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Measles vaccination below 9 months of age: Systematic literature review and meta-analyses of effects and safety

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Contents

Summary

Background

This report summarises the results of a systematic review of the literature into effects and safety of giving a first dose of measles containing vaccine (MCV1) to infants below the age of 9 months, in order to inform the discussion about an optimal age of the first dose in different epidemiological settings.

Methods

We performed a systematic literature review and meta-analyses of studies in which standard titre MCV1 was given to infants <9 months of age. We extracted data on the following outcomes: immunogenicity (humoral and cellular), vaccine efficacy and vaccine effectiveness (VE), duration of immunity, blunting of the response to subsequent doses of MCV and safety. We compared results with reference values for seroconversion (SC), VE and safety of MCV1 ≥ 9 months of age derived from previous reviews. Quality of all included studies was assessed using the GRADE methodology.

Results of the search and selection

From an initial 867 references identified by the search, we selected 138 studies for inclusion in the review.

Results of the review of included studies

In a meta-analyses of 20 papers, the proportion of infants who seroconverted (%SC) depended on the age at MCV1 vaccination. It increased from 50% (95% CI 29-71%) at age 4 months to 67% (95% CI 51-81%) at 5 months, 76% (95% CI 71-82%) at 6 months, 72% (95% CI 56-87%) at 7 months and 85% (69-97%) at 8 months. These SC proportions are lower than the WHO Immunological Basis for Immunization reference values of 92% and 98% for MCV1 at 9 months and 11 months, respectively. The %SC further depended on the vaccine strain used. Head-to-head studies found those vaccinated with Edmonston-Zagreb had a seroconversion rate 18% (95% CI 3-34%) higher than those vaccinated with Schwarz. Meta-analyses of studies reporting seroconversion stratified by presence or absence of maternal antibodies showed seroconversion to be significantly lower when maternal antibodies were present (mean difference in SC rate 33.2% (95% CI 20-46%)). The GMT was lower after MCV1 at <9 compared to ≥9 months of age (283 mIU/ml and 615 mIU/ml, respectively). Limited evidence on avidity of measles specific antibodies and cellular immunity (only one study for each outcome) found avidity was significantly lower after MCV1 at 6 months compared to MCV1 at 9 or 12 months of age, whilst T cell proliferation was not dependent on age at MCV1. The estimated pooled vaccine effectiveness (VE) of MCV1 <9 months of age against clinical measles was 72% (95% CI 53-91%). This VE is somewhat lower than the reference VE for MCV1 against clinical measles at 9-11 and ≥12 months (77% and 92%, respectively). Regarding duration of immunity, one of three relevant studies found significantly faster measles antibody waning with MCV1 vaccination <9 months compared to MCV1 vaccination >9 months of age. Concerning blunting of the response to subsequent doses of MCV, MCV1 <9 months was not found to affect seropositivity proportions after MCV2. Limited evidence from only one cohort of children suggested avidity to be lower after MCV2 when MCV1 was

given <9 months of age. Out of three studies reporting GMT after MCV2 when MCV1 was administered <9 months of age, one found GMT to be significantly lower than when the two-dose schedule began >9 months of age. Two studies reporting VE of two doses of MCV with MCV1 <9 months of age found no evidence of blunting (pooled VE 93%). The VE for two doses of MCV with the first dose ≥9 months found in a previous review was 94%. Regarding adverse events, fever occurred more often in infants receiving MCV1 <9 months of age than in infants vaccinated at older ages. Since there was no study with an age-matched unvaccinated control group it is not possible to relate this to the MCV. No reports of serious adverse events were found among 2,042 infants receiving MCV1 <9 months, but more observations are needed to draw reliable conclusions. Regarding the quality of studies, only five RCTs were found where infants were randomised to receive MCV1 at different ages. All remaining included studies were observational in this review. Mainly due to the observational nature of most of the included studies, the quality of evidence was low or very low for all outcomes.

Conclusions

The available evidence suggests that MCV1 administration <9 months of age is immunogenic, effective and safe. Humoral immunogenicity and VE of MCV1 <9 months were somewhat lower than reference values for MCV1 at 9-11 and ≥12 months. SC depended on age at MCV1, vaccine strain used and the presence of maternal antibodies. Limited evidence on cellular immunity did not find an effect of age at MCV1 whilst one study found faster waning of immunity compared to MCV1 ≥9 months. Some evidence of a blunted response to MCV2 after MCV1 <9 months of age was found considering GMTs and avidity, but not for the proportion seropositive, VE and cellular immunity. No severe adverse events were found among about 2000 infants receiving MCV1 <9 months. Research priorities include head-to-head immunogenicity studies of different measles vaccine strains, VE, avidity and cellular immunity studies for MCV1 <9 months of age and for a two dose schedule starting <9 months. The GRADE quality of evidence was low or very low for all outcomes considered.

Abbreviations

CCID	Cell culture infective dose
CI	Confidence interval
DIMDI	German Institute of Medical Documentation and Information
GMC	Geometric mean concentration
GMT	Geometric mean titre
HI	Hemagglutination inhibition
HIA	Hemagglutination inhibition assay
MCV1	Measles containing vaccine, dose one
MCV2	Measles containing vaccine, dose two
MCV3	Measles containing vaccine, dose three
pfu	Plaque forming unit
PRNT	Plaque reduction neutralization test
PubMED	Public MEDLINE
RCT	Randomized controlled trial
RIVM	National Institute for Public Health and the Environment (The Netherlands)
SC	Seroconversion
SP	Seropositive
TCID	Tissue culture infective dose
VE	Vaccine effectiveness/ efficacy

1 Introduction

Recent measles outbreaks in many countries show a bimodal age distribution with a high proportion of cases <9 months of age, as well as increasing numbers of cases among adolescents and or young adults. In countries with ongoing transmission, WHO recommends the first dose of a measles containing vaccine (MCV) at 9 months of age, while in countries where the risk of measles is lower, MCV1 is recommended at 12 months of age (2). Since 2013, all six WHO regions have measles elimination targets and offer two doses of MCV through routine immunisation programmes or supplementary immunisation activities (3).

Some researchers have suggested that the age of first measles vaccination can or should be given at a time point earlier than 9 months of age, based on the observations that infants of mothers with vaccine induced immunity against measles may have lower concentrations of maternal antibodies and lose protection by maternal antibodies at an earlier age (4). However, induction of protective responses depends on the presence of inhibitory maternal antibodies and immunological competence of the vaccine recipients, as well as on dose and strain of the measles vaccine used (5). Therefore, alterations of the MCV schedule must balance the potential risk of primary vaccine failure, which decreases the older a child is vaccinated, against the risk of measles infection prior to vaccination, which increases the later a child is vaccinated (1).

Given this early loss of vaccine induced maternal antibodies and the fact that today, many infants are born to vaccinated mothers, it is timely to review the evidence to assess whether adjustments of the recommended age of first MCV dose are pertinent. The first dose of MCV when given below the recommended age is often referred to as MCV0, implying two subsequent doses of MCV are needed for optimal protection. In this review, we refer to the first dose of MCV as MCV1, without making any implicit recommendation about the total number of doses needed for optimal protection.

2 Objective

We set out to conduct a systematic review and critical appraisal of the evidence on whether the effect of an MCV schedule starting younger than 9 months of age – in terms of immunogenicity, efficacy or effectiveness, duration of immunity, safety and blunting of the response to subsequent doses of MCV – is equal or less than the effect of the current MCV1 recommended at 9-12 months.

3 Methods

3.1 Review Questions

PICO (Population, Intervention, Comparator and Outcome) framework questions were pre-defined to inform the review objectives and are presented in Table 1.

Table 1. PICO framework for the effect of measles vaccination <9 months of age

Population	Intervention	Comparison	Outcome
Infants up to 24 months of age receiving an MCV1	Any currently licensed MCV1 administered to infants < 9 months of age.	Any currently licensed MCV administered to infants 9-24 months of age	1. Immunogenicity 2. Efficacy 3. Effectiveness 4. Duration of immunity 5. Safety 6. Blunting

3.1.1 Primary questions

a) Is the effect of MCV1 - in terms of immunogenicity, efficacy, effectiveness and duration of immunity - given to infants younger than 9 months of age equal or less than the effect of MCV1 administered at 9-24 months of age? What is the effect in infants aged 6-8 months?
b) Is the safety profile for infants vaccinated with MCV1 at below 9 months of age comparable with infants vaccinated with MCV1 at 9-24 months of age?
c) Does a dose of MCV1 administered <9 months of age blunt the immune response to a subsequent dose of measles vaccine?

3.1.2 Primary outcome measures

a) Immunogenicity

Humoral immunity

We will consider serological measles antibody responses in terms of the proportions seroconverted and seropositive, geometric mean titres (GMTs) and the avidity index assessed by:

- Plaque reduction neutralization test (PRNT);
- Enzyme-linked immunosorbent assay (ELISA);
- Hemagglutination inhibition (HI) assay;
- Complement fixation (CF) assay;
- Avidity assay.

- Seroconversion was defined by a ≥ four-fold increase in titres pre- and post-vaccination or by a change from a negative to a positive titre before and after vaccination (only for HIA). We did not consider the latter criterion adequate for PRNT seroconversions, as due to the sensitivity of the assay this would exclude all infants with pre-vaccination maternal antibodies (and limit the external validity of the results);
- Seropositivity was defined by cut-off values as described by the authors and by a PRNT titre >120 mIU/ml;
- GMTs were reported only when based on PRNTs with samples taken at least 6 weeks after the receipt of a MCV. For all reported GMTs based on non-PRNT assays, and for the avidity index, we used relative measures from within study comparisons, as these assays are not sufficiently comparable between laboratories.
- When multiple GMTs or proportions seroconversion/seropositive are reported at different time points, we used the highest values.

Cellular immunity
Here we used relative indicators reported from within study comparisons, e.g. the stimulation index for measles T-cell proliferation.

b) Efficacy

Vaccine efficacy against measles cases and measles deaths (laboratory confirmed or epidemiologically linked measles cases) as assessed from RCTs.

c) Effectiveness

Vaccine effectiveness against measles cases and measles deaths (laboratory confirmed or epidemiologically linked measles cases) as assessed from post-implementation field studies.

d) Duration of immunity

Trends in antibody levels over time since measles vaccination, taking into account exposure to wild-type measles virus.

e) Safety

Adverse events (AE) and serious adverse events (SAEs).

f) Blunting

Immune response to a subsequent dose of a measles containing vaccine.

3.1.3 Secondary questions

Is the effect modified by any of the following factors:

- Gender
- Vaccine strain and manufacturer
- Number of doses received
- Monovalent or combination vaccines
- Co-administration with other vaccines and or vitamin A
- Vaccination history of the mother including time since last MCV dose
- Presence of maternal antibodies
- Health status of the child
- Evidence of immunodeficiency
- Time between vaccination and sampling
- Nutritional status of the child
- Breastfeeding
- Duration of breastfeeding
- Geographical setting

3.2 Search strategy

Our search strategy had four components: a library database search; a search of two WHO library databases; snowballing from reference lists of included papers and key reviews; and a consultation of experts of the WHO SAGE M/R working group during a meeting in September 2015.

3.2.1 Searching literature databases

In collaboration with an RIVM librarian (W. ten Have), a primary search for articles that met the eligibility criteria was applied on the primary databases for biomedicine and health sciences outlined in Appendix A. The databases were searched using controlled vocabulary (i.e MeSH terms) with a pre-determined strategy as detailed in Appendix B. The results were limited to articles in English, Dutch, German, French and Spanish. No time limit was applied to dates of published records included in this study. To maximize the search sensitivity, the literature searches were checked to ensure that they contained papers cited in "The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants" paper by Cutts, 1995 (5), "The 2009 Immunological Basis for Immunization Series, Module 7 (Measles) by Moss and Scott (1) and "Measles vaccines: WHO position paper", 2009 (2). Regional and general databases for biomedicine and health sciences outlined in Appendix A were later searched to retrieve papers not found in the primary search. The search results were transferred to an EndNote library. Duplicate records were removed using the EndNote "Find duplicates" function, followed by a manual check.

3.2.2 Grey literature

The literature search was complemented by a search for relevant articles in the websites shown in Table 2, using the available search interfaces.

Table 2. Sources for manual search for relevant articles in journals and websites

Resources that were searched by hand
• WHO's Library Database (WHOLIS) (http://www.who.int/library/databases/en/) • WHO's IRIS (http://apps.who.int/iris/)

3.2.3 "Snowballing"

Bibliographies of papers that matched the eligibility criteria below were searched by hand to identify any further, relevant references. Reference lists of five key reviews of measles vaccination (1, 5-8) were also checked for additional references. References found were subject to the same screening and selection process as papers found in the primary search.

3.2.4 Expert network consultations

Members of the WHO SAGE M/R working group were consulted to suggest additional references during a meeting in September 2015.

3.3 Literature selection

All references found by the search strategy described above were screened by two reviewers (Laura Nic Lochlainn and Nicoline van der Maas) using a two-stage approach to reviewing the title, abstract and full text as outlined below.

3.3.1 First selection step: title and abstract

The two reviewers reviewed a random selection of ten percent of the retrieved articles by title and abstract according to the predefined set of inclusion criteria. There was consistent application of the inclusion criteria (≤10 percent disagreement). The reviewers therefore divided the remaining articles to continue the title and abstract screening separately. In case of uncertainty about inclusion or exclusion, the reviewers consulted each other for a second opinion. Disagreements were resolved by consultation with a third reviewer.

3.3.2 Second selection step: full article

The two reviewers screened a random selection of ten percent of records selected for full text screening in parallel. There was consistent application of the inclusion criteria (≤10 percent disagreement). The reviewers therefore divided the remaining articles and continued the full text screening separately. In case of uncertainty about inclusion or exclusion, the reviewers consulted each other for a second opinion. Disagreements were resolved by consultation with a third reviewer.

3.3.3 Eligibility criteria

After gathering the evidence, the eligibility criteria outlined below were applied to the results.

3.3.3.1 Types of studies

Randomized control trials (RCTs), quasi-randomised control trials (qRCTs), outbreak investigations, cohort and case control studies regarding vaccination schedules for currently licensed measles containing vaccines.

3.3.3.2 Types of participants

Infants <9 months of age receiving their first dose of a MCV.

3.3.3.3 Types of intervention

Any currently licensed measles containing vaccine administered to infants <9 months of age. A currently licensed measles containing vaccine can be:

- Monovalent vaccine: Schwarz, Moraten, Edmonston, Edmonston-Zagreb, Leningrad-16, Shanghai-191, CAM-70, AIK-C and TD97.

- Combination vaccine containing various combinations of the above measles strains with other viruses: measles and rubella (MR), measles, mumps and rubella (MMR), measles, mumps, rubella and varicella (MMRV).

3.3.3.4 Minimum data requirements

For inclusion in the review, the articles must report a minimum set of data as shown in Table 3.

Table 3. Minimal data requirements within articles for inclusion in review

Data requirements for all studies	
Age at vaccination	Exact age (months)
Safety	Adverse events case definition
Data requirements for immunogenicity studies only	
Vaccine strain used	Exact vaccine strain and or potency used
Immunogenicity results	Type of laboratory test used

3.3.4 Exclusion criteria

Ecological studies, case reports, non-human primate studies, meeting abstracts, editorials, newspaper articles and other forms of popular media were excluded.

High titre vaccines were excluded from the review, defined as vaccines with a $TCID_{50}$ or p.f.u. of ≥4.7 (F. Cutts, personal communication). Titres below this cut-off were assumed to be 'standard'. Study results derived from combining MCV with gamma globulin or obtained after intradermal (rather than subcutaneous) administration of MCV were also excluded from the review.

Failure to meet any one of the above eligibility criteria (section 3.3.3) also resulted in exclusion from the review. Data regarding the reasons for excluded studies (including reasons for exclusion for those excluded following review of the full text) was recorded at each stage. If more than one exclusion criterion was applicable, only one reason for exclusion was recorded, according to the priority order as by the list on the data extraction form.

The final decision for inclusion or exclusion of references was made by the WHO IVB team and researchers conducting the review. Any apparent discrepancies during the selection process were resolved by a third, independent reviewer.

3.4 Data extraction

Data regarding the characteristics of included studies, such as; participants; interventions (including comparators); and outcomes from relevant papers were extracted by one reviewer into a form. Another reviewer checked the data in the form, after which, it was entered into an Access database. For trials, data from per-protocol analyses were used rather than intention to treat results.

3.5 Quality appraisal

The review was carried out and reported according to the PRISMA guidelines (www.prismastatement.org). We used the Grades of Recommendation Assessment, Development and Evaluation (GRADE) guidelines (9) to classify the quality of the evidence found. Risk of bias across studies was assessed using the approach outlined by the GRADE working group (9). Study characteristics relevant for risk of bias were formulated per outcome by authors SH, LN, NvdM and BG and graded accordingly, using Review Manager 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and entered into GRADE evidence summary forms. For all studies, completeness of outcome data (attrition bias and reporting bias), representativeness of the study population, inclusion of a control group, comparability of the control group and ascertainment of exposure was assessed and plotted as risk of bias summary graphs. In addition, for vaccine effectiveness studies, laboratory confirmation of measles cases and study design were assessed as risk of bias criteria. Studies reporting safety data were additionally scored on whether adverse events were reported passively or actively. Randomized controlled trials were further scored on selection bias, performance bias and detection bias. Inconsistency and imprecision was assessed from the forest plots by considering the overlap and width of confidence intervals, respectively. Indirectness of evidence was not applicable in our review, as we reviewed each outcome separately.

3.6 Data analyses

Following the selection of literature to be included in the review, the WHO IVB group and the SAGE secretariat were consulted regarding the process to be followed for summarizing the studies.

We used Stata version 13 (StataCorp, Austin, USA) for all analyses.

- Where possible, results were stratified by age at administration of MCV1 in months. Where sufficient high quality data was available, results were pooled by meta-analyses. We examined heterogeneity between results of different studies visually in forest plots and quantitatively using the I^2 statistic. This value represents the percentage of the total variation which is due to variation between studies. We used random effects meta-analyses to create summary estimates per outcome. When multiple studies provided comparisons of responses to MCV1 in infants <9 months versus ≥ 9 months, separate meta-analyses of within-study comparisons was performed to create pooled estimates of differences. Where possible, random effects meta-regression was employed, to explore whether determinants of age at MCV1, vaccine strain and titre, continent, type of test, or decade of study explained heterogeneity between studies.

3.6.1 Analyses per outcome measure

Immunogenicity

- We employed random effects meta-analysis for proportions, using the Freeman-Tukey double arcsine transformation for standard errors. We made forest plots of the proportion seroconverted or seropositive by age of administration of MCV1. Here we only considered results obtained by applying the following definitions of seroconversion: ≥4 times increase in titre (with or without adjusting for pre-vaccination antibody decay), or a change from a negative

pre-vaccination titre to a positive post-vaccination titre. A list of accepted and rejected definitions can be found in Appendix D. Venous and capillary blood collected in tubes were defined as acceptable samples for serological analyses, dried blood spots were not. A minimum time between vaccination and blood sampling of four weeks was chosen to allow for development of an immune response to the vaccine. We analysed GMTs based on PRNT on a natural logarithmic scale by random effects meta-analysis. Studies reporting GMTs derived from methods other than PRNT or with a time between vaccination and sampling less than 4 weeks were excluded from this analysis.

- Avidity and GMTs by tests other than PRNT: Results were only used when within study comparison groups were presented (due to the lack of standardization of tests other than PRNT), and when sufficient data was available to calculate the standard error of the results. In these cases, the weighted mean difference (with 95% CI) between GMTs was calculated on a natural-logarithmic scale by random effects meta-analysis. Since differences on a log scale translate to ratios on the back transformed GMTs, the exponentiated overall estimates (and its 95% CI bounds) were interpreted as the GMT among infants receiving MCV1 at age x divided by the GMT among infants receiving MCV1 at age x+y. These are comparable to published data presented as a GMT ratio.

Cellular immunity

- We reviewed only results from measles specific cellular immunity tests, including blast transformation, T cell stimulation, proliferation tests and memory T cell assays. Results of cytokine studies were not included in the review. Given the lack of standardization of assays, we only considered within study comparisons of MCV1 < and ≥9 months of age.

Vaccine efficacy and vaccine effectiveness

- Vaccine efficacy and vaccine effectiveness (VE) were presented by age of administration of MCV1. Random effects meta-analyses was used to calculate pooled estimates for VE of MCV1 <9 months of age. Within-study comparisons of VE <9 and ≥9 months of age were analysed as weighted mean difference on natural logarithmic scale. Where available, multiple outcome measures for VE were considered (clinical measles, laboratory confirmed measles, measles hospitalisation and measles related deaths). Non-specific effects of measles vaccination (e.g. overall mortality) were not considered.

Duration of immunity

- We reviewed only results of studies with GMTs and corresponding confidence intervals that were within study comparisons (<9 and ≥9 months at MCV1) with different time points between MCV vaccination and sampling.

Safety

- We employed random effects meta-analysis for proportions, using the Freeman-Tukey double arcsine transformation for standard errors. We made forest plots of the proportion of infants with rash and fever by age of administration of MCV1 and vaccine strain. In addition, we made a forest plot of the difference in proportion of rash, fever, conjunctivitis, diarrhoea and local adverse reactions at the injection site between those receiving MCV1 <9 months of age and ≥ 9

months of age, only including within-study comparisons. Available evidence on serious AEFIs (e.g. anaphylaxis, convulsions) was summarized.

Blunting of the immune response to a subsequent dose of MCV

- Here we considered the proportion seropositive, GMT, avidity index and stimulation index after MCV2 or MCV3 by age of administration of MCV1, and made forest plots when a sufficient number of studies was available.

3.6.2 Comparison of review results with evidence of administration of MCV1 at older ages

The current review only considered MCV1 administered <9 months of age. Evidence on the effects of administration of MCV1 at older ages was obtained from the following sources:

- For the proportion seroconverted by age: “The 2009 Immunological Basis for Immunization Series, Module 7 (Measles)” by Moss and Scott (1);
- For safety: “The 2009 WHO measles position paper” (2);
- For vaccine effectiveness: The 2011 review “Field effectiveness of live attenuated measles-containing vaccines: a review of published literature” by Uzicanin and Zimmerman (10).

4 Results of the literature search

The search was carried out on 01.06.2015 (PubMed) and 02.06.2015 (DIMDI). It yielded a total of 861 references. The search of the WHO databases IRIS and LIS resulted in 526 hits, of which 15 unique references were eligible for full text screening. Of these, eight had been found by the PubMed/DIMDI search. Of the remaining seven, none were eligible for including in the review. By searching reference lists of included papers and of key reviews ("snowballing") 108 additional references were identified (Figure 1).

4.1 PRISMA flow chart

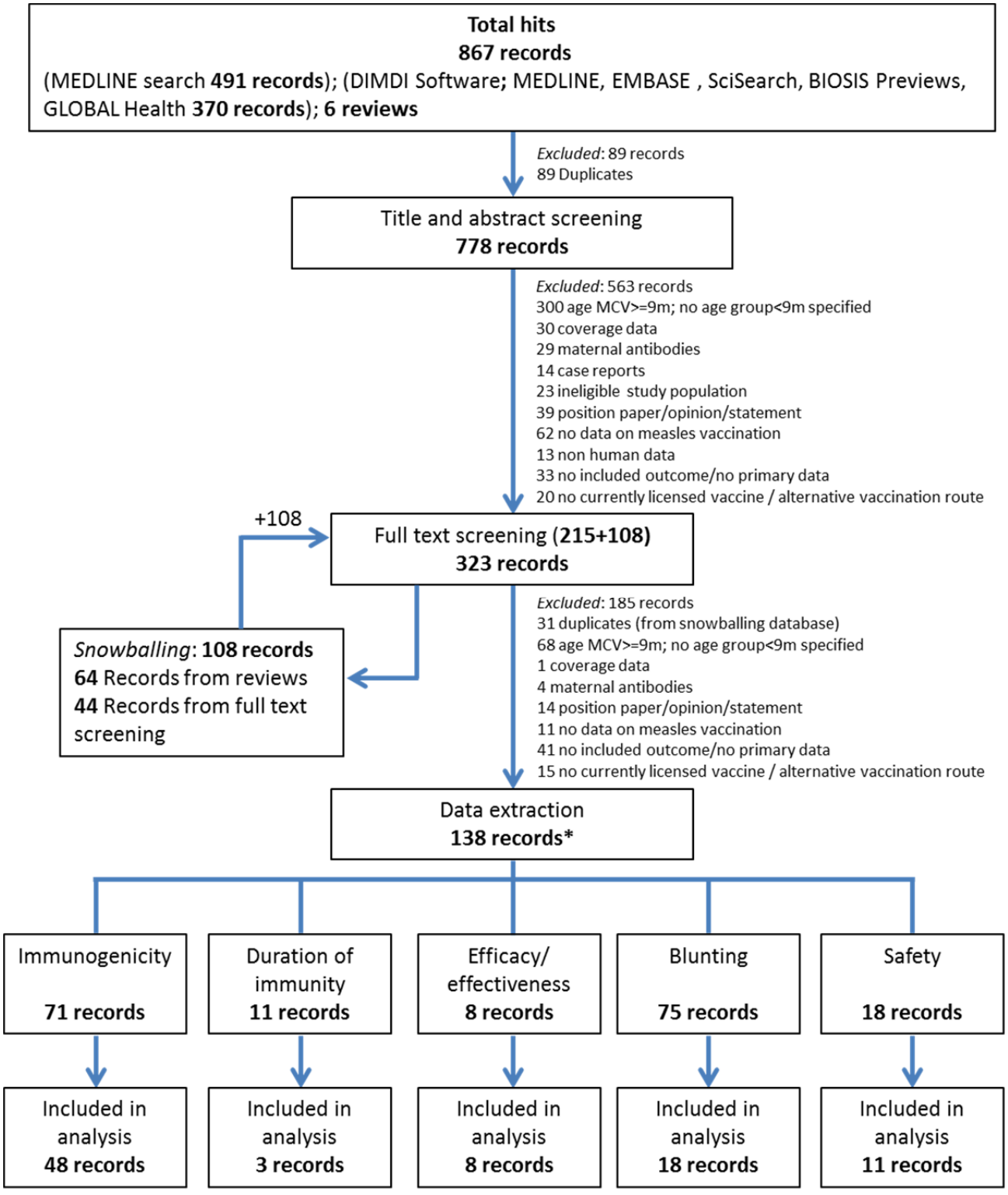

Figure 1. Flow chart of retrieved items, excluded and included items, and number of studies according to outcome measure.

*Of the 138 records, data was extracted from some studies for multiple outcomes.

