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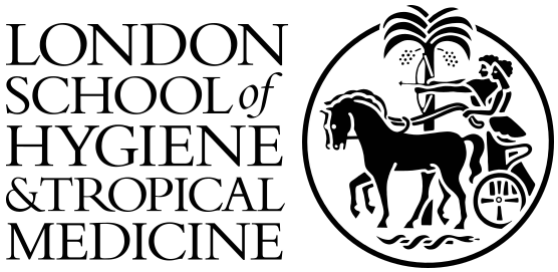

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Review

The effect of time since measles vaccination and age at first dose on measles vaccine effectiveness – A systematic review

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ABSTRACT

Background: In settings where measles has been eliminated, vaccine-derived immunity may in theory wane more rapidly due to a lack of immune boosting by circulating measles virus. We aimed to assess whether measles vaccine effectiveness (VE) waned over time, and if so, whether differentially in measles-eliminated and measles-endemic settings.

Methods: We performed a systematic literature review of studies that reported VE and time since vaccination with measles-containing vaccine (MCV). We extracted information on case definition (clinical symptoms and/or laboratory diagnosis), method of vaccination status ascertainment (medical record or vaccine registry), as well as any biases which may have arisen from cold chain issues and a lack of an age at first dose of MCV. We then used linear regression to evaluate VE as a function of age at first dose of MCV and time since MCV.

Results: After screening 14,782 citations, we identified three full-text articles from measles-eliminated settings and 33 articles from measles-endemic settings. In elimination settings, two-dose VE estimates increased as age at first dose of MCV increased and decreased as time since MCV increased; however, the small number of studies available limited interpretation. In measles-endemic settings, one-dose VE increased by 1.5% (95% CI 0.5, 2.5) for every month increase in age at first dose of MCV. We found no evidence of waning VE in endemic settings.

Conclusions: The paucity of data from measles-eliminated settings indicates that additional studies and approaches (such as studies using proxies including laboratory correlates of protection) are needed to answer the question of whether VE in measles-eliminated settings wanes. Age at first dose of MCV was the most important factor in determining VE. More VE studies need to be conducted in elimination settings, and standards should be developed for information collected and reported in such studies.

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1. Introduction

Measles elimination is defined as the absence of endemic measles virus transmission in a defined geographical area for ≥12 months, in the presence of a well-performing surveillance system [1,2]. An ambitious goal to eliminate measles by 2020 has been set by the six World Health Organization (WHO) Regions [1,3]. While several countries have eliminated measles, some have subsequently lost this status, and measles is not currently eliminated in any WHO Region [4]. Measles outbreaks are causing ongoing concern in many countries worldwide, including the Philippines [5], the Democratic Republic of the Congo [6], Ukraine, France [7] and the United States (US) [8]; such outbreaks demonstrate how challenging it is to control measles. The risk of importation of wild-type measles virus will likely continue for many years. As a result, vaccine-derived immunity will need to be sustained to protect those in eliminated settings.

Vaccine-derived antibodies are known to be less durable than those derived from infection with wild-type measles virus [9–12]. Levels of antibody induced by measles vaccination decrease over time [13], and, in settings where measles has been eliminated, could potentially wane more rapidly due to a lack of immune boosting by circulating measles virus [11]. Conversely, studies from areas that have sustained measles elimination indicate that vaccination provides protection for at least several decades [14], suggesting that if waning immunity ever becomes a public health problem (i.e. leads to sustained transmission or large outbreaks after measles virus introductions in which secondary vaccine failure plays a major role), it will emerge slowly over a long period [9,11].

In this systematic review, we aimed to investigate whether there is evidence that measles vaccine effectiveness (VE) wanes over time. Our goal was to assess VE by time since measles vaccination. We hypothesized there might be evidence of waning immunity in measles-eliminated settings but little evidence in measles-endemic settings. Furthermore, we hypothesized there may be a difference in VE following one dose of MCV in comparison to two doses of MCV.

2. Methods

2.1. Study design

We used a Population Intervention Comparison Outcome Study framework to define our research question. Our *population* was individuals ≥9 months of age; our *intervention* was administration of measles-containing vaccine (MCV); our *comparison* was the time since first and last MCV dose (or proxy); our *outcome* was VE or vaccine efficacy measured by the development of clinical measles, as diagnosed by symptoms and/or laboratory confirmation; and our *study designs* included ecological, randomized controlled trials (RCT), non-RCT, cohort, case-control, and outbreak investigations (case series). Our complete study protocol, including search and screening details, can be viewed on PROSPERO (#CRD42018109248).

With increasing measles activity, we selected VE as our outcome of interest because it is the primary measure of how well the measles vaccine works.

2.2. Literature search

We devised a search strategy according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15], which comprised bibliographic database and grey literature searches, citation scanning (snowballing) and expert consultation.

