Systematic review of available evidence on effectiveness and duration of protection of varicella vaccines

Table of Contents

1. OBJECTIVES

The WHO Strategic Advisory Group of Experts on Immunisation (SAGE) Working Group on Varicella and Herpes Zoster Vaccines (established in May 2012) was asked by SAGE to review the available evidence, identify the information gaps, and guide the work required to address these information gaps and formulate proposed recommendations in preparation for a SAGE review of the use of varicella vaccines. This will then lead to an update of the current (1998) WHO position paper on varicella vaccines.

In particular the Working Group was asked to assess:

- the effectiveness of varicella vaccines including that of vaccine combinations such as MMRV
- the duration of protection following immunization
- the impact of varicella vaccination on immunocompromised individuals

Therefore this review was conducted to identify and critically appraise the available evidence for these questions.

2. METHODS

2.1. Search strategy

A systematic search of published, peer-reviewed, English-language studies was conducted using the National Library of Medicine's online search utility PubMed. No restrictions were made to range of years, thus the start date was from the beginning of each candidate database to November 2013. Search strategies were designed to capture articles on varicella vaccination, as well as articles using the common names of licensed varicella vaccines and varicella-containing vaccines. Additional search criteria were used to narrow the results to more specific articles (e.g. articles on effectiveness of varicella vaccine in immunocompetent individuals). The three search strategies used are outlined below, where the first strategy searched for articles regarding the effectiveness of varicella vaccines in immunocompetent individuals, the second searched for articles regarding the duration of protection of varicella vaccines in immunocompetent individuals, and the third searched for articles regarding varicella vaccination of immunocompromised individuals, with a focus on HIV-infected individuals.

2.1.1. Search strategy for vaccine effectiveness

(effectiveness[All Fields]

AND ((((((((((((((((("chickenpox vaccine"[MeSH Terms] OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields])) OR (("chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All

Fields]))) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("chickenpox"[All Fields] AND "vaccines"[All Fields]) OR "chickenpox vaccines"[All Fields])) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("varicella"[All Fields] AND "vaccine"[All Fields]) OR "varicella vaccine"[All Fields])) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields]))) OR "measles, mumps, rubella, varicella vaccine"[Supplementary Concept]) OR ("Priorix-Tetra vaccine"[Supplementary Concept] OR "Priorix-Tetra vaccine"[All Fields] OR "priorix tetra vaccine"[All Fields])) OR proquad[All Fields]) OR varilrix[All Fields]) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR "varivax"[All Fields])) OR MMR+V[All Fields]) OR MMRV[All Fields]) OR okavax[All Fields]) OR changchun[Title/Abstract]) OR attenuated live varicella vaccine[Title/Abstract]) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND (containing vaccine[All Fields] OR containing vaccines[All Fields])))

NOT ((("herpes zoster vaccine"[MeSH Terms] OR "herpes zoster"[MeSH Terms]) OR herpes zoster vaccine[Title/Abstract]) OR herpes zoster[Title/Abstract])))

NOT ("immunocompromised host"[MeSH Terms] OR immunocompromised[Title/Abstract] OR immunosuppressed[Title/Abstract])

AND English

2.1.2. Search strategy for duration of protection

((((((((((("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]) AND failure[All Fields]) OR (breakthrough[All Fields] AND ("infection"[MeSH Terms] OR "infection"[All Fields] OR "communicable diseases"[MeSH Terms] OR ("communicable"[All Fields] AND "diseases"[All Fields]) OR "communicable diseases"[All Fields]))) OR (("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields]) AND persistence[All Fields])) OR (duration[All Fields] AND protection[All Fields])) OR (duration[All Fields] AND ("immunity"[MeSH Terms] OR "immunity"[All Fields]))) OR (("immunity"[MeSH Terms] OR "immunity"[All Fields]) AND protection[All Fields])) OR (protection[All Fields] AND wanes[All Fields])) OR (protection[All Fields] AND fades[All Fields])) OR (("immunity"[MeSH Terms] OR "immunity"[All Fields]) AND loss[All Fields])) OR (length[All Fields] AND ("time"[MeSH Terms] OR "time"[All Fields]) AND ("immunity"[MeSH Terms] OR "immunity"[All Fields])))

AND ((((((((((((((((("chickenpox vaccine"[MeSH Terms] OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields])) OR (("chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("chickenpox"[All Fields] AND "vaccines"[All Fields]) OR "chickenpox vaccines"[All Fields])) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("varicella"[All Fields] AND "vaccine"[All Fields]) OR "varicella vaccine"[All Fields])) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields]))) OR "measles, mumps, rubella, varicella vaccine"[Supplementary Concept]) OR ("Priorix-Tetra vaccine"[Supplementary Concept] OR "Priorix-Tetra vaccine"[All Fields] OR "priorix tetra vaccine"[All Fields])) OR proquad[All Fields]) OR varilrix[All Fields]) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR "varivax"[All Fields])) OR MMR+V[All Fields]) OR MMRV[All Fields]) OR okavax[All Fields]) OR changchun[Title/Abstract]) OR attenuated live varicella vaccine[Title/Abstract]) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND (containing vaccine[All Fields] OR containing vaccines[All Fields])))

NOT ((("herpes zoster vaccine"[MeSH Terms] OR "herpes zoster"[MeSH Terms]) OR herpes zoster vaccine[Title/Abstract]) OR herpes zoster[Title/Abstract]))

NOT ("immunocompromised host"[MeSH Terms] OR immunocompromised[Title/Abstract] OR immunosuppressed[Title/Abstract])

AND English

2.1.3. Search strategy for varicella vaccine in immunocompromised individuals

((("immunocompromised host"[MeSH Terms] OR immunocompromised[Title/Abstract] OR immunosuppressed[Title/Abstract]) OR "hiv"[MeSH Terms])

AND ((((((((((((((((("chickenpox vaccine"[MeSH Terms] OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields])) OR (("chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR

("chickenpox"[All Fields] AND "vaccines"[All Fields]) OR "chickenpox vaccines"[All Fields])) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR ("varicella"[All Fields] AND "vaccine"[All Fields]) OR "varicella vaccine"[All Fields])) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields]))) OR "measles, mumps, rubella, varicella vaccine"[Supplementary Concept]) OR ("Priorix-Tetra vaccine"[Supplementary Concept] OR "Priorix-Tetra vaccine"[All Fields] OR "priorix tetra vaccine"[All Fields])) OR proquad[All Fields]) OR varilrix[All Fields]) OR ("chickenpox vaccine"[MeSH Terms] OR ("chickenpox"[All Fields] AND "vaccine"[All Fields]) OR "chickenpox vaccine"[All Fields] OR "varivax"[All Fields])) OR MMR+V[All Fields]) OR MMRV[All Fields]) OR okavax[All Fields]) OR changchun[Title/Abstract]) OR attenuated live varicella vaccine[Title/Abstract]) OR (("herpesvirus 3, human"[MeSH Terms] OR "human herpesvirus 3"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[MeSH Terms] OR "chickenpox"[All Fields]) AND (containing vaccine[All Fields] OR containing vaccines[All Fields])))

NOT ((("herpes zoster vaccine"[MeSH Terms] OR "herpes zoster"[MeSH Terms]) OR herpes zoster vaccine[Title/Abstract]) OR herpes zoster[Title/Abstract]))

AND English

2.2. Study selection and data collection process

Article titles and abstracts were manually examined by a single reviewer (SJ) and appropriate articles were selected for further review. Postlicensure studies were the primary source of data, and the types of study designs included were: observational epidemiological studies, case-control studies and prospective/retrospective cohort studies. We excluded uncontrolled studies (i.e. case reports and case series studies), studies including only individuals with the outcome of interest in the analyses and animal studies. Additionally, we excluded studies involving post-exposure and prophylactic vaccine effectiveness and studies examining vaccine efficacy.

