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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Schenk J, Abrams S, Theeten H, Damme PV, Beutels P, Hens N. Immunogenicity and persistence of trivalent measles, mumps, and rubella vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2020; published online September 1. https://doi.org/10.1016/S1473-3099(20)30442-4.

Appendix

Schenk *et al*, Immunogenicity and persistence of trivalent measles, mumps and rubella vaccines: a systematic review and meta-analysis

Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8 and appendix 3 p10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2 page 5-9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8 and appendix 3 p10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8 and appendix 5 p12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9 and appendix 5 p12

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9, appendix 12 and 13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table S8, S9-14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	appendix 12 pp 22-24
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10, 12. Fig 2, 3, 4, S7, S12 and S13

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11 and appendix 10 and 11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 appendix 7, 9, 11 and 11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

Appendix 2: Search strategy

We searched the following electronic bibliographic databases: PudMed (incl. MEDLINE), Web of Science and EMBASE. We made use of controlled vocabulary, MeSH (PubMed), EMTREE (Embase) as well as Title/abstract in PubMed. In Web of Science only free-text searching is possible. Articles in English from the earliest dates to October 2018 were considered eligible. Furthermore, an additional manual search was performed by screening the reference lists from reviews and eligible publications to ensure that important publications are not omitted from our systematic review and meta-analysis. For the database Embase, we restricted only to Embase search (excluding MEDLINE) since MEDLINE was already covered by PubMed. The used search terms were related to immunogenicity (primary vaccine failure) and persistence (secondary vaccine failure) of the trivalent MMR vaccine.

The search strategy and results for each database are listed below.

PUBMED (including medline)

First search term: 22/06/2018 and second search term: 25/7/2018

Searching terms: Title/abstract (TA) and controlled vocabulary (SH)

Update

First and second search term until 31/12/2019: 66 and 55 extra hits

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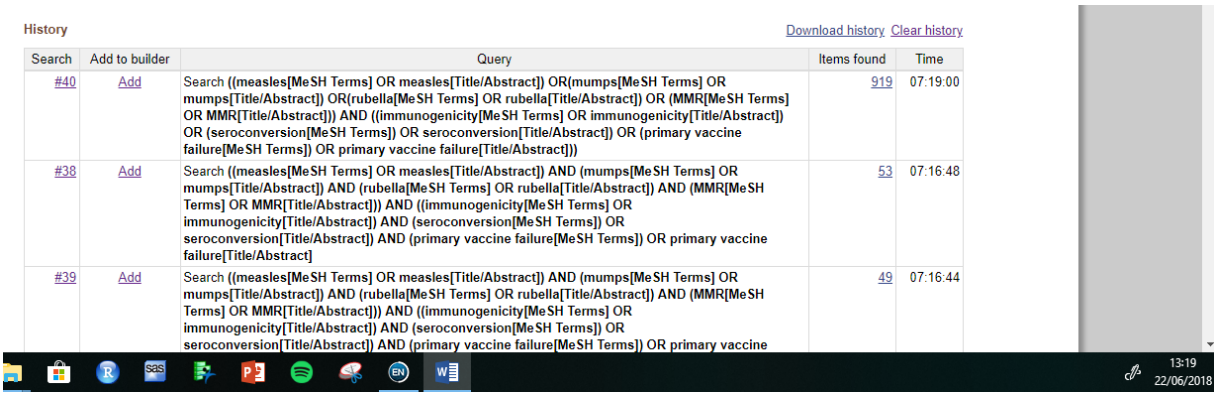
First search term:

1. SH:. (measles OR mumps OR rubella OR MMR) AND (immunogenicity OR seroconversion OR primary vaccine failure)
2. TA. (measles OR mumps OR rubella OR MMR) AND (immunogenicity OR seroconversion OR primary vaccine failure)

Search query:

((measles[MeSH Terms] OR measles[Title/Abstract]) OR(mumps[MeSH Terms] OR mumps[Title/Abstract]) OR(rubella[MeSH Terms] OR rubella[Title/Abstract]) OR (MMR[MeSH Terms] OR MMR[Title/Abstract])) AND ((immunogenicity[MeSH Terms] OR immunogenicity[Title/Abstract]) OR (seroconversion[MeSH Terms]) OR seroconversion[Title/Abstract]) OR (primary vaccine failure[MeSH Terms]) OR primary vaccine failure[Title/Abstract]))

In total 919 articles found (search #40 in picture below)



History

Download history Clear history

Search	Add to builder	Query	Items found	Time
#40	Add	Search ((measles[MeSH Terms] OR measles[Title/Abstract]) OR(mumps[MeSH Terms] OR mumps[Title/Abstract]) OR(rubella[MeSH Terms] OR rubella[Title/Abstract]) OR (MMR[MeSH Terms] OR MMR[Title/Abstract])) AND ((immunogenicity[MeSH Terms] OR immunogenicity[Title/Abstract]) OR (seroconversion[MeSH Terms]) OR seroconversion[Title/Abstract]) OR (primary vaccine failure[MeSH Terms]) OR primary vaccine failure[Title/Abstract]))	919	07:19:00
#38	Add	Search ((measles[MeSH Terms] OR measles[Title/Abstract]) AND (mumps[MeSH Terms] OR mumps[Title/Abstract]) AND (rubella[MeSH Terms] OR rubella[Title/Abstract]) AND (MMR[MeSH Terms] OR MMR[Title/Abstract])) AND ((immunogenicity[MeSH Terms] OR immunogenicity[Title/Abstract]) AND (seroconversion[MeSH Terms]) OR seroconversion[Title/Abstract]) AND (primary vaccine failure[MeSH Terms]) OR primary vaccine failure[Title/Abstract]	53	07:16:48
#39	Add	Search ((measles[MeSH Terms] OR measles[Title/Abstract]) AND (mumps[MeSH Terms] OR mumps[Title/Abstract]) AND (rubella[MeSH Terms] OR rubella[Title/Abstract]) AND (MMR[MeSH Terms] OR MMR[Title/Abstract])) AND ((immunogenicity[MeSH Terms] OR immunogenicity[Title/Abstract]) AND (seroconversion[MeSH Terms]) OR seroconversion[Title/Abstract]) AND (primary vaccine failure[MeSH Terms]) OR primary vaccine	49	07:16:44

13:19
22/06/2018

Figure S1: Details of the search strategy in PubMed for immunogenicity of MMR vaccine.

Second search term:

3. SH:. (measles OR mumps OR rubella OR MMR) AND (persistence OR waning OR immuni* OR secondary vaccine failure)
4. TA. (measles OR mumps OR rubella OR MMR) AND (persistence OR waning OR immuni* OR secondary vaccine failure)

Originally immuni* was in the search query but this gave a lot of hits and was too much to go through with only two reviewers (Search #1 in picture below). Therefore a test run without immuni* was done and we checked whether the articles, found in a previous performed extensive, though not systematic, search from our research team were identified (Abrams et al, 2014)[1]. All were found in the search query without immuni*, except two but those were found in the references from other included articles. Thus, we decided to go further without the search term immuni* which gave 761 hits (Search #2 in picture below).

Search query without immuni*:

((measles[MeSH Terms] OR measles[Title/Abstract]) OR(mumps[MeSH Terms] OR mumps[Title/Abstract]) OR(rubella[MeSH Terms] OR rubella[Title/Abstract]) OR (MMR[MeSH Terms] OR MMR[Title/Abstract])) AND ((persistence [MeSH Terms] OR persistence [Title/Abstract]) OR (waning [MeSH Terms]) OR waning [Title/Abstract]) OR (secondary vaccine failure[MeSH Terms]) OR secondary vaccine failure[Title/Abstract]))

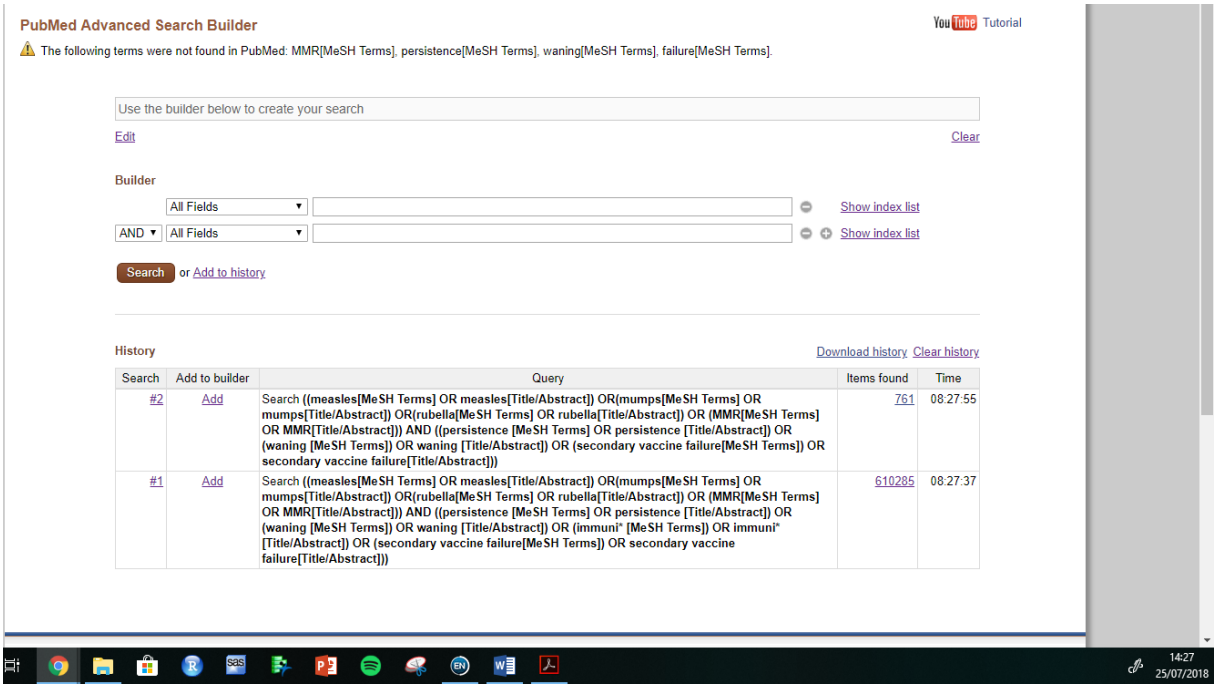


Figure S2: Details of the search strategy in PubMed for persistence of MMR vaccine.

Web of Science

First search term: 13/08/2018 and second search term: 20/8/2018

Searching terms: Search Terms: free text (FT). TI = title and TS = Topic

Update

First and second search term until 31/12/2019: 126 and 120 extra hits

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First search term:

1. FT: TS=(measles OR mumps OR rubella OR MMR) OR TI=(measles OR mumps OR rubella OR MMR)

2. FT: TS=(immunogenicity OR seroconversion OR primary vaccine failure) OR TI=(immunogenicity OR seroconversion OR primary vaccine failure)

This resulted in 847 hits (Result # 4, in picture below)

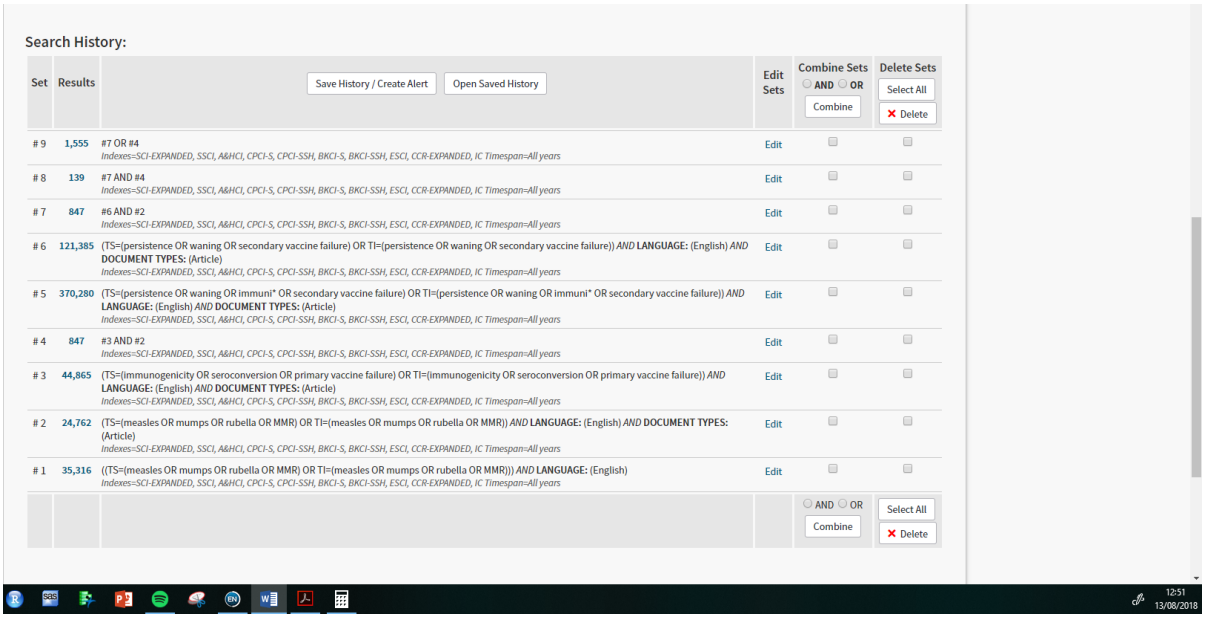

Figure S3: Details of the search strategy in WOS for immunogenicity of MMR vaccine.

