Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis

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Summary

Background Measles is an important cause of death in children, despite the availability of safe and cost-saving measles-containing vaccines (MCVs). The first MCV dose (MCV1) is recommended at 9 months of age in countries with ongoing measles transmission, and at 12 months in countries with low risk of measles. To assess whether bringing forward the age of MCV1 is beneficial, we did a systematic review and meta-analysis of the benefits and risks of MCV1 in infants younger than 9 months.

Methods For this systematic review and meta-analysis, we searched MEDLINE, EMBASE, Scopus, Proquest, Global Health, the WHO library database, and the WHO Institutional Repository for Information Sharing database, and consulted experts. We included randomised and quasi-randomised controlled trials, outbreak investigations, and cohort and case-control studies without restriction on publication dates, in which MCV1 was administered to infants younger than 9 months. We did the literature search on June 2, 2015, and updated it on Jan 14, 2019. We assessed: proportion of infants seroconverted, geometric mean antibody titre, avidity, cellular immunity, duration of immunity, vaccine efficacy, vaccine effectiveness, and safety. We used random-effects models to derive pooled estimates of the endpoints, where appropriate. We assessed methodological quality using the Grading of Recommendations, Assessment, Development, and Evaluation guidelines.

Findings Our search identified 1156 studies, of which 1071 were screened for eligibility. 351 were eligible for full-text screening, and data from 56 studies that met all inclusion criteria were used for analysis. The proportion of infants who seroconverted increased from 50% (95% CI 29–71) for those vaccinated with MCV1 at 4 months of age to 85% (69–97) for those were vaccinated at 8 months. The pooled geometric mean titre ratio for infants aged 4–8 months vaccinated with MCV1 compared with infants vaccinated with MCV1 at age 9 months or older was 0·46 (95% CI 0·33–0·66; I^2=99·9%, p<0·0001). Only one study reported on avidity and suggested that there was lower avidity and a shorter duration of immunity following MCV1 administration at 6 months of age than at 9 months of age (p=0·0016) or 12 months of age (p<0·001). No effect of age at MCV1 administration on cellular immunity was found. One study reported that vaccine efficacy against laboratory-confirmed measles virus infection was 94% (95% CI 74–98) in infants vaccinated with MCV1 at 4·5 months of age. The pooled vaccine effectiveness of MCV1 in infants younger than 9 months against measles was 58% (95% CI 9–80; I^2=84·9%, p<0·0001). The pooled vaccine effectiveness estimate from within-study comparisons of infants younger than 9 months vaccinated with MCV1 were 51% (95% CI –44 to 83; I^2=92·3% , p<0·0001), and for those aged 9 months and older at vaccination it was 83% (76–88; I^2=93·8% , p<0·0001). No differences in the risk of adverse events after MCV1 administration were found between infants younger than 9 months and those aged 9 months of older. Overall, the quality of evidence ranged from moderate to very low.

Interpretation MCV1 administered to infants younger than 9 months induces a good immune response, whereby the proportion of infants seroconverted increases with increased age at vaccination. A large proportion of infants receiving MCV1 before 9 months of age are protected and the vaccine is safe, although higher antibody titres and vaccine effectiveness are found when MCV1 is administered at older ages. Recommending MCV1 administration to infants younger than 9 months for those at high risk of measles is an important step towards reducing measles-related mortality and morbidity.

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See Comment page 1157

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Introduction

Measles is a highly contagious viral disease with a high burden of morbidity and mortality, particularly in children in low-income countries.[1,2] Between 2000 and 2017, improvements in measles control reduced the estimated global number of measles-related deaths by

Research in context

Evidence before this study

As part of WHO's Immunological Basis for Immunization series, the 2009 Measles Module found that the proportion of infants responding to their first measles-containing vaccine (MCV1) increases with age at vaccination. Evidence of the age-specific effects of measles vaccination is essential to guide policy decisions on the optimal age of MCV1 administration. At the time of our study, WHO recommended that, as part of routine immunisation, all children should receive two doses of a MCV, with the first dose administered at 9 months of age in high-risk settings. However, countries with high incidence of measles infection questioned whether administering MCV1 to infants younger than 9 months could improve measles prevention in this age group because infants in these settings have high measles-related mortality. Moreover, an increasing number of infants are born to immunised mothers and are thus susceptible to measles infection at an earlier age because they lose passive immunity earlier than infants whose mothers have naturally acquired immunity. We therefore did a systematic review and meta-analyses of the immunogenicity, effectiveness, and safety of MCV1 administered to infants younger than 9 months.

Added value of this study

To our knowledge, our systematic review and meta-analysis is the first to examine the immunogenicity, effectiveness, and safety of MCV1 administered to infants younger than 9 months. We found that MCV1 vaccination in this age group induces a good immune response, which increased with increasing age at vaccination. MCV1 administered to infants younger than 9 months confers protection and is safe, although higher antibody titres and vaccine effectiveness are seen in infants who are vaccinated later. Little evidence was available on antibody avidity, duration of immunity, and cellular immunity following MCV1 vaccination before 9 months of age.

Implications of all the available evidence

Findings from our systematic review were presented at the 2015 WHO Strategic Advisory Group of Experts (SAGE) on Immunization meeting, which recommended that a MCV could be administered as early as 6 months of age for infants at high risk of contracting measles. However, a dose of MCV given to those younger than 9 months should be considered a supplementary dose, and two additional MCV doses should be given for optimal protection, according to national immunisation schedules. This updated WHO recommendation is an important step towards reducing measles-related mortality and morbidity. Further evidence on the effect of different measles vaccination schedules, derived from clinical, immunological, epidemiological, and modelling studies, could aid in the design of optimal MCV vaccination schedules that are needed to achieve global targets for measles control and regional elimination goals.

