SUPPLEMENT ARTICLE

Field Effectiveness of Live Attenuated Measles-Containing Vaccines: A Review of Published Literature

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Background. Information on measles vaccine effectiveness (VE) is critical to help inform policies for future global measles control goals.

Methods. We reviewed results of VE studies published during 1960–2010.

Results. Seventy papers with 135 VE point estimates were identified. For a single dose of vaccine administered at 9–11 months of age and ≥12 months, the median VE was 77.0% (interquartile range [IQR], 62%–91%) and 92.0% (IQR, 86%–96%), respectively. When analysis was restricted to include only point estimates for which vaccination history was verified and cases were laboratory confirmed, the median VE was 84.0% (IQR, 72.0%–95.0%) and 92.5% (IQR, 84.8%–97.0%) when vaccine was received at 9–11 and ≥12 months, respectively. Published VE vary by World Health Organization region, with generally lower estimates in countries belonging to the African and SouthEast Asian Regions. For 2 doses of measles-containing vaccine, compared with no vaccination, the median VE was 94.1% (IQR, 88.3%–98.3%).

Conclusions. The VE of the first dose of measles-containing vaccine administered at 9–11 months was lower than what would be expected from serologic evaluations but was higher than expected when administered at ≥12 months. The median VE increased in a subset of articles in which classification bias was reduced through verified vaccination history and laboratory confirmation. In general, 2 doses of measles-containing vaccine provided excellent protection against measles.

The successful isolation of measles virus in 1954 by Enders and Peebles marked the eve of research that in the early 1960s resulted in availability of the first live attenuated measles-containing vaccines (MCVs). In 1963, the live attenuated MCV (Edmonston B strain) became licensed in the United States, and 2 additional attenuated live MCVs derived from the Edmonston strain became available in 1965 (Schwartz strain) and in 1968 (Moraten strain) [1]. The Moraten strain is currently the only MCV used in the United States; internationally, the most frequently used MCVs are of the Schwartz or the Edmonston-Zagreb strain and 2 other attenuated MCV strains derived from the original Edmonston strain [1]. Several other attenuated MCVs used in international settings are not related to the Edmonston strain, but are rather produced from locally derived wild-type measles virus strains; examples include the Leningrad-16 strain (Russian Federation), the Shanghai-191 strain (People's Republic of China), and CAM-70 and AIK-C strains (Japan) [1].

Serologic evaluations have demonstrated that, when handled and administered under ideal conditions, currently used attenuated MCVs elicit immune responses in the large majority of susceptible vaccine recipients. Age at vaccination is one of the key host-related determinants of vaccine efficacy as measured by antibody response after vaccination: frequently cited figures are that 85% of children develop protective antibody levels

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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when given 1 dose of MCV at 9 months of age, whereas 90%–95% respond when vaccinated at 12 months [2, 3]. Other host-related factors that may adversely affect immune response after measles vaccination include presence of passively acquired measles antibody, immunologic immaturity at vaccination, infection with human immunodeficiency virus type 1 (HIV-1), other immunosuppressive conditions, and in some circumstances, concurrent acute infections [3].

Routine measles vaccination remained sporadic in developing countries until the advent of the World Health Organization (WHO) Expanded Programme on Immunization (EPI) during the late 1970s. In 1983, the WHO EPI recommended routine vaccination with a single dose of MCV for children aged ≥9 months [1]. Most developing countries subsequently adopted that recommendation into their national immunization schedule and MCV use became more widespread, with single-dose measles vaccination programs remaining the standard practice in most parts of the world for almost 2 decades.

Measles-containing vaccines are generally recognized as safe and effective [1]. In 2005, >1 decade after the successful elimination of the indigenous measles virus circulation in Finland through a 2-dose routine vaccination program [4] and 3 years after region-wide measles elimination in the Americas [5], the WHO Global Immunization Vision and Strategy document established a goal of 90% global measles mortality reduction by 2010, compared with 2000 estimates [6]. Until 2009, strategies emphasized routine 1-dose vaccination and the second opportunity for vaccination mainly through Supplemental Immunization Activities (SIAs), primarily to reach previously unvaccinated children. During 2000–2008, these efforts resulted in a 78% decrease in estimated measles-related deaths worldwide, from an estimated 733,000 deaths in 2000 to 164,000 deaths in 2008 [7]. In 2009, a global recommendation was made for a 2-dose MCV scheduled for all children [8]. Currently, 5 of the 6 WHO Regions have established target dates for measles elimination, and the feasibility of a global eradication goal is being evaluated [9, 10]. As more ambitious measles control targets are being considered, we present here results of a literature review undertaken to summarize experience with effectiveness of measles-containing vaccines administered at different ages worldwide, to inform the formulation of future vaccination policies.

METHODS

Identification of Studies

Medline and PubMed were searched for articles on measles-containing vaccine effectiveness (VE), applying different combinations of the terms "measles," in conjunction with "vaccine," "mumps, rubella vaccine," "outbreak," "effectiveness," "efficacy," and "vaccine failure." Any additional articles that may not have been included in the initial search strategy were identified by reviewing references of articles obtained and the *Vaccines* textbook (5^{th} edition) [1].

