Primary Versus Secondary Failure After Varicella Vaccination: Implications for Interval Between 2 Doses

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Background: Two-dose varicella vaccination is recommended for optimal control of varicella in populations with high (>90%) 1-dose coverage. Optimal timing of the second dose may depend on whether breakthrough varicella results from primary vaccine failure (no protective immunity after vaccination) or secondary vaccine failure (waning protective immunity).

Methods: Published literature (1995 to 2012) on vaccine failure after varicella vaccination cited in PubMed and other online sources was reviewed.

Results: Nineteen publications detailed 21 varicella outbreaks with breakthrough varicella rates ranging from 0% to 42%; the publications showed no consistent trend between breakthrough varicella rate and time since vaccination.

Conclusions: Literature to date indicates a relatively high rate of primary vaccine failure and limited evidence of secondary vaccine failure among 1-dose varicella vaccine recipients, suggesting that a short interval between 2 doses might be preferable in countries considering implementation of universal varicella vaccination to reduce breakthrough varicella. However, any potential disruption to well-established vaccination schedules should be considered.

Key Words: varicella vaccination, vaccine failure, dose interval

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As a result of the societal and clinical impact of varicella, universal routine vaccination has been implemented in several countries worldwide. In the United States, where 1-dose varicella universal routine vaccination was introduced in 1995, there have been substantial reductions in the number of varicella cases, varicella-related ambulatory visits, hospitalizations and deaths.[1–3] Outside of the United States, implementation of varicella universal routine vaccination in Germany, Italy (7 regions as of January 2012) and Uruguay has also resulted in decreased rates of hospitalizations and complications.[4–8] However, in a recent review, 1-dose varicella vaccination was estimated to be only ~85% effective in preventing disease, resulting in cases of breakthrough varicella.[9]

Breakthrough varicella is defined as the appearance of a pruritic maculopapulovesicular rash with onset >42 days after vaccination without any other apparent cause.[10] Whilst breakthrough varicella is generally milder (eg, involves fewer lesions, mostly papules, a lower rate of fever and shorter duration) than natural varicella, it is still a cause for concern due to varicella zoster virus (VZV) transmission from the breakthrough rash. Additionally, it can establish latency to cause herpes zoster.[11] Breakthrough varicella is caused by primary or secondary vaccine failure. Primary vaccine failure could be defined as the failure to seroconvert or the failure to mount a protective immune response after vaccination despite seroconversion, whereas secondary vaccine failure is the gradual waning of immunity over time.

In response to cases of breakthrough varicella, several countries have implemented recommendations for a 2-dose varicella vaccination schedule. Indeed, the second dose of varicella vaccine has been shown to increase effectiveness from 86% to 98%.[12] However, the optimal timing for the second dose is currently unknown. Knowledge on the relative contributions of primary and secondary vaccine failure to the incidence of breakthrough varicella would influence decision making because a trend toward more primary than secondary vaccine failure would favor a shorter interval and vice versa. As more countries consider implementing varicella vaccination, it is important to know whether a short (months between doses) or a long (years between doses) immunization schedule will provide optimal control of the disease. Therefore, a review of the literature has been carried out to assess the incidence and causes of varicella vaccine failure.

Search Strategy and Selection Criteria

Published literature (PubMed, conference abstracts, Google Scholar and Medscape) on live-attenuated vaccine failure associated with 1 and 2 doses of varicella-containing vaccine was reviewed (1995 to January 2012). Limits included: English, humans, clinical trials, randomized controlled trial, meta-analyses and reviews. Search terms encompassed: "varicella vaccine failure," "waning varicella immunity," "breakthrough varicella," "(measles mumps rubella varicella or MMRV) vaccine failure," "varicella vaccine seroconversion" and "varicella vaccine catch-up." Exclusion criteria included studies in immunocompromised patients, as the varicella vaccine is not routinely given to this patient group, and postoutbreak control.

Cited articles were chosen on the relevance of their contents (eg, content on breakthrough varicella, varicella outbreaks, postvaccination antibody titers, vaccine failure, etc.), and each article was studied for references that were missed by the initial search. This was not intended as a systematic review.

One-dose Varicella Vaccine Effectiveness

Since 1995, there have been 19 publications describing 21 varicella outbreaks in vaccinated populations in day-care centers and elementary schools worldwide and 1 meta-analysis of 16 of these outbreaks (Table 1).[13–32] Of these publications, 14 are from the United States where varicella universal routine vaccination has been employed since 1995. However, published outbreak reports represent just a small number of the outbreaks that actually occurred and most likely represent a bias toward outbreaks where issues occurred (ie, a large number of cases). Indeed, a total of 190 outbreaks were reported to the Centers for Disease Control and Prevention from 24 jurisdictions throughout the United States in 2004.[33] This indicates that vaccine failure after 1-dose varicella vaccination is more prevalent than the published literature would suggest.

In published outbreaks, vaccination coverage rates for 1 dose of varicella-containing vaccines were 30–97% (Table 1).[13–32] In these studies, vaccine effectiveness varied from 20% to 100% against disease of any severity and 85.5% to 100% for moderate/severe disease (Table 1).[13–32] Breakthrough varicella rates ranged from 0% to 42%, which appeared to have no association with vaccination coverage. For instance, the study with the lowest coverage (30%) showed the highest effectiveness (100%), as no vaccinated child developed breakthrough varicella[15]; however, this could be explained by study size as only 20 children attended the day-care center involved. It is therefore possible that vaccine coverage in a population experiencing an outbreak of varicella may not correlate with vaccine effectiveness.