80%, from 545 174 to 109 638.[3] However, increases in the coverage of measles vaccination have slowed over the past 5–6 years. As a result, measles outbreaks still occur, predominantly in areas where weak immunisation systems have led to suboptimal immunity.[2,4]

WHO recommends that children receive two doses of a measles-containing vaccine (MCV) as part of routine immunisation. In countries where measles-related mortality is high in the first year of life, the first MCV dose (MCV1) is recommended at 9 months of age, whereas in countries with low measles transmission, MCV1 is recommended at 12 months of age.[1] A second dose of a MCV (MCV2) is offered in 171 (88%) WHO member states.[5]

Measles incidence has increased in several WHO regions in infants younger than 9 months, adolescents, and adults. The increase in young infants has been particularly apparent in Europe,[6] Asia,[7,8] and Africa,[9] and this trend might worsen because of declining immunity and increased transmission in adolescents and adults. Another explanation for the increase of measles in young infants is that mothers who have vaccine-induced antibodies lose passive immunity approximately 3 months earlier than infants with mothers who have naturally acquired immunity.[10–12] Since measles in young infants is more severe than in older children,[13] they disproportionally contribute to the burden of measles-related morbidity and mortality.

In response to these observations, suggestions have been made to offer MCV1 to infants younger than 9 months in areas with high measles virus transmission.[14] The optimal timing for the first MCV depends on the age at which the infant is at greatest risk of infection, the age when their immune system is sufficiently mature to respond to the vaccine, and the age when maternal antibodies, which interfere with the vaccine response, are no longer present.[13,15] Additionally, the uptake of the first MCV at different ages is of relevance. Before initiating our review, WHO guidelines for measles vaccination and public assessment reports by the European Medicines Agency did not provide recommendations for MCV use in infants younger than 9 months.[1,16,17]

We, therefore, reviewed and analysed the evidence on immunogenicity, efficacy, effectiveness, duration of immunity, and safety of MCV1 vaccination to infants younger than 9 months.

Methods

Search strategy and selection criteria

Our search strategy for this systematic review and meta-analysis consisted of four components: a library database search of MEDLINE, EMBASE, Scopus, Proquest, and

Global Health; a search of the WHO library database (WHOLIS) and the WHO Institutional Repository for Information Sharing database (IRIS); consulting WHO Measles and Rubella working-group experts in September 2015; and screening bibliographies of included articles and five key reviews.[13,15,18–20] Additional references found in this way were subject to the same screening and selection process as articles found in the primary search. The results were restricted to articles in English, Dutch, German, French, and Spanish. We did not set any time limit to dates of published articles in our search. We did the literature search on June 2, 2015, and updated it on Jan 14, 2019.

We developed search terms for each database using controlled vocabulary (appendix pp 2–7) to capture publications on the effects and safety of MCV1 in infants younger than 9 months. We searched for randomised and quasi-randomised controlled trials, outbreak investigations, and cohort and case-control studies on vaccination schedules of currently licenced MCVs. When the first dose of a MCV is given below the recommended age, it is typically referred to as MCV0, implying that two subsequent MCV doses are needed for optimal protection. We, however, refer to MCV1 for all first MCV doses, without making any recommendation about the total number of doses needed for optimal protection. Our search aimed to find articles containing data on immunogenicity, vaccine efficacy, vaccine effectiveness, and duration of immunity and safety of MCV1 administered to infants younger than 9 months. When studies on the effects of administration of MCV1 in this age group also contained data on MCV1 in older infants, we also extracted these data and did within-study comparisons for antibody titres, vaccine effectiveness, and safety. Studies that did not meet the inclusion criteria or study type and those that reported vaccines with non-standard high viral titres were excluded. A complete list of the exclusion and inclusion criteria is available in the appendix (p 8).

After deleting duplicate studies, two reviewers selected 10% of the retrieved articles at random and independently reviewed the title and abstract according to the predefined set of inclusion criteria. The application of the inclusion criteria was consistent (≤10% disagreement between the two reviewers), indicating high concordance.[21] The reviewers divided the remaining articles to continue the title and abstract screening separately. This selection process was also applied to the full-text screening of included articles eligible for data extraction (≤10% disagreement between the two reviewers). In case of uncertainty about inclusion or exclusion, the reviewers consulted each other. Discrepancies during the selection process were resolved by a third reviewer.

Data analysis

We considered the following outcome measures for immunogenicity: proportion of infants seroconverted, geometric mean antibody titres, avidity index, T-cell stimulation index for cellular immunity, duration of immunity, vaccine efficacy, and vaccine effectiveness. For data on vaccine efficacy from randomised controlled trials, per-protocol results were extracted. We also extracted information on study characteristics. For safety outcomes, we considered serious adverse events following immunisation (AEFI) and proportions of infants with fever, rash, diarrhoea, conjunctivitis, and local reactions.

The included articles were divided among four reviewers who extracted study characteristics and outcomes using a predefined form. The form included 128 fields to capture data relating to the author, study year, type of study, country, study population, vaccine type, vaccine titre, test used, test definitions, summary estimates, 95% CIs, and SEs, among others. Data in all forms were checked by at least two reviewers against the original publication, and subsequently entered into a Microsoft Access database. We used the Grading of Recommendation Assessment, Development and Evaluation (GRADE) guidelines[22] to classify the quality of the evidence found. We used eight indicators to assess risk of bias within and between studies: (1) representativeness, (2) attrition bias, (3) reporting bias, (4) laboratory confirmation of measles virus infection, (5) confirmation of vaccination status, (6) comparability of control group with vaccinated group, (7) time between vaccination and sampling, and (8) study design. These study characteristics were reviewed per outcome by four reviewers using Review Manager 5.1 (The Nordic Cochrane Centre; Copenhagen, Denmark) and entered into GRADE evidence summary forms.

