610

PRIMARY VERSUS SECONDARY FAILURE FOLLOWING VARICELLA VACCINATION: IMPLICATIONS FOR INTERVAL BETWEEN TWO DOSES – LITERATURE REVIEW

Paolo Bonanni,[1] Anne Gershon,[2] Michael Gershon,[2] Andrea Kulcsár,[3] Vana Papaevangelou,[4] Bernard Rentier,[5] Catherine Sadzot,[5] Jacque Senterre,[5] Vytautas Usonis,[6] Timo Vesikari,[7] Catherine Weil-Olivier,[8] Peter de Winter,[9] Peter Wutzler[10]

[1]University of Florence, Florence, Italy; [2]Columbia University, New York, USA; [3]Szent László Hospital, Budapest, Hungary; [4]University of Athens Medical School, "P & A Kyriakou" Children's Hospital, Athens, Greece; [5]University of Liège, Liège, Belgium; [6]Vilnius University Clinic of Paediatrics, Vilnius, Lithuania; [7]University of Tampere Medical School, Tampere, Finland; [8]University Paris VII, Paris, France; [9]Spaarne Hospital, Hoofddorp, The Netherlands; [10]Friedrich-Schiller University, Jena, Germany

BACKGROUND

- Varicella universal mass vaccination (UMV) has been implemented in several countries including the USA, Uruguay, Israel, Germany and Greece.
- Following a large number of varicella outbreaks in children vaccinated with the one-dose varicella vaccination schedule and recommendations by the Advisory Committee on Immunisation Practices and the European Working Group on Varicella,[1,2] a two-dose schedule was established in the USA and a number of European countries.
- Breakthrough varicella (defined as disease occurring >42 days post-vaccination) results from either primary vaccine failure (PVF) or secondary vaccine failure (SVF) (Figure 1).
  - PVF is the failure to mount a protective immune response after vaccination.
  - SVF is the gradual loss of immunity after an initial immune response over a period of years after vaccination.
- There is no consensus between countries regarding the interval between the two doses: 3–5 years in the USA and 6 weeks–12 months in Germany.
- The optimal interval between doses should be guided by the relative importance of PVF and SVF, and currently this is unknown.
- This prompted a review of the evidence for PVF and SVF after varicella vaccination.

METHODS

- Published literature (PubMed®, conference abstracts, Google™ and Medscape®) on live-attenuated vaccine failure associated with one and two doses of all varicella-containing vaccines, was reviewed (1995–October 2009).
- Additionally, a further search, since abstract submission, was carried out in February 2010.
- Search terms included: primary OR secondary vaccine failure, waning immunity, seroconversion and breakthrough varicella.

RESULTS AND DISCUSSION

- A total of 52 relevant publications were identified (48 in original search and abstract), with 4 new publications indentified in the February 2010 search. Of these, 19 publications included results from vaccinees who had received two doses of vaccine.

Incidence of breakthrough varicella

- 22 publications (21 in abstract) showed breakthrough varicella rates of 0–42% in 23 outbreak settings, with no consistent trend between breakthrough varicella rate and coverage between publications (Table 1).
- Vaccine effectiveness (VE) estimates varied from 20–100% in these publications, with no apparent relationship between VE and coverage rate or number of doses received (Table 1).
- A meta-analysis of 14 outbreaks was published in 2007; it revealed that VE was 72.5%, indicating a combined PVF and SVF rate of 27.5%.[3]

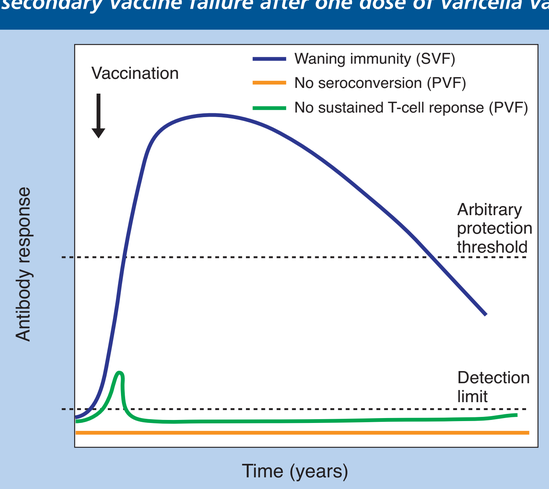
Evidence for PVF after one dose of varicella vaccine in children

- Based on seroconversion/seroresponse rates alone, PVF rates range between 0 and 24% depending on the assay used for antibody testing (Table 2).
  - However, the assays used to assess antibodies after vaccination are only a proxy for PVF, and the choice of assay may affect the result.
  - The fluorescent antibody to membrane antigen (FAMA) assay is considered to be the 'gold standard' for VZV antibody measurements and correlates with protection in household exposure studies.
  - A seroconversion rate of 76% with FAMA indicates high instances of PVF.[4]
  - High seroconversion rates assessed by the glycoprotein ELISA (gpELISA) may represent an initial immune response that is not strong enough to generate the sustained memory T-cell response required for protection (Figure 1).[4]
- A case-controlled 8-year study has shown that VE drops from 97% in the first year after vaccination to 86% in the second year and then remains stable.[5]
- A 3-year study has shown that 81% of breakthrough varicella occurs within the first year after vaccination, which is more suggestive of PVF than SVF.[6]

