National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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

8 September 2017

Laura Nic Lochlainn and Susan Hahné

Centre for Infectious Disease Control (CIb)
National Institute for Public Health and the Environment (RIVM)
Bilthoven, the Netherlands

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Summary

Background

This report summarises the results of an updated systematic review of the literature and meta-analyses into the benefits and risks of giving a first dose of measles containing vaccine (MCV) to infants below 6 months of age 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 for studies in which standard titre MCV was given to infants <6 months of age. We extracted data on the following outcomes: immunogenicity (humoral and cellular), vaccine efficacy or effectiveness (VE), duration of immunity, blunting and safety. Where appropriate, meta-analyses and meta-regression was performed. We compared results with results from our 2015 review of MCV1 <9 months of age. Quality of all included studies was assessed using the GRADE methodology.

Results of the search and selection

From an initial search carried out in June 2015, 867 references were identified. Following an updated search in April 2017, an additional 186 references were identified. A total of 19 studies from both searches were included in the review.

Results of the review of included studies

The proportion of infants seroconverting increased from 50% (95% CI 29-71) at 4 months of age to 67% (51-81%) at 5 months of age. The proportion of infants seroconverting was found to be further dependent on the vaccine strain used. Seropositivity also increased with age and was strain dependent. GMTs were higher after MCV<6 compared to ≥6 months of age, but results for MCV<6 months were derived from only two studies. There was limited evidence on cellular immunity, vaccine efficacy and effectiveness, duration of immunity, blunting and safety to draw conclusions.

Conclusions

We found humoral immunity after MCV1<6 months of age was dependent on age of MCV1 and presence of maternal antibodies. There was limited evidence available for cellular immunity, vaccine effectiveness, duration of immunity, safety and blunting following MCV1<6 months of age.

Abbreviations

CI	Confidence interval
GMC	Geometric mean concentration
GMT	Geometric mean titre
HI	Hemagglutination inhibition
HIA	Hemagglutination inhibition assay
MCV	Measles containing vaccine
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)
TCID	Tissue culture infective dose
VE	Vaccine effectiveness/ efficacy
WHO	World Health Organization

1 Introduction

The World Health Organization (WHO) recommends a two dose measles containing vaccine (MCV) schedule, with the first dose of MCV (MCV1) at 9 months of age in countries with ongoing measles transmission, and at 12 months when MCV coverage is high and the risk of measles in infancy is low. The recommendations for the age of the second MCV dose (MCV2) are based on programmatic considerations, e.g. the age at which the highest coverage of MCV2 and, hence, the highest population immunity, can be achieved (1).

Measles outbreaks now show a bimodal age distribution in many countries, with a high proportion of cases occurring below the WHO recommended age for MCV1. In addition, many measles cases are occurring among adolescents and/or young adults (2).

In 2015, the National Institute for Public Health and the Environment (RIVM) in the Netherlands conducted a systematic literature review of effects and safety of MCV below 9 months of age for the Strategic Advisory Group of Experts (SAGE) on Immunization (3). Based on this review, and other evidence, SAGE made recommendations that infants from 6 months of age receive a supplementary dose of measles containing vaccine in the following situations (1);

- during a measles outbreak as part of intensified service delivery;
- during campaigns in settings where the risk of measles among infants <9 months of age remains high;
- for internally displaced populations and refugees, and populations in conflict zones;
- for individual infants at high risk of contracting measles; for infants travelling to countries experiencing measles outbreaks;
- for infants known to be human immunodeficiency virus (HIV)-infected or exposed.

However, recent outbreaks have found many cases are occurring in children less than 6 months of age. As a result, countries have requested information for MCV <6 months in order to assess whether infants less than 6 months can be protected against measles while maintaining robust population immunity.

Several strategies exist to protect children younger than six months of age against measles. The first, and most important, is to reduce measles virus transmission overall such that the risk of exposure in young infants is minimal to none. Second, MCV could be administered prior to 6 months of age under some circumstances, although the proportion of children who develop protective antibodies is expected to be lower than following vaccination at a later age. Third, measles antibody levels could

be increased in women of child bearing age, although this should be done prior to pregnancy as MCVs are contra-indicated during pregnancy.

2 Objective

To conduct an update of the 2015 systematic review of the evidence on whether the effect of MCV below 6 months of age – in terms immunogenicity, efficacy or effectiveness, duration of protection, safety and blunting – is equal or less than the effect of MCV at 6-8 months of age.

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 <6 months of age

Population	Intervention	Comparison	Outcome
Infants up to 6 months of age receiving an MCV	Any currently licensed MCV administered to infants < 6 months of age.	Any currently licensed MCV administered to infants 6-8 months of age	1. Immunogenicity 2. Efficacy 3. Effectiveness 4. Duration of immunity 5. Safety 6. Blunting

3.1.1 Primary questions

- What is the immunogenicity, duration of immunity, efficacy and effectiveness of MCV1 (M, MR and MMR) when given to infants younger than 6 months of age (as compared infants aged 6-8 months).
- Does a dose of MCV1 administered <6 months of age blunt the immune response to a subsequent dose of measles vaccine?
- Is the safety profile for infants vaccinated with MCV1 at <6 months of age comparable with infants vaccinated with MCV1 at 6-8 months of age?

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

Reduced immune response to a subsequent dose of a measles containing vaccine.

3.2 Search strategy

An initial search was carried out on 01 June 2015 for any articles published in relevant databases reporting MCV <9 months (3). An updated search was carried out on 13 April 2017 for articles published after 01 January 2015 reporting MCV<6 months.

3.2.1 Searching literature databases

The initial search was carried out as previously described (3) and results of the initial search were screened for studies reporting MCV<6 months.

The updated search for MCV<6 months was carried out in the following primary databases outlined in Appendix A: Databases and websites used for literature search. The databases were searched using controlled vocabulary (i.e MeSH terms) with a pre-determined strategy as detailed in Appendix B: Database search strategy. Secondary databases were also searched for relevant studies. A time limit of records published after 01 January 2015 was applied to capture any articles published since the initial 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.

3.3 Literature selection

All articles found by the updated search were screened by one reviewer (Laura Nic Lochlainn) using a two-stage approach by reviewing the title, abstract and full text as outlined below.

3.3.1 First selection step: title and abstract

The title and abstract of each article were reviewed to see if they met criteria for inclusion. In case of uncertainty about inclusion or exclusion, a second opinion was sought.

3.3.2 Second selection step: full article

Articles which met criteria for inclusion were reviewed for full text screening. In case of uncertainty about inclusion or exclusion, a second opinion was sought.

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 <6 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 <6 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 2.

Table 2: 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, modelling studies, 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 (3). Studies derived from combining MCV with gamma globulin or obtained after intradermal (rather than subcutaneous) administration of MCV were also excluded from the review.

Studies reporting on the non-specific effects of measles vaccination (e.g. overall mortality) were not considered.

The reasons for excluding studies (including reasons for exclusion following review of the full text) were recorded at each stage.

3.4 Data extraction

The characteristics of included studies were extracted into a data extraction form and entered into an Access database. For any trial data, per-protocol analyses were used rather than intention to treat results.

3.5 Data analyses

We used Stata version 14 (StataCorp, Austin, USA) for all analyses. Where possible, results were stratified by age at administration of MCV in months. Where sufficient data was available, results were pooled by meta-analyses. We examined heterogeneity between results of different studies with forest plots and quantitatively using the I^2 statistic. We used random effects meta-analysis to estimate the weighted average of the pooled effects. Where possible, random effects meta-regression was employed, to explore whether determinants of age at MCV, vaccine strain and titre, continent, or decade of study explained heterogeneity between studies.

3.5.1 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 by age of administration of MCV. 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 (only for HIA tests).
- We analysed GMTs based on PRNT by age of administration of MCV (<6 months or 6-8 months), 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 6 weeks were excluded from this analysis.

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 MCV <6 months or 6-8 months of age.

Vaccine efficacy and vaccine effectiveness

- Vaccine efficacy and vaccine effectiveness (VE) were summarized. Where available, multiple outcome measures for VE were considered (clinical measles, laboratory confirmed measles, measles hospitalisation and measles related deaths).

Duration of immunity

- We reviewed only results of studies with GMTs and corresponding confidence intervals that were within study comparisons and had different time points between MCV vaccination and sampling. We plotted the GMT measures by time between vaccination and sampling to look at the effect of time on the GMT values.

Safety

- We summarized available evidence of adverse events following immunization (AEFIs).

Blunting

- Here we considered the proportion seropositive, GMT, avidity index and stimulation index after MCV2 or MCV3 by age of administration of MCV.

3.5.2 Comparison of review results with evidence of administration of MCV at older ages

The current review considered MCV administered <6 months of age. Evidence on the effects of administration of MCV at 6-8 months of age was obtained from Nic Lochlainn et al., 2015 (3).

4 Results of the literature search

An initial literature search carried out on 01 June 2015 yielded a total of 867 references (**Error! Reference source not found.**). An updated search carried out on 13 April 2017 yielded a total of 186 references (Figure 2). A total of 18 studies from both searches (17 and 1, respectively) were included in the review.

4.1 PRISMA flow charts

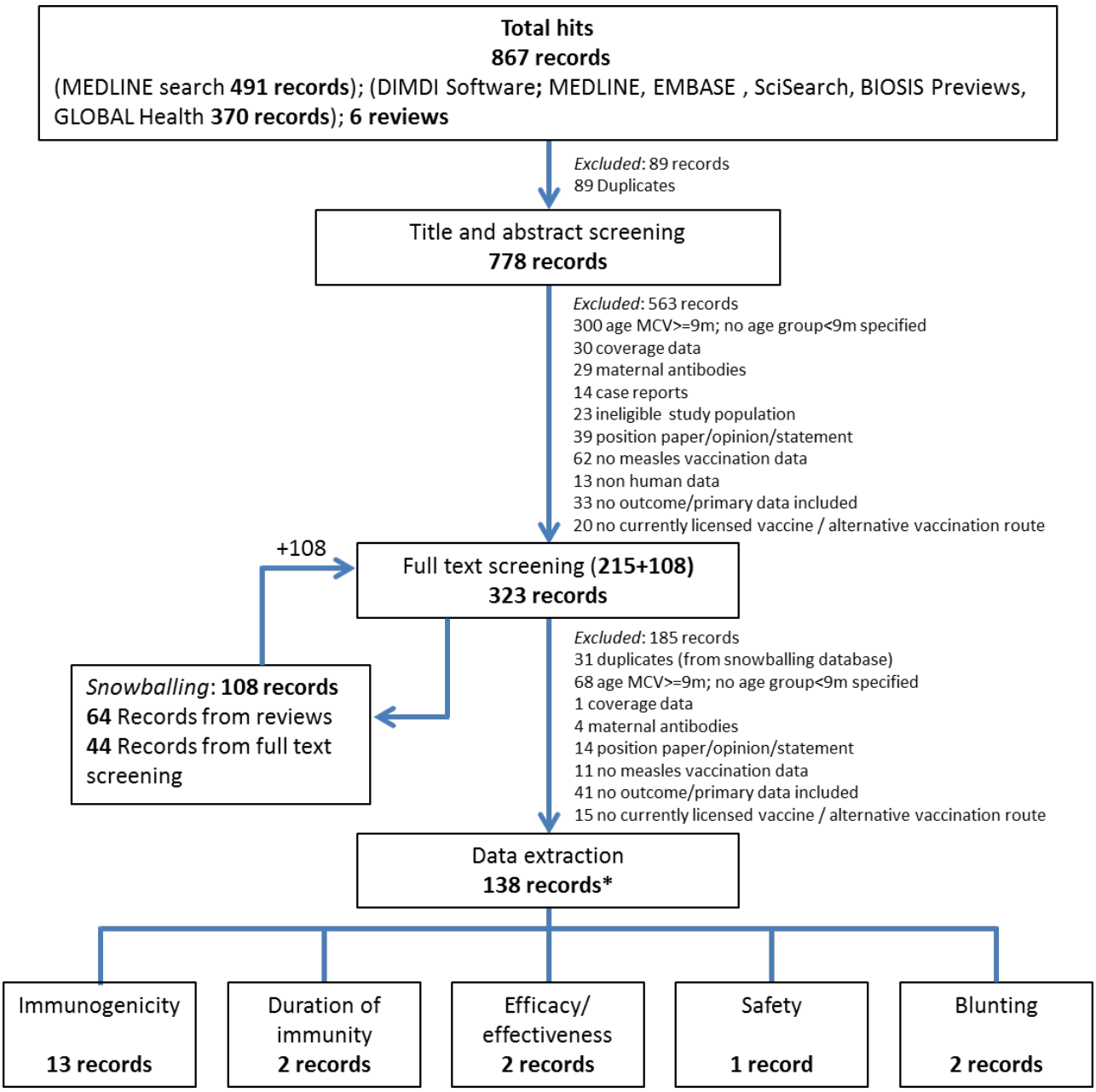

Figure 1: Flow chart of the initial literature search (2015) with excluded and included items, and number of studies according to outcome measure.
*Data were extracted from some studies for multiple outcomes.