See Online for appendix

Where possible, results were stratified by month of MCV1 vaccination. Where data were reported with a numerator and a denominator, results were pooled by meta-analyses. We examined heterogeneity between results of different studies in forest plots and using the I^2 statistic to estimate the percentage of the total variation due to between-study variation.[23] Where possible, univariable and multivariable random-effects meta-regression was used to investigate whether determinants including age at MCV1, vaccine strain and titre, continent, type of test, or the decade in which the study data were collected explained heterogeneity between studies.

For our immunogenicity outcome measures, we included data derived from testing venous and capillary blood samples collected in tubes, with a minimum of 4 weeks between vaccination and blood sampling. For the proportion of infants seroconverted, we only included results when seroconversion was defined as a fourfold or greater increase in antibody titre or a change from a negative pre-vaccination titre to a positive post-vaccination titre (appendix pp 9–10). We used random-effects meta-analysis for the proportion of infants seroconverted using the Freeman-Tukey double arcsine transformation for SEs.[24]

We analysed geometric mean titres on a natural logarithmic scale by random-effects meta-analysis, using only studies reporting plaque reduction neutralisation

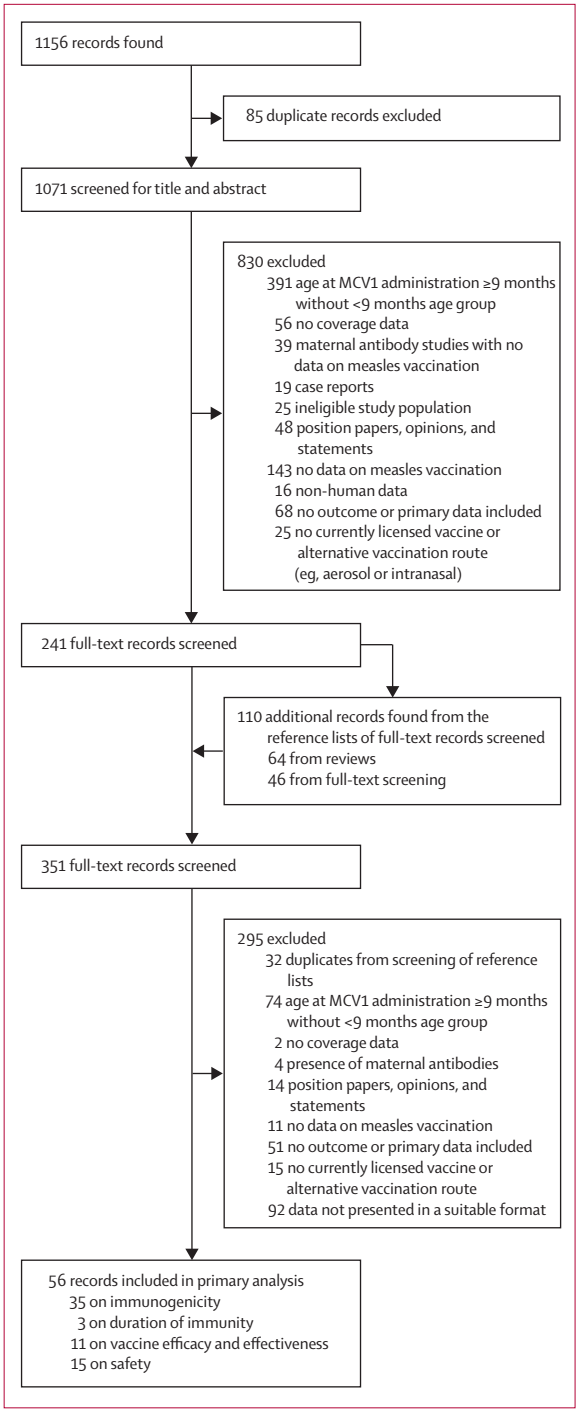

Figure 1: **Study profile**
Some of the 56 records included in the primary analysis had data on more than one outcome. MCV1=first dose of measles-containing vaccine.

testing (PRNT). However, for within-study comparisons of administration of MCV1 to infants younger than 9 months and those aged 9 months or older, we used geometric mean titres by PRNT and other tests. We estimated the weighted mean difference between log-geometric mean titres assessed after MCV1 administration in each of the two age groups by random-effects meta-analysis. The pooled difference was exponentiated to calculate the pooled geometric mean titre ratio. This ratio was applied to the geometric mean titre of antibodies in the younger age group to obtain an estimated geometric mean titre of MCV1 in the older age group.

For studies with data on avidity and cellular immunity, we only assessed those with within-study comparisons of MCV1 administration to infants aged below or above 9 months. For studies reporting the T-cell stimulation index, which is the ratio of mean T-cell counts per minute in antigen wells divided by the mean counts per minute in corresponding control wells, we considered a T-cell stimulation index of 3·0 or greater as positive.

For our assessment of immunity duration, we reviewed studies that reported geometric mean titres and their corresponding CIs or SEs of within-study comparisons of MCV1 vaccination in infants younger than 9 months versus those aged at least 9 months. We calculated ratio differences of geometric mean titres reported at different time intervals between MCV1 vaccination and sampling.