We searched MEDLINE, Embase, Global Health, BIOSIS Previews and Science Citation Index, and asked content experts to recommend relevant articles. We placed no restriction on year, but removed animal studies, conference abstracts/presentations, or non-research articles.

To search grey literature, we utilized a variety of online catalogues and repositories, and web search engines. We considered the first 100 results of each query for the most relevant webpages.

Our search strategy is detailed in Supplementary Materials 1.

2.3. Study screening

We used DistillerSR software (Evidence Partners, Ottawa, Ontario, Canada) throughout screening. Two independent reviewers screened the titles and abstracts identified by the literature search in singular. Reviewers pilot tested 100 titles and abstracts to ensure compliance with the screening criteria. We included articles for full-text screening if they reported on VE or vaccine efficacy in any context.

During full-text screening, we determined the measles-eliminated or -endemic status from Regional Verification Commission reports on progress towards and achievement of measles elimination and expert consultations. We included all countries that adhered to the WHO definition of "eliminated" [1,2], regardless of how long the country had held the status. We screened all full-text articles in duplicate with a third reviewer consulted for conflicts. We calculated a Cohen's Kappa for full-text screening agreement between reviewers after the first 20 articles, and reviewers discussed their understanding of the inclusion/exclusion criteria if agreement was low (i.e. <0.7) prior to proceeding. We excluded studies that related only to the following: failure of individuals to mount an immune response to MCV (primary vaccine failure [16]); a non-generalizable population; vaccinations given to infants <9 months of age; experimental or high-titre vaccines; vaccines combined with immunoglobulin and/or vitamin A; vaccination through any administration route other than subcutaneous or intramuscular; age groups >10 years; results that were influenced by a supplemental immunisation activity (SIA); lack of information relevant to the research question; or in an unsupported format or language (case studies, letters, conference abstracts/presentations, modelling studies, non-English). We snowballed and excluded relevant studies which did not contain primary data.

For articles to pass full-text screening, we required them to include VE or vaccine efficacy (overall or by age/age group), and time between MCV and measles diagnoses.

2.4. Data extraction, synthesis and risk of bias

We used two independent reviewers to extract all data from eligible studies including median age and/or age range of measles diagnosis, method of vaccination status verification, age at MCV, among others. Extracted ages at each dose of MCV were linked to the method of vaccine status verification. We developed our data extraction form *a priori*; the two reviewers pilot tested the first two articles from measles-endemic settings, and consulted a third reviewer for disagreements. When data on the age at first dose of MCV was not included in an article, we attempted additional research to supplement this information.

One reviewer performed a risk of bias assessment for each study using an adapted Cochrane ROBINS-I tool [17,18]. We identified three criteria that that could contribute to a high risk of bias: cold chain issues identified in the paper; width of age groups ≥10 years; and an unclear (i.e. did not have an upper and/or a lower bound) or absent age at first dose. We conducted sensitivity analyses for each criterion, removing all of the articles at high risk of bias.

In endemic and eliminated settings, we plotted age at first dose of MCV and time since first dose of MCV against VE estimates. Median ages at diagnosis were used in analyses in measles-eliminated settings, and age ranges in measles-endemic settings due to data limitations.