3. RESULTS

3.1. Vaccine effectiveness

3.1.1. Search results

The systematic search on vaccine effectiveness resulted in 147 post-licensure studies being identified. Of these, 37 abstracts met inclusion criteria and included data on vaccine effectiveness (VE). Additionally, a meta-analysis (Bayer, 2007[1]) and a systematic review of Varivax (Seward, 2008[2]) were identified, and bibliographies

from these two articles were screened for relevant references, which identified an additional study (Dworkin, 2002). In addition, two articles were included through suggestion by the SAGE Working Group (Quian, 2010; Nguyen, 2010). Therefore, a total of 40 articles were included in the assessment of VE (Table 1). The studies assessed VE in a variety of settings, which included childcare centres, schools, households, and community clinical practices. Most studies assessed varicella VE using clinically diagnosed cases, generally occurring during outbreak investigations. However, some studies used laboratory-verified varicella cases in their VE assessment.

3.1.2. Single dose vaccine effectiveness

Most post-licensure studies were performed in the United States and as a result, most VE estimates were for the Varivax vaccine. Studies conducted in other countries generally assessed Varilrix, Okavax, and various other varicella vaccines. Some studies assessed multiple types of varicella vaccines and/or one- or two-dose regimens. Other studies did not specify the vaccine used or were unable to distinguish between vaccines because more than one vaccine was licensed in the country where the study was performed. Table 1 presents the included post-licensure studies, the vaccines assessed in these respective studies, the estimated VE arranged by varicella severity, and the studies definition of severity (since some studies defined varicella severity differently).

Within the studies listed in Table 1, single dose varicella VE against all grades of disease severity ranged from 20 – 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type. Single dose varicella VE against moderate and severe disease ranged from 78 – 100%, with an approximate mean VE of 95%, irrespective of vaccine type. Whereas, the single dose varicella VE against severe disease ranged from 85 – 100%. In addition, of the eighteen studies reporting a VE value, seventeen reported a VE of 100% with only one study reporting a VE of 85%[3] (Table 1). Many additional studies did not specifically report a VE value, but instead reported that no cases of hospitalization or severe complications were observed, thus a VE of 100% can be considered in these studies. Overall, this indicates that a single dose of varicella vaccine is moderately effective (approximately 80%) for preventing disease of any severity, highly effective (approximately 95%) for preventing moderate and severe disease, and highly effective (approximately 99%) for preventing severe disease only.

3.1.3. Two dose vaccine effectiveness

There were fewer studies that assessed VE after two doses of varicella vaccine, with seven studies providing nine VE estimates against all grades of disease severity. Of these nine, six estimate were specific for two doses of the Varivax vaccine[4-8], with only one specific for two doses of the Priorix-Tetra (MMRV) vaccine[9]. The remaining two estimates were non-specific and represented estimates for any varicella vaccine[9,10] (Table 1). Furthermore, one VE estimate against moderate disease only[9] and two VE estimates against severe disease only[4,5] were provided (Table 1).

Two-dose varicella VE against all grades of disease severity ranged from 84 – 98%, with an approximate mean VE of 93%, irrespective of vaccine type. Spackova et al. provided the one estimate available for two doses of the Priorix-Tetra vaccine, which was 93% against all grades of disease severity[9]. In addition, Spackova et al. was the only study reporting a VE estimate against moderate disease, and reported a VE estimate of 95% for two doses of the Priorix-Tetra[9]. Both two dose VE estimates against severe disease only were 100%, and both were for the Varivax vaccine[4,5]. Overall, two doses of any varicella vaccine provided better protection against all grades of disease severity when compared to one dose of any varicella vaccine (93% vs. 80%, respectively).

Table 1. Summary of identified studies reporting varicella vaccine effectiveness

No.	Study	Vaccine (dose)	Vaccine Effectiveness			Disease Severity Categorization
			All Varicella	**Moderate to Severe Varicella**	**Severe Varicella**	
1	Arnedo-Pena et al., 2006[11] Spain	Varilrix (one dose)	70%	97%	100%	Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions
2	Buchholz et al., 1999[12]	Varivax (one dose)	1 group = 71% 2 group = 100%	1 group = 93% 2 group = 100%	N/A	Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions
3	CDC Michigan, 2003 (2004)[13]	Varivax (one dose)	85%	98%	N/A	Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions or presence of complication/hospitalization
4	CDC Nebraska, 2004 (2006)[14]	Varivax (one dose)	81%	93%	N/A	Mild: <50 skin lesions Moderate: 50--500 skin lesions Severe: >500 skin lesions or any complications or hospitalization
5	Cenoz et al., 2013[4] Spain	Varivax (one and two dose)	1st dose = 87% 2nd dose = 97%	N/A	1 dose = 100% (no cases of hospitalization or complications) 2 doses = 100%	No specific details provided
6	Clements et al., 1999[15]	Varivax (one dose)	83% (69 – 91%)	100%	100% (no cases with >50 vesicles)	Mild: <50 skin lesions Moderate: 51-200 skin lesions Severe: >200 skin lesions
7	Dworkin et al., 2002[16]	Varivax (one dose)	School A = 89% School B = 84%			No specific details provided
8	Fu et al., 2010[17] China	Varilrix; Changchun; Shanghai (one dose)	Varilrix = 86% Changchun = 80% Shanghai = 93%	N/A	N/A	No specific details provided
9	Galil, Fair et al., 2002[18]	Varivax (one dose)	79%	95%	100% (no cases with >500 vesicles)	Mild: <50 lesions Moderate: 51-500 lesions Severe: >500 lesions or presence of a serious complication
10	Galil, Lee et al., 2002[19]	Varivax; (one dose)	44%	86%	(no cases with severe complications or	Mild: <50 lesions Moderate: 51-500 lesions