We reviewed findings from studies on vaccine efficacy and vaccine effectiveness and used random-effects meta-analyses on the log-relative risk or log-odds ratio. The pooled log-relative risk was exponentiated to calculate a pooled vaccine effectiveness (1–RR) of MCV1 administered to infants younger than 9 months. We excluded studies that used the screening method, as it approximates vaccine effectiveness by comparing the proportion of vaccinated children among those with disease with the proportion of vaccinated children in the general population, precluding pooling of results. For within-study comparisons of vaccine effectiveness following MCV1 vaccination in infants younger than 9 months versus those aged at least 9 months, both estimates of vaccine effectiveness were separately pooled with random-effects weighting based on infants younger than 9 months.

Within-study comparisons of safety of MCV1 vaccination in infants younger than 9 months with those aged at least 9 months were analysed by pooling the risk differences of rash, fever, conjunctivitis, diarrhoea, and local adverse reactions. Available evidence on serious AEFI (eg, anaphylaxis, convulsions) was summarised.

We used Stata 15.0 statistical software (StataCorp 2017 Release 15; College Station, TX, USA) for all analyses.

Role of the funding source

PMS and TG are employees of the funder of the study and participated in data interpretation and writing of the report. The funder had no role in study design, data collection, and data analysis. All authors had full access to the study data, and the analysis, interpretation, and the decision to publish was solely the responsibility of the authors.

Results

Our search retrieved 1156 records, of which 85 were duplicates and were excluded. The titles and abstracts of the remaining 1071 published articles were screened and 241 articles were found to meet the inclusion criteria and were assessed for eligibility via full-text evaluation (figure 1). 110 additional publications were found through screening the bibliographies of the assessed full-text articles. 295 records in total did not meet the inclusion criteria after this second full-text review. Data from the remaining 56 studies were included in the primary analysis. 35 articles reported relevant information on immunogenicity, three on duration of immunity, two on vaccine efficacy, nine on vaccine effectiveness, and 15 on safety information (appendix pp 11–14).

The estimated proportion of infants who seroconverted was based on 20 studies[25–44] that presented data by age at MCV1 vaccination, ranging from 4 to 8 months. The pooled estimate of the proportion of infants who seroconverted increased from 50% (95% CI 29–71) at age 4 months, to 67% (51–81) at 5 months, 76% (71–82) at 6 months, 72% (56–87) at 7 months, and 85% (69–97) at 8 months (figure 2, appendix pp 15–16). Heterogeneity in the proportion of infants who seroconverted was moderate to high. The forest plots by age at MCV1 and vaccine strain and titre are shown in the appendix (pp 17–21).

Many studies in our search presented results for MCV1 vaccination in a range of ages, rather than by month of vaccination and were therefore not included in our meta-analyses. However, we did additional sensitivity analyses by pooling and comparing seroconversion data from 24 studies presenting data on MCV1 by month of vaccination and age ranges.[25,26,28,29,31,36–40,45–49] The data presented as age ranges were in accordance with our estimates per month of vaccination (appendix pp 22–23).

Multivariable meta-regression analysis showed age (point estimate 0·086, 95% CI 0·022–0·15, p=0·010), the vaccine strain Edmonston-Zagreb-Mexico (0·21, 0·076–0·39, p=0·0043), and vaccine titre (0·13, 0·035–0·22, p=0·0083) as independent determinants of seroconversion, increasing the proportion of infants who seroconverted when vaccinated with MCV1 before 9 months of age. Type of test, continent of study, and decade of data collection were not found to be independent determinants (appendix pp 24–25).

Data from four studies[25,28,36,45] allowed us to pool in a meta-analysis head-to-head comparisons of infants vaccinated with the Schwarz MCV strain with those vaccinated with the Edmonston-Zagreb MCV strain at 6 months of age. 18% (95% CI 2–34, p=0·023) more infants seroconverted when vaccinated with Edmonston-Zagreb strain at 6 months than when vaccinated with the Schwarz strain (appendix p 26). There were insufficient data for head-to-head comparisons of other strains of the measles vaccine or to compare other ages of MCV1 vaccination.

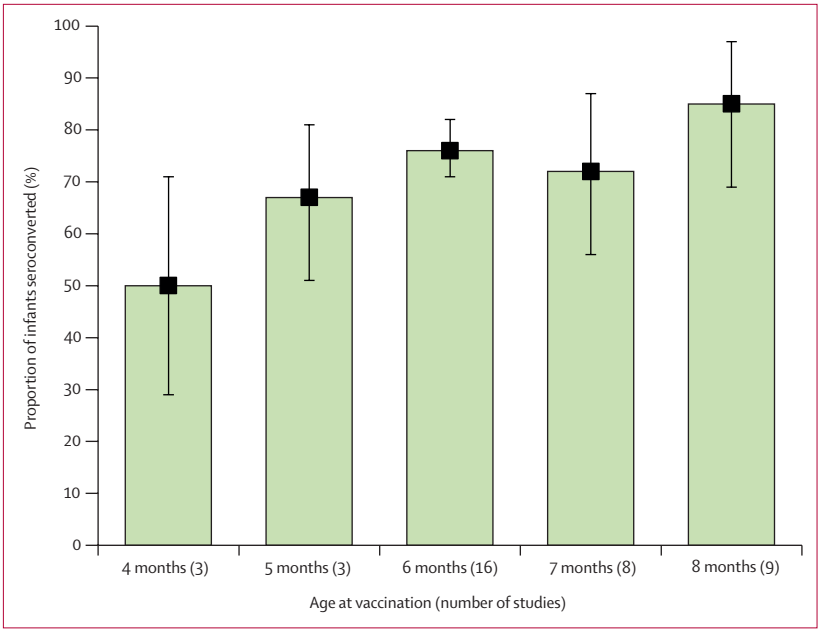

Figure 2: **Pooled estimates of proportion of infants seroconverted, by age of MCV1 (4–8 months) with 95% CIs**
MCV1=first dose of measles-containing vaccine.