Inclusion Criteria

We considered any reports that provided estimates of measles-containing VE that were available in the English language since vaccine licensure in 1963 until May 2010. We included only articles that evaluated the effectiveness of measles-containing vaccines administered under routine field conditions by estimating the VE using ≥1 methods described by Orenstein et al [11].

Data Extraction and Statistical Analyses

We abstracted data from each article that included (but was not limited to) the following key variables: year and type of study (ie cohort, case-control, or screening method), country and WHO Region, ages that were assessed and their birth cohorts, age at first and second dose of vaccine, vaccine type and strain (when available), VE point estimate, and VE 95% confidence intervals (CIs; when available).

VE point estimates for the overall study sample (where provided) were assessed, as were estimates stratified by age of receipt of the first dose of a measles-containing vaccine at 9–11 months of age and at ≥12 months of age. A specific article may include several point estimates because of assessments of VE for different age groups. Some articles presented an overall VE point estimate for all ages considered in the study and separate VE point estimates for ≥2 age strata in the same study group. Furthermore, a number of articles presented VE estimates resulting from >1 study type, including cohort, case-control, and screening studies. In such situations, each of the VE point estimates was separately included in the summary table along with the explanatory information.

We explored the distribution of the published VE estimates by age of vaccination and by geographic region on a subset of the VE point estimates produced by case-control or cohort studies included in this review. For this analysis, we calculated summary statistics (mean, median, and interquartile range [IQR]) for the published VE point estimates stratified by age of receipt of the first dose of MCV (MCV1) worldwide and by WHO region (ie, regions of Africa [AFR], the Americas [PAHO], SouthEast Asia [SEAR], Europe [EUR], Eastern Mediterranean [EMR], and Western Pacific [WPR]). Finally, we separately summarized the distribution of the published VE estimates by age of vaccination for VE estimates produced by case-control or cohort studies in which case patients had either laboratory confirmed measles, or in which cases were epidemiologically linked to a laboratory-confirmed outbreak and in which vaccination status for all study participants was ascertained using a written vaccination record. All summary statistics for the aforementioned analyses were calculated using JMP Software (SAS Institute).

We did not include point estimates that were only speculated in some of the articles as an attempt to address possible study biases (eg, possible misclassification based on vaccination status, disease, and susceptibility status). VE estimates that included children who received vaccine at ≤8 months of age were not included, because this is not a routinely recommended age for measles vaccination [3, 12].

RESULTS

Overall, we identified 71 English-language papers published during 1969–2010 that presented ≥1 VE estimate of a live attenuated MCV, with a total of 135 VE point estimates including 122 for MCV1 and 14 for a second dose of MCV (MCV2) (Table 1).

One-Dose MCV VE

Of 122 reported MCV1 VE point estimates, 16 (13%) were reported from a case-control study, 92 (75%) from a cohort study, and 14 (12%) from a study that used the screening method to evaluate VE. All WHO regions were represented among abstracted MCV1 VE estimates, but few studies were published from SEAR and EMR. For 84 (69%) of the 122 MCV1 point estimates identified, vaccine type and vaccine strain were not specified. Thirty-four (28%) MCV1 VE point estimates had information on vaccine strain and type; of these, 3 (9%) were from use of the live attenuated strain (Edmonston [1], multiple live-attenuated strains [1], or unspecified [1]); the remaining 31 (91%) point estimates with strain and type information were from use of a live further attenuated measles virus strain (AIK-C [1], L-16 [1], Moraten [6], Schwarz [16], multiple live further attenuated strains [1], and unspecified [2]).

To assess whether some factors related with the period during that the study was conducted may have influenced the VE estimates, we explored the distribution of MCV1 VE point estimates by grouping them into 2 intervals (1969–1989 and 1990–2009) and by the decade. The group of 48 MCV1 VE point estimates from studies conducted during 1969–1989 had the median value of 88.3% (IQR, 77.3%–94.9%; range, 37%–100%), compared with the median VE of 91.0% (IQR, 83.3%–95.0%; range, 26.0%–100%) in the group of 74 MCV1 VE point estimates from studies conducted during 1990–2009. Similarly, there was little difference in distribution of MCV1 VE point estimates by the decade of the study (data not shown).

Distribution of the reported MCV1 VE by age of vaccination was explored taking into consideration 106 nonnegative MCV1 VE point estimates reported from studies with case-control or cohort designs (Table 2). When MCV1 was administered at any age ≥9 months, the median reported VE was 91.0% (IQR, 79.0%–95.0%; range, 25.0%–100.0%). When MCV1 was administered at age 9–11 months, the median reported VE was 77.0% (IQR, 68.0%–91.0%); by WHO region, the median MCV1 VE point estimates ranged from 73.0% in AFR to 96.0% in EUR. The median VE for MCV1 given at >12 months was 92.0% (IQR, 88.0%–96.0%); by region, it ranged from 88% in AFR to 94% in AMR and SEAR (Table 2).