					hospitalization)	Severe: >500 lesions or presence of a serious complication
11	Gould et al., 2009[5]	Varivax (one and two dose)	1st dose = 83% 2nd dose = 88%	N/A	1st dose = 100% 2nd dose = 100%	Mild: 3–50 lesions Moderate: 51–249 lesions Severe: >=250 lesions or hospitalization
12	Haddad et al., 2005[20]	Varivax (one dose)	School A = 87% School B = 87%	School A = 90% School B = 99%	No VE% reported; one vaccinated child reported with severe varicella (>500 lesions) that required hospitalization	Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions or fever lasting >5 days or presence of complication/hospitalization
13	Hohle et al., 2011[21] Germany	Unspecified (one dose)	83.2%	N/A	N/A	No specific details provided
14	Huang et al., 2011[3] Taiwan	Varivax and Varilrix (one dose)	83%	N/A	85%	Severe: any hospitalized case
15	Izurieta et al., 1997[22]	Varivax (one dose)	86% (73 – 92%)	100% (96 – 100%)	100% (96 – 100%)	Mild: <50 lesions Moderate: 50 – 250 lesions Severe: >250 lesions
16	Kilic et al., 2008[23] Turkey	Okavax (one dose)	90%	100%	100%	Mild: <=50 lesions, fever <3 days, no complications Moderate/Severe: >50 lesions, fever >=4 days, or complications
17	Lai et al., 2011[24]	Varivax and Varilrix (one dose)	By grade 69% 73% 100%	85.5%	N/A	Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions
18	Lee et al., 2004[25]	Varivax (one dose)	56%	90% (moderate disease only)	100% (no cases with >500 vesicles)	Mild: <50 lesions Moderate: 51-500 lesions Severe: >500 lesions
19	Lee et al., 2008[26]	Varivax (one dose)	81%			Mild: <50 lesions Moderate: 50-500 lesions Severe: >500 lesions
20	Liese et al., 2013[10]	Varilrix Varivax Priorix-Tetra (one and two dose)	One dose Varilrix only 72% One dose any vaccine = 86% 2 doses any vaccine = 94.3% (76.4 – 98.6)	One dose Varilrix only = 95% One dose any vaccine = 98%	N/A due to low number of cases (no cases in vaccinated individuals and 3 in unvaccinated)	Severity assessed with a 15-point clinical scale that takes into the account the number and character of lesions, the height of the fever, the presence of complications, and a subjective assessment: Mild: <= 7 points Moderate: 8-15 points

						Severe: >= 16 points
21	Lopez et al., 2006[27]	Varivax (one dose)	82%	97%	(no cases of hospitalization)	Mild: <50 lesions Mild/Moderate: 50-249 lesions Moderate: 250-500 lesions Severe: >500 lesions or presence of complication/hospitalization
22	Lu et al., 2012[28] China	Unspecified (one dose)	89%	99%	(no cases with complications or hospitalization)	Mild: <50 lesions Moderate-Severe: >=50 lesions
23	Mahamud et al., 2012[6]	Varivax (one and two dose)	School A: 1-dose = 81% 2-dose = 95% School B: 1-dose = 80% 2-dose = 84%	N/A	N/A	Mild: <50 lesions Mild/Moderate: 50-249 lesions Moderate: 250-499 lesions Severe: >=500 lesions or presence of complication/hospitalization
24	Marin et al., 2005[29]	Varivax (one dose)	89%	96%	100%	Mild: <50 lesions Moderate: 50 – 500 lesions Severe: >500 lesions; presence of complication/hospitalization
25	Miron et al., 2005[30] Israel	Varilrix (one dose)	20%	93%	(no cases with severe complications or hospitalization)	Mild: <=50 lesions, fever <3 days, no complications Moderate/Severe: >50 lesions, fever >=4 days, or complications
26	Parker et al., 2008[31]	Varivax (one dose)	86.6%	100%	100%	Mild: <50 lesions Mild/Moderate: 50-249 lesions Moderate: 250-500 lesions Severe: >500 lesions or presence of complication
27	Passwell et al., 2004[32] Israel	Varilrix (one dose)	92%	N/A	N/A	No specific details provided
28	Seward et al., 2004[33]	Varivax (one dose)	79%	92%	100%	Mild: <50 lesions Moderate: 50 – 500 lesions or complication requiring a health care clinic visit Severe: >500 lesions or complication resulting in hospitalization or death

29	Shapiro et al., 2011[7]	Varivax; 2 out of 22 controls with 2 doses received MMRV (one and two dose)	One dose VE = 86.0% Two dose VE = 98%	N/A	N/A	No specific details provided
30	Sheffer et al., 2005[34] Israel	Varilrix (one dose)	88%	100%	100%	No specific details provided
31	Spackova et al., 2010[9]	Varilrix; Varivax; Priorix-Tetra (one and two dose)	Overall VE% = 72% (59 – 81%) One dose VE = 61% (44 – 73%) Two dose VE = 95% (79 – 99%) Varivax one dose = 83% (55 – 93%) Varilrix one dose = 49% (21 – 67%) Priorix-Tetra one dose = 62% (23 – 81) Priorix-Tetra two dose = 93% (71 – 98)	Overall VE% = 89% (78 – 94%) Varivax one dose = 94% (61 – 99%) Varilrix one dose = 80% (52 – 92%) Priorix-Tetra one dose = 78% (33 – 93) Priorix-Tetra two dose = 95% (68 – 99) Moderate disease only	Overall VE% = 100% (no severe varicella cases, defined as hospitalized cases, reported) Varivax = 100% Varilrix = 100%	Mild: <50 lesions Moderate: >=50 lesions Severe: any hospitalized case
32	Tafuri et al., 2010[35] Italy	Unspecified (one dose)	82%	N/A	N/A	Mild: <50 lesions without complications Moderate/Severe: >50 lesions, or presence of serious complication, hospitalization or death
33	Tafuri et al., 2013[36] Italy	Varilrix Varivax Priorix_tetra (one dose)	60% (in day care center) 69% (in elementary school)	100%	100%	Mild: <50 lesions without complications Moderate/Severe: >50 lesions, or presence of serious complication, hospitalization or death
34	Tugwell et al., 2004[37]	Varivax (one dose)	72%	N/A	(no cases with >500 vesicles)	No specific details provided
35	Vally et al., 2007[38] Australia	Varilrix/Varivax (one dose)	78.0%	100%	100% (no severe varicella cases)	No specific details provided
36	Vazquez et al., 2001[39]	Varivax (one dose)	85%	97%	100%	Severity assessed with a 15-point clinical scale that takes into the

						account the number and character of lesions, the height of the fever, the presence of complications, and a subjective assessment: Mild: <= 7 points Moderate: 8-15 points Severe: >= 16 points
37	Vazquez et al., 2004[40]	Varivax (one dose)	87% (81 – 91%)	98%	N/A	Severity assessed with a 15-point clinical scale that takes into the account the number and character of lesions, the height of the fever, the presence of complications, and a subjective assessment
38	Wang et al., 2013[41] China	Varilrix; Baike; Changsheng; Keygen; Shanghai (one dose)	Overall VE (all five vaccines) = 83.4% (71.4 – 90.3%) One dose Baike VE = 91%* One dose Changsheng VE = 77%* *significant difference (p<0.008)	N/A	N/A	No specific details provided
39	Quian, 2010[63]	Varilrix	80%		100%	Mild:< 50 lesions Moderate: 51-150 lesions Severe: >150 lesions or hospitalization
40	Nguyen, 2010[8]	Varivax (one and two dose)	1 dose = 79% 2 doses =95%			Mild: <50 lesions and afebrile Moderate/Severe: > 50 lesions; vesicular rash