Results from meta-regression of studies reporting on seroconversion by age of MCV1 administration stratified by the presence or absence of maternal antibodies showed that seroconversion was significantly reduced when maternal antibodies were present, with a mean difference in the proportion of infants who seroconverted of 33% (95% CI 20–46, p<0·0001; appendix p 35).

We identified five eligible studies[29,50–53] with results on geometric mean titres from PRNT testing with accompanying CIs or SEs. The pooled geometric mean titre estimate following MCV1 vaccination in infants younger than 9 months was 248 mIU/mL (95% CI 142–433; I^2=96·4%, p<0·0001; appendix p 27).

For within-study comparisons of geometric mean titres of infants aged 4–8 months at vaccination with MCV1 with infants vaccinated at age 9 months or older, six studies[32,35,50,54–56] presenting data on geometric mean titres (by PRNT and other tests) were included. The pooled geometric mean titre ratio for infants vaccinated with MCV1 at age 4–8 months compared with infants vaccinated at age 9 months or older was 0·46 (95% CI 0·33–0·66; figure 3). Applying this ratio to the pooled geometric mean titre estimate of 248 mIU/mL for infants younger than 9 months at vaccination gave an estimated geometric mean titre for infants aged 9 months or older of 539 mIU/mL (95% CI 376–751). Heterogeneity between studies was very high and significant (I^2=99·9%, p<0·001).

Only one study[57] reported an avidity index after MCV1 vaccination of infants younger than 9 months and those aged 9 months and older. The avidity index in infants vaccinated with MCV1 at 6 months was 0·9, at 9 months it

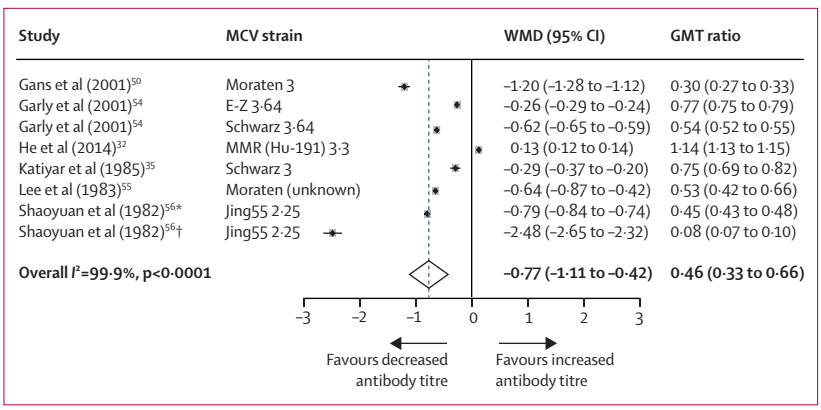

Figure 3: **Random-effects meta-analysis of within-study comparisons of GMTs (by PRNT and other tests) following MCV1 administration in infants aged 4–8 months *vs* infants aged ≥9 months**
Vaccine titres are expressed as $TCID_{50}$ unless otherwise specified. GMT ratios are derived through exponentiation of the WMD between log-GMTs. E-Z=Edmonston-Zagreb. GMT=geometric mean titre. MCV1=first dose of measles-containing vaccine. MMR=measles-mumps-rubella. PRNT=plaque reduction neutralisation testing. TCID=median tissue culture infectious dose. WMD=weighted mean difference of log-GMTs. *Subgroup with maternal antibodies. †Subgroup without maternal antibodies.

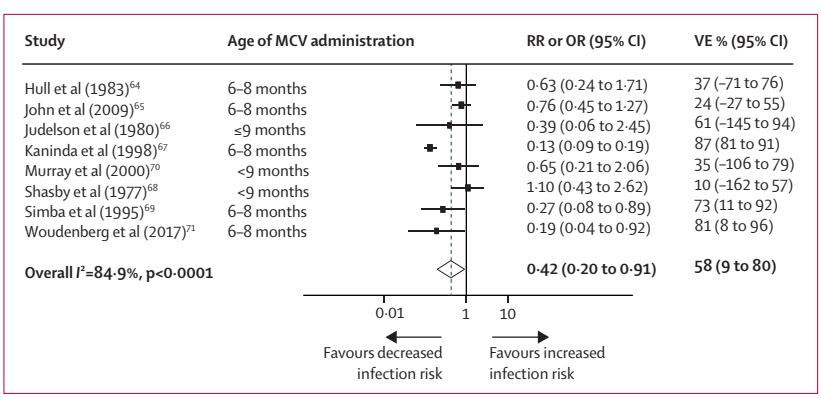

Figure 4: **Random-effects meta-analysis of VE following MCV1 in infants aged <9 months**
MCV1=first dose of measles-containing vaccine. RR=risk ratio. OR=odds ratio. VE=vaccine effectiveness.

was 1·0, and at 12 months it was 1·8. The avidity index was significantly lower following MCV1 vaccination at 6 months than at 9 months (p=0·0016) and 12 months (p<0·001). The avidity index was also significantly lower in children vaccinated at 9 months than at 12 months (p=0·001).[57]