Outside of outbreak studies, the effectiveness of a single dose of vaccine against disease of any severity reported by varicella surveillance in the United States and case-control studies falls in the range of 71% to 87%.[2,9,12,34,35] A review of 19 studies (including outbreak reports) from the United States found that the median 1-dose effectiveness was 85%.[9] Additionally, 2 studies from Israel indicated vaccine effectiveness of 88% and 92%.[36,37] One-dose vaccine effectiveness determined by a meta-analysis of 16 outbreaks worldwide was 72%.[14] A large epidemiological study from Taiwan that investigated the incidence of breakthrough varicella in over 1,000,000 vaccinated children found that 1-dose vaccine effectiveness was 82.6%.[38] Together, these data represent a rough average of 80% vaccine effectiveness for 1 dose of varicella vaccine against any varicella disease and an approximate vaccine failure rate of 20%. As with outbreak studies, effectiveness against severe/moderate disease was a lot higher than for disease of any severity.[9,35,37]

Vaccine Failure

Differentiating between primary and secondary vaccine failure in outbreak analyses is difficult, as measurement of antibody levels postvaccination cannot determine whether the affected individual had primary or secondary vaccine failure. Additionally, secondary vaccine failure can have a similar clinical presentation to primary vaccine failure in those whose immunity has waned completely.[39]

Several risk factors have been proposed to increase varicella vaccine failure and are debated in the literature, including vaccine titer,[40] immunization at a young age (particularly below 12–15 months),[18,19,26,34,38,41–44] time since vaccination with other live virus vaccines,[34,42,43] history of eczema,[22,27,43] asthma[23,26] vaccine brand[30] and the use of oral or inhaled corticosteroids.[26,34,42,43]

A placebo-controlled trial conducted before the licensure of GlaxoSmithKline Vaccine's varicella vaccine set the scene for assessing the impact of varicella vaccination at population level.[40] In this study, infants and toddlers aged 10–30 months received placebo or varicella vaccine at (high) release titer (10,000–15,850 plaque forming units [pfu]) or (low) expiry titer (630–1260 pfu). The seroconversion rates for the high and low titer vaccines were 100% and 99.4%, respectively, when measured by immunofluorescence assay (IFA).

The protection rate over a period of 29 months (mean) was 88% for the high titer and 55% for the low titer vaccines against any varicella disease. Overall, vaccine efficacy was lower for those vaccinated at 10–18 months (64%) than those vaccinated at 19–24 months of age (82%). These results indicated that vaccine titer and age at the time of vaccination are major determinants of clinical protection, which is lower than what could be expected from the high IFA seroconversion rates.

The importance of time since vaccination as a cause of vaccine failure is discussed further below.

Evidence for Primary Vaccine Failure

As shown in Table 2,[40,45–72] across all studies 0–24% of subjects failed to seroconvert after primary vaccination, depending on age group, vaccine titer and vaccine lot. Importantly, the assays used to assess antibody titers vary between publications, which appeared to affect the outcome. For instance, assessment of seroconversion rates with enzyme-linked immunosorbent assay (ELISA) and IFA methods generally reported high seroconversion rates (>90%), whereas assessment with the validated fluorescent antibody to membrane antigen (FAMA) assay generally showed lower seroconversion rates of 76–84%.[52,57] Indeed, the FAMA assay is the only assay that has been validated in a real-life setting, where a positive titer correlated with protection following household exposure to varicella.[73,74] Additionally, 6-week postvaccination FAMA antibody titers have also been inversely correlated with the likelihood of developing breakthrough varicella over 10 years of follow-up.[50] The high seroconversion rates (>90%) as assessed by ELISA and IFA methods have been proposed to be due to an initial burst of immunity after vaccination that may not be adequate to instigate a memory T-cell response.[75] Interestingly, this could be overcome by a higher dose of vaccine,[40] or with a second dose of varicella vaccine, which has been shown to boost VZV-specific cell-mediated immune responses in children after vaccination.[71,76]

Using the glycoprotein ELISA employed by Merck & Co., Inc. (NJ) to measure VZV antibody concentrations, an arbitrary value of ≥5 glycoprotein ELISA units 6 weeks postvaccination correlates with a 3.5-fold reduced risk of breakthrough varicella, although this has never been verified in contact settings or correlated to the FAMA assay.[53] Additionally, the correlate of protection could not be ascertained from this study as it did not include a control

TABLE 1. Publications and Characteristics of Selected Varicella Outbreaks in Vaccinated Populations

Reference	Location	Vaccination Policy	Vaccine	N	Vaccination Coverage (%)	BV Cases* (%)	VE† Any Disease (%)	VE† Moderate/ Severe Disease (%)
Buchholz[1] 1999[15]	Los Angeles, USA	URV	Varivax	20	30	0	100	100
Arnedo-Pena 2006[13]	Castellón, Spain	Selective	Varilrix	269	36	23	70	97
Miron 2005[28]	Northern Israel	Selective	Varilrix	242	37	42	20	93
Izurieta 1997[23]	Georgia, USA	URV	Varicella vaccine‡	148	45	13	86	100
Lee 2004[25]	Minnesota, USA	URV	Varivax	249	47	25	56	90
Marin 2005[27]	Maine, USA	URV	Varivax	296	47	8	89	96
Tafuri 2010[31]	Puglia, Italy	URV	Varilrix	102	54	13	82	NR
Spackova 2010[30]	Various, Germany	URV	Varivax, Varilrix, Priorix-Tetra	631	62§	21	62 [94]§	89§
Dworkin 2002[18]	Illinois, USA	URV	Varivax	209	68	6	88	NR
Lai 2011[24]	Taipei, Taiwan	URV	Varivax	392	71	10	69–100¶	85.5
Galil 2002[19]	Pennsylvania, USA	URV	Varivax	131	73	36	44	86
Haddad[1] 2005[22]	Utah, USA	URV	Varivax	558	77	4	87	90
Galil 2002[20]	New Hampshire, USA	URV	Varivax	88	80	34	79	95
Centers for Disease Control and Prevention 2006[17]	Nebraska, USA	URV	Varivax	142	81	13	81	93
Parker 2008[29]	Maine, USA	URV	Varivax	341	81	13	87	100
Haddad[2] 2005[22]	Utah, USA	URV	Varivax	924	83	5	87	99
Buchholz[2] 1999[15]	Los Angeles, USA	URV	Varivax	39	87	24	71	93
Lopez 2006[26]	Arkansas, USA	URV	Varivax	545	96§	8	82	97
Centers for Disease Control and Prevention 2004[16]	Michigan, USA	URV	Varivax	507	96	12	85	98
Gould 2009[21]	Arkansas, USA	URV	Varivax	871	97 [39]	15	85 [89]	100
Tugwell 2004[32]	Oregon, USA	URV	Varivax	218	97	9	72	NR
Bayer 2007[14]	Meta-analysis		Varivax	—	—	—	73	NR

Data collated from the literature. Studies are listed in order of vaccine coverage. Superscript numbers (1 and 2) in references represent different cohorts within the same publication. Numbers in square brackets indicate 2-dose coverage and VE after 2 doses were available.

*Percentage of vaccinated children who develop breakthrough varicella.

†Effectiveness after 1 dose.

