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Effectiveness of Two-dose Varicella Vaccination: Bayesian Network Meta-analysis

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ABSTRACT

Purpose: A 2-dose varicella vaccination strategy has been introduced in many countries worldwide, aiming to increase vaccine effectiveness (VE) against varicella infection. In this network meta-analysis, we aimed to provide a comprehensive evaluation and an overall estimated effect of varicella vaccination strategies, via a Bayesian model.
Methods: For each eligible study, we collected trial characteristics, such as: 1-dose vs. 2-dose, demographic characteristics, and outcomes of interest. For studies involving different doses, we aggregated the data for the same number of doses delivered into one arm. The preventive effect of 1-dose vs. 2-dose of varicella vaccine were evaluated in terms of the odds ratio (OR) and corresponding equal-tailed 95% confidence interval (95% CI).
Results: A total of 903 studies were retrieved during our literature search, and 25 interventional or observational studies were selected for the Bayesian network meta-analysis. A total of 49,265 observed individuals were included in this network meta-analysis. Compared to the 0-dose control group, the OR of all varicella infections were 0.087 (95% CI, 0.046–0.164) and 0.310 (95% CI, 0.198–0.484) for 2-doses and one-dose, respectively, which corresponded to VE of 69.0% (95% CI, 51.6–81.2) and VE of 91.3% (95% CI, 83.6–95.4) for 1- and 2-doses, respectively.
Conclusions: A 2-dose vaccine strategy was able to significantly reduce varicella burden. The effectiveness of 2-dose vaccination on reducing the risk of infection was demonstrated by sound statistical evidence, which highlights the public health need for a 2-dose vaccine recommendation.

Keywords: Varicella; Chickenpox; Vaccination; Effectiveness; Meta-analysis; Systematic review

INTRODUCTION

Varicella-zoster virus infections pose a significant global disease burden.[1] Following the introduction of universal childhood vaccination against varicella, the number and rates of varicella cases and mortality have declined markedly.[2,3] However, despite early success, reports of varicella outbreaks in highly immunized groups have increased concern about 1-dose vaccination strategies in recent years.[4] Breakthrough varicella can be attributed to either primary or secondary vaccine ineffectiveness. Primary vaccine ineffectiveness is

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Hong K, Kim YK; Data curation: Hong K; Formal analysis: Hong K; Funding acquisition: Kim YK; Investigation: Hong K, Yoon Y, Kim YK; Methodology: Hong K, Lee YH, Yoon Y; Project administration: Lee YH, Yoon Y; Resources: Lee YH, Yoon Y; Software: Hong K; Supervision: Choe YJ, Kim YK; Validation: Hong K, Kim YK; Writing - original draft: Hong K, Choe YJ, Kim YK; Writing - review & editing: Hong K, Choe YJ, Kim YK.

characterized by the inability to achieve seroconversion or to generate a protective immune response following vaccination, even after seroconversion has occurred.[5] On the other hand, secondary vaccine ineffectiveness refers to the gradual decline in immunity over time. In response, a 2-dose vaccination strategy has been introduced in many countries to increase vaccine effectiveness (VE) against varicella infection.[6]

In South Korea, a 1-dose varicella vaccination was introduced in the 1990s; however, the number of varicella cases has not decreased substantially, which is similar to other countries.[7] A modelling study based on changing population demographics demonstrated that a 2-dose varicella vaccination schedule would significantly reduce varicella in the long term[8]; however, the debate is still ongoing in the country. At present, the second dose has become widely accessible without incurring any 'out-of-pocket' expenses.[9] A comprehensive evaluation of the VE of 1-dose vs. 2-doses schedules for varicella vaccines is therefore needed.

With global efforts to pursue effective preventive strategies against varicella, several observational studies have been conducted. Timely analyses of existing epidemiological data can help public health agencies to better understand the benefits of vaccination strategies. However, conventional systematic reviews are limited in that they simultaneously compare multiple studies conducted in different settings. Network meta-analyses that combine both direct and indirect information can be useful in such situations.[10]

This network meta-analysis aimed to provide a comprehensive evaluation of the effectiveness of 1-dose vs. 2-dose varicella vaccination strategies, and to provide an overall estimated effect, via a Bayesian model using fixed effects.