4.2 Overview of studies included in the review

A summary table of studies with eligible data is shown in Table 4. Table 14 in Appendix E summarises the basic characteristics of all references with data extracted for inclusion in this review

Table 4. Summary of studies included in the review by outcome

Author, year of study (Ref)	Country	MCV1 age (months)	Vaccine Strain	Immunogenicity					Duration of immunity	Vaccine effectiveness	Blunting	Safety
				SC	SP	GMT	Cellular	Avidity				
Abanamy 1992 (11)	Saudi Arabia	6, 9	Schwarz, Edmonston-Zagreb	Yes	-	-	-	-	-	-	Yes	-
Anonymous 1977 (12)	Kenya	4,5,6,7,8,11	Schwarz	Yes	-	-	-	-	-	-	-	-
Anonymous 1981 (13)	Tanzania	4-5, 6-7, 8-9, 10-11, 12-13, 14-15	Schwarz	Yes	-	-	-	-	-	-	-	-
Benn 1997 (14)	Guinea-Bissau	6, 9	Schwarz	-	-	-	-	-	-	-	Yes	-
Berry 1992 (15)	Peru	5-6, 8-9	Schwarz, Edmonston-Zagreb	-	Yes	-	-	-	-	-	-	-
Bolotovski 1994 (16)	Uzbekistan	6, 9	AIK-C, Edmonston-Zagreb, Leningrad 16, Schwarz	Yes	-	-	-	-	-	-	-	-
Carson 1995 (17)	Canada	6-8.5	Connaught	Yes	-	-	-	-	-	-	Yes	-
Carson 2005 (18)	Canada	6	AIK-C, Connaught	-	-	-	-	-	-	-	Yes	-
Cutts 1994 (19)	DRC	<5,5, 5-6, 6, 6-7, 7-8, >9	Edmonston-Zagreb	Yes	Yes	Yes	-	-	-	-	-	-
Davis 1987 (20)	USA	<9, ≥9, ≥15	Unknown	-	-	-	-	-	-	Yes	-	-

Deivanayagam 1990 (21)	India	6,6-8,7,8,	Schwarz	-	-	-	-	-	-	-	-	-
Diaz-Ortega 1986 (22)	Mexico	8,9-10,11-12,13-14,15-16,17-18	Schwarz	Yes	-	-	-	-	-	-	-	-
Dick 1975 (23)	South Africa	6,7,8,9,10,11,12	Moraten	-	-	-	-	-	-	-	-	Yes
Ekunwe 1985 (24)	Nigeria	6,7,8,9-12,13-19,20-26	Edmonston	Yes	-	-	-	-	-	-	-	-
Fernandez de Castro 1986 (25)	Mexico	6-9	Edmonston-Zagreb, Schwarz	Yes	-	-	-	-	-	-	-	-
Gans 1998 (26)	USA	6,9,12	Moraten	-	-	-	Yes	-	-	-	-	-
Gans 1999 (27)	USA	6,9,12	Moraten	-	-	-	Yes	-	-	-	Yes	-
Gans 2001 (28)	USA	6,9,12	Moraten	-	Yes	Yes	Yes	-	-	-	Yes	-
Gans 2004 (29)	USA	6,9,12	Moraten	-	-	-	-	-	-	-	Yes	-
Gans 2013 (6)	USA	6,9,12	Moraten	Yes	-	-	-	-	-	-	Yes	-
Garly 2001 (30)	Guinea-Bissau	6,9	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	-	-	Yes	-
Goan 1978 (31)	Bosnia and Herzegovina	<9, 9-11, 12-14, >15	Edmonston-Zagreb	-	Yes	-	-	-	-	-	-	-
He 2014 (32)	China	8,12	Hu-191	Yes	Yes	-	-	-	Yes	-	Yes	Yes
Helfand 2008 (33)	Malawi	6,9	Edmonston-Zagreb	-	Yes	-	-	-	-	-	Yes	Yes
Hull 1983 (34)	Gambia	<6, 6-8, 9-11, 12-14, >15	Moraten	-	-	-	-	-	-	Yes	-	-
Hussey 1995 (35)	South Africa	6,9	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	-	-	-	-
Jensen 1994 (36)	Guinea-Bissau	4-5,6-8,9-12	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	-	-	-	-
Job 1984 (37)	India	6,7,8,9,10,11,12,13-15	Moraten	Yes	-	-	-	-	-	-	-	-
Job 1991 (38)	Haiti	6,8	Edmonston-Zagreb, Schwarz	-	-	-	-	-	-	-	-	Yes
John 2009 (39)	India	6,6-8,>8,9	Unknown	-	-	-	-	-	-	Yes	-	-
Johnson 1994 (40)	USA	6,15	Moraten	Yes	Yes	-	-	-	-	-	-	Yes

Judelsohn 1980 (41)	USA	≤9, >10	Unknown	-	-	-	-	-	-	Yes	-	-
Kaninda 1998 (42)	Niger	6-8,9	Schwarz	-	-	-	-	-	-	Yes	Yes	-
Katiyar 1985 (43)	India	6,7,8,9-12,13-15	Schwarz	Yes	-	-	-	-	-	-	-	-
Khalil 1999 (44)	Saudi Arabia	6	Edmonston-Zagreb	-	Yes	-	-	-	-	-	Yes	-
Khanum 1987 (45)	Bangladesh	3-4,4-5,5-6	Edmonston-Zagreb, Schwarz	Yes	-	-	-	-	-	-	-	-
Kiepiela 1991 (46)	South Africa	3-5,4-8,5-6,6-8,8-9,9-10,9-11	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	-	-	-	-
Ko 1999 (47)	England	5	Schwarz	-	-	Yes	-	-	-	-	-	Yes
Lee 1983 (48)	Taiwan	6,7,8,9,10,11, >12	Moraten	-	Yes	-	-	-	-	-	-	-
Mandara 1985 (49)	Tanzania	6-7,8-9,10-11,12-13,14-15,16-21	Schwarz	Yes	-	-	-	-	-	-	-	-
Markowitz 1990 (7)	Mexico	6,9	Edmonston-Zagreb, Edmonston-Zagreb Mexico, Schwarz	Yes	Yes	-	-	-	-	-	-	Yes
Martins 2014 (50)	Guinea-Bissau	4,9	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	-	Yes	Yes	-
Nair 2007 (51)	USA	6,9	Moraten	-	-	-	-	Yes	-	-	Yes	-
Ndumbe 1995 (52)	Cameroon	3,4,5,6,7,8	Connaught, Schwarz	Yes	Yes	-	-	-	-	-	-	-
Njie-Jobe 2012 (53)	Gambia	4,9	Edmonston-Zagreb	-	Yes	-	Yes	-	-	-	Yes	-
Nkrumah 1998 (54)	Ghana	6,9	AIK-C, Schwarz	Yes	-	-	-	-	-	-	-	Yes
Pabst 1999 (55)	Canada	6	AIK-C, Connaught	Yes	Yes	-	Yes	-	-	-	-	Yes
Pan American Health Organization 1982 {Anonymous, 1982 #2}	Several Latin American countries	6,12	Moraten	Yes	-	-	-	-	-	-	-	-
Pongrithsukda 1991	Thailand	4-7	Edmonston-	-	-	Yes	-	-	-	-	-	-

{Pongrithsukda, 1991 #78}			Zagreb									
Porter 1990 (57)	Malawi	6-9	Unknown	-	-	-	-	-	-	Yes	-	-
Rogers 1991 (58)	Papua New Guinea	4,5,6,6-7,7,<8, 8-29	Edmonston-Zagreb	Yes	-	-	-	-	-	-	-	-
Sakatoku 1994 (59)	Ghana	3,4,5,6,7,8,9, 10,11	Schwarz	-	Yes	-	-	-	-	-	-	-
Schatzmayr 1982 (60)	Brazil	7,8,9,10,11,12-14,15-18,16-24,25	Schwarz	Yes	-	-	-	-	-	-	-	-
Semba 1995 (61)	Indonesia	6	Schwarz	Yes	-	-	-	-	-	-	-	Yes
Shaoyuan 1982 (62)	China	4-6,6,7,7-8,8-12,9-10,11-12,>13	Jing55	-	-	-	-	-	Yes	-	-	-
Shasby 1977 (63)	USA	<9,9-11,12,>13	Unknown	-	-	-	-	-	-	Yes	-	-
Simasathien 1997 (64)	Thailand	6,9	Edmonston-Zagreb	-	Yes	-	-	-	-	-	-	-
Simba 1995 (65)	Tanzania	6-8,>9	Unknown	-	-	-	-	-	-	Yes	-	-
Soula 1991 (66)	Mali	4-8,12-24	Schwarz	-	-	-	-	-	-	-	-	Yes
Stewien 1978 (67)	Brazil	7,8,9,10,11,12	Schwarz	Yes	-	-	-	-	-	-	-	-
Tidjani 1989 (68)	Togo	4-5	AIK-C	-	Yes	-	-	-	-	-	-	-
Whittle 1984 (69)	Gambia	4-6	Edmonston-Zagreb	-	Yes	-	-	-	-	-	-	-
Whittle 1988 (70)	Gambia	4,5	Edmonston-Zagreb, Schwarz	-	-	Yes	-	-	-	-	-	-
Whittle 1990 (71)	Gambia	4,9	Edmonston-Zagreb, Schwarz	-	Yes	-	-	-	Yes	-	-	-

5 Results on outcomes

5.1 Immunogenicity

5.1.1 Seroconversion

We found 29 studies in which an adequate definition of seroconversion (SC) was applied (see methods 3.6.1 and Appendix D). Among these papers, 20 presented data on the proportion of infants who seroconverted (%SC) by month of MCV1 vaccination ranging from 4 to 8 months. There was only one study presenting the proportion SC after MCV1 at 3 months of age, but with conflicting data for the 3 months estimate (52). We therefore cannot present SC estimates for MCV1 at age 3 months. Meta-analyses found seroconversion increased from 50% (95% CI 29-71%) at age 4 months to 67% (95% CI 51-81%) at 5 months, 76% (95% CI 71-82%) at 6 months, 72% (95% CI 56-87%) at 7 months and 85% (69-97%) at 8 months. The estimates of the %SC by age of MCV1 ranging from 4 to 8 months, pooled across strain and titre, is presented in Figure 2 and Figure 3, which also includes the proportions seroconverted following MCV1 ranging from 4 to 8 months reported by Moss and Scott. As a reference, the proportion SC reported by Moss and Scott after MCV1 at 9 months, 91.9% (95%CI 59-100) and 11 months, 97.8% (95%CI 88-100) were included in Figure 3 (1).

The estimates of the proportion SC by age of MCV1 and strain, pooled by titre, are presented in Figure 4 and Table 5. The forest plots by age of MCV1 and strain are presented in Appendix F (Figures 18-22).

Age and vaccine strain, but not titre, type of test or continent of study, were independent determinants of the proportion SC among infants receiving MCV1 <9 months of age in meta-regression analysis (results in Appendix F Table 9).

A head to head comparison of the Schwarz and Edmonston-Zagreb vaccines at 6 months of age were pooled in a meta-analyses. A mean difference increase of 18% (95% CI 3-34%) was found of the proportion seroconverted if vaccinated with Edmonston-Zagreb (11, 16, 45, 72) (results in Appendix F Figure 24). Insufficient data was available for pooling head to head comparisons of other strains or for other ages of MCV1 vaccination.

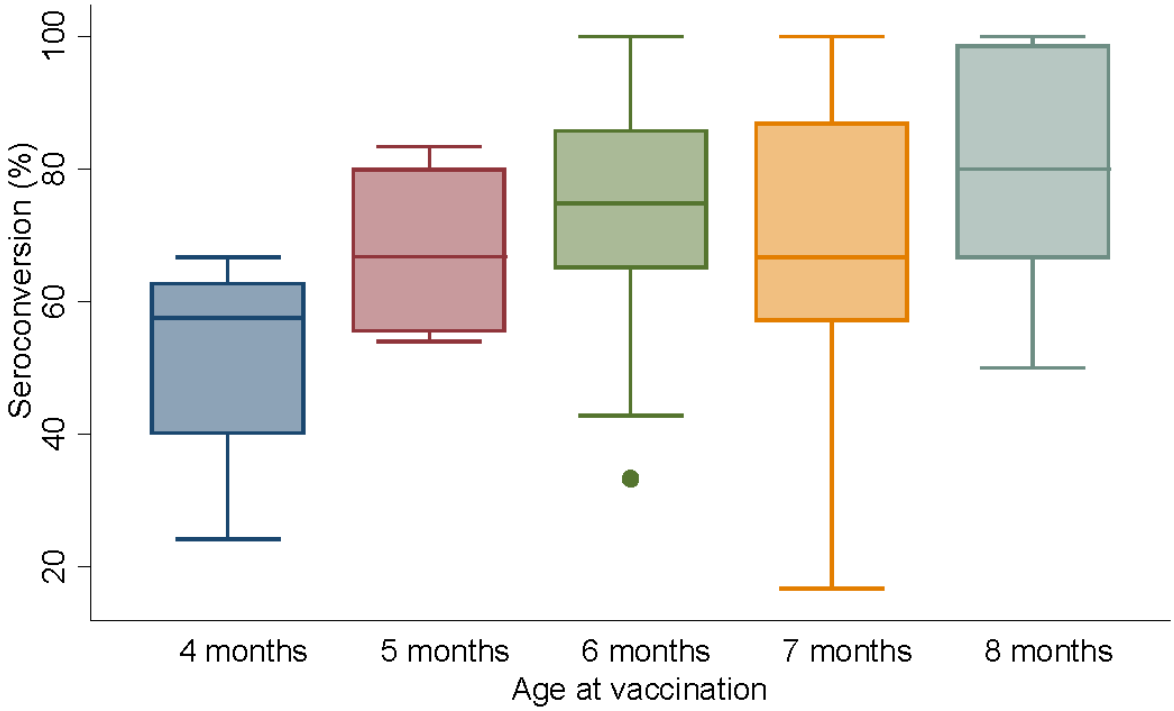

Figure 2. Proportion seroconverted by age of MCV1 (4-8 months): median and range derived from 20 studies.

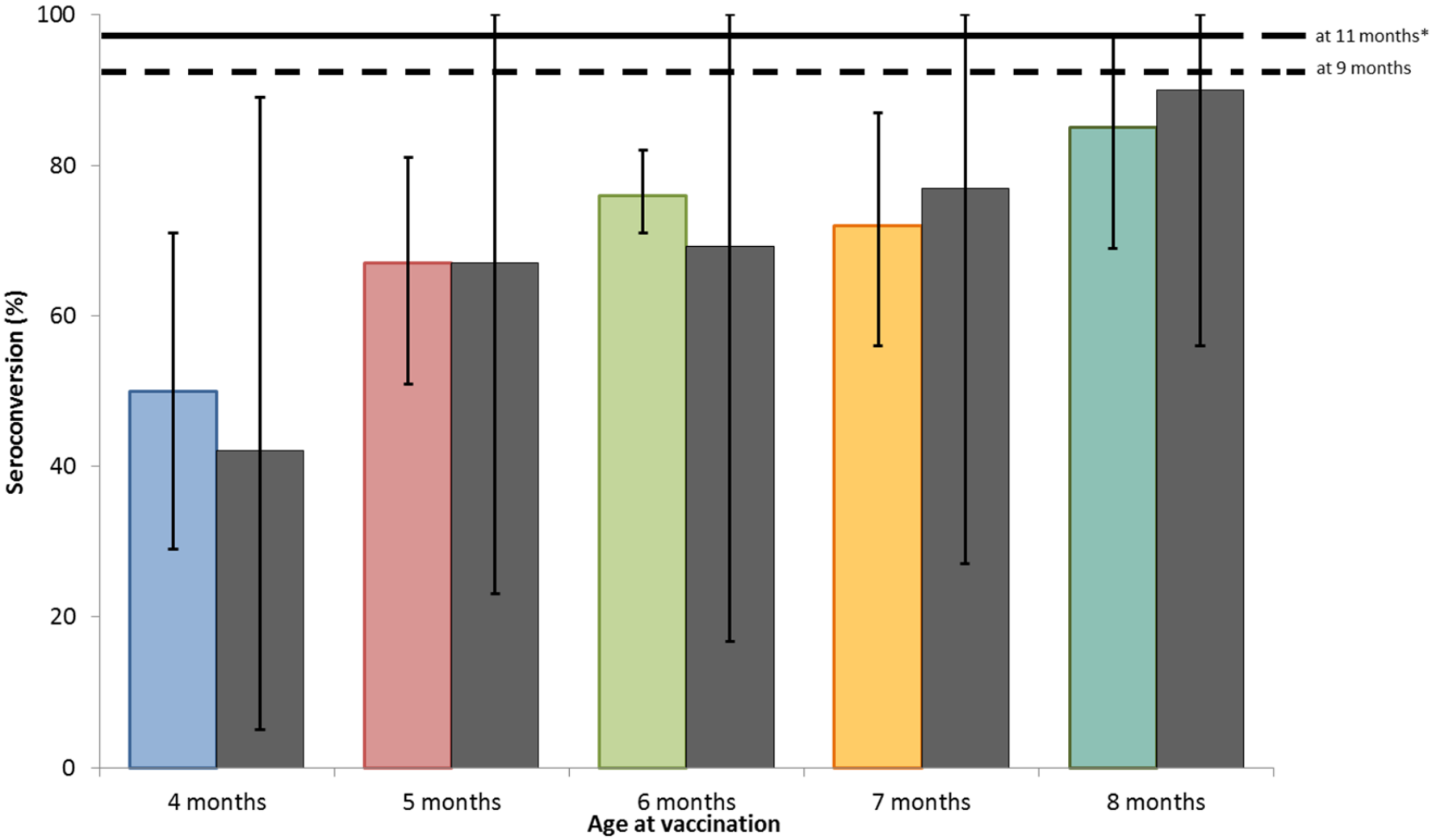

Figure 3. Proportion seroconverted by age of MCV1 (4-8 months), pooled estimates derived from 20 studies (coloured blocks) and the proportion seroconverted by age of MCV1 (4-8 months) from the Moss & Scott review (1) (grey blocks). Error bars present 95% confidence intervals.

*The horizontal lines represent the median proportion of infants responding to MCV1 at 9 months (dashed line) and 11 months (filled line) Moss & Scott, 2009(1)

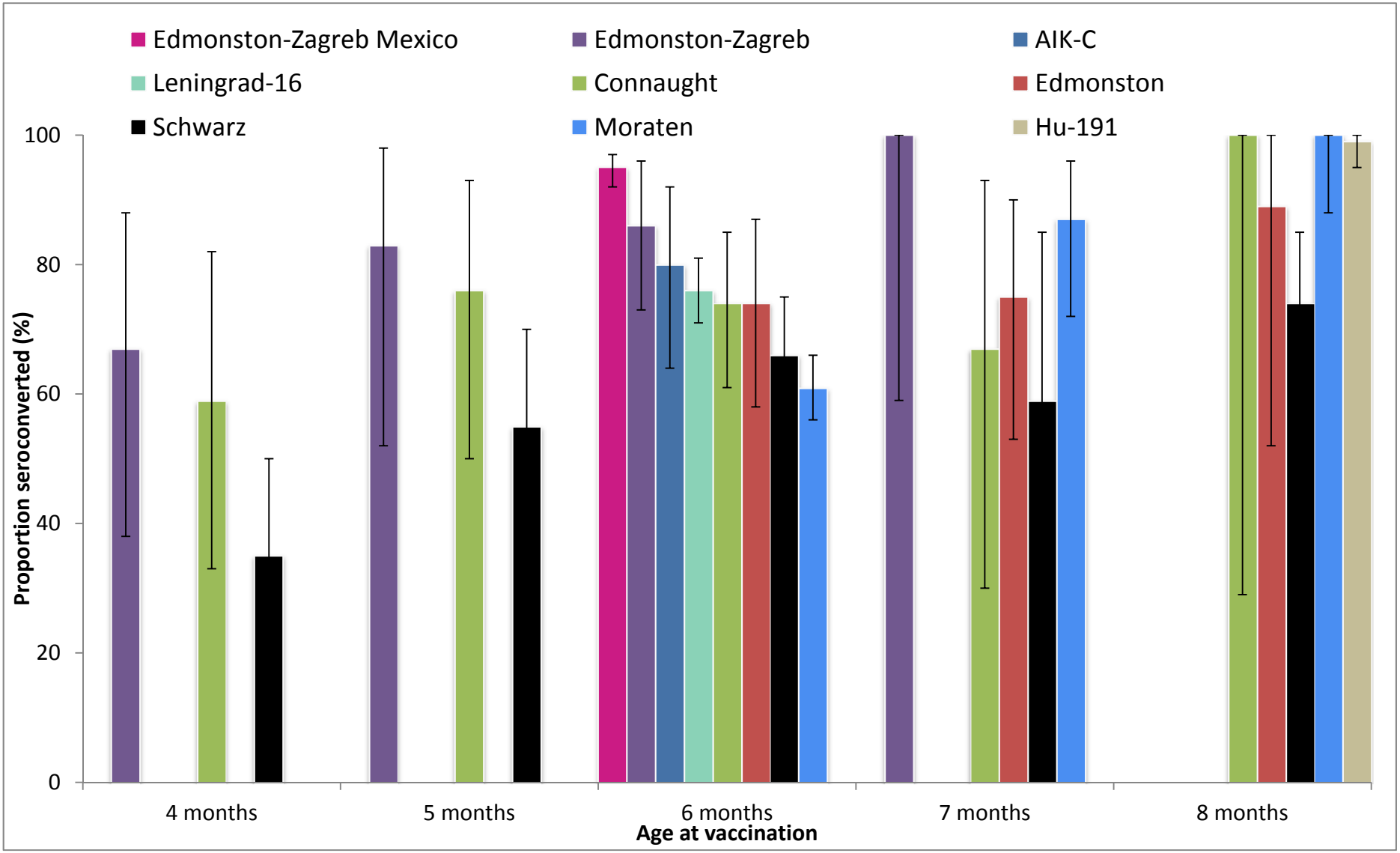

Figure 4. Proportion seroconverted by age of MCV1 (4-8 months), pooled estimates where multiple studies were available, derived from 20 studies. Error bars present 95% confidence intervals.

*The horizontal lines represent the median proportion of infants responding to MCV1 at 9 months (dashed line) and 11 months (filled line) Moss & Scott, 2009(1).

Table 5. Proportion seroconverted by age of MCV1 (4-8 months) and strain.

Age of MCV1 (months)	Strain	% Seroconverted	95% CI	References
4	Connaught	59	33-82	**(52)**
	Edmonston-Zagreb	67	38-88	**(58)**
	Schwarz	35	21-50	**(12, 52)**
5	Connaught	76	50-93	**(52)**
	Edmonston-Zagreb	83	52-98	**(58)**
	Schwarz	55	39-70	**(12, 52)**
6	AIK-C	80	64-92	**(16, 54, 55)**
	Connaught	74	74-85	**(52, 55)**
	Edmonston	74	58-87	**(7, 11, 16, 19, 24, 58)**
	Edmonston-Zagreb	86	73-96	**(7, 11, 16, 19, 58)**
	Edmonston-Zagreb Mexico	95	92-97	**(7)**
	Leningrad-16	76	71-81	**(16)**
	Moraten	61	56-66	**(37, 40, 56, 73)**
	Schwarz	66	56-75	**(7, 11, 12, 16, 43, 52, 61)**
7	Connaught	67	30-93	**(52)**
	Edmonston	75	53-90	**(24)**
	Edmonston-Zagreb	100	59-100	**(58)**
	Moraten	87	72-96	**(37)**
	Schwarz	59	31-85	**(12, 43, 52, 60, 67)**
8	Connaught	100	29-100	**(52)**
	Edmonston	89	52-100	**(24)**
	Hu-191	99	95-100	**(32)**
	Moraten	100	88-100	**(37)**
	Schwarz	71	44-93	**(12, 22, 43, 52, 60, 67)**

5.1.2 Geometric mean antibody concentrations

We identified eight studies in which GMT results from PRNT testing at least four weeks after MCV1 with accompanying confidence intervals or standard errors. Figure 5 shows the results of meta-analysis of GMTs after MCV1 <9 months. The (exponentiated) pooled GMT estimate was 283 mIU/ml (95% CI 161-497 mIU/ml).

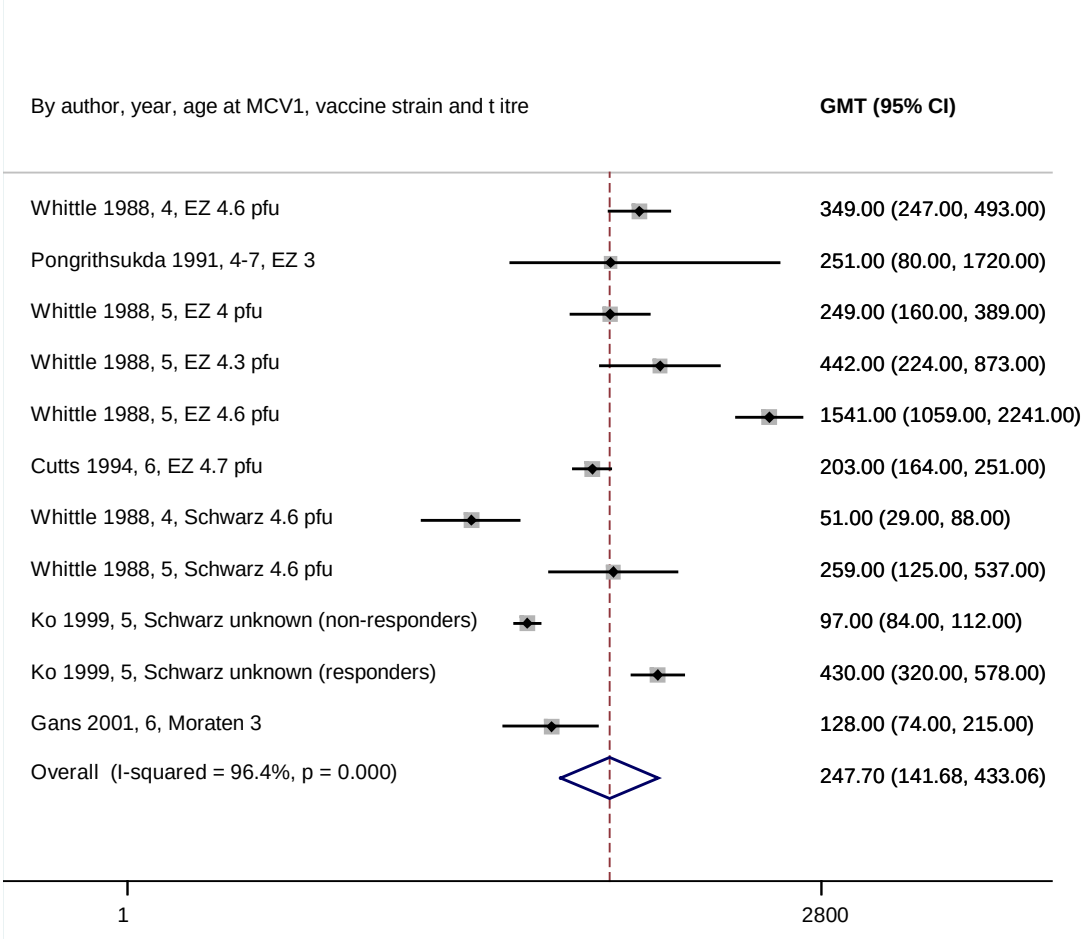

Figure 5. Random effects meta-analysis of PRNT geometric mean titres after MCV1 in infants aged <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. GMT: geometric mean titre. CI: confidence interval.

Figures 6 shows the meta-analysis of within-study comparisons between infants aged 4-8 months versus 9 months and older. For these within study-comparisons, GMT data resulting from PRNT and other tests were eligible. This resulted in inclusion of six studies for the within-study comparisons. Data from these studies are displayed in Table 6. In this analysis, the overall effect estimate is a weighted mean difference on the logarithmic scale. Therefore, the exponentiated effect estimate indicates the ratio of GMTs in infants aged 4-8 months and infants aged ≥9 months. Most studies had a negative overall effect estimate, corresponding with a ratio below 1, indicating lower GMT values in the <9 month-old compared to the ≥9 month old infants. The pooled ratio of GMTs for MCV1 in 4-8 month olds to the GMTs for MCV1 in ≥9 month olds was 0.46 (95% CI 0.33-0.66). Applying this ratio to the pooled GMT estimate of 283 for <9 months olds gives an estimated GMT for ≥9 month old infants of 615 mIU/ml (95% CI 429-858 mIU/ml). Heterogeneity between studies was very high and statistically significant.

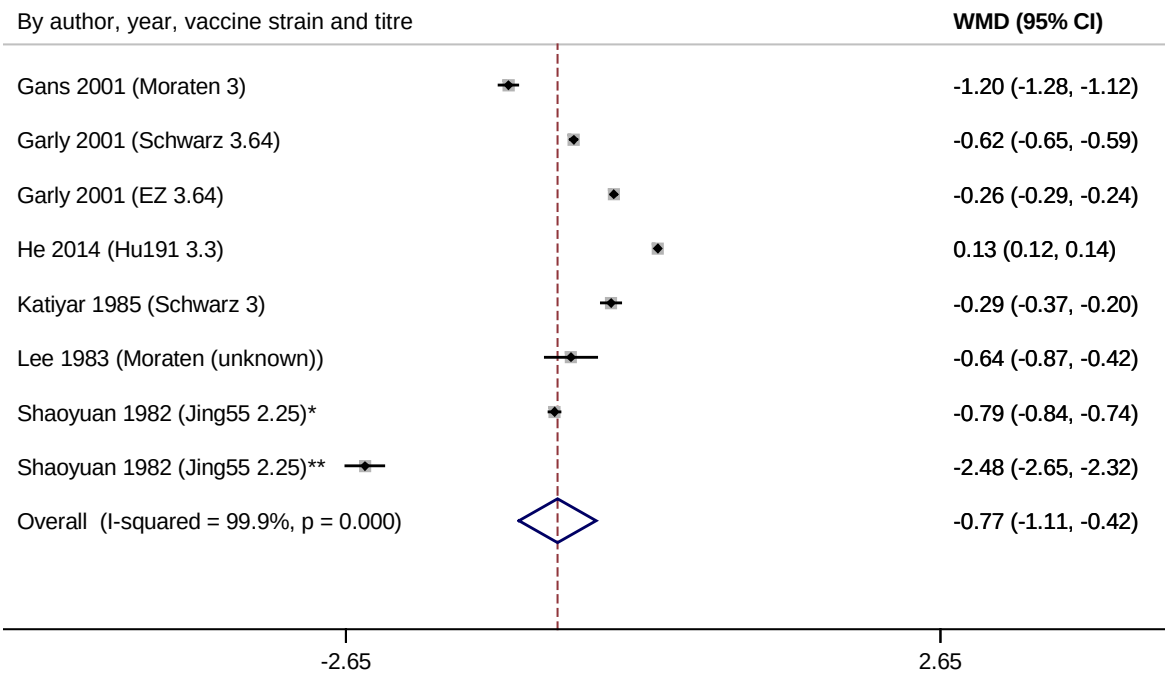

Figure 6. Random effects meta-analysis of within-study comparisons of geometric mean titres (by PRNT and other tests) after MCV1 in infants aged 6 versus 9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. WMD: weighted mean difference. CI: confidence interval.*subgroup with maternal antibodies, ** subgroup without maternal antibodies

Table 6. Studies reporting comparisons of GMTs after MCV1 <9 and ≥9 months of age.

Author and year	Strain	Age at MCV1 (months)	N	GMT	95% CI
Gans 2001	Moraten	6	73	128	74-215
		9	61	426	241-657
Garly 2001	Edmonston-Zagreb	6	77	1174	962-1433
		9	208	1525	1349-1723
Garly 2001	Schwarz	6	83	1338	1055-1697
		9	301	2491	2231-2781
He 2014	Hu191	8	140	2790	2590-3000
		12	140	2450	2300-2600
Katiyar 1985	Schwarz	6	12	0,928	0,629-1,227
		9-12	27	1,238	1,025-1,45
Lee 1983	Moraten	6	14	168,9	80-357
		9	22	321,8	189-547
Shaoyuan 1982*	Jing55	4-6	30	4,49	-2,15-11,13
		9-10	16	53,83	48,3-59,36
Shaoyuan 1982**	Jing55	4-6	107	8,93	3,29-14,57
		9-10	353	19,71	13,79-25,63

*subgroup with maternal antibodies, ** subgroup without maternal antibodies

5.1.3 Avidity

There was only one study reporting avidity after MCV1 given <9 months of age (51). Here the avidity index (AI) was 0.9, 1.0 and 1.8 after MCV1 at 6, 9 and 12 months of age, respectively. The AI was significantly lower after MCV1 at 6 compared to 9 and 12 months (p=0.0016 and 0.0001, respectively). It was also lower comparing MCV1 at 9 to 12 months (p=0.001).

5.1.4 Cellular immunity

Five studies reported measles specific cellular immunity results after MCV1 <9 months of age (26-28, 53, 55). Only the studies by Gans et al (1998, 1999 and 2001) contained data for within study analyses, comparing infants receiving MCV1 at < and ≥9 months of age. These studies are based on the same cohort of infants. We therefore report only the 2001 results. Here there was no effect of age on the proportion of infants with an SI ≥3.0. This proportion was 72%, 69% and 65% in 74, 58 and 47 infants receiving MCV1 at 6, 9 and 12 months of age, respectively. There was also no effect of the presence of maternal antibodies on the level of T cell proliferation (28).

5.2 Efficacy and effectiveness

We found only one RCT studying the efficacy of MCV1 <9 months of age. Results are reported in two papers by Martins et al. (50, 74). In this study, efficacy of MCV1 at 4.5 months of age was assessed against several outcomes: clinical measles, laboratory confirmed measles, measles hospitalisation and measles death (efficacy 91% (62-98%), 94% (74-98%) (74), 100% (76-100%) (50) and 100% (-42-100%) (74), respectively). Results of the Martins study have to be interpreted with caution since the follow-up time was limited (4.5 months). Eight studies assessed vaccine effectiveness (VE) after MCV1 <9 months of age against clinical measles. The pooled VE estimate for MCV1 <9 months of age against clinical measles was 72% (95% CI 53-91%) (Figure 7). The review by Uzicanin and Zimmerman found a VE against clinical measles of 77% (IQR 62-91%) and 92% (IQR 86-96%) for MCV1 administered at 9-11 and ≥12 months of age, respectively (10).

VE estimates seemed to decrease after longer follow-up times (Figure 7). However, age of MCV1 above or below 9 months, nor time since vaccination, was a significant determinant of VE in meta-regression (results in Appendix F, Table 15). The pooled VE estimate for MCV1 given at 6 to 8 months of age was 61% (95% CI 28-95%). This is lower than the overall <9 months VE since it excludes the Martins study where a relatively high VE of MCV1 at 4.5 months was found.

To estimate the difference between the VEs of MCV1 at < and ≥9 months, we performed meta-analysis of studies with within study comparisons (including a VE estimate for both age groups). Data from these studies is presented in Table 7. Results of the analyses are in Appendix F, Figure 25. Applying the resulting ratio of RRs (2.64) with its corresponding confidence limits to our overall VE estimate for MCV1 <9 months, this gave an estimated difference of the VE between MCV1 <9 and ≥ 9 months of 18% (95% CI 15-20%).