‡Commercial name not available.

§Coverage/VE include 2-dose vaccine recipients.

¶Across 3 school grades.

BV indicates breakthrough varicella; NR, not reported; URV, universal routine vaccination; VE, vaccine effectiveness.

group. Indeed, using this value as a threshold for protection, there is a wide range of primary vaccine failure (5–24%) after 1-dose varicella vaccination with a single brand.[55,64] The reason for such variance is unclear.

Of interest there is data suggesting that some children without detectable antibodies are still protected against infection by cell-mediated immunity.[77] This would imply that antibodies do not play a direct role in immunity to VZV. Indeed, it is unclear whether varicella antibodies play a direct role in vaccine-specific protection or whether they are just a surrogate marker for vaccine-specific T-cell responses that accompany seroconversion.[78] However, if 1-dose vaccine effectiveness is approximately 80% and seroconversion is a proxy marker for protection, most cases of breakthrough varicella can be accounted for by primary vaccine failure.

Two case-control studies from the United States and China examined whether vaccine effectiveness is time dependent.[34,79] In the 8-year study from the United States, vaccine effectiveness dropped from 97% in the first year postvaccination to 86% in the second year and then remained stable.[34] In the study from China, effectiveness was also shown to drop after the first year and then remain stable; however, this result was not statistically significant.[79] These effectiveness measures conflict with a 3-year retrospective study from Taiwan where 81% of cases occurred during the first year postvaccination.[80] However, these studies all indicate 1-dose primary vaccine failure in populations with circulating VZV because the varicella breakthrough rate does not increase over time.

Evidence for Secondary Vaccine Failure

Increased incidence and severity of breakthrough varicella with time is an indicator of secondary vaccine failure. Of the 29 publications that reported on breakthrough varicella rates with time (Table 3),[10,13,16,18,19,22,23,25–28,30,32,34,41,43,44,46,50,53,54,66,70,73,74,79–82] 9 showed an increased risk with time of breakthrough varicella; this increased risk was generally observed around 4–5 years postvaccination. However, 7 of these publications were outbreak studies, which by design are based on limited population size and therefore not adequately powered to detect any drop in protection according to time since vaccination.

A large retrospective study of over 11,000 children found that time since vaccination is an important risk factor for breakthrough varicella, with both incidence and severity increasing over a 10-year period.[10] Whilst a strength of this study is that decreasing exposure levels were controlled for, this study did not use laboratory confirmation for cases of breakthrough varicella, which, as the disease tends to be very mild, can be confused with other causes of papulovesicular rashes. Indeed, one of the strengths of the case-control study conducted in the United States, which showed no secondary vaccine failure after the first year postvaccination, was that the authors required VZV DNA-positive samples from lesions for diagnosis of varicella.[34]

In a meta-analysis of varicella outbreaks, the authors modeled vaccine effectiveness against time since vaccination (up to 6 years) from 4 outbreaks.[14] This analysis found that the pattern of vaccine effectiveness fitted models of waning immunity with a linear or exponential course.[14] However, other longer-term studies

TABLE 2. Varicella Zoster Virus Seroconversion/Seroresponse Rates 4–6 Weeks After 1 Dose of Varicella Vaccine in Children

Reference	Vaccine(s)	Total Children Vaccinated	Seroconversion/ Seroresponse Rate (%)	Assay* (Threshold)
Clements 1995[46]	V (Varivax)	465	95	ELISA† and gpELISA†
Gatchalian 2004[47]	V (Okavax)	100	96	Commercial ELISA (12 mIU/mL)
Michalik 2008[57]	V (Varivax)	148	76	FAMA (>1:4 dilution)
Kim 2010[52]	V (Varilrix, Varivax, Vari-L, SuduVax)	67	84	
Johnson 1997[50]	V (Varivax)	281	94–98‡	FAMA (>1:2 dilution)
Watson 1995[71]	V (Varicella vaccine§)	419	100	gpELISA (≥0.3 units/mL)
Ngai 1996[58]	V (Varivax)	2196	99	gpELISA (≥0.6 units/mL)
Li 2002[53]	V (Varivax)	1164	99	
Vessey 2001[70]	V (Varivax)	1164	99	
Watson 1996[72]	V (Varivax)	111	100	
Shinefield 2005[65]	MMRV (ProQuad) or V (Varivax)	783	81–93	gpELISA (≥5.0 units/mL)
Shinefield 2005[64]	MMRV (ProQuad) or V (Varivax)	480	91–99	
Merck 2001[55]	V (Varivax)	6889	76	
Shinefield 2002[66]	V (Varivax)	603	93–95¶	
Silber 2007[67]	V (Varivax)	3771	93	
Nolan 2008[59]	V (Varivax)	411	83	
Gillet 2009[48]	V IM or SC (Varivax)	752	86–88	
Ramikissoon 1995[61]	V (Varivax)	200	100	Indirect IFA (≥1:4 dilution)
Tan 1996[69]	V (Varilrix)	191	98–100‡	
Kanra 2000[51]	V (Varilrix)	114	97	
Barzaga 2002[45]	V (Varilrix)	246	97	
Nolan 2002[60]	MMRV (Priorix-Tetra) or V (Varilrix)	160	93–96	
Stück 2002[68]	V (Varilrix)	61	96	
Schuster 2008[63]	V (Varilrix)	970	96	
Gillet 2009[49]	MMRV (Priorix-Tetra) or V (Varilrix)	458	96–100	
Rümke 2011[62]	MMRV (Priorix-Tetra)	372	98.4–98.9	
Varis 1996[40]	V (Varilrix)	325	99–100	Indirect IFA
Meruice 1996[56]	V (Varilrix)	1372	99	
Lim 1998[54]	V (Varilrix)	181	99	

Data collated from the literature.
*FAMA is the only assay validated in a real-life setting.
†No threshold for seroconversion/seroresponse specified.
‡Different vaccine lots.
§Commercial name not available.
¶Concomitant versus nonconcomitant administration with MMR.
gpELISA indicates glycoprotein ELISA; IM, intramuscular; SC, subcutaneous; V, monovalent varicella vaccine.

with up to 20 years of follow-up[73,74] found long-term persistence of antibodies or have shown that the rate and severity of breakthrough varicella does not increase with time, suggesting a limited rate of secondary vaccine failure.[41,50,66,74,81]