MATERIALS AND METHODS

This systematic review and network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] We searched the PubMed, Embase, Cochrane, and KoreaMed databases for articles that included the following search terms in their titles, abstracts, or keyword lists published between January 1990 and September 2021: "Chickenpox Vaccine[mh:noexp] OR (Chickenpox[mh] AND Vaccination[mh:noexp]) chickenpox vaccin*[tiab] OR chicken pox vaccin*[tiab] OR varicella vaccin*[tiab] (chickenpox[ti] OR chicken pox[ti] OR varicella[ti]) AND vaccin*[ti] varilrix[tiab] OR varivax[tiab] OR proquad[tiab] OR priorix[tiab] OR okavax[tiab] OR suduvax[tiab]", as described in **Supplementary Table 1**. A combination of eligible studies was retrieved and their abstracts were checked for other relevant publications. Two independent reviewers (KH and YJC) examined titles, abstracts, and full articles to determine the eligibilities of the identified studies. All discrepancies were resolved through discussions.

All potentially eligible studies identified using the search strategy were screened. Original studies that met the following criteria were reviewed for the selection criteria: (i) trials comparing the VE of 1-dose or 2-dose vaccination and (ii) observational studies assessing the VE of 1-dose or 2-dose vaccination. The outcomes of interest included the occurrence of clinically-diagnosed varicella, laboratory-confirmed varicella, hospitalization due to varicella, and varicella-associated deaths.

The extraction was conducted by a single investigator (KH). For each eligible study, we collected the trial characteristics, 1-dose vs. 2-dose nature, demographic characteristics, and outcomes of interest. For studies involving different doses, we aggregated the data for the same number of doses delivered into one arm. We plotted the network for each outcome of interest using a Bayesian network meta-analysis model and generated posterior samples of parameters using the Markov chain Monte Carlo algorithm. The network graph is composed of "nodes" that symbolize the interventions under scrutiny and "edges" that signify the existing direct comparisons between these interventions. Additionally, the extent of available evidence can be visually conveyed by assigning various node sizes and line thicknesses to "weight" the nodes and edges. The preventive effects of 1-dose vs. 2-doses of varicella vaccine were evaluated in terms of the odds ratio (OR) and corresponding equal-tailed 95% confidence interval (95% CI).

RESULTS

The initial search resulted in 903 relevant publications, out of which 351 were eliminated due to duplicate records. Subsequently, 552 studies underwent screening based on their title and abstract, and 493 of these were excluded for various reasons (such as being case reports, animal experiments, reviews, editorials, letters, or comments). This left us with 59 studies for a comprehensive review of the full-text information. Out of these potential studies, 34 were further excluded: 17 did not provide the necessary data, 9 did not include outcomes relevant to our research, and 8 were unrelated to our research topics. Ultimately, 25 studies met our inclusion criteria and were included in this meta-analysis (**Fig. 1**). The inter-rater reliability agreement for study selection was a Cohen's kappa of 0.951 (95% CI, 0.909–0.994).