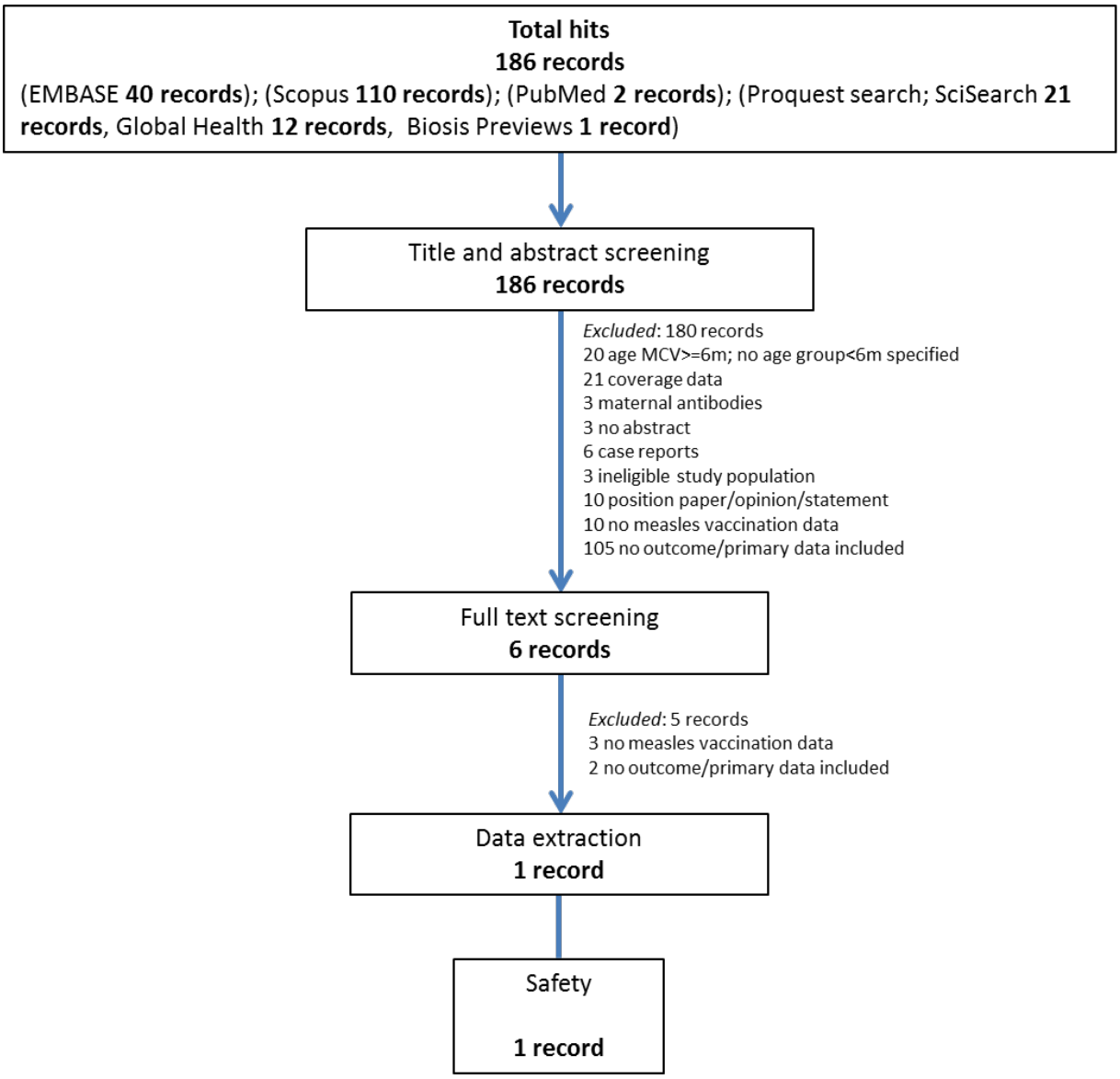

Figure 2: Flow chart of the updated literature search (2017) with excluded and included items, and number of studies according to outcome measure.

4.2 Overview of studies included in the review

A summary table of studies with eligible data is shown in Table 3.

Table 3: Summary of studies included in the review by outcome

Author, year of study (ref)	Country	MCV age (months)	Vaccine Strain	Immunogenicity	Vaccine effectiveness	Duration of immunity	Safety	Blunting	Maternal antibodies
Anonymous 1977 (4)	Kenya	4,5,6,7,8,11	Schwarz	Yes	-	-	-	-	Yes
Anonymous 1981 (5)	Tanzania	4-5, 6-7, 8-9, 10-11, 12-13, 14-15	Schwarz	Yes	-	-	-	-	-
Cutts 1994 (6)	DRC	<5,5,5-6,6,6-7,7-8,>6-8-8	Edmonston-Zagreb	Yes	-	Yes	-	-	-
Do, 2017 (7)	Guinea-Bissau	4.5, 9	Edmonston-Zagreb	-	-	-	Yes	-	-
Hull 1983 (8)	Gambia	<6,6-8,9-11,12-14,>15	Moraten	-	Yes	-	-	-	-
Jensen 1994 (9)	Guinea-Bissau	4-5,6-8,9-12	Edmonston-Zagreb	Yes	-	-	-	-	-
Khanum 1987 (10)	Bangladesh	3-4,4-5,5-6	Edmonston-Zagreb, Schwarz	Yes	-	-	-	Yes	-
Kiepiela 1991 (11)	South Africa	3-5,4-8,5-6,6-8,8-9,9-10,9-11	Edmonston-Zagreb, Schwarz	Yes	-	-	-	-	-
Ko 1999 (12)	England	5	Schwarz	Yes	-	-	Yes	-	-
Martins 2008 (13)	Guinea-Bissau	4.5,9	Edmonston-Zagreb	-	-	-	-	Yes	-
Martins 2014 (14)	Guinea-Bissau	4.5,9	Edmonston-Zagreb	-	Yes	-	-	Yes	-
Ndumbe 1995 (15)	Cameroon	3,4,5,6,7,8	Connaught, Schwarz	Yes	-	-	-	-	Yes
Njie-Jobe 2012 (16)	Gambia	4,9	Edmonston-Zagreb	-	-	-	-	Yes	-
Rogers 1991 (17)	Papua New	4,5,6,6-7,7,<8,8-29	Edmonston-	Yes	-	-	-	-	-

	Guinea		Zagreb						
Sakatoku 1994 (18)	Ghana	3,4,5,6,7,8,9,10,11	Schwarz	Yes					
Tidjani 1989 (19)	Togo	4-5	AIK-C	Yes	-	-	-	-	-
Whittle 1988 (20)	Gambia	4,5	Edmonston-Zagreb, Schwarz	Yes	-	-	-	-	-
Whittle 1990 (21)	Gambia	4,9	Edmonston-Zagreb, Schwarz	Yes	-	Yes	-	-	-

5 Results on outcomes

5.1 Immunogenicity

5.1.1 Seroconversion

We found five studies in which an adequate definition of seroconversion (SC) was applied (4, 10, 15, 17, 22). The pooled estimates of the proportion SC by age of MCV ranging from 4 to 5 months, stratified by strain, are presented in Figure 3.

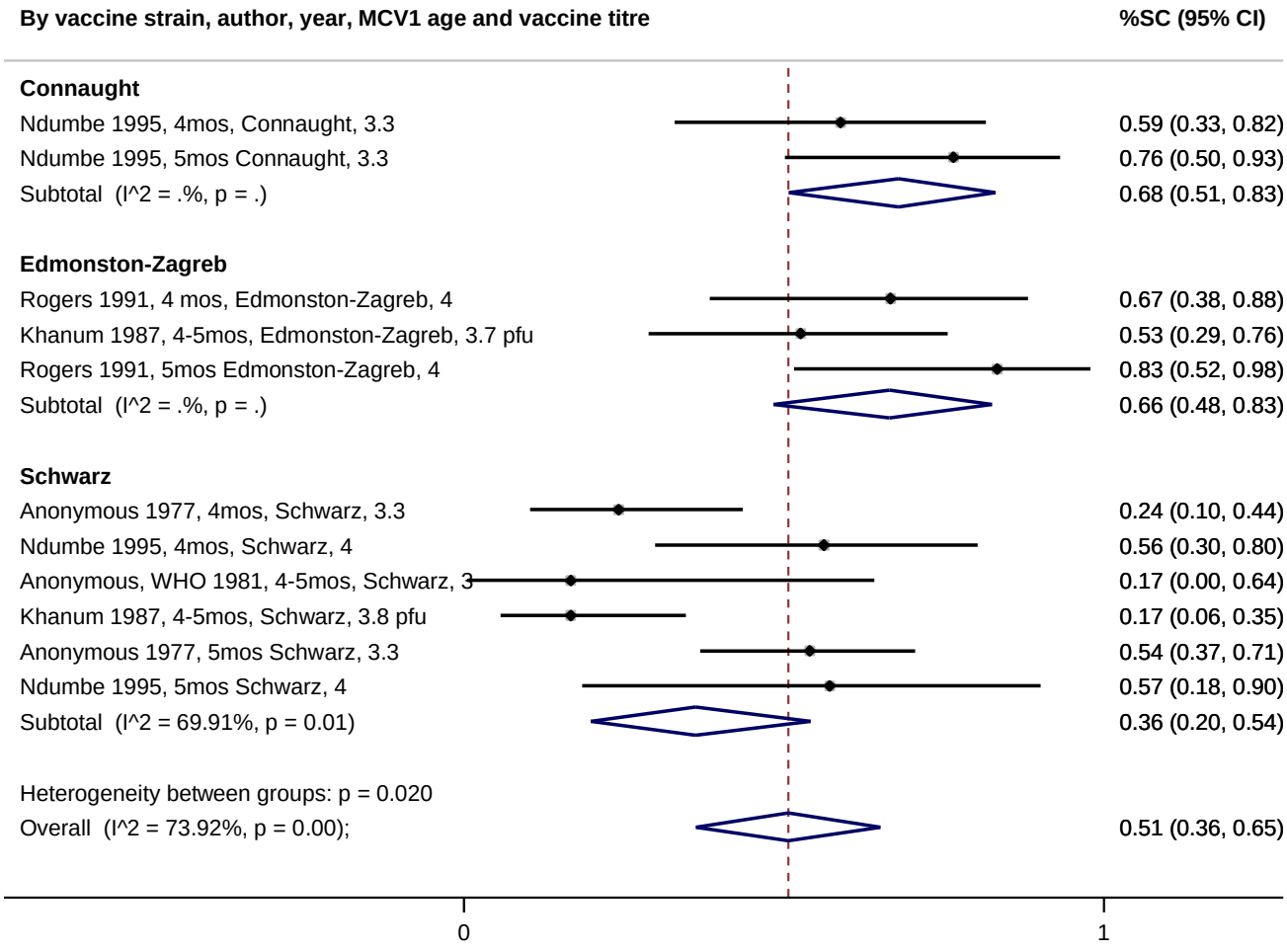

Figure 3: Overall proportion of infants seropositive following MCV1 <6 months by vaccine strain, derived from five studies.

The pooled estimates of the proportion SC by age of MCV ranging from 4 to 5 months are presented in Figure 4, and stratified by strain in Figure 5. As a reference, we included the proportion SC reported by Nic Lochlainn *et al*., for MCV1 at 6 months [76% (95%CI 71-82)] (3) and as reported by Moss and Scott for MCV1 at 9 months [92% (95%CI 59-100)] and at 11 months [98% (95%CI 88-100)] (23).

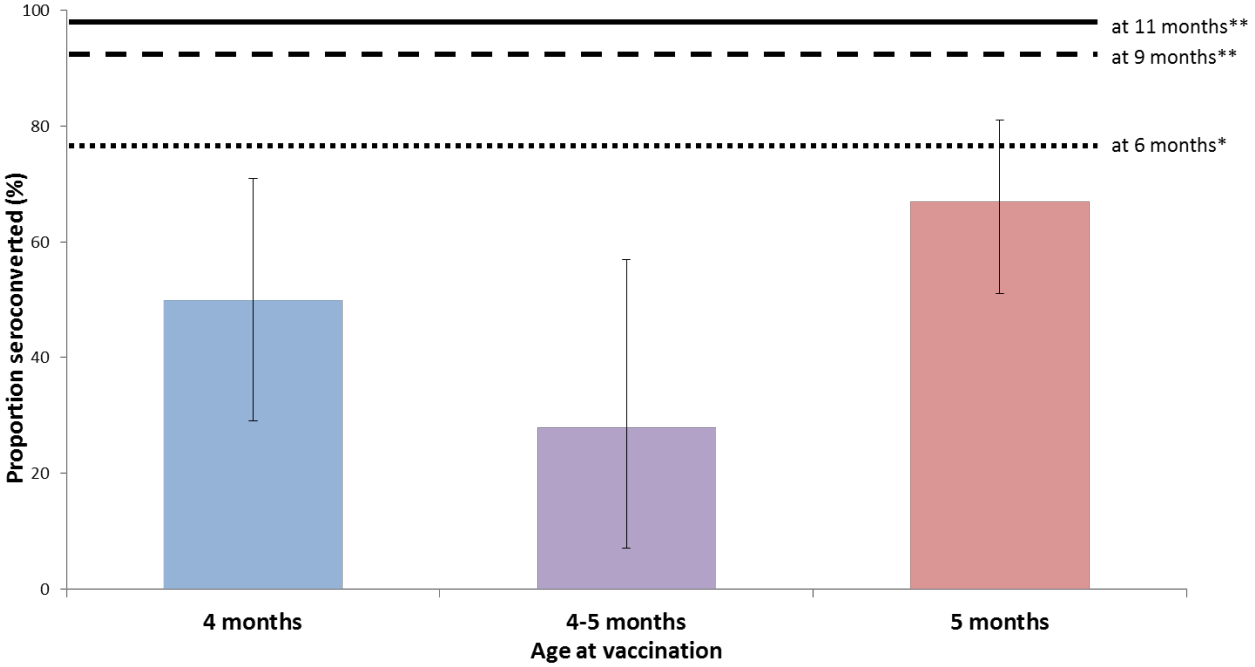

Figure 4: Proportion seroconverted by age of MCV1 below 6 months, pooled estimates derived from five studies. Error bars present 95% confidence intervals. *This horizontal line represents the proportion of infants seroconverted following MCV1 at 6 months (small dashed line) Nic Lochlainn et al., 2015 (3). **The horizontal lines represent the median proportion of infants seroconverted following MCV1 at 9 months (wide dashed line) and 11 months (filled line) Moss & Scott, 2009 (23).

The estimates of the proportion SC by age of MCV and strain are also presented in Table 4: Proportion seroconverted by age of MCV (4-5 months) and strain.

Age of MCV (months)	Strain	% Seroconverted	95% CI	References
4	Edmonston-Zagreb	67	38-88	(17)
	Connaught	59	33-82	(15)
	Schwarz	35	21-50	(4, 15)
4-5	Edmonston-Zagreb	53	29-76	(10)
	Schwarz	15	4-30	(5, 10)
5	Edmonston-Zagreb	83	52-98	(17)
	Connaught	76	50-93	(15)

Schwarz	55	39-70	(4, 15)

. The forest plots by age of MCV and strain are presented in Appendix D: Supplementary results (Figure 11 to Figure 13).

In meta-regression analysis, there were no independent determinants on the proportion SC among infants receiving MCV <6 months of age (data not shown).