When the analysis was restricted to include only the 44 MCV1 VE estimates from those case-control or cohort studies in which the vaccination status for all study participants was ascertained using an official record and in which laboratory confirmation was used to confirm measles diagnosis among case patients participating in the study or the outbreaks with which these cases were epidemiologically associated, the median VE of MCV1 given at age 9–11 months was 84.0% (IQR, 72.0%–95.0%), at age ≥12 months was 92.5% (IQR, 84.8%–97.0%), and at any age ≥9 months was 92.0% (IQR, 84.0%–96.8%; Table 2). Of note, 41 (93%) of the 44 MCV1 VE point estimates considered in this group were predominantly clustered in 3 WHO regions: AMR, EUR, and WPR (AMR, 24 [54.5%]; EUR, 7 [15.9%]; WPR, 10 [22.7%]; AFR, 2 [4.5%]; SEAR, 1 [2.2%]).

Two-Dose MCV VE

Overall, in the 71 articles reviewed, we identified 14 VE point estimates that presented information on MCV2, representing AMR ($n = 6$), EUR ($n = 6$), and WPR ($n = 2$) (This excludes 1 point estimate from a study in which methodology did not meet the inclusion criteria for this review). Nine of the 14 MCV2 VE point estimates were from an unspecified type vaccine and vaccine strain, 2 were from a live further attenuated strain, and 1 each of Schwarz and Moraten.

We identified 8 case-control or cohort studies that evaluated MCV2 VE, compared with no vaccination [40, 44, 55, 58, 59, 60, 79, 82]; on the basis of these studies, the overall median VE of receipt of MCV2, compared with no vaccination, was 94.1% (IQR, 88.3%–98.3%).

We identified 5 case-control or cohort studies that evaluated the effectiveness of MCV2, compared with receipt of MCV1; one study reported an incremental VE of 67% [44], and the other 4 reported MCV2 VE point estimates of 94%–100% [4, 42, 45, 61].

DISCUSSION

Results of this literature review suggest that the VE of MCV1 administered at 9–11 months of age is generally lower than 85%, which is the usual expected rate of immune response after vaccination at that age [3]. In contrast, effectiveness of MCV1 administered at age of ≥12 months is close to the usually cited values of 90%–95% [3]. Published MCV1 effectiveness estimates vary by geographic region, which may be related to the age of vaccination and other factors. Lower

Table 1. Summary of All Measles-Containing Vaccine (MCV) Vaccine Effectiveness (VE) Point Estimates

WHO region	Year[a]	Country	Reference	Study design	Laboratory[b]	Vaccination record[c]	Vaccine strain, if indicated	Vaccine effectiveness point estimate, % (95% CI): 1 dose: Received at 9-11 months (CI) [additional information where multiple estimates calculated, if specified]	1 dose: Received at ≥ 12 months (CI) [additional information where multiple estimates calculated, if specified]	1 dose: Age not specified[d] (CI) [additional information where multiple estimates calculated, if specified]	2 doses: 2 doses vs 0 (CI)	2 doses: 2 doses vs 1 (CI)
AFR												
	1981	Gambia	Hull et al [13]	Cohort	–	√		–	–	89 (77–94) [>9 months]	–	–
	1981	Gambia	Hull et al	Cohort	–	√		85 (52–94) [vaccinated at 9-11 months]	–	–	–	–
	1981	Gambia	Hull et al	Cohort	–	√		–	86 (41–95) [vaccinated at 12-14 months]	–	–	–
	1981	Gambia	Hull et al	Cohort	–	√		–	90 (76–95) [vaccinated at >15 months]	–	–	–
	1986	Mozambique	Cutts et al. [14]	Cohort	–	√		40 (28–56)	–	–	–	–
	1986	Mozambique	Cutts et al	Cohort	–	√		59 (37–72)	–	–	–	–
	1986	Mozambique	Cutts et al	Cohort	–	√		37 (<0–69)	–	–	–	–
	1987	Zimbabwe	Marufu et al [15]	Screening	–	–	Schwarz	73 [Year of study 1987]	–	–	–	–
	1987	Zimbabwe	Marufu et al	Screening	–	–	Schwarz	82 [Year of study 1988]	–	–	–	–
	1987	Zimbabwe	Marufu et al	Screening	–	–	Schwarz	77 [Year of study 1989]	–	–	–	–
	1987	Zimbabwe	Mudzamiri et al [16]	Cohort	–	–	Schwarz	78 (54–90)	–	–	–	–
	1988	Burundi	Chen et al [17]	Cohort	–	√		73	–	–	–	–
	1990	Niger	Malfait et al [18]	Case-control	–	√	Schwarz	92 (82–96)	–	–	–	–
	1990	Niger	Malfait et al	Cohort	–	√	Schwarz	26 (0–84) [Vaccinated at 9-11 months]	–	–	–	–