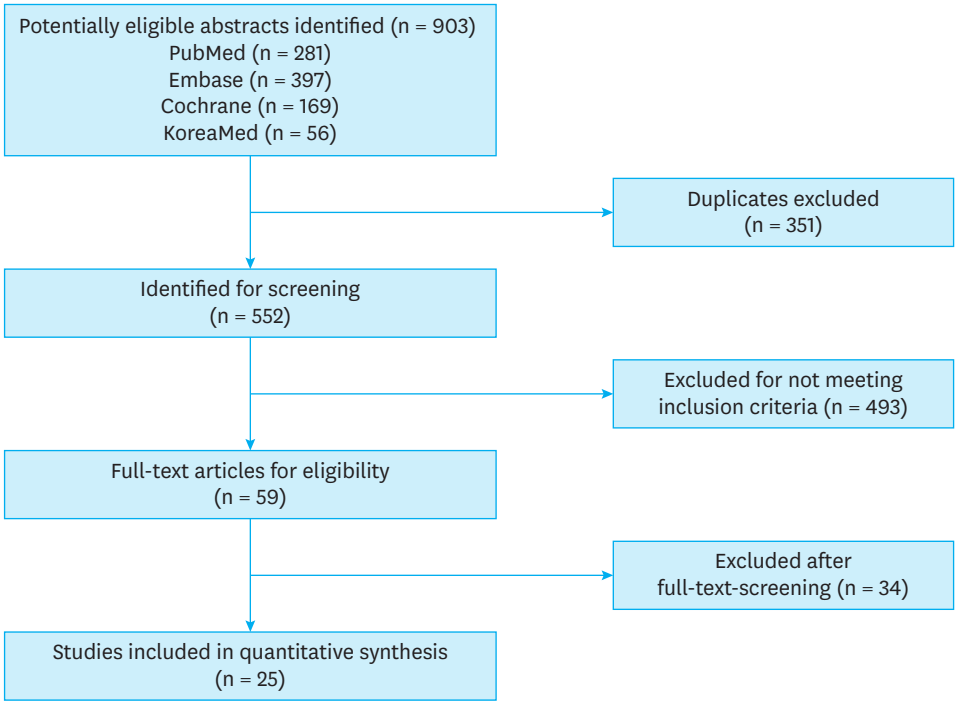

Fig. 1. Results of the literature search and evaluation of the identified studies.

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Table 1. Selected publications included in the meta-analysis

No.	Author (Year)	Design	Periods	Country	No.	Intervention
1	Xu et al.[21] (2021)	Retrospective case-control	2019	China	11,813	1-dose, 2-dose varicella vaccination
2	Hao et al.[17] (2019)	Prospective clinical trial	2016	China	5,997	1-dose varicella vaccination
3	Quinn et al.[22] (2019)	Retrospective case-control	2008–2015	Australia	78	1-dose varicella vaccination
4	Kurugöl and Gökçe[33] (2018)	Retrospective case-control	2016	Turkey	124	1-dose varicella vaccination
5	Latasa et al.[29] (2018)	Retrospective case-control	2003–2015	Spain	7,585	1-dose varicella vaccination
6	Giaquinto et al.[26] (2018)	Retrospective cohort	2006–2013	Italy	7,623	1-dose varicella vaccination
7	Andrade et al.[31] (2018)	Matched case-control	2013–2015	Brazil	469	1-dose varicella vaccination
8	Hattori et al.[30] (2017)	Matched case-control	2015–2016	Japan	225	1-dose, 2-dose varicella vaccination
9	Lee et al.[32] (2016)	Retrospective case-control	2013	Korea	537	1-dose varicella vaccination
10	Perella et al.[15] (2016)	Retrospective case-control	2009–2011	U.S.	533	1-dose, 2-dose varicella vaccination
11	Thomas et al.[16] (2014)	Retrospective case-control	2010–2011	U.S.	498	1-dose, 2-dose varicella vaccination
12	Prymula et al.[34] (2014)	Prospective clinical trial	2005–2006	Europe	5,803	1-dose, 2-dose varicella vaccination
13	Wang et al.[20] (2013)	Retrospective case-control	2010–2011	China	869	1-dose varicella vaccination
14	Liese et al.[24] (2013)	Matched case-control	2008–2010	Germany	864	1-dose varicella vaccination
15	Cenoz et al.[28] (2013)	Retrospective case-control	2010–2012	Spain	486	1-dose, 2-dose varicella vaccination
16	Mahamud et al.[13] (2012)	Retrospective case-control	2011	U.S.	82	1-dose, 2-dose varicella vaccination
17	Lu et al.[19] (2012)	Retrospective case-control	2010	China	916	1-dose, 2-dose varicella vaccination
18	Shapiro et al.[6] (2011)	Matched case-control	2006–2010	U.S.	211	1-dose, 2-dose varicella vaccination
19	Nguyen et al.[18] (2010)	Retrospective case-control	2006	U.S.	342	1-dose, 2-dose varicella vaccination
20	Tafuri et al.[27] (2010)	Retrospective case-control	2009	Italy	41	1-dose varicella vaccination
21	Spackova et al.[25] (2010)	Retrospective case-control	2008–2009	Germany	631	1-dose, 2-dose varicella vaccination
22	Gould et al.[35] (2009)	Retrospective case-control	2006	U.S.	871	1-dose, 2-dose varicella
23	Parker et al.[14] (2006)	Retrospective case-control	2005–2006	U.S.	240	1-dose varicella vaccination
24	Vally et al.[23] (2007)	Retrospective case-control	2002	Australia	211	1-dose varicella vaccination
25	Kuter et al.[12] (2004)	Prospective cohort	2000	U.S.	2,216	1-dose, 2-dose varicella vaccination