3.2. Duration of protection

3.2.1. Search results

The systematic search on duration of protection resulted in 157 abstracts being identified. Of these, 21 abstracts met inclusion criteria and included data on duration of protection, time to breakthrough infection and/or vaccine failure. Additionally, several studies identified through the effectiveness search strategy (see Section 2.1.1) contained information applicable to the duration of protection of varicella vaccines, and were therefore included (i.e. CDC Michigan, 2004; Cenoz, 2013; Fu, 2010; Haddad, 2005; Lee, 2008; Marin, 2005; Tugwell, 2004; Vaquez, 2004;). Two additional articles were included through suggestion by the SAGE Working Group (Baxter, 2013; Kuter, 2004). Therefore, a total of 31 articles were reviewed in the assessment of waning immunity of varicella vaccines. These studies examined both one- and two-dose varicella vaccinations and had a follow-up period of up to 20 years in duration. Majority of studies looked at waning immunity in children, however, two studies examined adult populations.

3.2.2. Single dose duration of protection

There appears to be conflicting information available on the waning immunity of a single dose of vaccine, where some studies suggest that there is waning of vaccine-induced immunity over time, while others indicate long-term protection. Table 2 lists the studies identified through the systematic search, and summarizes whether time since vaccination was significantly related to the development of breakthrough varicella infection. There was variability in what studies defined as a significant duration of time since vaccination. Different studies defined different cohorts, ranging from greater than two years to greater than five years since vaccination, when calculating significance. Other studies did not define cohorts, and instead treated time since vaccination as a continuous parameter. Overall, these differences in definition make it difficult to compare studies directly.

Table 2 also summarizes whether the studies determined the mean time from vaccination to the development of breakthrough varicella. Although there was variability with regards to the mean time to breakthrough varicella, majority of studies indicated that breakthrough varicella could develop over a range of times, from 8 weeks to 11.8 years post-vaccination. In general, there appeared to be a peak of breakthrough disease occurring around four to five years after vaccination. These studies attributed this peak to children starting school about four years after receiving the vaccination, and thus being exposed to VZV more frequently.

Although there is conflicting information on whether waning immunity after a single dose of vaccine was evident, the identified studies did generally agree that breakthrough disease did not become more severe with time. That is, breakthrough disease was generally milder when compared to individuals who were not vaccinated. Majority of studies reported breakthrough disease as mild (i.e. <50 lesions/non-vesicular rash, afebrile, shorter duration), whereas fewer studies reported some

breakthrough cases of moderate to severe disease. However, unvaccinated individuals were still more likely to develop moderate to severe disease than vaccinated individuals in these studies.

In addition to the identified studies listed in Table 2, a meta-analysis was identified (Bayer, 2007), which concluded waning immunity of a single dose of varicella vaccine[1]. This conclusion was formed from four outbreak studies (included in Table 2), which provided enough data for independent statistical calculation. Since these were outbreak studies, the sample size was limited and thus the conclusions may not be accurate. Furthermore, all four studies identified waning immunity and the meta-analysis did not include any studies that did not detect waning immunity, therefore the results of the meta-analysis may have been biased.

Overall, there is conflicting evidence on whether there is waning immunity after a single dose of vaccine, and if so, it is unknown how long a single dose of vaccine is effective for. There is also difficulty in elucidating whether the cause of waning immunity is due to primary or secondary vaccine failure. Vazquez et al. report a substantial difference in VE between one year and two years post-vaccination, but no significant difference between two years and eight years post-vaccination[40]. This drop after the first year was partially attributed to primary vaccine failure[40], however it is difficult to confirm this without specific serological testing.

The duration of protection offered by a single dose of vaccine has been difficult to study and has resulted in conflicting results for a number of reasons. Several long-term studies suggested that the results were difficult to interpret due to circulating wild-type VZV, which could go unnoticed through sub-clinical disease, thereby resulting in natural boosting and prolongation of the duration of protection, which is incorrectly interpreted to be provided by a single dose of vaccine. Furthermore, the amount of wild-type VZV circulating also depends on the vaccine coverage rate of a particular area, thus making it difficult to compare and interpret studies. In short, the duration of protection offered by a single dose of varicella vaccine is difficult to study and remains incompletely understood for the time being.

3.2.3. Two dose duration of protection

Although there is conflicting evidence on the duration of protection offered by a single dose of varicella vaccine, majority of the identified studies supported the introduction of a second dose of vaccine. This was largely based on the effectiveness of a second dose of vaccine in reducing severe breakthrough disease. In a ten-year follow-up study, Kuter at al. reported that children receiving two doses of vaccine developed no severe disease and additionally, were 3.3 times less likely to develop breakthrough disease of any severity[42]. Kuter et al. also noted that recipients of two doses did not develop any breakthrough infection seven to ten years post-vaccination, whereas there were some breakthrough cases during this same time frame in single dose recipients[42]. Additionally, Knuf et al. indicated that a two-dose regimen of the Priorix-Tetra vaccine (MMRV) resulted in less breakthrough infection overall when compared to a single dose of Varivax given concomitantly with the MMR vaccine[43]. Furthermore, all breakthrough cases developed with the two-dose regiment were milder (i.e. <50 lesions). Also, Baxter et al. conducted a 14-year follow-up of patients

receiving two doses of vaccine and noted no waning immunity during this entire 14-year period[44]. Baxter et al. also noted that there were no breakthrough cases in children receiving two doses of vaccine[44], thus supporting the introduction of a second dose of varicella vaccine.

Overall, there were fewer studies directly comparing single and two-dose regimens than studies examining the duration of protection offered by a single dose only. Moreover, there were some studies that did not distinguish between single- and two-dose recipients when reporting VE and breakthrough infection rates, thus making it difficult to elucidate the effect of introducing a second dose of vaccine. Additionally, the studies exploring two-dose regimens included recipients who received the second dose of vaccine at any time after the first dose, thus there was variability in interval time between receiving the two doses. For example, Knuf et al. included patients who received the second dose 42-56 days after the first dose[43], and Baxter et al. examined patients who received the second dose at four to six years of age[44]. Overall, this could make it difficult in determining the duration of protection provided by a second dose of vaccine, as well as determining what the optimal time interval between doses should be in order to provide the maximal benefit.

