The Pediatric Infectious Disease Journal Publish Ahead of Print
DOI: 10.1097/INF.0b013e31828b7def

Primary Versus Secondary Failure Following Varicella Vaccination: Implications for Interval between Two Doses

Paolo Bonanni[1], MD, Anne Gershon[2], MD, Michael Gershon[3], MD, Andrea Kulcsár[4], MD, Vassiliki Papaevangelou[5], MD, PhD, Bernard Rentier[6], DSc, PhD, Catherine Sadzot-Delvaux[6], PhD, Vytautas Usonis[7], MD, Dr habil, Timo Vesikari[8], MD, PhD, Catherine Weil-Olivier[9], MD, Peter de Winter[10], PhD, and Peter Wutzler[11], MD

[1]Department of Public Health, University of Florence, Florence, Italy;
[2]Department of Pediatrics, Division of Pediatric Infectious Disease, Columbia University, New York, USA;
[3]Faculty of Anatomy and Cell Biology, Columbia University, New York, USA;
[4]Ward for Pediatric Infectious Diseases, Szent László Hospital, Budapest, Hungary;
[5]Second Department of Pediatrics, University of Athens Medical School, "P & A Kyriakou" Children's Hospital, Athens, Greece;
[6]GIGA-Virology and Immunology-CHU Liège, University of Liège, Belgium;
[7]Clinic of Paediatrics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;
[8]Vaccine Research Center, University of Tampere Medical School, Tampere, Finland;
[9]Department of General Pediatrics, University of Paris VII, Paris, France;
[10]Department of Pediatrics, Spaarne Hospital, Hoofddorp, The Netherlands
[11]Institute of Virology and Antiviral Therapy, Jena University Hospital Friedrich-Schiller University, Jena, Germany

Abbreviated Title: Dose Interval for Varicella Vaccination

Running Head: Varicella Vaccine

Corresponding Author: Prof. Dr med. P. Wutzler

Institute of Virology and Antiviral Therapy, Jena University Hospital, Friedrich Schiller University, Hans-Knöll-Strasse 2 (Beutenberg Campus), 07745 Jena, Germany

Email: Peter.Wutzler@med.uni-jena.de

Tel: 03641/9395700; Fax: 03641/9395702

Key words: varicella vaccination, vaccine failure, dose interval

Conflicts of Interest and Source of Funding

Manuscript preparation: This work was supported by an unrestricted educational grant from GlaxoSmithKline Biologicals SA.

GlaxoSmithKline Biologicals SA (GSK) also provided input into and commented upon the development of the manuscript. All authors are members of the Working Against Varicella in Europe (WAVE) group, sponsored by GSK. Potential conflicts of interest: PB has been consultant for Pfizer, GSK, Sanofi Pasteur MSD and Novartis Vaccines. PB has also given lectures on vaccination topics sponsored by Pfizer, GSK, and Sanofi Pasteur MSD. AG receives research funding from Merck. MG has received funding from the National Institutes of Health. AK has been consultant for Novartis. AK has also given lectures on vaccination topics sponsored by GSK, Sanofi, Novartis and Pfizer. VP has been consultant for GSK and has received honoraria from GSK and Novartis Vaccines. VP has also received support from GSK and Pfizer for participation to congress. BR has no conflicts of interest to declare. CSD has been consultant for GSK and has received honoraria from GSK. VU has given lectures for Sanofi Pasteur, GSK, MSD and Pfizer. VU has been a consultant for Sanofi Pasteur, Baxter, GSK, MSD and Pfizer, and has received support from these companies to attend scientific meetings. TV has received honoraria/lecture fees from GSK, Merck. TV has received support from GSK for participation in congress. CWO has been member of boards of GSK, Pfizer and Sanofi Pasteur MSD and has received honoraria/lecture fees from GSK. CWO has received support from Roche, Pfizer and Sanofi Pasteur MSD for participation in meetings. PdW has no conflicts of interests to declare. PW has received honoraria/lecture fees from GSK, Novartis, Astra-Zeneca and Berlin-Chemie. PW has been a consultant for GSK and Sanofi Pasteur MSD and holds a number of shares in GSK.

Abstract

Background: Two-dose varicella vaccination is recommended for optimal control of varicella in populations with high (>90%) one-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 (1995–2012) on vaccine failure following 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 amongst one-dose varicella vaccine recipients, suggesting that a short interval between two 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.