The detailed characteristics of the included studies are summarized in **Table 1**. The 25 eligible studies yielded 49,265 observed individuals that were included in this network meta-analysis. Eight studies from the U.S.,[2,6,12-16] 4 from China,[17-21] 2 each from Australia,[22,23] Germany,[24,25] Italy,[26,27] and Spain,[28,29] and one each from Brazil, Japan,[30] Korea,[32] and Turkey[33] were analyzed. One study was conducted in multiple countries across Europe.[34] The observation period was from 2000 to 2016. Seventeen retrospective case-control studies were included,[2,13-16,19-23,25,27-29,32,33,35] followed by 4 matched case-control studies,[6,24,30,31] 2 prospective clinical trials,[17,34] and one prospective and one retrospective cohort study.[12,26] Participants were allocated to one of the following groups: 0-dose, 1-dose, or 2-dose. In the network analysis diagram, each node represents the number of varicella vaccine doses: 0-dose, 1-dose, or 2-dose (**Fig. 2**).

Table 2 shows a summary of VE for all infections, as well as outbreak mitigation. The 1-dose vs. 0-dose VE ranged between 64.7% (95% CI, 43.3–78.0) and 94.4% (95% CI, 92.9–95.7), whereas the 2-dose vs. 0-dose VE ranged between 93.6% (95% CI, 75.6–98.3) and 98.3% (95% CI, 97.3–99.0). Three studies showed a VE of 2-dose vs. 1-dose, with a range between 38% (95% CI, 15–66) and 76% (95% CI, 44–90).

Our forest plot revealed that 2-dose network nodes were significantly superior to 1-dose nodes (**Fig. 3**). Compared to the 0-dose group, the OR of all varicella infection for the 2-dose group was 0.087 (95% CI, 0.046–0.164), and for the 1-dose group the OR was 0.310 (95% CI, 0.198–0.484). This corresponded to a one-dose VE of 69.0% (95% CI, 51.6–81.2) and a 2-dose VE of 91.3% (95% CI, 83.6–95.4).

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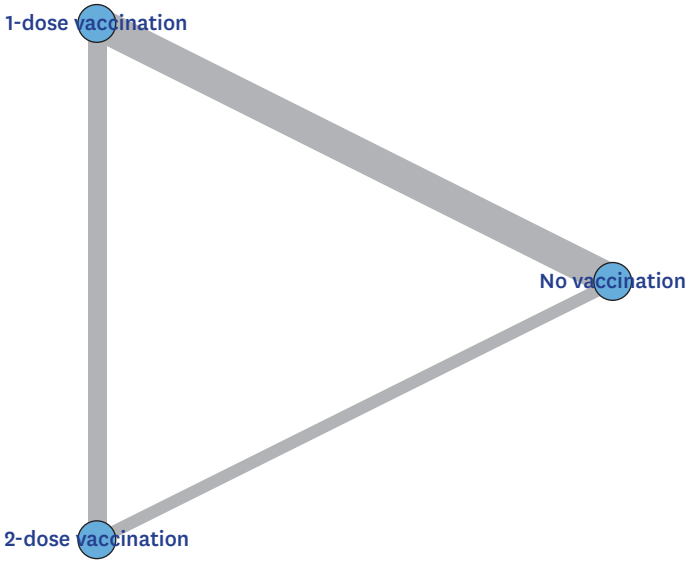

Fig. 2. Network geometry of varicella vaccine effectiveness studies.