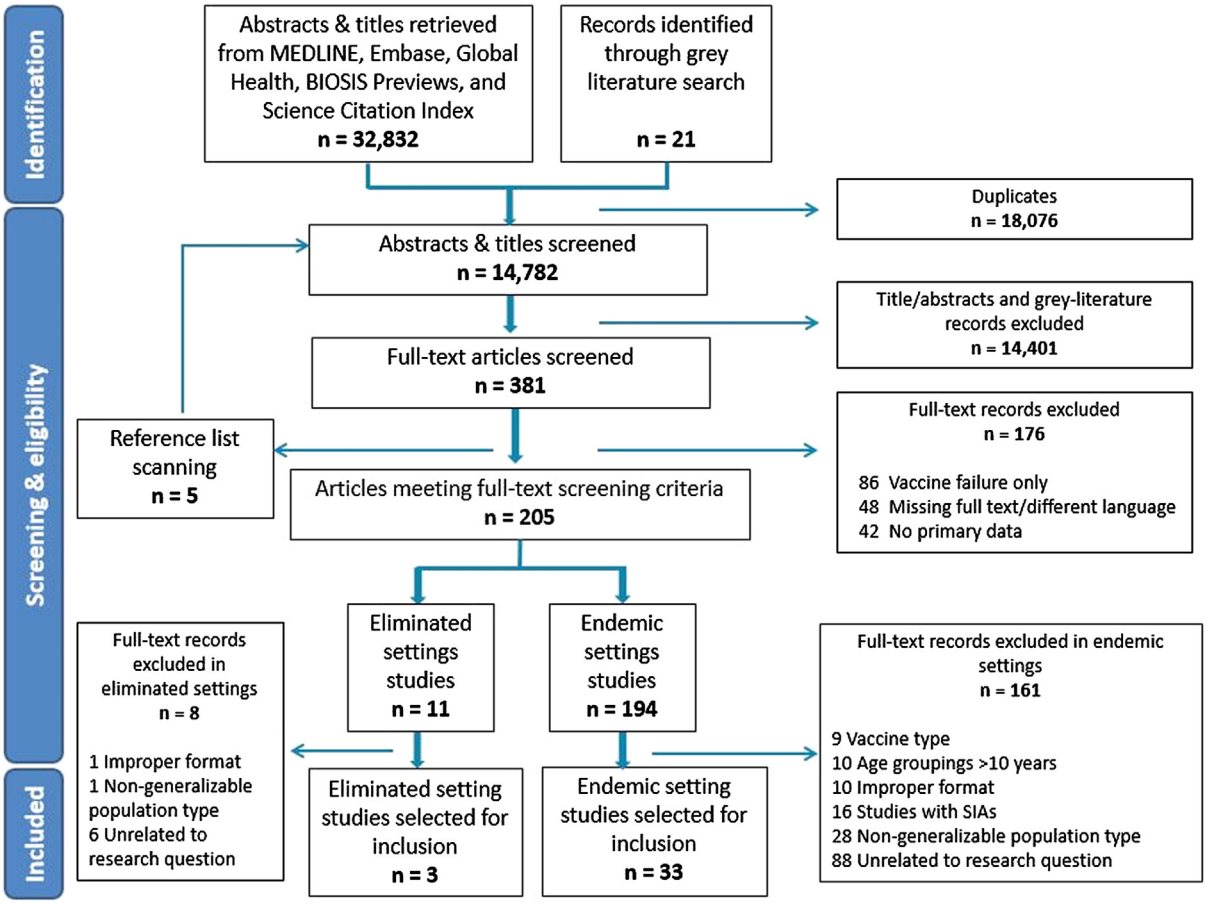

Fig. 1. PRISMA diagram.

Table 1
Articles selected for inclusion from measles-eliminated settings (N = 3).

Selected article	Title	Characteristic					
		Country	Study period	Setting	Year of elimination	Number of measles cases in study	Median age at exposure
De Serres et al. [19]	Higher risk of measles when the first dose of a 2-dose schedule is given at 12–14 versus 15 months of age	Canada	2011	School	1998*	110	15
Hahné et al. [20]	Measles outbreak among previously immunized healthcare workers, the Netherlands, 2014	The Netherlands	2014	Community	2012†	8	27
Choe et al. [21]	An outbreak of measles in a University in Korea, 2014	Republic of Korea	2014	School	2006‡	85	20

* King et al. [32].
† WHO [33].
‡ Heywood et al. [34].

In endemic settings, we evaluated whether VE was significantly associated with age at first dose of MCV by linear regression analysis of all data and for the subgroups of individuals exposed to measles at <5 years and ≥5 years of age. This age was used as a cut-off to mitigate the large number of data points in individuals <5 years and account for age as a potential confounding variable. Data were weighted by study precision, calculated using the VE confidence intervals (CI). Furthermore in endemic settings, we evaluated whether time since first dose of MCV was significantly associated with VE by linear regression using the following categories: less than one year; one to less than two years; two to less than five years; five to <10 years; and ≥10 years. Because time since first dose was provided as a range, it could not be treated as a continuous predictor. We used the shortest time since first dose category (varied for sensitivity analyses) as the referent category in each model. For all models in endemic settings, we determined the best-fitting model by comparing linear regression to Poisson and negative binomial, and evaluating Akaike & Bayesian Information Criteria. Data were weighted by precision.

All analyses were performed in STATA v.12.1 (StataCorp, College Station, Texas, US).

3. Results

Following the removal of duplicates and addition of five articles from snowballing references, we screened 14,782 titles/abstracts and grey-literature documents (Fig. 1). We identified 381 full-text articles eligible for full-text screening. Of these, we excluded: 86 articles as they pertained only to vaccine failure (did not report VE); 48 articles written in a language other than English (n = 39) or the full-text was irretrievable (n = 9); and 42 articles because they did not contain primary data.

Of the remaining 205 articles, 11 were in measles-eliminated settings, and 194 in -endemic settings. From the 11 studies in measles-eliminated settings, three met full-text inclusion criteria (Fig. 1, Table S2). Of the 194 studies in measles-endemic settings, 33 met full-text inclusion criteria (Fig. 1, Table S2). Our Cohen's Kappa for full-text screening was 0.62.