Five studies[39,50,58–60] reported on measles-specific cellular immunity following MCV1 vaccination of infants younger than 9 months. Three studies[50,58,59] contained data on within-study comparisons. These studies compared the same cohort of infants receiving MCV1 under the age of 9 months and when aged 9 months and older. Therefore, we only analysed the most recent results from this cohort.[50] Age of administration of MCV1 had no significant effect on measles-specific cellular immunity, including no effect on the proportion of infants with a T-cell stimulation index of 3·0 or higher. The proportion of infants with a positive T-cell stimulation index was 53 (72%) of 74 who received MCV1 at 6 months, 40 (69%) of 58 who received it at 9 months, and 31 (65%) of 47 who received it at 12 months. The presence of maternal antibodies was also not found to have an effect on the level of T-cell proliferation: 16 infants with passive antibody titres greater than 50 mIU had an average T-cell stimulation index of 8·2 (SE 1·9) and 31 infants whose passive antibody titres were 4–50 mIU had an average index of 7·9 (0·9).[50] We identified three studies[32,56,61] that compare geometric mean titres over time after receipt of MCV1 before and after 9 months of age. One study[61] showed an increase in geometric mean titres in infants aged 4 or 9 months at 5, 14, and 32 months after MCV1 administration. However, this effect could reflect measles transmission in the study population. The second study[56] reported geometric mean titre ratios at 12 months versus 1 month after vaccination in infants vaccinated at 6, 7, and 13 months and older. For infants vaccinated with MCV1 at 6 months of age, geometric mean titres significantly declined from 1 month to 12 months after vaccination, with a geometric mean titre ratio of 0·60 (95% CI 0·41–0·86). A similar geometric mean titre ratio of 0·59 (0·50–0·69) was found for infants who were vaccinated at age 13 months or older. Infants vaccinated with MCV1 at 7 months of age had a lower geometric mean titre ratio of 0·35 (0·19–0·62) 12 months following vaccination. However, there was no significant difference between the three ratios, as evidenced by the overlapping CIs of the three age groups.[56] The third study[32] reported geometric mean titres ratios at 10 months versus 1 month after MCV1 vaccination at 8 or 12 months of age and found that antibody waning was significantly higher in infants who had been vaccinated at 8 months of age (ratio 0·76, 95% CI 0·70–0·81) than in those vaccinated at 12 months (0·91, 0·86–0·97).

We found only one randomised controlled trial examining vaccine efficacy of MCV1 administered to infants younger than 9 months, results from which are reported in two articles.[62,63] In this trial, the efficacy of MCV1 at 4·5 months of age was assessed against several outcomes for 85 infants. MCV1 administration to infants aged 4·5 months was sufficient to prevent 91% (95% CI 62 to 98) of cases of clinically diagnosed measles (two in the treatment group and 41 in the control group),[63] 94% (74 to 98) of cases of laboratory-confirmed measles (two in the treatment group and 60 in the control group),[63] 100% (46 to 100) of cases of measles requiring hospital treatment (none in the treatment group and 14 in the control group),[62] and 100% (–42 to 100) of deaths due to measles virus infection (none in the treatment group and seven in the control group).[63] Of note, the trial had a short follow-up time of 4·5 months.

Eight studies[64–71] assessed vaccine effectiveness after MCV1 administration to infants younger than 9 months against clinically diagnosed measles and the pooled estimate for vaccine effectiveness was 58% (95% CI 9–80; figure 4). There was considerable heterogeneity between studies, with vaccine effectiveness estimates ranging from –10% to 87%. One study of vaccine effectiveness[72] against clinically diagnosed measles following MCV1 vaccination at 6 to 9 months of age was not included in this pooled

	Age at follow-up (months)	Study weight (%)	MCV1 at <9 months					MCV1 at ≥9 months				
			Age at MCV1 (months)	Vaccinated infants (n/N)	Unvaccinated infants (n/N)	RR (95% CI)	VE (95% CI)	Age at MCV1 (months)	Vaccinated infants (n/N)	Unvaccinated infants (n/N)	RR (95% CI)	VE (95% CI)
Hull et al (1983)[64]	47	16·73	6–8	3/11	46/107	0·63 (0·24 to 1·71)	37% (–71 to 76)	>9	11/224	46/107	0·11 (0·06 to 0·21)	89% (79 to 94)
John et al (2009)[65]	120	18·64	6–8	46/395	17/111	0·76 (0·45 to 1·27)	24% (–27 to 55)	>8	4/65	17/111	0·38 (0·13 to 1·08)	62% (–8 to 87)
Judelsohn et al (1980)[66]	120	12·43	≤9	4/31	1/3	0·39 (0·06 to 2·45)	61% (–145 to 94)	>9	53/1428	1/3	0·11 (0·02 to 0·56)	89% (44 to 98)
Kaninda et al (1998)[67]	59	19·10	6–8	32/453	1136/1843	0·11 (0·08 to 0·16)	89% (84 to 92)	>9	127/3037	948/1843	0·08 (0·07 to 0·10)	92% (90 to 93)
Shasby et al (1977)[68]	108	15·96	<9	6/16	6/17	1·06 (0·43 to 2·62)	–6% (–162 to 57)	9–11	38/268	6/17	0·40 (0·20 to 0·82)	60% (18 to 80)
Murray and Rasmussen (2000)[70]	36	17·14	<9	2/6	54/106	0·65 (0·21 to 2·06)	35% (–106 to 79)	>9	13/153	54/106	0·15 (0·09 to 0·27)	85% (73 to 91)
Pooled estimates*	..	..	..	..	..	0·49 (0·17 to 1·44)	51% (–44 to 83)	..	..	..	0·17 (0·12 to 0·24)	83% (76 to 88)

I^2=92·3%, p<0·0001 for MCV1 at <9 months. I^2=93·8%, p<0·0001 for MCV1 at <9 months. MCV1=first dose of measles-containing vaccine. RR=relative risk. VE=vaccine effectiveness. *From meta-analysis of RR.

Table: **Meta-analysis of within-study comparisons of vaccine effectiveness for MCV1 administered to infants <9 months of age and ≥9 months of age. Weighting is based on the study population of infants younger than 9 months with random effects.**

estimate, as it used the screening method, which precluded data pooling. The vaccine effectiveness from this study was 93% (87–95).