Long-term studies do not indicate significant waning immunity after varicella vaccination, as they have shown that there is no increase in breakthrough varicella between 4 and 8 years after vaccination.[34,41,70,79] A mathematical model fitted to the rate of breakthrough varicella in subjects of 3 clinical trials showed that, in the worst-case scenario (88% protected after vaccination, that is, 12% primary vaccine failure), the incidence of breakthrough varicella would increase in the first few years postvaccination and then plateau at 3% per year for up to 6 years postvaccination.[83] Although this was extrapolated from a clinical trial which used a low titer vaccine lot currently not in production, it does appear to fit the patterns observed in case-control studies.[34,79]

It should be emphasized that the results of long-term studies can be difficult to evaluate in areas where wild-type virus still circulates, as this can provide natural boosting to the immune system, reducing secondary vaccine failure. Therefore, as circulating wild-type virus is reduced by universal routine vaccination, secondary vaccine failure could increase. In fact, time since vaccination was only identified as a risk factor for breakthrough varicella in 2002,[19] 7 years into the United States vaccination program. Moreover, it can be difficult to interpret long-term studies in countries where coverage rates change considerably over the years. As coverage rates plateau in the future, further long-term surveillance studies are required to fully assess the rate of secondary vaccine failure.

Evidence for Optimal Interval Between Doses

It has been suggested that high antibody titers are required for optimal protection against varicella, rather than seroconversion *per se,* and that 2 doses are required to achieve this.[84,85] Numerous studies have assessed antibody titers in children after administration of 2 doses of vaccine given at various intervals (4 weeks to 6 years; Table 4).[49,58,62–65,71,86–93] These studies indicate that geometric mean antibody concentrations increase roughly 10-fold (range 5- to 39-fold) after the second dose of vaccine in children, irrespective of timing between doses. Such a large increase in antibody titers after the second dose suggests inadequate priming after the first dose and thus minimal induction of memory cells, resulting in vaccinees who are not fully protected after 1 dose.[94]

The boosting effect in geometric mean antibody concentrations observed with the short interval for the second dose is atypical of most live viral vaccines[75] and suggests that

TABLE 3. Publications Showing Evidence For and Against Secondary Vaccine Failure

Reference	N	Vaccine	Maximum Follow-up (yr)	Average Annual BV Rate (%)	Cumulative BV Rate (%)	Time Since Vaccination a Risk Factor?
No evidence for secondary vaccine failure						
Clements 1995[46]	426	Varivax	5	2.7	19	No
Izurieta 1997[23]*	148	Varicella vaccine†	—	—	13	No
Johnson 1997[50]	281	Varivax	10	1.7	17	No
Takayama 1997[82]	593	Oka strain†	8	1–4	34	No
Lim 1998[54]	168	Varilrix	2.9	—	11	No
Ozaki 2000[81]	973	Live varicella vaccine (Oka strain)‡	10	—	21	No
Saiman 2001[74]	120	Varivax, Varilrix	20	—	10	No§
Vessey 2001[70]	937	Varivax	7	0.2–2.3	7	No
Ampofo 2002[73]	461	Varivax, Varilrix	20	—	9	No§
Dworkin 2002[18]*	209	Varivax	—	—	6	No
Li 2002[53]	1087	Varivax	7	0.2–2.2	6	No
Shinefield 2002[66]	603	Varivax	5	1.1–1.4	6–7	No
Tseng 2003[80]	1248	Varivax	2.6	2.1–2.8	2	No—First year after vaccination only
Vázquez 2004[34]¶	1008	Varivax	8	—	—	No—First year after vaccination only
Marin 2005[27]*	296	Varivax	—	—	8	No
Lopez 2006[26]*‖	545	Varivax	—	—	8	No
Black 2008[41]	7449	Varivax	8	—	16	No—First 4 yr after vaccination only
Lee 2008[43]	9025	Varivax	5	6–8	5	No
Spackova 2010[30]*‖	631	Varivax, Varilrix, Priorix-Tetra	4.6	—	21	No
Fu 2010[79]¶	1000	Varilrix, Shanghai, Changchun	5	—	—	No
Evidence for secondary vaccine failure						
Galil 2002[19]*	131	Varivax	—	—	26	Yes
Centers for Disease Control and Prevention 2004[16]*	507	Varivax	—	—	12	Yes—Time since vaccination >4 yr
Lee 2004[25]*	249	Varivax	—	—	25	Yes—Time since vaccination >5 yr
Tugwell 2004[32]*	218	Varivax	—	—	9	Yes—Time since vaccination >5 yr
Haddad 2005[22]*	1482	Varivax	—	—	5	Yes—Time since vaccination >5 yr
Miron 2005[28]*	242	Varilrix	—	—	42	Yes—Time since vaccination >2 yr
Arnedo-Pena 2006[13]*	269	Varilrix	—	—	23	Yes—Time since vaccination >25 mo
Chaves 2007[10]	11,356	Varivax	10	—	10	Yes
Kurugol 2011[44]	1683	Varilrix and Okavax	10	3–63	28	Yes—Time since vaccination >5 yr

Data collated from the literature.
*Outbreak studies.
†Commercial name not available.
‡Biken Institute, Osaka, Japan.
§Vaccinees were adults who had received 1, 2 or 3 doses of the vaccine.
¶Case-control study.
‖Vaccinees were children who had received 1 or 2 doses of the vaccine.
BV indicates breakthrough varicella.

an incomplete immune response is mounted after the first dose. In addition to the large booster effect of the second dose, the generally mild nature of breakthrough varicella would also seem to suggest that priming of the immune system takes place following vaccination.[75,94] In this respect, a second dose would not be a booster for waning immunity but would instigate completion of the necessary immune response.