Second search term:

1. FT: TS=(measles OR mumps OR rubella OR MMR) OR TI=(measles OR mumps OR rubella OR MMR)
2. FT: TS=(persistence OR waning OR secondary vaccine failure) OR TI=(persistence OR waning OR secondary vaccine failure)

This resulted in 778 hits (Results #3 in picture below)

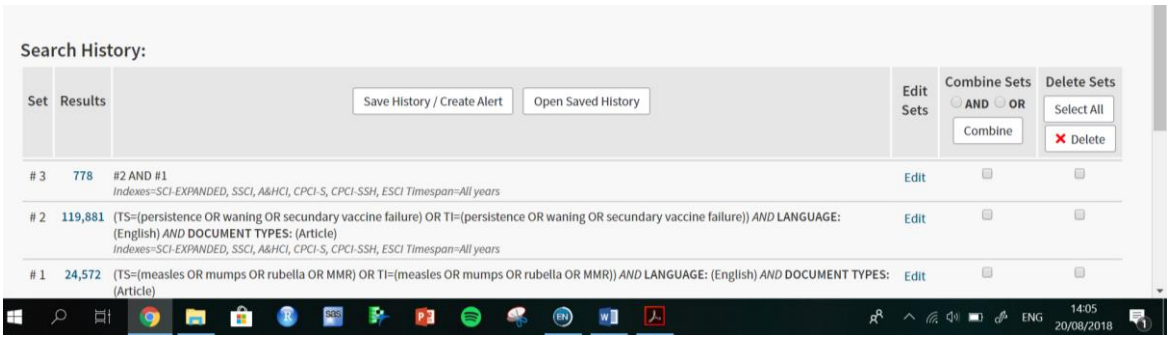

Figure S4: Details of the search strategy in WOS for persistence of MMR vaccine.

Embase

First search term: 2/10/2018 and second search term: 2/10/2018

Searching terms: Search Terms: free text (FT) and controlled vocabulary (SH)

Update

First and second search term until 31/12/2019: 138 and 83 extra hits

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First search term:

1. FT: (measles OR mumps OR rubella OR MMR) AND (immunogenicity OR seroconversion OR primary vaccine failure)
2. SH: (measles OR mumps OR rubella OR MMR) AND (immunogenicity OR seroconversion OR primary vaccine failure)

There was the option to search only in Embase, or including Medline. We choose only Embase, because Medline was already covered in Pudmed. Only humans and English articles were used in the search term to reduce the amount articles.

This resulted in 1460 hits.

Due to bad picture quality, no screenshot is available from the Embase search

Second search term:

1. FT: (measles OR mumps OR rubella OR MMR) AND (persistence OR waning OR secondary vaccine failure)
2. SH: (measles OR mumps OR rubella OR MMR) (persistence OR waning OR secondary vaccine failure)

There was the option to search only in Embase, or including Medline. We choose only Embase, because Medline was already covered in Pudmed. Only humans and English articles were used in the search term to reduce the amount articles.

This resulted in 676 hits. Also due to bad picture quality, no screenshot is available from the Embase search.

Appendix 3: Inclusion and exclusion criteria extended

The reviewers (JS and SA) read the abstract of each identified publication when the total number of potentially eligible publications is less than 2000. Otherwise, the reviewers selected potentially eligible titles first and read thereafter the abstracts of publications with titles that potentially fit the inclusion criteria. The full-text of articles was reviewed in case there was doubt after screening of the title and abstract. The full-text of all eligible articles was read and data was retrieved to perform the meta-analyses.

We excluded cross-sectional serological surveys (as they do not evaluate seroconversion after vaccination or persistence of vaccine-induced humoral immunity with time since an MMR vaccination), outbreak studies and case-reports (as it is not the same type of data that we collected for the waning part). Studies with an unclear description are defined as studies that could potentially be included but for which both researchers (JS and SA) found that the description of the methodology therein was unclear or when studies did not contain useable data were excluded.

"The study is a clinical trial, cohort, longitudinal study" reflects the broad range of studies we wanted to include. With clinical trial we wanted to make it broad, including phase I/II as well as phase III randomized (controlled) trials, but the studies had to have clearly investigated the immunogenicity (seroconversion) of a combined MMR vaccine, either as a single primary goal or as a by-product in the comparison of such trivalent MMR vaccines with quadrivalent formulations including a varicella component, with a combination of mono- and/or bivalent vaccines or with co-administration together with other vaccines. Longitudinal studies are required for the evaluation of the duration (persistence/waning) of humoral protection, i.e., (repeated) measurements (based on collected blood samples) done at different time points in order to evaluate how many individuals were still seropositive at a given time after receiving a dose of the MMR vaccine

More details in PROSPERO protocol. [2]

Appendix 4: Exponential waning rates

The annual waning rate indicates to what extent the seropositivity decreases over time. It is the proportion seropositives at time point t+1 which is a factor $e^{(-waning\ rate)}$ from the proportion seropositives at time point t. Thus $1 - e^{(-waning\ rate * \Delta t)}$ is the chance of seropositivity loss, where Δt is the time (in years) after MMR vaccination.

We used three different methods to estimate the exponential waning rates because not all studies reported the same type of data. More specifically, in some studies repeated measurements on the same individuals were done over time, thereby imposing association in the data which needs to be adequately addressed in the statistical analysis. More details regarding the information we exactly extracted from the eligible studies for waning and which method is used, is displayed in **Tables S12** (p 36)**, S13** (p 38) **and S14** (p40).

All studies evaluated the amount of IgG antibodies, or seropositivity for that matter, after receiving an MMR dose (first or second dose), at different time points. We estimated the exponential waning rate from a model describing (exponential) decay in seropositivity (either generalized linear model or generalized estimating equations). For studies that only provided a single time point at which the number of seropositives was reported, starting from a group of individuals that were all seroconverted, an empirical estimate of the waning rate was calculated as follows:

$$\gamma = -\frac{(1-p)}{t}$$

, where p is the proportion of seropositives at time point t (with time the time after vaccination).

Appendix 5: Methodology meta-analysis

In a fixed effects meta-analysis model, we assume that the only reason why k independent effect size estimates $\hat{\theta}_i$, $i = 1,\ldots,k$, each estimating the (true) effect size θ, deviate from the true value due to sampling error:

$$\widehat{\theta_i} = \theta + e_i$$

$$y_i = \theta_i + e_i$$

where y_i denotes the observed effects, in this case either the seroconversion rates or the retrieved waning rates, in the i-th study, $\theta_i$the corresponding unknown true effect and $e_i$is the sampling error with $e_i \sim N(0, v_i)$. Thus, y_i is assumed to be unbiased and normally distributed estimated of their corresponding true effect. As the effect estimates are proportions in case of estimating seroconversion rates, a bias correction, normalizing, and variance stabilizing transformation is necessary to ensure that these assumptions are at least approximately true. Therefore, we used the Freeman-Tukey double arscine variance-stabilizing transformation[3] which enables calculating an overall proportion from a set of proportions, together with inverse-variance weighting. For waning, the retrieved waning rates were log-transformed.

Due to differences in study methods and sample characteristics, variability or heterogeneity may be introduced among the true effects which can be treated as purely random, forming a meta-analysis random effects model:

$$\theta_i = \mu + u_i,$$

$$y_i = \mu + u_i + e_i,$$

with $u_i \sim N(0, \tau^2)$. It is assumed that the true effects are normally distributed with mean μ and variance τ^2. Here, we used the DerSimonian-Laird estimator for the between-study variability[4,5]. Confidence intervals for the combined effect are constructed using the Knapp and Hartung method (2003)[6], which is an adjustment to the standard errors for taking into account the uncertainty in τ^2. This is performed for both seroconversion and waning rates. We investigated the heterogeneity in the estimated overall seroconversion and waning rates using the I^2 statistic[7].

As secondary analysis, we also subdivided the studies per vaccine strain for measles and mumps in order to estimate the strain-specific seroconversion rates. A subdivision based on method of detection (ELISA or other test) is also carried out in order to see whether it influenced the seroconversion rate of measles, mumps or rubella. We also tested whether MMR dose (MMR1 or MMR2), age of administration (below 1 year, between 1-2 years and above two years) or region affected the seroconversion rate of measles, mumps and rubella. Differences in the amount of heterogeneity are suspected to be present within the different vaccine strains of measles and mumps,

method of detection, MMR dose and age of administration. Theretofore, a single mixed-effect model with strain as fixed effect is fitted for measles, mumps and rubella. The model goes as follows:

$$\theta_i = \beta_0 + \beta_j x_{ij} + u_i,$$

$$y_i = \beta_0 + \beta_j x_{ij} + u_i + e_i,$$

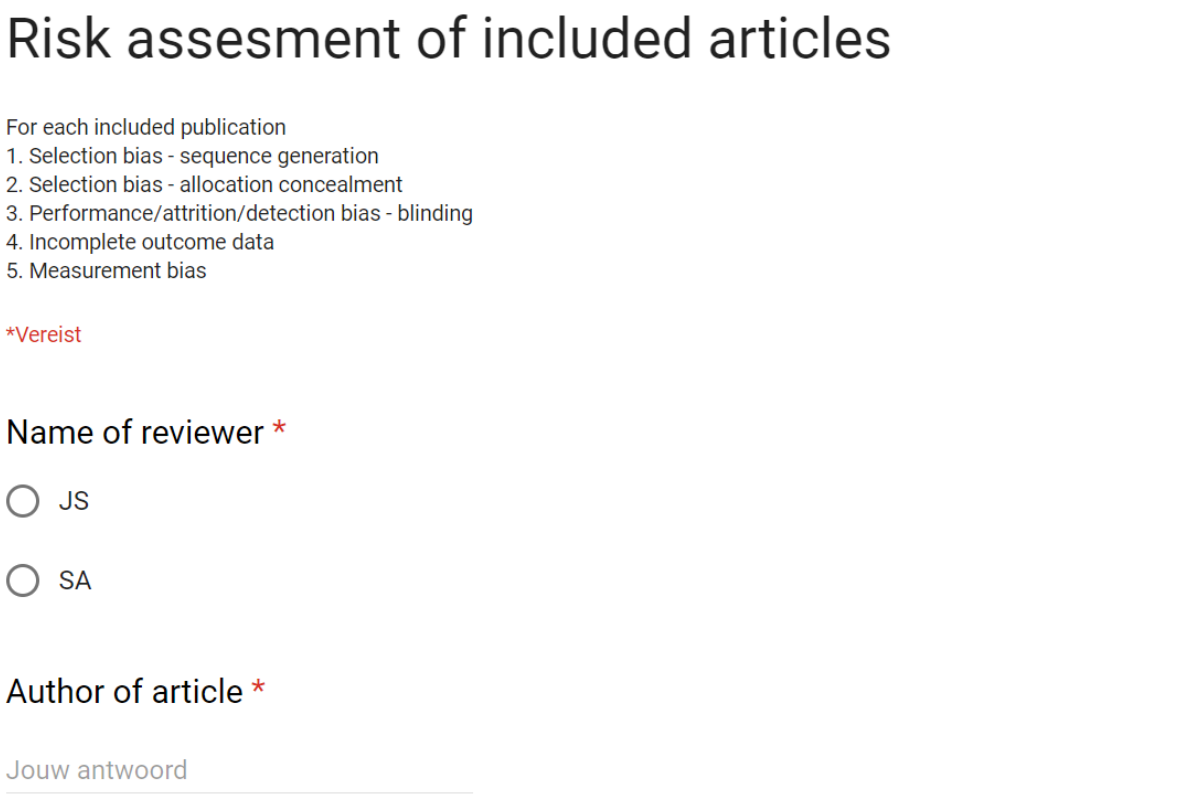
where x_{ij}denotes the value of the j-th moderator, here strain type of measles/ mumps or type of detection method, for the i-th study and $u_i \sim N(0, \tau^2)$. Here, τ^2denotes the amount of residual heterogeneity among the true effects, meaning the variability among the true effects that is not accounted for by the moderators included in the model. We examine here to what extent the moderators included in the model influence the size of the average true effect by using an omnibus test implemented in metafor R package.[8]

Appendix 6: Risk of bias assessment form

We used five domains for risk of bias as specified by Cochrane Risk of Bias Tool to assess the potential sources for risk of bias[9]

1. Selection bias – sequence generation
2. Selection bias – allocation concealment
3. Attribution/performance/detection – blinding of all outcomes
4. Attribution bias – incomplete data
5. Measurement bias – Clear description of quantification method and cut-off values

The category "not applicable" was added to the risk of bias assessment because not all questions were applicable for all studies.