There were three methods of vaccine status verification identified in the 36 included articles: medical record, vaccine registry, and patient/parent account. A total of 18 studies utilised medical records, 2 vaccine registries, and 3 patient/parent accounts. An additional 7 studies used a combination of medical record and

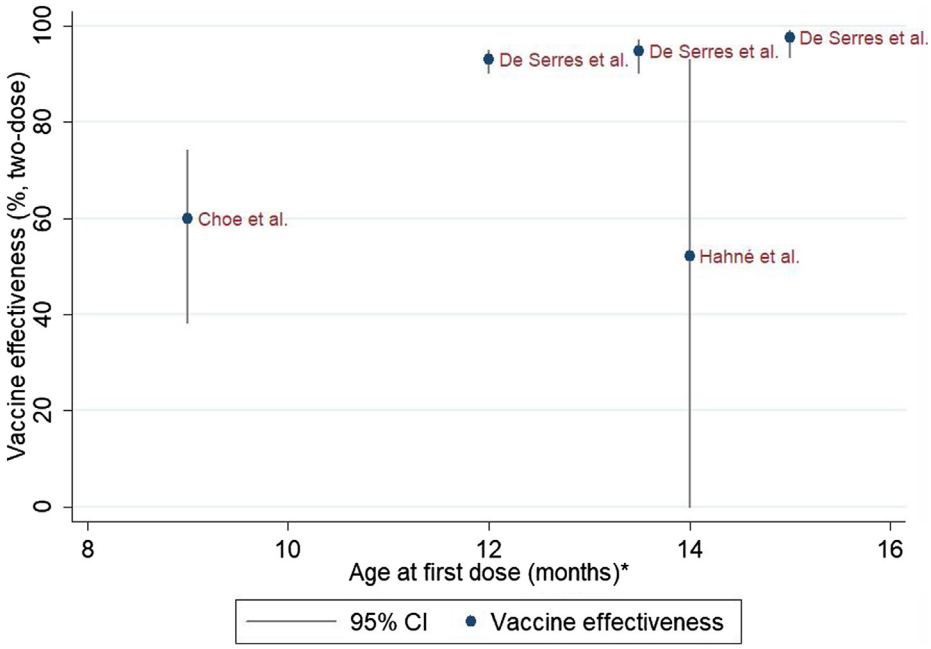

Fig. 2. Vaccine effectiveness by age at first dose of measles-containing vaccine in measles-eliminated settings. *Cases in Choe et al. [21] were vaccinated between 9 and 15 months (indicated as 9 months in the figure). Cases in Hahné et al. [20] were vaccinated at 14 months. Cases in De Serres et al. [19] were vaccinated at 12 months, 13–14 months, and ≥15 months (the latter indicated as 15 months in the figure).

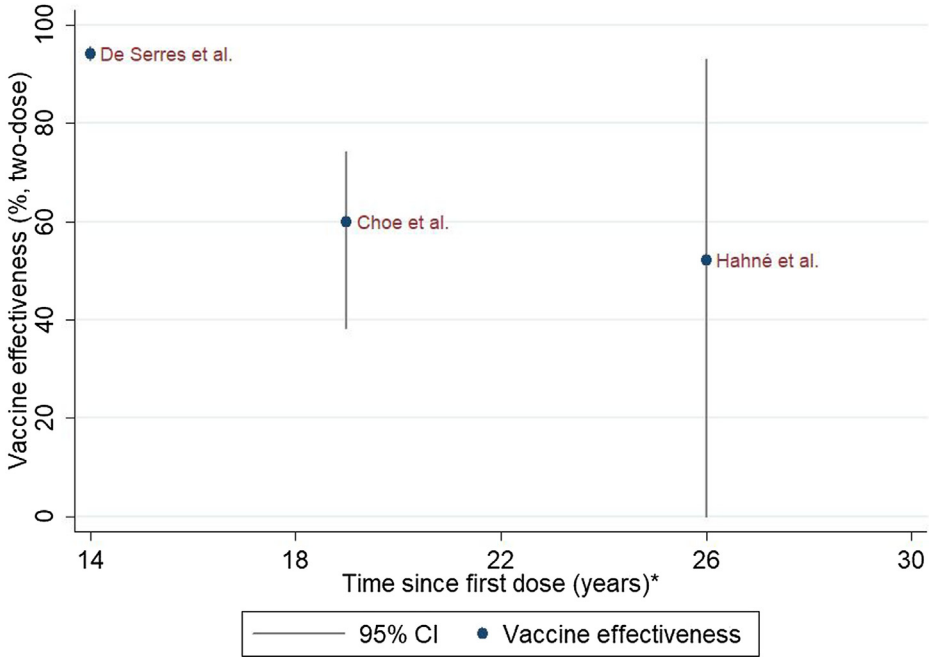

Fig. 3. Vaccine effectiveness by the duration of time since the first dose of measles-containing vaccine in measles-eliminated settings. *Values have been rounded for Choe et al. [21] and Hahné et al. [20].

patient/parent account, 2 a combination of vaccine registry and medical records, 3 were missing, and 1 other.