On this basis, the literature suggests that a second dose should be given soon after the first dose to cover the individuals with primary vaccine failure and those who did not mount an adequate response for protection despite an initial antibody response (also termed primary vaccine failure by the definition laid out in this article). Furthermore, evidence also suggests that antibody titers fall during the first year postvaccination,[52,57] which, even if this reflects a type of rapid waning immunity, indicates that the second dose should be given soon after the first because antibody titers are correlated with protection.[50,53] Therefore, administering the second dose of the vaccine within the second year of life may be optimal. The second dose should be given at least 4 weeks after the first, as clinical trials have not assessed shorter intervals (Table 4).[49,58,62,63,65,71,86–93] One study in adolescents and adults, who have always been given 2 doses of vaccine due to the lowered immunogenicity of the vaccine in this age group, found that delaying the second dose to 8 weeks compared with 4 weeks induced higher antibody titers.[95] Additionally, a recent study of 2 doses of MMRV has shown that higher antibodies titers are induced if the second dose is given 12 months versus 4 weeks after the first dose (Table 4).[49,58,62,63,65,71,86–93] However, there were 2 cases of

TABLE 4. Geometric Mean Antibody Concentrations After 2 Doses of VZV-containing Vaccines in Children

Reference	Dose 1	Dose 2	Dose Interval	Fold Increase in GMC From First to Second Dose
Schuster 2008[63]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	6 wk	23.7
Czajka 2009[86]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	6–8 wk	26.6*
Gillet 2009[49]	MMRV(Priorix-Tetra)	V(Varilrix)	6–8 wk	12.6–14.1
Gillet 2009[49]	MMR+V(Priorix and Varilrix)	V(Varilrix)	6–8 wk	9.8–13.1
Knuf 2006[89]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	6–8 wk	>20
Kuter 2004[90]	V(Varivax)	V(Varivax)	12 wk	11.0
Ngai 1996[58]	V(Varivax)	V(Varivax)	12 wk	11.6
Shinefield 2005[65]	MMRV(ProQuad)	MMRV(ProQuad)	12 wk	29.4–39.4†
Shinefield 2005[64]	MMRV(ProQuad)	MMRV(ProQuad)	12 wk	45.2
Goh 2007[87]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	12 wk	10.0
Goh 2007[87]	MMR+V(Priorix and Varilrix)	MMR+V(Priorix and Varilrix)	12 wk	5.0
Reisinger 2006[91]	MMR+V(M-M-R-II and Varivax)	MMRV(ProQuad)	3 yr	12.4
Reisinger 2006[91]	MMR+V(M-M-R-II and Varivax)	MMR+V(M-M-R-II and Varivax)	3 yr	8.5
Vesikari 2007[92]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	5 yr	9.8
Watson 1995[71]	V(Varicella vaccine‡)	V(Varicella vaccine‡)	4–6 yr	8.5
Halperin 2009[88]	MMR+V(Priorix and Varilrix)	MMRV(Priorix-Tetra)	6 wk to 5 yr	27.2
Halperin 2009[88]	MMR+V(Priorix and Varilrix)	MMR+V(Priorix and Varilrix)	6 wk to 5 yr	26.2
Rümke 2011[62]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	4 wk	7.8
Rümke 2011[62]	MMRV(Priorix-Tetra)	MMRV(Priorix-Tetra)	1 yr	22.6

Data collated from the literature.
*Pooled analysis of 3 studies.[63,89,93]
†Dose range study for MMRV vaccine.
‡Commercial name not available.
GMC indicates geometric mean antibody concentration; V, monovalent varicella vaccine.

breakthrough varicella 5 and 10 months after the first dose in the 12-month interval group, and no cases in the 4-week interval group, despite a similar rate of varicella contact.[62]

Implementation of a Short-interval 2-dose Schedule

Short-interval 2-dose varicella immunization schedules should reduce the period of time that a child with primary vaccine failure is unprotected, reducing the risk of breakthrough disease. There are a number of different options for implementation of short-interval 2-dose varicella vaccination in the second year of life: 1) vaccination with 2 doses of monovalent vaccine; 2) vaccination with 2 doses of MMRV vaccine; 3) vaccination with a combination of 2 doses of MMR and varicella vaccine and/or MMRV. However, implementation of a short interval between doses should always be evaluated with respect to the overall vaccination schedule. A public health evaluation of the advantages and disadvantages of alternative vaccination schedules should be carefully performed.

For ease of scheduling, a combination of MMRV or monovalent vaccines can be used to allow flexibility for the administration of 2 doses of varicella vaccine. For instance, in Germany, both MMRV and monovalent vaccines are licensed under 2-dose schedules.[96] This option is especially pertinent for the United States, where the second dose of MMR is currently suggested for children aged 4–6 years.[97] In this instance, the use of a monovalent vaccine would allow the second dose to be administered in the second year of life. This is currently permitted in the United States varicella vaccination schedule as long as there is a minimum of 3 months between doses.[98] Another possibility that may be considered to implement the short-interval 2-dose schedule for varicella is shifting the age at which the second dose of MMR is administered from 4−6 years to 18 months of age. This option may minimize administration costs for the immunization program (less patient visits/administration costs, for example, needles and reduced time dedicated by healthcare professionals) and will help support improved coverage for both MMR and varicella vaccination.

Reduction in Risk With Short- Versus Long-interval Immunization Schedules

Assuming no waning immunity and breakthrough varicella rates of 1–3% per year (Table 3),[10,13,16,18,19,22,23,25–28,30,32,34,41,43,44,46,50,53,54,66,70,73,74,79–82] changing the timing of the second dose from age 4–6 years to the second year of life could prevent around 2-fold cumulative cases of breakthrough varicella. Undoubtedly, this figure is an overestimation as increasing varicella vaccination coverage would reduce the opportunity for contracting the disease; however, a high primary vaccine failure rate could allow continued circulation of the virus. Additionally, implementation of a short immunization schedule would be especially important for countries that introduce varicella vaccination because wild-type virus circulates more in those countries than in countries that have already reduced incidence of the disease due to varicella vaccination.

Effectiveness of 2-dose Schedules

Two-dose schedules have been implemented in a variety of countries worldwide, including the United States and Germany. Unlike the United States, Germany employs short-interval varicella vaccination where both doses are given in the second year of life. Recent outbreak reports from Germany and the United States have varied on the effectiveness of a second dose of varicella vaccine. In Germany, a second dose of MMRV within the second year of life (66% second-dose coverage) increased vaccine effectiveness from 62% to 94% in outbreak situations.[30] Long-term follow-up of clinical trials where 2 doses were given in a short interval (3 months between doses) also showed that 2 doses provide more protection than a single dose.[90] In the United States, where a longer schedule is used, 2 studies have shown that a second dose of vaccine increases vaccine effectiveness by up to 98%.[12,99] The short schedule should theoretically protect children earlier in life as it allows early revaccination of children with primary vaccine failure.[98] As the duration of immunity to 2 doses of varicella vaccine is currently unknown, continued surveillance and prospective studies are required.