Risk assesment of included articles

For each included publication
1. Selection bias - sequence generation
2. Selection bias - allocation concealment
3. Performance/attrition/detection bias - blinding
4. Incomplete outcome data
5. Measurement bias

*Vereist

Name of reviewer *

JS

SA

Author of article *

Jouw antwoord

Title of article *

Jouw antwoord

Year of publication *

Jouw antwoord

Article concerning seroconverion or waning or MMR vaccine? *

- ◯ Seroconversion
- ◯ Waning

Risk of bias in words

Brief summary of:
1. Selection bias - sequence generation
2. Selection bias - allocation concealment
3. Performance/attrition/detection bias - blinding
4. Incomplete outcome data
5. Measurement bias: clear description of test used with cut-offs values.

Catogorize into high, low and unclear

Selection bias - sequence generation. Did the study used a randomized sequence of assigments?

Jouw antwoord

Selection bias - allocation concealment. Was there stricted implementation of an allocation sequence without foreknownlegde of intervention assigments?

Jouw antwoord

Performance/attrition/detection bias - blinding. Blinding of all outcomes?

Jouw antwoord

Incomplete outcome data?

Jouw antwoord

Measurement bias. Clear description of quantificiation method used and cut-off values?

Jouw antwoord

Summarized into high, low and unclear risk of bias *

	No - High risk of bias	Yes - Low risk of bias	Unclear	Not applicable
Selection bias: adequate sequence generation? Did the study used a randomized sequence of assigments?	○	○	○	○
Selection bias: allocation concealment. Was there stricted implementation of an allocation sequence without foreknownlegde of intervention assigments?	○	○	○	○
Blinding?	○	○	○	○
Incomplete outcome data addressed?	○	○	○	○
Measurement bias	○	○	○	○

Appendix 7: Seroconversion rates per dose and per age

We tested whether the seroconversion rates after first and second MMR dose for measles, mumps and rubella were differ or not; and whether it depended on age of administration. Stratified by strain, studies investigated 51 of 69 seroconversion after the first MMR dose for measles, for mumps 46 of 62, leaving out Rubini strain, and 50 of 66. It was unclear from two studies which dose it investigated. Three studies[10-12] concerning seroconversion after a second MMR dose did not take into account the pre-vaccination serostatus of the participants ,or it was not clear, thus were excluded from further meta-analysis. The meta-analysis estimates per MMR dose are displayed in **table S1**.

The age of administration ranges from 8 months to 44 years, a subdivision is made of age below 1, between 1 and 2 years; and above 2 years. The meta-analysis estimates for seroconversion per age and sample size (leaving out Rubini) in each group (below 1, between 1-2 and above 2 years) are displayed in **table S2**. There is no significant difference between the seroconversion rate per age group for measles, mumps and rubella (p= 0·379, 0·467 and 0·453, respectively)

We did not perform a subgroup analysis regarding the effect of age at vaccination on waning due to limited studies available.

Table S1: Overall seroconversion rates for measles, mumps and rubella per dose, stratified by strain, with 95% confidence interval.

	MMR1 (95% CI)	MMR2 (95% CI)
Measles	96·2 (94·3-98·6)	95·5 (91·2-98·7)
Mumps	93·1 (90·1-95·2)	94·7 (89·5-98·9)
Rubella	98·7 (97·6-99·5)	96·1 (91·6-99·1)

Table S2: Overall seroconversion rates for measles, mumps and rubella per age, stratified by strain, with 95% confidence interval and sample size per age group.

	Below 1 year (95% CI), N	Between 1 – 2 years (95% CI), N	Above 2 years (95% CI), N
Measles	91·5 (82·5-97·4), 4	96·1 (94·4-97·6), 52	96·6 (93·4-98·9), 17
Mumps	96·6 (90·0-99·0), 5	92·9 (90·5-95·1), 46	94·9 (90·5-95·6), 14
Rubella	97·3 (89·9-99·7), 5	98·3 (97·0-99·3), 50	96·49 (93·5-99·2), 15

Appendix 8: Seroconversion rates per different strain

Different strains for measles, mumps and rubella are used in the different MMR vaccines available on the market. Therefore, we performed a meta-analysis subgrouping the studies based on the measles and mumps strain types, but not for the rubella component as the majority of the studies used RA 27/3 (see appendix pp 11-12 for details).

The eligible studies for seroconversion included the Schwarz strain (used 27 times), Edmonston-Enders (19 times), Edmonston-Zagreb (16 times) and further seven measles strains. The seroconversion estimates per measles strain are displayed in **figure S9** (p 42). However, differences between measles strains were not significant ($p = 0{\cdot}602$).

Of the various attenuated mumps strains developed over the years the majority of the studies used the Jeryl Lynn mumps strain (23 times), followed by RIT 4385, derived from Jeryl Lynn (17 times), Urabe Am 9 (7 times), Leningrad-Zagreb (6 times), Rubini (5 times) Hoshino (4 times) and other four mumps strains. The rubella component in the majority of the MMR vaccines is the Wistar RA 27/3 strain in 58 studies while eight studies used other strains such as Cendehill, Takashi and BDRII. The seroconversion estimates per mumps strain are displayed in the main text (**figure 3**). Significant differences exist between mumps strains ($p< 0{\cdot}0001$), mainly due to Rubini. After excluding Rubini, the difference did not persist ($p = 0{\cdot}664$).

We did not perform a subgroup analysis to study differences in waning rates for the different strains as most of the eligible studies, except for two publications, used vaccines with the same measles and mumps strains.

Appendix 9: Different estimators for τ^2

Several estimators for the between-study variance component have been proposed whereof the DerSimonian and Laird (1986)[5] (DL) method is the most commonly implemented approach and default in many software programs. Veronike et al (2016)[13] have done a comprehensive overview of the different methods used for estimating the between-study variance and uncertainty. Here, we compared different estimators (DL, ML and REML) for the between-study variance (**tables S3 and S4**). Details for each estimator are described by Veronike and colleagues (2016)[13]. We found no substantial differences between the seroconversion rates and waning rates using different estimators for τ^2.

Table S3: Overall seroconversion rates for measles, mumps and rubella using different estimators for between-study variance, with 95% confidence interval.

	DL (95% CI)	ML (95% CI)	REML (95% CI)
Measles	96·0 (94·5-97·4)	96·0 (94·5-97·4)	96·0 (94·5-97·4)
Mumps	93·3 (91·1-95·2)	93·3 (91·2-95·2)	93·3 (91·2-95·2)
Rubella	98·3 (97·3-99·2)	98·4 (97·2-99·2)	98·4 (97·2-99·2)

Table S4: Overall waning rates for measles, mumps and rubella using different estimators for between-study variance, with 95% confidence interval.

	Estimator for τ^2	Dose 1 (95% CI)	Dose 2 (95% CI)	Overall (95% CI)
Measles	DL	0·008 (0·002-0·024)	0·009 (0·003-0·021)	0·009 (0·005-0·016)
	ML	0·007 (0·002-0·023)	0·009 (0·004-0·021)	0·007 (0·004-0·015)
	REML	0·007 (0·002-0·023)	0·009 (0·004-0·021)	0·008 (0·003-0·015)
Mumps	DL	0·039 (0·028-0·056)	0·016 (0·008-0·031)	0·024 (0·016-0·039)
	ML	0·039 (0·028-0·056)	0·016 (0·008-0·031)	0·024 (0·016-0·039)
	REML	0·039 (0·028-0·056)	0·015 (0·008-0·031)	0·024 (0·016-0·038)
Rubella	DL	0·014 (0·012-0·017)	0·010 (0·009-0·012)	0·012 (0·010-0·014)
	ML	0·014 (0·012-0·17)	0·010 (0·008-0·12)	0·012 (0·010-0·014)
	REML	0·014 (0·012-0·18)	0·010 (0·008-0·12)	0·012 (0·010-0·014)

Appendix 10: Seroconversion per test of detection

We tested whether the serological test used influences the seroconversion rate using a single mixed model with type of test as a covariate (see appendix pp 11-12 for details). We subdivided the test into ELISA and other tests because of the small sample size for the latter, ELISA being used to detect IgG antibody for measles 49 of 65 cases, for mumps 47 of 58, leaving out Rubini, cases and for rubella 45 of 62 cases. No significant difference between ELISA or other serological test was found for mumps (p=0·138) rubella (0·742). We found a significant difference for measles (p = 0·043). The overall seroconversion rates per test for measles, mumps and rubella are displayed in **table S5.**

Table S5: Overall seroconversion rates for measles, mumps and rubella, stratified per strain, subdividing by method of detection using a single fixed model, with 95% confidence interval.

	ELISA (95% CI)	**Other (95% CI)**
Measles	96·8 (95·2-98·2)	93·2 (89·4-96·3)
Mumps	94·1 (91·7-95·9)	89·7 (83·2-94·8)
Rubella	98·3 (96·9-99·3)	98·6 (96·3-99·5)

Appendix 11: Seroconversion and persistence per region

We tested whether the region where the study was done, influences the seroconversion rate using a single mixed model with region as covariate (see appendix pp 11-12 for details). The meta-analysis estimates for seroconversion rates per region and sample size for measles, mumps (leaving out Rubini) and rubella (taking all strain together and; MMR1 and MMR2) are displayed in **table S6**. There is no significant difference between the seroconversion rate per age region for measles, mumps and rubella (p= 0·899, 0·554 and 0·437, respectively).

We did not perform a subgroup analysis to study differences in waning rates for the different regions as most of them were conducted in Europe and a few in North America; and due to limited studies available.

Table S6: Overall seroconversion rates for measles, mumps and rubella per region using a single fixed model, with 95% confidence interval and sample size per region (N).