Evidence for SVF

- Twenty-eight publications (25 in abstract) determined the risk of breakthrough varicella with time (Table 3), where an increased risk of breakthrough varicella is an indicator of SVF.
  - Nine publications indicated an increased risk of breakthrough varicella with time. However, eight publications were outbreak analyses with limited power to detect differences. There was no consistent trend between rates of breakthrough varicella and time since vaccination.
  - Nineteen publications (16 in abstract) did not show any drop in protection according to time since vaccination, with a study-specific period of follow-up ranging from 1 year up to 20 years' follow-up. By design however, these studies were based on a limited population size and therefore, were not adequately powered to detect any drop of protection according to time since vaccination.
- It has been suggested, by authors of the Michalik *et al*. study, that it is difficult to differentiate between PVF and SVF in outbreak studies.[4]

Figure 1. Diagram indicating the antibody responses behind primary and secondary vaccine failure after one dose of varicella vaccine



PVF, primary vaccine failure; SVF, secondary vaccine failure

Evidence for the optimal interval between doses

- In several studies, two doses of varicella vaccine were administered with a variety of intervals (4 weeks–6 years).
  - These studies indicate that geometric mean antibody concentrations (GMCs) increase roughly 10-fold after the second dose of varicella vaccine in children (Table 4), irrespective of the time between doses (See poster 620, Vinals C, *et al*.).

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

Reference	Vaccination coverage (%)	BV cases* (%)	VE** (%)
Buchholz 1999 *Pediatrics* (1)	30	0	100
Arnedo-Pena 2006 *PIDJ*	36	23	70
Miron 2005 *PIDJ*	37	42	20
Izurieta 1997 *JAMA*	45	13	86
Lee 2004 *J Infec Dis*	47	25	56
Marin 2005 *Pediatrics*	47	8	89
Forssman 2008 *ICID*	54	20	54
Tafuri 2010 *Vaccine*	54	40	82
Kurugol 2008 *ESPID*	55	31	-
Spackova 2009 *Vaccine*	62†	21	62 [94]†
Dworkin 2002 *Clin Infect Dis*	70	6	88
Galil 2002 *J Infect Dis*	73	26	44
Haddad 2005 *Pediatrics* (1)	77	4	87
Galil 2002 *NEJM*	80	34	79
CDC 2006 *MMWR*	81	13	81
Parker 2008 *J Infect Dis*	81	14	87
Haddad 2005 *Pediatrics* (2)	84	5	87
CDC 2004 *MMWR*	87	12	85
Buchholz 1999 *Pediatrics* (2)	87	24	71
Lopez 2006 *Pediatrics*	95†	8	82
Gould 2009 *PIDJ*	97†	15	85 [89]†
Tugwell 2004 *Pediatrics*	97	9	72
Kubinyiova 2008 *ESPID*	-	13	72†
Bayer 2007 *Vaccine*	Meta-analysis		73

BV, breakthrough varicella; VE, vaccine effectiveness
Numbers in round brackets represent different cohorts within the same publication.
*Percentage of vaccinated children who develop breakthrough varicella
**Effectiveness against any form of disease after one dose
†Includes two-dose vaccination recipients. Figure in square brackets indicate VE after two doses

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

Reference	Seroconversion/ seroresponse rate (%)	Assay (threshold)
Clements 1995 *PIDJ*	95	ELISA† and gpELISA†
Michalik 2008 *J Infect Dis*	76	FAMA (>1:4 dilution)
Johnson 1997 *Pediatrics*	94–98	FAMA (>1:2 dilution)
Watson 1995 *J Infect Dis*	100	gpELISA (≥0.3 units/ml)
Ngai 1996 *PIDJ* Li 2002 *PIDJ* Vessey 2001 *J Pediatr* Watson 1996 *J Infect Dis*	99 99 99 100	gpELISA (≥0.6 units/ml)
Shinefield 2005a *PIDJ* Shinefield 2005b *PIDJ* Merck 2001 *Varivax® package circular* Shinefield 2002 *PIDJ* Silber 2007 *PIDJ*	81–93 91–99 76 93–95 93	gpELISA (≥5.0 units/ml)
Nolan 2002 *Vaccine* Schuster 2008 *PIDJ* Gillet 2009 *Vaccine*	93–96 96 96–100	Indirect IFA (≥4 units)
Kanra 2000 *Pediatr Int* Meurice 1996 *J Infect Dis* Lim 1998 *Arch Dis Child* Ramikissoon 1995 *S Afr Med J*	98 99 99 100	Indirect IFA†

ELISA, enzyme-linked immunosorbent assay; FAMA, fluorescent antibody to membrane antigen; gpELISA, glycoprotein ELISA; IFA, Immunofluorescence assay
†No threshold for seroconversion/seroresponse specified