Table 2. Summary of varicella VE

No.	Author (Year)	VE formula	Endpoint	Calculated VE, % (95% CI)		
				0 vs. 1	1 vs. 2	0 vs. 2
1	Xu et al.[21] (2021)	1-RR	All infection	91.0 (81.6–95.8)	-	98.0 (95.5–99.2)
2	Hao et al.[17] (2019)	1-IRR	All infection	87.1 (66.9–9.45)	-	-
3	Quinn et al.[22] (2019)	1-OR	Hospitalization	64.7 (43.3–78.0)	-	-
4	Kurugöl and Gökçe[33] (2018)	1-RR	Outbreak	33.6	-	-
5	Latasa et al.[29] (2018)	1-OR	All infection	93.1 (90.9–94.8)	-	-
6	Giaquinto et al.[26] (2018)	1-RR	All infection	94 (91–95)	-	-
7	Andrade et al.[31] (2018)	1-mOR	All infection	86 (72–92)	-	-
8	Hattori et al.[30] (2017)	1-mOR	All infection	76.7 (58.6–86.9)	-	94.2 (85.7–97.6)
9	Lee et al.[32] (2016)	1-OR	All infection	13 (–17.3–35.6)	-	-
10	Perella et al.[15] (2016)	1-RR	All infection	75.6 (38.7–90.3)	-	93.6 (75.6–98.3)
11	Thomas et al.[16] (2014)	1-OR	Outbreak	83.2 (69.2–90.8)	63.6 (32.6–80.3)	93.9 (86.9–97.1)
12	Prymula et al.[34] (2014)	1-HR	All infection	65.4 (57.2–72.1)	-	-
13	Wang et al.[20] (2013)	1-OR	All infection	83.4 (71.4–90.3)	-	-
14	Liese et al.[24] (2013)	1-mOR	All infection	71.5 (49.1–84.0)	-	-
15	Cenoz et al.[28] (2013)	1-OR	All infection	93 (34–100)	-	-
16	Mahamud et al.[13] (2012)	1-OR	Outbreak	80.9 (67.2–88.9)	-	94.7 (89.2–97.4)
17	Lu et al.[19] (2012)	1-RR	Outbreak	89	-	-
18	Shapiro et al.[6] (2011)	1-mOR	All infection	86.0 (–44.5–99)	-	98.3 (83.5–100)
19	Nguyen et al.[18] (2010)	1-RR	Outbreak	-	76 (44–90)	-
20	Tafuri et al.[27] (2010)	1-RR	Outbreak	82.4	-	-
21	Spackova et al.[25] (2010)	1-RR	Outbreak	71 (57–81)	-	-
22	Gould et al.[35] (2009)	1-RR	Outbreak	-	38 (15–66)	-
23	Parker et al.[14] (2006)	1-RR	Outbreak	86.6 (82.0–90.1)	-	-
24	Vally et al.[23] (2007)	1-RR	Outbreak	78 (15.4–94.3)	-	-
25	Kuter et al.[12] (2004)	1-RR	All infection	94.4 (92.9–95.7)	-	98.3 (97.3–99.0)

Abbreviations: VE, vaccine effectiveness; RR, relative risk; OR, odds ratio; mOR, matched odds ratio.

DISCUSSION

This systematic review and network meta-analysis provided a detailed summary of the VE of the varicella vaccine. Compared to 0-dose and 1-dose, a 2-dose vaccination strategy was shown to be highly effective against varicella infection over most time periods and continents. The vaccine also provided a high effectiveness in terms of infection prevention

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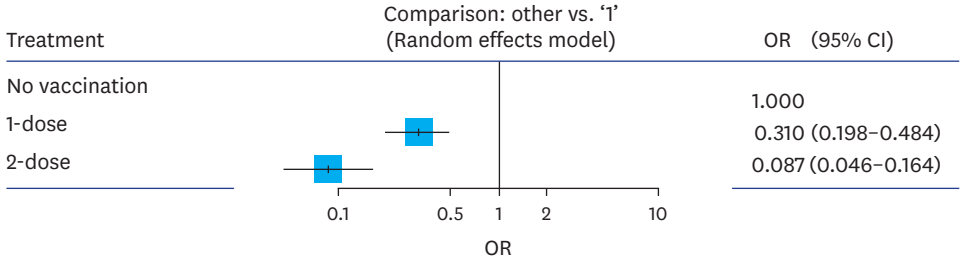

Fig. 3. Bayesian network meta-analysis of the effectiveness of 1-dose or 2-dose varicella vaccination vs. no vaccination.
Abbreviations: OR, odds ratio; CI, confidence interval.