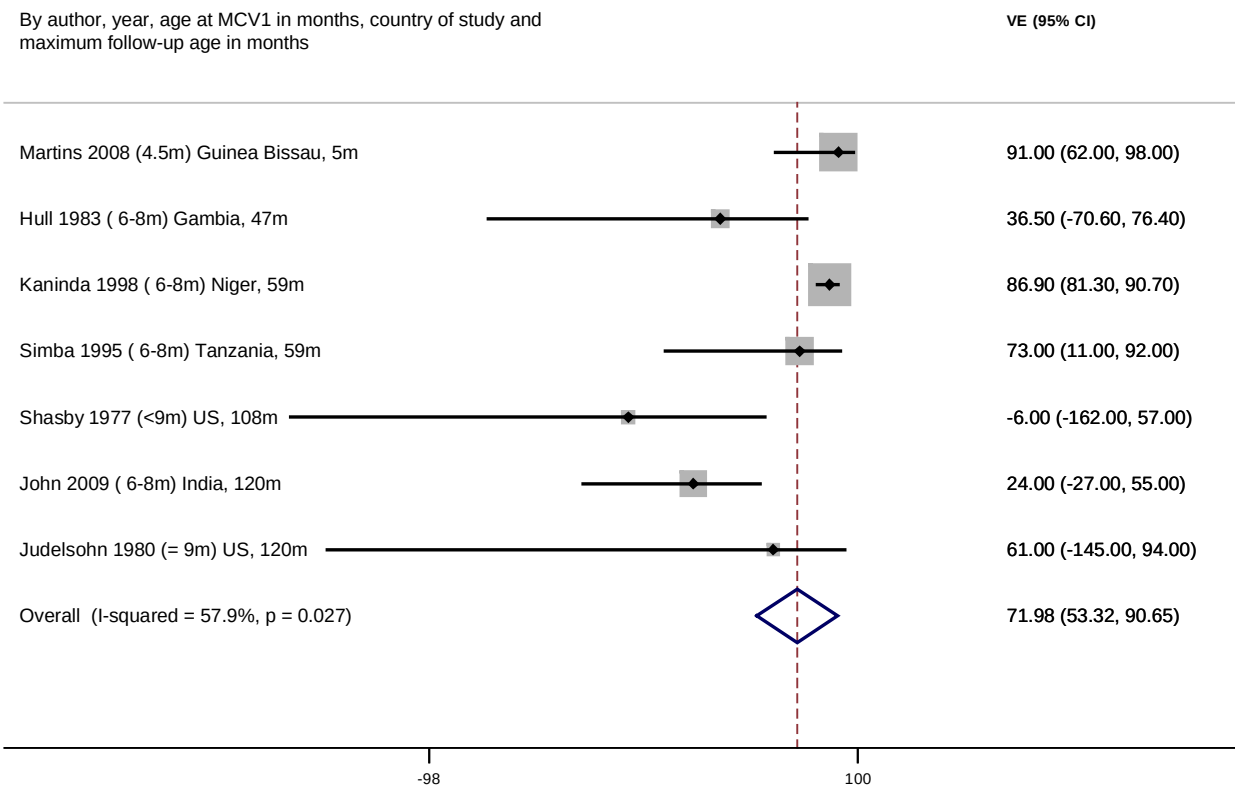

Figure 7. Random effects meta-analysis of vaccine effectiveness after MCV1 in infants <9 months of age. VE: vaccine effectiveness except for Martins et al (vaccine efficacy). CI: confidence interval. Note: One study of VE against clinical measles for MCV1 at 6 to 9 months was not included in this pooled estimate since its method (screening method) did not allow pooling. The VE was 93% (95% CI 87-95%) (57).

Table 7. Studies reporting comparisons of VE after MCV1 <9 and ≥9 months of age.

Author and year	Age at MCV1	N (measles cases vaccinated and unvaccinated)	Maximum follow-up age (months)	Median time since vaccination (months)	VE	95% CI
Hull 1983	6-8	49	47	11	37	-71-76
	>9	57	47	8	89	79-94
John 2009	6-8	63	120	56	24	-27-55
	>8	21	120	55	62	-8-87
Judelsohn 1980	≤ 9	5	144	93	61	-145-94
	>9	22	144	90	89	79-94
Kaninda 1998	6-8	1168	59	26	87	81-91
	>9	1075	59	25	95	93-95
Shasby 1977	<9	12	120	81	-6	-162-57
	9-11	44	120	80	59	18-80
Simba 1995	6-8	(case-control)	59	27	73	11-92
	>9	(case-control)	59	24	84	61-93

5.3 Duration of immunity

We identified three studies (71) (32, 62) reporting GMTs over time, in infants receiving MCV1 <9 months and ≥9 months of age, which allowed assessing differences in duration of immunity. The study by Whittle *et al* showed an increase in GMTs over time after receipt of MCV1 at 6 or 9 months of age, which may indicate the occurrence of measles infections (71). Shaoyuan *et al* compared GMT one year and one month post vaccination, and we calculated a ratio difference of 0.59 (95%CI 0.50-0.69) for children receiving MCV1 ≥13 months old and a similar ratio of 0.60 (95% CI 0.41-0.86) after MCV1 at 6 months old. For MCV1 receipt at 7 months, measles antibodies appeared to wane faster, but this was not significant (ratio 0.35, (95% CI 0.19-0.62)) (62). He *et al* did find significantly more antibody waning at 10 months post-vaccination in infants aged 8 months versus 12 months at the time of MCV1 administration (GMT ratio 10 months/ 1 month post-MCV1 0.91 (95% CI 0.86-0.97) for 12 month-olds and 0.76 (95% CI 0.70-0.81) for 8 month-olds) (32).

5.4 Blunting

Proportion seropositive

We found 12 papers with information on the proportion of infants seropositive after a two dose schedule starting below <9 months (Figure 9). The pooled proportion seropositive after MCV2 with MCV1 given <9 months was 97% (95% CI 95-99%). Meta-analysis of within-study comparisons of the proportion of infants seropositive after MCV1 given <9 and ≥9 months resulted in a pooled estimate of 2% (95% CI -1-5) fewer seropositives when MCV1 was given < 9 months of age. Table 8 and Figure 39 in Appendix F show these within-study comparisons.

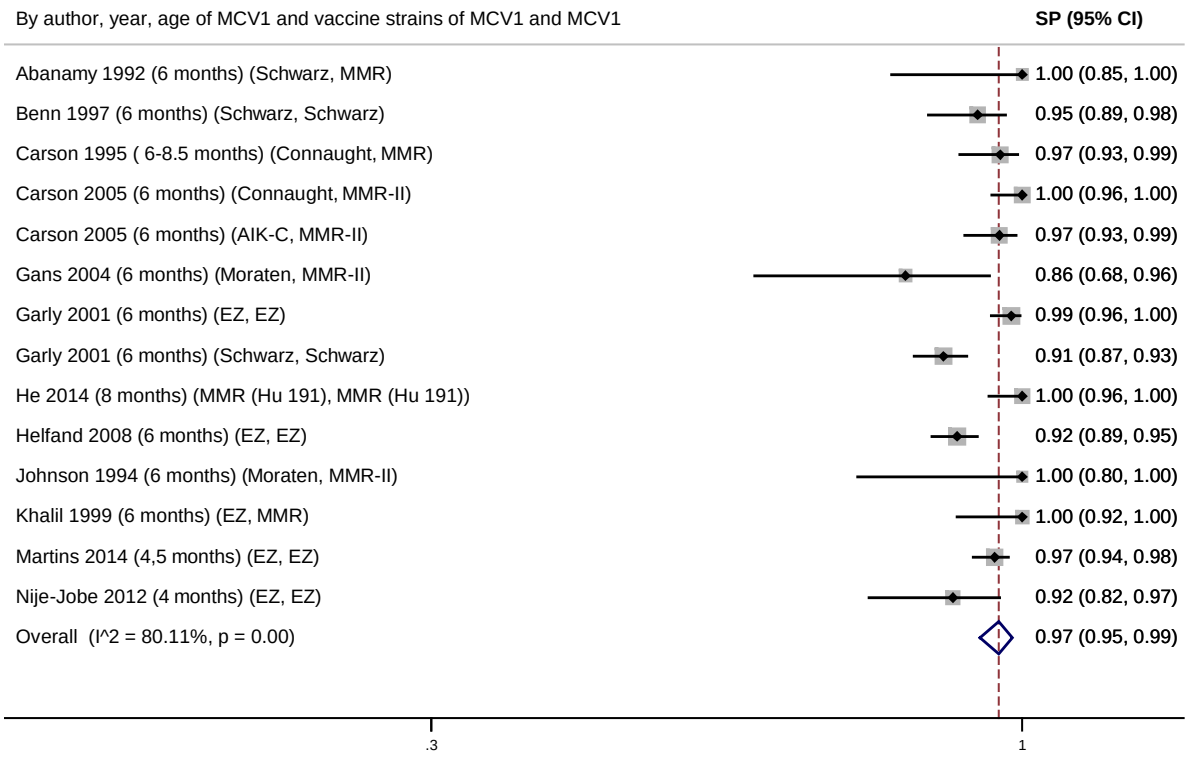

Figure 8 Random effects meta-analysis of the percentage seropositive after MCV2 in infants <9 months of age at the time of MCV1. SP: seropositive. CI: confidence interval.

Table 8 Studies with within study comparison of the proportion seropositive (SP) after a two dose schedule with MCV1 <9 and ≥9 months of age.

Author and year	Strain MCV1	Strain MCV2	Age at MCV1 / age at MCV2 (months)	SP (%)	95% CI
Gans 2004	Moraten	MMR-II	6/12	86	68-96
			9/12	90	70-99
He 2014	MMR (Hu-191)	MMR (Hu-191)	8/18	100	96-100
			12/22	100	97-100
Martins 2014	Edmonston-Zagreb	Edmonston-Zagreb	4.5/9	97	94-98
			9/18	98	95-100
Njie-Jobe 2012	Edmonston-Zagreb	Edmonston-Zagreb	4/9	92	82-97
			9/36	100	92-100

GMTs, avidity and duration of immunity

We found four papers reporting GMT levels (including a measure of variance) after a two or three dose MCV schedule starting <9 months of age, with a control group starting the MCV schedule ≥ 9 months of age (29, 32, 73, 75). Two of these studies report on the same cohort of infants (29, 73). Three studies reported GMTs post-MCV2 with MCV1 administered <9 months versus ≥9 months (29, 32, 75). One out of these three studies reported significantly lower GMTs with the MCV schedule starting <9 months compared to MCV1 ≥9 months of age (75). Post-MCV3 GMTs were not significantly different for schedules starting <9 versus ≥9 months of age, based on one study (73).

We found two papers reporting avidity results after two or three doses of MCV with a first dose <9 months of age (51, 73). These results are derived from the same cohort of infants at different follow-up times. The 2007 study, with about 10 individuals per group, reports the comparison between three schedules of MCV: 6-12 months, 9-12 months and 12 months (51). The comparison of the avidity index (AI) after the first and second dose of the schedule starting at 6 months does indicate avidity maturation. However, the AI after MCV1 at 6 and 12 months was comparable to the AI after only one dose of MCV at 12 months. It was lower than the AI after the two dose schedule starting at 12 months, reported in the 2013 study (73). The studies do not report statistical significance of this difference.

The 2013 paper reports on the comparison of the same schedules as above, with a booster dose at 5 years of age and a follow-up period up to 10 years of age (73). The two schedules starting below 12 months of age included three doses of MCV. The AI at age 5-10y was lower when the first dose was received at 6 months compared to MCV1 at 9 or 12 months, irrespective of the presence of maternal antibodies ($p \leq 0.01$). The AI of the three schedules (6m-12m-5y, 9m-12m-5y, 12m-5y) were 1.4, 1.7 and 2.2, respectively.

These findings suggest that starting measles vaccination <9 months of age results in lower avidity antibodies even after one or two booster vaccinations, compared to starting at ≥9 months of age, both in infants with and without maternal antibodies.

No studies were found describing duration of immunity after MCV2 when MCV1 was administered <9 months.

Vaccine effectiveness

We found two studies of the VE after a two dose schedule with the first dose administered <9 months of age (20, 42). Davis et al found a VE of 100% after a two dose MCV schedule in school-age children during an outbreak, regardless of whether the schedule started <9 or ≥9 months of age (20). Kaninda et al found a VE of 93.3% (95% CI 85.9-96.8%) up to the age of five years for a two-dose schedule with MCV1 at 6-8 months and MCV2 at 9 months of age (42). The pooled VE of these two studies for a two dose schedule with MCV1 <9m is 93% (88-99%). The VE for two doses with MCV1 ≥9 months reported by Uzicanin and Zimmerman was 94% (IQR 88-98%) (10).

Cellular immunity

We found seven studies reporting measles specific cellular immunity results after two or three doses of MCV with a first dose starting <9 months of age (6, 18, 27-29, 53, 76). Carson et al. (2005)

compared results between AIK-C and Connaught MCV1 vaccination at 6 months of age after MMR revaccination at 15 months in both groups (18). In total, 70% of the infants studied developed evidence of T-cell specific responses after two doses of MCV. Since there was no control group in whom MCV1 was administered ≥9 months of age, this result is difficult to interpret. The cell-mediated immunity studies by Gans et al. suggest measles specific T-cell responses are sustained at 5-10 years of age after a 2 or 3 dose schedule irrespective of whether MCV1 was given at 6, 9 or 12 months of age (73, 76). Njie-Jobe reported specifically about memory T-cell responses after two different MCV schedules: 4-9-36 months and 9-36 months. No differences between memory responses were found between the study groups after vaccination at time points up to 48 months of age (53).

5.5 Safety

A total of 18 studies reported proportions of adverse events after MCV1 <9 months. Fever and rash were the most frequently reported adverse events. Meta-analysis of proportions of fever showed 10%, 5% and 3% in infants age 6 months, 7-8 months and 9 months and older, respectively. Rash occurred in 9%, 6% and 2% of infants in the respective age groups (Figure 9).

Meta-regression did not show age, vaccine strain or titre to be significant determinants of fever or rash (n=32 and n=26, respectively, Appendix F Tables 19-20). Appendix F Figures 27-32 show the results of meta-analyses by vaccine strain and titre, including subgroup estimates per vaccine strain. Studies not included in the meta-analysis, as ages were reported as a range, support the observation that fever occurs more often in younger infants. Reported proportions with fever were 22-30% in 3-8 month-olds (52), 37-54% in 4-6 month-olds (45), 13.3% in 4-7 month-olds (77)and 9.1% in 4-8 month-olds (66).

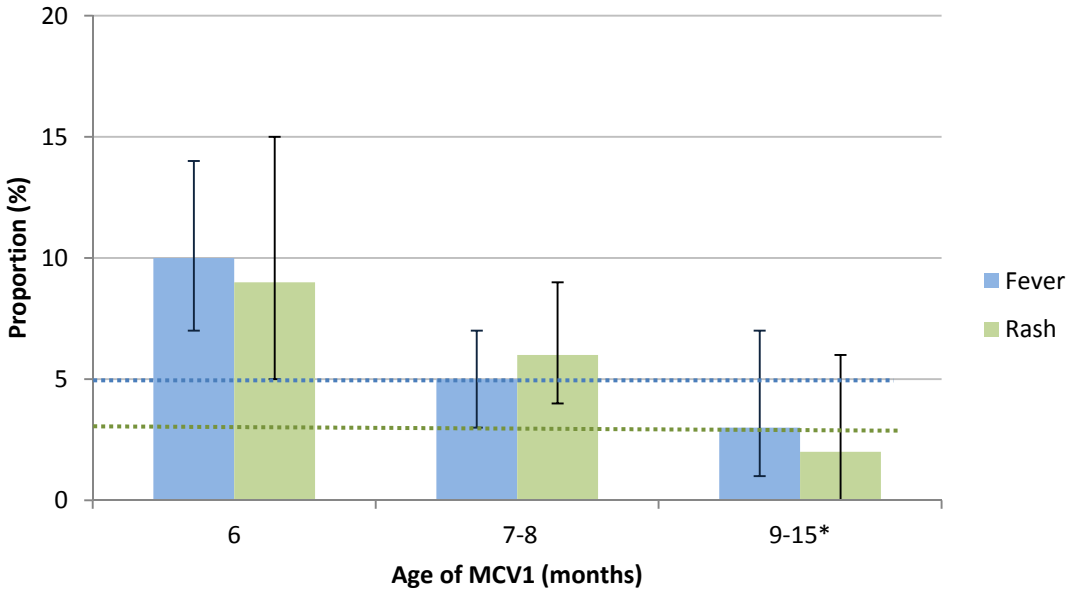

Figure 9. Proportion of infants experiencing fever or rash following MCV1 by age of administration. Error bars present 95% confidence intervals. The dashed reference lines represent proportions of fever and rash as mentioned in the WHO position paper (1). *: as our literature search focused on studies of MCV1 <9 months of age, the data we present on adverse events ≥9 months of age are likely not representative of all available evidence on MCV1 ≥9 months of age.

Meta-analyses of within-study comparisons for adverse events after MCV1 administration below or above 9 months of age were possible for outcomes fever, rash, diarrhoea, conjunctivitis and local reactions. Forest plots of these analyses are shown by strain and titre in Appendix F Figures 33-37, showing 3% (95%CI 1-5%) higher risk of fever after MCV1 in infants <9 months of age, 2% (95% CI -1-5%) higher risk of rash and 4% (95% CI 0-7%) higher risk of diarrhoea. Figure 10 shows a summary of the meta-analyses of risk differences of adverse events in within-study comparisons.

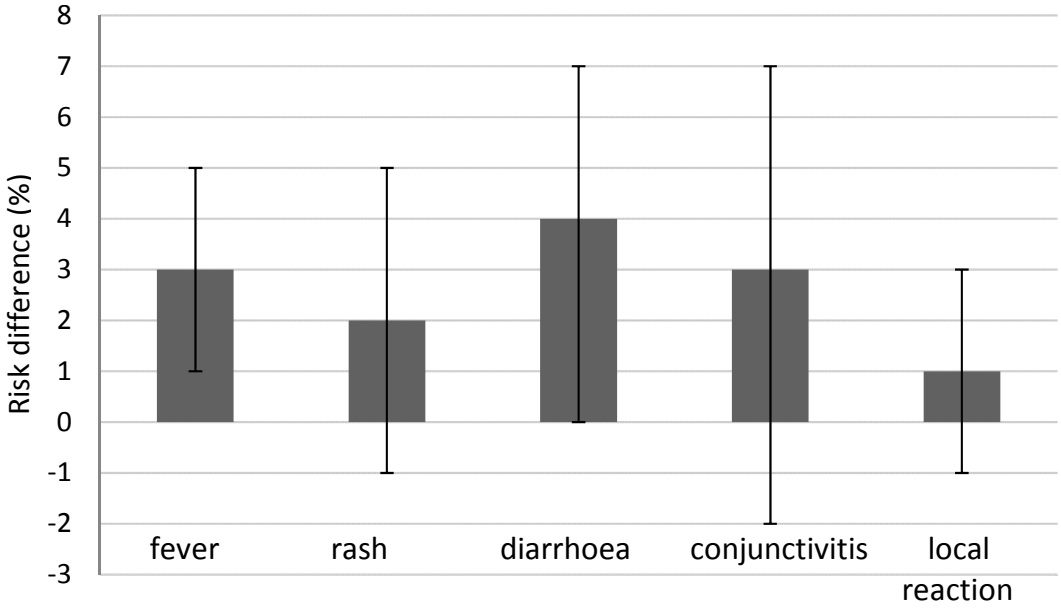

Figure 10. Risk difference of adverse events following MCV1 in infants < 9 months compared to infants ≥9 months of age, from within-study comparisons. A positive risk difference indicates higher risk in infants below 9 months of age. Error bars present 95% confidence intervals.

Seven papers reported that no severe adverse events (e.g. convulsions or anaphylaxis) were observed in their study populations <9 months of age (15, 16, 23, 25, 32, 52, 78). However, the combined number of observations (N=2042) is too low to find rare outcomes.

5.6 Secondary questions

5.6.1 Presence of maternal antibodies and seroconversion

We found 16 studies comparing the proportion seroconverted in infants with and without maternal antibodies vaccinate with MCV1 <9 months. Studies reporting outcomes per age in months and data suitable for meta-analysis (n/N or effect size with CI or SE) were pooled in random-effects meta-analyses (N=9). Figure 11 shows a summary of the results of the meta-analysis of the proportion seroconverted stratified by presence of maternal antibodies. The proportion seroconverted is higher in infants without maternal antibodies compared to those with maternal antibodies. Meta-regression showed that the presence of maternal antibodies decreases seroconversion by 33.2% on average (95% CI 20.1-45.6%), in infants <9 months of age, adjusted for age. Forest plots and meta-regression results are found in Appendix F, Figures 38-39 and Table 18.

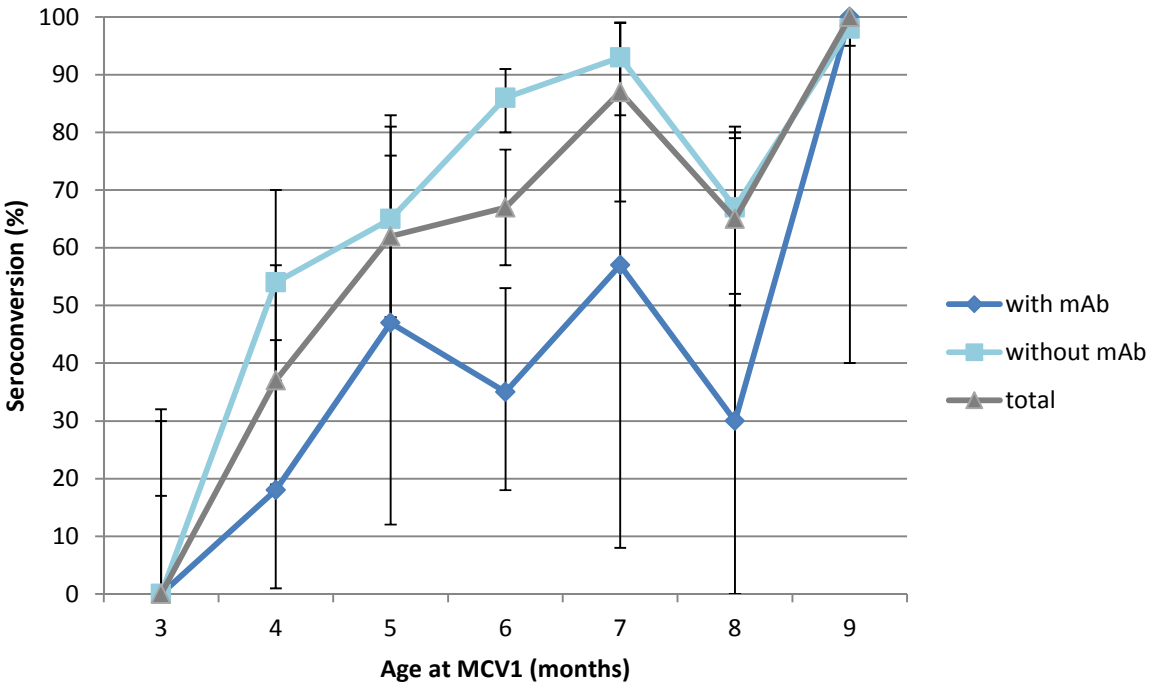

Figure 11. Results of random effects meta-analysis of the proportion seroconversion by month of age of MCV1, stratified by presence of maternal antibodies (based on 66 observations from 16 studies).

Studies with ages grouped in ranges that could not be used for pooling, support the notion of less frequent seroconversion after MCV1 in infants with maternal antibodies (16, 22, 25, 62).

5.6.2 Presence of maternal antibodies and GMT

Three studies reported post-MCV1 geometric mean antibody titres stratified by presence of maternal antibodies with a confidence interval in infants <9 months of age (28, 54, 62). As these studies employed different techniques (PRNT and HIA), results were not pooled. These studies did not find a significant difference in GMT post- MCV1 between infants with and without maternal antibodies pre-vaccination.

5.6.3 Co-administration of vitamin A

Two studies were found in our literature search that reported on outcomes of MCV1 before 9 months of age stratified by co-administration of vitamin A (14, 61). In both studies, MCV1 was given to 6 month old infants. Meta-analysis of percentage seroconverted in infants with and without vitamin A co-administered showed no significant differences.

6 GRADE quality of evidence found

The quality of evidence, using eight indicators for each outcome was systematically assessed scoring all studies included in the review (Appendix C). For all outcomes, the quality of evidence found was low or very low (see summary table of evidence, Appendix C, 2).

7 Discussion

In our review and meta-analyses of effects and safety of MCV1 <9 months of age we encountered several methodological limitations of the identified studies. Firstly, vaccination success is most often reported as seroconversion and seropositivity. However, both indicators have their limitations. The proportion seroconverted, when defined as at least a fourfold increase in titre, can include infants with a low absolute titre after vaccination who may not be protected. Conversely, it may not count good vaccine responses in the context of high pre-vaccination antibodies. When seroconversion is defined as a change from a negative to a positive result, the proportion seroconverted can include infants with only marginal increases in titres. The proportion seropositive post vaccination is also problematic as an indicator since it can include infants with high maternal antibodies who did not have an adequate vaccine response. Furthermore, cut-off values used between studies vary. For measles, the correlate for protection is primarily based on one small study (79). For both seroconversion and seropositivity it is problematic that antibody tests such as HIA and ELISA are not standardized and only PRNT is assumed to be somewhat comparable between laboratories. Due to lack of standardisation, comparison of avidity and cellular immunity results from different laboratories is even more problematic.

Since the primary aim of our review was to assess response to MCV we chose seroconversion as the main indicator. Results in terms of seropositivity are presented in Annex F, Figures 40-45. We critically assessed definitions used for seroconversion, and excluded papers where this was not defined or inadequate.

Many studies found in our search presented results for age ranges and were therefore not included in our meta-analyses. However, by pooled data by month were consistent with data given in ranges (Annex F, Figure 23).

The results of seroconversion rates by month of age were dependent on the limited availability of data, e.g., no seroconversion studies using Edmonston-Zagreb strains were available for vaccination at 8 months. Had these studies been available, it is likely that the overall proportion seroconverted at 8 months of age would have been higher than what was currently found. Data on seroconversion following MCV1 including the Edmonston-Zagreb Mexico strain (at 3.7 and 4.6 p.f.u.) was only available at 6 months (72). Availability of studies using this strain at different ages would have likely influenced our results.

We found few studies reporting VE, cellular immunity, blunting and safety following MCV1 administered below 9 months of age. This paucity of data, together with large heterogeneity between studies, warrants caution when interpreting our results.

Besides measles-specific immunogenicity, overall morbidity and mortality can also be affected by age of MCV1 (2). In addition, serological results pose difficulties in interpretation: it is unknown whether all seropositive infants are truly protected against measles infection, and if so, for how long. Similarly, the susceptibility to measles infection of seronegative infants after MCV1 is uncertain as well, as cellular immunity may still be induced. Further, the severity of disease may be less in ‘vaccine failures’.

8 Conclusions

We presented results found by performing a systematic review and meta-analyses of the evidence on the effects and safety of administering MCV1 below the age of 9 months. Even though a wealth of peer-reviewed articles were found, the number that could be used for specific outcome indicators was limited due to either absence of evidence (e.g. on avidity, VE, cellular immunity) or due to the criteria we applied (for e.g. definition for seroconversion). We believe the latter were necessary to deliver the best possible estimates.

In terms of effects of MCV1 <9 months of age, we firstly considered humoral immunogenicity. Here we found a significant effect of age of MCV1, whereby all indicators considered (proportion seroconverted, GMT and avidity) were significantly lower in infants who received MCV1 <9 months compared to MCV1 administered ≥9 months. The evidence on avidity was only derived from one study (51). These findings underline the importance of a two dose schedule when MCV1 is given <9 months of age with timely receipt of MCV2. In contrast, the limited evidence available on cellular immunity suggested this is not affected by receipt of MCV1 <9 months of age. The clinical relevance of this is uncertain. Regarding seroconversion, an effect of vaccine strain was found whereby in head-to-head studies Edmonston-Zagreb resulted in higher seroconversion rates than Schwarz.

The pooled estimated VE of MCV1 <9 months was 72% (95% CI 53-91%), which is somewhat lower than the VE of 77% for MCV1 at 9-11 months found in a previous review (10). Our meta-analysis of studies with within study comparisons found a significant difference of 18% between the VE of MCV1 < and ≥9 months. These results are consistent with the lower humoral immunogenicity found for MCV1 <9 months. The effect of age at MCV vaccination on VE may even extend after 12 months: de Serres et al. found a difference of 4.5% in VE for MCV1 administered at ≥15 compared to 12 months (80).

Regarding duration of immunity we found three study with within study comparisons of which one found significantly faster waning when MCV1 was administered <9 months compared to ≥9 months.

Regarding blunting of the response to subsequent doses after MCV1 <9 months, a limited number of studies was available. Here we did not find an effect of receipt of MCV1 <9 months of age on the proportion of infants seropositive after MCV2. The importance of this may be limited as it may just represent an adequate response to MCV2 given ≥9 months of age. To further assess the presence of blunting, we considered avidity, duration of immunity, cellular immunity and VE after an early two dose schedule. Here limited evidence available suggested blunting is indeed induced by early receipt of MCV1: avidity and GMTs were lower after subsequent doses of MCV when the first dose was received <9 months. This finding needs to be interpreted with caution since it is derived from only a few studies with a limited number of infants. The clinical significance of the relatively low avidity after two or three doses of MCV with a first dose at 6 months is unknown. The strain used for MCV1 in this study was Moraten, which we found was associated with a relatively low seroconversion rate at age 6 months. There is no evidence to suggest that the blunting effect is caused by immunological tolerance. It is likely due to a suboptimal response to the first dose when given early. In contrast to the evidence found for existence of a blunting effect on humoral immunity, there was no such effect on cellular immunity. The clinical relevance of this discrepancy is uncertain. Regarding vaccine

effectiveness, pooling of the two studies assessing the VE of a two dose schedule with the first dose <9 months resulted in a VE of 93% (95% CI 88-99%) . The VE for two doses with MCV1 ≥9 months found in a previous review was 94% (IQR 88-98%) (10).

Our review of safety of MCV1 at <9 compared to ≥9 months of age suggested a somewhat higher frequency of fever, rash and local reactions. The risk difference in fever was statistically significant. However, all study designs found were prone to confounding effects of other causes of these events which are related to age. Zero severe events were found among over 2000 infants receiving MCV1 <9 months of age, which is a low number to assess rare events .

The GRADE quality of evidence was low or very low for all outcomes considered.

9 Recommendations for future research

In our review, we encountered several areas with paucity of published studies in children below 9 months of age. These include studies on antibody avidity and cellular immunity after MCV1, blunting of the response to MCV2 after MCV1 <9 months (especially concerning antibody avidity and cellular immunity) and vaccine effectiveness of MCV1 and MCV2 after MCV1 <9 months of age. In addition, more observations are needed to estimate the incidence of severe adverse events following MCV1 below 9 months of age. A review of the available evidence concerning severity of disease in vaccine failures after MCV1<9 months of age (e.g. up to 2 years of age) would be very informative as well.

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79. Chen RT, Markowitz LE, Albrecht P, Stewart JA, Mofenson LM, Preblud SR, et al. Measles antibody: reevaluation of protective titers. J Infect Dis. 1990;162(5):1036-42.
80. De Serres G, Boulianne N, Defay F, Brousseau N, Benoit M, Lacoursiere S, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12-14 months versus 15 months of age. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;55(3):394-402.