Table 3. Publications showing evidence for SVF, or no evidence for SVF

Reference	Maximum follow-up (years)	Cumulative BV rate (%)	Time since vaccination a risk factor?
No evidence for SVF			
Clements 1995 *PIDJ*	5	19	No
Izurieta 1997 *JAMA**	–	13	No
Johnson 1997 *Pediatrics*	10	17	No
Takayama 1997 *Acta Paediatr Jpn*	8	34	No
Lim 1998 *Arch Dis Child*	2.9	–	No
Ozaki 2000 *Vaccine*	10	21	No
Saiman 2001 *Infect Cont Hosp Epi*	20	10	No†
Vessey 2001 *J Pediatr*	7	7	No
Ampofo 2002 *Clin Infect Dis*	20	9	No†
Dworkin 2002 *Clin Infect Dis**	–	6	No
Shinefield 2002 *PIDJ*	5	6–7	No
Tseng 2003 *Am J Infect Cont*	2.6	2	No – First year after vaccination only
Vasquez 2004 *JAMA*	8	–	No – First year after vaccination only
Marin 2005 *Pediatrics**	–	8	No
Lopez 2006 *Pediatrics**‡	–	8	No
Black 2008 *J Infect Dis*	8	16	No – First 4 years after vaccination only
Lee 2008 *J Infect Dis*	5	5	No
Spackova 2009 *Vaccine*‡	4.6	21	No
Fu et al 2010 *PIDJ*	5	–	No
Evidence for SVF			
Galil 2002 *J Infect Dis**	–	26	Yes
CDC 2004 *MMWR**	–	12	Yes – Time since vaccination >4 years
Lee 2004 *J Infect Dis**	–	25	Yes – Time since vaccination >5 years
Tugwell 2004 *Pediatrics**	–	9	Yes – Time since vaccination >5 years
Haddad 2005 *Pediatrics**	–	5	Yes – Time since vaccination >5 years
Miron 2005 *PIDJ**	–	42	Yes – Time since vaccination >2 years
Arnedo-Pena 2006 *PIDJ**	–	23	Yes – Time since vaccination >25 months
Chaves 2007 *NEJM*	10	10	Yes
Kurugol 2009 *ESPID**	–	31	Yes – Time since vaccination >5 years

BV, breakthrough varicella; SVF, secondary vaccine failure
*Outbreak studies
†Vaccinees were adults who had received 1, 2 or 3 doses of the vaccine
‡Vaccinees were children who had received 1 or 2 doses of the vaccine

Table 4. Antibody titres after two doses of varicella vaccine

Reference	Dose interval	Fold increase in GMC from first to second dose
Kuter 1995 *Vaccine*	4 weeks*	4.8
Kosuwon 2004 *SE Asian J Trop Med Pub Health*	6 weeks*	4.5
Schuster 2008 *PIDJ*	6 weeks	12.1
Gillet 2009 *Vaccine*	6–8 weeks	10.9
Kuter 1995 *Vaccine*	8 weeks*	9.9
Burgess 1999 *Vaccine*	8 weeks*	4.4
Kuter 2004 *PIDJ*	12 weeks	11.0
Ngai 1996 *PIDJ*	12 weeks	11.6
Shinefield 2005 *PIDJ*	12 weeks	36.3
Reisinger 2006 *Pediatrics*	3 years	10.5
Vesikari 2007 *PIDJ*	5 years	9.8
Watson 1995 *J Infect Dis*	4–6 years	8.5

GMC, geometric mean antibody concentration
*Adult population

CONCLUSION

- **The assays and thresholds used to assess varicella vaccine responses are not necessarily predictive of vaccine failure.**
- **Amongst recipients of one dose of varicella vaccine, the literature indicates a relatively high rate of PVF and limited convincing evidence of SVF. Furthermore, vaccine efficacy/effectiveness decreases after the first year post-vaccination and then remains stable, a pattern predictive of PVF.**
- **This suggests that the second dose of varicella vaccine should be given as close to the first as possible (minimum of 4 weeks), to prevent a large number of people remaining vulnerable to infection and reduce the risk of breakthrough varicella.**

All authors are members of the Working Against Varicella in Europe (WAVE) group. Meetings of this group and the development of this poster were supported by an unrestricted educational grant from GlaxoSmithKline Biologicals.

KEY REFERENCES

1. Advisory Committee on Immunization Practices *MMWR* 2007; **56**: RR-4.
2. Rentier B, *et al. Pediatr Infect Dis J* 2004; **23**: 379–89.
3. Bayer O, *et al. Vaccine* 2007; **25**: 6655–60.
4. Michalik DE, *et al. J Infect Dis* 2008; **197**: 944–9.
5. Vasquez M, *et al. JAMA* 2004; **291**: 851–5.
6. Tseng HF, *et al. Am J Infect Control* 2003; **31**: 151–6.

Presenting author:
Peter Wutzler
Peter.Wutzler@med.uni-jena.de