Conclusion

All published evidence (1995 to 2012) for varicella vaccine failure strongly supports a 2-dose schedule in order to obtain effective control of the disease.[12,29,30,90,100] A review of the literature indicated a relatively high rate of primary vaccine failure among recipients of 1-dose varicella vaccine and limited convincing evidence of secondary vaccine failure. Furthermore, vaccine effectiveness decreases after the first year postvaccination and then remains stable, a pattern predictive of primary vaccine failure. This suggests that the second dose of varicella vaccine should be given as close to the first as possible (minimum interval of 4 weeks based on clinical trials), to prevent a large number of people remaining vulnerable to infection and to reduce the risk of breakthrough varicella. However, individual countries should consider how shortening the interval between doses could impact second-dose vaccination coverage, especially if this warrants an additional visit to the doctor for vaccination. A comparison of vaccine efficacy between the United States and Germany, which employ different varicella vaccination schedules, is warranted in the future. Our findings need to be placed in the context of an important limitation of the selection criteria employed in this review. Published outbreak reports represented only a small number of the varicella outbreaks that actually occurred. Our review did not assess vaccine failure from the varicella outbreaks reported only to the Centers for Disease Control and Prevention. Therefore, we expect that vaccine failure after 1-dose varicella vaccination is more prevalent than what published literature would suggest. To conclude, we propose that a short interval between 2 doses of the varicella vaccine might be preferable to reduce breakthrough varicella, especially in countries that will introduce varicella vaccination and where the wild-type virus circulates predominantly.

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REFERENCES

1. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N Engl J Med*. 2005;352:450–458.
2. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. *JAMA*. 2002;287:606–611.
3. Shah SS, Wood SM, Luan X, et al. Decline in varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against varicella. *Pediatr Infect Dis J*. 2010;29:199–204.
4. Siedler A, Arndt U. Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. *Euro Surveill*. 2010;15:19530.
5. Giammanco G, Ciriminna S, Barberi I, et al. Universal varicella vaccination in the Sicilian paediatric population: rapid uptake of the vaccination programme and morbidity trends over five years. *Euro Surveill*. 2009;14:19321.
6. Spackova M, Muehlen M, Siedler A. Complications of varicella after implementation of routine childhood varicella vaccination in Germany. *Pediatr Infect Dis J*. 2010;29:884–886.
7. Quian J, Rüttimann R, Romero C, et al. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997-2005. *Arch Dis Child*. 2008;93:845–850.
8. Pozza F, Piovesan C, Russo F, et al. Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. *Vaccine*. 2011;29:9480–9487.
9. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis*. 2008;197(suppl 2):S82–S89.
10. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med*. 2007;356:1121–1129.
11. Gershon AA, Katz SL. Perspective on live varicella vaccine. *J Infect Dis*. 2008;197(suppl 2):S242–S245.
12. Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011;203:312–315.
13. Arnedo-Pena A, Puig-Barberà J, Aznar-Orenga MA, et al. Varicella vaccine effectiveness during an outbreak in a partially vaccinated population in Spain. *Pediatr Infect Dis J*. 2006;25:774–778.
14. Bayer O, Heininger U, Heiligensetzer C, et al. Metaanalysis of vaccine effectiveness in varicella outbreaks. *Vaccine*. 2007;25:6655–6660.
15. Buchholz U, Moolenaar R, Peterson C, et al. Varicella outbreaks after vaccine licensure: should they make you chicken? *Pediatrics*. 1999;104(3 Pt 1):561–563.
16. Centers for Disease Control and Prevention. Outbreak of varicella among vaccinated children--Michigan, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:389–392.
17. Centers for Disease Control and Prevention. Varicella outbreak among vaccinated children--Nebraska, 2004. *MMWR Morb Mortal Wkly Rep*. 2006;55:749–752.
18. Dworkin MS, Jennings CE, Roth-Thomas J, et al. An Outbreak of Varicella among children attending preschool and elementary school in Illinois. *Clin Infect Dis*. 2002;35:102–104.
19. Galil K, Fair E, Mountcastle N, et al. Younger age at vaccination may increase risk of varicella vaccine failure. *J Infect Dis*. 2002;186:102–105.
20. Galil K, Lee B, Strine T, et al. Outbreak of varicella at a day-care center despite vaccination. *N Engl J Med*. 2002;347:1909–1915.
21. Gould PL, Leung J, Scott C, et al. An outbreak of varicella in elementary school children with two-dose varicella vaccine recipients–Arkansas, 2006. *Pediatr Infect Dis J*. 2009;28:678–681.
22. Haddad MB, Hill MB, Pavia AT, et al. Vaccine effectiveness during a varicella outbreak among schoolchildren: Utah, 2002-2003. *Pediatrics*. 2005;115:1488–1493.
23. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. *JAMA*. 1997;278:1495–1499.
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, et al. An elementary school outbreak of varicella attributed to vaccine failure: policy implications. *J Infect Dis*. 2004;190:477–483.
26. 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–e1077.
27. Marin M, Nguyen HQ, Keen J, et al. Importance of catch-up vaccination: experience from a varicella outbreak, Maine, 2002-2003. *Pediatrics*. 2005;115:900–905.
28. Miron D, Lavi I, Kitov R, et al. Vaccine effectiveness and severity of varicella among previously vaccinated children during outbreaks in day-care centers with low vaccination coverage. *Pediatr Infect Dis J*. 2005;24:233–236.
29. 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. *J Infect Dis*. 2008;197(suppl 2):S101–S107.
30. Spackova M, Wiese-Posselt M, Dehnert M, et al. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. *Vaccine*. 2010;28:686–691.
31. Tafuri S, Martinelli D, De Palma M, et al. 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;28:1594–1597.
32. Tugwell BD, Lee LE, Gillette H, et al. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics*. 2004;113(3 Pt 1):455–459.