3.2.4. Duration of protection in adults

The systematic search of the literature revealed only two studies that examined the duration of protection of varicella vaccines in the adult population. Ampofo et al. and Saiman et al. looked at adult populations with age ranges of 22-41 (mean 30) and 19-45 (mean 26) years, respectively. Ampofo et al. reported that, on average, the mean time since vaccination to develop breakthrough infection was 3.3 years, concluding that time since vaccination was not related to developing breakthrough disease[45]. This study did not distinguish between subjects receiving one, two or three doses of varicella vaccine. Saiman et al.'s 20-year follow-up study also did not distinguish between whether subjects received one or two doses, but also concluded that waning immunity did not occur, with a 3.6-year mean time to breakthrough infection[46]. Both studies also reported that breakthrough disease was milder and did not increase in severity with time[45,46], which is consistent with the studies conducted in children.

Although both studies reported consistent results, both studies were not randomized or controlled and were fairly small (i.e. 461 and 120 subjects), however both studies followed their subjects for up to 20 years. Overall, due to the limited number and size of studies exploring duration of protection in adults, it is difficult to determine with confidence whether waning immunity occurs in adults. With that said, the complementary results from the two identified studies indicate that varicella vaccines provide long-term protection.

Table 2. Summary of identified studies examining waning immunity of varicella vaccines

No.	Study	Vaccine (Dose)	Population	Maximum follow-up	Mean time to breakthrough	Summary
1	Ampofo et al., 2002[45]	Varivax, Varilrix (one, two, or three dose)	Adults (22-41 years, mean 30 years)	20 years	3.3 years (8 weeks – 11.8 years)	Time since vaccination not related to breakthrough varicella
2	Arnedo-Pena et al., 2006[11]	Varilrix (one dose)	Children	-	-	time lapsed since vaccination was significantly associated with vaccine failure in children, if time had been >25 months since vaccination ($p<0.017$).
3	Baxter et al., 2013[44]	Varivax (one or two dose)	Children (2 years)	14 years		NO indication of waning over the 14-year period. Disease was mild. No child developed breakthrough varicella after the second dose. Breakthrough disease steadily decreased with time, and was milder than unvaccinated cases.
4	CDC Michigan 2003, (2004)[13]	Varivax (one dose)	Children (Kindergarten – Grade 3)	-	-	Children vaccinated >= 4 years before the outbreak were nearly five times more likely to develop breakthrough disease than children vaccinated within 4 years of the outbreak (RR, 4.65; 95% CI 1.48-14.61).
5	Cenoz et al., 2013[4]	Varivax (one and two dose)	Children (15 months – 10 years)		35 weeks – 6 years	Time since vaccination was associated with an increased risk of breakthrough varicella among children who had received a dose of vaccine (OR, 2.07; 95% CI 1.13-3.80). Breakthrough cases were milder.
6	Chaves et al., 2007[47]	Varivax (one dose)	Children (2-18 years)	10 years	-	Children who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than those who had been vaccinated less than 5 years previously (RR, 2.6; 95% CI 1.2-5.8)
7	Fu et al., 2010[17]	Varilrix; Changchun; Shanghai (one dose)	Children (mean 7.2 years)	7 years	-	The difference in VE with respect to time since vaccination was not statistically significant, however VE was highest during the year after vaccination and was lower thereafter.
8	Galil et al., 2002[19]	Varivax (one dose)	Children (6 months – 8.9 years)	-	35.5 months	Children vaccinated three years or more before the outbreak were at greater risk for vaccine failure than those who had been vaccinated more recently (RR, 2.6; 95% CI 1.3-5.3)
9	Gershon et al, 1989[48]	Varivax, Varilrix (one or two dose)	Children (3-12 years)	6 years	15 months (1-43 months)	In children in remission from leukemia, there was no relation between time since vaccination and either the attack rate or severity of breakthrough varicella.
10	Haddad et al., 2005[20]	Varivax (one dose)	Children (5-12 years)	-	-	Children vaccinated >5 years before the outbreak were more likely to develop breakthrough varicella (RR, 3.0; 95% CI 1.4-6.4). One breakthrough case was severe enough to warrant hospitalization.

11	Huang et al., 2011[3]	Varivax, Varilrix (one dose)	Children (mean 1.6 years)	8 years	2.3 years (? – 8.72 years)	Breakthrough varicella was significantly more likely to occur at age 5 and 6 years of age among vaccines who received vaccination between 12-23 months (P<0.001)
12	Johnson et al., 1989[49]	Varivax (one dose)	Children (12-24 months)	3 years	18-30 months	Vaccination leads to antibody persisitence for two years and a low rate of reinfection (6%), which are generally mild (<70 lesions, afebrile)
13	Knuf et al., 2012[43]	MMRV or 2MMR+V (one or two dose)	Children (12-18 months)	3 years	8-28 months from second dose	MMRVx2 = 2 breakthrough cases MMRV+V = 5 breakthrough cases Fewer cases in two dose recipients, which were all milder (<50 lesions), indicating that 2-dose MMRV has the potential to reduce secondary vaccine failure than single dose vaccine.
14	Kurogol et al., 2011[50]	Varilrix, Varilrix (one dose)	Children (2-15.5 years)	10 years	72 months	Risk of varicella breakthrough when vaccinated more than 5 years previously was 3.7 times greater than when vaccinated less than 5 years previously (OR 3.7, 95% CI 2.82-4.79) Also, frequency of breakthrough varicella increased with time since vaccination (3.1% within first year to 63.0% for ten years post-vaccination)
15	Kuter et al., 1991[42]	Varivax (one dose)	Children (1-14 years)	7 years	-	95% remained varicella free after seven years, and breakthrough varicella was mild (average number of lesions 53, with 50% cases having non-vesicular rash)
16	Kuter et al., 2004[51]	Varivax (one dose vs two dose)	Children (1 – 12 years)	9-10 years	Most cases occurred between years 2 and 5*.	The risk of developing breakthrough infection was 3.3-fold lower (P<0.001) in children who received two doses. Either one or two dose varicella vaccination results in long-term protection *There are no cases in years 7 to 10 for 2 dose vaccination
17	Lee et al., 2004[25]	Varivax (one dose)	Children (4 – 11 years)	-	5 years	Student vaccinated >5 years before the outbreak had a greater risk of breakthrough varicella than did those vaccinated within <4 years (RR, 2.6; 95%CI 1.3-5.4)
18	Lee et al., 2008[26]	Varivax (one dose)	Children (5 – 10 years)	-	Ranged from <1 year to >7 years (no specific details)	Time >5 years since vaccination was not a risk factor for breakthrough varicella when compared to those with time <5 years since vaccination (RR, 0.95; 95% CI 0.94-1.10).
19	Liese et al., 2013[10]	Varivax, Varilrix, Priorix-Tetra (one or two dose)	Children (1-7 years)	60 months	28 months (5-57 months)	The difference in vaccine effectiveness over time was not significant. However, interpret with caution because study was not powered to measure difference. N.B. there was a trending decrease over time, with increasing 95% CI's. Breakthrough cases were generally milder
20	Lopez et al,	Varivax	Children	101 months	59 months	Time since vaccination was not a significant risk factor for development of