Table 1. (Continued)

AFR (continued)												
1990	Niger	Malfait et al	Cohort	–	√	Schwarz		94 (84–98) [Vaccinated at 12-23 months]	–	–	–
1990	Niger	Malfait et al	Cohort	–	√	Schwarz		88 (76–94) [Vaccinated at 24-59 months]	–	–	–
1990	Niger	Malfait et al	Cohort	–	√	Schwarz			89 (81–94) [Vacci-nated at 9-59 months]	–	–
1990	Niger	Malfait et al	Screening	–	–	Schwarz	87 (80–92) [Children aged 9-11 months]	–	–	–	–
1990	Niger	Malfait et al	Screening	–	–	Schwarz		90 (83-94) [Children aged 12-23 months]	–	–	–
1990	Uganda	Weeks et al [19]	Cohort	–	–		55 [location 1]	–	–	–	–
1990	Uganda	Weeks et al	Cohort	–	–		75 [location 2]	–	–	–	–
1991	Tanzania	Simba et al [20]	Case -control	√	√		84 (61-93)	–	–	–	–
1993	Chad	Ndikuyeze et al [21]	Cohort	–	–		71 (59-80)	–	–	–	–
1995	Niger	Kaninda et al [22]	Cohort	–	√	Schwarz	95 (93-95)	–	–	–	–
1996	Kenya	Borus et al [23]	Screening	–	–		84	–	–	–	–
1996	Zimbabwe	Mahomva et al [24]	Cohort	–	√	Schwarz	68	–	–	–	–
1999	Uganda	Mupere et al [25]	Cohort	√	√		74 (64-81)	–	–	–	–
2000	Ethiopia	Talley et al [26]	Cohort	–	–		72 (55-89)	–	–	–	–
2003	South Africa	McMorrow et al [27]	Screening	–	–		85 (63-94) [location 1, PPV[e] 80%]	–	–	–	–
2003	South Africa	McMorrow et al	Screening	–	–		94 (84-97) [location 1, PPV 90%]	–	–	–	–
2003	South Africa	McMorrow et al	Screening	–	–		89 (77-95) [location 2, PPV 80%]	–	–	–	–
2003	South Africa	McMorrow et al	Screening	–	–		95 (90-98) [location 2, PPV 90%]	–	–	–	–

Table 1. (Continued)

WHO region	Year[a]	Country	Reference	Study design	Laboratory[b]	Vaccination record[c]	Vaccine strain, if indicated	Vaccine effectiveness point estimate, % (95% CI): 1 dose: Received at 9-11 months (CI) [additional information where multiple estimates calculated, if specified]	1 dose: Received at ≥ 12 months (CI) [additional information where multiple estimates calculated, if specified]	1 dose: Age not specified[d] (CI) [additional information where multiple estimates calculated, if specified]	2 doses: 2 doses vs 0 (CI)	2 doses: 2 doses vs 1 (CI)
AMR												
	1969	United States	Lerman et al[f] [28]	Cohort	√	√	Edmonston	99	–	–	–	–
	1970	United States	Landrigan [29]	Cohort	–	√	LA (n.s.)[g]	96	–	–	–	–
	1970	United States	Wyll et al [30]	Cohort	–	–		91	–	–	–	–
	1972	United States	Andrews et al [31]	Cohort	–	–		–	96	–	–	–
	1973	United States	Ziskin et al [32]	Cohort	√	√		–	94 [Location 1]	–	–	–
	1973	United States	Ziskin et al	Cohort	√	√		–	87 [Location 2]	–	–	–
	1976	United States	Marks et al [33]	Cohort	–	√		75 [vaccinated at 9-11 months]	–	–	–	–
	1976	United States	Marks et al	Cohort	–	√		90 [vaccinated at 11 months]	–	–	–	–
	1976	United States	Marks et al	Cohort	–	√		–	96 [vaccinated at 12 months]	–	–	–
	1976	United States	Marks et al	Cohort	–	√		–	97 [vaccinated at 13 months]	–	–	–
	1976	United States	Marks et al	Cohort	–	√		–	97 [vaccinated at 14 months]	–	–	–
	1984	Canada	Guasparini et al [34]	Cohort	√	√		–	92 [Assessed for children in grades K-2]	–	–	–
	1984	Canada	Guasparini et al	Cohort	√	√		–	84 [Assessed for children in grades 3-7]	–	–	–
	1984	Canada	Guasparini et al	Cohort	√	√		–	39 [Assessed for children in grades 8-12]	–	–	–

Table 1. (Continued)