33. Centers for Disease Control and Prevention. Public health response to varicella outbreaks--United States, 2003–2004. *MMWR Morb Mortal Wkly Rep*. 2006;55:993–995.
34. Vázquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. *JAMA*. 2004;291:851–855.
35. Vázquez M, LaRussa PS, Gershon AA, et al. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med*. 2001;344:955–960.
36. Passwell JH, Hemo B, Levi Y, et al. Use of a computerized database to study the effectiveness of an attenuated varicella vaccine. *Pediatr Infect Dis J*. 2004;23:221–226.
37. 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. *Pediatr Infect Dis J*. 2005;24:434–437.
38. Huang WC, Huang LM, Chang IS, et al. Varicella breakthrough infection and vaccine effectiveness in Taiwan. *Vaccine*. 2011;29:2756–2760.
39. Hirose M, Hidaka Y, Miyazaki C, et al. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Infect Dis*. 1997;29:187–190.
40. Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. *J Infect Dis*. 1996;174(suppl 3):S330–S334.
41. Black S, Ray P, Shinefield H, et al. Lack of association between age at varicella vaccination and risk of breakthrough varicella, within the Northern California Kaiser Permanente Medical Care Program. *J Infect Dis*. 2008;197(suppl 2):S139–S142.
42. Verstraeten T, Jumaan AO, Mullooly JP, et al.; Vaccine Safety Datalink Research Group. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics*. 2003;112:e98–103.
43. Lee LE, Ho H, Lorber E, et al. Vaccine-era varicella epidemiology and vaccine effectiveness in a public elementary school population, 2002-2007. *Pediatrics*. 2008;121:e1548–e1554.
44. Kurugol Z, Halicioglu O, Koc F, et al. Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey. *Int J Infect Dis*. 2011;15:e475–e480.
45. Barzaga NG, Florese RH, Bock HL. Reactogenicity and immunogenicity of a varicella vaccine in healthy seronegative and seropositive subjects. *Southeast Asian J Trop Med Public Health*. 2002;33:259–267.
46. Clements DA, Armstrong CB, Ursano AM, et al. Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents. *Pediatr Infect Dis J*. 1995;14:874–879.
47. Gatchalian S, Tabora C, Bermal N, et al. Immunogenicity and safety of a varicella vaccine (Okavax) and a trivalent measles, mumps, and rubella vaccine (Trimovax) administered concomitantly in healthy Filipino children 12-24 months old. *Am J Trop Med Hyg*. 2004;70:273–277.
48. Gillet Y, Habermehl P, Thomas S, et al. Immunogenicity and safety of concomitant administration of a measles, mumps and rubella vaccine (M-M-RvaxPro) and a varicella vaccine (VARIVAX) by intramuscular or subcutaneous routes at separate injection sites: a randomised clinical trial. *BMC Med*. 2009;7:16.
49. Gillet Y, Steri GC, Behre U, et al. Immunogenicity and safety of measles-mumps-rubella-varicella (MMRV) vaccine followed by one dose of varicella vaccine in children aged 15 months-2 years or 2-6 years primed with measles-mumps-rubella (MMR) vaccine. *Vaccine*. 2009;27:446–453.
50. Johnson CE, Stancin T, Fattlar D, et al. A long-term prospective study of varicella vaccine in healthy children. *Pediatrics*. 1997;100:761–766.
51. Kanra G, Ceyhan M, Ozmert E. Safety and immunogenicity of live attenuated varicella vaccine in 9-month-old children. *Pediatr Int*. 2000;42:674–677.
52. Kim SH, Lee HJ, Park SE, et al. Seroprevalence rate after one dose of varicella vaccine in infants. *J Infect*. 2010;61:66–72.
53. Li S, Chan IS, Matthews H, et al. Inverse relationship between six week postvaccination varicella antibody response to vaccine and likelihood of long term breakthrough infection. *Pediatr Infect Dis J*. 2002;21:337–342.
54. Lim YJ, Chew FT, Tan AY, et al. Risk factors for breakthrough varicella in healthy children. *Arch Dis Child*. 1998;79:478–480.
55. Merck. Package circular for VARIVAX™ (Varicella Virus Vaccine Live) 2001. Available at: http://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf. Accessed January 12, 2013.
56. Meurice F, De Bouver JL, Vandevoorde D, et al. Immunogenicity and safety of a live attenuated varicella vaccine (Oka/SB Bio) in healthy children. *J Infect Dis*. 1996;174(suppl 3):S324–S329.
57. Michalik DE, Steinberg SP, Larussa PS, et al. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. *J Infect Dis*. 2008;197:944–949.
58. Ngai AL, Staehle BO, Kuter BJ, et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. *Pediatr Infect Dis J*. 1996;15:49–54.
59. Nolan T, Bernstein DI, Block SL, et al.; LAIV Study Group. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Pediatrics*. 2008;121:508–516.
60. Nolan T, McIntyre P, Roberton D, et al. Reactogenicity and immunogenicity of a live attenuated tetravalent measles-mumps-rubella-varicella (MMRV) vaccine. *Vaccine*. 2002;21:281–289.
61. Ramkissoon A, Coovadia HM, Jugnundan P, et al. Immunogenicity and safety of a live attenuated varicella vaccine in healthy Indian children aged 9-24 months. *S Afr Med J*. 1995;85:1295–1298.
62. Rümke HC, Loch HP, Hoppenbrouwers K, et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. *Vaccine*. 2011;29:3842–3849.
63. Schuster V, Otto W, Maurer L, et al. Immunogenicity and safety assessments after one and two doses of a refrigerator-stable tetravalent measles-mumps-rubella-varicella vaccine in healthy children during the second year of life. *Pediatr Infect Dis J*. 2008;27:724–730.
64. Shinefield H, Black S, Digilio L, et al. Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *Pediatr Infect Dis J*. 2005;24:665–669.
65. Shinefield H, Black S, Williams WR, et al.; Dose Selection Study Group for Proquad. Dose-response study of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *Pediatr Infect Dis J*. 2005;24:670–675.
66. Shinefield HR, Black SB, Staehle BO, et al.; Kaiser Permanente Medical Team for Varivax. 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. *Pediatr Infect Dis J*. 2002;21:555–561.
67. Silber JL, Chan IS, Wang WW, et al. Immunogenicity of Oka/Merck varicella vaccine in children vaccinated at 12-14 months of age versus 15-23 months of age. *Pediatr Infect Dis J*. 2007;26:572–576.
68. Stück B, Stehr K, Bock HL. Concomitant administration of varicella vaccine with combined measles, mumps, and rubella vaccine in healthy children aged 12 to 24 months of age. *Asian Pac J Allergy Immunol*. 2002;20:113–120.
69. Tan AY, Connett CJ, Connett GJ, et al. Use of a reformulated Oka strain varicella vaccine (SmithKline Beecham Biologicals/Oka) in healthy children. *Eur J Pediatr*. 1996;155:706–711.
70. Vessey SJ, Chan CY, Kuter BJ, et al. Childhood vaccination against varicella: persistence of antibody, duration of protection, and vaccine efficacy. *J Pediatr*. 2001;139:297–304.
71. Watson B, Rothstein E, Bernstein H, et al. Safety and cellular and humoral immune responses of a booster dose of varicella vaccine 6 years after primary immunization. *J Infect Dis*. 1995;172:217–219.
72. Watson BM, Laufer DS, Kuter BJ, et al. Safety and immunogenicity of a combined live attenuated measles, mumps, rubella, and varicella vaccine (MMR(II)V) in healthy children. *J Infect Dis*. 1996;173:731–734.
73. Ampofo K, Saiman L, LaRussa P, et al. Persistence of immunity to live attenuated varicella vaccine in healthy adults. *Clin Infect Dis*. 2002;34:774–779.
74. Saiman L, LaRussa P, Steinberg SP, et al. Persistence of immunity to varicella-zoster virus after vaccination of healthcare workers. *Infect Control Hosp Epidemiol*. 2001;22:279–283.
75. Arvin A, Gershon A. Control of varicella: why is a two-dose schedule necessary? *Pediatr Infect Dis J*. 2006;25:475–476.
76. Watson B, Boardman C, Laufer D, et al. Humoral and cell-mediated immune responses in healthy children after one or two doses of varicella vaccine. *Clin Infect Dis*. 1995;20:316–319.
77. Ludwig B, Kraus FB, Allwinn R, et al. Loss of varicella zoster virus antibodies despite detectable cell mediated immunity after vaccination. *Infection*. 2006;34:222–226.
78. Amanna IJ, Messaoudi I, Slifka MK. Protective immunity following vaccination: how is it defined? *Hum Vaccin*. 2008;4:316–319.
79. Fu C, Wang M, Liang J, et al. The effectiveness of varicella vaccine in China. *Pediatr Infect Dis J*. 2010;29:690–693.
80. Tseng HF, Tan HF, Chang CK. Varicella vaccine safety, incidence of breakthrough, and factors associated with breakthrough in Taiwan. *Am J Infect Control*. 2003;31:151–156.