	2006[27]	(one or two dose)	(K – grade 5)		(0-101 months)	breakthrough varicella. Most breakthrough cases experienced mild disease
21	Lu et al., 2012[28]	Unspecified (one or two dose)	Children (5.9-8.6 years)	-	5.1 years	Time since vaccination (<5 vs. >5 years) was not associated with breakthrough varicella.
22	Marin et al., 2005[29]	Varivax (one dose)	Children (5 – 9 years)	-	-	Time since vaccination was categorized as <3 years and >3 years before the start of the outbreak, and was found to not be significantly associated with vaccine failure and breakthrough varicella.
23	Miron et al., 2005[30]	Varilrix (one dose)	Children (3-6 years)			Vaccine protection was poor for children vaccinated >2 years before the outbreak (RR, 17; 95% CI 2.18-118). 94% of breakthrough cases were mild.
24	Saiman et al., 2001[46]	Varivax, Varilrix (one or two dose)	Adult HCW (19 – 45 years, mean 26 years)	20.6 years (mean 4.6 years)	3.6 years (6 months – 8.4 years)	All breakthrough cases were mild (mean number of vesicles = 40). There was no increase in incidence or severity of varicella with time, thus waning immunity did not seem to occur.
25	Shinefield et al., 2002[52]	Varivax (MMR+V) (one dose)	Children (1 – 6 years)	5 years	-	MMR+V induces persistent immunity and long-term protection against breakthrough. Breakthrough cases were milder. Annual breakthrough rates of 0.4-2.2%.
26	Takayama et al., 1997[53]	Oka Strain / Japan (one dose)	Children (10 months – 15 years)	8 years	Ranging from within 1 year to 8 years	Time since vaccination was not significantly related to breakthrough disease, but disease was milder.
27	Tugwell et al., 2004[37]	Varivax (one dose)	Children (5-12 years)	-	4.8 years	Students vaccinated >5 years before the outbreak were 6.7 times as likely to develop breakthrough disease as those vaccinated <5 years before the outbreak (95% CI 2.2-22.9)
28	Vazquez et al, 2004[40]	Varivax (one dose)	Children (13 months – 16 years)	8 years	-	Vaccine effectiveness decreased significantly after the first year, although most breakthrough cases were mild. VE year 1 = 97%, VE years 2 to 8 = 84%. VE remained good during the entire 8 years, and VE against mod/severe disease remains excellent.
29	Vessey et al., 2001[54]	Varivax (one dose)	Children (1-12 years)	7 years	-	Varicella vaccine is highly effective in inducing persistent and long-term protection against breakthrough varicella infection. Time since vaccination was not significant. Annual breakthrough rate ranged from 0.2-2.3%/year.
30	Watson et al., 1993[55]	Varivax (unspecified)	Children (1 – 17 years)	8 years	44 months (2-96 months)	Milder disease (median 18 lesions). Breakthrough disease was seen during each year, peaking during the fourth and fifth years, but does not seem to increase generally with time and does not get more severe.
31	Zhang et al., 2012[56]	Varivax, Varilrix, Changchun but mainly Shanghai (one or two dose)	Children (3 – 15 years)	>10 years	3.91 +/- 1.50 years (1 - >10 years)	Time since vaccination was associated with an increased risk of breakthrough disease (OR, 1.59; 95% CI 1.14-2.21). Breakthrough disease was milder. 98.9% cases received one dose, and 1.1% received two dose of vaccine. 91.9% received domestic vaccine, and 8.14% received imported vaccine.

3.3 Varicella vaccine and immunocompromised individuals

3.3.1. Search results

The systematic search on varicella vaccine and immuncompromised individuals resulted in 173 abstracts being identified. Of these, 17 abstracts met inclusion criteria with regards to all groups of immunocompromised individuals (i.e. leukemia and other malignancies, organ transplant, HIV infection, etc.). For the purpose of this review, it was decided to initially focus on HIV patients, thus the search results were refined to include two articles specific to HIV infection (Armenian, 2006; Bekker, 2006). Several additional articles were included through suggestion by the SAGE Working Group (Levin, 2006; Son, 2010), which included two systematic reviews (Sartori, 2004; Levin, 2008), providing a general overview of various groups of immunocompromised individuals (including HIV-infected individuals). Therefore, a total of six articles were reviewed in the assessment of the immunogenicity and effectiveness of varicella vaccination in HIV-infected patients.

3.3.2. Varicella vaccine effectiveness in HIV-infected individuals

There were few studies providing data on vaccine effectiveness in HIV-infected individuals, and most studies included immunogenicity data as well by providing seroconversion rates. For example, Levin et al. (2006) reported seroconversion rates with a range of 59-72% after two doses of varicella vaccine in HIV-infected children with CD4% >15% and a CD4 T cell counts of >200 cells/uL[57]. After one year, the seroconversion rates persisted and ranged from 43-65%, and at two and three years, less than 50% of vaccine recipients had detectable antibody, which is similar to antibody levels after natural infection[57]. Additionally, Bekker et al., reported a seroconversion rate of 60% after two doses of varicella vaccine in HIV-infected children with CD4 T cell counts of >700 cells/uL[58]. This was again found to be similar to levels found with natural infection in HIV-infected individuals, but less than levels found in HIV-negative siblings (where 100% seroconverted)[58]. Lastly, Armenian et al. reported that after a single dose of vaccine, a varicella virus-specific lymphocyte proliferative response was detected in all subjects at four weeks post-vaccination, which remained positive in 90% of subjects at one year post-vaccination[59].

There are few studies reporting data on vaccine effectiveness in HIV-infected individuals, with most studies reporting only seroconversion rates and not observed breakthrough infection rates. Additionally, majority of these studies have small sample sizes and were conducted under very controlled settings, making the results difficult to extrapolate. With that said, Son et al. conducted a longitudinal cohort study, evaluating data from between 1989 to 2007 and was able to calculate vaccine effectiveness to be 82% (95% CI 24-99%)[60]. Son et al. also reports that 3% of vaccinated HIV-infected children developed breakthrough varicella, which occurred at 3.9 and 4.7 years after vaccination with one- and two-dose regimens, respectively[60]. Although this study was larger than others, it still only consisted of 72 vaccinated HIV-infected children. Therefore, in order to confidently report data on varicella

vaccine effectiveness in HIV-infected individuals, additional studies evaluating larger sample sizes for a longer follow-up period would be benefical.

In general, the reviews (Sartori, 2004; Levin, 2008) agreed that vaccination against varicella was beneficial for immunocompromised individuals but only after a careful consideration of the risk and benefits involved. The reviews recommended that vaccine administration should take place in a controlled clinical setting and preferably during periods of reduced immunosuppression in order to minimize risk, and although not always possible, it was also recommended that it would be most beneficial if immunocompromised individuals were vaccinated before immune compromise developed[61,62]. Overall, further investigation with larger sample sizes and longer follow-up periods is required to answer the many questions on the effectiveness of varicella vaccines in immunocompromised individuals.