Appendix A: Databases, websites and journals used for literature search

Databases

Primary: databases for biomedicine and health sciences:

- MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed)
- EMBASE (http://www.elsevier.com/online-tools/embase)
- Web of Science
- BIOSIS Previews
- Global Health (medicine, infectiology).

Secondary: regional databases for biomedicine and health sciences:

- African Index Medicus (http://indexmedicus.afro.who.int/)
- Index Medicus for Eastern Mediterranean Region (www.emro.who.int/his/vhsl)
- Indexing of Indian Medical Journals (IndMED) (www.indmed.nic.in)
- KoreaMed (www.koreamed.org/)
- LILACS (Literatura Latino-Americana em Ciências da Saúde – Latin American and Caribbean Health Sciences Literature) (http://regional.bvsalud.org/php/index.php?lang=en)
- Index Medicus for the South-East Asia Region (IMSEAR) (http://imsear.li.mahidol.ac.th/)
- Panteleimon for Russia and Ukraine (www.panteleimon.org/maine.php3)
- Western Pacific Region Index Medicus (WPRIM) (http://www.wprim.org/)
- PASCAL (http://www.inist.fr/?PASCAL-73&lang=en)

General databases:

- Google Scholar (http://scholar.google.com)

Appendix B: Database search strategy

Database	Strategy
PubMed MEDLINE, *conducted on 01-06-2015*	1 (((measles or mmr* or schwarz or moraten or edmonston or edmonston-zagreb or Leningrad-16 or Shanghai-191 or CAM-70 or AIK-C or TD97) and (vaccine* or vaccination* or immunization* or immunisation*)) or (mr vaccine* or mmrv)).ti. (4317) 2 *measles vaccine/ or *measles-mumps-rubella vaccine/ or (measles vaccine/ and (*vaccination/ or *immunization programs/)) (5372) 3 (*measles virus/im or *measles/im) and (vaccination/ or immunization schedule/) (464) 4 1 or 2 or 3 (6383) 5 (before 9 months or ("less than" adj4 9 months) or (earlier adj4 9 months) or "under 9 months" or " below 9 months" or ("younger than" adj4 9 months)).tw. (379) 6 (("0" adj6 month*) or ("1" adj6 month*) or ("2" adj6 month*) or ("3" adj6 month*) or ("4" adj6 month*) or ("5" adj6 month*) or ("6" adj6 month*) or ("7" adj6 month*) or ("8" adj6 month*)).tw. (656671) 7 ("at birth" or newborn* or (one adj4 month*) or (two adj4 month*) or (three adj4 month*) or (four adj4 month*) or (five adj4 month*) or (six adj4 month*) or (seven adj4 month*) or (eight adj4 month*)).tw. (392499) 8 ((first adj4 month*) or (second adj4 month*) or (third adj4 month*) or (fourth adj4 month*) or (fifth adj4 month*) or (sixth adj4 month*) or (seventh adj4 month*) or (eighth adj4 month*)).tw. (64481) 9 (weeks adj4 age).tw. (39088) 10 ((("0" adj6 month*) or ("1" adj6 month*) or ("2" adj6 month*) or ("3" adj6 month*) or ("4" adj6 month*) or ("5" adj6 month*) or ("6" adj6 month*) or ("7" adj6 month*) or ("8" adj6 month*) or ("at birth" or newborn* or (one adj4 month*) or (two adj4 month*) or (three adj4 month*) or (four adj4 month*) or (five adj4 month*) or (six adj4 month*) or (seven adj4 month*) or (eight adj4 month*)) or ((first adj4 month*) or (second adj4 month*) or (third adj4 month*) or (fourth adj4 month*) or (fifth adj4 month*) or (sixth adj4 month*) or (seventh adj4 month*) or (eighth adj4 month*)) or (weeks adj4 age)) adj6 (vaccin* or immun* or dose* or antibod*)).tw. (33638) 11 ("4.5 months" or (first dose and (before adj3 months))).tw. (4314) 12 ((early adj3 vaccination) or (early adj3 immunization) or (early adj3 immunisation) or (early adj3 mv) or (early adj3 schedule) or give earlier or early mv or primary mv or given earlier or early infancy).tw. (6072) 13 4 and (5 or 10 or 11 or 12) (597) 14 (immunogenicity or efficacy or effectiveness).tw. or (immunogenicity or efficacy or effectiveness).kw. or (optimal age or optimum age).ti. (813145) 15 measles cases.tw. or (measles/ and incidence/) or measles/mo or ((infant mortality/ or mortality/) and measles vaccine/) or (measles adj4 (death* or mortality)).tw. (2087) 16 antibodies, viral/bl or antibodies, neutralizing/bl or immunoglobulin g/bl or enzyme-linked immunosorbent assay/ or hemagglutination inhibition tests/ or neutralization tests/ (191192)

	17 (plaque reduction neutralization test or prnt or "enzyme-linked immunosorbent assay" or elisa or hemagglutination inhibition assay or "hi assay" or complement fixation assay or "cf assay" or avidity).tw. (158579) 18 measles virus/im or measles/im or measles vaccine/im or *measles vaccine/ad or antibody formation/ or antibodies, viral/im or antibody affinity/ or immunity, active/ or T-lymphocytes/im or immunity, cellular/ or lymphocyte activation/ or cytopathogenic effect, viral/ or (stimulation index and t-cell proliferation).tw. (281268) 19 (antibody response* or antibody titer* or antibody titre* or antibody level* or immune response* or T-cell response* or cell-mediated immunity or (humoral adj3 immunity) or measles igg or seroconversion or "response to vaccination" or (response adj3 measles vaccination)).tw. (267856) 20 ((improve adj3 survival) or (improves adj3 survival) or mortality reduction or child mortality or (prevention adj3 measles) or (risk adj3 measles)).tw. (25666) 21 (reactogenicity or safety or adverse events or adverse effects or side effects or fever or local reaction* or convulsion* or purpura or rash).tw. or (reactogenicity or safety or adverse events or adverse effects or side effects or fever or local reaction* or convulsion* or purpura or rash).kw. (733256) 22 (aseptic meningitis or seizures or encephalopathy or anaphylaxis or hypersensitivity or allergic reaction* or joint pain or arthropathy or arthralgia or arthritis or cough or diarrhoea or diarrhea).tw. (419068) 23 measles vaccine/ae or measles-mumps-rubella vaccine/ae or (measles vaccine/ and (adverse events or chemically induced or complications or contraindications or toxicity or poisoning or drug effects).fs.) (2014) 24 ((adverse and (effect* or event*)) or (side effect* or hypersensitiv* or sensitiv* or safe* or pharmacovigil*)).tw. (1925385) 25 13 and (14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24) (548) 26 (english or dutch or german or french or spanish).lg. (21901714) 27 25 and 26 (521) 28 exp animals/ not humans/ (4043807) 29 (macaque* or primate* or rodent* or mice or mouse or murine or rat or rats).ti. (1251069) 30 (case reports or news or letter or comment or editorial).pt. (3118360) 31 27 not (28 or 29 or 30) (492) 32 remove duplicates from 31 (491)
DIMDI *conducted on 02-06-2015* MEDLINE(ME66) EMBASE (EM74) SciSearch (IS74) BIOSIS Previews (BA70) GLOBAL Health (AZ72)	Five database(s) with 112352471 documents selected **Number of hits search expression** c= 1 112352471 me66; em74; is74; ba70; az72 s= 2 15143 (ft=(measles; mmr*; schwarz; moraten; edmonston; edmonston-zagreb; leningrad-16; shanghai-191; cam-70; aik-c; td97)/ti and ft=(vaccine*; vaccination*; immunization*; immunisation*)/ti) or ft=(mr vaccine*; mmrv)/ti

3 10886 ct=(measles vaccine; measles-mumps-rubella vaccine;
measles mumps vaccine; measles rubella vaccine; measles rubella mumps
vaccine; measles killed vaccine; measles mumps rubella varicella vaccine;
measles vaccination)/w=1
4 4516 ct=(measles vaccine; measles mumps vaccine; measles
rubella vaccine; measles rubella mumps vaccine; measles killed vaccine;
measles mumps rubella varicella vaccine) and ct=(vaccination; immunization
programs)/w=1
5 447 ct=(measles virus; measles)/qf=im/w=1 and ct=(vaccination; immunization schedule)
6 21595 2 or 3 or 4 or 5
7 1035 ft=(before 9 months; "less than" # # # # 9 months;
earlier # # # # 9 months; "under 9 months"; "below 9 months"; "younger than" # # # # 9 months)/(ti; ab)
8 2752769 ft=("0" # # # # # # month*; "1" # # # # # # month*;
"2" # # # # # # month*; "3" # # # # # # month*; "4" # # # # # # month*; "5"
month*; "6" # # # # # # month*; "7" # # # # # # month*; "8" #
month*)/(ti; ab)
9 1301760 ft=("at birth"; newborn*; one # # # # month*; two #
month*; three # # # # month*; four # # # # month*; five # # # # month*; six # # # # month*; seven # # # # month*; eight # # # # month*)/(ti; ab)
10 210889 ft=(first # # # # month*; second # # # # month*;
third # # # # month*; fourth # # # # month*; fifth # # # # month*; sixth # # # # month*; seventh # # # # month*; eighth # # # # month*)/(ti; ab)
11 111265 ft=(weeks # # # # age)/(ti; ab)
12 10672 ft=("4.5 months")/(ti; ab) or (ft=(first dose)/(ti;
ab) and ft=(before # # # months)/(ti; ab))
13 21236 ft=(early # # # vaccination; early # # # immunization; early # # # immunisation; early # # # mv; early # # # schedule; give earlier; early mv; primary mv; given earlier; early infancy)/(ti; ab)
14 2984 6 and (7 or 8 or 9 or 10 or 11 or 12 or 13)
15 3561220 ft=(immunogenicity; efficacy; effectiveness)/(ti;
ab; ut) or ft=(optimal age; optimum age)/ti
16 43235 ct=immunogenicity
17 6600 ft=measles cases/(ti; ab) or (ct=measles and ct=incidence) or ct=measles/qf=mo or (ct=(infant mortality; mortality)

and
ct=measles vaccine) or ft=(measles # # # # (death*; mortality))/(ti; ab)
18 485282 ct=(antibodies, viral; virus antibody; antibodies,
neutralizing; neutralizing antibody; immunoglobulin g)/qf=bl or
ct=(enzyme-linked immunosorbent assay; hemagglutination inhibition tests;
neutralization tests; complement fixation test)
19 710142 ft=(plaque reduction neutralization test; prnt;
"enzyme-linked immunosorbent assay"; elisa; hemagglutination inhibition
assay; "hi assay"; complement fixation assay; "cf assay"; avidity)/(ti; ab)
20 578819 ct=(measles virus; measles; measles vaccine;
t-lymphocytes; antibodies, viral)/qf=im or ct=measles vaccine/qf=ad/w=1 or
ct=(antibody formation; antibody affinity; humoral immunity; immunity,
active; active immunization; immunity, cellular; cellular immunity;
lymphocyte activation; cytopathogenic effect, viral; cytopathogenic effect)
or (ft=(stimulation index)/(ti; ab) and ft=(t-cell proliferation)/(ti; ab))
21 1133438 ft=(antibody response*; antibody titer*; antibody
titre*; antibody level*; immune response*; t-cell response*; cell-mediated
immunity; humoral # # # immunity; measles igg; seroconversion; "response #
vaccination"; response # # # measles vaccination)/(ti; ab)
22 232869 ft=(improv* # # # survival; improves # # #
survival; mortality reduction; child mortality; prevention # # # measles;
risk # # # measles)/(ti; ab)
23 2952372 ft=(reactogenicity; safety; adverse events;
adverse effects; side effects; fever; local reaction*; convulsion*;
purpura; rash)/(ti; ab) or ft=(reactogenicity; safety; adverse events;
adverse effects; side effects; fever; local reaction*; convulsion*;
purpura; rash)/(ti; ab)
24 1704886 ft=(aseptic meningitis; seizures; encephalopathy;
anaphylaxis; hypersensitivity; allergic reaction*; joint pain; arthropathy;
arthralgia; arthritis; cough; diarrhoea; diarrhea)/(ti; ab)
25 4803 ct=(measles vaccine; measles-mumps-rubella vaccine;
measles mumps vaccine; measles rubella vaccine; measles rubella mumps
vaccine; measles killed vaccine; measles mumps rubella varicella
vaccine)/qf=ae or (ct=measles vaccine and qf=(adverse events; adverse drug
reaction; side effect; chemically induced; complications; complication;

	contraindications; toxicity; drug toxicity; poisoning; drug effects)) 26 8181234 (ft=adverse/(ti; ab) and ft=(effect*; event*)/(ti; ab)) or ft=(side effect*; hypersensitiv*; sensitiv*; safe*; pharmacovigil*)/(ti; ab) 27 2529 14 and (15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26) 28 105236272 la=(english; dutch; german; french; spanish) 29 2392 27 and 28 30 15403591 ct d (animals; animal) not (ct d (animals; animal) and ct=(humans; human)) 31 5833282 ft=(macaque*; primate*; rodent*; mice; mouse; murine; rat; rats)/ti 32 20070407 DT=(CASE REPORTS; NEWS; NEWS ITEM; LETTER; COMMENT; EDITORIAL; MEETING ABSTRACT; MEETING; CONFERENCE ABSTRACT; CONFERENCE PAPER) 33 2245 29 NOT (30 OR 31 OR 32) 34 1015 check duplicates: unique in s=33 35 645 34 AND BASE=ME66 36 370 34 NOT 35
WHO LIS	Words or phrase: measles$ AND Words or phrase: vaccin$ OR immunization$ OR immunisation$
WHO IRIS	Search: All of WHO IRIS For: Measles Current filters: Title: measles AND vaccine OR Title: measles AND vaccines OR Title: measles AND immunization OR Title: measles AND immunisation

Appendix C: GRADE data quality assessment

1. Quality of evidence across studies per outcome

Table 6. Quality of evidence table for immunogenicity: observational studies

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**No**		⊕⊕◯◯ Low
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**Serious (-1)**	**Wide confidence intervals, mainly for GMT**	
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	Yes (+1)	**% Seroconversion and seropositivity increase with age (significant in metaregression)**	
Plausible confounding would change the effect	No		

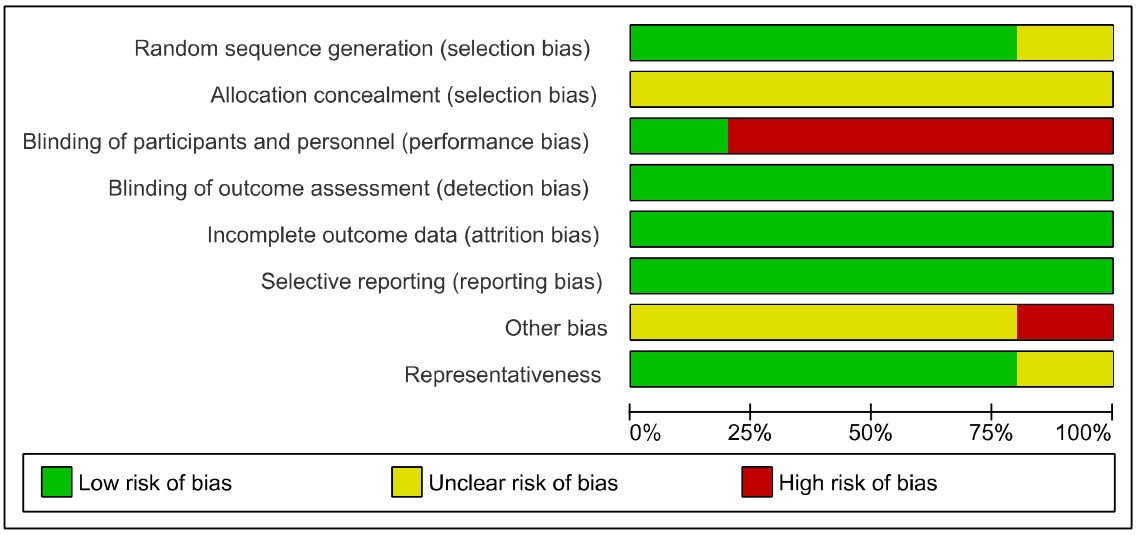

Figure 12. Risk of bias graph for immunogenicity: observational studies

Table 7. Quality of evidence table immunogenicity: RCTs

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**No**		⊕⊕⊕◯ Moderate
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**serious (-1)**	**Mainly for GMTs**	
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	No		
Plausible confounding would change the effect	No		

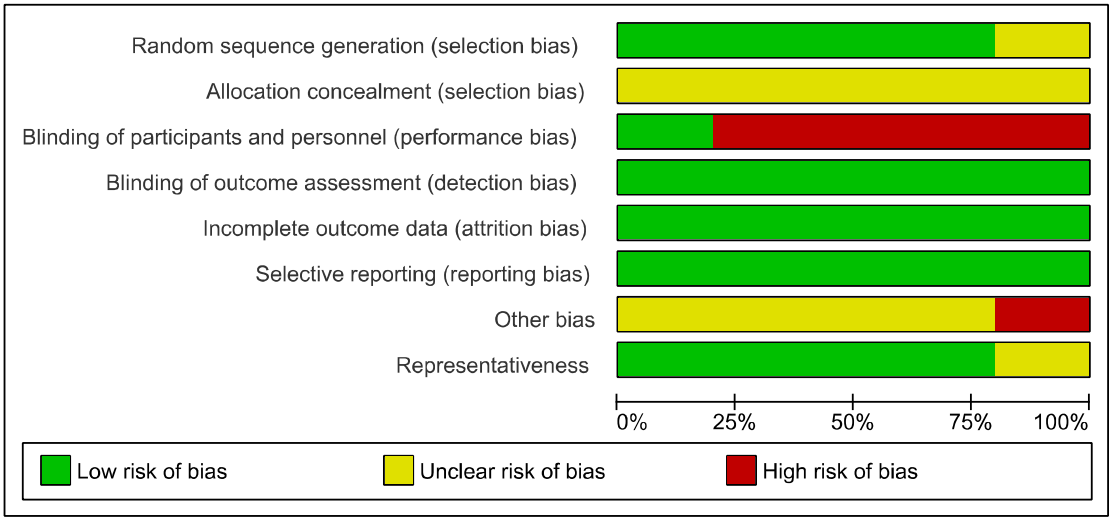

Figure 13. Risk of bias graph for immunogenicity: RCTs

Table 8. Quality of evidence table for duration of immunity

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**No**		⊕⊕◯◯ Low
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**No**		
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	No		
Plausible confounding would change the effect	No		

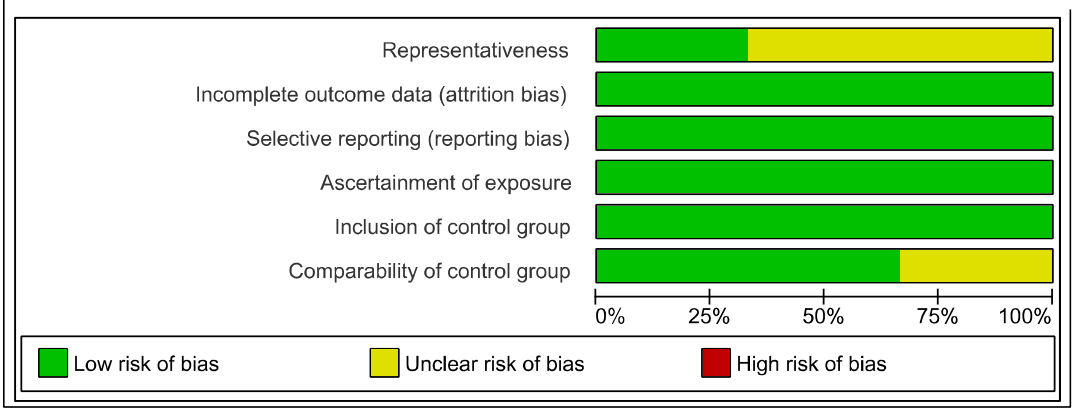

Figure 14. Risk of bias graph for duration of immunity

Table 9. Quality of evidence table for vaccine effectiveness/efficacy

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**serious (-1)**	**Main risk of bias is the lack of laboratory confirmation of measles cases**	⊕○○○ Very Low
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**serious (-1)**		
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	No		
Plausible confounding would change the effect	No		

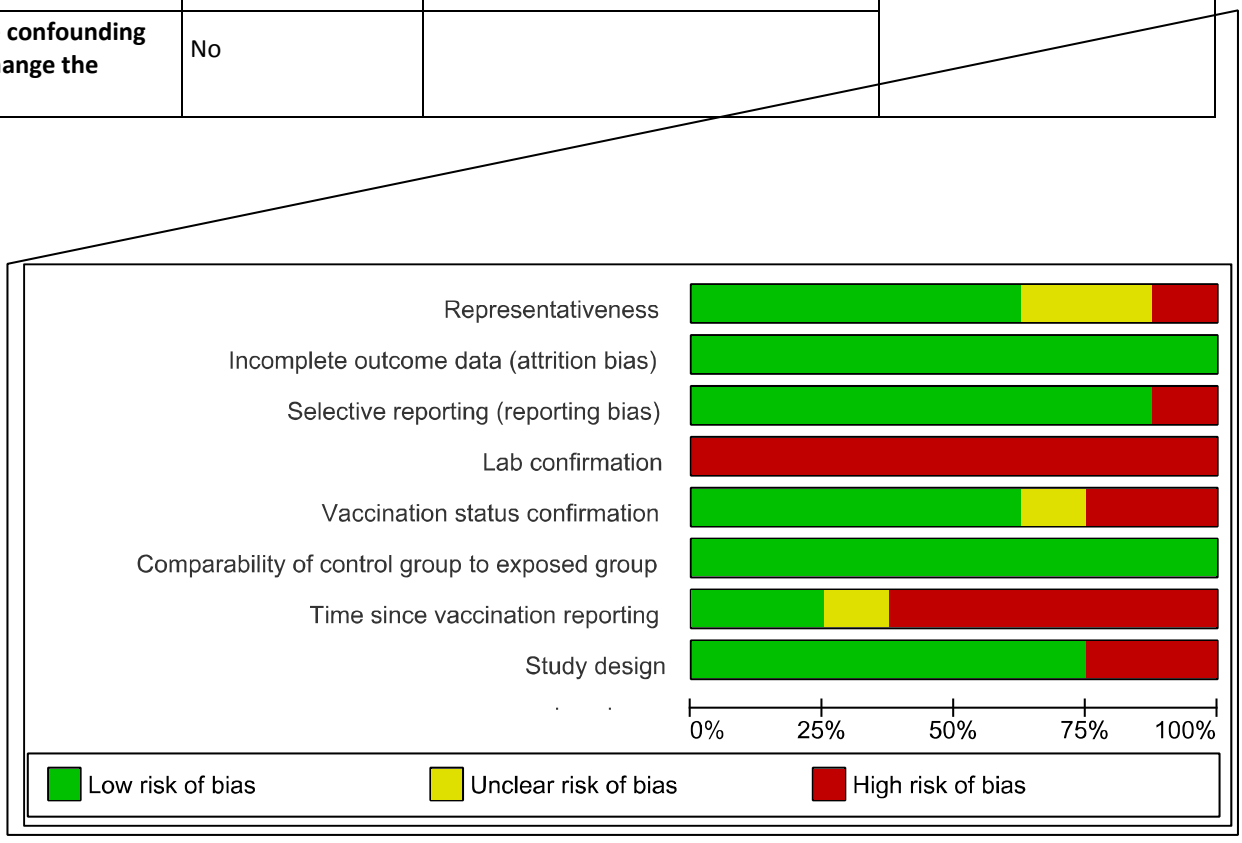

Figure 15. Risk of bias graph for vaccine effectiveness

Table 10. Quality of evidence table for blunting

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**No**		⊕⊕◯◯ Low
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**No**		
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	No		
Plausible confounding would change the effect	No		

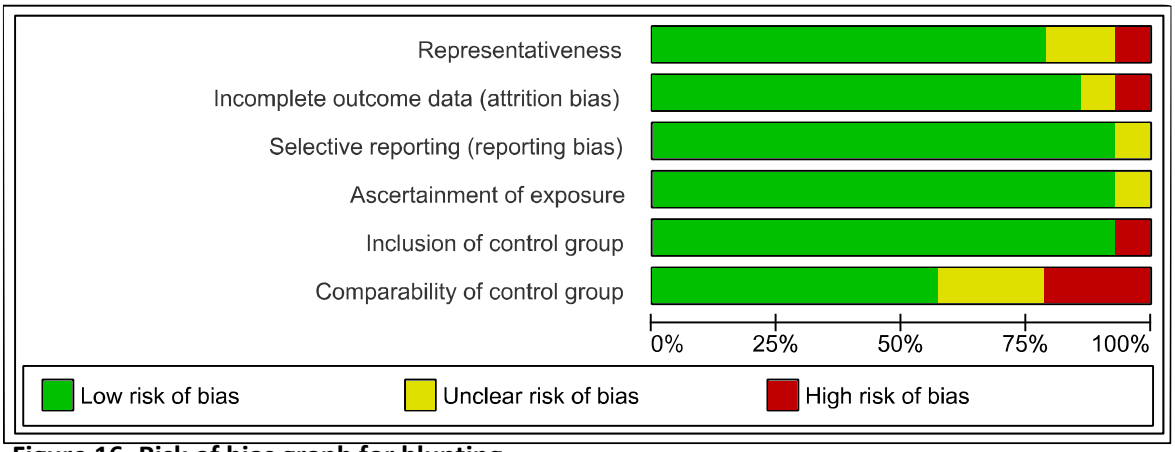

Figure 16. Risk of bias graph for blunting

Table 11. Quality of evidence table for safety

Quality criteria	Rating	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence
Outcome # 1:			
Risk of bias	**Serious limitations**	**Most studies lack an unvaccinated control group of the same age**	⊕◯◯◯ Very low
Inconsistency	**No**		
Indirectness	**No**		
Imprecision	**No**		
Publication Bias	**Unlikely**		
Large effect	No		
Dose-response gradient	No		
Plausible confounding would change the effect	No		

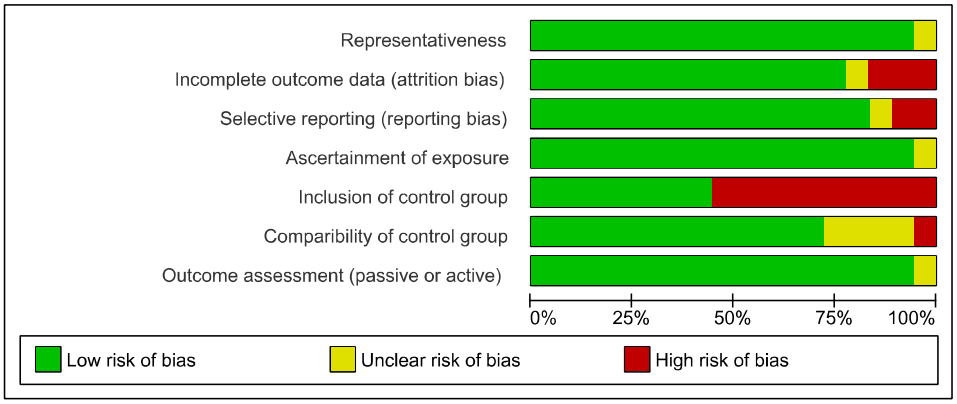

Figure 17. Risk of bias graph for safety

2. GRADE Evidence Profile Table

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute		
Immunogenicity												
41	Observational	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	Many studies had high loss to follow-up. Dose-response gradients for age and seroconversion/ seropositivity.	#	#	#	#	⊕⊕◯◯ Low	IMPORTANT
5	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	Lack of methodological information on performance bias	#	#	#	#	⊕⊕⊕◯ Moderate	IMPORTANT
Duration of immunity												
3	Observational	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Very few studies available	#	#	#	#	⊕⊕◯◯ Low	IMPORTANT
Vaccine effectiveness/ efficacy												
8	Observational	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious[1]		#	#	#	#	⊕◯◯◯ Very low	IMPORTANT
Blunting												
14	Observational	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Aside from seropositivity, very few data available on blunting	#	#	#	#	⊕⊕◯◯ Low	IMPORTANT

Safety												
18	Observational	Serious Limitations[3]	No serious inconsistency	No serious indirectness	No serious imprecision	In many studies, clear case definitions (e.g. for fever) are lacking	#	#	#	#	⊕◯◯◯ Very low	IMPORTANT

1: very wide confidence intervals
2: mainly due to lack of laboratory confirmation of measles cases
3: most studies lack an unvaccinated control group of the same age; this is important for safety results because fever and rash occur more often in younger infants due to other causes.
#: no summary estimates per intervention or control group are applicable

Appendix D: Definitions for seroconversion

Table 12. Definitions of seroconversion accepted for inclusion into the review

Author	Definitions accepted for seroconversion	Type of sample	Type of test
Abanamy 1992	Greater or equal than fourfold rise in titre	Serum	Other
Allal 1977	Increase in antibody greater or equal than 1/4	Serum	HIA
Anonymous 1977	Greater or equal than fourfold rise	Blood cells	Other
Anonymous, WHO 1981	From seronegative to seropositive	Fingerstick	HIA
Bolotovski 1994	From negative to positive or a greater or equal than fourfold titre rise above expected decay	Fingerstick	HIA
Carson 1995	PRNT: fourfold increase in measles antibody titre	Serum	PRNT
Cutts 1994	Fourfold rise in titre pre/(expected) post vaccination 6w and 6m post vaccination	Fingerstick	PRNT
Diaz-Ortega 1986	Fourfold increase or change from seronegative to seropositive	Fingerstick	HIA
Ekunwe 1985	Fourfold rise in antibody titre	Fingerstick	HIA
Fernandez de Castro 1986	Greater or equal than fourfold increase pre/post vaccination	Serum	HIA
Gans 2013	Greater or equal than fourfold increase in GMT (1998 paper)	Serum	PRNT
He 2014		Serum	ELISA
Job 1984	Seronegative to seropositive	Fingerstick	HIA
Johnson 1994	Seronegative to seropositive	Serum	Other
Katiyar 1985	Greater than fourfold rise in HAI titre	Serum	HIA
Khanum 1987	Fourfold increase in HI	Heel prick	HIA
Mandara 1985	Fourfold rise in titre post-vaccination	Serum	HIA
Markowitz 1990	Change from negative (<40miu) pre-vaccination to positive post-vaccination or fourfold increase in level above calculated titre expected 8 or 18w post-vaccination	Fingerstick	PRNT
Ndumbe 1995	Prevaccination <200 mu/ml and postvaccination positive or greater or equal fourfold increase 6w postvaccination	Serum	ELISA
Nkrumah 1998	Seronegative to seropositive, or greater or equal 4-fold increase in titre given decay	Serum	HIA
Pabst 1999	4fold increase in titer, adjusted for decay of maternal antibodies	Serum	PRNT
Pan American Health Organization 1982	Greater or equal than fourfold increase in titre or greater or equal 1:10	Serum	HIA
Pongrithsukda 1991	No detectable to detectable Ab	Serum	PRNT
Rogers 1991	Fourfold increase	Blood cells	ELISA
Schatzmayr 1982	Not reported	Serum	HIA
Semba 1995	Greater or equal than fourfold titre rise	Serum	PRNT