3.1. Elimination settings

Studies performed in elimination settings were De Serres et al., describing a 2011 measles outbreak in a Canadian secondary school 13 years after measles elimination [19], Hahné et al. describing a 2014 measles outbreak among healthcare workers in the Netherlands two years following measles elimination [20], and Choe et al. describing a 2014 measles outbreak in a university in the Republic of Korea, eight years following measles elimination [21] (Table 1).

3.1.1. VE estimates reported

De Serres et al. reported various VE estimates, including by number of MCV doses and by age at first dose of MCV. In comparison, Hahné et al. and Choe et al. calculated only a two-dose VE estimate using a single age at first dose of MCV. Therefore, we focused on two-dose VE estimates as the only estimate common to all three articles. We used median age of diagnosis to measles as this was common to all three articles.

The VE estimates were presented by both age at first dose of MCV and age of diagnosis, and ranged between 52.0% and 98.8%. De Serres et al. had the largest number of cases with 110 cases, followed by Choe et al. with 85 cases and Hahné et al. with 8 cases (Table 1).

3.1.2. Age at first dose of MCV

The study by De Serres et al. suggested a small but significant increase in VE with increasing age of first dose of MCV (Fig. 2). However, the other studies were not useful in confirming this relationship. Choe et al. did not report an age at first dose; however, following additional online research, we found that the first dose of MCV was administered in the Republic of Korea between nine and 15 months prior to 1997 [22]. All individuals studied by Choe et al. would have received their childhood vaccinations prior to 1997, and would therefore have received their first dose of MCV within this range. Furthermore, the point estimate for Hahné et al. was low with extremely wide confidence intervals (52%, 95% CI −207, 93).

3.1.3. Time since first dose of MCV

Two-dose VE decreased as time since first dose of MCV increased (Fig. 3). The tight confidence intervals exhibited by De Serres et al. were in concordance with the highest VE and shortest time since MCV. Both Choe et al. and Hahné et al. demonstrated wider confidence intervals with longer time since first MCV.

3.1.4. Risk of bias and sensitivity analyses

Although Choe et al. had broad width of age at diagnosis bands and an absent age at first dose (Table S3), due to the small number of papers we did not perform sensitivity analyses.

3.2. Endemic settings

The 33 studies included from endemic settings were published between 1982 and 2018. From these, 10 articles were published in Africa [23–32], nine from Europe [33–41], six from Asia [42–47], six from Oceania [48–53] and two from North America [54,55] (Table 2). The articles included an RCT (n = 1) [38] and studies focussed on measles in communities (n = 22) [23–32,35,36,41–43,45,46,50,52–54,55], schools (n = 9) [33–35,37,39,40,44,48,51], or households (n = 2) [47,49]. One study was performed in both a community and school [35], and was therefore treated as two studies.

3.2.1. VE estimates

The majority of VE estimates reported were one-dose VE estimates, with few two-dose and even fewer overall estimates provided. The one-dose estimates spanned from 26.0% to 100.0% (Fig. 4), and two-dose from 93.0% to 100.0%.

The ages at first dose of MCV in the 33 selected articles ranged between 9 months and >24 months. Case counts of measles varied greatly between the studies, with VE estimates calculated from eight to 10,285 cases. Few median ages of diagnosis were reported;

Table 2
Articles selected for inclusion from measles-endemic settings (N = 33).