Five studies[64–68,70] had within-study comparisons of vaccine effectiveness in infants younger than 9 months when vaccinated with MCV1 and those aged 9 months and older. The pooled estimates of vaccine effectiveness for MCV1 in the younger age group was 51% (95% CI –44 to 83) compared with a vaccine effectiveness of 83% (76 to 88; table) for infants aged 9 months or older at vaccination.

Eight studies[32,34,36,73–77] reported within-study comparisons for adverse events of fever, rash, diarrhoea, conjunctivitis, and local reactions after MCV1 vaccination in infants younger than 9 months or in those aged 9 months and older. No significant differences were found in the risks of fever, rash, diarrhoea, or local reactions between infants younger than 9 months vaccinated with a MCV1 and those vaccinated at 9 months or older (appendix pp 28–32).

We found nine articles with information on serious AEFI in infants administered MCV1 before 9 months of age; none reported an event from any of the 3848 infants studied.[28,32,37,46,73,78–81]

For immunogenicity outcomes of studies in which MCV1 was administered to infants younger than 9 months, we graded the quality of evidence for 23 observational studies as low (appendix pp 33–34), whereas the quality of evidence from 12 randomised controlled trials in which infants younger than 9 months were randomised to receive MCV1 was moderate. For the outcome on duration of immunity, the quality of evidence from two observational studies was graded as low and the quality of evidence from one randomised controlled trial was moderate. Findings on vaccine efficacy were derived from two articles reporting on the same trial; the evidence from the trial was moderate. For vaccine effectiveness, we graded the quality of evidence from nine observational studies as very low. Five observational studies reported safety data, but many did not have clear case definitions for AEFI; therefore, we graded their quality of evidence as very low. Ten trials that reported safety data also did not have clear case definitions for AEFI and the quality of evidence was low. Overall, we deemed the quality of evidence to be important for decision-making on the age of early MCV1 administration (appendix pp 33–34).

Discussion

To our knowledge, our study is the first systematic review of the benefits and risks of administering MCV1 to infants younger than 9 months. From our results, MCV1 vaccination in this age group is immunogenic, although less so than in infants aged 9 months and older. Furthermore, we did not find evidence that administration of MCV1 to infants younger than 9 months was less safe than administration to older infants.

Humoral immunogenicity was dependent on age at MCV1 administration. The proportion of infants who seroconverted increased from 50% after MCV1 vaccination at 4 months of age to 85% at 8 months. Our findings are consistent with those from an earlier review,[18] in which the proportion of infants who seroconverted after vaccination with MCV1 at 9 months of age was 92% (95% CI 59–100), and 98% (95% CI 88–100) for those vaccinated at 11 months of age. Antibody titres were lower in infants who were vaccinated when younger than 9 months than in those

vaccinated at age 9 months or older. This age effect might not be present when groups of infants older than 9 months are compared. A study by Kontio and colleagues[82] found no difference in antibody responses when MCV1 was given to infants aged 12 months compared with infants aged 18 months. Evidence for antibody avidity was only available from one study[57] and suggested that there was reduced avidity following MCV1 administration to infants younger than 9 months. The clinical relevance of this finding is uncertain. By contrast, the scarce evidence available on cell-mediated immune responses to early MCV administration suggested that it is not affected by administering MCV1 before 9 months of age. Regarding duration of immunity, we found only three studies with within-study comparisons, one of which[32] found faster waning of antibodies when MCV1 was administered to infants younger than 9 months than to those aged 9 months or older.

The pooled vaccine effectiveness estimate following MCV1 vaccination of infants younger than 9 months was 58%, which is lower than the vaccine effectiveness of 77% (IQR 62–91) for MCV1 administration at 9–11 months found in a previous review.[83] However, it is difficult to compare vaccine effectiveness estimates between studies because of differences in the vaccine strains used, the methods, and the epidemiological contexts, which is also reflected by the large heterogeneity between estimates of vaccine effectiveness. Therefore, we also did a meta-analysis examining the differences in vaccine effectiveness resulting from within-study comparisons of early and late administration of MCV1. We found a difference of 32% between vaccine effectiveness in infants younger than 9 months when vaccinated with MCV1 than those vaccinated at age 9 months and older. This finding is consistent with the reduced humoral immunogenicity we found at earlier ages of MCV1 administration. The effect of age at MCV1 vaccination on vaccine effectiveness might extend beyond 12 months of age, as de Serres and colleagues[84] found a difference of 4·5% in vaccine effectiveness for MCV1 administered to infants aged 15 months and older compared with infants vaccinated with MCV1 at 12 months of age. However, this study assumed comparable levels of measles exposure between the two groups. To assess the public health impact of the somewhat reduced vaccine effectiveness following early MCV1 administration, it is important to consider the risk of exposure and that the severity of disease and infectiousness might be reduced even if the vaccine does not provide complete immunity.[13,85]

Our review of safety of MCV1 vaccination found no significant differences in the risk of fever, diarrhoea, rash, or local reactions for infants younger than 9 months receiving MCV1 compared with those receiving the vaccine at ages 9 months and older. No serious AEFI were found in 3848 infants younger than 9 months when receiving MCV1. Although these safety findings are reassuring, too few infants were vaccinated to assess the risk of rare AEFI.

The main strengths of our review are its systematic strategy and broad search terms used to identify studies in different databases and in multiple languages, and the rigorous methods used to extract and appraise the data. The assessment of multiple outcomes within our systematic review, including the review of the effects of early administration of MCV1 on the response to subsequent MCV vaccination (which we show in an accompanying review),[86] has resulted in a comprehensive overview of the benefits and risks of MCV1 administration to infants younger than 9 months. Whereas the scope of our review was restricted to evaluating MCV1 administration in this age group, wherever reported, we included data on comparison groups with MCV1 administered to infants aged 9 months and older to quantify and meta-analyse within-study differences in outcomes for different timing of MCV1 vaccination.