Shaikh 1992	Greater or equal than fourfold rise in HI titre or from negative to positive	Serum	HIA
Soula 1991	Lower Ab titer of 1/10 before vaccination and equal or higher post vaccination	Serum	HIA
Stewien 1978	Greater or equal than fourfold titre increase between pre and post vaccination sample	Serum	HIA

Table 13. Definitions of seroconversion not accepted for inclusion into the review

Author	Definitions not accepted for seroconversion	Type of sample	Type of test
Breman 1975	No definition given	Serum	HIA
Cutts 1994	Optical density ratio pre/post >= 1.47	Other	ELISA
Deivanayagam 1990	Conversion from negative to positive or >= twofold rise in titre	Serum	HIA
Gendrel 1988	Greater or equal than twofold rise of dilutions	Dried blood spots	HIA
Halsey 1985	From negative to >= 1:10	Dried blood spots	HIA
Hussey 1995	Fourfold rise at 2 weeks, 2fold rise at 3 m or conc >= 200 miu/ml post-vacc with <200 prevacc	Serum	PRNT
Job 1991	Greater or equal than 200 mlu/ml	Dried blood spots	PRNT
King 1978	No definition given	Dried blood spots	HIA
Kumar 1998	Titer <= 10 (NT), see erratum	Serum	PRNT
Kurubi 2009	No definition given	Serum	ELISA
Lhuillier 1989	No definition given	Serum	HIA
McGraw 1986	Titre >= 10	Dried blood spots	HIA
Mirchamsy 1991	Fourfold increase in HI titre	Other	HIA
Ogunmekan 1981	No definition given	Other	HIA
Sabin 1984	In ref 1 (no full text available)	Red blood cells	PRNT
Sakatoku 1994	Seropos/ total samples = INVALID definition! (other calc used for data input, data still usable)	Serum	HIA
Simasathien 1997	Positive 9 month NT and >= 6 month sample	Serum	PRNT
Vidyashankar 2002	No definition given	Serum	ELISA
Whittle 1988	No definition given	Other	PRNT
Wilkins 1979	No definition given	Serum	HIA
Youwang 2001	Negative to positive or >= fourfold rise following reimmunisation	Dried blood spots	ELISA

Appendix E: Basic characteristics of all studies included in the review

Table 14. Basic characteristics of all references with data extracted for inclusion in this review

Author	Country	MCV1 age (months)	Vaccine Strain	Vaccine Titre	Study Period	Immuno-genicity	VE	Duration of immunity	Safety	Blunting	Maternal antibodies
Abanamy 1992	Saudi Arabia	6, 9	Schwarz, Edmonston-Zagreb	3	-	Yes	-	-	-	-	-
Allal 1977	Algeria	6-9, 10-13	Schwarz	3	1974 - 1975	Yes	-	-	-	-	-
Anonymous 1977	Kenya	4,5,6,7,8,11	Schwarz	3.3	1974 - 1975	Yes	-	-	-	-	Yes
Anonymous, WHO 1981	Tanzania	4-5, 6-7, 8-9, 10-11, 12-13, 14-15	Schwarz	3	1977 -	-	-	-	-	-	-
Benn 1997	Guinea-Bissau	6, 9	Schwarz	3.7 pfu	1993 - 1995	-	-	-	-	Yes	-
Berry 1992	Peru	5-6, 8-9	Schwarz, Edmonston-Zagreb	4.2 pfu	1989 - 1990	-	-	-	-	-	-
Bhatnagar 1981	India	8, 10, 12, 15	Schwarz	Unknown	-	-	-	-	-	-	-
Bolotovski	Uzbekistan	6, 9	AIK-C,	3.5 pfu, 3.65	-	Yes	-	-	-	-	-

1994			Edmonston-Zagreb, Leningrad 16, Schwarz	pfu, 4 pfu, 4.36 pfu, 4.4 pfu, 4.7 pfu							
Breman 1975	Ivory Coast	6-8, 9-24	Unknown	Unknown	-	-	-	-	-	-	-
Carson 1995	Canada	6-8	Connaught	3.3	1991 - 1993	-	-	-	-	Yes	Yes
Cutts 1994	DRC	<5,5, 5-6, 6, 6-7, 7-8, >9	Edmonston-Zagreb	4.45 pfu, 4.7 pfu	1990 - 1990	Yes	-	Yes	-	-	-
David 1987	USA	<9, ≥9, ≥15	Unknown	Unknown	1985	-	-	-			
Deivanayagam 1990	India	6,6-8,7,8,	Schwarz	3	1988 -	-	-	-	-	-	Yes
Diaz-Ortega 1986	Mexico	8,9-10,11-12,13-14,15-16,17-18	Schwarz	3	1983 - 1984	Yes	-	-	-	-	Yes
Dick 1975	South Africa	6,7,8,9,10,11,12	Moraten	3	-	-	-	-	Yes	-	-
Ekunwe 1985	Nigeria	6,7,8,9-12,13-19,20-26	Edmonston	Unknown	1982 - 1983	Yes	-	-	-	-	Yes
Fernandez de Castro 1986	Mexico	6-9	Edmonston-Zagreb, Schwarz	3.3	1983 - 1984	Yes	-	-	-	-	Yes
Gans 1999	USA	6,9,12	Moraten	3	-	-	-	-	-	Yes	-
Gans 2004	USA	6,9,12	Moraten	3	-	-	-	-	-	Yes	-

Gans 2001	USA	6,9,12	Moraten	3	-	Yes	-	-	-	Yes	Yes
Gans 2013	USA	6,9,12	Moraten	3	-	Yes	-	-	-	Yes	-
Garly 2001	Guinea-Bissau	6,9	Edmonston-Zagreb, Schwarz	3.65	1995 - 1996	Yes	-	-	-	Yes	-
Gendrel 1988	Gabon	3-5, 5-6	Schwarz	3.4, 4.4	31717 - March 1987	-	-	-	-	-	-
Goan 1978	Bosnia and Herzegovina	<9, 9-11, 12-14, >15	Edmonston-Zagreb	3	-	-	-	-	-	-	-
Halsey 1985	Haiti	6,7,8,9,10,11,12	Moraten	Unknown	1982 -	-	-	-	-	-	-
He 2014	China	8,12	Hu-191	3.3	-	-	-	-	Yes	Yes	-
Helfand 2008	Malawi	6,9	Edmonston-Zagreb	3.1 pfu	2000 - 2002	-	-	-	Yes	Yes	-
Hull 1983	Gambia	<6, 6-8, 9-11, 12-14, >15	Moraten	Unknown	1981 - 1981	-	Yes	-	-	-	-
Hussey 1995	South Africa	6,9	Edmonston-Zagreb, Schwarz	4.3 pfu	-	-	-	-	-	-	-
Jensen 1994	Guinea-Bissau	4-5,6-8,9-12	Edmonston-Zagreb, Schwarz	3.7 pfu, 4.6 pfu	1984 - 1987	-	-	-	-	-	-
Job 1984	India	6,7,8,9,10,11,12,	Moraten	3.4	1981 -	-	-	-	-	-	-

		13-15			1981						
Job 1991	Haiti	6,8	Edmonston-Zagreb, Schwarz	4.4 pfu, 4.6 pfu	1987 - 1989	-	-	-	Yes	-	-
John 2004	India	Unknown	unknown			-	-	-	-	-	-
John 2009	India	6,6-8,>8,9	Unknown	Unknown	1999 - 2006	-	Yes	-	-	-	-
Johnson 1994	USA	6,15	Moraten	3.9	-	Yes	-	-	Yes	-	-
Judelsohn 1980	USA	≤9, >10	Unknown	Unknown	1978 - 1978	-	Yes	-	-	-	-
Kaninda 1998	Niger	6-8,9	Schwarz	Unknown	1995 - 1995	-	Yes	-	-	-	-
Katiyar 1985	India	6,7,8,9-12,13-15	Schwarz	3	-	Yes	-	-	-	-	-
Khalil 1999	Saudi Arabia	6	Edmonston-Zagreb	4.3 pfu	1995 - 35156	-	-	-	-	Yes	-
Khanum 1987	Bangladesh	3-4,4-5,5-6	Edmonston-Zagreb, Schwarz	3.7 pfu, 3.8 pfu	-	Yes	-	-	-	Yes	-
Kiepiela 1991	South Africa	3-5,4-8,5-6,6-8,8-9,9-10,9-11	Edmonston-Zagreb, Schwarz	3.3, 3.9	1988 -	-	-	-	-	-	-
King 1978	Tanzania	<7, 7-9,10-12,13-18,16-24,25-30,31-36,	Moraten	Unknown	1975 - 1975	-	-	-	-	-	-

		>36									
Ko 1999	England	5	Schwarz	Unknown	1993 - 1994	Yes	-	-	Yes	-	-
Kumar 1998	USA	6,15	Edmonston	Unknown	-	-	-	-	-	-	Yes
Kurubi 2009	Papua New Guinea	6	Edmonston-Zagreb	Unknown	-	-	-	-	-	-	-
Lee 1983	Taiwan	6,7,8,9,10,11,>12	Moraten	Unknown	-	Yes	-	-	-	-	-
Lhuillier 1989	Ivory Coast	5-7,8-10	Schwarz	3	-	-	-	-	-	-	-
Mandara 1985	Tanzania	6-7,8-9,10-11,12-13,14-15,16-21	Schwarz	3	-	Yes	-	-	-	-	-
Markowitz 1990	Mexico	6,9	Edmonston-Zagreb, Edmonston-Zagreb Mexico, Schwarz	3.7 pfu,3.8 pfu, 4.5 pfu, 4.6 pfu	1987 - 1987	Yes	-	-	Yes	Yes	-
Martins 2014	Guinea-Bissau	4,9	Edmonston-Zagreb, Schwarz	3.65 pfu,Unknown	2003 - 2006	-	Yes	-	-	Yes	-
McGraw 1986	USA	7-8,9-10-11-12	Moraten	Unknown	1982 - 1984	-	-	-	-	Yes	-
Mirchamsy	Iran	7,8,9-24	AIK-C,	4	-	Yes	-	-	-	-	-

1991			Edmonston-Zagreb								
Mouchon 1990	Cameroon	6,7,8,9,10	Schwarz	3	-	-	-	-	-	-	-
Nair 2007	USA	6,9	Moraten			-	-	-	-	Yes	-
Ndumbe 1995	Cameroon	3,4,5,6,7,8	Connaught, Schwarz	3.3, 4	1991 - 1992	Yes	-	-	-	-	Yes
Njie-Jobe 2012	Gambia	4,9	Edmonston-Zagreb	3,6 pfu	2002 -	-	-	-	-	Yes	-
Nkrumah 1998	Ghana	6,9	AIK-C, Schwarz	3.7 pfu, 4 pfu	-	Yes	-	-	Yes	-	Yes
Ogunmekan 1981	Nigeria	5,6,7,8,9	Moraten	Unknown	-	-	-	-	-	-	-
Pabst 1999	Canada	6	AIK-C, Connaught	3.3, 3.7	1995 - 1996	Yes	-	-	Yes	-	Yes
Pan American health Organization 1982	Several Latin American countries	6,12	Moraten	Unknown	-	-	-	-	-	-	-
Pongrithsukda 1991	Thailand	4-7	Edmonston-Zagreb	3	-	Yes	-	-	-	Yes	Yes
Porter 1990	Malawi	6-9	Unknown	Unknown	1988 - 1988	-	-	-	-	-	-
Rogers 1991	Papua New	4,5,6,6-7,7,<8,	Edmonston-	4	1989 -	Yes	-	-	-	-	-

	Guinea	8-29	Zagreb		1989						
Sabin 1984	Mexico	4,5,6	Edmonston-Zagreb	3.7 pfu	1982 -	-	-	-	-	-	-
Sakatoku 1994	Ghana	3,4,5,6,7,8,9,10,11	Schwarz	3	1986 - 1988	-	-	-	-	-	-
Schatzmayr 1982	Brazil	7,8,9,10,11,12-14,15-18,16-24,25	Schwarz	3	-	-	-	-	-	-	-
Semba 1995	Indonesia	6	Schwarz	4	1992 - 1993	-	-	-	Yes	-	Yes
Shaikh 1992	India	<9,9-12,13-18,>19	Edmonston-Zagreb	3	-	-	-	-	-	-	Yes
Shaoyuan 1982	China	4-6,6,7,7-8,8-12,9-10,11-12,>13	Jing55	2.25	-	Yes	-	-	-	-	Yes
Shasby 1977	USA	<9,9-11,12,>13	Unknown	Unknown	1976 -	-	Yes	-	-	-	-
Simasathien 1997	Thailand	6,9	Edmonston-Zagreb	3.8 pfu	-	-	-	-	-	-	-
Simba 1995	Tanzania	6-8,>9	Unknown	Unknown	1991 - 1991	-	Yes	-	-	-	-
Soula 1991	Mali	4-8,12-24	Schwarz	3	1988 - 1989	Yes	-	-	Yes	Yes	-
Stewien 1978	Brazil	7,8,9,10,11,12	Schwarz	3	1976 -	-	-	-	-	-	-

					1976						
Tidjani 1989	Togo	4-5	AIK-C	3.7	1987 - 1989	-	-	-	-	-	-
Vidyashankar 2002	India	6,6-8,7,8,9,9-11,10,11	Schwarz	Unknown	1991 - 1992	-	-	-	-	-	-
Whittle 1984	Gambia	4-6	Edmonston-Zagreb	4.6 pfu	-	Yes	-	-	-	-	-
Whittle 1988	Gambia	4,5	Edmonston-Zagreb, Schwarz	4 pfu, 4.3 pfu, 4.6 pfu	-	Yes	-	-	-	-	-
Whittle 1990	Gambia	4,9	Edmonston-Zagreb, Schwarz	3.8 pfu, 4.6 pfu	1985 -	Yes	-	Yes	-	-	-
Wilkins 1979	USA	6,7,8,9,10,11,12, 13,14,15,16,17	Schwarz	Unknown	1965 - 1976	-	-	-	-	-	-
Youwang 2001	China	6,7,>8	Hu-191	3.8	1991 - 1998	-	-	-	-	-	-
Zanetta 2001	Brazil	6,7,8,9,10,11,12	Schwarz	Unknown	1997 - 1997	-	-	-	-	-	-

Appendix F: Supplementary results

Forest plots for seroconversion

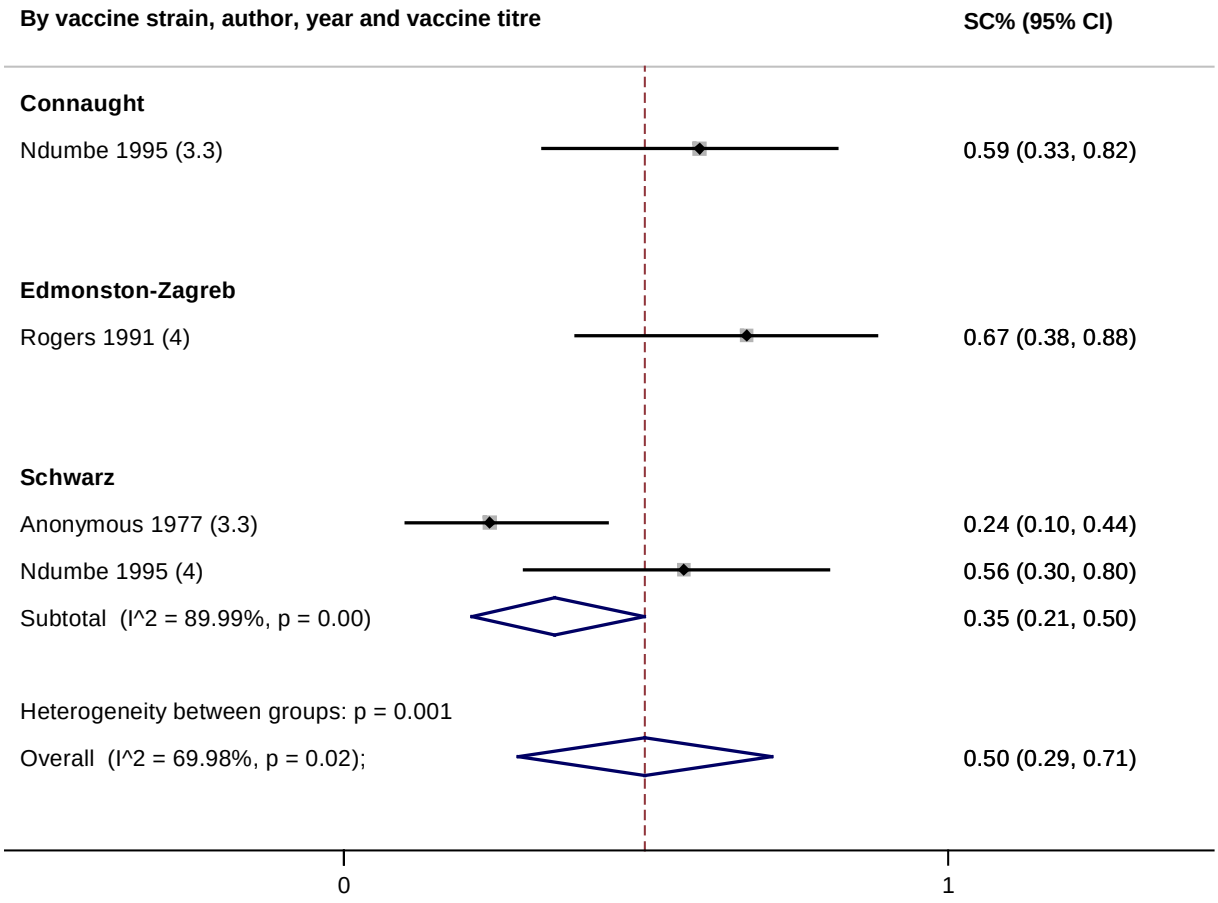

Figure 18. Random effects meta-analysis of the percentage seroconverted after MCV1 in 4 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. SC: seroconversion. CI: confidence interval.

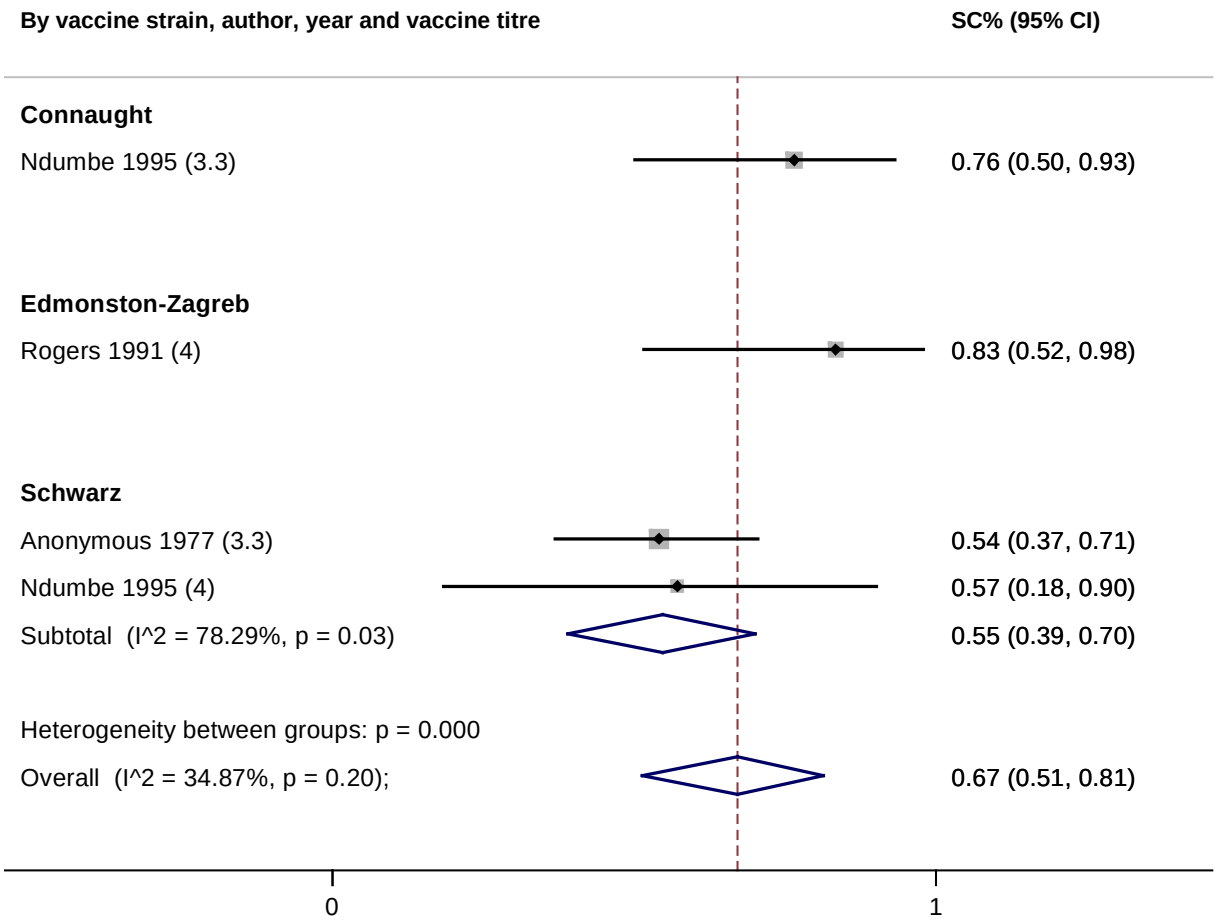

Figure 19. Random effects meta-analysis of the percentage seroconverted after MCV1 in 5 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. SC: seroconversion. CI: confidence interval.

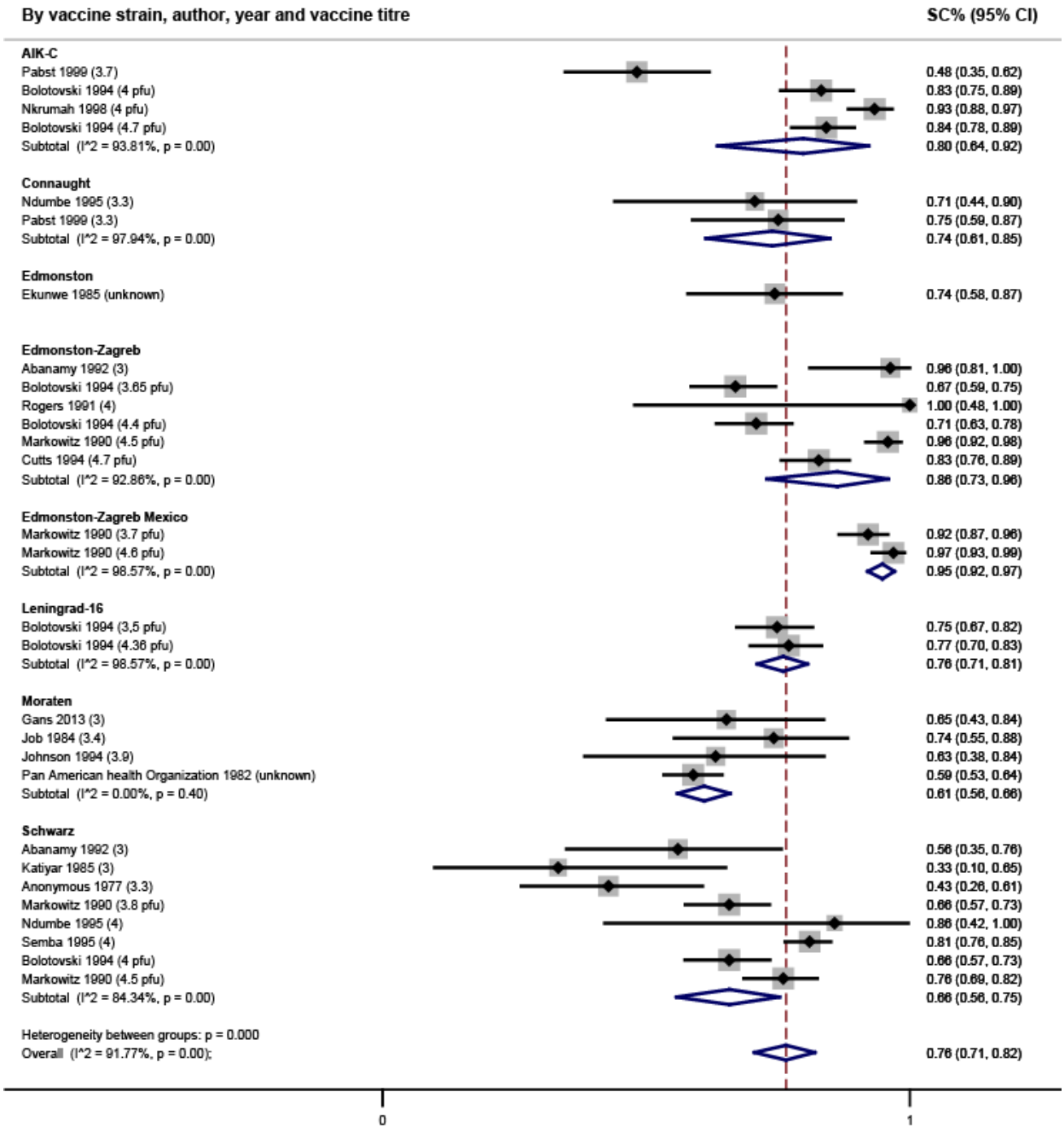

Figure 20. Random effects meta-analysis of the percentage seroconverted after MCV1 in 6 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. SC: seroconversion. CI: confidence interval.

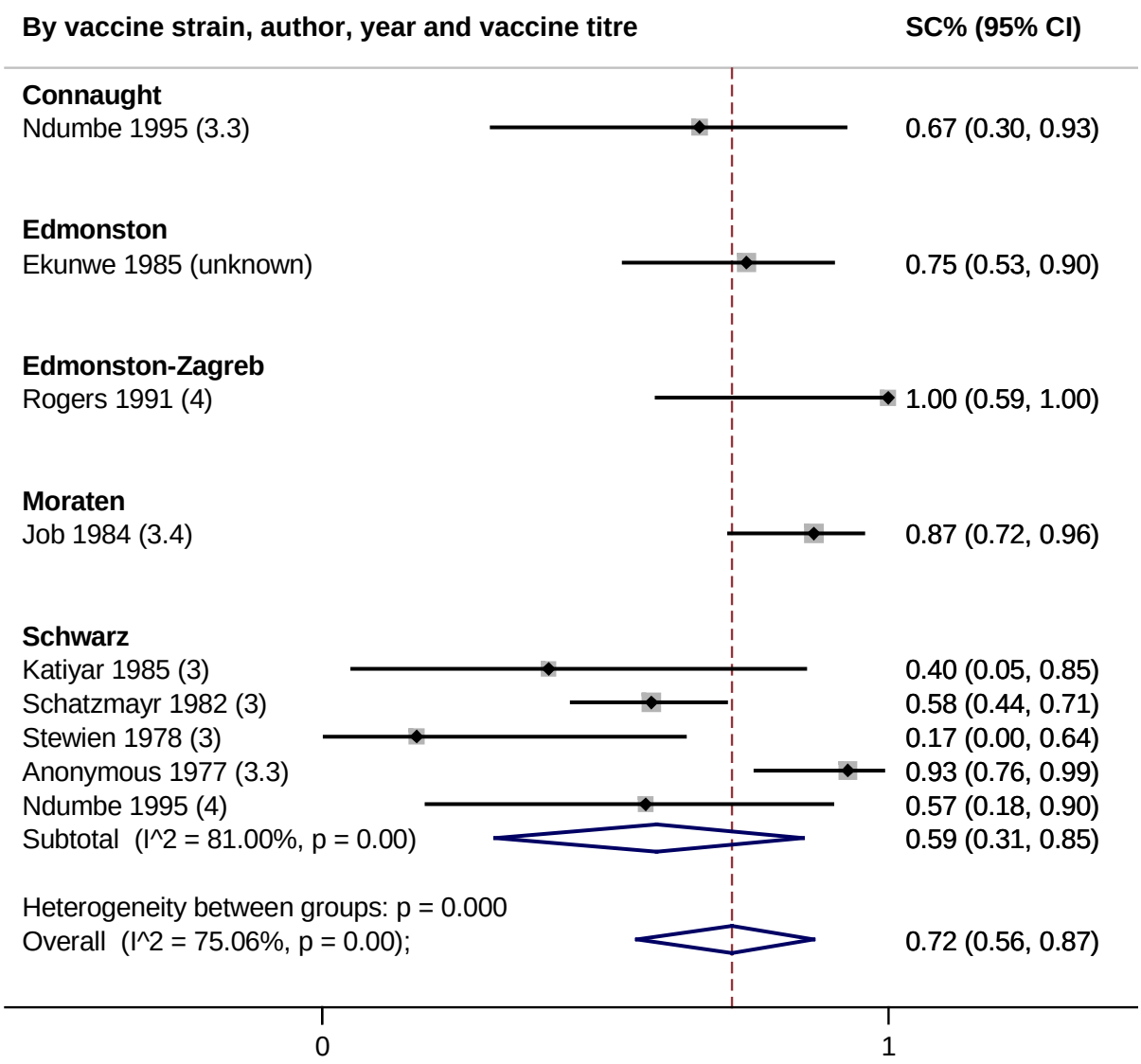

Figure 21. Random effects meta-analysis of the percentage seroconverted after MCV1 in 7 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. SC: seroconversion. CI: confidence interval.