Introduction

As a result of the societal and clinical impact of varicella, universal routine vaccination has been implemented in several countries worldwide. In the USA, where one-dose varicella universal routine vaccination was introduced in 1995, there have been substantial reductions in the number of varicella cases, varicella-related ambulatory visits, hospitalisations and deaths (1-3). Outside of the USA, implementation of varicella universal routine vaccination in Germany, Italy (seven regions as of January 2012) and Uruguay has also resulted in decreased rates of hospitalisations and complications (4-8). However, in a recent review one-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 (e.g. 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 (HZ) (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 two-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, since a trend towards more primary than secondary vaccine failure would favour 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) immunisation 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 one and two doses of varicella-containing vaccine was reviewed (1995–January 2012). Limits included: English, humans, clinical trials, randomised 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'; 'varicella vaccine catch-up'. Exclusion criteria included studies in immunocompromised patients, as the varicella vaccine is not routinely given to this patient group, and post-outbreak control.

Cited articles were chosen on the relevance of their contents (e.g. content on breakthrough varicella, varicella outbreaks, post-vaccination antibody titres, 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 centres and elementary schools worldwide and one meta-analysis of 16 of these outbreaks (Table 1) (13-32). Of these publications, 14 are from the USA 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 towards outbreaks where issues occurred (i.e. 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 USA in 2004 (33). This indicates that vaccine failure following one-dose varicella vaccination is more prevalent than the published literature would suggest.

In published outbreaks, vaccination coverage rates for one dose of varicella-containing vaccines were 30–97% (Table 1) (13-32). In these studies, vaccine effectiveness varied from 20–100% against disease of any severity and 85.5–100% 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 centre 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 USA 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

USA found that the median one-dose effectiveness was 85% (9). Additionally, two 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 one-dose vaccine effectiveness was 82.6% (38). Together, these data represent a rough average of 80% vaccine effectiveness for one 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 post-vaccination 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 titre (40), immunisation 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 prior to 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 titre (10,000–15,850 plaque forming units [pfu]) or (low) expiry titre (630–1260 pfu). The seroconversion rates for the high and low titre 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 titre and 55% for the low titre 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 titre 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.

_ENREF_28_ENREF_28_ENREF_28The 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 following primary vaccination, depending on age group, vaccine titre and vaccine lot. Importantly, the assays used to assess antibody titres 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 titre correlated with protection following household exposure to varicella (73, 74). Additionally, six-

week post-vaccination FAMA antibody titres 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 enzyme-linked immunosorbent assay (gpELISA) employed by Merck & Co., Inc. (NJ, USA) to measure VZV antibody concentrations, an arbitrary value of ≥5 gpELISA units six weeks post-vaccination 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 group. Indeed, using this value as a threshold for protection, there is a wide range of primary vaccine failure (5–24%) after one-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 one-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 USA and China examined whether vaccine effectiveness is time dependent (34, 79). In the eight-year study from the USA, vaccine effectiveness dropped from 97% in the first year post-vaccination 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 three-year retrospective study from Taiwan where 81% of cases occurred during the first year post-vaccination (80). However, these studies all indicate one-dose primary vaccine failure in populations with circulating VZV, since 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]), nine showed an increased risk with time of breakthrough varicella; this increased risk was generally observed around 4–5 years post-vaccination. However, seven 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 USA, which showed no secondary vaccine failure after the first year post-vaccination, 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 modelled vaccine effectiveness against time since vaccination (up to six years) from four 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 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 four and eight years after vaccination. (34, 41, 70, 79). A mathematical model fitted to the rate of breakthrough varicella in subjects of three clinical trials showed that, in the worst-case scenario (88% protected after vaccination i.e. 12% primary vaccine failure), the incidence of breakthrough varicella would increase in the first few years post-vaccination and then plateau at 3% per year for up to six years post-vaccination (83). Although this was extrapolated from a clinical trial which used a low titre vaccine lot currently not in production, it does appear to fit the patterns observed in case-control studies (34, 79).

It should be emphasised 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), seven years into the USA vaccination programme. 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 titres are required for optimal protection against varicella, rather than seroconversion *per se,* and that two doses are required to achieve this (84, 85). Numerous studies have assessed antibody titres in children after administration of two doses of vaccine given at various intervals (four weeks to six years; Table 4 (49, 58, 62-65, 71, 86-93). These studies indicate that geometric mean antibody concentrations (GMCs) increase roughly 10-fold (range 5–39-fold) after the second dose of vaccine in children, irrespective of timing between doses. Such a large increase in antibody titres 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 one dose (94).