Selected article	Title	Characteristic				
		Country of study	Study period	Study setting	Number of measles cases in study	Age range
Barrabeig et al. [33]	MMR vaccine effectiveness in an outbreak that involved day-care and primary schools	Spain	2006–2007	Daycare/school	17	≥15 mo
Bhuniya et al. [42]	Measles outbreak among the Dukpa tribe of Buxa hills in West Bengal, India: epidemiology and vaccine efficacy	India	2011	Community	68	9–59 mo
Cheah, Lane, and Passaris [48]	Measles vaccine efficacy study in a Canberra high school: A study following a measles outbreak	Australia	1991	School	35	13–15 yrs
Fernandes and Gill [34]	Prevention of measles: vaccine efficacy and potential effectiveness of a vaccination programme on entry to school	U.K.	1985	School	35	3–8 yrs
Guris et al. [49]	Measles vaccine effectiveness and duration of vaccine-induced immunity in the absence of boosting from exposure to measles virus	Palau	1993	Households	8	10 yrs
Harrison and Durham [50]	The 1991 measles epidemic: how effective is the vaccine?	New Zealand	1991	Community		1–19 yrs
Hennessey et al. [35]	Measles epidemic in Romania, 1996–1998: Assessment of vaccine effectiveness by case-cohort and cohort studies	Romania	1996–1998	Community/ school	312	9 mo – 15 yrs
Hull, Williams, and Oldfield [23]	Measles mortality and vaccine efficacy in rural west Africa	Gambia	1981	Community		9–47 mo
Hutchins et al. [54]	Evaluation of an early two-dose measles vaccination schedule	U.S.	1989–1996	Community	43	15–59 mo
Janaszek, Gay, and Gut [36]	Measles vaccine efficacy during an epidemic in 1998 in the highly vaccinated population of Poland	Poland	1998	Community	2255	1–28 yrs
John et al. [43]	Two doses of measles vaccine: Are some states in India ready for it	India	1999–2006	Community	129	1–19 yrs
Kaninda et al. [24]	Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995	Niger	1995	Community		9–59 mo
Kim et al. [47]	Efficacy of measles vaccine during the 1993 measles epidemic in Korea	Republic of Korea	1993	Households	16	1–5 yrs
Lamb [25]	Epidemic measles in a highly immunized rural west African (Gambian) village	Gambia	1984–1985	Community	32	1–9 yrs
Lyons, Jones, and Salmon [37]	Successful control of a school based measles outbreak by immunization	U.K.	1991	School	77	10–16 yrs
Mahomva, Moyo, and Mbengeranwa [26]	Evaluation of a measles vaccine efficacy during a measles outbreak in Mbare, City of Harare, Zimbabwe	Zimbabwe	1996	Community	28	9–35 mo
Malfait et al. [27]	Measles epidemic in the urban community of Niamey: transmission patterns, vaccine efficacy and immunization strategies, Niger, 1990 to 1991	Niger	1990–1991	Community	3583	9–59 mo
Marufu et al. [28]	Questioning the level of efficacy of the measles vaccine in use in Zimbabwe	Zimbabwe	1987–1989	Community	110	10–23 mo
McDonnell, Jorm, and Patel [51]	Measles outbreak in western Sydney	Australia	1993	School	38	5–9 yrs
McIntyre et al. [55]	Measles and measles vaccine efficacy in a remote island population	U.S.	1977–1978	Community	87	1–9 yrs
Mudzamiri et al. [29]	Measles vaccine efficacy in Masvingo District, Zimbabwe	Zimbabwe	1987–1994	Community	31	12–23 mo
Mupere et al. [30]	Measles vaccination effectiveness among children under 5 years of age in Kampala, Uganda	Uganda	1999	Community	70	9–59 mo
Nsubuga et al. [31]	Factors contributing to measles transmission during an outbreak in Kamwenge District, Western Uganda, April to August 2015	Uganda	2015	Community	41	9 mo – 52 yrs
Ong et al. [44]	A 24-year review on the epidemiology and control of measles in Singapore, 1981–2004	Singapore	2004	School	9	8–14 yrs
Pillsbury and Quinn [52]	An assessment of measles vaccine effectiveness, Australia, 2006–2012	Australia	2006–2012	Community	189	1–15 yrs
Puri et al. [45]	Measles vaccine efficacy evaluated by case reference technique	India	Not reported	Community	109	12–35 mo
Ramsay, Morratt, and O'Connor [38]	Measles vaccine: a 27-year follow-up	U.K.	1964–1990	Longitudinal RCT	53	12–25 yrs
Schmid et al. [39]	Measles outbreak linked to a minority group in Austria, 2008	Austria	2008	School	150	5–20 yrs

(*continued on next page*)

Table 2 (*continued*)

Selected article	Title	Characteristic				
		Country of study	Study period	Study setting	Number of measles cases in study	Age range
Sharma, Chawla, and Datta [46]	Field evaluation of measles vaccine efficacy in Najafgarh Zone of Delhi	India	1987	Community		12–35 mo
Sheppeard et al. [53]	Vaccine failures and vaccine effectiveness in children during measles outbreaks in New South Wales, March-May 2006	Australia	2006	Community	25	1–7 yrs
Velicko et al. [40]	Nationwide measles epidemic in Ukraine: the effect of low vaccine effectiveness	Ukraine	2005–2006	School		15–29 yrs
Weekly Epidemiological Record [32]	Expanded programme on immunization: measles vaccine efficacy	Ivory Coast	1982	Community	68	24–25 mo
Weekly Epidemiological Record [41]	Expanded programme on immunization: measles vaccine efficacy	Poland	1984	Community	10,285	1–4 yrs

Blank cells represent missing or unclear values.