AMR (continued)											
1984	United States	Nkowane et al [35]	Cohort	√	√		–	94 (91-97)	–	–	–
1985	United States	Davis et al [36]	Cohort	√	√		–	97	–	–	–
1986	United States	Mast et al [37]	Cohort	√	√		–	93 (81-98)	–	–	–
1986	United States	Robertson et al [38]	Cohort	√	√		70 (22-88) [vaccinated at 9-11 months]		–	–	–
1986	United States	Robertson et al	Cohort	√	√			92 (81-96) [Vaccinated at >12 months]	–	–	–
1988	United States	Hersh et al [39]	Cohort	√	√		–	80 (51-92) [vaccinated at 12-14 months]	–	–	–
1988	United States	Hersh et al	Cohort	√	√		–	94 (86-98) [vaccinated at >15 months]	–	–	–
1989	Canada	De Serres et al [40]	Cohort	√	√	Moraten	84 (65-92) [vaccinated at 9-11 months]	–		100 (85-100)	
1989	Canada	De Serres et al	Cohort	√	√	Moraten	–	85 (78-90) [vaccinated at 12 months]	–	–	–
1989	Canada	De Serres et al	Cohort	√	√	Moraten	–	92 (82-96) [vaccinated a 13 months]	–	–	–
1989	Canada	De Serres et al	Cohort	√	√	Moraten	–	95 (84-98) [vaccinated at 14 months]	–	–	–
1989	Canada	De Serres et al	Cohort	√	√	Moraten	–	94 (85-97) [vaccinated at 15-17 months]	–	–	–
1989	Canada	De Serres et al	Cohort	√	√	Moraten	–	97 (89-99) [vaccinated at >18 monnths]	–	–	–
1989	United States	King et al [41]	Cohort	–	√		–	95 (89-97)	–	–	–
1994	United States	Vitek et al [42]	Cohort	√	–		–	92 [location 1]			100
1994	United States	Vitek et al	Cohort	√	–		–	91 [location 2]	–	–	–
1995	Canada	Rivest et al [43]	Case-control	√	√		–	–	96 (32-100)	–	–
1995	Canada	Rivest et al	Case-control	√	√		–	92 (-54-100) [vaccinated at 12 months]	–	–	–

Table 1. (Continued)

WHO region	Year[a]	Country	Reference	Study design	Laboratory[b]	Vaccination record[c]	Vaccine strain, if indicated	Vaccine effectiveness point estimate, % (95% CI)				
								1 dose			2 doses	
								Received at 9-11 months (CI) [additional information where multiple estimates calculated, if specified]	Received at ≥ 12 months (CI) [additional information where multiple estimates calculated, if specified]	Age not specified[d] (CI) [additional information where multiple estimates calculated, if specified]	2 doses vs 0 (CI)	2 doses vs 1 (CI)
AMR (continued)												
	1995	Canada	Rivest et al	Case-control	√	√		–	96 (27-100) [vaccinated at 13 months]	–	–	–
	1995	Canada	Rivest et al	Case-control	√	√		–	97 (43-100) [vaccinated at 14 months]	–	–	–
	1995	Canada	Rivest et al	Case-control	√	√		–	98 (60-100) [vaccinated at >15 months]	–	–	–
	1995	Canada	Sutcliffe et al [44][h]	Cohort	–	–		–		–	89	67
	1998	United States	Lynn et al [45]	Cohort	√	√					94 (60-99)	
	2003	United States	Yeung et al [46]	Cohort	√	√		–	–		99 (92-99)	
EMR										–	–	–
	1990	Pakistan	Murray et al [47]	Cohort	–	√		–	–	89 (76-91)	–	–
	1990	Pakistan	Murray et al	Cohort	–	√		76 (48-89)	–	–	–	–
	1990	Pakistan	Murray et al	Cohort	–	√		–	87 (66-95) [vaccinated 12-14 months]	–	–	–
	1990	Pakistan	Murray et al	Cohort	–	√		–	92 (75-97) [vaccinated >15 months]	–	–	–
	1995	Egypt	Kotb et al [48][i]	Case-control	–	√		–	–	53	–	–
EUR										–	–	–
	1988	Romania	Agocs et al [49]	Cohort	–	√	L-16	96 (68-100)	–	–	–	–

Table 1. (Continued)