	Europa (95% CI), N	**Asia (95% CI), N**	**The Americas (95% CI), N**	**More than one region + Australia (95% CI), N**
Measles	95·7 (91·7-98·6), 14	95·1 (91·1-97·9), 17	95·5 (91·1-98·6), 12	97·5 (90·4-100·0), 4
Mumps	94·5 (90·4-97·6), 15	93·0 (88·5-96·6), 16	91·5 (85·4-96·2), 10	97·1 (89·5-100·0), 4
Rubella	98·7 (96·8-99·8), 15	97·6 (95·3-99·3), 16	96·9 (93·7-99·1), 10	99·8 (96·3-100·0), 4

Appendix 12: Risk of bias assessment

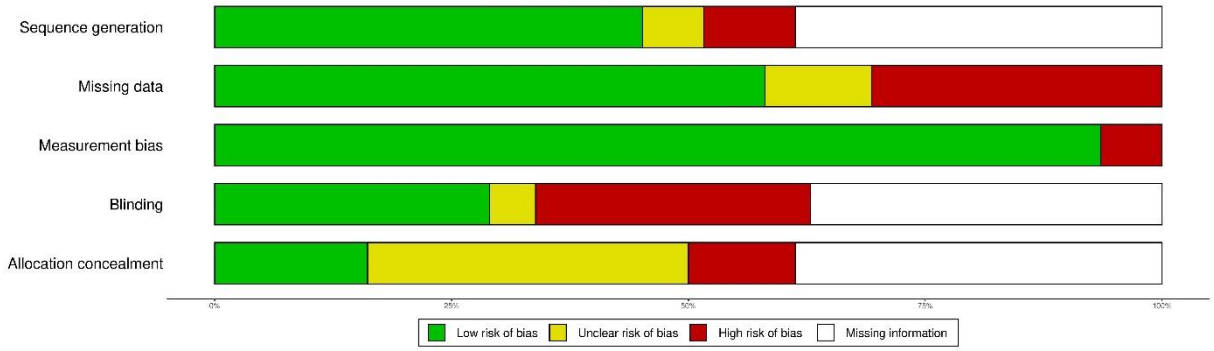


Figure S5: Risk of assessment. The proportion of all studies (n= 62) categorized to have high (red), low (green), unclear (yellow) risk of bias or not applicable (white) is plotted for each of the 5 categories: measurement bias, incomplete outcome data, blinding, allocation concealment and sequence generation based on the Higgens et al (2008)[9] risk assessment guideline.

Table S7: Individual risk of bias assessment. Red – High risk; Yellow – Unclear; Green – Low risk; blue – not applicable (NA).

Author	Sequence generation	Allocation concealment	Blinding	Missing data	Measurement bias
dos Santos et al (2019)[21]	Low	Low	Low	High	Low
Nakayama et al (2019)[22]	Low	Low	High	High	Low
The MMR-158 study group (2019)[20]	Low	Unclear	Low	High	Low
Carryn et al (2019)[68]	Low	Unclear	Low	Unclear	Low
Abu-Elyazeed et al (2018)[10]	Low	Low	Low	Low	Low
Bavdekar et al (2018)[24]	Low	Low	Low	Low	Low
Joshi et al (2018)[23]	Low	High	High	Low	Low
Sood et al (2017)[25]	Low	Low	High	Low	Low
Wiedmann et al (2015)[26]	Low	Unclear	Low	Low	Low
Diaz-Ortega et al (2014)[11]	Low	Unclear	Low	Low	Low
He et al (2014)[27]	Low	Low	High	Low	Low
Prymula et al (2014)[28]	Low	Low	Low	Low	Low
Tabatabaei et al (2013)[29]	NA	NA	NA	Low	High
Poethko-Müller et al (2012)[18]	NA	NA	NA	Low	Low
Lee et al (2011)[31]	High	High	High	Low	Low
Rumke et al (2011)[33]	Low	High	High	Low	Low
Saffar et al (2011)[30]	NA	NA	NA	High	Low

Diaz Ortega et al (2010)[34]	Low	Unclear	Unclear	Unclear	Low
Gomber et al (2010)[32]	NA	NA	NA	High	Low
LeBaron et al (2009a)[69]	NA	NA	NA	Low	Low
LeBaron et al (2009b)[70]	NA	NA	NA	Low	Low
Davidkin et al (2008)[19]	NA	NA	NA	High	Low
Khalil et al (2008)[35]	NA	NA	NA	High	Low
LeBaron et al (2007)[71]	NA	NA	NA	Low	Low
Lim et al (2007)[37]	NA	NA	NA	Low	Low
dos Santos et al (2006)[38]	Low	Unclear	Low	Low	Low
Feiterna-Sperling et al (2005)[39]	Low	Unclear	High	Low	Low
Kremer et al (2005)[72]	NA	NA	NA	Low	Low
Redd et al (2004)[40]	Low	Low	Low	Low	High
Yadav et al (2003)[41]	NA	NA	NA	High	Low
Lee et al (2002)[42]	Unclear	Unclear	High	Low	Low
Nolan et al (2002)[44]	Low	Unclear	High	Unclear	Low
Stuck et al (2002)[43]	Low	Unclear	High	Low	Low
208136/007 (2001)[47]	Low	Unclear	Unclear	Unclear	Low
208136/016 (2001)[48]	Low	Unclear	High	Unclear	Low
Ceyhan et al (2001)[45]	High	Unclear	High	High	Low
Gothefors et al (2001)[46]	Low	Unclear	High	Low	Low
Crovari et al (2000)[50]	High	Unclear	Low	High	Low
Klinge et al (2000)[49]	NA	NA	NA	High	Low
Gatchalian et al (1999)[52]	High	Unclear	High	High	Low
Khalil et al (1999)[51]	Low	Low	High	Unclear	Low
Broliden et al (1998a)[73]	NA	NA	NA	Low	Low
Broliden et al (1998b)[74]	NA	NA	NA	Low	Low
Mitchell et al (1998)[54]	NA	NA	NA	High	Low
Schwarzer et al (1998)[55]	Low	High	High	High	Low
Usonis et al (1998)[53]	Low	High	Low	Low	Low
Forleo-Neto et al (1997)[56]	NA	NA	NA	High	Low
Mitchell et al (1996)[12]	NA	NA	NA	High	Low
Bhargava et al (1995)[57]	NA	NA	NA	Low	Low
Boulianne et al (1995)[17]	NA	NA	NA	Low	Low
Davidkin et al (1995)[75]	NA	NA	NA	Low	Low
Miller et al (1995)[76]	NA	NA	Low	Low	Low
Cohn et al (1994)[58]	Unclear	Unclear	Low	High	Low
Edees et al (1991)[59]	Low	Unclear	Low	Low	Low
Dunlop et al (1989)[60]	High	High	High	Low	High

Robertson et al (1988)[61]	High	High	High	Unclear	Low
Böttiger et al (1987)[62]	NA	NA	NA	Low	Low
Christenson et al (1983)[63]	Unclear	Unclear	Unclear	Low	Low
Isozakiet et al (1982)[64]	NA	NA	NA	Low	Low
Lerman et al (1981)[65]	Low	Unclear	Low	High	Low
Bloom et al (1975)[67]	Unclear	Low	Low	High	Low
Ehrenkranz et al (1975)[66]	Low	Unclear	Low	Low	Low

Appendix 13: Publication bias

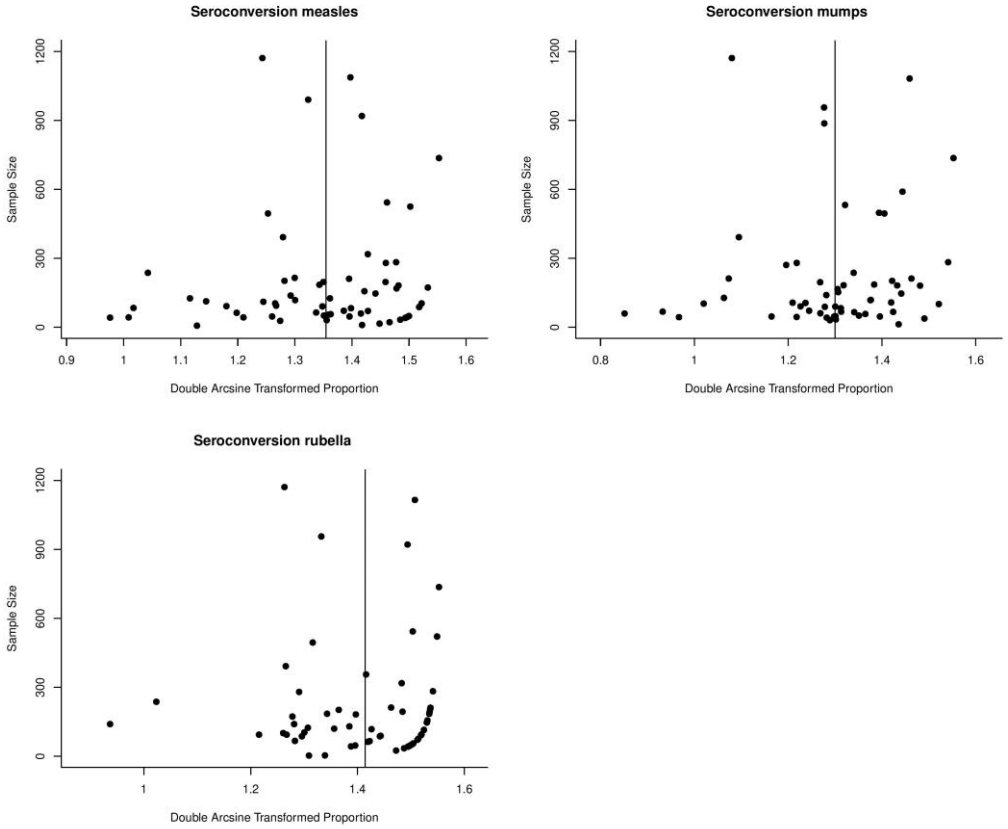


Figure S6: Funnel plot. Funnel plots of the double arscine transformed proportion versus the sample size for the respective proportion for seroconversion rates of measles, mumps (leaving out Rubini) and rubella.

When combining proportions, it is recommend to plot the study size versus the logit transformed proportions.[14] The funnel plot in Figure S6 shows that there is asymmetry for seroconversion rate for measles, mumps and rubella as the dots are not symmetrically distributed on both sides of the combined effect line. However, when publication bias was tested in a formal way, using the test developed by Peters and collogues (2006)[15] , we found no publication bias for seroconversion of measles (p=0·580), mumps (0·274) and rubella (0·861).

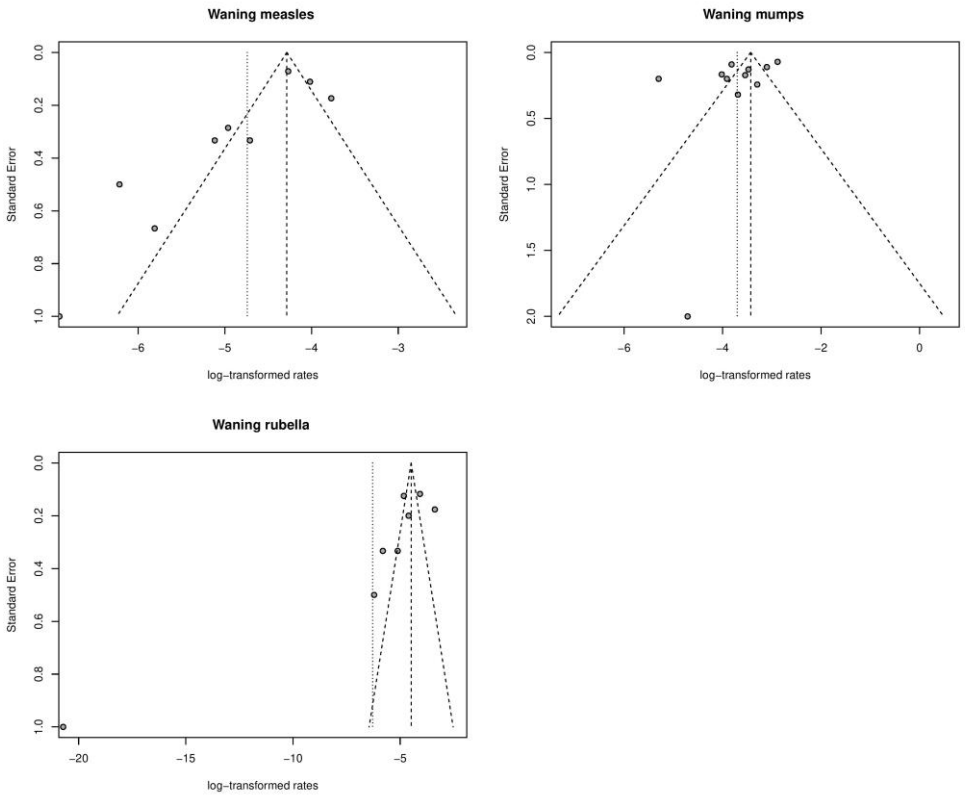


Figure S7: Funnel plot. Funnel plots of the log-transformed rates versus standard error for the respective rates for waning rates of measles, mumps and rubella.