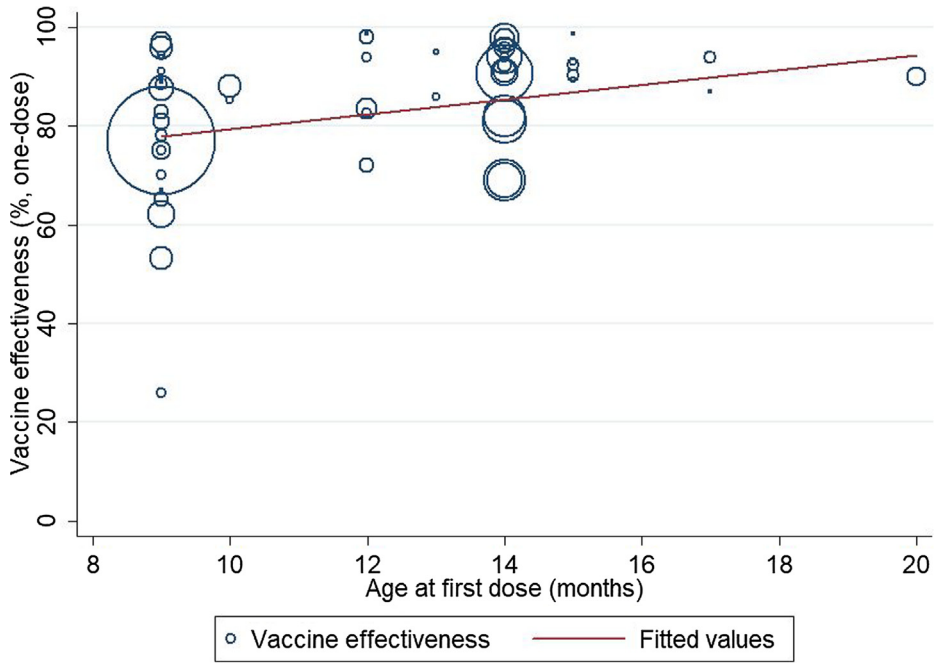

Fig. 4. Vaccine effectiveness by age at first dose of measles-containing vaccine in measles-endemic settings. Red line represents linear regression trend line. Circle sizes correspond to precision (larger circles = higher precision). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

therefore, we were limited to using age-ranges in analyses. Lastly, not every article contained a case count and/or confidence interval, restricting the VE estimates included in syntheses.

3.2.2. Age at first dose of MCV

We observed a wide range of ages at first dose, spanning from 6 to greater than 24 months (Fig. S1). Although we included articles which contained ages at first dose less than 9 months, we only extracted information from 9 months and onwards.

One-dose VE increased as age at first dose of MCV increased (Fig. 4). The relationship between the two variables of interest was statistically significant with an age at first dose coefficient of 0.015 (95% CI 0.005, 0.025), indicating an increase of 1.5% VE with each increasing month of age at first dose of MCV. In subgroup analyses, the findings were 0.014 (95% CI −0.008, 0.036) for the <5 age group, and 0.007 (95% CI −0.027, 0.040) for the ≥5 age group.

Analyses were also performed for two-dose VE estimates, where available. Four studies and nine estimates were used to assess VE by both age at first and second dose; these studies were conducted in Romania [35], Australia [52], Ukraine [40], and Poland [36]. We observed a significant increase in VE as age at first dose increased [0.014 (95% CI 0.000, 0.027), p = 0.046], and a similar but non-significant result as age at second dose increased [0.015 (95% CI 0.000, 0.029), p = 0.050].

3.2.3. Time since first dose of MCV

No clear pattern emerged for the relationship between VE and time since first dose of MCV (Fig. S2). Of all the categorical comparisons, only the "5 to less than 10 years" time since first dose of MCV category using <1 year as the referent was significant (Table S3).

We also performed time since first dose analyses for two-dose VE estimates, where available. We used the category of "1 to less than 10 years" as the referent, and observed non-significant differences for both the "10 to less than 20 years" category [0.4% (95% CI

−1.9%, 2.7%) and "≥20 years" category [−5.2% (95% CI −13.4%, 3.1%)].

3.2.4. Risk of bias and sensitivity analyses

Only one article was affected by width of the age of diagnosis band issues [33] (Table S4). We were therefore unable to perform sensitivity analyses on this criterion. Nine articles stated there were cold chain issues [26,28–30,40,42,46,48,55] and 20 had unclear or absent data on age at first dose of MCV [23–26,30,32,34–36,38,41–46,50,51,54,55]. Sensitivity analyses were performed on these criteria to assess whether age at first dose of MCV or time since first dose of MCV trend significance changed following removal of the affected articles (Tables S5 and S6). Neither criterion changed the outcome of age at first dose of MCV or time since first dose of MCV analyses; therefore, analyses proceeded with all 33 included articles.

4. Discussion

Our over-whelming finding is a lack of sufficient quality data to ascertain whether measles vaccination-induced immunity wanes in elimination settings. This is surprising given that measles immunisation is recommended in every country, and measles elimination is a target in every WHO region [3].

In measles-eliminated settings, definitive conclusions cannot be drawn from the small number of heterogeneous studies to assess whether VE decreased with increasing time since MCV. In measles-endemic settings we anticipated finding little evidence of waning. Our results concurred with this hypothesis with one exception, the time period from 5 to less than 10 years since MCV administration.