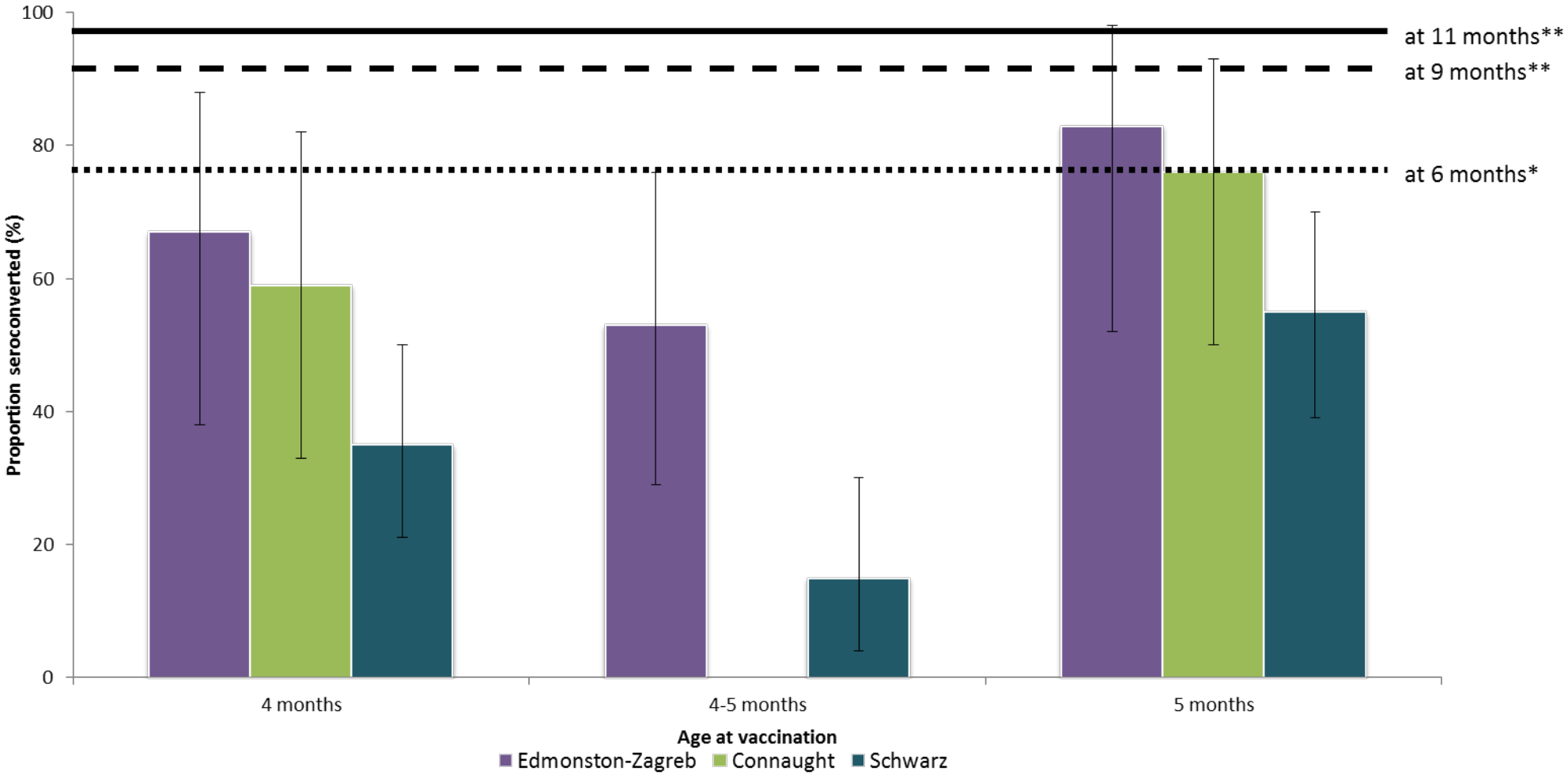

Figure 5: Proportion seroconverted by age of MCV (4-5 months), pooled estimates derived from five studies. Error bars present 95% confidence intervals.
* This horizontal line represents the proportion of infants seroconverted following MCV1 at 6 months (small dashed line) Nic Lochlainn et al., 2015 (3).
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	Schwarz	35	21-50	(4, 15)
4-5	Edmonston-Zagreb	53	29-76	(10)
	Schwarz	15	4-30	(5, 10)
5	Edmonston-Zagreb	83	52-98	(17)
	Connaught	76	50-93	(15)
	Schwarz	55	39-70	(4, 15)

5.1.2 Geometric mean antibody concentrations

We identified two studies (12, 20) with GMT results from PRNT testing at least six weeks after MCV <6 months with accompanying confidence intervals or standard errors.

The study by Whittle *et al*., (20) examined GMTs of infants vaccinated at 4 or 5 months with different titres of the Schwarz or Edmonston-Zagreb strains. The study by Ko *et al*., (12) examined GMTs of infants vaccinated at 5 months with standard titre Schwarz strain. However, they stratified their results by GMT antibody levels prior to vaccination.

Figure 6 shows the pooled GMT estimates for infants vaccinated with MCV <6 months of age (275 (95% CI 126-600)). We also included the pooled GMT estimates for infants vaccinated with MCV >6 months of age which was 247 (95% CI 148-412).

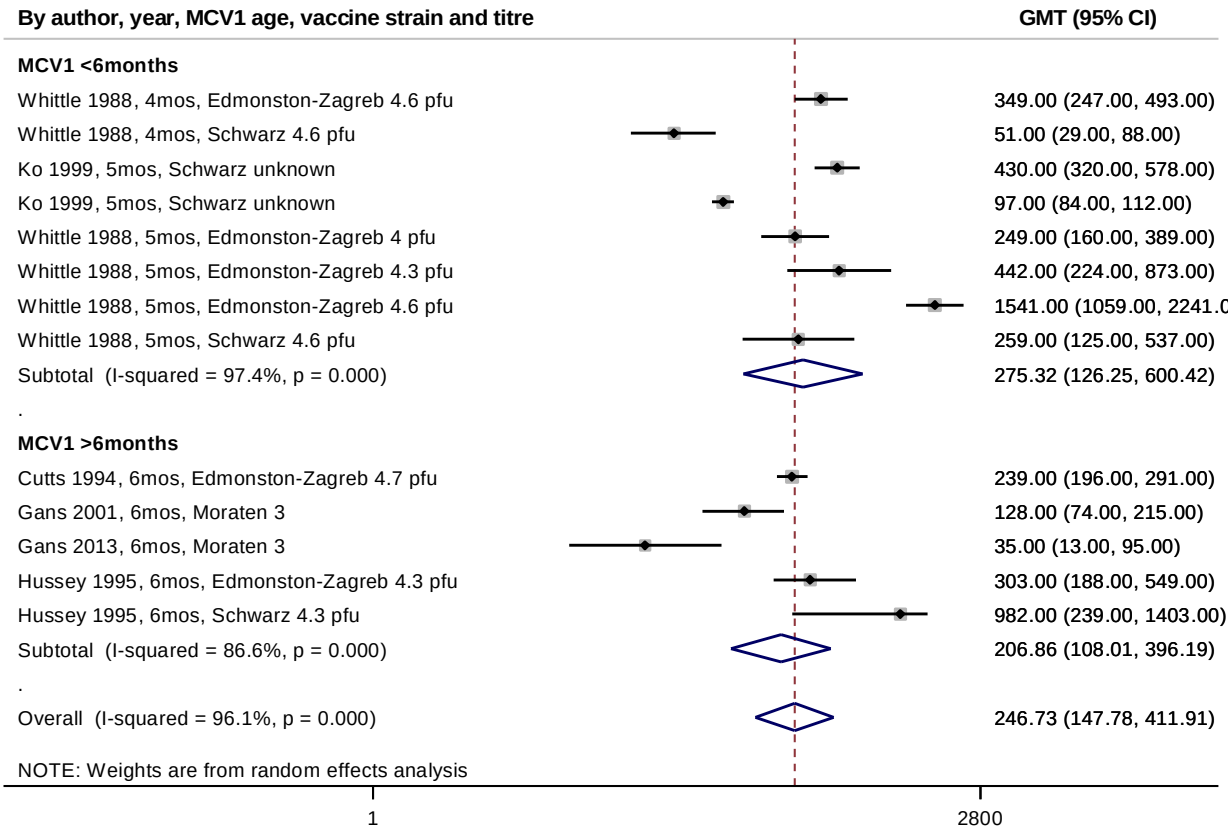

Figure 6. Random effects meta-analysis of PRNT geometric mean titres after MCV in infants <6 months or 6-8 months of age. Titres are expressed as TCID50 unless specified otherwise. GMT: geometric mean titre. CI: confidence interval.

5.1.3 Avidity

There were no studies examining avidity following MCV vaccination below 6 months of age.

5.1.4 Cellular immunity

We found one study by Njie-Jobe *et al.,* (16) which found that infants vaccinated with MCV1 (Edmonston-Zagreb) at 4 months had higher IFN-γ memory T-cell responses at 9 months compared to the unimmunized group. They found that 14 and 44 months following vaccination, IFN-γ memory responses were similar in the group with two MCVs at 4 and 9 months and the group with MCV1 at 9 months. They also found that the presence of maternal antibodies had no effect on memory T-cell responses nor did the number of MCVs the infants received.

5.1.5 Seropositivity

We found eight studies reporting seropositivity for measles antibodies following MCV1<6 months (9, 15, 16, 18, 19, 21, 24, 25). The estimates of the proportion seropositive by age of MCV ranging from 3 to 5 months, pooled across strain and titre are presented in Figure 7. The overall pooled estimate for seropositivity following MCV1 <6 months was 68% (95%CI 58-78). The pooled seropositivity estimates stratified by age at MCV and strain in are presented in Figure 8. The corresponding forest plot is available in Appendix D: Supplementary results (Figure 15 to Figure 19).

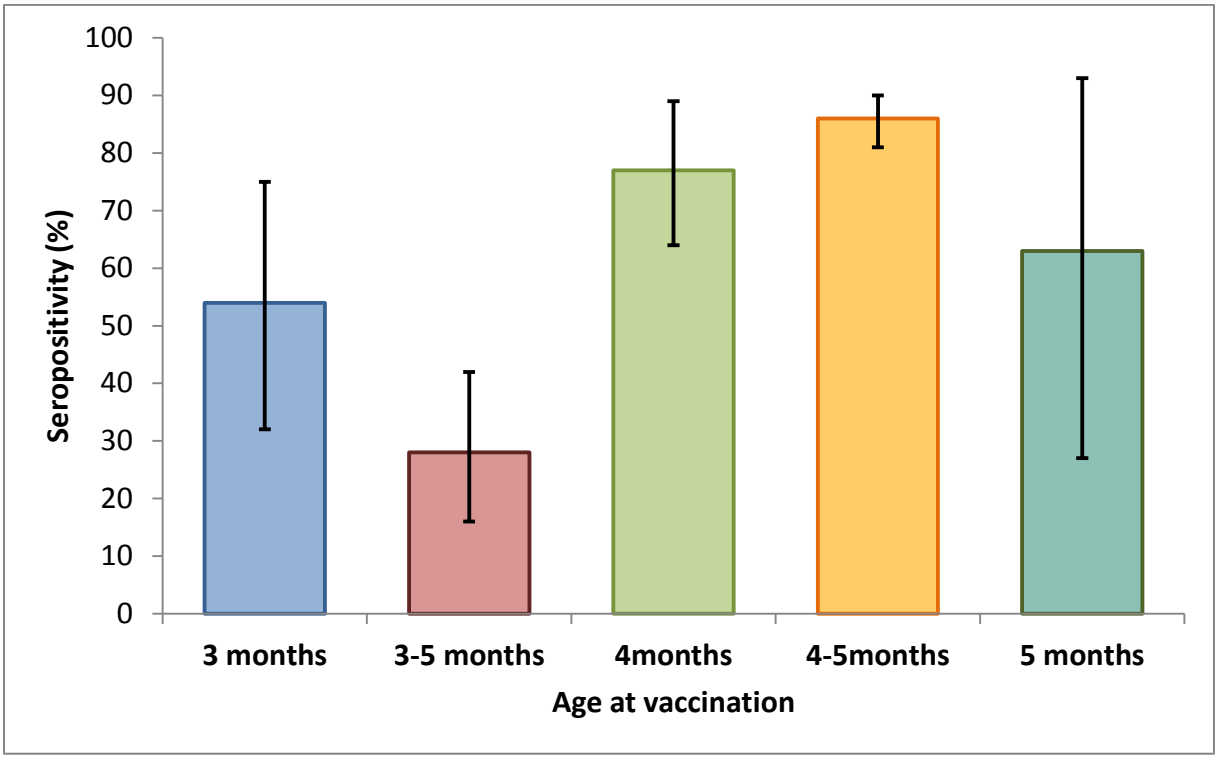

Figure 7: Proportion seropositive by age of MCV (3-5 months), pooled estimates derived from seven studies. Error bars present 95% confidence intervals.

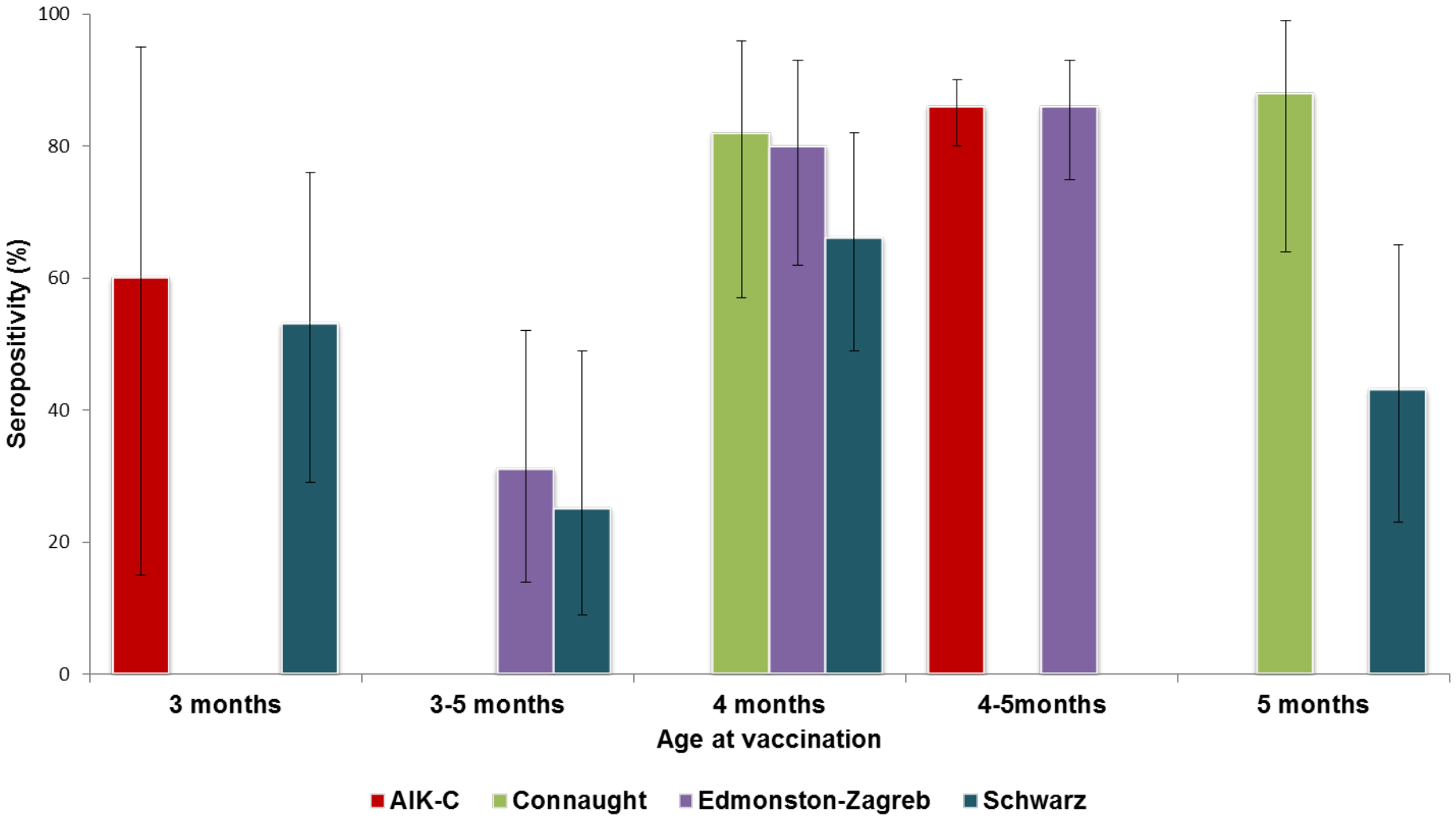

Figure 8. Proportion seropositive by age of MCV (3-5 months) and vaccine strain derived from seven studies. Error bars present 95% confidence intervals.