The boosting effect in GMCs observed with the short interval for the second dose is atypical of most live viral vaccines (75), and suggests that 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 paper). Furthermore, evidence also suggests that antibody titres fall during the first year post-vaccination (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, since antibody titres 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 two doses of vaccine due to the lowered immunogenicity of the vaccine in this age group, found that delaying the second dose to eight weeks compared with four weeks induced higher antibody titres (95). Additionally, a recent study of two doses of MMRV has shown that higher antibodies titres 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 two cases of 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 two-dose schedule

Short-interval two-dose varicella immunisation 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 two-dose varicella vaccination in the second year of life: 1) vaccination with two doses of monovalent vaccine; 2) vaccination with two doses of MMRV vaccine; 3) vaccination with a combination of two 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 two doses of varicella vaccine. For instance, in Germany, both MMRV and monovalent vaccines are licensed under two-dose schedules (96). This option is especially pertinent for the USA, 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 USA varicella vaccination schedule as long as there is a minimum of three months between doses (98). Another possibility that may be considered to implement the short-interval two-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 minimise administration costs for the immunisation program (less patient visits/administration costs e.g. needles and reduced time dedicated by health care professionals) and will help support improved coverage for both MMR and varicella vaccination.

Reduction in risk with short- *versus* long-interval immunisation 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 two-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 immunisation schedule would be especially important for countries that introduce varicella vaccination, since 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 two-dose schedules

Two-dose schedules have been implemented in a variety of countries worldwide, including the USA and Germany. Unlike the USA, Germany employs short-interval varicella vaccination where both doses are given in the second year of life. Recent outbreak reports from Germany and the USA 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 two doses were given in a short interval (three months between doses) also showed that two doses provide more protection than a single dose (90). In the USA, where a longer schedule is used, two 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 re-vaccination of children with primary vaccine failure (98). As the duration of immunity to two doses of varicella vaccine is currently unknown, continued surveillance and prospective studies are required.

Conclusion

All published evidence (1995–2012) for varicella vaccine failure strongly supports a two-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 amongst recipients of one-dose varicella vaccine and limited convincing evidence of secondary vaccine failure. Furthermore, vaccine effectiveness decreases after the first year post-vaccination 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 four 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 USA 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 CDC. Therefore we expect that vaccine failure following one-dose varicella vaccination is more prevalent than what published literature would suggest. To conclude, we propose that a short interval between two 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 pre-dominantly.

Acknowledgements

The authors would like to thank Prof. Jacques Senterre for his contribution to this work. The authors would also like to thank Dr Elizabeth Hutchinson who carried out the

literature search and provided medical writing assistance on behalf of Fishawack Communications Ltd; and Amrita Ostawal (consultant writer to GlaxoSmithKline group of companies) for medical writing assistance.

Trademarks

Priorix-Tetra and *Varilrix* are trademarks of GlaxoSmithKline group of companies. *M-M-R*-II, *ProQuad* and *Varivax* are trademarks of Merck and Co., Inc. Changchun and Shanghai are manufactured by Changchun Institute of Biologic Products (Changchun, China) and Shanghai Institute of Biologic Products (Shanghai, China), respectively. *Okavax* is a trademark of Varicella Biken; The Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan.

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, Ratner AJ. 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, Ruttimann 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, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis*. 2008;197 Suppl 2:S82-89.

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:S242-245.

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-Barbera 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, von Kries R. Metaanalysis of vaccine effectiveness in varicella outbreaks. *Vaccine*. 2007;25:6655-6660.

15. Buchholz U, Moolenaar R, Peterson C, Mascola L. Varicella outbreaks after vaccine licensure: should they make you chicken? *Pediatrics*. 1999;104:561-563.

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, Britz P, Seward J. 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, Hedberg CW, Ehresmann KR. 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:e1070-1077.

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, Hendler A. 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:S101-107.

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, 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;28:1594-1597.

32. Tugwell BD, Lee LE, Gillette H, et al. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics*. 2004;113:455-459.

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. Vazquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. *JAMA*. 2004;291:851-855.

35. Vazquez 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, Tsai FY, Chang LY. Varicella breakthrough infection and vaccine effectiveness in Taiwan. *Vaccine*. 2011;29:2756-2760.

39. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. 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:S330-334.

41. Black S, Ray P, Shinefield H, Saddier P, Nikas A. 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:S139-142.

42. Verstraeten T, Jumaan AO, Mullooly JP, et al. 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:e1548-1554.

44. 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:e475-480.