The funnel plots for persistence studies for measles, mumps and rubella are displayed in Figure S7. The funnel plots for waning show asymmetry especially for measles and rubella. Publication bias is formally tested by the Egger's test[16]. Indeed, publication bias exist for the persistence studies concerning the measles component (p=0·013), even when excluding studies with large sample size (p=0·033). This was done merely to check whether these studies and the results therein altered the meta-analytic results/estimates drastically which it did not. There were more studies published demonstrating a low waning rate compared to studies that demonstrated a high waning rate. [17,18]

There is a gap between the persistence studies concerning the rubella component (Figure S7 lower left panel). This asymmetry is mainly due to one study[19] where there were no seronegative individuals for the rubella component after 20 years after second MMR dose but no publication exist for the persistence studies concerning the rubella component (p=0·056).

The funnel plot for the persistence of the mumps component shows asymmetry duo to two studies[68,69] that have smaller waning rate compared to the others but when testing formally, no publication bias exist for the persistence studies concerning mumps (p=0·187).

Appendix 14: Supplementary tables

Table S8: Characteristics of included studies. Study concerning seroconversion or waning (sero/waning), average age at immunisation (Age), the administered vaccine (Vaccine), timepoints after vaccination at which blood samples are drawn (Time), type of study (Study design), country where study took place (Country). CT: clinical trial, RCT: randomised controlled trial, PC: prospective study, F: follow up study, R: review, RT: randomised trial.

	Sero or waning	Age	Vaccine	Route off Administratior	Time	Study design	Country
MMR-158 study group (2019)[20]	sero	4-6 yrs	MMR II (Merck) / Priorix	s.c.	42 d	RCT	US, South Korea, Taiwan
dos Santos et al (2019)[21]	sero	12-19 mon	Priorix / NA	s.c.	42-60 d	RT	Brazil
Nakayama et al (2019)[22]	sero	12-14 mon	JCV-001	s.c.	NA	RCT	Japan
Joshi et al (2018)[23]	sero	15-18 mon	Cadila MMR	s.c.	42 d	CT	US
Bavdekar et al (2018)[24]	sero	15-18 mon	MMR (SIIPL)	DSJI / N-S	35 d	RT	India
Abu-Elyazeed et al (2018)[10]	sero	≥ 7 yrs	Priorix / MMR-II (Merck)	NA	42 d	RCT	US
Sood et al (2017)[25]	sero	15-18 mon	Cadila / Serum MMR (Serum Institute of India, Pune)	s.c.	42 d	RT	India
Wiedmann et al (2015)[26]	sero	11 to 19 mon	MMRII /(r)HA (Merck)	s.c.	6 wks	CT	US
He et al (2014)[27]	sero	8/12 mon	NA	s.c.	30-35 d	CT	China
Diaz-ortega et al (2014)[11]	sero	6-7 yrs	Serum MMR / MMR-II (Merck)	NA	4 wks	CT	Mexico
Prymnula et al (2014)[28]	sero	12-22 mon	Priorix	s.c.	42 d	RCT	Europa
Tababtabaei et al (2013)[29]	sero	12-15 mon	MMR (Razi Institute)	NA	4-7 wks	PC	Iran
Saffar et al (2011)[30]	sero	1.5/4-6 yrs	MMR (Razi Institute)	NA	4-6 wks	PC	Iran
Lee et al (2011)[31]	sero	12-23 mon	Priorix / MMR-II (Merck)	NA	5-8 wks	CT	Korea
Gomber et al (2011)[32]	sero	4-6 yrs	Tresivac	s.c.	4-6 wks	PC	India
Rumke et al (2011)[33]	sero	11-13 mon	NA	s.c.	6 wks	RT	Germany, Belgium, Netherlands
Diaz-ortega et al (2010)[34]	sero	18-25 yrs	Triviraten/MMR-II (Merck)	Aerosol / s.c.	2 mon, 1 yr	RCT	Mexico

Khalil et al (2008)[35]	sero	12 mon	NA	NA	1 mon	F	Saudi Arabia
Lim et al (2007)[37]	sero	12-18 mon	Priorix	s.c.	42 d	CT	Singapore
Dos Santos et al (2006)[38]	sero	7-12 yrs	Tresivac / MMR-II (Merck) / Trimovax	s.c.	21-30 d	RT	Brazil
Feiterna-Sperling et al (2005)[39]	sero	12-24 mon	MMR Berna / MMR-Vax	i.m.	6-8 wks	RT	Germany
Redd et al (2004)[40]	sero	9/12/15 mon	MMR-II (Merck)	NA	24 mon	PC	US
Yavad et al (2003)[41]	sero	9-10/15-18 mon	Serum MMR (Serum Institute of India, Pune)	s.c.	6-8 wks	PC	India
Lee et al (2002)[42]	sero	12-18 mon	Priorix / MMR-II (Merck)	s.c.	40-63 ds	CT	Taiwan
Stuck et al (2002)[43]	sero	12-24 mon	Priorix / MMR-II (Merck) / Triviraten	s.c.	60 d	RCT	Germany
Nolan et al (2002)[44]	sero	12 mon	Priorix	NA	60 d	RCT	Australia
Ceyhan et al, (2001)[45]	sero	12 mon	Trimovax	s.c.	6 wks	PC	Turkey
Gothefors et al (2001)[46]	sero	11-12 yrs	SB MMR (priorix) / MMR-II (Merck)	NA	39-63 d	RT	Sweden
208136/016, (2001)[47]	sero	12-24 mon	Priorix	s.c.	42 d	RCT	Belgium & Australia
208136/007, (2001)[48]	sero	12-24 mon	Priorix	s.c.	42 d	RCT	Australia & Canada & Italy & Colombia & Mexico
Klinge et al (2000)[49]	sero	9-17 mon	MMR-Vax	i.m. / s.c.	4-6 wks	PC	Germany
Crovari et al (2000)[50]	sero	12-27 mon	Priorix / Triviraten	s.c.	60 d	RT	Italy
Khalil et al (1999)[51]	sero	12 mon	Triviraten/ MMR-II (Merck)	s.c.	8 wks	CT	Saudi Arabia
Gatchalian et al (1999)[52]	sero	12-24 mon	SB MMR (priorix) / MMR-II (Merck)	s.c.	40-63 d	RT	Philippines
Usonis et al (1999)[53]	sero	12-24 mon	Priorix / MMR-II (Merck)	s.c.	42 d	CT	Lithuania
Mitchell et al (1998)[54]	sero	12-24 mon	MMR-II (Merck)	NA	1/3/12 mon	PC	Canada
Schwarzer et al (1998)[55]	sero	12-24 mon	Triviraten / MMR-Vax	s.c.	6-9 wks	RT	Germany
Forleo-Neto et al (1997)[56]	sero	9/15 mon	Trimovax	s.c.	6 wks	PC	Brazil
Mitchell et al (1996)[12]	sero	17-44 yrs	MMR-II (Merck)	NA	1 mon	PC	Canada
Bhargava et al (1995)[57]	sero	15-24 mon	NA	NA	4 wks	F	India
Cohn et al (1994)[58]	sero	10-30 yrs	MMR-II (Merck)	NA	8 wks	PC	US
Edees et al (1991)[59]	sero	13-15 mon	Trimovax	NA	6 wks	C	UK
Dunlop et al (1989)[60]	sero	15 mon	Trimovax	s.c.	6 wks	CT	UK
Robertson et al (1988)[61]	sero	13 mon	NA	NA	6 wks s	CT	UK

Bottiger et al (1987)[62]	sero	18 mon/ 12 yrs	MMR-II (Merck)	NA	NA	PC	Sweden
Christenson et al (1983)[63]	sero	18 mon	NA	NA	2 mon & 1 yr	CT	Sweden
Isozaki et al (1982)[64]	sero	1-5 yrs	NA	NA	6 wks	C	Japan
Lerman et al (1981)[65]	sero	15 mon - 4 yrs	MMR-II (Merck)	s.c.	6 wks	RCT	US
Ehrenkranz et al (1975)[66]	sero	1-7 yrs	NA	s.c.	8 wks	RCT	Dominican Republic
Bloom et al (1975)[67]	sero	1-4 yrs	NA	s.c.	NA	RT	US
Carryn et al (2019)[68]	waning	12-22 mon	Priorix	s.c.	1,2,4,6,8,10 yrs	F	12 countries in Europe
Poethko-Muller et al (2012)[18]	waning	0-17 yrs	NA	NA	0-2/ 3-6/ > 6 yrs	F	Germany
LeBaron et al (2009a)[69]	waning	4-15 yrs	MMR-II (Merck)	NA	1-6 mon & 2,5,7,10,12 yrs	F	US
LeBaron et al (2009b)[70]	waning	4-15 yrs	MMR-II (Merck)	NA	1-6 months & 2,5,7,10,12 yrs	F	US
Davidkin et al (2008)[19]	waning	14-18 mon / 6 yrs	MMR-II (Merck)	NA	1/8/15 yrs	F	Finland
LeBaron et al (2007)[71]	waning	4-15 yrs	MMR-II (Merck)	NA	1-6 mon & 2,5,7,10,12 yrs	F	US
Kremer et al (2006)[72]	waning	12 yrs	Pluserix / MMR-II (Merck)	NA	2/9 & 10/17 yrs	F	Luxembourg
Broliden et al (1998a)[73]	waning	12 yrs	MMR-II (Merck)	NA	NA	F	Sweden
Broliden et al (1998b)[74]	waning	12 yrs	MMR-II (Merck)	NA	NA	F	Sweden
Bouilianne et al (1995)[17]	waning	12-24 mon	MMR-II (Merck) / Trivirix	NA	6-7 yrs	RT	Canada
Davidkin et al (1995)[75]	waning	14-18 mon / 6 yrs	MMR-II (Merck)	NA	3 mon & 1-6, 9 yrs	F	Finland
Miller et al (1995)[76]	waning	12-18 mon	MMR-II(Merck)/ Pluserix / Immravax	NA	4 yrs	F	UK

Sero or waning, study concerned seroconversion or waning; Age, average age at immunisation; Vaccine, administered vaccine; Route of administration, s.c. subcutaneous, i.m. intramuscular, DSJI/N-S disposable syringe jet injector versus needle-syringe; Time, timepoint(s) after vaccination when blood was drawn; Study design, CT: clinical trial, RCT: randomised controlled trial, PC: prospective study, F: follow up study, R: review, RT: randomised trial, Country, country(ies) where study took place. wks, weeks; mon, months; yrs, years.

Table S9: Characteristics of included seroconversion studies for measles component. Number of subjects involved in the study (N) together with number of positives (n), the measles strain used (Strain), the test used to quantify the antibody titre levels (Test), and cut-off based on which individuals are classified to be seropositive (Sero+), and dose of MMR (MMR dose). EZ, Edmonston-Zagreb; EE, Edmonston-Enders; S, Schwarz; O, Others; NT: neutralisation test; HI: hemoagglutination inhibition test; SN: serum neutralisation; IFA: immunofluorescent assay. Note that the number of strains is higher than the number of eligible studies because some studies considered more than one MMR vaccine.