4. CONCLUSION

Varicella vaccination is effective in preventing varicella disease in immunocompetent individuals. A single dose of varicella vaccine appears to be moderately effective (approximately 80%) for preventing disease of any severity, highly effective (approximately 95%) for preventing moderate and severe disease, and highly effective (approximately 99%) for preventing severe disease only. In addition, a second dose of varicella vaccine appears to be highly effective in preventing disease of any severity (approximately 93%). Individuals receiving two doses of vaccine developed breakthrough disease less often, and when breakthrough disease did occur it was generally milder when compared to unvaccinated individuals.

The duration of protection provided by a single dose of varicella vaccine is not clearly understood at the moment, which is largely due to the conflicting evidence available. As a result, it is unclear whether varicella vaccines provide long-term protection or whether immunity wanes with time. This is partially due to the fact that multiple factors are involved with waning immunity, making it difficult to confidently evaluate the effectiveness of varicella vaccines over time. With that said, the two-dose regimen appears to be highly effective against any disease severity and particularly effective against severe disease only (i.e. no severe cases have been reported after receiving two doses of vaccine), and the few studies that specifically evaluated the duration of protection provided by two doses demonstrated long-term protection. Furthermore, the introduction of a second dose of vaccine has been suggested to be beneficial for decreasing the amount of primary vaccine failure. As a result, majority of studies included in this review support the introduction of a second dose into routine immunization schedules.

In general, more data is required to confidently understand the effectiveness of varicella vaccines in immunocompromised individuals. Using HIV-infected children as an example, very few studies were available, and those that were available reported seroconversion rates only. This was largely due to small sample sizes and tightly controlled settings under which the studies were conducted. With that said, the few studies reviewed in this review collectively indicated that varicella vaccination may be beneficial for HIV-infected children in reducing the risk of contracting varicella disease, thereby reducing varicella-related complications and mortality. However, in

order to have better estimates of vaccine effectiveness in HIV-infected individuals (and immunocompromised individuals in general), studies with larger sample sizes and longer periods of follow-up will be required.

There are some self-identified limitations with this systematic review. The literature search was conducted using only the PubMed database, which potentially could miss detecting studies not listed in PubMed. Furthermore, the use of MeSH terms as part of the search strategy may have resulted in missing additional articles that were not catalogued using MeSH terms, however searching titles/abstracts for keywords in addition to MeSH terms would have likely captured these potential articles. There was only one reviewer of the initial literature results, which may have resulted in mistakenly not including articles that fit the criteria. Bibliographies of pertinent reviews were screened for additional relevant articles, which helped incorporate additional articles not identified through the initial search. Finally, only studies written in English were included, which may have resulted in some studies using alternative varicella vaccines to not be included in this systematic review. Although majority of studies used the Varivax vaccine, there were several studies that used Varilrix as well as several domestically produced vaccines (i.e. Keygen, Changchun, Shanghai, etc), thereby capturing some data on a variety of different varicella vaccine formulations.

In summary, varicella vaccination is effective in preventing varicella disease and the evidence has demonstrated that a two-dose regimen is better than a single dose. However, further work is required to continue evaluating the long-term protection and to better understand the role of varicella vaccines in immunocompromised individuals.

REFERENCES

1. Bayer O, Heininger U, Heiligensetzer C, von Kries R. Metaanalysis of vaccine effectiveness in varicella outbreaks. Vaccine 2007;25:6655-60.

2. Seward JF, Marin M, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. The Journal of infectious diseases 2008;197 Suppl 2:S82-9.

3. Huang WC, Huang LM, Chang IS, Tsai FY, Chang LY. Varicella breakthrough infection and vaccine effectiveness in Taiwan. Vaccine 2011;29:2756-60.

4. Cenoz MG, Martinez-Artola V, Guevara M, Ezpeleta C, Barricarte A, Castilla J. Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain. Human vaccines & immunotherapeutics 2013;9:1172-6.

5. Gould PL, Leung J, Scott C, et al. An outbreak of varicella in elementary school children with two-dose varicella vaccine recipients--Arkansas, 2006. The Pediatric infectious disease journal 2009;28:678-81.

6. Mahamud A, Wiseman R, Grytdal S, et al. Challenges in confirming a varicella outbreak in the two-dose vaccine era. Vaccine 2012;30:6935-9.

7. Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. The Journal of infectious diseases 2011;203:312-5.

8. Nguyen MD, Perella D, Watson B, Marin M, Renwick M, Spain CV. Incremental effectiveness of second dose varicella vaccination for outbreak control at an elementary school in Philadelphia, pennsylvania, 2006. The Pediatric infectious disease journal 2010;29:685-9.

9. Spackova M, Wiese-Posselt M, Dehnert M, Matysiak-Klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. Vaccine 2010;28:686-91.

10. Liese JG, Cohen C, Rack A, et al. The effectiveness of varicella vaccination in children in Germany: a case-control study. The Pediatric infectious disease journal 2013;32:998-1004.

11. Arnedo-Pena A, Puig-Barbera J, Aznar-Orenga MA, et al. Varicella vaccine effectiveness during an outbreak in a partially vaccinated population in Spain. The Pediatric infectious disease journal 2006;25:774-8.

12. Buchholz U, Moolenaar R, Peterson C, Mascola L. Varicella outbreaks after vaccine licensure: should they make you chicken? Pediatrics 1999;104:561-3.

13. Outbreak of varicella among vaccinated children--Michigan, 2003. MMWR Morbidity and mortality weekly report 2004;53:389-92.

14. Varicella outbreak among vaccinated children--Nebraska, 2004. MMWR Morbidity and mortality weekly report 2006;55:749-52.

15. Clements DA, Moreira SP, Coplan PM, Bland CL, Walter EB. Postlicensure study of varicella vaccine effectiveness in a day-care setting. The Pediatric infectious disease journal 1999;18:1047-50.

16. Dworkin MS, Jennings CE, Roth-Thomas J, Lang JE, Stukenberg C, Lumpkin JR. An Outbreak of Varicella among children attending preschool and elementary school in Illinois. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2002;35:102-4.

17. Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. The Pediatric infectious disease journal 2010;29:690-3.

18. Galil K, Fair E, Mountcastle N, Britz P, Seward J. Younger age at vaccination may increase risk of varicella vaccine failure. The Journal of infectious diseases 2002;186:102-5.

19. Galil K, Lee B, Strine T, et al. Outbreak of varicella at a day-care center despite vaccination. The New England journal of medicine 2002;347:1909-15.

20. Haddad MB, Hill MB, Pavia AT, et al. Vaccine effectiveness during a varicella outbreak among schoolchildren: Utah, 2002-2003. Pediatrics 2005;115:1488-93.