We encountered several methodological limitations. Although 351 peer-reviewed articles were eligible for full-text screening, only 56 were eligible for inclusion in our analyses. The number of studies that could be used for specific outcome indicators was small because of absence of evidence reported (eg, on avidity, vaccine effectiveness, duration of immunity, cellular immunity, influence of maternal antibodies) or because of the inclusion criteria we applied (eg, definition of seroconversion, time between vaccination and sampling, and type of sample tested). We consider that our criteria were necessary to deliver the most robust estimates.

The main indicator of humoral immunogenicity we used was seroconversion since our aim was to assess the response to MCV1. Our definition might include infants with a low absolute titre of antibodies to measles virus following vaccination who might not be protected, or infants with only marginal increases in antibody titres whose tests change from negative to positive. Conversely, adequate vaccine responses might have been disregarded in infants with high titres of pre-vaccination antibodies. The use of seropositivity as an indicator avoids these pitfalls, but high concentrations of persistent maternal antibodies might be falsely considered as adequate vaccine responses. Furthermore, using seropositivity relies on insufficient evidence on the threshold antibody titre that is needed for protection, which is primarily based on one small study.[87] For both seroconversion and seropositivity, it is also problematic that only the PRNT method is assumed to be somewhat comparable between laboratories (provided that standard operating procedures are followed and a reference serum is included), whereas antibody tests such as the haemagglutination inhibition assay and ELISA are not always standardised. This absence of standardisation applies even more so to avidity and cellular immunity results from different laboratories.

The seroconversion results by month of age and vaccine titre in our review were based on few studies (n=20). We

found an effect of vaccine strain on seroconversion in head-to-head comparison studies, with a higher proportion of infants who seroconverted after vaccination with a MCV containing the Edmonston-Zagreb strain than with the Schwarz strain. Also, data on seroconversion following vaccination with the Edmonston-Zagreb-Mexico strain (at a titre of 3·7 and 4·6 plaque-forming units) was only available for infants vaccinated at 6 months of age.[36] The scarcity of studies using this strain at different ages probably influenced our results.

We found few studies that reported on vaccine efficacy, vaccine effectiveness, antibody avidity, duration of immunity, cellular immunity, or safety following MCV1 administered to infants younger than 9 months. This paucity of data, together with the large heterogeneity between studies, warrants caution when interpreting our results. Therefore, we would encourage further studies on vaccine effectiveness and immunogenicity of early MCV1. The assessment of whether the immune response to a subsequent dose could be impaired when MCV1 is given to infants younger than 9 months is discussed in our accompanying manuscript.[86]

Explanations of the reduced immunogenicity and effectiveness of early MCV1 administration include neutralisation of the vaccine by persistent maternal antibodies and immaturity of the infant's immune system. Our additional meta-analyses of the proportion of infants who seroconverted stratified by presence or absence of maternal antibodies showed indeed that seroconversion was significantly less frequent when maternal antibodies were present.

The optimal age of MCV1 administration needs to consider the risk of suboptimal immunogenicity, which decreases with the child's age at vaccination,[88] and the risk of contracting infection with measles virus before vaccination, which increases the more vaccination is delayed.[18] As an increasing proportion of infants are now born to immunised mothers, they will have lower concentrations of maternal antibodies to the measles virus and are likely to become susceptible to measles infection at an earlier age. However, if the schedule is to be optimised, there will be policy implications for use of MCV in infants younger than 9 months, which is considered off-label use. Therefore, a standard global recommendation and guidance for vaccinating infants younger than 9 months with MCV is needed. Preliminary results from our review were discussed at the meeting of WHO's Strategic Advisory Group of Experts (SAGE) on Immunization in October 2015. On the basis of our findings, WHO subsequently made recommendations for the first dose of MCV to be administered as early as 6 months of age in the following circumstances: (1) during a measles outbreak as part of intensified service delivery; (2) during supplementary immunisation activities in settings where the risk of measles in infants is high (eg, in endemic countries having regular outbreaks); (3) for internally displaced populations and refugees, and populations in conflict zones; (4) for individual children at high risk of contracting measles virus infection (eg, contact with patients with measles or in settings with increased risk of exposure during outbreaks, such as daycare facilities); (5) for infants travelling to countries with ongoing measles outbreaks; and (6) for infants known to be HIV-positive.[1,11] Our results underline the importance of additional doses when MCV1 is given to infants younger than 9 months. Because of reduced immunogenicity and effectiveness of a dose given to this age group, WHO considers this dose as supplementary and recommends that two additional doses be given according to national schedules.[1]

In summary, the results of our review suggest that administering MCV1 to infants younger than 9 months induces a good immune response, confers protection, and is safe. The updated WHO recommendations on MCV administration at 6 months of age for infants at high risk of measles infection are therefore an important step towards reducing measles-related mortality and morbidity. Further evidence on the effect of different vaccination schedules, derived from clinical, immunological, epidemiological, and modelling studies, could help with the design of optimal MCV vaccination schedules needed to achieve global control targets and regional elimination goals.

Contributors

LMN and SJMH designed the study. LMN, NvdM, BdG, and SJMH reviewed the literature and extracted the data. BdG, LMN, NvdM, and SJMH checked the extracted data. BdG, LMN, and SJMH planned and completed the analysis and maintained the database. PMS and TG provide feedback and edits of the manuscript. All authors contributed intellectually to the work.

Declaration of interests

We declare no competing interests.

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