during outbreak periods, which is in line with the findings of other systematic reviews evaluating varicella VE at different doses. Marin et al.[36] conducted a systematic review to evaluate the VE of 1-dose and 2-dose vaccination strategies. They found that pooled one-dose VE was 81% against all varicella, and 2-dose VE was 92% against all varicella. Zhang et al.[37] reported improved VE for 2 doses of varicella vaccines in their systematic review, which included both randomized control trials (RCTs) and observational studies. A recent study by Pawaskar et al.[38] conducted a relative efficacy study of varicella vaccines using a network meta-analysis of RCTs and showed a difference in VE between multiple products; however, the 2-dose strategy was superior in all scenarios. In a previous study in Korea, 1-dose of varicella vaccine exhibited an 86.1% VE (95% CI, 81.4–89.5) during the first year after vaccination and 49.9% VE (95% CI, 43.3–55.7) over the 6-year follow-up period post-vaccination, indicating a 7.2% annual decline in VE.[39]

The majority of our findings were consistent with those of previous research, except that we also identified 3 studies that measured the VE of 2-dose vs. one-dose varicella vaccination in outbreak settings. During outbreaks in schools, Thomas et al.[16] showed an incremental VE of 78.6% from 1-dose to 2-dose strategies in mitigating infections. Likewise, Nguyen et al.[17] also showed an adjusted incremental 2-dose VE of 76%. Gould et al.[35] showed that the varicella infection rates among 2-dose recipients (10.4%) and one-dose recipients (14.6%) were not significantly different, but 2-dose recipients had fewer skin lesions than one-dose recipients, suggesting an additional clinical benefit of 2-dose vaccination.

This study had several key limitations. First, by comparing the risk of varicella infection in observational studies (except for 2 prospective trials), the observed VE patterns might have been driven by other confounding factors such as behavior and access to medical care. Second, we did not directly assess the factors that may have led to higher numbers of varicella cases. Yearly trends or random occurrences of outbreaks may have had direct effects on VE values, and it can be challenging to assess the preventive effectiveness when observing studies from outside. Lastly, our findings may not be generalizable because the only available published data were from countries that have licensed and used varicella vaccines in their routine practices.

In conclusion, our systematic review and network meta-analysis showed that a 2-dose vaccine strategy significantly reduced varicella infection burden. Children receiving 2-dose vaccination had lower risks of varicella infection and better protection during outbreaks than children who received 1-dose vaccination. The effectiveness of 2-dose vaccination on reducing infection risk was shown with sound statistical evidence, which highlights the public health need for 2-dose varicella vaccination recommendations.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Search strategy

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요약

목적: 수두 감염에 대한 백신 효과성을 높이기 위해 수두백신 2회접종 전략이 여러 국가에 도입이 되었다. 본 연구에서는 Bayesian 모델을 통해 수두 예방 접종 전략의 종합적인 평가와 효과를 제공하고자 한다.
방법: 체계적 문헌고찰을 통해 수집된 연구에 대해 1회 및 2회 접종, 인구특성 및 관심대상결과와 같은 결과값들을 수집했다. 다양한 접종 횟수를 포함하는 연구의 경우 동일한 투여 횟수에 대한 데이터를 하나의 그룹으로 집계했다. 수두 백신의 1회 및 2회 접종의 예방 효과는 오즈 비 (OR) 및 해당하는 95% 신뢰 구간 (95% CI)을 기준으로 평가하였다.
결과: 문헌 검색을 통해 총 903개의 연구가 검색되었고, Bayesian 네트워크 메타 분석을 위해 25개의 개입 또는 관찰 연구가 선택되었다. 총 49,265명의 관찰 대상자가 이 연구에 포함되었다. 미접종군과 비교하여, 모든 수두 감염의 OR은 각각 2회 및 1회 접종에 대해 0.087 (95% CI, 0.046-0.164) 및 0.310 (95% CI, 0.198-0.484)이었으며, 이는 각각 1회 및 2회의 VE가 각각 69.0% (95% CI, 51.6-81.2) 및 91.3% (95% CI, 83.6-95.4)에 해당한다.
결론: 체계적인 검토 및 네트워크 메타 분석 결과, 2회 접종 백신 전략은 수두 감염 부담을 크게 감소시키는 것을 확인하였고, 2회 접종을 받은 어린이들은 1회 접종을 받은 어린이들보다 수두 감염 위험이 낮았으며, 유행 발생 시 더 나은 보호를 받는 것을 확인하였다.

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