5.2 Vaccine efficacy and vaccine effectiveness

We identified two studies following MCV1 <6 months; one reporting vaccine efficacy (13) and one reporting vaccine effectiveness (8).

Hull *et al*., reported on the vaccine effectiveness of the Moraten strain following a measles outbreak in the Gambia in 1981 (8). They found vaccine effectiveness of 54% (95%CI 0-84%) among infants vaccinated with MCV1 below 5 months (n=5), and vaccine effectiveness of 37% (95%CI 0-74%) among infants vaccinated with MCV1 at 6-8 months (n=11) (8).

Martins *et al*., reported on the interim analysis of a randomised clinical trial in Guinea-Bissau using the Edmonston-Zagreb strain. The outcomes of interest were vaccine efficacy against measles infection, admission to hospital for measles, and measles mortality before standard vaccination at 9 months of age (13). They found vaccine efficacy of MCV1 (Edmonston-Zagreb) at 4.5 months was 91% (95%CI 62-98) (n=43), vaccine efficacy against measles related hospitalisation was 100% (95%CI 46-100)] and against measles related death [100% (95%CI -42-100)].

5.3 Duration of immunity

We identified two studies (12, 14) reporting findings following MCV below and above 6 six months.

Ko *et al*., stratified their findings by infants' response to MCV1 (Schwarz) at 5 months and compared them four to six weeks following MCV2 (MMR II, Wellcome) at 13 months. They found one infant who responded to MCV1 but showed no further rise in GMT following MCV2. However, the remaining 15 infants who responded to MCV1 had significantly higher responses four to six weeks following MCV2 at 13 months, compared to those who did not respond to MCV1 (12).

Martins *et al*., examined the GMTs of infants following vaccination with MCV1 at 4.5 months and MCV2 at 9 months using standard-titer Edmonston-Zagreb (14). Overall, they found that at 24 months, infants vaccinated early maintained high protective antibody levels (14).

5.4 Blunting

We found two studies (14, 16) reporting seropositivity following MCV1 <6 months and MCV2 >9 months of age.

Martins *et al*., found infants at 24 months of age had measles seropositivity of 97% (95%CI 94-98) following MCV1 at 4.5 months and MCV2 at 9 months (14).

Nije-Jobe *et al*., found measles seropositivity at 9.5 moths to be 98% following MCV1 at 4 months and MCV2 at 9 months of age (16). Twelve months following MCV3 at 36 months, antibody titres had dropped but all infants had protective levels of antibody.

5.5 Safety

We found two studies (7, 12) reporting on safety following MCV1 below 6 months.

Ko *et al*., reported two episodes of rash with fever among 53 study participants following MCV1 (Schwarz) at 5 months. However, the authors stated that one infant had a rash throughout the recording period and unlikely to be due to the vaccination. The second infant developed a rash 19 days after MMR vaccination, a saliva specimen collected five days after rash onset was negative for measles IgM and IgG. No adverse events were reported.

A study by Do *et al*., relates to the RCT in Guinea-Bissau previously reported by Martins *et al.,* (13, 14). However, here they report on AEFIs among 1,592 infants who were randomized to receive MCV1 (Edmonston-Zagreb) at 4.5 months. Overall, they found reduced skin reaction among infants who received MCV1 at 4.5 months of age [Hazard Ratio 0.76 (95% CI 0.60-0.95)]. Also, they found no significant difference between groups randomized to receive MCV1 at 4.5 months or 9 months for AEFIs 7 and 14 days post vaccination (7).

5.6 Secondary questions

5.6.1 Presence of maternal antibodies and seroconversion

We found two studies comparing the proportion seroconverted in infants with maternal antibodies following MCV <6 months (4, 15).

Figure 9 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. These differences were, however, not significant. 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. Forest plots can be found in Appendix D: Supplementary results Figure 20 and Figure 21.

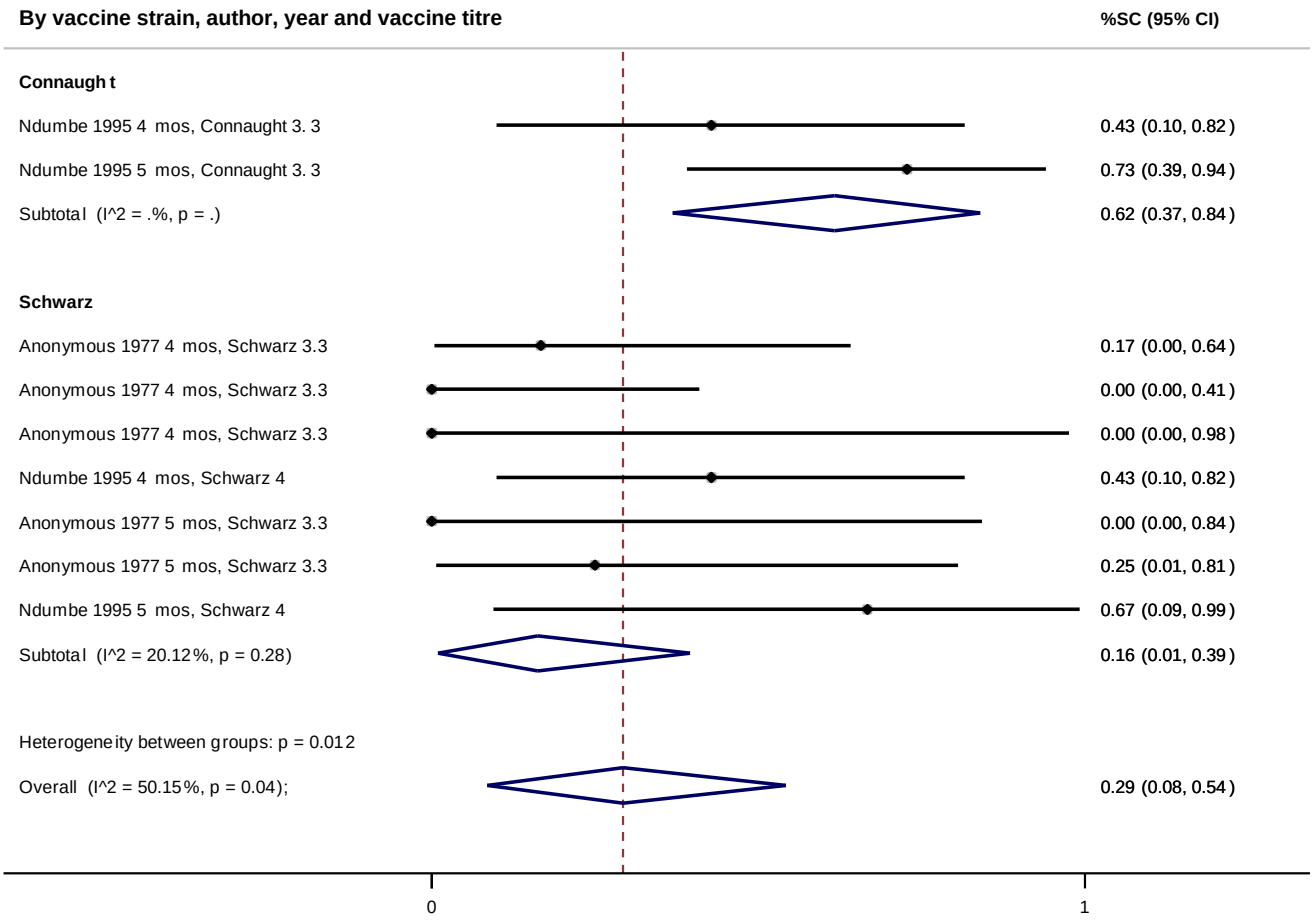

Figure 9. Overall proportion of seroconverted infants with maternal antibodies following MCV below 6 months.

Figure 10 shows 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.

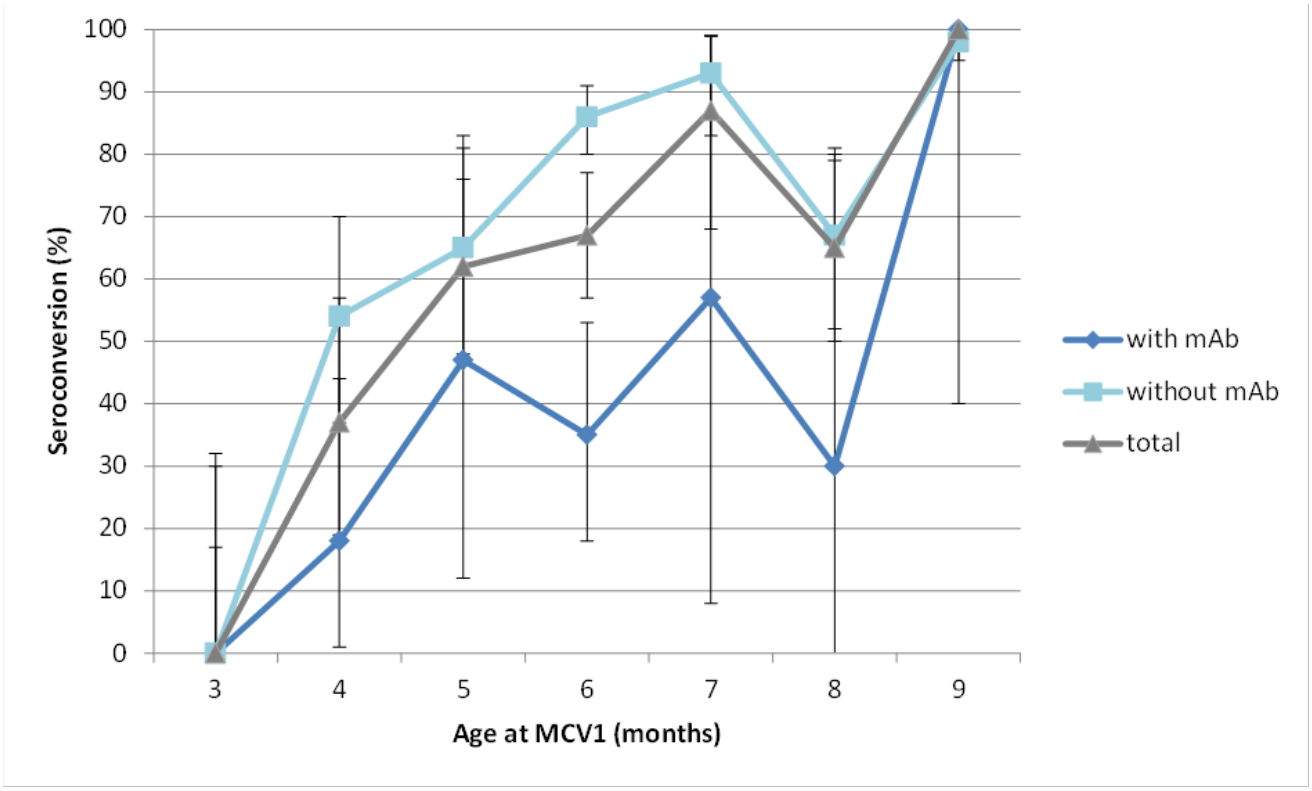

Figure 10: Proportion seroconverted by month of MCV, stratified by presence of maternal antibodies.

6 GRADE quality of evidence found

Seventeen of nineteen included studies were observational. Therefore, for all outcomes, the quality of evidence was found to be moderate, low or very low but of importance. See Table 5 in Appendix C: GRADE data quality assessment.

7 Discussion

In our review, we encountered a number of areas with paucity of studies of infants vaccinated with MCV1 <6 months of age. These include studies on antibody avidity, vaccine effectiveness, cellular immunity, duration of immunity and blunting to subsequent MCVs following MCV <6 months. In addition, more observations are needed to estimate the incidence of AEFIs following MCV below 6 months of age. This paucity of data, together with heterogeneity between studies, warrants caution when interpreting our results.

In terms of humoral immunity among infants vaccinated below 6 months of age, the proportion seroconverted and seropositive increased with age, and was also dependent on strain. We found that GMTs were higher among infants vaccinated below 6 months, but there was variation by strain and age of MCV1 vaccination. Furthermore, these findings are based on only two studies among infants vaccinated below 6 months and five observations from three studies among infants vaccinated above 6 months.

For vaccine efficacy and effectiveness and safety, there were few eligible studies and, those eligible had small sample sizes.

Metaregression did not find significant findings for any of the outcomes. The quality of evidence was found to be moderate, low or very low for all outcomes considered but of importance.

8 Conclusions

We found humoral immunogenicity following MCV1<6 months of age was dependent on age of MCV1 and low levels of maternal antibodies. There was limited evidence available for cellular immunity, vaccine effectiveness, duration of immunity, safety and blunting.

9 Recommendations for future research

In order to obtain reliable evidence to inform decisions, a trial, with a long follow-up after subsequent doses of MCV in an endemic area with MCV1 at 4-6-9 month would be helpful. Observational case-control studies in high endemicity areas where MCV1 has been given at 6 months of age in the past e.g. South Africa or Papua New Guinea, could provide useful humoral and vaccine effectiveness data. Finally, seroepidemiological studies in low and middle income countries could

provide a better understanding of population immunity towards measles and other vaccine preventable diseases.

10 Acknowledgements

We thank the Members of the WHO IVB team for the opportunity to conduct this review. We would also like to Wim ten Have (RIVM librarian) for contribution towards this review.