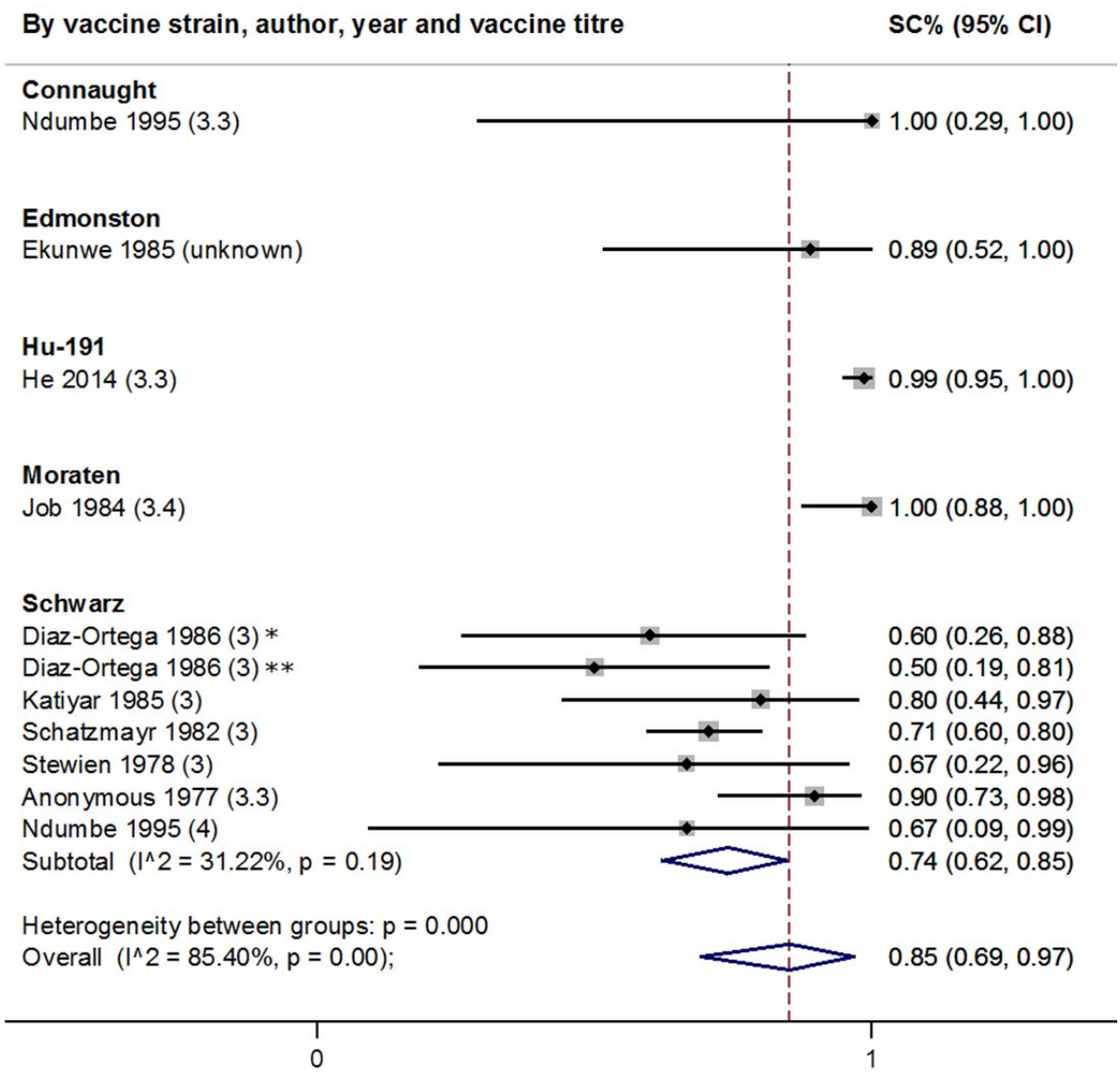

Figure 22. Random effects meta-analysis of the percentage seroconverted after MCV1 in 8 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. SC: seroconversion. CI: confidence interval.

Diaz-Ortega 1986 examined two Schwarz vaccines (3 $TCID_{50}$) from *RIT and **Mérieux

Analysis of grouped age data

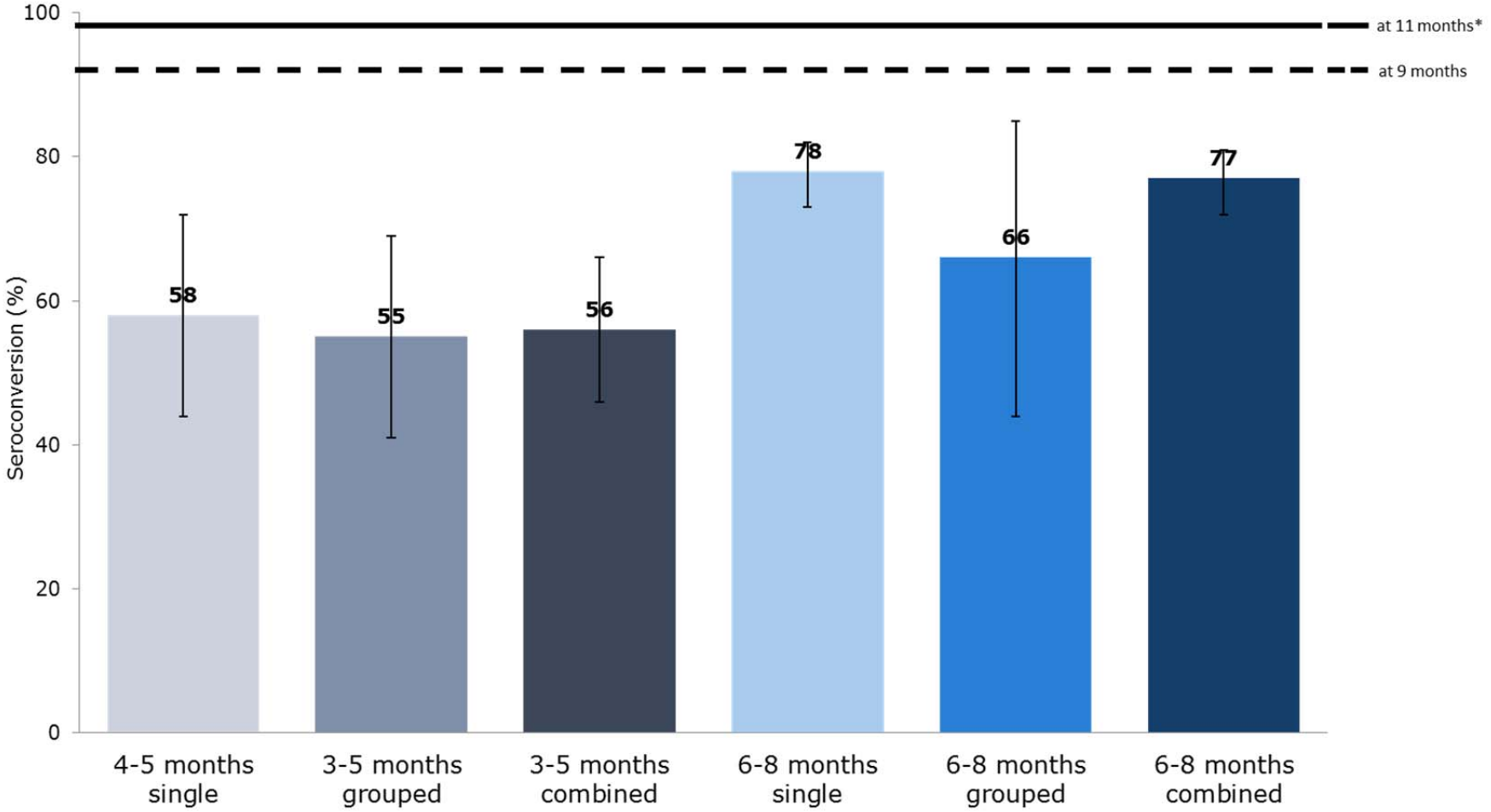

Figure 23. Proportion seroconverted by age of MCV1 (3-8 months), pooled estimates derived from 25 studies. Error bars present 95% confidence intervals.

*The horizontal lines represent the median proportion of infants responding to MCV1 at 9 months (dashed line) and 11 months (filled line) Moss & Scott, 2009(1)

Forest plots for head-to-head vaccine comparisons

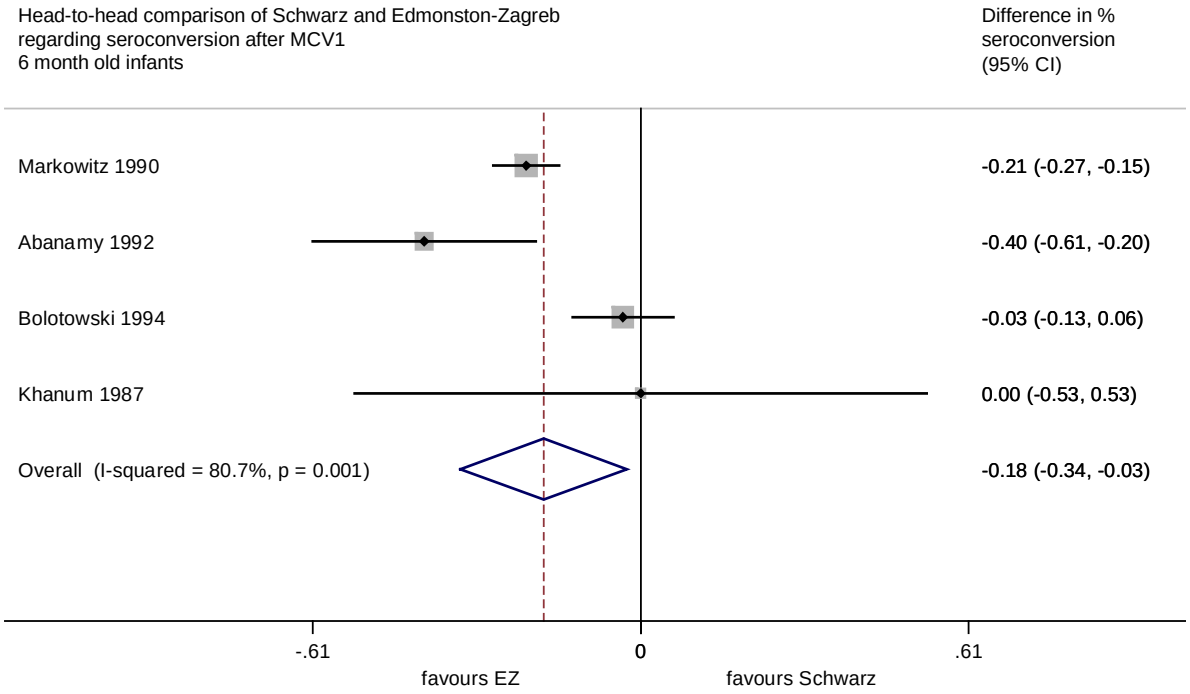

Figure 24. Random effects meta-analysis of the difference in proportion seroconverted after either Edmonston-Zagreb or Schwarz strain vaccination at 6 months of age. CI: confidence interval. EZ: Edmonston-Zagreb.

Meta-regression results for association between time since vaccination or age of MCV1

Table 15 Meta-regression of the association between time since vaccination or age at MCV1 and the natural logarithm of the relative risk of measles compared to unvaccinated children (ln(1-VE)).

Independent variable	Coefficient	95% CI		P value
Median time since vaccination (months)	0.0177	-0.004	0.0391	0.099
Age at MCV1 (1= before 9 months, 2= after or at 9 months)	-0.5459	-1.8052	0.7134	0.374

Forest plots for within-study comparisons for vaccine effectiveness

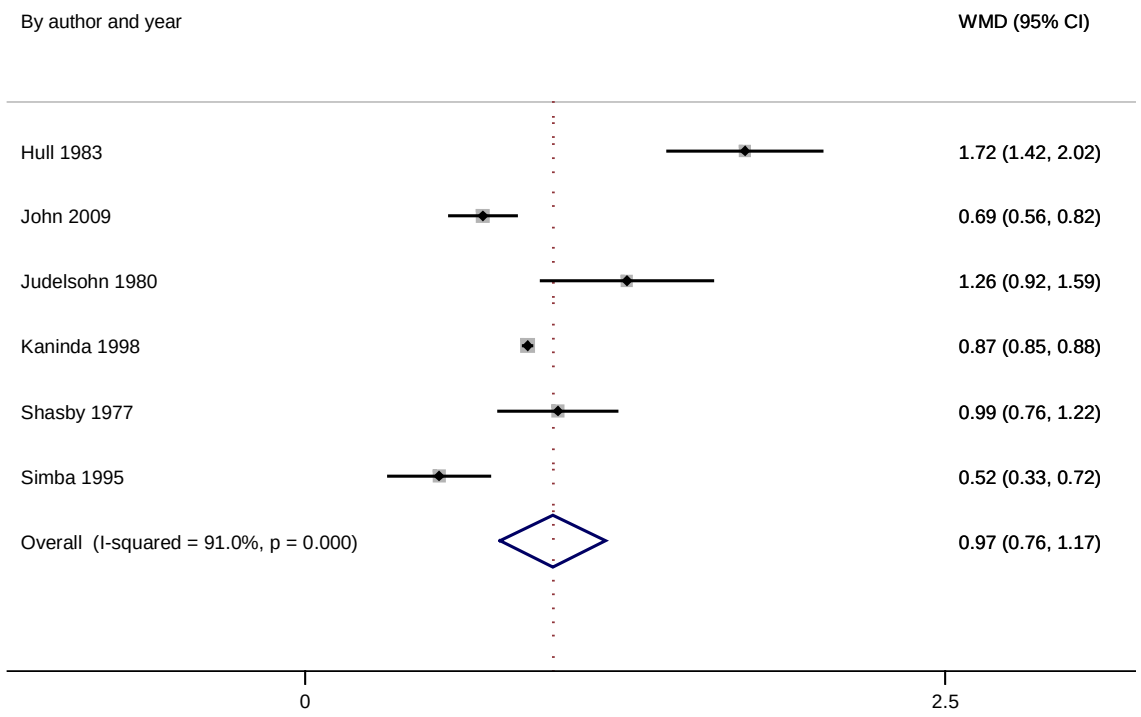

Figure 25 Random effects meta-analysis of the difference in (the natural logarithm of) the relative risk of clinical measles infection after MCV1 <9 versus ≥ 9 months of age. WMD: weighted mean difference. CI: confidence interval. Since this analysis was done on a logarithmic scale, the exponentiated weighted mean difference is to be interpreted as a ratio of RR≥9 to RR<9 months.

Forest plots for within-study comparisons for duration of immunity

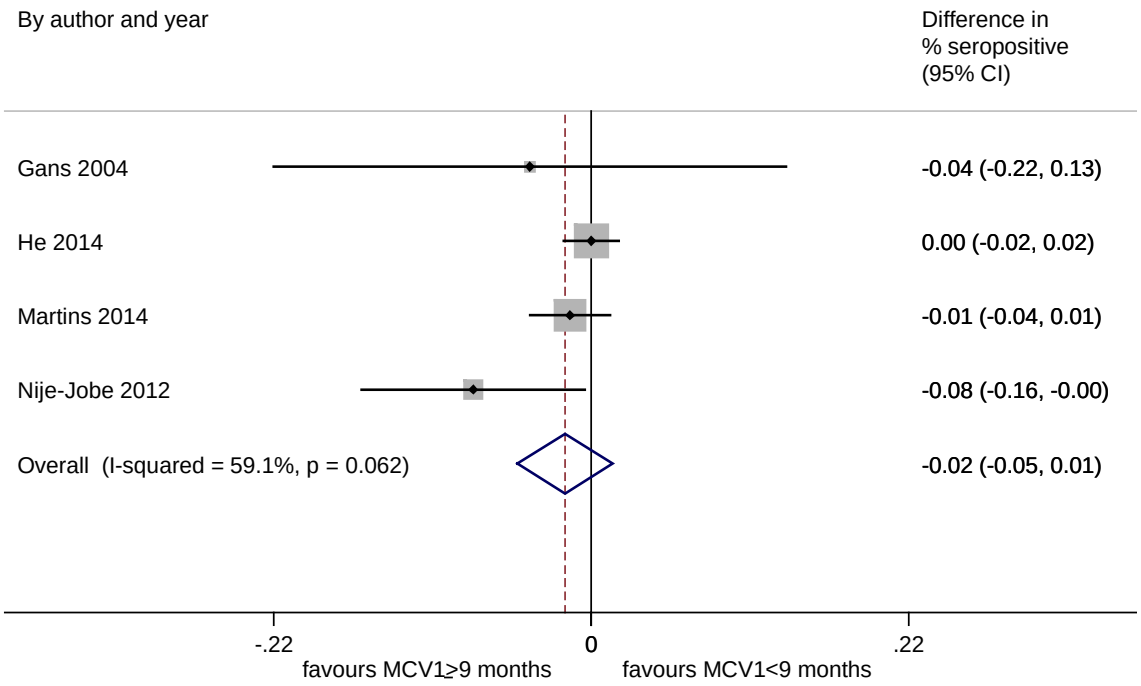

Figure 26 Random effects meta-analysis of the difference in proportion seropositives after MCV2 when MCV1 was given <9 versus ≥ 9 months of age. CI: confidence interval.

Forest plots for safety

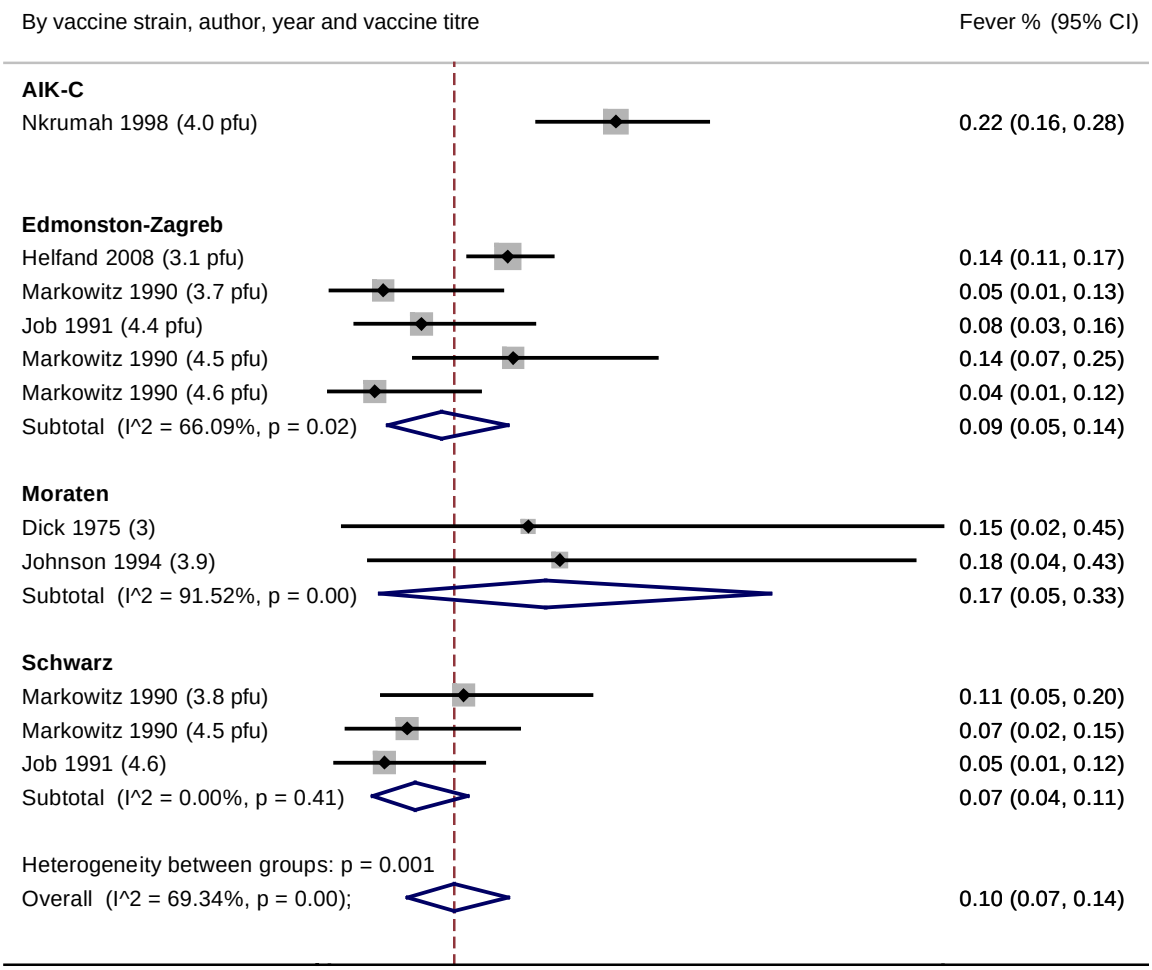

Figure 27. Random effects meta-analysis of the percentage of infants with fever after MCV1 in 6 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. CI: confidence interval.

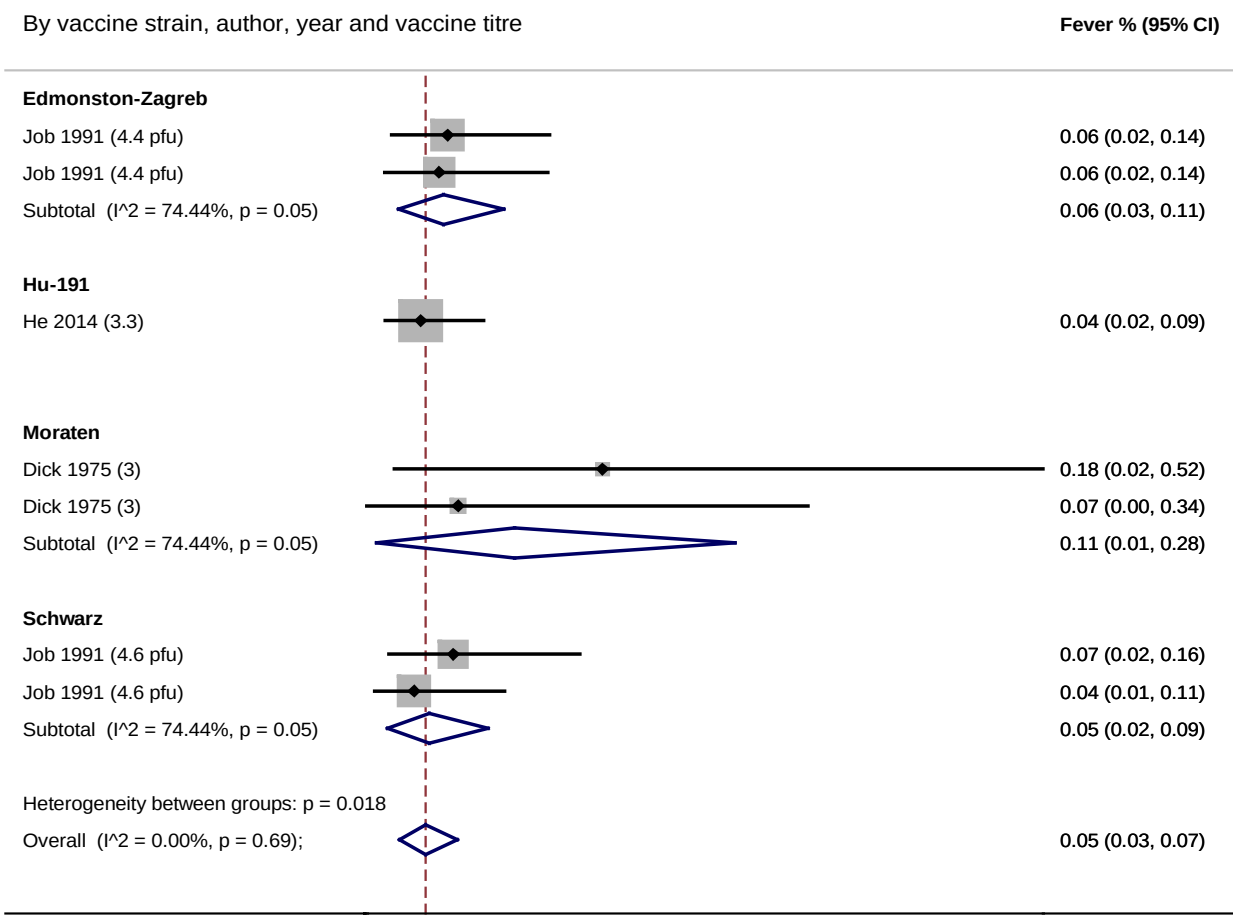

Figure 28 Random effects meta-analysis of the percentage of infants with fever after MCV1 in 7 to 8 month old infants. Studies occurring twice in the plot present estimates for 7 month-olds (upper line) and 8 month olds (lower line). Titres are expressed as $TCID_{50}$ unless specified otherwise. CI: confidence interval.

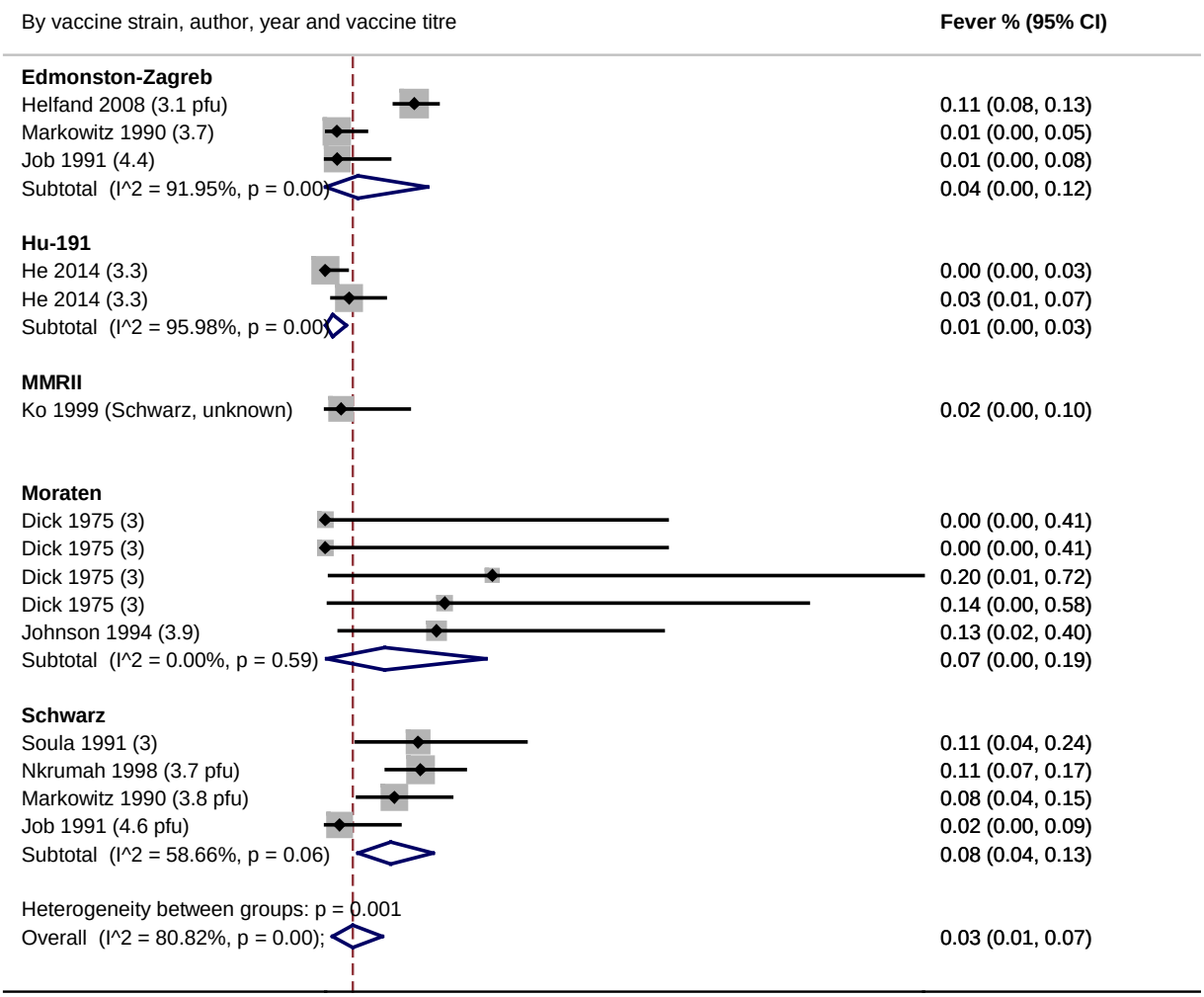

Figure 29. Random effects meta-analysis of the percentage of infants with fever after MCV1 in infants aged 9 months and older. As our literature search focused on studies of MCV1 <9 months of age, the data we present on adverse events ≥9 months of age are likely not representative of all available evidence on MCV1 >9 months of age. Titres are expressed as TCID50 unless specified otherwise. CI: confidence interval.

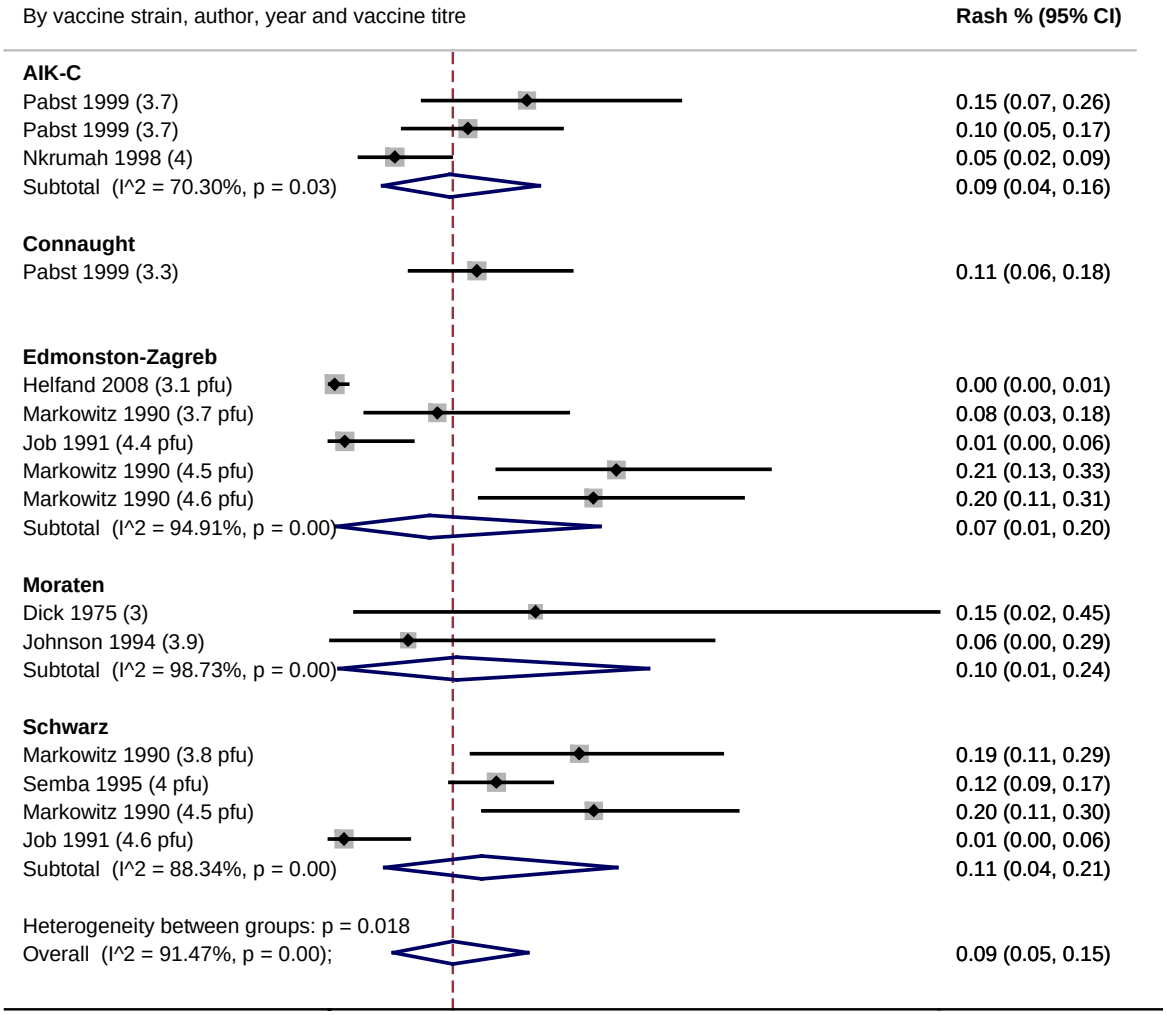

Figure 30. Random effects meta-analysis of the percentage of infants with rash after MCV1 in 6 month old infants. Titres are expressed as $TCID_{50}$ unless specified otherwise. CI: confidence interval.