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, Leboulleux D, Desauziers E. 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, Eymin C, Fiquet A. 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, Rome LP, Kumar ML. 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, Lee BW. 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 12 January 2012.

56. Meurice F, De Bouver JL, Vandevoorde D, Woods S, Bogaerts H. Immunogenicity and safety of a live attenuated varicella vaccine (Oka/SB Bio) in healthy children. *J Infect Dis*. 1996;174 Suppl 3:S324-329.

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. 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, Descamps D. 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. Rumke 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-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. 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, Matthews H, Kuter BJ. 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 Vaccine*. 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, Law B, De Serres G. 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, Willems P. 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. 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. 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 (MeMuRu-OKA-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.

97. Marin M, Broder KR, Temte JL, Snider DE, Seward JF. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59:1-12.

98. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56:1-40.

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.

Table 1 Publications and characteristics of selected varicella outbreaks in vaccinated populations

Reference	Location	Vaccination policy	Vaccine	N	Vaccination coverage (%)	BV cases[a] (%)	VE[b] Any disease (%)	VE[b] Moderate/ severe disease (%)
Buchholz 1999[1] (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[c]	21	62 [94][c]	89[c]
Dworkin 2002 (18)	Illinois, USA	URV	*Varivax*™	209	68	6	88	NR
Lai 2011 (24)	Taipei, Taiwan	URV	*Varivax*™	392	71	10	69–100[d]	85.5
Galil 2002 (19)	Pennsylvania, USA	URV	*Varivax*™	131	73	36	44	86

Haddad 2005[1] (22)	Utah, USA	URV	*Varivax*™	558	77	4	87	90
Galil 2002 (20)	New Hampshire, USA	URV	*Varivax*™	88	80	34	79	95
CDC 2006(17)	Nebraska, USA	URV	*Varivax*™	142	81	13	81	93
Parker 2008 (29)	Maine, USA	URV	*Varivax*™	341	81	13	87	100
Haddad 2005 [(2)] (22)	Utah, USA	URV	*Varivax*™	924	83	5	87	99
Buchholz 1999 [(2)] (15)	Los Angeles, USA	URV	*Varivax*™	39	87	24	71	93
Lopez 2006 (26)	Arkansas, USA	URV	*Varivax*™	545	96[c]	8	82	97
CDC 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

BV, breakthrough varicella; NR, not reported; URV, universal routine vaccination; VE, vaccine effectiveness; Data collated from the literature. Studies are listed in order of vaccine coverage. Superscript numbers after references represent different cohorts within the same publication. Numbers in square brackets indicate two-dose coverage and VE after two doses where available. [a]Percentage of vaccinated children who develop breakthrough varicella; [b]effectiveness after one dose; [c]coverage/ VE include two-dose vaccine recipients; [d]across three school grades; *commercial name not available

Table 2 VZV seroconversion/seroresponse rates 4–6 weeks after one dose of varicella vaccine in children

Reference	Vaccine(s)	Total children vaccinated	Seroconversion/ seroresponse rate (%)	Assay[a] (threshold)
Clements 1995 (46)	V (*Varivax*™)	465	95	ELISA[b] and gpELISA[b]
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[c]	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[d]	

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	
Tan 1996 (69)	V (*Varilrix*™)	191	98–100[c]	
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	Indirect IFA (≥4 units)
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	
Meruice 1996 (56)	V (*Varilrix*™)	1372	99	Indirect IFA†
Lim 1998 (54)	V (*Varilrix*™)	181	99	

ELISA, enzyme-linked immunosorbent assay; FAMA, fluorescent antibody to membrane antigen; gpELISA, glycoprotein enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; IM, intramuscular; MMRV, measles-mumps-rubella-varicella vaccine; SC, subcutaneous; V, monovalent varicella vaccine; data collated from the literature; [a]FAMA is the only assay validated in a real-life setting; [b]no threshold for seroconversion/seroresponse specified; [c]different vaccine lots; [d]concomitant *versus* non concomitant administration with MMR; *commercial name not available

Table 3 Publications showing evidence for and against secondary vaccine failure

Reference	N	Vaccine	Maximum follow-up (years)	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)[a]	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[b]
Vessey 2001 (70)	937	*Varivax*™	7	0.2–2.3	7	No