EUR (continued)											
1991	Wales	Lyons et al [50]	Case-control	√	√		–	99 (90-100)	–	–	–
1991	Wales	Lyons et al	Cohort	√	√		–	97 (90-100)	–	–	–
1992	Ireland	Tohani et al [51]	Cohort		√		–	94 (91-96)	–	–	–
1992	Wales	Morse et al [52]	Cohort	√	√		–	92	–	–	–
1995	Italy	BCPN [53]	Screening	–	–		–	96 (93-98)	–	–	–
1996	Luxembourg	Mossong et al [54]	Cohort	√	√		–	95 (90-97)	–	–	–
1996	Romania	Hennessey et al [55]	Case-control	–	√	Schwarz	–	–	94 (86-98)	–	–
1996	Romania	Hennessey et al	Cohort	–	√	Schwarz	88 (82-92)		–	–	–
1996	Romania	Hennessey et al	Cohort	–	√	Schwarz	–	91 (87-94) [vaccinated at 12-15 months]	–	96 (92-98)	–
1996	Romania	Hennessey et al	Cohort	–	√	Schwarz	–	90 (84-94) [vaccinated at 16-24 months]	–	–	–
1996	Romania	Hennessey et al	Cohort	–	√	Schwarz	–	79 (68-87) [vaccinated at >24 months]	–	–	–
1996	Romania	Hennessey et al	Cohort	–	√	Schwarz	–		89 (85-96)	–	–
1997	Poland	Janaszek et al [56]	Screening	–		Multiple LFA (n.s.)[j]	–	90	–	99 (99-100)	–
2001	Bavaria	Arenz et al [57]	Cohort	–	–		–	–	90	–	–
2001	Bavaria	Arenz et al	Screening	–	–		–	–	97	–	–
2004	Georgia	Doshi et al [58]	Cohort	–	√		–	86 (54-96)	–	88 (34-98)	–
2006	Germany	Wichmann et al [59]	Cohort	√	√		98 (92-100)	–	–	99 (97-100)	–
2006	Ukraine	Velicko et al [60]	Case-control	√	√	Multiple LA (n.s.)	–	92 (79-97)	–	93 (81-98)	–
2008	Australia	Schmid et al [61]	Cohort	√	√		–	97 (80-100)	–	–	100
SEAR										–	–
1987	India	Sharma et al [62]	Cohort	–	–		53 (35-71)	–	–	–	–

Table 1. (Continued)

WHO region	Year[a]	Country	Reference	Study design	Laboratory[b]	Vaccination record[c]	Vaccine strain, if indicated	Vaccine effectiveness point estimate, % (95% CI): 1 dose			2 doses	
								Received at 9-11 months (CI) [additional information where multiple estimates calculated, if specified]	Received at ≥ 12 months (CI) [additional information where multiple estimates calculated, if specified]	Age not specified[d] (CI) [additional information where multiple estimates calculated, if specified]	2 doses vs 0 (CI)	2 doses vs 1 (CI)
SEAR (continued)												
	1989	India	Chawla et al [63]	Cohort	–	–			–	86 (75-97)	–	–
	1989	India	Chawla et al	Cohort	–	–		77	–	–	–	–
	1989	India	Chawla et al	Cohort	–	–		–	88 [vaccinated at 12-14 months]	–	–	–
	1989	India	Chawla et al	Cohort	–	–		–	100 [vaccinated at >15 months]	–	–	–
	1995	Bangladesh	Akramuzzaman et al [64]	Case-control	–	–		80 (60-90)	–	–	–	–
	1999	India	John et al [65]	Cohort	√	–		–	–	62	–	–
	2000	Thailand	Lertpiriyasuwat et al [66]	Cohort	√	√		91 (42-99)	–	–	–	–
	2001	India	Puri et al [67]	Cohort	–	–		62 (46-73)	–	–	–	–
	2006	India	John et al [68]	Cohort	√	–		–	–	43	–	–
WPR										–	–	–
	1978	Marshell Islands	McIntyre et al [69]	Cohort	√	√	LFA (n.s.)	–	84 (74-89)	–	–	–
	1985	Taiwan	Gao et al [70]	Cohort	√	√	LA (n.s.)	40	–	–	–	–
	1991	Australia	Cheah et al [71]	Cohort	√	√	Schwarz	–	72 (46-86)	–	–	–
	1992	Australia	Anonymous [72]	Cohort	–	–		–	100	–	–	–
	1993	Australia	Herceg et al [73]	Cohort	–	–		–	90 (75-96)	–	–	–
	1993	Australia	McDonnell et al [74]	Case-control	–	√		96 (64-99)	–		–	–

Table 1. (Continued)

WPR (continued)

1993	Australia	McDonnell et al	Case-control	–	√		–	95 (81-99) [vaccinated at 12-14 months]	–	–	–
1993	Australia	McDonnell et al	Case-control	–	√		–	93 (80-98) [vaccinated at >15 months]	–	–	–
1993	Australia	McDonnell et al	Case-control	–	√			–	94 (83-98)	–	–
1993	Australia	Srirajalingam et al [75]	Cohort	–	–		–	91 (80-96)	–	–	–
1993	Korea	Kim et al [76]	Cohort	–	–	AIK-C	–	92 (84-96)	–	–	–
1993	Palau	Guris et al [77]	Cohort	√	√		–	86	–	–	–
1994	Australia	Patel et al [78]	Cohort	√	√		–	97 (78-100)	–	–	–
1994	Taiwan	Lee et al [79]	Cohort	√	√		–	79 (6-95)	–	88 (41-98)	–
1997	Canada	Gidding et al [80]	Cohort	√	√		–	81	–	–	–
2002	Japan	Mori et al [81]	Cohort	√	√		–	77 (52-88) [location 1]	–	–	–
2002	Japan	Mori et al	Cohort	√	–		–	99 (95-100) [location 2]	–	–	–
2003	Marshell Islands	Marin et al [82]	Cohort	√	√		92 (67-98)	–	–	95 (82-98)	–
2004	Singapore	Ong et al [83]	Cohort	√	√		–	98	–	–	–
2006	Wales	Sheppeard et al [84]	Screening	–	–		–	96 (78-99)	–	–	–

NOTE. [a] Year of study (earliest indicated)

[b] Laboratory confirmation of all cases, or cases epidemiologically linked to a lab-confirmed outbreak

[c] Vaccination history ascertained from a written record

[d] >9 months of age

[e] Proportion of the population vaccinated

[f] This study reported VE of 66% for vaccine given at a single provider's office where it was exposed to warm temperatures

[g] Live attenuated (not specified)

[h] This study reported VE point estimate of -200 for MCV1 administered at ≥12 months of age.