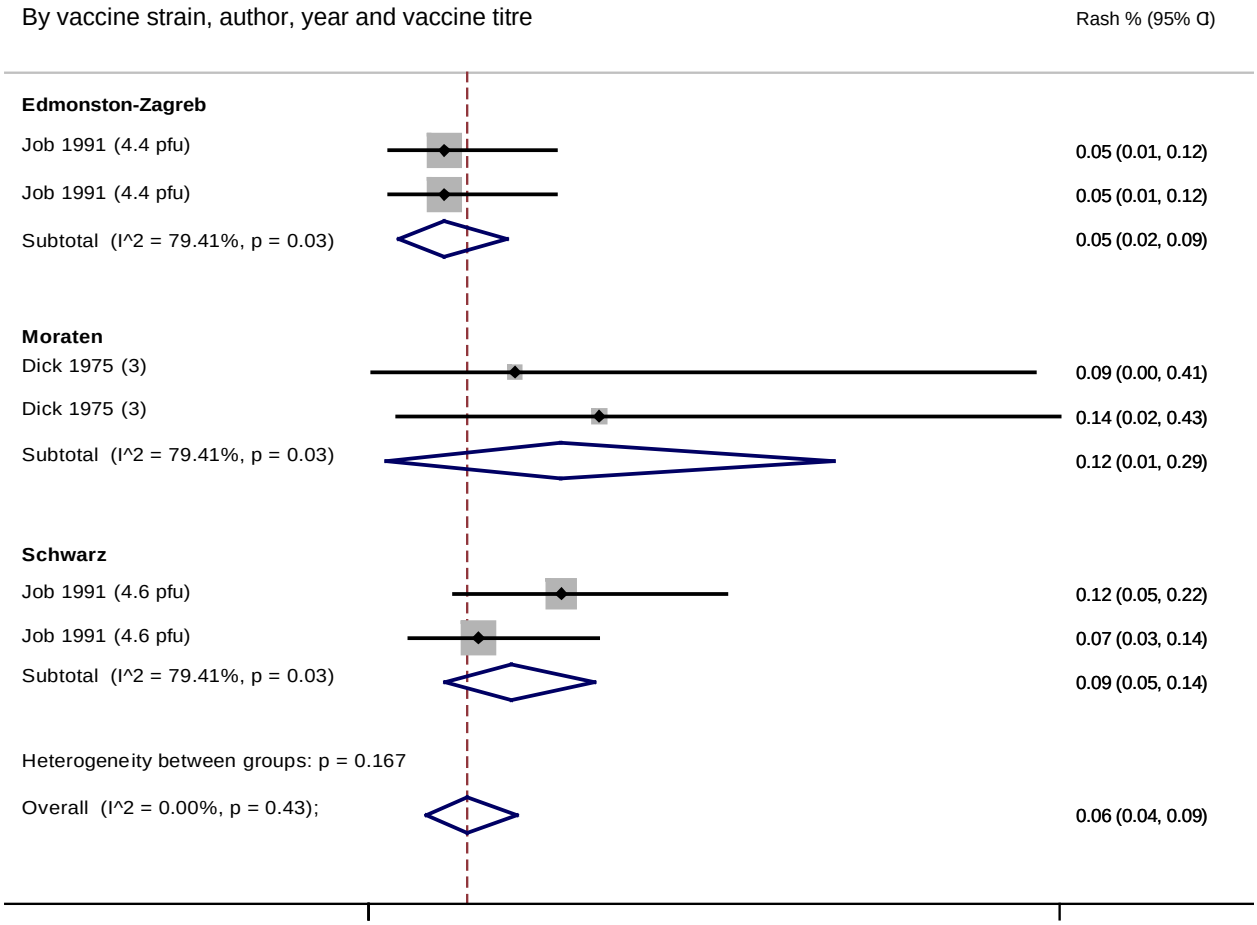

Figure 31. Random effects meta-analysis of the percentage of infants with rash after MCV1 in 7 to 8 month old infants. Studies occurring twice in the plot present estimates for 7 month-olds (upper line) and 8 month olds (lower line). Titres are expressed as $TCID_{50}$ unless specified otherwise. CI: confidence interval.

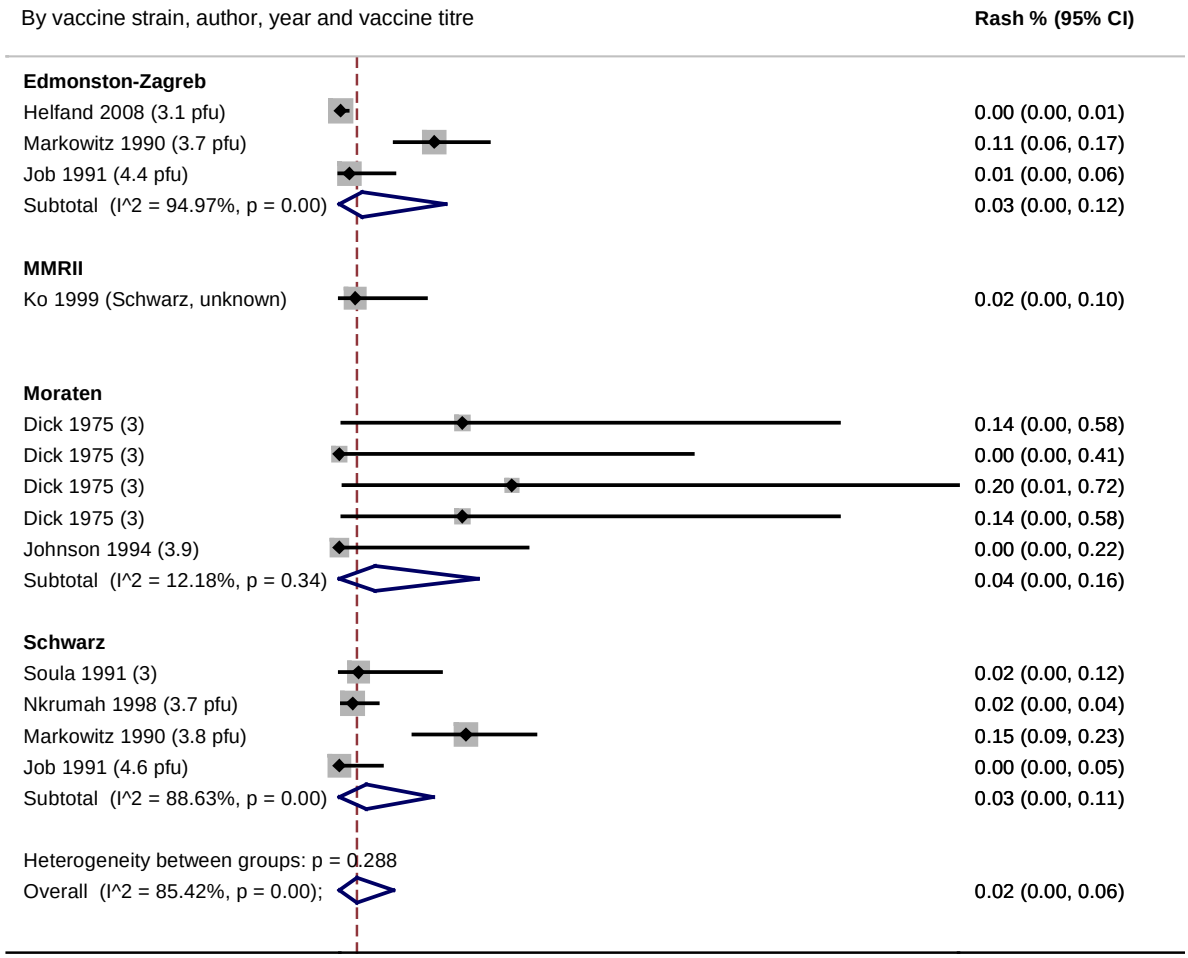

Figure 32. Random effects meta-analysis of the percentage of infants with rash after MCV1 in infants aged 9 months and older. As our literature search focused on studies of MCV1 <9 months of age, the data we present on adverse events ≥9 months of age are likely not representative of all available evidence on MCV1 >9 months of age. Titres are expressed as $TCID_{50}$ unless specified otherwise. CI: confidence interval.

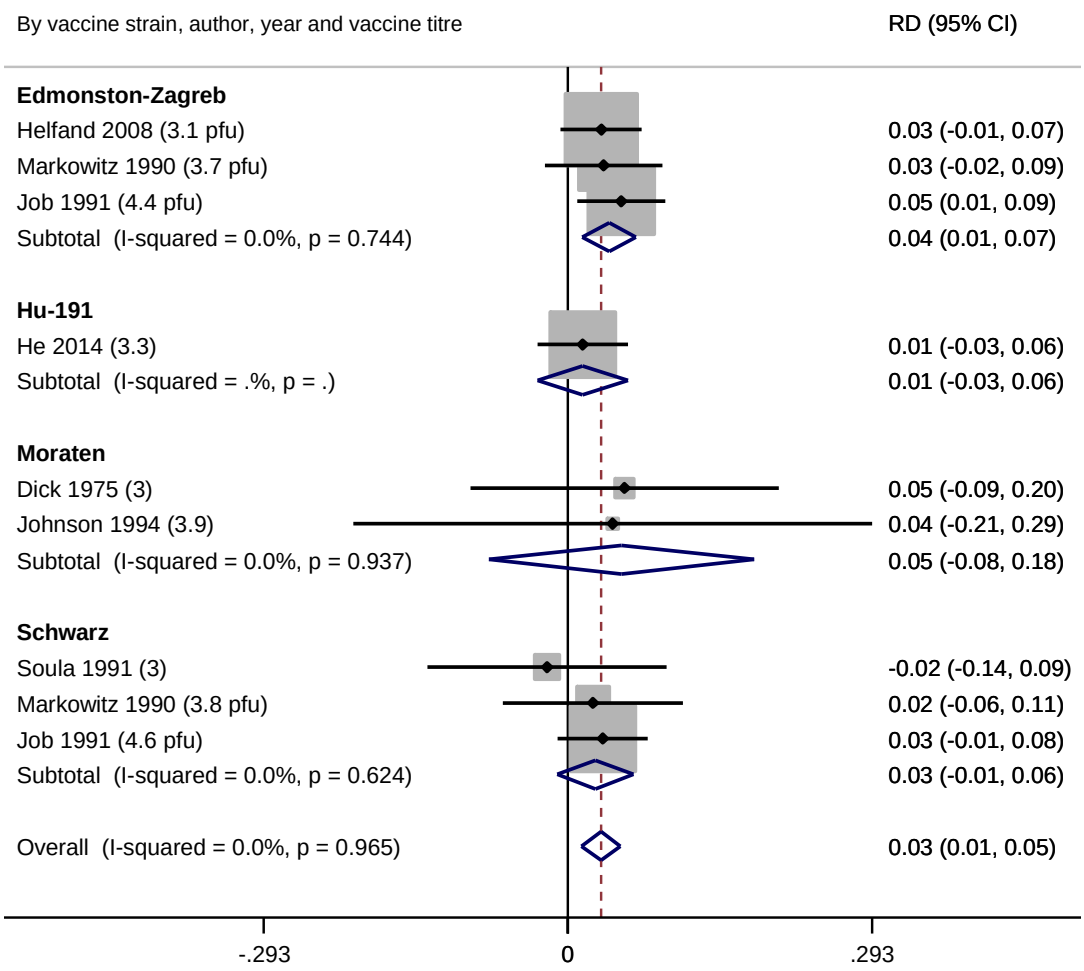

Figure 33. Random effects meta-analysis of within-study comparisons of fever after MCV1 in infants aged above or <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. RD: risk difference. CI: confidence interval. A positive risk difference indicates a higher risk in infants <9 months of age.

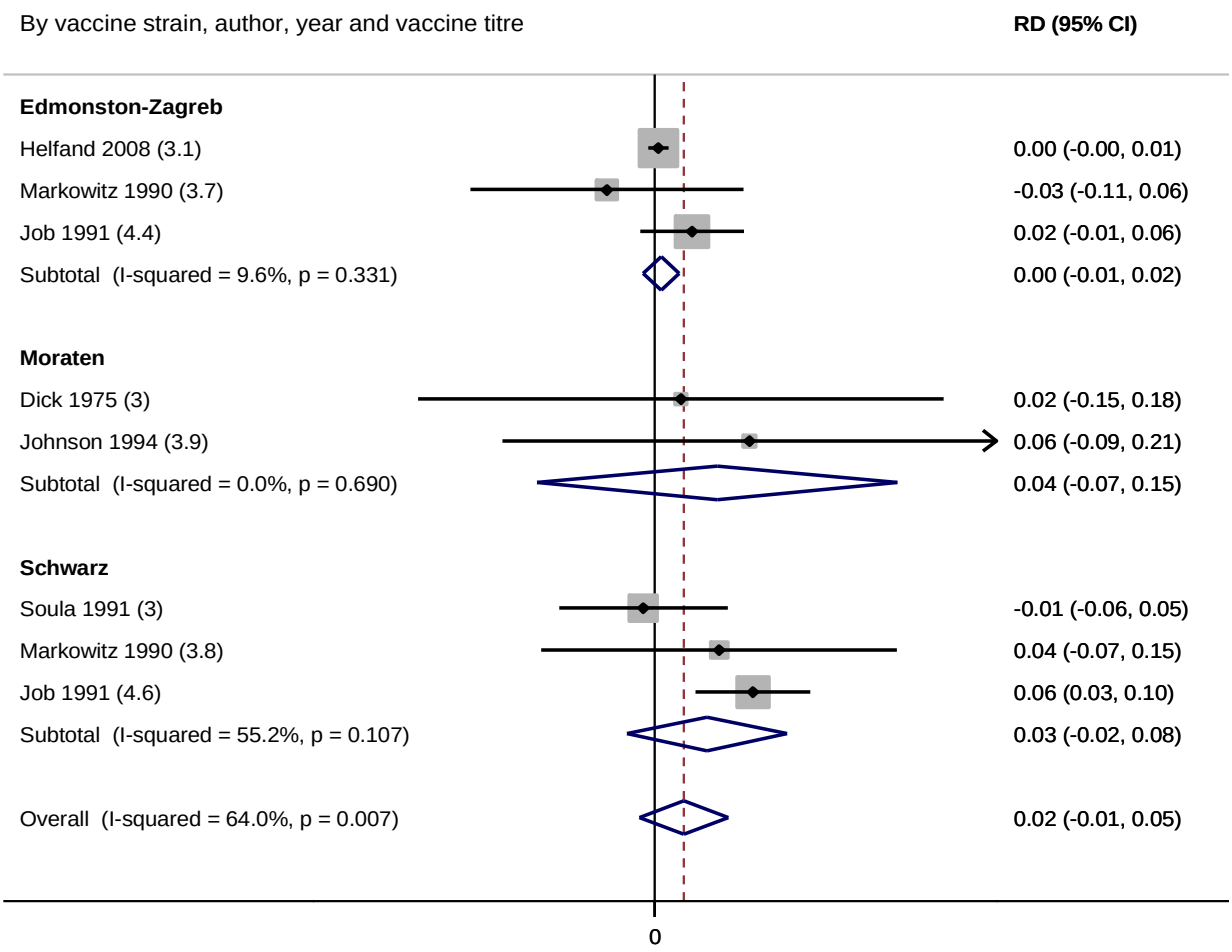

Figure 34. Random effects meta-analysis of within-study comparisons of rash after MCV1 in infants aged above or <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. RD: risk difference. CI: confidence interval. A positive risk difference indicates a higher risk in infants <9 months of age.

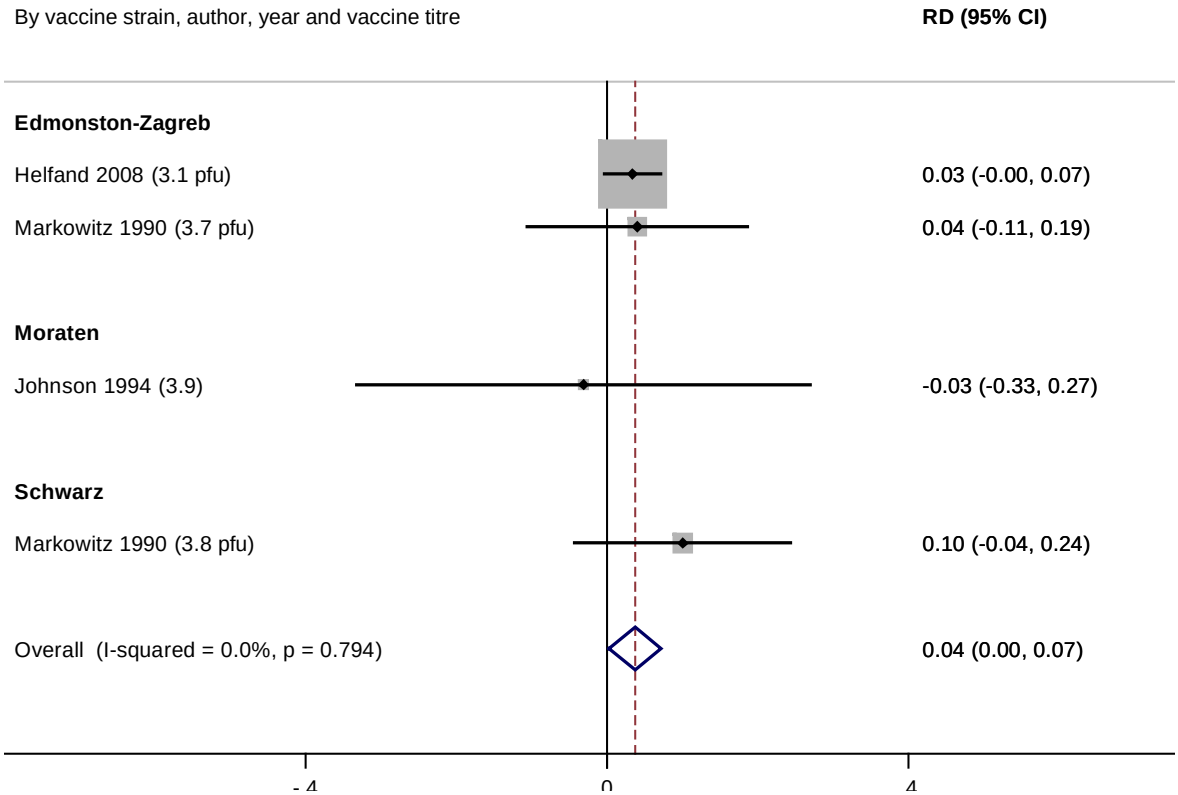

Figure 35. Random effects meta-analysis of within-study comparisons of diarrhoea after MCV1 in infants aged above or <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. RD: risk difference. CI: confidence interval. A positive risk difference indicates a higher risk in infants <9 months of age.

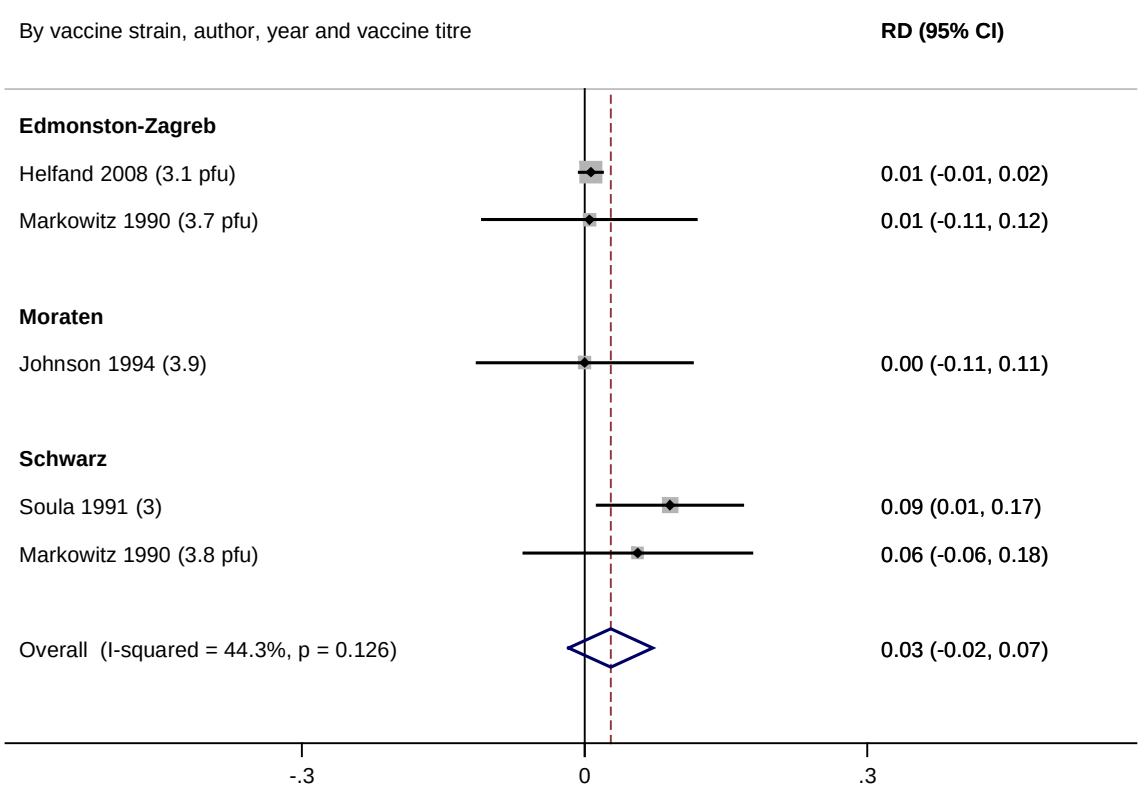

Figure 36 Random effects meta-analysis of within-study comparisons of conjunctivitis after MCV1 in infants aged above or <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. RD: risk difference. CI: confidence interval. A positive risk difference indicates a higher risk in infants <9 months of age.

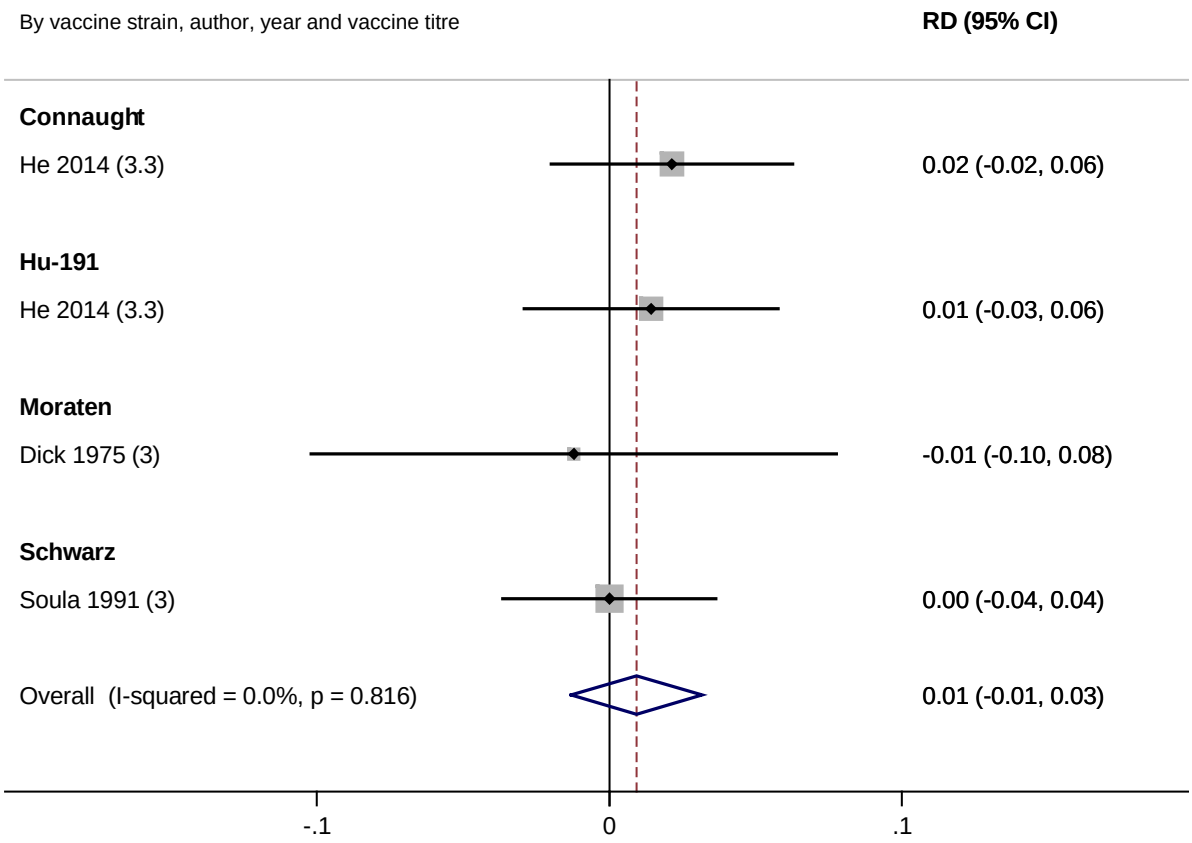

Figure 37. Random effects meta-analysis of within-study comparisons of local reactions at the injection site (redness, swelling) after MCV1 in infants aged above or <9 months. Titres are expressed as $TCID_{50}$ unless specified otherwise. RD: risk difference. CI: confidence interval. A positive risk difference indicates a higher risk in infants <9 months of age.

Forest plots of seroconversion with and without maternal antibodies

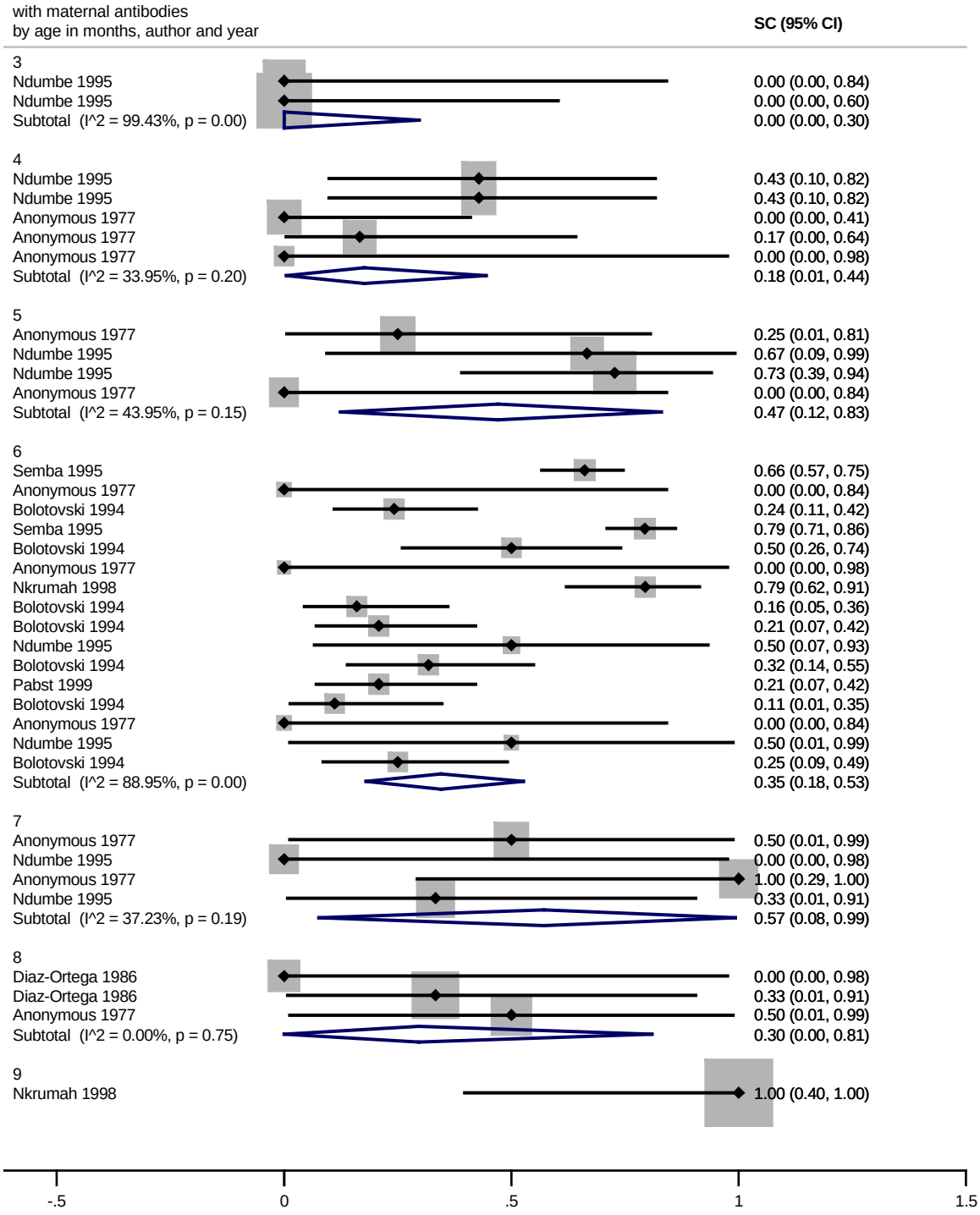

Figure 38. Random effects meta-analysis of the percentage seroconverted in infants with maternal antibodies present pre-vaccination, by age of MCV1 in months. As seroconversion was measured by different techniques in these studies (PRNT, HIA and ELISA), these are crude estimates and only suited for a general comparison between infant with and without maternal antibodies.