21. Hohle M, Siedler A, Bader HM, Ludwig M, Heininger U, Von Kries R. Assessment of varicella vaccine effectiveness in Germany: a time-series approach. Epidemiology and infection 2011;139:1710-9.

22. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. JAMA : the journal of the American Medical Association 1997;278:1495-9.

23. Kilic A, Unuvar E, Yilmaz C, Yildiz I, Oguz F, Sidal M. The effectiveness of varicella vaccination during an outbreak in a children's day-care center. Vaccine 2008;26:3371-2.

24. Lai CC, Chen SC, Jiang DD. An outbreak of varicella among schoolchildren in Taipei. BMC public health 2011;11:226.

25. Lee BR, Feaver SL, Miller CA, Hedberg CW, Ehresmann KR. An elementary school outbreak of varicella attributed to vaccine failure: policy implications. The Journal of infectious diseases 2004;190:477-83.

26. Lee LE, Ho H, Lorber E, Fratto J, Perkins S, Cieslak PR. Vaccine-era varicella epidemiology and vaccine effectiveness in a public elementary school population, 2002-2007. Pediatrics 2008;121:e1548-54.

27. Lopez AS, Guris D, Zimmerman L, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? Pediatrics 2006;117:e1070-7.

28. Lu L, Suo L, Li J, et al. A varicella outbreak in a school with high one-dose vaccination coverage, Beijing, China. Vaccine 2012;30:5094-8.

29. Marin M, Nguyen HQ, Keen J, et al. Importance of catch-up vaccination: experience from a varicella outbreak, Maine, 2002-2003. Pediatrics 2005;115:900-5.

30. Miron D, Lavi I, Kitov R, Hendler A. Vaccine effectiveness and severity of varicella among previously vaccinated children during outbreaks in day-care centers with low vaccination coverage. The Pediatric infectious disease journal 2005;24:233-6.

31. Parker AA, Reynolds MA, Leung J, et al. Challenges to implementing second-dose varicella vaccination during an outbreak in the absence of a routine 2-dose vaccination requirement--Maine, 2006. The Journal of infectious diseases 2008;197 Suppl 2:S101-7.

32. Passwell JH, Hemo B, Levi Y, Ramon R, Friedman N, Lerner-Geva L. Use of a computerized database to study the effectiveness of an attenuated varicella vaccine. The Pediatric infectious disease journal 2004;23:221-6.

33. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA : the journal of the American Medical Association 2004;292:704-8.

34. Sheffer R, Segal D, Rahamani S, et al. Effectiveness of the Oka/GSK attenuated varicella vaccine for the prevention of chickenpox in clinical practice in Israel. The Pediatric infectious disease journal 2005;24:434-7.

35. Tafuri S, Martinelli D, De Palma M, Germinario C, Prato R. Report of varicella outbreak in a low vaccination coverage group of otherwise healthy children in Italy: the role of breakthrough and the need of a second dose of vaccine. Vaccine 2010;28:1594-7.

36. Tafuri S, Martinelli D, Prato R, Germinario C. Vaccine effectiveness evaluation during a varicella outbreak among children of primary schools and day-care centers in a region which adopted UMV. Human vaccines & immunotherapeutics 2013;9:184-8.

37. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. Pediatrics 2004;113:455-9.

38. Vally H, Dowse GK, Eastwood K, Cameron S. An outbreak of chickenpox at a child care centre in Western Australia. Costs to the community and implications for vaccination policy. Australian and New Zealand journal of public health 2007;31:113-9.

39. Vazquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. The New England journal of medicine 2001;344:955-60.

40. Vazquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. JAMA : the journal of the American Medical Association 2004;291:851-5.

41. Wang Z, Yang H, Li K, et al. Single-dose varicella vaccine effectiveness in school settings in China. Vaccine 2013;31:3834-8.

42. Kuter BJ, Weibel RE, Guess HA, et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine 1991;9:643-7.

43. Knuf M, Zepp F, Helm K, et al. Antibody persistence for 3 years following two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. European journal of pediatrics 2012;171:463-70.

44. Baxter R, Ray P, Tran TN, et al. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. Pediatrics 2013;131:e1389-96.

45. Ampofo K, Saiman L, LaRussa P, Steinberg S, Annunziato P, Gershon A. Persistence of immunity to live attenuated varicella vaccine in healthy adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2002;34:774-9.

46. Saiman L, LaRussa P, Steinberg SP, et al. Persistence of immunity to varicella-zoster virus after vaccination of healthcare workers. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 2001;22:279-83.

47. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. The New England journal of medicine 2007;356:1121-9.

48. Gershon AA, Steinberg SP. Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. The New England journal of medicine 1989;320:892-7.

49. Johnson C, Rome LP, Stancin T, Kumar ML. Humoral immunity and clinical reinfections following varicella vaccine in healthy children. Pediatrics 1989;84:418-21.

50. Kurugol Z, Halicioglu O, Koc F, Koturoglu G, Aksit S. Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2011;15:e475-80.

51. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. The Pediatric infectious disease journal 2004;23:132-7.

52. Shinefield HR, Black SB, Staehle BO, et al. Vaccination with measles, mumps and rubella vaccine and varicella vaccine: safety, tolerability, immunogenicity, persistence of antibody and duration of protection against varicella in healthy children. The Pediatric infectious disease journal 2002;21:555-61.

53. Takayama N, Minamitani M, Takayama M. High incidence of breakthrough varicella observed in healthy Japanese children immunized with live attenuated varicella vaccine (Oka strain). Acta paediatrica Japonica; Overseas edition 1997;39:663-8.

54. Vessey SJ, Chan CY, Kuter BJ, et al. Childhood vaccination against varicella: persistence of antibody, duration of protection, and vaccine efficacy. The Journal of pediatrics 2001;139:297-304.

55. Watson B, Piercy S, Soppas D, et al. The effect of decreasing amounts of live virus, while antigen content remains constant, on immunogenicity of Oka/Merck varicella vaccine. The Journal of infectious diseases 1993;168:1356-60.

56. Zhang X, Yan Y, Liu F, et al. The epidemiology and risk factors for breakthrough varicella in Beijing Fengtai district. Vaccine 2012;30:6186-9.

57. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. The Journal of infectious diseases 2006;194:247-55.

58. Bekker V, Westerlaken GH, Scherpbier H, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. AIDS (London, England) 2006;20:2321-9.

59. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. The Pediatric infectious disease journal 2006;25:368-70.

60. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. The Journal of infectious diseases 2010;201:1806-10.

61. Sartori AM. A review of the varicella vaccine in immunocompromised individuals. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2004;8:259-70.

62. Levin MJ. Varicella vaccination of immunocompromised children. The Journal of infectious diseases 2008;197 Suppl 2:S200-6.

63. Quian RJ, Protasio PA, Dall'orso VP, et al. Varicella outbreak in a village in Uruguay. Revista chilena de infectologia : organo oficial de la Sociedad Chilena de Infectologia. 2010;27(1):47-51.