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Appendix A: Databases and websites used for literature search

Databases
Primary: databases for biomedicine and health sciences • EMBASE; • Scopus; • ProQuest search; • SciSearch; • Global Health; • Biosis Previews **Secondary: regional and clinical trials-databases** • ClinicalTrials.gov • EU Clinical Trials Register **General databases** • Google & Google Scholar

Appendix B: Database search strategy

Database	Search strategy
Scopus search strategy ***conducted on 13-04-2017***	1. (TITLE(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 TITLE(vaccine* OR vaccination* OR immunization* OR immunisation*)) OR TITLE((mr-vaccine*) OR mmrv) 5.310 2. (KEY(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 KEY(vaccine* OR vaccination* OR immunization* OR immunisation*)) OR KEY((mr-vaccine*) OR mmrv) 18.578 3. #1 OR #2 19.129 4. TITLE-ABS-KEY((before-6-months) OR ((less-than) W/4 (6-months)) OR (earlier W/4 (6-months)) OR (under-6-months) OR (below-6-months) OR ((younger-than) W/4 (6-months))) 7.732 5. TITLE-ABS-KEY((0-month*) OR (1-month*) OR (2-month*) OR (3-month*) OR (4-month*) OR (5-month*) OR (1-2-month*) OR (1-3-month*) OR (1-4-month*) OR (1-5-month*) OR (1-6-month*) OR (2-3-month*) OR (2-4-month*) OR (2-5-month*) OR (2-6-month*) OR (3-4-month*) OR (3-5-month*) OR (3-6 month*) OR (4-5-month*) OR (4-6-month*) OR (5-6-month*)) 523.440 6. TITLE-ABS-KEY((at-birth) OR newborn* OR (one W/4 month*) OR (two W/4 month*) OR (three W/4 month*) OR (four W/4 month*) OR (five W/4 month*)) 1.135.587 7. TITLE-ABS-KEY((first-month*) OR (second-month*) OR (third-month*) OR (fourth-month*) OR (fifth-month*) OR (first-two-month*) OR (first-three month*) OR (first-four-month*) OR (first- five month*) OR (first-six month*) OR (first-2-month*) OR (first-3-month*) OR (first-4-month*) OR (first-5-month*) OR (first-6-month*)) 83.485 8. TITLE-ABS-KEY(weeks W/4 age) 62.473 9. TITLE-ABS-KEY(4.5-months) OR (TITLE-ABS-KEY(first-dose) AND TITLE-ABS-KEY(before W/6 months)) 5.381 10. TITLE-ABS-KEY((early W/3 vaccination) OR (early W/3 immunization) OR (early W/3 immunisation) OR (early W/3 mv) OR (early W/3 schedule) OR (give-earlier) OR (early-mv) OR (primary-mv) OR (given-earlier) OR (early-infancy)) 11.722 11. #3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 2.749 12. TITLE-ABS-KEY(immunogenic* OR efficacy OR effectiveness OR effectivity OR (immunological-impact) OR immunogenicity) OR TITLE((optimal-age) OR (optimum-age)) 2.464.775 13. TITLE-ABS-KEY((measles-cases) OR (measles AND incidence) OR ((mortality OR death) AND (measles-vaccin*))) OR TITLE-ABS-KEY(measles W/4 (death* OR mortality OR incidence)) 5.584

	14. TITLE-ABS-KEY((plaque-reduction-neutralization-test*) OR prnt OR (enzyme-linked-immunosorbent-assay) OR (enzyme-linked-immunospot-assay) OR elisa OR (hemagglutination-inhibition-assay) OR (hi-assay) OR (complement-fixation-assay) OR (cf-assay) OR avidity OR (virus-anitibod*) OR (neutralizing-antibod*) OR (immunogloublin-g) OR (virus-neutralization) OR serodiagnosis) 416.590 15. (KEY(measles-vaccine) AND KEY(drug-administration)) OR KEY((antibody-production) OR (antibody-affinity) OR (cellular-immunity) OR (lymphocyte-activation) OR (cytopathogenic-effect) OR ((stimulation-index) AND (t-cell-proliferation))) 295.402 16. TITLE-ABS-KEY((antibody-response*) OR (antibody-titer*) OR (antibody-titre*) OR (antibody-level*) OR (immune-response*) OR (t-cell-response*) OR (cell-mediated-immunity) OR (humoral W/3 immunity) OR (measles-igg) OR seroconversion OR (response-to-vaccination) OR (response W/3 (measles-vaccination))) 459.447 17. TITLE-ABS-KEY((improve W/3 survival) OR (improves W/3 survival) OR (mortality-reduction) OR (child-mortality) OR (prevention W/3 measles) OR (risk W/3 measles)) 41.525 18. TITLE-ABS-KEY(reactogenicity OR safety OR (adverse-events) OR (adverse-effects) OR (side-effects) OR fever OR (local-reaction*) OR convulsion* OR purpura OR rash) 2.157.671 19. TITLE-ABS-KEY((aseptic-meningitis) OR seizures OR encephalopath* OR anaphylaxis OR hypersensitivity OR (allergic-reaction*) OR (joint-pain) OR arthropathy OR arthralgia OR arthritis OR cough OR diarrhoea OR diarrhea) 1.048.606 20. KEY((measles-vaccine) OR (measles-mumps-rubella-vaccine) OR (measles-rubella vaccine) OR (measles-mumps-vaccine)) AND KEY((adverse-drug-reaction*) OR (adverse-effect*) OR (adverse-event*) OR (side-effect*) OR (chemically-induced) OR complications OR contraindications OR toxicity OR poisoning OR (drug-effects)) 2.073 21. TITLE-ABS-KEY(adverse W/5 (effect* OR event*)) OR TITLE-ABS-KEY((side-effect*) OR hypersensitiv* OR sensitiv* OR safe* OR pharmacovigil*) 4.963.102 22. #11 AND (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) 2.105 23. LANGUAGE(english OR dutch OR german OR french OR spanish) 61.514.152 24. #23 AND #24 1.992 25. KEY(animal*) NOT KEY(human*) 779.838 26. TITLE(macaque* OR primate* OR rodent* OR mice OR mouse OR murine OR rat OR rats) 1.547.016 27. DOCTYPE(ed) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(le) 4.795.798 28. #25 AND NOT (#26 OR #27 OR #28) 1.832 29. PUBYEAR AFT 2014 OR (PUBYEAR IS 2014 AND ORIG-LOAD-DATE AFT 20150101) 7.080.060 30. #29 AND #30 141

ProQuest search strategy ***conducted on 13-04-2017***	S31 S30 NOT (Medline OR Embase) Databases: 5 databases searched S30 S28 AND S29 Databases: 5 databases searched S29 YR(2015-2017) OR (YR(2014) AND PD(20150101-20170410)) Databases: 5 databases searched S28 S24 NOT (S25 OR S26 OR S27) Databases: 5 databases searched S27 DTYPE(editorial OR erratum OR NOTE OR news OR letter OR comment OR (case-report)) Databases: 5 databases searched S26 TI(macaque* OR primate* OR rodent* OR mice OR mouse OR murine OR rat OR rats) Databases: 5 databases searched S25 SU(animal*) NOT SU(human*) Databases: 5 databases searched S24 S22 AND S23 Databases: 5 databases searched S23 LA(english OR dutch OR german OR french OR spanish) Databases: 5 databases searched S22 S11 AND (S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21) Databases: 5 databases searched S21 TI,AB,SU(adverse W/5 (effect* OR event*)) OR TI,AB,SU((side-effect*) OR hypersensitiv* OR sensitiv* OR safe* OR pharmacovigil*) Databases: 5 databases searched S20 SU((measles-vaccine) OR (measles-mumps-rubella-vaccine) OR (measles-rubella vaccine) OR (measles-mumps-

	vaccine)) AND SU((adverse-drug-reaction*) OR (adverse-effect*) OR (adverse-event*) OR (side-effect*) OR (chemically-induced) OR complications OR contraindications OR toxicity OR poisoning OR (drug-effects)) Databases: 5 databases searched S19 TI,AB,SU((aseptic-meningitis) OR seizures OR encephalopath* OR anaphylaxis OR hypersensitivity OR (allergic-reaction*) OR (joint-pain) OR arthropathy OR arthralgia OR arthritis OR cough OR diarrhoea OR diarrhea) Databases: 5 databases searched S18 TI,AB,SU(reactogenicity OR safety OR (adverse-events) OR (adverse-effects) OR (side-effects) OR fever OR (local-reaction*) OR convulsion* OR purpura OR rash) Databases: 5 databases searched S17 TI,AB,SU((improve W/3 survival) OR (improves W/3 survival) OR (mortality-reduction) OR (child-mortality) OR (prevention W/3 measles) OR (risk W/3 measles)) Databases: 5 databases searched S16 TI,AB,SU((antibody-response*) OR (antibody-titer*) OR (antibody-titre*) OR (antibody-level*) OR (immune-response*) OR (t-cell-response*) OR (cell-mediated-immunity) OR (humoral W/3 immunity) OR (measles-igg) OR seroconversion OR (response-to-vaccination) OR (response W/3 (measles-vaccination))) Databases: 5 databases searched S15 (SU(measles vaccine) AND SU(drug-administration)) OR SU((antibody-production) OR (antibody-affinity) OR (cellular-immunity) OR (lymphocyte-activation) OR (cytopathogenic-effect) OR ((stimulation-index) AND (t-cell-proliferation))) Databases: 5 databases searched S14 TI,AB,SU((plaque-reduction-neutralization-test*) OR prnt OR (enzyme-linked-immunosorbent-assay) OR (enzyme-linked-immunospot-assay) OR elisa OR (hemagglutination-inhibition-assay) OR (hi-assay) OR (complement-fixation-assay) OR (cf-assay) OR avidity OR (virus-anitibod*) OR (neutralizing-antibod*) OR (immunogloublin-g) OR (virus-neutralization) OR

	serodiagnosis) Databases: 5 databases searched S13 TI,AB,SU((measles-cases) OR (measles AND incidence) OR ((mortality OR death) AND (measles-vaccin*))) OR TI,AB,SU(measles W/4 (death* OR mortality OR incidence)) Databases: 5 databases searched S12 TI,AB,SU(immunogenic* OR efficacy OR effectiveness OR effectivity OR (immunological-impact) OR immunogenicity) OR TI((optimal-age) OR (optimum-age)) Databases: 5 databases searched S11 S3 AND (S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10) Databases: 5 databases searched S10 TI,AB((early W/3 vaccination) OR (early W/3 immunization) OR (early W/3 immunisation) OR (early W/3 mv) OR (early W/3 schedule) OR (give-earlier) OR (early-mv) OR (primary-mv) OR (given-earlier) OR (early-infancy)) Databases: 5 databases searched S9 TI,AB(4.5-months) OR (TI,AB,SU(first-dose) AND TI,AB,SU(before W/6 months)) Databases: 5 databases searched S8 TI,AB(weeks W/4 age) Databases: 5 databases searched S7 TI,AB((first-month*) OR (second-month*) OR (third-month*) OR (fourth-month*) OR (fifth-month*) OR (first-two-month*) OR (first-three month*) OR (first-four-month*) OR (first-five month*) OR (first-six month*) OR (first-2-month*) OR (first-3-month*) OR (first-4-month*) OR (first-5-month*) OR (first-6-month*)) Databases: 5 databases searched S6 TI,AB((at-birth) OR newborn* OR (one W/4 month*) OR (two W/4 month*) OR (three W/4 month*) OR (four W/4 month*) OR (five W/4 month*)) Databases: 5 databases searched

	S5 TI,AB((0-month*) OR (1-month*) OR (2-month*) OR (3-month*) OR (4-month*) OR (5-month*) OR (1-2-month*) OR (1-3-month*) OR (1-4-month*) OR (1-5-month*) OR (1-6-month*) OR (2-3-month*) OR (2-4-month*) OR (2-5-month*) OR (2-6-month*) OR (3-4-month*) OR (3-5-month*) OR (3-6 month*) OR (4-5-month*) OR (4-6-month*) OR (5-6-month*)) Databases: 5 databases searched S4 TI,AB((before-6-months) OR ((less-than) W/4 (6-months)) OR (earlier W/4 (6-months)) OR (under-6-months) OR (below-6-months) OR ((younger-than) W/4 (6-months))) Databases: 5 databases searched S3 S1 OR S2 Databases: 5 databases searched S2 (SU(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 SU(vaccine* OR vaccination* OR immunization* OR immunisation*)) OR SU((mr-vaccine*) OR mmrv) Databases: 5 databases searched S1 (TI(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 TI(vaccine* OR vaccination* OR immunization* OR immunisation*)) OR TI((mr-vaccine*) OR mmrv) Databases: 5 databases searched
EMBASE search strategy ***conducted 12-04-2017***	#33 #31 AND #32 3,110,358 #32 [2015-2017]/py OR (2014:py AND [1-5-2015]/sd) 491 #31 #27 NOT (#28 OR #29 OR #30) 2,307,149 #30 'case report':it OR news:it OR letter:it OR note:it OR comment:it

	OR editorial:it OR erratum:it 1,566,204 #29 macaque*:ti OR primate*:ti OR rodent*:ti OR mice:ti OR mouse:ti OR murine:ti OR rat:ti OR rats:ti 5,117,094 #28 [animals]/lim NOT [humans]/lim 528 #27 #25 AND #26 28,603,685 #26 english:la OR dutch:la OR german:la OR french:la OR spanish:la 557 #25 #12 AND (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 2,872,739 #24 adverse:ti,ab AND (effect*:ti,ab OR event*:ti,ab) OR 'side effect*':ti,ab OR hypersensitiv*:ti,ab OR sensitiv*:ti,ab OR safe*:ti,ab OR pharmacovigil*:ti,ab 298 #23 'measles vaccine'/de OR 'measles mumps rubella vaccine'/de OR 'measles rubella vaccine'/de OR 'measles mumps vaccine'/de AND ('adverse events':de OR 'side effects':de OR 'chemically induced':de OR complications:de OR contraindications:de OR toxicity:de OR poisoning:de OR 'drug effects':de) 3,220 #22 'measles vaccine'/de OR 'measles mumps rubella vaccine'/de OR 'measles rubella vaccine'/de OR 'measles mumps vaccine'/de AND ('adverse drug reaction'/lnk OR 'side effect'/lnk) 654,400 #21 'aseptic meningitis':ti,ab OR seizures:ti,ab OR encephalopathy:ti,ab OR anaphylaxis:ti,ab OR hypersensitivity:ti,ab OR 'allergic reaction*':ti,ab OR 'joint pain':ti,ab OR arthropathy:ti,ab OR arthralgia:ti,ab OR arthritis:ti,ab OR cough:ti,ab OR diarrhoea:ti,ab OR diarrhea:ti,ab