[i] This study also reported separate values for vaccine effectiveness at 9 months (26%) and at >9 months (72%)

[j] Live further attenuated

than expected VE estimates were primarily reported by studies conducted in countries belonging to the African and the South-East Asian regions of the WHO, where MCV1 is usually scheduled for children aged ≥9 months of age. In contrast, studies conducted in the American, European, and Western Pacific regions, where countries more frequently recommend MCV1 at ≥12 months of age, more frequently documented higher VE estimates. There was little difference in distribution of published MCV1 VE point estimates with regard to the period during which the study was conducted that would suggest that more recent VE estimates may be generally higher than the historic VE estimates because of factors, such as programmatic improvements related to efforts to strengthen immunization infrastructure (eg, better cold chain and better vaccine handling), or because of certain host factors, such as younger age of loss of maternal antibody in children born to vaccinated mothers [85].

The retrospective nature of VE evaluation studies often precludes precise identification of the reasons for reduced effectiveness. Generally, the reasons related to low VE estimates can be grouped into 3 broad categories, including (1) issues related to study methods; (2) program-related factors, such as appropriate vaccine storage, handling, and administration; and (3) host-related factors, most notably, age at vaccination.

Previously described reasons that could result in biasing the VE estimates and that are inherent to study methods include misclassification of case status because of inaccurate diagnosis, misclassification of the vaccination status, and lack of comparability between the cases and the noncases considered in the VE evaluation study with regard to potential confounding factors (eg, differences in risk of exposure to measles during the outbreak and differences in susceptibility to measles because of an unaccounted history of infection) [11]. Several articles included in this review acknowledge that ≥1 of these reasons may have led to an underestimate of the VE, including possible issues with misclassification of the disease status [14, 21, 24], misclassification of vaccination status [34, 80, 81], and bias resulting from possible differences among study participants in risk for measles infection because of inability to ascertain history of measles disease [17]. One study identified the small number of cases as a potential reason for a low VE point estimate in the cohort study that evaluated VE for children aged 9–11 months; a case-control analysis undertaken in the same study population yielded a VE in the expected range [18].

Program-related factors were most frequently hypothesized as possible reasons for low reported VE estimates. These included cold chain issues [15, 19, 25, 26, 62, 69, 70], inadequate vaccine handling [25, 69], poor vaccine storage [71, 81], and inadequate vaccine administration [71]. However, only one study reported actual observed programmatic reasons that may have resulted in low VE; these reasons included inadequate vaccination practices and frequent power cuts that may have compromised cold chain [14].

A number of authors discussed various host factors that may have been related to lower MCV1 VE estimates reported in their studies, including young age at vaccination with MCV1 and subsequent interference from maternally derived measles IgG antibodies [15, 47, 62, 67], malnutrition [67], and HIV infection [26, 27].

Waning immunity was considered as a possible explanation for a low MCV1 VE point estimate in 1 of the 3 age strata considered in one study, but it was not found to be a probable explanation for the low VE estimate because it was not coupled with a high attack rate among vaccinated children [33] and because both waning immunity and primary vaccine failure were discussed in 2 separate studies conducted in India as possible reasons for low MCV1 VE [65, 67]. However, no evidence of waning immunity was found in studies that investigated large outbreaks in island populations that occurred after long intervals without documented measles virus circulation [77, 82].

Intensity of exposure resulting from crowding was recognized as a possible reason for reduced MCV1 VE in 2 studies that reported low MCV1 VE [24, 38]. Crowding also may have been a factor for observed lower VE in other settings. In a study conducted during a large measles outbreak in a boarding school, Yeung et al [46] documented an apparently lower 2-dose VE among students who received both doses outside the United States (94%; 95% CI, 69.6%–98.3%) than among those who received both doses in the United States (99.1%; 95% CI, 95.5%–98.8%); the authors hypothesized that the reasons for this apparent difference may include the cold chain, mishandling of vaccine with respect to constitution, less accurate vaccination histories, or greater intensity of exposure during the outbreak.

The results from 14 studies that presented two-dose VE estimates indicate that in general, two doses of vaccine provide excellent protection against measles. However, three of eight MCV2 VE point estimates in which effectiveness of 2-dose vaccination was compared with no vaccination yielded an MCV2 estimate of <90%. All three of these studies also reported reduced MCV1 VE point estimates, but possible reasons for such results were not discussed [44, 58, 79].