Ampofo 2002 (73)	461	*Varivax*™, *Varilrix*™	20	–	9	No[b]
Dworkin 2002 (18)[a]	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)[c]	1008	*Varivax*™	8	–	–	No – First year after vaccination only
Marin 2005 (27)[a]	296	*Varivax*™	–	–	8	No
Lopez 2006 (26)[a,d]	545	*Varivax*™	–	–	8	No
Black 2008 (41)	7449	*Varivax*™	8	–	16	No – First 4 years after vaccination only
Lee 2008 (43)	9025	*Varivax*™	5	6–8	5	No
Spackova 2010 (30)[a,d]	631	*Varivax*™, *Varilrix*™, *Priorix-Tetra*™	4.6	–	21	No
Fu 2010 (79)[c]	1000	*Varilrix*™,	5	–	–	No

		Shanghai, Changchun				
Evidence for secondary vaccine failure						
Galil 2002 (19)[a]	131	*Varivax*™	–	–	26	Yes
CDC 2004 (16)[a]	507	*Varivax*™	–	–	12	Yes – Time since vaccination >4 years
Lee 2004 (25)[a]	249	*Varivax*™	–	–	25	Yes – Time since vaccination >5 years
Tugwell 2004 (32)[a]	218	*Varivax*™	–	–	9	Yes – Time since vaccination >5 years
Haddad 2005 (22)[a]	1482	*Varivax*™	–	–	5	Yes – Time since vaccination >5 years
Miron 2005 (28)[a]	242	*Varilrix*™	–	–	42	Yes – Time since vaccination >2 years
Arnedo-Pena 2006 (13)[a]	269	*Varilrix*™	–	–	23	Yes – Time since vaccination >25 months
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 years

BV, breakthrough varicella; data collated from the literature; [a]outbreak studies; [b]vaccinees were adults who had received one, two or three doses of the vaccine; [c]case-control study; [d]vaccinees were children who had received one or two doses of the vaccine; *(Biken Institute, Osaka, Japan); [#]Commercial name not available

Table 4 GMCs after two 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 weeks	23.7
Czajka 2009 (86)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	6–8 weeks	26.6[a]
Gillet 2009 (49)	MMRV (*Priorix-Tetra*™)	V (*Varilrix*™)	6–8 weeks	12.6–14.1
Gillet 2009 (49)	MMR+V (*Priorix*™ and *Varilrix*™)	V (*Varilrix*™)	6–8 weeks	9.8–13.1
Knuf 2006 (89)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	6–8 weeks	>20
Kuter 2004 (90)	V (*Varivax*™)	V (*Varivax*™)	12 weeks	11.0
Ngai 1996 (58)	V (*Varivax*™)	V (*Varivax*™)	12 weeks	11.6
Shinefield 2005 (65)	MMRV (*ProQuad*™)	MMRV (*ProQuad*™)	12 weeks	29.4–39.4[b]
Shinefield 2005 (64)	MMRV (*ProQuad*™)	MMRV (*ProQuad*™)	12 weeks	45.2
Goh 2007 (87)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	12 weeks	10.0
Goh 2007 (87)	MMR+V (*Priorix*™ and *Varilrix*™)	MMR+V (*Priorix*™ and *Varilrix*™)	12 weeks	5.0

Reisinger 2006 (91)	MMR+V (*M-M-R*™-II and *Varivax*™)	MMRV (*ProQuad*™)	3 years	12.4
Reisinger 2006 (91)	MMR+V (*M-M-R*™-II and *Varivax*™)	MMR+V (*M-M-R*™-II and Varivax™)	3 years	8.5
Vesikari 2007 (92)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	5 years	9.8
Watson 1995 (71)	V (Varicella vaccine*)	V (Varicella vaccine*)	4–6 years	8.5
Halperin 2009 (88)	MMR+V (*Priorix*™ and *Varilrix*™)	MMRV (*Priorix-Tetra*™)	6 weeks–5 years	27.2
Halperin 2009 (88)	MMR+V (*Priorix*™ and *Varilrix*™)	MMR+V (*Priorix*™ and *Varilrix*™)	6 weeks–5 years	26.2
Rümke 2011 (62)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	4 weeks	7.8
Rümke 2011 (62)	MMRV (*Priorix-Tetra*™)	MMRV (*Priorix-Tetra*™)	1 year	22.6

GMC, geometric mean antibody concentration; MMRV, measles-mumps-rubella-varicella vaccine; MMR, measles-mumps-rubella vaccine; V, monovalent varicella vaccine; VZV, varicella zoster virus; data collated from the literature; [a]pooled analysis of three studies(63, 89, 93); [b]dose range study for MMRV vaccine; *commercial name not available.