	N	n	Strain	Test	Sero+	MMR dose
MMR-158 study group (2019)*[20]	1019	1017	S/O	ELISA	≥ 200 mIU/ml	MMR2
dos Santos et al (2019)[21]	1563	1410	S/NA	ELISA	≥ 321 mIU/ml	MMR1
Nakayama et al (2019)[22]	49	49	O	NT	titre ≥ 1:4	MMR1
Joshi et al (2018)[23]	22	22	EZ	ELISA	200 mIU/ml	MMR1
Bavdekar et al (2018)[24]	111	105	EZ	ELISA	≥ 1·10 ISR	MMR1
Abu-Elyazeed et al (2018)**[10]	869	861	S/EE	ELISA	≥ 200 mIU/ml	MMR2
Sood et al (2017)[25]	87	87	EZ	ELISA	200mUI/ml	MMR1
Wiedmann et al (2015)[26]	1087	1055	EE	ELISA	≥ 255 mIU/ml	MMR1
He et al (2014)[27]	280	277	Hu 191	ELISA	≥ 200 mIU/ml	MMR1
Diaz-ortega et al (2014)**[11]	253	253	S/EZ	PRN	≥ 120 mIU/ml	MMR2
Prymnula et al (2014)[28]	919	898	S	ELISA	NA	MMR1
Tababtabaei et al (2013)[29]	237	177	O	ELISA	NA	MMR1
Saffar et al (2011)[30]	113	94	O	ELISA	≥ 275 mIU/ml	MMR2
Lee et al (2011)[31]	91	90	S/EE	ELISA	150 mIU/ml	MMR1
Gomber et al (2011)[32]	66	43	EZ	ELISA	> 12 U/ml	MMR2
Rumke et al (2011)[33]	104	95	S	ELISA	150 mIU/ml	MMR1
Diaz-ortega et al (2010)[34]	92	87	S/EZ	ELISA	≥ 120 mIU/ml	MMR2
Khalil et al (2008)[35]	57	55	NA	EIA	> 0.200 OD	MMR1
Lim et al (2007)[37]	104	104	S	ELISA	150 mIU/ml	MMR1
Dos Santos et al (2006)[38]	132	131	S/EZ/EE	ELISA	NA	MMR2
Feiterna-Sperling et al (2005)[39]	408	400	EZ/EE	ELISA	> 350 mIU/ml	MMR1
Redd et al (2004)[40]	990	931	EE	EIA	NA	MMR1
Yavad et al (2003)[41]	202	186	NA	ELISA	> 0.2 EU	MMR1
Lee et al (2002)[42]	49	49	S/EE	ELISA	150 mIU/ml	MMR1
Stuck et al (2002)[43]	153	145	S/EZ/EE	ELISA	> 150 mIU/ml	MMR1

Nolan et al (2002)[77]	72	70	S	ELISA	> 150 mIU/ml	MMR1
Ceyhan et al, (2001)[45]	937	756	S	ELISA	0.29 IU/ml	MMR1
Gothefors et al (2001)[46]	17	16	S	ELISA	NA	MMR2
208136/016, (2001)[47]	63	55	S	ELISA	150 mIU/ml	MMR1
208136/007, (2001)[48]	543	537	S	ELISA	150 mIU/ml	MMR1
Klinge et al (2000)[49]	118	110	EE	ELISA	≥ 200 U/l	MMR1
Crovari et al (2000)[50]	682	677	E/ES	ELISA	150 mIU/ml	MMR1
Khalil et al (1999)[51]	85	60	EE/EZ	EIA	> 300 mIU/ml	MMR1
Gatchalian et al (1999)[52]	119	118	S/EE	ELISA	> 150 mIU/ml	MMR1
Mitchell et al (1998)[54]	126	102	O	EIA	EIA absorbance values ≥ 200 units	MMR1
Schwarzer et al (1998)[55]	313	312	EE/EZ	ELISA	250 mIU/ml	MMR1
Usonis et al (1999)[53]	252	250	S/EE	ELISA	> 150 mIU/ml	MMR1
Forleo-Neto et al (1997)[56]	111	100	S	HI	titers ≥ 1/10	MMR1
Bhargava et al (1995)[57]	89	89	EZ	ELISA	NA	MMR1
Cohn et al (1994)[58]	43	38	EE	IFA	> 12.0 titre	NA
Edees et al (1991)[59]	138	128	S	HI	> 20 titre	MMR1
Dunlop et al (1989)[60]	197	188	S	HI	NA	MMR1
Robertson et al (1988)[61]	215	200	S	HI	≥ 20 titre	MMR1
Bottiger et al (1987)[62]	126	126	EE	HI	NA	MMR1
Bottiger et al (1987)[62]	92	79	EE	HI	NA	MMR2
Christenson et al (1983)[63]	126	121	M	HI	>10 tite	MMR1
Isozaki et al (1982)[64]	60	59	O	HI	$< 2^3$	MMR1
Lerman et al (1981)[65]	91	87	EE	HI	NA	MMR1
Ehrenkranz et al (1975)[66]	71	70	S	HI	titre ≥ 1/2	NA
Bloom et al (1975)[67]	182	181	S	HI	< 1:2	MMR1

*MMR2 study seroresponse rate defined as an IgG antibody concentration >= 200 mIU/ml for anti-measles but did not account for pre-vaccination concentrations since most of the participants were expected to be seroresponsive before there second dose of MMR vaccine.

** MMR2 studies excluded from analysis because no clear proportion seronegative were mentioned.

Table S10: Characteristics of included seroconversion studies for mumps component. Number of subjects involved in the study (N) together with number of positives (n), the mumps strain used (Strain), the test used to quantify the antibody titre levels (Test), and cut-off based on which individuals are classified to be seropositive (Sero+), and dose of MMR (MMR dose). LZ: Leningrad-Zagreb; NT: neutralisation test; HI: hemoagglutination inhibition test; SN: serum neutralisation; IFA: immunofluorescent assay. Note that the number of strains is higher than the number of eligible studies because some studies considered more than one MMR vaccine.

	N	n	Strain	Test	Sero+	MMR dose
MMR-158 study group (2019)*[20]	1019	1019	rit 4385/Jeryl Lynn	ELISA	≥ 10 EU/ml	MMR2
dos Santos et al (2019)[21]	1563	1221	rit 4385/NA	ELISA	≥ 457 U/ml	MMR1
Nakayama et al (2019)[22]	45	48	rit 4385	ELISA	NA	MMR1
Joshi et al (2018)[23]	101	101	Hoshino	ELISA	8 EU/ml	MMR1
Bavdekar et al (2018)[24]	295	291	Liningrad-Zagreb	ELISA	≥ 1.10 ISR	MMR1
Abu-Elyazeed et al (2018)**[10]	869	860	rit 4385/Jeryl Lynn	ELISA	≥ 10 EU/ml	MMR2
Sood et al (2017)[25]	273	256	Hoshino/LZ	ELISA	8 EU/ml	MMR1
Wiedmann et al (2015)[26]	1082	1069	Jeryl Lynn	ELISA	≥ 10 U/ml	MMR1
He et al (2014)[27]	280	247	S79	ELISA	≥ 100 U/ml	MMR1
Diaz-ortega et al (2014)**[11]	253	251	Jeryl Lynn/LZ	ELISA	≥ 500 U/ml	MMR2
Prymnula et al (2014)[28]	887	813	rit 4385	ELISA	NA	MMR1
Tababtabaei et al (2013)[29]	237	225	Hoshino	ELISA	NA	MMR1
Saffar et al (2011)[30]	116	95	Hoshino	ELISA	≥ 22 U/ml	MMR2
Lee et al (2011)[31]	92	80	rit 4385/Jeryl Lynn	ELISA	231 U/ml	MMR1
Gomber et al (2011)[32]	13	13	liningrad-Zagreb	ELISA	> 12 U/ml	MMR2
Rumke et al (2011)[33]	103	75	rit 4385	ELISA	231 U/ml	MMR1
Diaz-ortega et al (2010)[34]	222	125	Rubini/Jeryl Lynn	ELISA	≥ 100 U/ml	MMR1
Lim et al (2007)[37]	108	106	rit 4385	ELISA	231 U/ml	MMR1
Dos Santos et al (2006)[38]	191	185	Liningrad-Zagreb /Jeryl Lynn/Urabe am 9	ELISA	NA	MMR2
Feiterna-Sperling et al (2005)[39]	408	343	Jeryl Lynn/Other	ELISA	> 1/500	MMR1
Redd et al (2004)[40]	956	876	Jeryl Lynn	ELISA	NA	MMR1
Yavad et al (2003)[41]	202	198	Others	ELISA	NA	MMR1
Lee et al (2002)[42]	200	189	rit 4385/Jeryl Lynn	ELISA	231 mIU/ml	MMR1
Stuck et al (2002)[43]	154	103	rit 4385/Jeryl Lynn/Rubini	ELISA	> 231 U/ml	MMR1
Nolan et al (2002)[77]	119	115	rit 4385	ELISA	≥ 231 U/ml	MMR1

Ceyhan et al, (2001)[45]	937	917	Urabe am 9	ELISA	0.83 IU/ml	MMR1
Gothefors et al (2001)[46]	69	67	rit 4385/Jeryl Lynn	ELISA	NA	MMR2
208136/016, (2001)[47]	61	56	rit 4385	ELISA	231 U/ml	MMR1
208136/007, (2001)[48]	532	500	rit 4385	ELISA	231 U/ml	MMR1
Klinge et al (2000)[49]	118	114	Jeryl Lynn	ELISA	≥ 1: 200	MMR1
Crovari et al (2000)[50]	645	535	rit 4385/Rubini	ELISA	231 U/ml	MMR1
Khalil et al (1999)[51]	85	49	Rubini/Jeryl Lynn	EIA	≥ 1: 500 titres	MMR1
Gatchalian et al (1999)[52]	140	127	rit 4385/Jeryl Lynn	ELISA	> 231 U/ml	MMR1
Mitchell et al (1998)[54]	128	98	Jeryl Lynn	EIA	≥ 200 units	MMR1
Schwarzer et al (1998)[55]	320	316	Rubini/Jeryl Lynn	ELISA	titer >=500	MMR1
Usonis et al (1999)[53]	249	233	rit 4385/Jeryl Lynn	ELISA	> 231 U/ml	MMR1
Forleo-Neto et al (1997)[56]	181	180	Urabe am 9	NT	titers > 1/60	MMR1
Bhargava et al (1995)[57]	89	82	Liningrad-Zagreb	ELISA	NA	MMR1
Edees et al (1991)[59]	107	94	Urabe am 9	NT	> 120 titre	MMR1
Dunlop et al (1989)[60]	186	180	Urabe am 9	ELISA	NA	MMR1
Robertson et al (1988)[61]	212	210	Urabe am 9	ELISA	≥ 160 titre	MMR1
Bottiger et al (1987)[62]	140	129	Jeryl Lynn	HI	NA	MMR1
Bottiger et al (1987)[62]	131	106	Jeryl Lynn	HI	NA	MMR2
Christenson et al (1983)[63]	265	259	Jeryl Lynn	SN	>2 SN titre	MMR1
Isozaki et al (1982)[64]	60	34	Urabe am 9	NT	NT values < 2^2	MMR1
Lerman et al (1981)[65]	91	81	Jeryl Lynn	IFA	NA	MMR1
Ehrenkranz et al (1975)[66]	72	68	Jeryl Lynn	SN	SN titers ≥ 1:2	NA
Bloom et al (1975)[67]	182	179	Jeryl Lynn	vero cell microtiter serum	SN titer < 1:2	MMR1

*MMR2 study seroresponse rate defined as an IgG antibody concentration >= 10 EU/ml for anti-mumps but did not account for pre-vaccination concentrations since most of the participants were expected to be seroresponsive before there second dose of MMR vaccine. ** MMR2 studies excluded from analysis because no clear proportion seronegative were mentioned.

Table S11: Characteristics of included seroconversion studies for rubella component. Number of subjects involved in the study (N) together with number of positives (n), the rubella strain used (Strain), the test used to quantify the antibody titre levels (Test), and cut-off based on which individuals are classified to be seropositive (Sero+), and dose of MMR (MMR dose). NT: neutralisation test; HI: hemoagglutination inhibition test; SN: serum neutralisation; ISR: immune status ratio. Note that the number of strains is higher than the number of eligible studies because some studies considered more than one MMR vaccine.