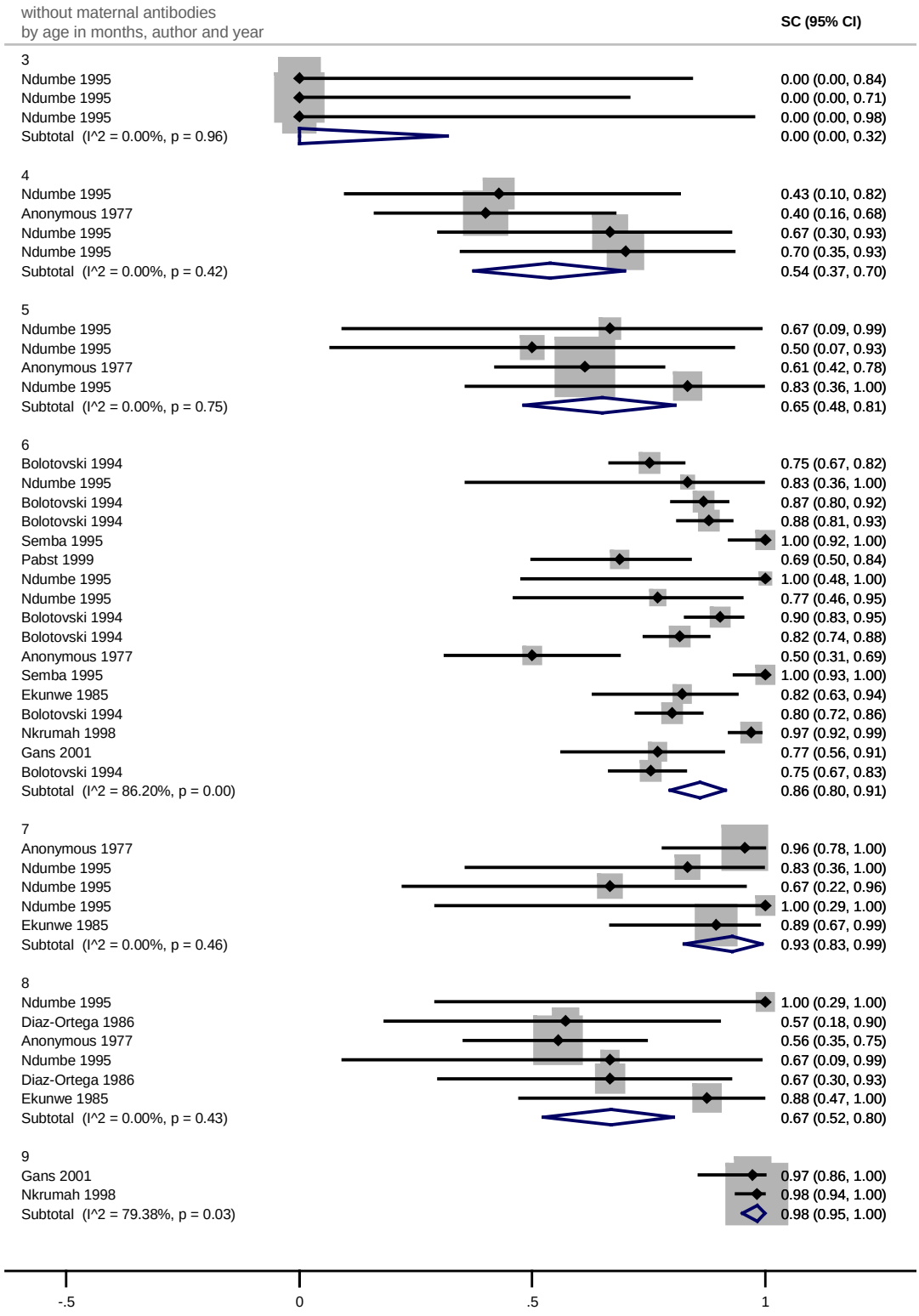

Figure 39. Random effects meta-analysis of the percentage seroconverted in infants without maternal antibodies present pre-vaccination, by age of MCV1 in months.

Forest plots for seropositivity

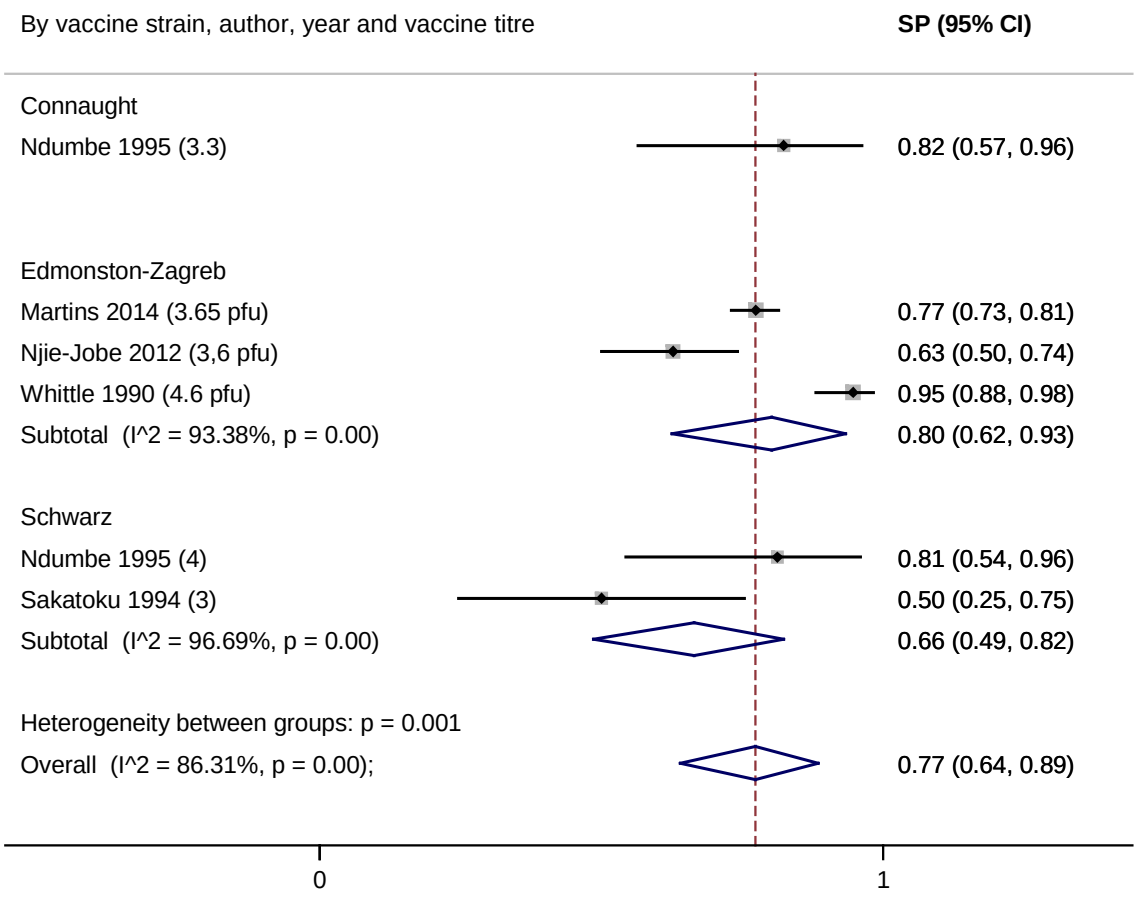

Figure 40. Random effects meta-analysis of the percentage seropositive after MCV1 in 4 month old infants. Titres are expressed as TCID50 unless specified otherwise. SP: seroconversion. CI: confidence interval.

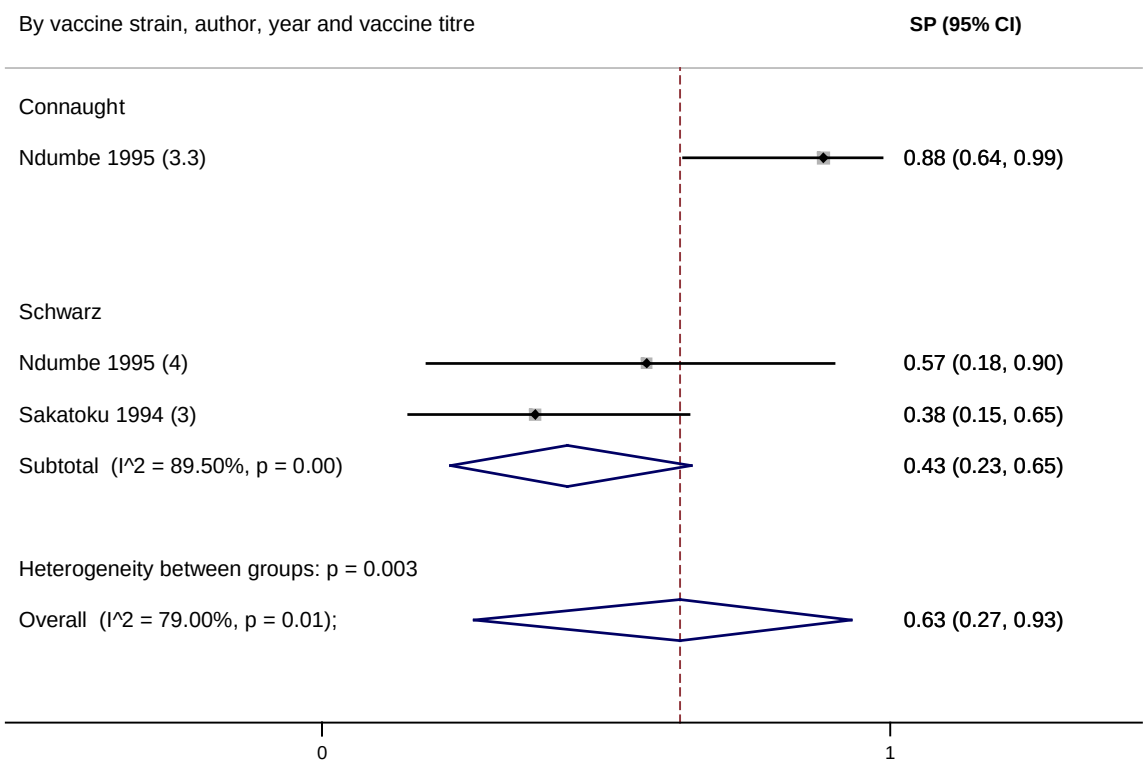

Figure 41. Random effects meta-analysis of the percentage seropositive after MCV1 in 5 month old infants. Titres are expressed as TCID50 unless specified otherwise. SP: seroconversion. CI: confidence interval.

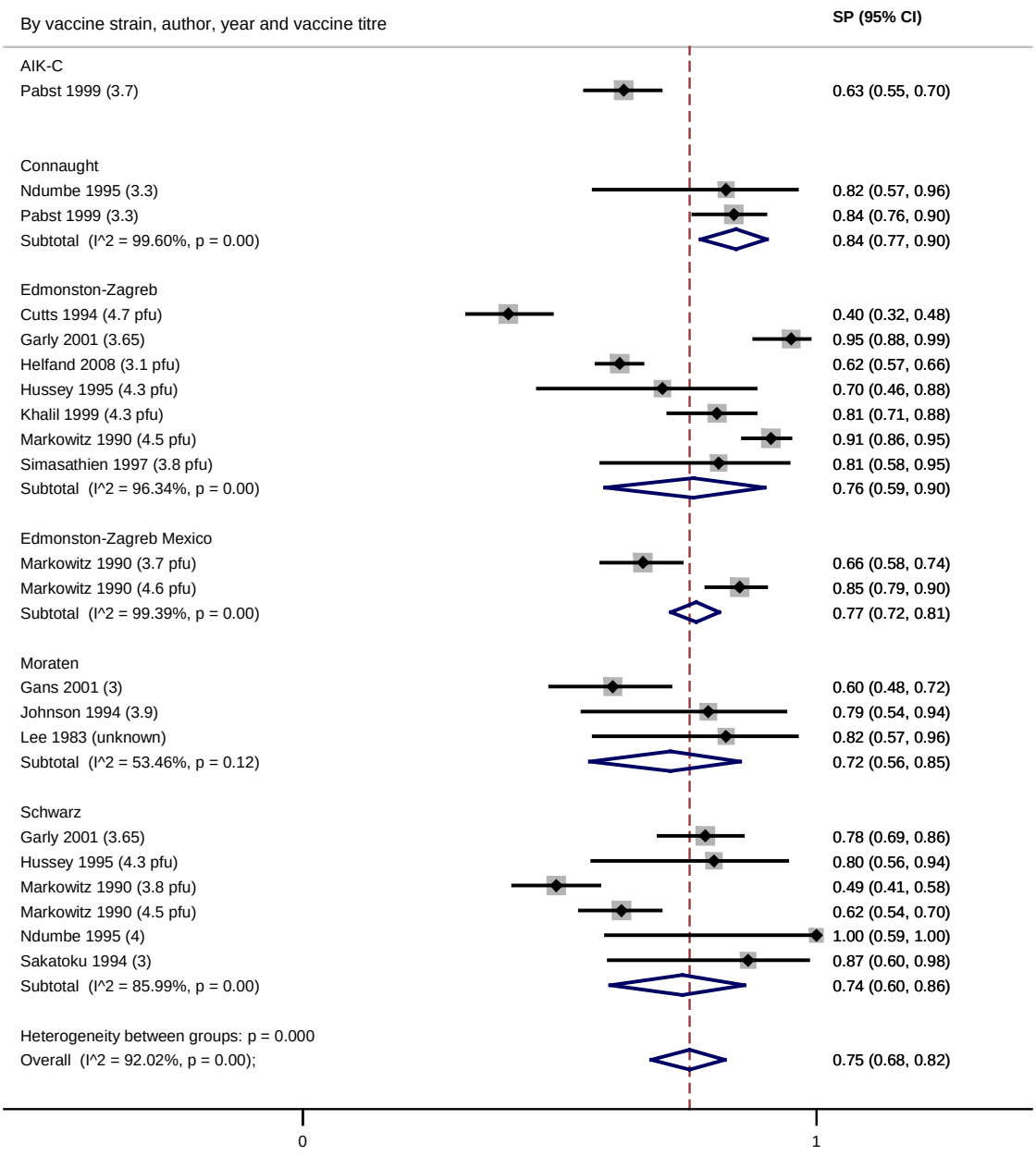

Figure 42. Random effects meta-analysis of the percentage seropositive after MCV1 in 6 month old infants. Titres are expressed as TCID50 unless specified otherwise. SP: seroconversion. CI: confidence interval.

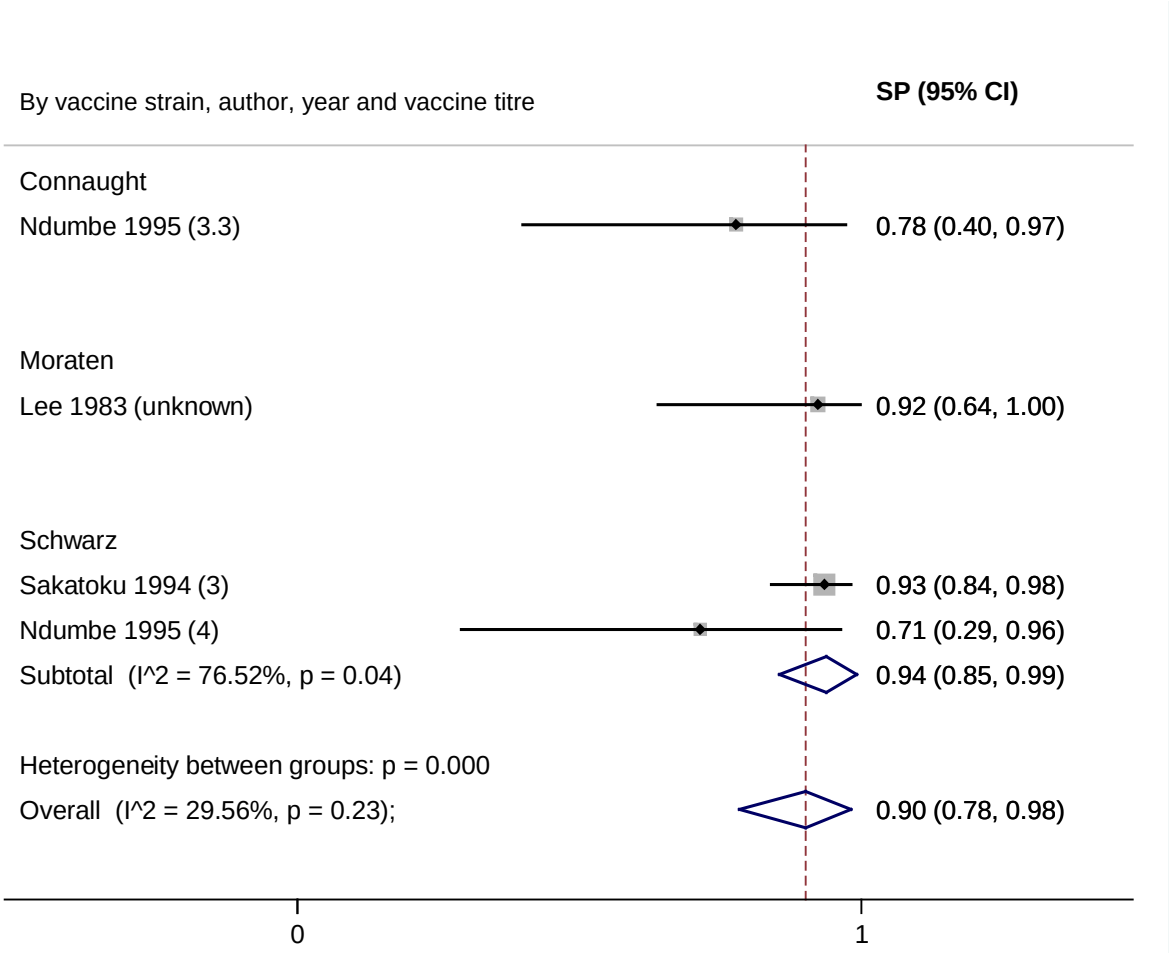

Figure 43. Random effects meta-analysis of the percentage seropositive after MCV1 in 7 month old infants. Titres are expressed as TCID50 unless specified otherwise. SP: seroconversion. CI: confidence interval.

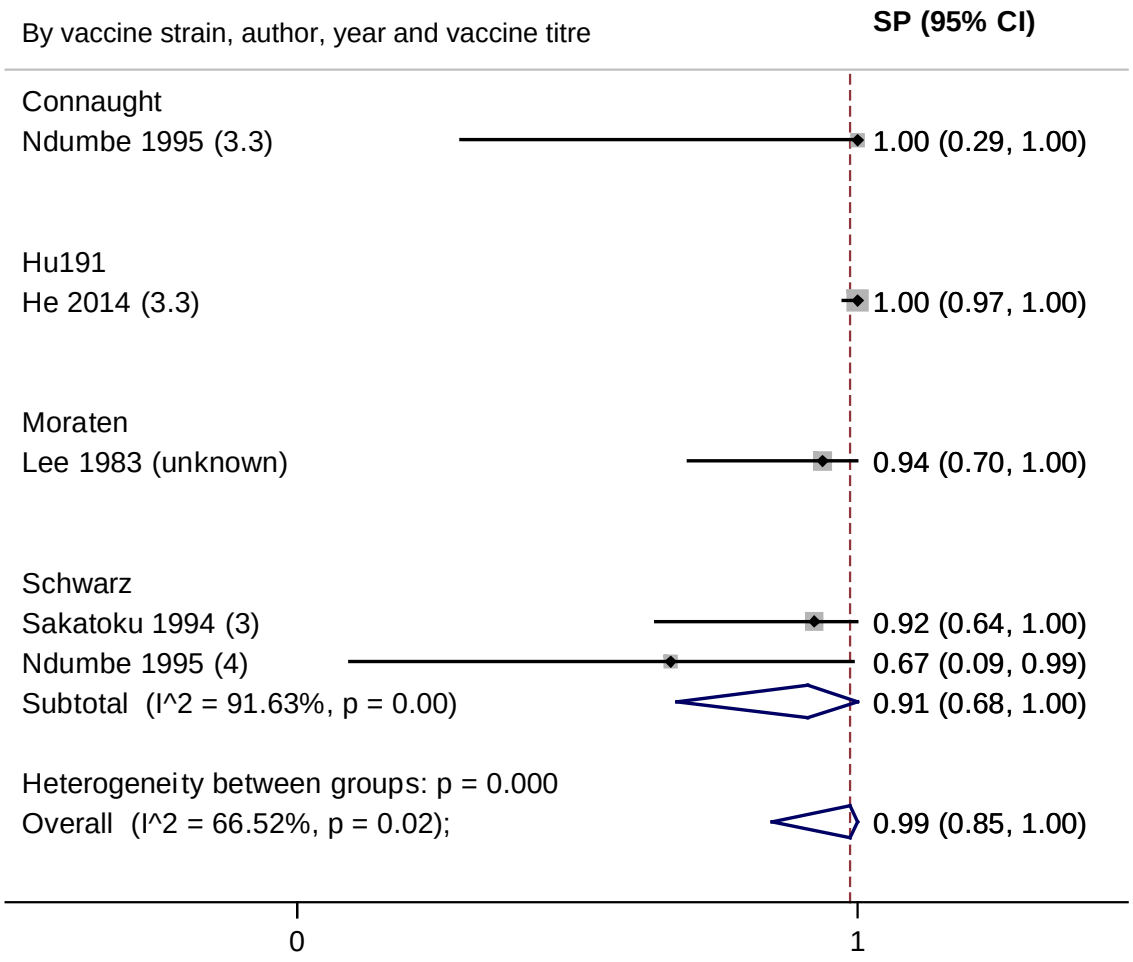

Figure 44. Random effects meta-analysis of the percentage seropositive after MCV1 in 8 month old infants. Titres are expressed as TCID50 unless specified otherwise. SP: seroconversion. CI: confidence interval.

Summary of results of meta-analysis for seropositivity

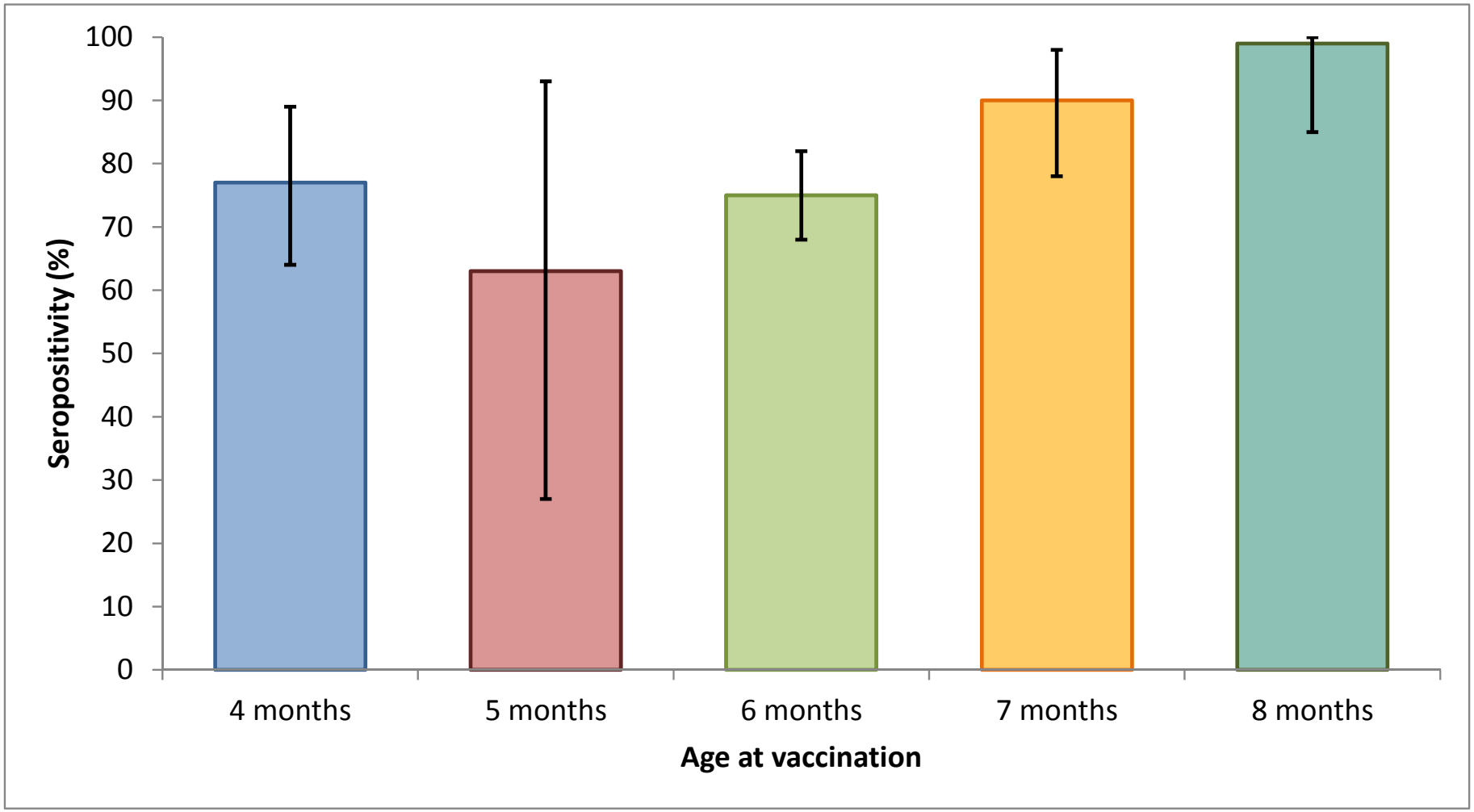

Figure 45. Summary of results of meta-analysis of the proportion seropositive after MCV1 by month of age when MCV1 was administered

Meta-regression results for seroconversion

Table 16 Univariable meta-regression analysis of the association between age of MCV1 in months and seroconversion after MCV1 (N=56)

Independent variable	Coefficient	95% CI		P value
Age at MCV1 (months)	0,0610	0,0041	0,1178	0.036
Vaccine strain				
Schwarz	Reference	-	-	-
Edmonston-Zagreb	0,1271	0,0185	0,2356	0,023
Edmonston-Zagreb Mexico	0,2368	0,1074	0,3662	0,001
AIK-C	0,1493	0,0124	0,2861	0,033
Moraten	0,0329	-0,1146	0,1803	0,657
Edmonston	0,1035	-0,1585	0,3655	0,432
Leningrad-16	0,0963	-0,0736	0,2663	0,261
Connaught	0,0553	-0,1632	0,2739	0,614
Hu191	0,3226	0,0857	0,5594	0,009
$TCID_{50}$ or pfu titre				
3	Reference	-	-	-
3.3	0,0902	-0,0928	0,2732	0.326
3.4	0,2303	-0,0364	0,4971	0.089
3,5 pfu	0,1119	-0,1674	0,3912	0.424
3.65 pfu	0,0326	-0,2497	0,3149	0.817
3.7	-0,1543	-0,5049	0,1964	0.380
3.7 pfu	0,2344	0,0140	0,4549	0.038
3.8 pfu	-0,0234	-0,2449	0,1980	0.832
3.9	-0,0048	-0,5138	0,5041	0.985
4	0,1347	-0,0732	0,3426	0.199
4 pfu	0,1731	-0,0250	0,3713	0.085

4.36 pfu	0,1338	-0,1425	0,4101	0.335
4.4 pfu	0,0719	-0,2025	0,3463	0.600
4.5 pfu	0,2040	0,0213	0,3868	0.029
4.6 pfu	0,2917	0,0730	0,5104	0.010
4.7 pfu	0,1189	-0,0783	0,3161	0.231
unknown	0,0235	-0,1914	0,2384	0.827
Continent				
Africa	Reference	-	-	-
Asia	0,0698	-0,0459	0,1854	0.232
North America	0,0746	-0,0410	0,1903	0.201
South America	-0,1044	-0,2774	0,0685	0.232
Type of test				
PRNT	Reference	-	-	-
ELISA	0,0157	-0,1415	0,1729	0.842
HIA	-0,0528	-0,1467	0,0411	0.265
OTHER	-0,1450	-0,3063	0,0163	0.077
Decade of study				
1970s	Reference	-	-	-
1980s	0,1035	-0,0931	0,3000	0.296
1990s	0,1942	0,0205	0,3680	0.029
2010s	0,3299	0,0611	0,5986	0.017

Table 17. Multivariable meta-regression model including MCV1 age, vaccine strain, vaccine titre and continent, final model (N=56)

Independent variable	Coefficient	95% CI		P value
MCV1 age	0,1145	0,0391	0,1899	0.004
Vaccine strain:				
Schwarz	Reference	-	-	-
Edmonston-Zagreb	0,1107	-0,0092	0,2306	0.070
Edmonston-Zagreb Mexico	0,2119	0,0724	0,3514	0.004
AIK-C	0,1690	-0,0078	0,3458	0.060
Moraten	0,1604	-0,0510	0,3717	0.133
Edmonston	0,1983	-0,1623	0,5588	0.274
Leningrad-16	0,1033	-0,0984	0,3050	0.307
Connaught	0,0475	-0,2086	0,3037	0.710
Hu191	0,1817	-0,4084	0,7717	0.538
Decade of study				
1970s	Reference	-	-	-
1980s	-0,0374	-0,4144	0,3397	0.843
1990s	0,0733	-0,2322	0,3788	0.631
2010s	-0,1229	-0,7106	0,4647	0.675
Continent				
Africa	Reference	-	-	-
Asia	0,0488	-0,1054	0,2029	0.527
North America	-0,0029	-0,1566	0,1509	0.970
South America	-0,0602	-0,3063	0,1859	0.624
Type of test				
PRNT	Reference	-	-	-
ELISA	0,0317	-0,2018	0,2651	0.786

HIA	-0,0836	-0,2594	0,0922	0.343
Other test	-0,0360	-0,2918	0,2197	0.778
Independent variable	**Coefficient**	**95% CI**		**P value**
MCV1 age	0,1145	0,0391	0,1899	0.004
Vaccine strain:				
Schwarz	Reference	-	-	-
Edmonston-Zagreb	0,1107	-0,0092	0,2306	0.070
Edmonston-Zagreb Mexico	0,2119	0,0724	0,3514	0.004
AIK-C	0,1690	-0,0078	0,3458	0.060
Moraten	0,1604	-0,0510	0,3717	0.133
Edmonston	0,1983	-0,1623	0,5588	0.274
Leningrad-16	0,1033	-0,0984	0,3050	0.307
Connaught	0,0475	-0,2086	0,3037	0.710
Hu191	0,1817	-0,4084	0,7717	0.538
Decade of study				
1970s	Reference	-	-	-
1980s	-0,0374	-0,4144	0,3397	0.843
1990s	0,0733	-0,2322	0,3788	0.631
2010s	-0,1229	-0,7106	0,4647	0.675
Continent				
Africa	Reference	-	-	-
Asia	0,0488	-0,1054	0,2029	0.527
North America	-0,0029	-0,1566	0,1509	0.970
South America	-0,0602	-0,3063	0,1859	0.624
Type of test				
PRNT	Reference	-	-	-

ELISA	0,0317	-0,2018	0,2651	0.786
HIA	-0,0836	-0,2594	0,0922	0.343
Other test	-0,0360	-0,2918	0,2197	0.778

Meta-regression results for maternal antibodies and seroconversion

Table 18 Meta-regression of the association between maternal antibodies and seroconversion, final model (N=66)

Independent variable	Coefficient	95% CI		P value
Maternal antibodies (0=absent, 1=present)	-0.3317	-0.4557	-0.2078	<0.001
Age at MCV1 (months)	0.0689	0.0164	0.1213	0.011

Meta-regression results for safety

Table 19 Meta-regression of the association between age of MCV1 in months and fever after MCV1, final model (N=32)

Independent variable	Coefficient	95% CI		P value
Age at MCV1 (months)	-0.0122	-0.0229	-0.001	0.026
Vaccine strain: Schwarz	Reference	-	-	-
Vaccine strain: Edmonston-Zagreb	0.0014	-0.0461	0.0489	0.953
Vaccine strain: Moraten	0.0066	-0.0590	0.0723	0.843
Vaccine strain: other	0.0068	-0.0014	0.0001	0.811
Vaccine titre (pfu&TCID$_{50}$ combined)	-0.0006	-0.0014	0.0001	0.096

Table 20 Meta-regression of the association between age of MCV1 in months and rash after MCV1, final model (N=26)

Independent variable	Coefficient	95% CI		P value
Age at MCV1 (months)	-0.0106	-0.0304	0.0092	0.276
Vaccine strain: Schwarz	Reference	-	-	-
Vaccine strain: Edmonston-Zagreb	-0.0366	-0.1033	0.0301	0.266
Vaccine strain: Moraten	-0.0138	-0.1584	0.1308	0.844
Vaccine strain: other	-0.0176	-0.0923	0.0571	0.628
Vaccine titre (pfu&TCID$_{50}$ combined)	-0.0009	-0.0019	0.0001	0.081