	1,665,283 #20 reactogenicity:ti,ab,de OR safety:ti,ab,de OR 'adverse events':ti,ab,de OR 'adverse effects':ti,ab,de OR 'side effects':ti,ab,de OR fever:ti,ab,de OR 'local reaction*':ti,ab,de OR convulsion*:ti,ab,de OR purpura:ti,ab,de OR rash:ti,ab,de 43,213 #19 (improve NEAR/3 survival):ti,ab OR (improves NEAR/3 survival):ti,ab OR 'mortality reduction':ti,ab OR 'child mortality':ti,ab OR (prevention NEAR/3 measles):ti,ab OR (risk NEAR/3 measles):ti,ab 363,768 #18 'antibody response*':ti,ab OR 'antibody titer*':ti,ab OR 'antibody titre*':ti,ab OR 'antibody level*':ti,ab OR 'immune response*':ti,ab OR 't-cell response*':ti,ab OR 'cell-mediated immunity':ti,ab OR (humoral NEAR/3 immunity):ti,ab OR 'measles igg':ti,ab OR seroconversion:ti,ab OR 'response to vaccination':ti,ab OR (response NEAR/3 'measles vaccination'):ti,ab 135,798 #17 'measles vaccine'/de AND 'drug administration'/lnk OR 'antibody production' OR 'antibody affinity'/de OR 'cellular immunity'/de OR 'lymphocyte activation'/de OR 'cytopathogenic effect'/de OR ('stimulation index':ti,ab AND 't-cell proliferation':ti,ab) 252,501 #16 'plaque reduction neutralization test*':ti,ab OR prnt:ti,ab OR 'enzyme-linked immunosorbent assay':ti,ab OR 'enzyme-linked immunospot assay':ti,ab OR elisa:ti,ab OR 'hemagglutination inhibition assay':ti,ab OR 'hi assay':ti,ab OR 'complement fixation assay':ti,ab OR 'cf assay':ti,ab OR avidity:ti,ab 505,122 #15 'virus antibody'/de OR 'neutralizing antibody'/de OR 'immunoglobulin g'/de OR 'enzyme-linked immunosorbent assay'/de OR 'enzyme-linked immunospot assay'/de OR 'hemagglutination inhibition test'/de OR 'virus neutralization'/de OR 'serodiagnosis'/de 2,983 #14 'measles cases':ti,ab OR ('measles'/de AND 'incidence'/de) OR ('infant mortality'/de OR 'mortality'/de OR 'death'/de AND 'measles vaccine'/de) OR (measles NEAR/4 (death* OR mortality

	OR incidence)):ti,ab 1,873,549 #13 immunogenicity:ti,ab,de OR efficacy:ti,ab,de OR effectiveness:ti,ab,de OR effectivity:ti,ab,de OR 'immunological impact':ti,ab,de OR 'immunogenicity'/de OR 'vaccine immunogenicity'/de OR 'drug efficacy'/de OR 'optimal age':ti OR 'optimum age':ti 690 #12 #4 AND (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) 8,458 #11 (early NEAR/3 vaccination):ti,ab OR (early NEAR/3 immunization):ti,ab OR (early NEAR/3 immunisation):ti,ab OR (early NEAR/3 mv):ti,ab OR (early NEAR/3 schedule):ti,ab OR 'give earlier':ti,ab OR 'early mv':ti,ab OR 'primary mv':ti,ab OR 'given earlier':ti,ab OR 'early infancy':ti,ab 4,252 #10 '4.5 months':ti,ab OR ('first dose':ti,ab AND (before NEAR/6 months):ti,ab) 55,279 #9 (weeks NEAR/4 age):ti,ab 55,196 #8 'first month*':ti,ab OR 'second month*':ti,ab OR 'third month*':ti,ab OR 'fourth month*':ti,ab OR 'fifth month*':ti,ab OR 'first two month*':ti,ab OR 'first three month*':ti,ab OR 'first four month*':ti,ab OR 'first five month*':ti,ab OR 'first six month*':ti,ab OR 'first 2 month*':ti,ab OR 'first 3 month*':ti,ab OR 'first 4 month*':ti,ab OR 'first 5 month*':ti,ab OR 'first 6 month*':ti,ab 501,381 #7 'at birth':ti,ab OR newborn*:ti,ab OR (one NEAR/4 month*):ti,ab OR (two NEAR/4 month*):ti,ab OR (three NEAR/4 month*):ti,ab OR (four NEAR/4 month*):ti,ab OR (five NEAR/4 month*):ti,ab 626,924 #6 '0 month*':ti,ab OR '1 month*':ti,ab OR '2 month*':ti,ab OR '3 month*':ti,ab OR '4 month*':ti,ab OR '5 month*':ti,ab OR '1-2 month*':ti,ab OR '1-3 month*':ti,ab OR '1-4 month*':ti,ab OR '1-5

	month*':ti,ab OR '1-6 month*':ti,ab OR '2-3 month*':ti,ab OR '2-4 month*':ti,ab OR '2-5 month*':ti,ab OR '2-6 month*':ti,ab OR '3-4 month*':ti,ab OR '3-5 month*':ti,ab OR '3-6 month*':ti,ab OR '4-5 month*':ti,ab OR '4-6 month*':ti,ab OR '5-6 month*':ti,ab 6,537 #5 'before 6 months':ti,ab OR ('less than' NEAR/4 '6 months'):ti,ab OR (earlier NEAR/4 '6 months'):ti,ab OR 'under 6 months':ti,ab OR 'below 6 months':ti,ab OR ('younger than' NEAR/4 '6 months'):ti,ab 9,863 #4 #1 OR #2 OR #3 2,126 #3 'measles'/mj OR 'measles virus'/mj AND ('vaccination'/mj OR 'immunization'/mj) 8,081 #2 'measles vaccine'/mj OR 'measles mumps rubella vaccine'/mj OR 'measles rubella vaccine'/mj OR 'measles mumps vaccine'/mj OR ('measles vaccine'/de AND ('vaccination'/mj OR 'immunization'/mj)) 5,167 #1 measles:ti OR mmr*:ti OR schwarz:ti OR moraten:ti OR edmonston:ti OR 'edmonston zagreb':ti OR 'leningrad 16':ti OR 'shanghai 191':ti OR 'cam 70':ti OR 'aik c':ti OR td97:ti AND (vaccine*:ti OR vaccination*:ti OR immunization*:ti OR immunisation*:ti) OR 'mr vaccine*':ti OR mmrv:ti
Secondary databases ***conducted on 25-04-2017***	Global strategy & dependent on the search possibilities of the different databases: measles AND vaccine/vaccines/vaccination/immunization/immunisation sometimes with additional: months/before/early

Appendix C: GRADE data quality assessment

Table 5: 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												
13	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
1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	Lack of methodological information on performance bias	#	#	#	#	⊕⊕⊕◯ Moderate	IMPORTANT
Duration of immunity												
2	Observational	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Very few studies available	#	#	#	#	⊕⊕◯◯ Low	IMPORTANT
Vaccine effectiveness/ efficacy												
2	Observational	Serious limitations[2]	No serious inconsistency	No serious indirectness	Serious[1]		#	#	#	#	⊕◯◯◯ Very low	IMPORTANT
Blunting												
2	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												
1	Observational	Serious Limitations[3]	No serious inconsistency	No serious indirectness	No serious imprecision	Lack clear case definitions (e.g. for fever)	#	#	#	#	⊕◯◯◯ Very low	IMPORTANT
1	RCT	No serious limitations	No serious inconsistency	No serious indirectness		Lack of methodological information on performance bias	#	#	#	#	⊕⊕⊕◯ Moderate	IMPORTANT

1: very wide confidence intervals

2: mainly due to lack of laboratory confirmation of measles cases

3: Study lacks 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: Supplementary results