	N	n	Strain	Test	Sero+	MMR dose
MMR-158 study group (2019)*[20]	1019	1019	RA27/3	ELISA	≥ 10 IU/ml	MMR2
dos Santos et al (2019)[21]	1563	1421	RA27/3	ELISA	≥ 10 IU/ml	MMR1
Nakayama et al (2019)[22]	49	49	Takahashi	HI	titre ≥ 1:8	MMR1
Joshi et al (2018)[23]	86	87	RA27/3	ELISA	8 IU/m;	MMR1
Bavdekar et al (2018)[24]	305	303	RA 27/3	ELISA	≥ 1·10 ISR	MMR1
Abu-Elyazeed et al (2018)**[10]	869	866	RA27/3	ELISA	≥ 10 IU/ml	MMR2
Sood et al (2017)[25]	279	262	RA27/3	ELISA	8 IU/ml	MMR1
Wiedmann et al (2015)[26]	1115	1111	RA27/3	ELISA	≥ 10 IU/ml	MMR1
He et al (2014)[27]	280	259	BDRII	ELISA	≥ 20 IU/ml	MMR1
Diaz-ortega et al (2014)**[11]	253	253	RA27/3	ELISA	≥ 10 IU/ml	MMR2
Prymnula et al (2014)[28]	921	916	RA27/3	ELISA	NA	MMR1
Tababtabaei et al (2013)[29]	237	173	Takahashi	ELISA	NA	MMR1
Saffar et al (2011)[30]	140	91	Takahashi	ELISA	≥ 11 IU/ml	MMR2
Lee et al (2011)[31]	91	91	RA27/3	ELISA	4UI/ml	MMR1
Gomber et al (2011)[32]	25	25	RA27/3	ELISA	> 10 IU/ml	MMR2
Rumke et al (2011)[33]	104	97	RA27/3	ELISA	4UI/ml	MMR1
Diaz-ortega et al (2010)[34]	301	301	RA27/3	ELISA	≥ 10 IU/ml	MMR2
Lim et al (2007)[37]	115	115	RA27/3	ELISA	4 IU/ml	MMR1
Dos Santos et al (2006)[38]	282	256	RA27/3	ELISA	NA	MMR2
Feiterna-Sperling et al (2005)[39]	406	403	RA27/3	ELISA	> 7 IU/ml	MMR1
Redd et al (2004)[40]	956	903	RA27/3	ELISA	NA	MMR1
Yavad et al (2003)[41]	202	194	RA27/3	ELISA	NA	MMR1
Lee et al (2002)[42]	202	202	RA27/3	ELISA	4 IU/ml	MMR1
Stuck et al (2002)[43]	154	153	RA27/3	ELISA	> 4 IU/ml	MMR1
Nolan et al (2002)[77]	72	72	RA27/3	ELISA	≥ 4 IU/ml	MMR1
Ceyhan et al, (2001)[45]	937	885	RA27/3	ELISA	5.1 IU/ml	MMR1
Gothefors et al (2001)[46]	7	7	RA27/3	ELISA	NA	MMR2
208136/016, (2001)[47]	63	62	RA27/3	ELISA	4UI/ml	MMR1

208136/007, (2001)[48]	543	541	RA27/3	ELISA	4UI/ml	MMR1
Klinge et al (2000)[49]	118	116	RA27/3	ELISA	≥ 10 U/ml	MMR1
Crovari et al (2000)[50]	677	677	RA27/3	ELISA	4 IU/ml	MMR1
Khalil et al (1999)[51]	85	84	RA27/3	EIA	≥ 7 IU/ml	MMR1
Gatchalian et al (1999)[52]	130	130	RA27/3	ELISA	> 4 IU/ml	MMR1
Mitchell et al (1998)[54]	124	116	RA27/3	EIA	≥ 200 units	MMR1
Schwarzer et al (1998)[55]	320	316	RA27/3	ELISA	> 8 IU/ml	MMR1
Usonis et al (1999)[53]	228	228	RA27/3	ELISA	> 4 IU/ml	MMR1
Forleo-Neto et al (1997)[56]	192	192	RA27/3	HI	titre ≥ 1/10	MMR1
Mitchell et al (1996)** [12]	356	348	RA27/3	EIA	10 U/ml	MMR2
Bhargava et al (1995)[57]	89	88	RA27/3	ELISA	NA	MMR1
Edees et al (1991)[59]	120	115	RA27/3	HI	> 20 titre	MMR1
Dunlop et al (1989)[60]	205	205	RA27/3	HI	NA	MMR1
Robertson et al (1988)[61]	185	185	RA27/3	HI	≥ 20 titre	MMR1
Bottiger et al (1987)[62]	130	129	RA27/3	HI	NA	MMR1
Bottiger et al (1987)[62]	211	211	RA27/3	HI	NA	MMR2
Christenson et al (1983)[63]	140	129	RA27/3	HIG	>9 titre	MMR1
Isozaki et al (1982)[64]	66	65	rubella-TO 336 001	HI	HI value < 2^3	MMR1
Lerman et al (1981)[65]	91	91	RA27/3	HI	NA	MMR1
Ehrenkranz et al (1975)[66]	67	62	Cendehill	HI	titre ≥ 1:8	NA
Bloom et al (1975)[67]	182	177	Cendehill	HI	HI value < 1:8	MMR1

*MMR2 study seroresponse rate defined as an IgG antibody concentration >= 10 IU/ml for anti-rubella but did not account for pre-vaccination concentrations since most of the participants were expected to be seroresponsive before there second dose of MMR vaccine.

** MMR2 studies excluded from analysis because no clear proportion seronegative were mentioned.

Table S12: Characteristics of included waning studies for measles component. Number of subjects involved (N) together with number of positives (n) at the different time points a blood sample was taken, which MMR dose, strain, the retrieved waning rate (rate) , and the used method. EE: Edmonston-Enders; S: Schwarz.

	n	N	Time points blood sample (years)	MMR dose	Strain	Rate, 95% CI	Method
Carryn et al (2019)[68]	231	232	0	1	S	0·007 (0·003-0·011)	gee
	230	232	1	1			
	227	232	2	1			
	222	232	4	1			
	217	232	6	1			
	220	232	8	1			
	219	232	10	1			
Poethko-Muller et al (2012)[18]	1876	2000	1	1	NA	0·018 (0·015-0·022)	glm
	1846	2000	4·5	1			
	1886	2000	6	1			
	1949	2000	1	2		0·014 (0·012-0·016)	glm
	1901	2000	4.5	2			
	1853	2000	6	2			
Davidkin et al (2008)[19]	81	85	15	2	EE	0·003 (0·0008-0·008)	empirical estimate
Kremer et al (2006)[72]*	44	47	10	1	EE	0·007 (0·002- 0·011)	
	42	47	17	1			
	36	38	2	2		0·018 (0·005- 0·031)	
	33	38	9	2			
LeBaron et al (2007)[71]	309	312	4·5	1	EE	0·002 (0·0004-0·006)	empirical estimate
	304	304	0.08	1	EE	0·006 (0·002-0·007)	gee
	302	302	0·5	1			
	243	243	2	1			
	173	174	5	1			
	160	161	7	1			
	145	154	10	1			
	307	308	0·08	2	EE	0·009 (0·002-0·015)	gee
	304	306	0·5	2			
	256	266	2	2			
	201	210	5	2			

Broliden et al (1998b)[74]	373	378	10	1	EE	0·001 (0·0004-0·003)	empirical estimate
Bouilianne et al (1995)[17]	212	241	5·5	1	EE	0·023 (0·016-0·033)	empirical estimate
Miller et al (1995)[76]	462	475	4	1	S/EE	0·007 (0·003-0·018)	empirical estimate

*Not included in meta-analysis because N is less than 50 (exclusion criteria stated in protocol)

Table S13: Characteristics of included waning studies for mumps component. Number of subjects involved (N) together with number of positives (n) at the different time points a blood sample was taken, which MMR dose, strain, the retrieved waning rate (rate) , and the used method.

	n	N	Time points blood sample (years)	MMR dose	Strain	Rate, 95% CI	Method
Carryn et al (2019)[68]	232	232	0	1	rit 4385	0·005 (0·002-0·007)	gee
	216	232	1	1			
	212	232	2	1			
	210	232	4	1			
	223	232	6	1			
	214	232	8	1			
	218	232	10	1			
Poethko-Muller et al (2012)[18]	1664	2000	1	1	NA	0·056 (0·05-0·063)	glm
	1572	2000	4·5	1			
	1627	2000	6	1			
	1897	2000	1	2	NA	0·022 (0·019-0·025)	glm
	1821	2000	4·5	2			
	1824	2000	6	2			
LeBaron et al (2009a)[69]	149	154	0·5	2	Jeryl Lynn	0·009 (0·004-0·014)	gee
	148	154	2	2			
	148	154	5	2			
	136	154	7	2			
	137	154	10	2			
	136	154	12	2			
	180	189	0·5	2	Jeryl Lynn	0·018 (0·012-0·025)	gee
	178	189	2	2			
	178	189	5	2			
	151	189	7	2			
Davidkin et al (2008)[19]	65	90	15	2	Jeryl Lynn	0·020 (0·012-0·028)	empirical estimate
Broliden et al (1998a)[73]	168	229	10	1	Jeryl Lynn	0·031 (0·024-0·040)	empirical estimate
Davidkin et al (1995)[75]	103	120	0	1	Jeryl Lynn	0·037 (0·019-0·054)	gee

	88	120	1	1			
	94	120	2	1			
	82	120	3	1			
	91	120	4	1			
	114	120	0	2	Jeryl Lynn	0·025 (0·010-0·040)	gee
	110	120	1	2			
	103	120	4	2			
Miller et al (1995)[76]	392	470	4	1	Urabe 9 am/ Jeryl Lynn	0·045 (0·035-0·055)	empirical estimate
Bouilianne et al (1995)[17]	205	241	5·5	1	Jeryl Lynn	0·029 (0·021-0·041)	empirical estimate

Table S14: Characteristics of included waning studies for rubella component. Number of subjects involved (N) together with number of positives (n) at the different time points a blood sample was taken, which MMR dose, strain, the retrieved waning rate (rate), and the used method.

	n	N	Time points blood sample (years)	MMR dose	Strain	Rate, 95% CI	Method
Carryn et al (2019)[68]	230	232	1	1	RA27/3	0·003 (0·0007-0·006)	gee
	231	232	2	1			
	231	232	4	1			
	230	232	6	1			
	226	232	8	1			
	224	232	10	1			
Poethko-Muller et al (2012)[18]	1922	2000	1	1	RA27/3	0·017 (0·014-0·020)	glm
	1897	2000	4·5	1			
	1833	2000	6	1			
	1980	2000	1	2	RA27/3	0·008 (0·006-0·010)	glm
	1923	2000	4·5	2			
	1930	2000	6	2			
LeBaron et al (2009b)[70]	143	144	0·5	1	RA27/3	0·010 (0·006- 0·014)	gee
	127	144	2	1			
	130	144	7	1			
	122	144	10	1			
	128	144	12	1			
	185	189	0·5	2	RA27/3	0·034 (0·022-0·046)	gee
	166	189	2	2			
	151	189	7	2			
Davidkin et al (2008)[19]	90	90	15	2	RA27/3	0·000 (0·000- 0·000)	empirical estimate
Miller et al (1995)[76]	471	475	4	1	RA27/3	0·002 (0·000-0·003)	empirical estimate
Bouilianne et al (1995)[17]	233	241	5·5	1	RA27/3	0·006 (0·002-0·010)	empirical estimate

Appendix 15: Supplementary figures

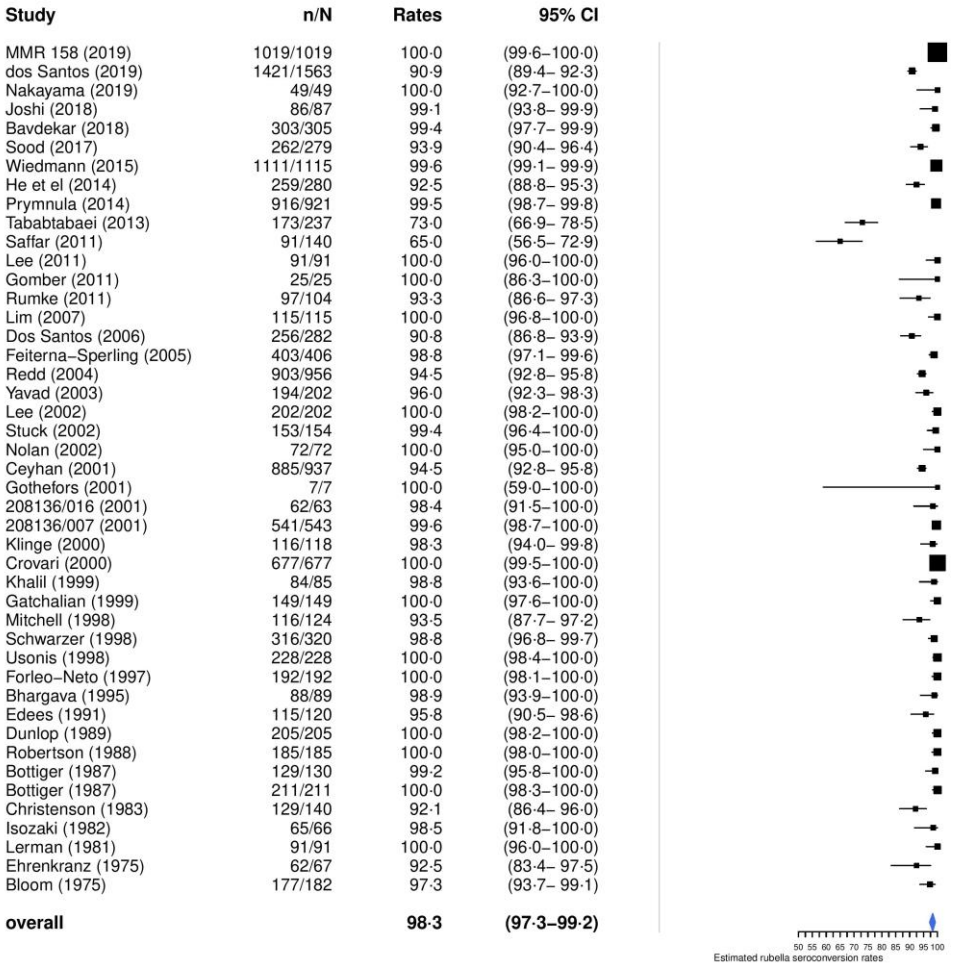


Figure S8: Forest plot of the seroconversion rate for rubella. The overall seroconversion rate estimate was obtained from a meta-analysis random effects model with the DerSimonian-Laird estimator. I^2 = 93 ·0% (95% CI 89 ·1, 94 ·8). The 95% confidence intervals (CI) for the individual studies were Clopper-Pearson exact intervals. Abbreviations: n, number of seropositive; N, total number.