81. Ozaki T, Nishimura N, Kajita Y. Experience with live attenuated varicella vaccine (Oka strain) in healthy Japanese subjects; 10-year survey at pediatric clinic. *Vaccine*. 2000;18:2375–2380.
82. 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 Paediatr Jpn*. 1997;39:663–668.
83. Brisson M, Edmunds WJ, Gay NJ, et al. Analysis of varicella vaccine breakthrough rates: implications for the effectiveness of immunisation programmes. *Vaccine*. 2000;18:2775–2778.
84. White CJ, Kuter BJ, Ngai A, et al. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatr Infect Dis J*. 1992;11:19–23.
85. Kosuwon P, Sutra S, Kosalaraksa P. Advantage of a two-dose versus one-dose varicella vaccine in healthy non-immune teenagers and young adults. *Southeast Asian J Trop Med Public Health*. 2004;35:697–701.
86. Czajka H, Schuster V, Zepp F, et al. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. *Vaccine*. 2009;27:6504–6511.
87. Goh P, Lim FS, Han HH, et al. Safety and immunogenicity of early vaccination with two doses of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine in healthy children from 9 months of age. *Infection*. 2007;35:326–333.
88. Halperin SA, Ferrera G, Scheifele D, et al. Safety and immunogenicity of a measles-mumps-rubella-varicella vaccine given as a second dose in children up to six years of age. *Vaccine*. 2009;27:2701–2706.
89. Knuf M, Habermehl P, Zepp F, et al. Immunogenicity and safety of two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. *Pediatr Infect Dis J*. 2006;25:12–18.
90. Kuter B, Matthews H, Shinefield H, et al.; Study Group for Varivax. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J*. 2004;23:132–137.
91. Reisinger KS, Brown ML, Xu J, et al.; Protocol 014 Study Group for ProQuad. A combination measles, mumps, rubella, and varicella vaccine (ProQuad) given to 4- to 6-year-old healthy children vaccinated previously with M-M-RII and Varivax. *Pediatrics*. 2006;117:265–272.
92. Vesikari T, Baer M, Willems P. Immunogenicity and safety of a second dose of measles-mumps-rubella-varicella vaccine in healthy children aged 5 to 6 years. *Pediatr Infect Dis J*. 2007;26:153–158.
93. GlaxoSmithKline. GlaxoSmithKline clinical trial register: 104020 (MeMuRuOKA-043). Available at: http://www.gsk-clinicalstudyregister.com/. Accessed 1.
94. Wutzler P, Knuf M, Liese J. Varicella: efficacy of two-dose vaccination in childhood. *Dtsch Arztebl Int*. 2008;105:567–572.
95. Kuter BJ, Ngai A, Patterson CM, et al. Safety, tolerability, and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy adolescents and adults. Oka/Merck Varicella Vaccine Study Group. *Vaccine*. 1995;13:967–972.
96. Wiese-Posselt M, Hellenbrand W. Changes to the varicella and pertussis immunisation schedule in Germany 2009: background, rationale and implementation. *Euro Surveill*. 2010;15:19548.
97. Marin M, Broder KR, Temte JL, et al.; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-3):1–12.
98. Marin M, Güris D, Chaves SS, et al.; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40.
99. Nguyen MD, Perella D, Watson B, et al. Incremental effectiveness of second dose varicella vaccination for outbreak control at an elementary school in Philadelphia, pennsylvania, 2006. *Pediatr Infect Dis J*. 2010;29:685–689.
100. Gershon AA. Varicella vaccine–are two doses better than one? *N Engl J Med*. 2002;347:1962–1963.

Erratum

Serotype Childhood Invasive Pneumococcal Disease has Unique Characteristics Compared to Disease Caused by Other *Streptococcus pneumoniae* Serotypes: ERRATUM

In the article on page 614, volume 32, issue 6 of *The Pediatric Infectious Disease Journal* there was an error in the title. The article title should appear as "Serotypeº1 Childhood Invasive Pneumococcal Disease has Unique Characteristics Compared to Disease Caused by Other *Streptococcus pneumoniae* Serotypes". Please note the inclusion of the 1.

REFERENCE

1. Fuchs I, Dagan, R, Givon-Lavi N, et al. Serotype Childhood Invasive Pneumococcal Disease has Unique Characteristics Compared to Disease Caused by Other *Streptococcus pneumoniae* Serotypes. *Pediatr Infect Dis J.* 2013;32:614-618.