under 6 months of age.
- The current policy on vaccination of infants from 6 months of age is already broad and inclusive, so there is no need to expand the current recommendations.
- Findings support the importance of sustained high population immunity achieved through high coverage as the primary strategy for protecting infants under 6 months of age, supported by high quality surveillance and coverage monitoring.
- Further research is needed to address the substantial information gap and to better understand the transmission source, the disease burden and the role of factors such as maternal immunity and blunting among affected infants less than 6 months of age. Community-based outbreak investigations to determine actual sources of infection for children <6 months of age are encouraged. A better understanding of measles virus transmission to young infants (e.g. from school-age siblings or parents) would enable effective targeting of these transmission drivers.
- Improved data quality and tools to be able to interpret data according to data quality, completeness of surveillance and other contextual factors at country and region levels are needed.
- Clinical trials in infants <6 months may be informative to improve the evidence concerning effectiveness, safety and long term effects on the effectiveness of subsequent MCV doses (i.e. MCV1 and MCV2). In addition, studies in countries which have introduced MCV1 at 6 months could add to the body of evidence