The results of this literature review are subject to at least 4 broad categories of limitations. First, our search was limited to published English-language studies and did not consider an unknown number of publications in other languages. Second, because our review focused on published results only, it is also possible that our results are subject to

Table 2. Effectiveness of the First Dose of Measles Containing Vaccine (MCV1 VE) by Age of 1st Dose 9–11 Months and ≥12 Months[a]

	No. of MCV1 VE point estimates	MCV1 VE point estimates summary statistics				
			Interquartile range		Range	
		Median	25th percentile	75th percentile	Min	Max
Age of 1st dose						
9–11 months, all regions	35	77.00%	68.00%	91.00%	26.00%	99.00%
By WHO region						
AFR	16	73.00%	57.00%	81.00%	26.00%	95.00%
AMR	7	90.00%	75.00%	95.90%	70.00%	99.00%
EMR	1	1 point estimate of 76%				
EUR	3	96.0%	88.0%	98.0%	88.0%	98.0%
SEAR	5	77.0%	57.5%	85.5%	53.0%	91.0%
WPR	3	92.0%	39.8%	96.0%	39.8%	96.0%
≥12 months, all regions	61	92.0%	88.0%	96.0%	39.0%	100.0%
By WHO region						
AFR	4	88.0%	86.0%	92.0%	86.0%	94.0%
AMR	27	94.0%	92.0%	96.0%	39.0%	98.0%
EMR	2	89.5%	87.0%	92.0%	87.0%	92.0%
EUR	11	92.0%	90.0%	97.0%	79.0%	99.3%
SEAR	2	94.0%	88.0%	100.0%	88.0%	100.0%
WPR	15	91.0%	81.3%	97.0%	72.0%	100.0%
Any age, (≥9months)[b]	106	91.0%	79.0%	95.0%	25.0%	100.0%
Lab confirmed/vx hx ascertained by record estimates						
Age of 1st dose						
9–11 months	9	84.0%	72.0%	95.0%	40.0%	99.0%
≥12 months	34	92.5%	84.8%	97.0%	39.0%	99.0%
Any age, (≥9months)	44	92.0%	84.0%	96.8%	39.0%	99.0%

NOTE. [a] Includes point estimates by case-control and cohort methodology.

[b] Includes point estimates in 9–11 months and ≥12 months categories, and those which do not fall within the 9–11 months and ≥12 months distinct categories

publication bias; unpublished studies may have yielded results different from those that were published. Third, the review included observational study results with numerous limitations inherent to study design, varying degrees of completeness and quality of presented data, and an uneven distribution of studies between and in geographic regions. A concerted effort was made to tabulate the original VE estimates as reported in the source articles, to convey, at least in part, the diversity of the included studies. Finally, we were able to identify relatively few studies that evaluated MCV2 VE.

The small number of published studies that evaluated MCV2 VE may be at least partly related to a small number of measles outbreaks among vaccinated individuals in areas with mature 2-dose vaccination programs. Indeed, sustained high 2-dose measles vaccination coverage was documented as the key strategy in achieving and sustaining measles elimination in Finland [4], the United States [85], and throughout the the Americas [5]. Postelimination measles outbreaks in these settings have mainly been associated with gaps in vaccine-induced immunity in select communities, which is a finding that usually precludes a need for VE evaluation [86–88]. In contrast, during 2000–2010, some countries that were formerly a part of the Soviet Union experienced large measles outbreaks among adolescents and adults in spite of mature 2-dose vaccination programs and high reported vaccination coverage since the early 1980s; this raised concerns about both accuracy of the historic vaccination records and VE [55, 56].

Since 2009, the WHO has recommended two doses of MCV for all children [8]. As more advanced global, regional, and national measles control goals are being considered, increasing use of measles-containing vaccine should be anticipated to result not only in decreasing disease incidence but also in a greater proportion of vaccinated individuals among cases in future measles outbreaks [11]. Therefore, further efforts will be needed to encourage investigation of outbreaks, including VE evaluations. As vaccination efforts continue to be scaled up globally, VE evaluations will be critical to maintain confidence in vaccination programs and to quickly identify any subpopulations and settings where certain host- or program-related factors may be leading to reduced VE. Measles outbreaks occurring in settings with high prevalence of HIV infection and AIDS deserve particular attention for future VE evaluations because of previously recognized issues with lower vaccine immunogenicity and uncertainties about duration of vaccine-derived immunity in HIV-infected children [3].

In summary, published VE studies indicate the importance of recommending 2 doses of measles vaccine to achieve and sustain the measles mortality reduction and regional elimination goals. To ensure appropriate monitoring of measles VE in areas that have been traditionally under-represented in the published literature, such as the African, SouthEast Asian, and Eastern Mediterranean Regions, further efforts are needed to support capacity building for epidemiologic investigation of measles outbreaks, scale up laboratory support for measles diagnostics and surveillance, and increase availability and reliability of written vaccination records.

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