Forest plots for seroconversion by MCV1 age

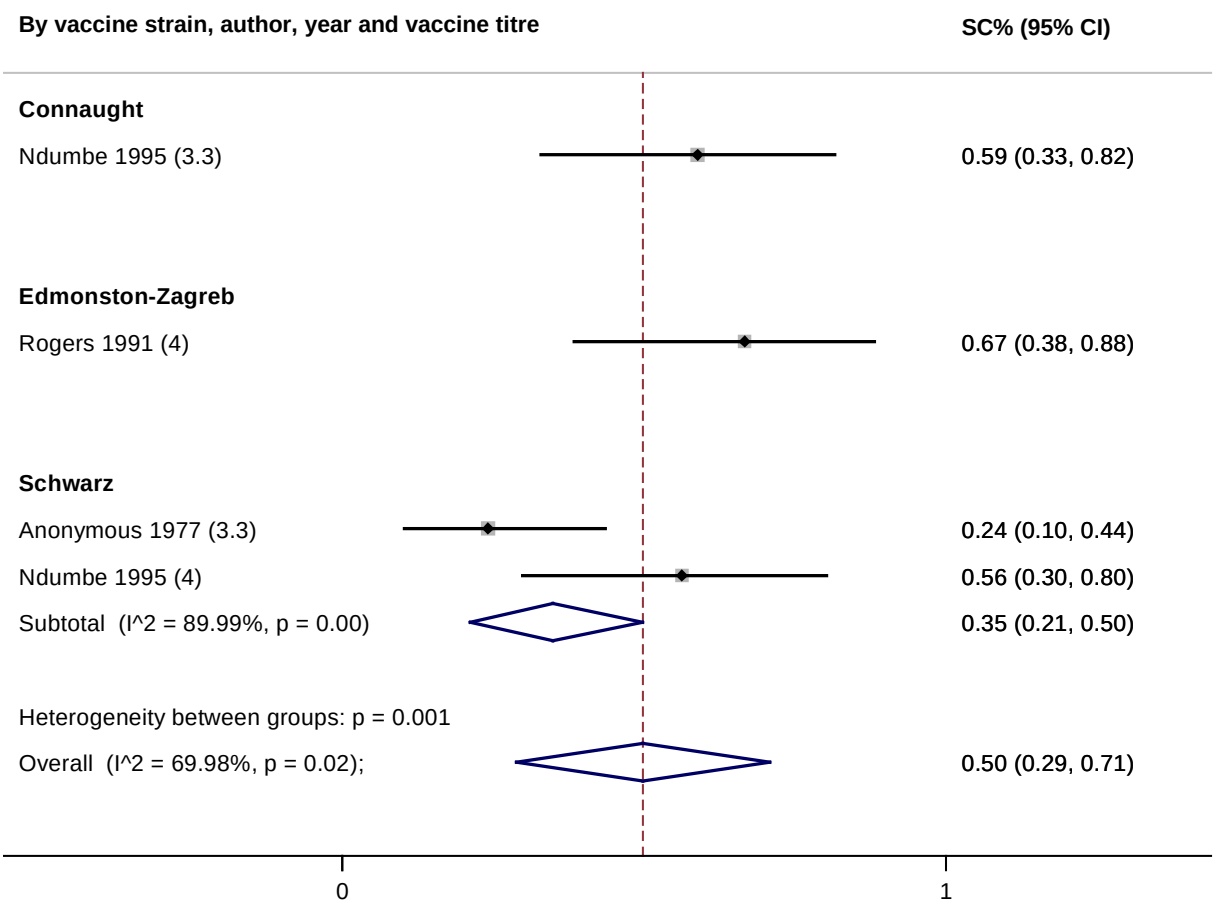

Figure 11: Proportion of seroconverted infants following MCV1 at 4 months

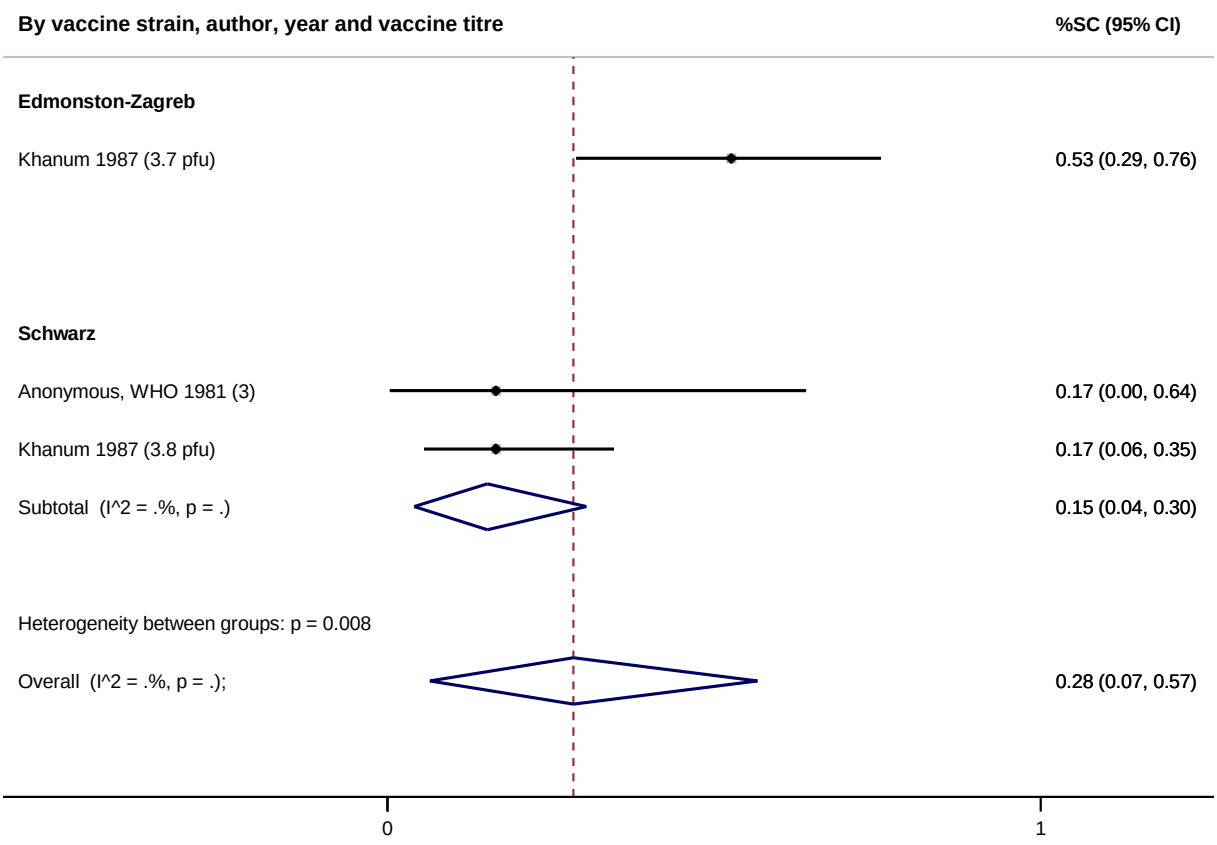

Figure 12: Proportion of seroconverted infants following MCV1 at 4-5 months

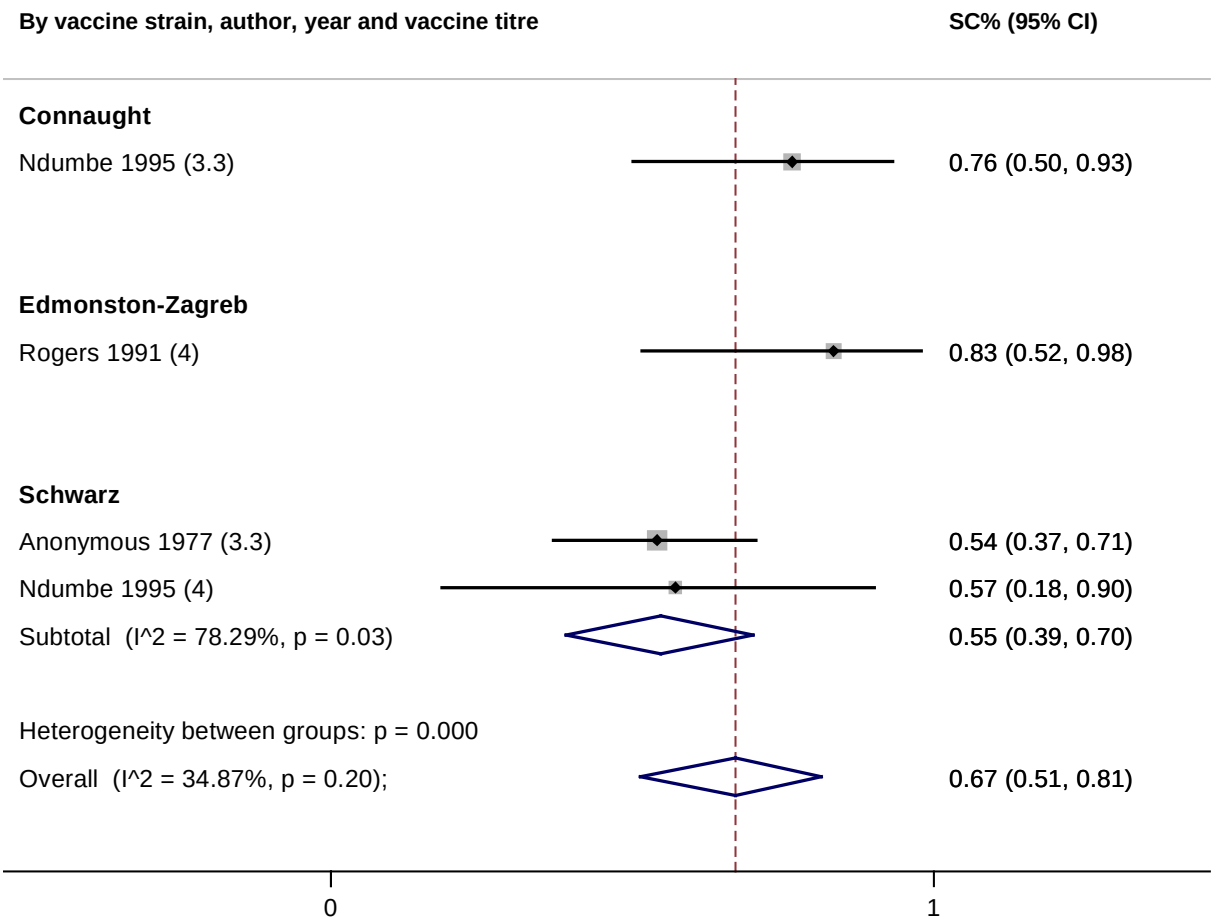

Figure 13: Proportion of seroconverted infants following MCV1 at 5 months

Forest plots for seropositivity by MCV1 age

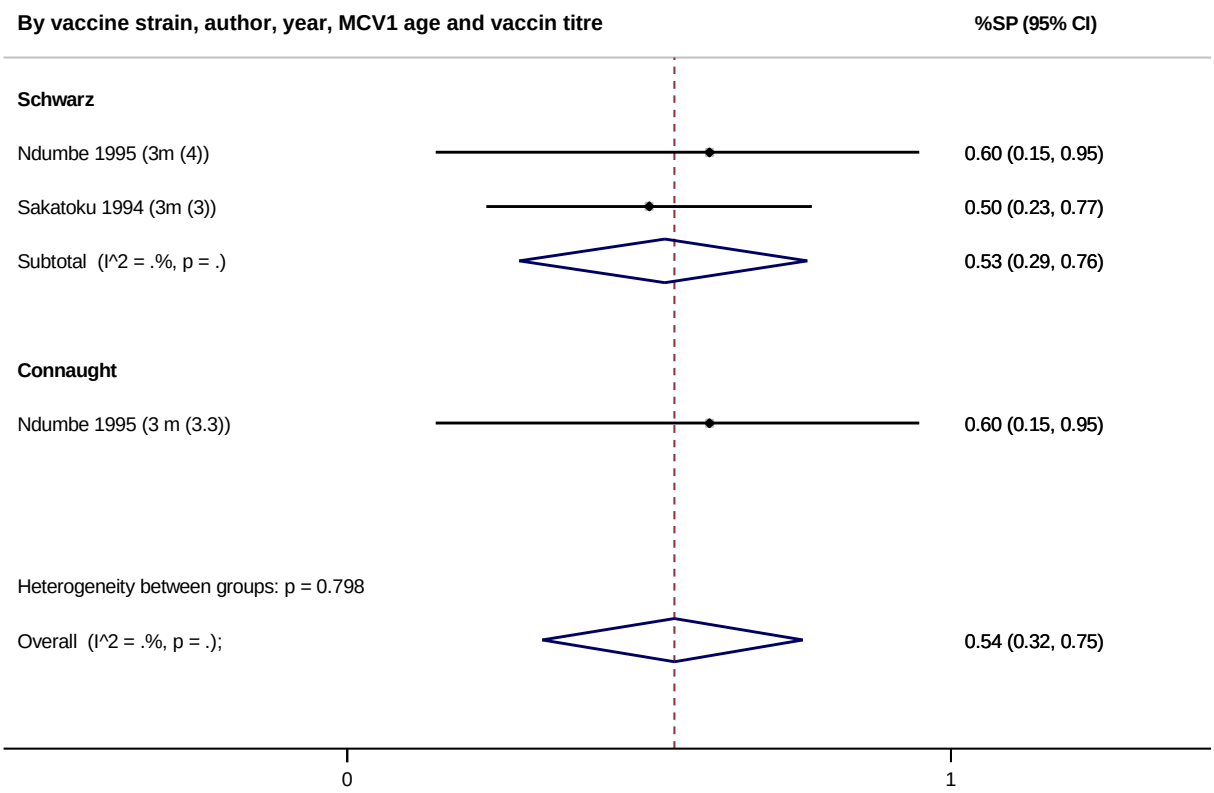

Figure 14: Proportion of seropositive infants following MCV1 at 3 months

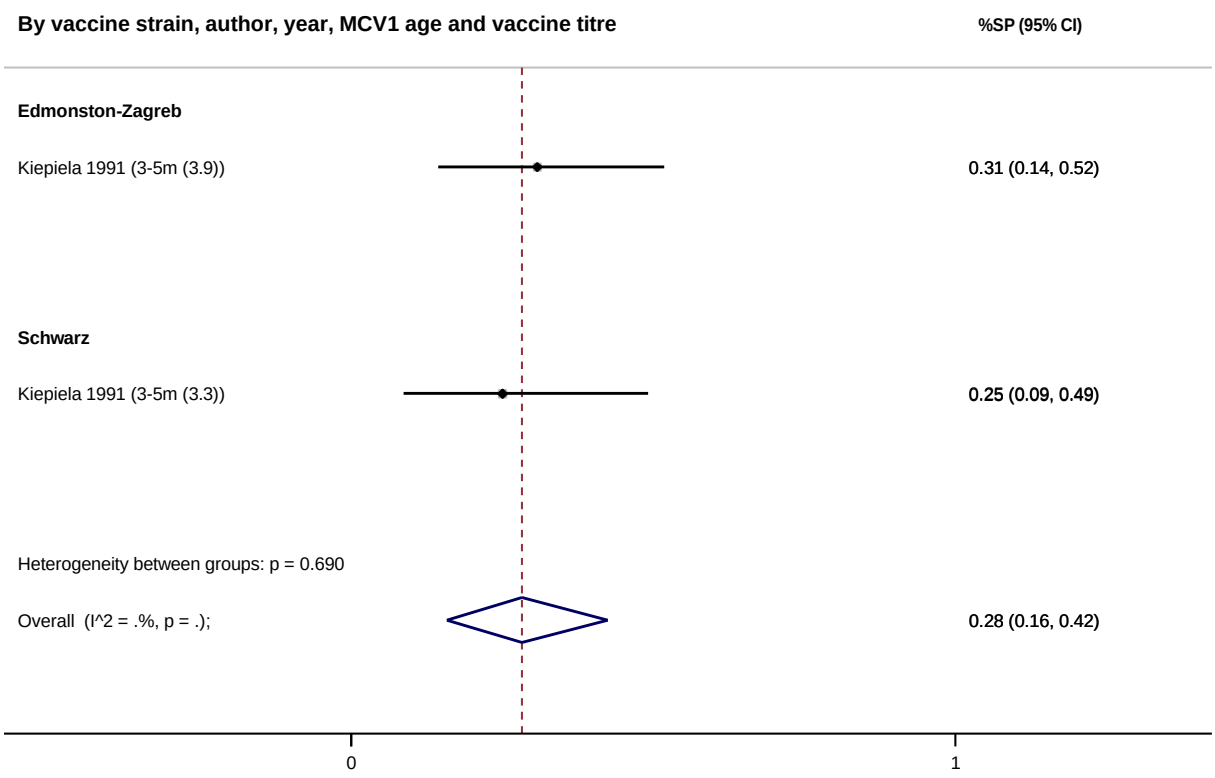

Figure 15: Proportion of seropositive infants following MCV1 at 3-5 months

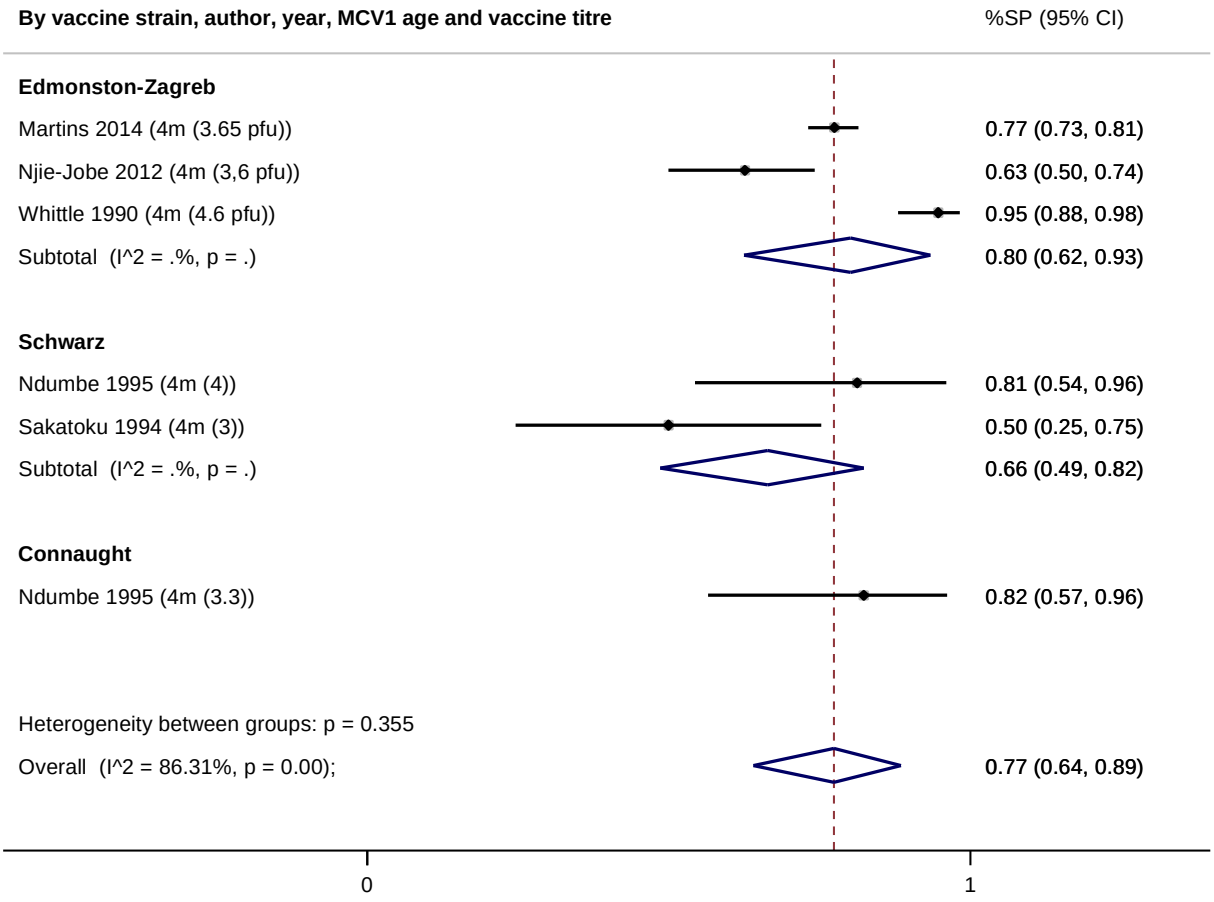