Our initial hypothesis that waning would only be evident in measles-eliminated settings, in which a large proportion of the population is immune through vaccination was based on previous studies demonstrating that antibody levels generated by MCV are lower than those generated by infection, and decrease over time [11,56]. We also hypothesized that antibody levels would wane faster in elimination settings because of the lack of boosting by circulating measles virus [14]. In countries such as the US, incidence of measles had been low for a long time prior to measles elimination, so the vast majority of the population has not been exposed to wild measles viruses for more than 30 years. Measles elimination has, however, been sustained despite multiple introductions of measles virus, demonstrating that vaccination provides robust protection for at least several decades [11]. Although it is possible that waning immunity in vaccinated individuals may not lead to substantial future outbreaks, the question remains unanswered since every country currently benefits from the immunity of older age groups, which is naturally-acquired through past measles virus infection. No country has yet experienced the epidemiologic situation of having an entire population immune only through immunisation. Finland, which was the first country worldwide to achieve measles elimination status in 1994, is likely the country with the highest proportion of birth cohorts that were born in an elimination setting. Studies on this population have demonstrated the effects of time and the potential for waning antibody levels [57,58].

Our results demonstrate that age at first dose of MCV may be the most influential driver in determining VE, confirming previous findings [19,59–62]. In both measles-endemic and eliminated settings, we observed a trend of increasing VE with increasing age at first dose of MCV. The timing of administration of the first dose of MCV balances several considerations. If the first dose is administered too early, immune responses can be blunted due to infant immunologic immaturity and maternal antibody interference [60]. However, if administered too late, infants can be placed at risk of measles virus infection [63,64]. The age at first dose of MCV in high burden settings is recommended by the WHO to be at 9 months, or possibly 6 months if an outbreak is occurring, to balance these factors [65]. In low burden settings, the first dose of MCV is administered between 12 and 15 months, favouring a higher seroconversion rate, but lengthening the duration of susceptibility to measles [65].

Most immunisation schedules now include a second dose of MCV. The introduction of the second dose helps immunize those with primary vaccine failure; however, immune boosting immediately following this dose may be short-lived [66]. The immune response, and, by proxy, VE, heavily depend on the age at which the first dose is administered. This latter finding is of great consequence for global vaccination policy given that the Americas achieved elimination by ensuring the first dose was given at 12 months but most of the world is giving the first dose at 9 months, and the most populous country in the world (China) is giving it as young as 8 months [67].

This systematic review has several limitations. Because of limited resources, we only included English articles in the review. However, our search did not reveal any non-English studies set in elimination settings. The small number of articles in measles-eliminated settings may simply reflect the small number of measles cases in these settings. However, our search strategy may also not have captured all existing data to address our research question if we missed VE estimates from investigations that were not published in peer-reviewed or grey literature. The method of defining cases was only available at an aggregate level, and could not be assessed at an individual level. It was also challenging to estimate waning VE amongst populations that have been eliminated for long periods of time, as only one of our three included studies in elimination settings was performed ≥10 years post-elimination [19]. It was not easy to compare results in measles-eliminated or –endemic settings because of great heterogeneity in setting, and data variability and gaps. Additionally, study heterogeneity prevented us from assessing laboratory confirmation in risk of bias analyses, due to the great spatial and temporal variability across studies. Including a large percentage of observational studies in our review introduced a variety of potential biases. We were unable to accurately assess exposure to measles virus in countries which may have previously been classified as eliminated, but subsequently lost their status. Misclassification of measles diagnoses may have occurred, due to the fact not all studies included laboratory confirmation in their case definitions. Lastly, non-differential misclassification of vaccination status may have occurred if information was not directly mentioned in the article, for example if an SIA was performed.

Given that the data in eliminated settings is exceedingly weak, we strongly recommend that public health authorities conduct more VE studies to monitor what happens as previously infected older birth cohorts die, and community protection becomes increasing reliant solely on immunisation. With this change in cohorts, it is essential researchers conduct studies examining the degree of waning and how quickly population antibody levels fall in the absence of circulating measles to inform elimination efforts. We also recommend development of a standardized approach to collecting and reporting information in studies of VE. The critical importance of age at first dose as a determinant of VE deserves much more attention in the development of country, regional and global strategies towards measles elimination and, ultimately, measles eradication.

5. Contributors

SLH, SB, SK, CJ, LF, ACT, SJMH, JMH, AD, DND, WAO, WJM, MJ, NKA, and NSC did the study design. SLH, SB, SK, CJ, LF, and NSC collected the data. SLH and YL did the statistical analysis. SLH wrote the first draft of the manuscript with input from SB, YL, CJ, LF, ACT, SJMH, JMH, DND, WAO, WJM, MJ, and NSC. All authors approved the final version and attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.10.090.

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