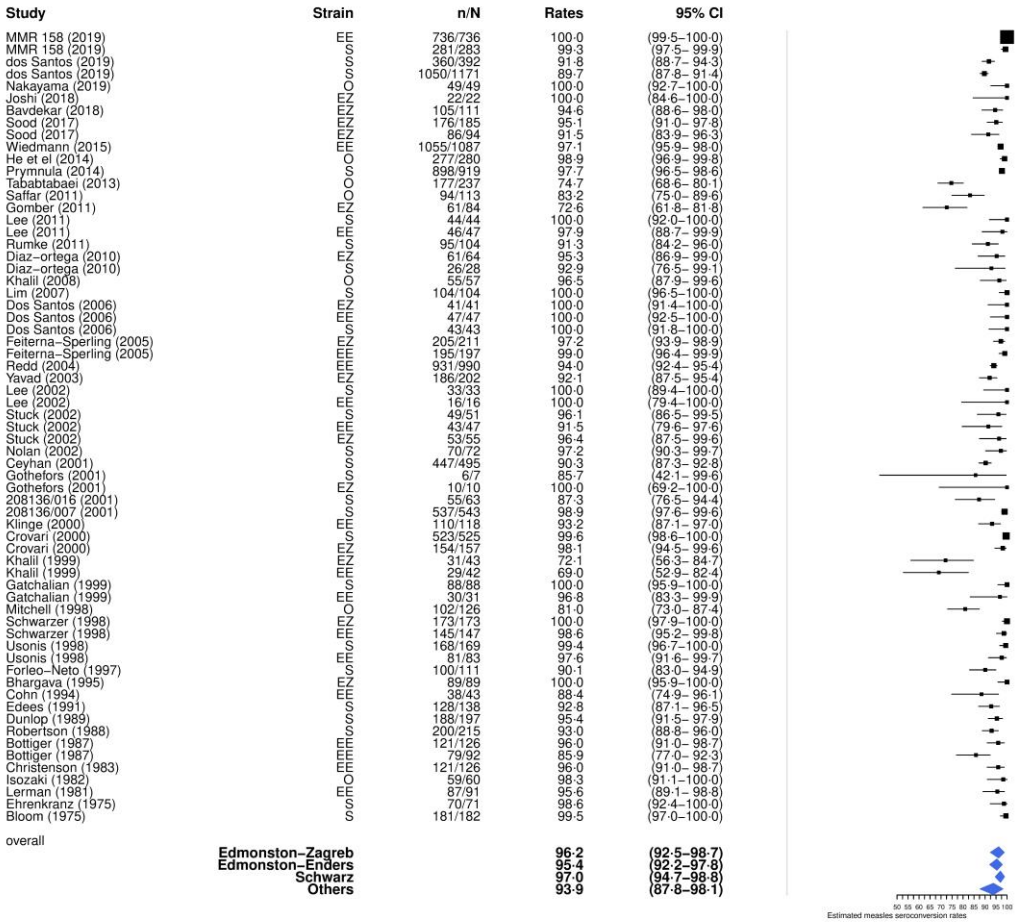


Figure S9: Forest plot of the seroconversion rate for measles per strain. The overall seroconversion rate estimate per strain was obtained from a single mixed model, strain as fixed effect, with the DerSimonian-Laird estimator. I^2 = 91·2% (95% CI 89·3, 94·9). The 95% confidence intervals (CI) for the individual studies were Clopper-Pearson exact intervals. Abbreviations: n, number of seropositive; N, total number; EZ, Edmonston-Zagreb; EE, Edmonston-Enders; S, Schwarz; O, Others.

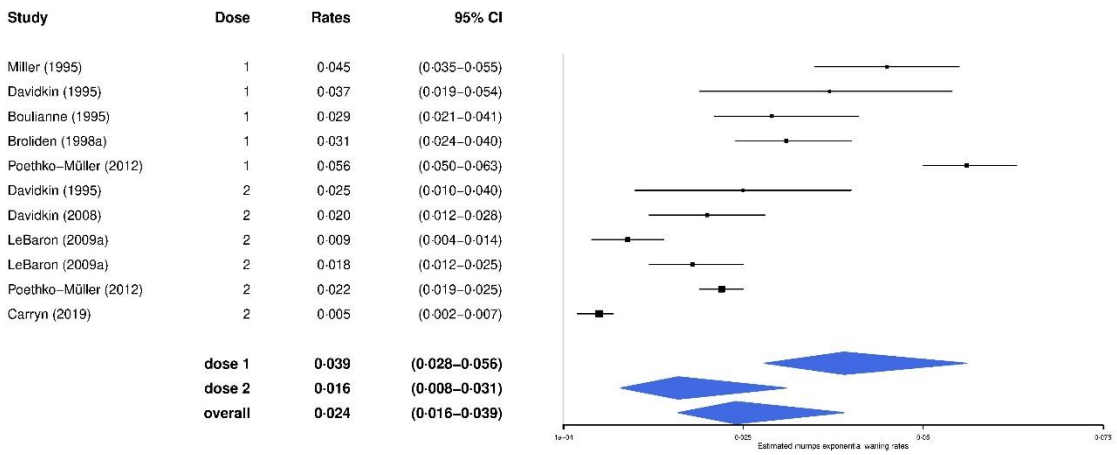


Figure S10: Forest plot of the waning rate for mumps. The waning rate estimates for dose 1, 2 and both combined for mumps was obtained from a meta-analysis random effect model, with DerSimonian-Laird estimator. I^2 = 94 ·7% (95% CI 92 ·4-96 ·5) for both doses combined.

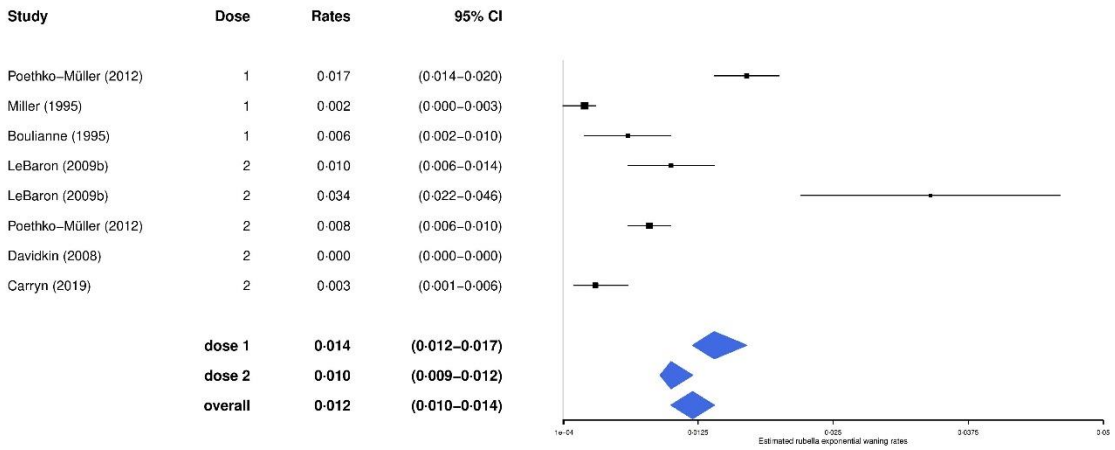


Figure S11: Forest plot of the waning rate for rubella. The waning rate estimates for dose 1, 2 and both combined for rubella was obtained from a meta-analysis fixed effect model, with DerSimonian-Laird estimator. I^2 = 93 ·3% (95% CI 88 ·6-96 ·0) for both doses combined.

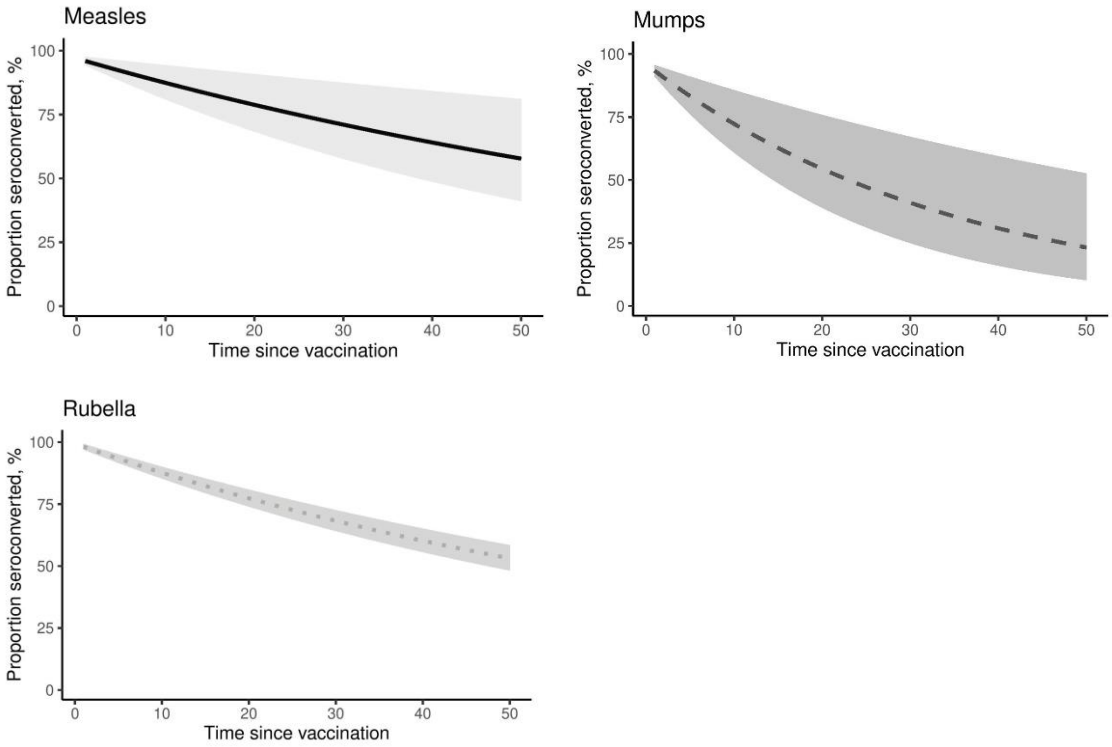


Figure S12: Loss of vaccine-induced immunity over time based on the overall meta-analysis results: simulated evolution of the proportion seroconverted for persons vaccinated in year 0 against measles, mumps and rubella with a single dose of MMR vaccine. The full, dashed and dotted lines are corresponding to measles, mumps and rubella. The shaded areas are the 95% bootstrap confidence intervals.

Figure S12 is a simple hypothetical projection based on the overall meta-analysis results to display how the proportion seroconverted in a group of 100 vaccinated individuals would evolve over a time span of 50 years, with a single dose of MMR vaccine and no exposure to wild types viruses at any time after vaccination. For example, 35 years after vaccination, about 30% ($= \left[1 - (0 \cdot 960 * e^{(-0 \cdot 009 * 35)})\right] * 100\%$) (95% CI: 14·2-46·1) of individuals became seronegative for measles, with 96·0% the overall seroconversion rate for measles after an MMR dose and 0·009 the overall annual waning rate for vaccine-induced measles immunity.

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