Figure 16: Proportion of seropositive infants following MCV1 at 4 months

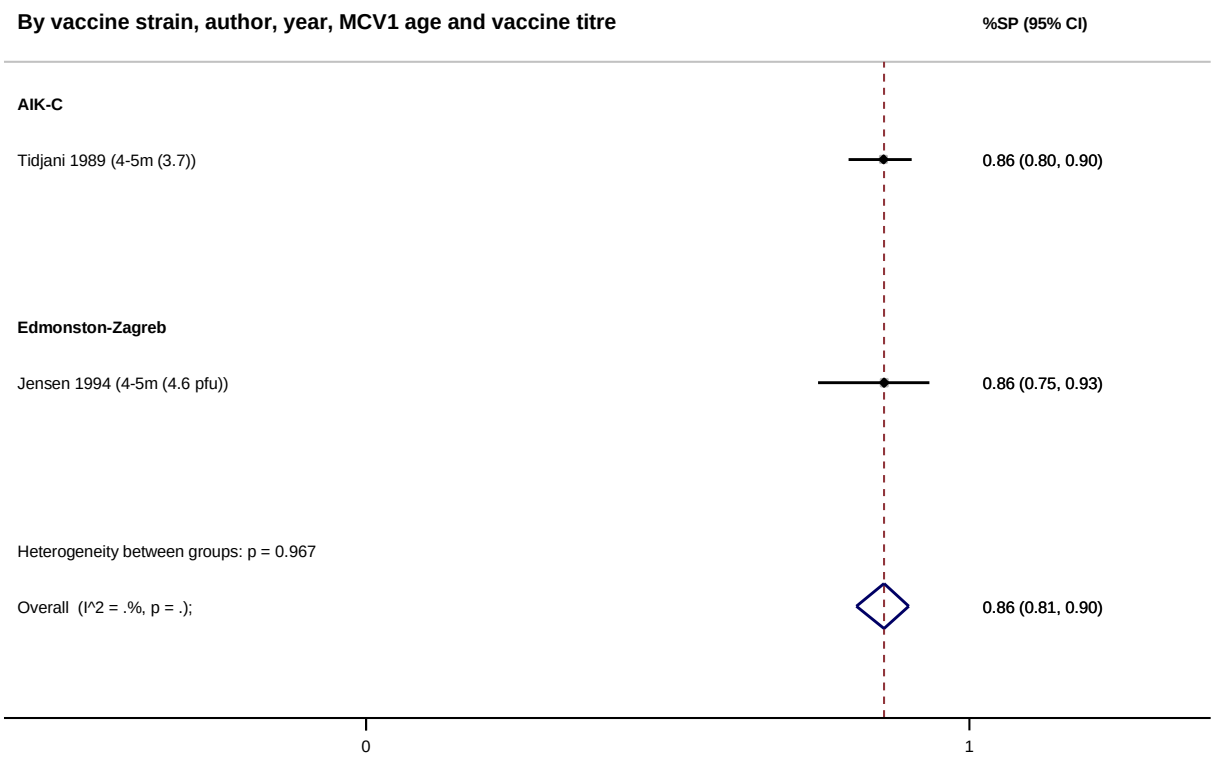

Figure 17: Proportion of seropositive infants following MCV1 at 4-5 months

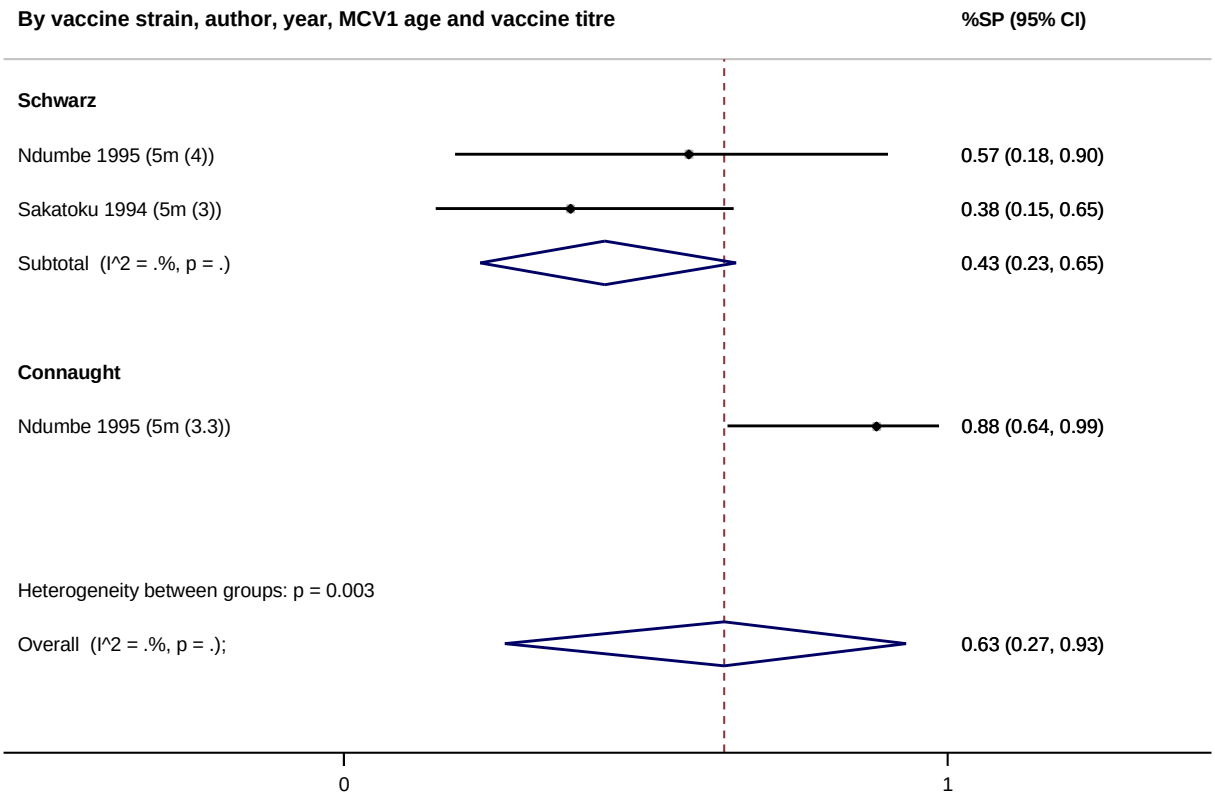

Figure 18: Proportion of seropositive infants following MCV1 at 5 months

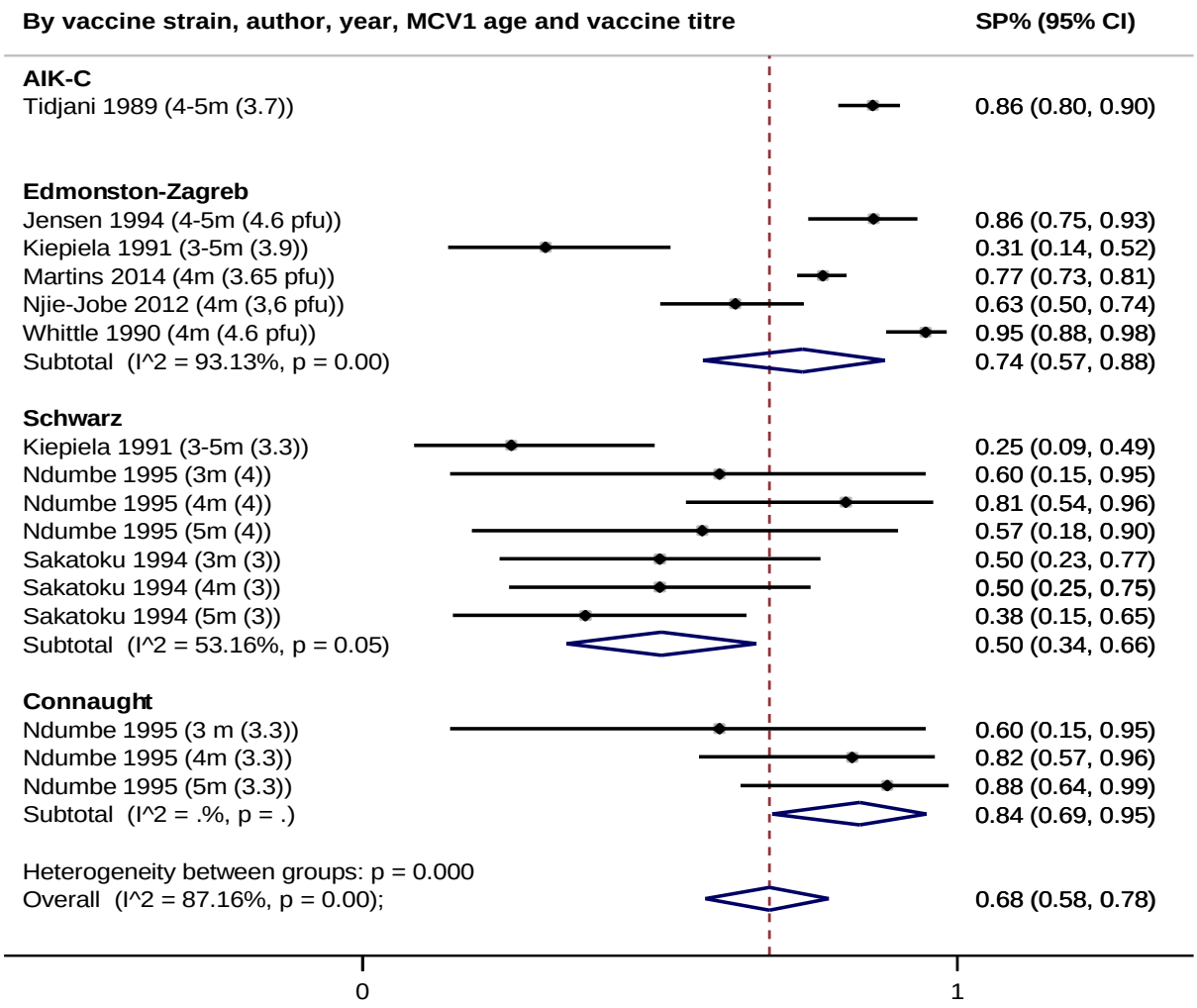

Figure 19: Overall seropositivity following MCV1 below six months

Forest plots for seroconversion by MCV1 age with maternal antibodies

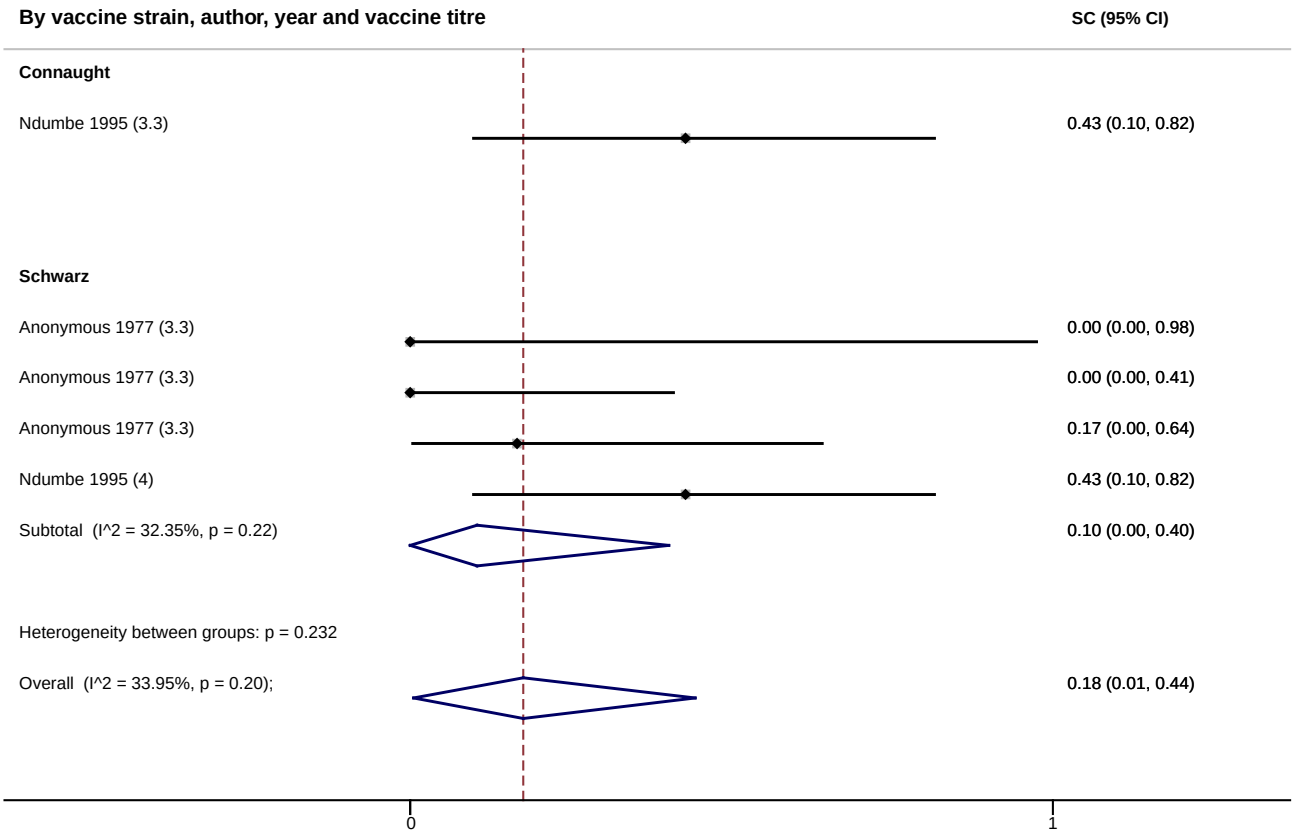

Figure 20: Proportion of seroconverted infants following MCV1 at 4 months with maternal antibodies

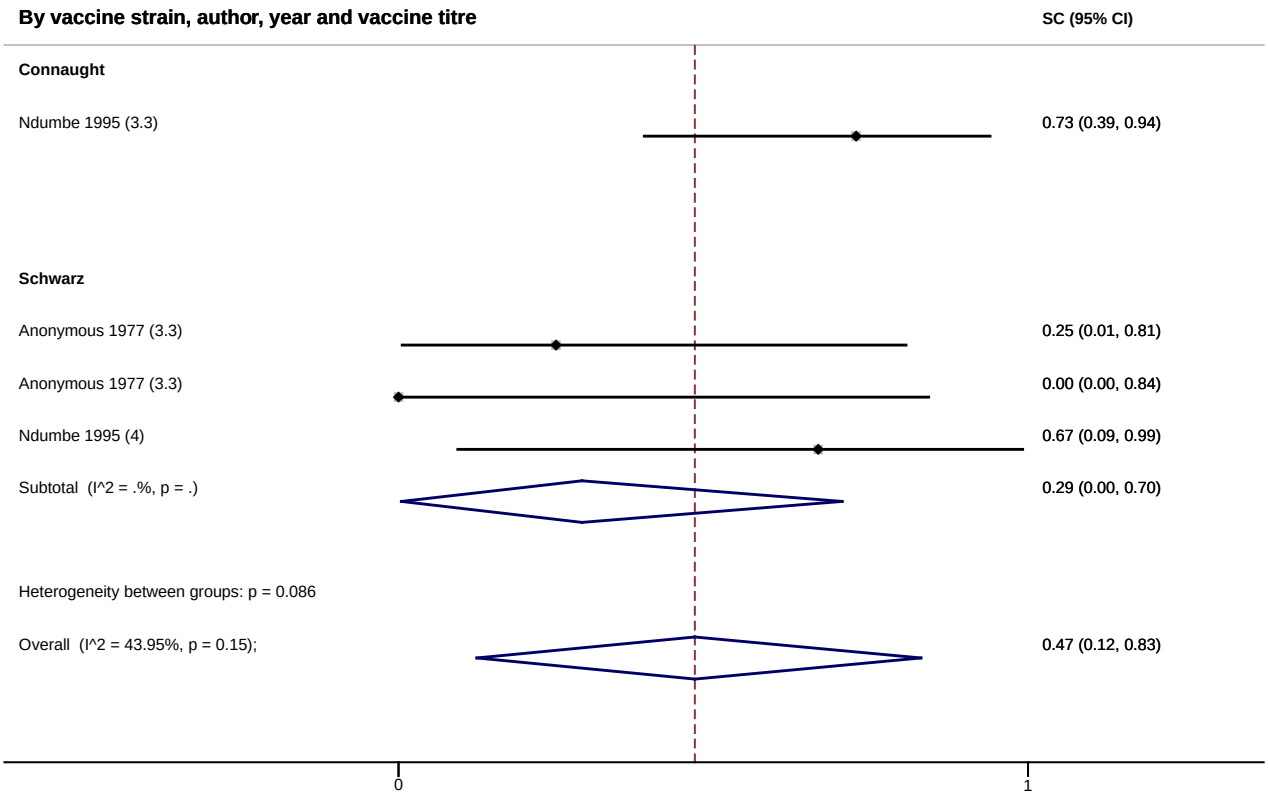

Figure 21: Proportion of seroconverted infants following MCV1 at 5 months with maternal antibodies