RESEARCH PAPER

Human Vaccines & Immunotherapeutics 10:3, 667–670; March 2014; © 2014 Landes Bioscience

Determinants of varicella breakthrough

Results of a 2012 case control study

Silvio Tafuri[1,*], Rocco Guerra[1], Maria Giovanna Cappelli[1], Domenico Martinelli[2], Rosa Prato[2], and Cinzia Germinario[1]

[1]Department of Biomedical Science and Human Oncology; Aldo Moro University of Bari; Bari, Italy; [2]Department of Medical and Surgical Science; University of Foggia; Foggia, Italy

Keywords: vaccine failure, breakthrough, varicella, UMV, varicella vaccine schedule

Abbreviations: GP, general practitioner; UMV, universal mass vaccination

This study aims to evaluate the determinants of breakthrough infection after one dose of varicella vaccine.

We designed a retrospective case-control study. Breakthrough cases were children, aged 1–15, who presented varicella symptoms ≥42 days after the first dose of varicella vaccine (breakthrough). Controls were children, aged 1–15 years, who attended the same class (in a school or in a kindergarten) than the cases in the year of the breakthrough onset; they received a dose of varicella vaccine ≥42 days before the case rash onset and they did not develop varicella symptoms.

We enrolled 45 cases and 135 controls. 40% of cases (n = 18; 95% CI = 25.4–54.6) presented at least one risk factor; this proportion was 39.2% (95% CI = 30.9–47.6) among the controls (chi-square = 0.0078; *P* = 0.93). Time between vaccination and virus exposure was longer among cases. Logistic regression showed that breakthrough disease was associated with duration of time from vaccination.

Introduction

Since the availability of a live varicella attenuated vaccine in 1974, many countries have introduced the Universal Mass Vaccination (UMV) for varicella. In Italy, 2005 and 2012 National Immunization Plans recommended the vaccination for adolescents and young adults without a history of chickenpox; moreover, several Italian Regions adopted a UMV.[1]

However, the unwanted phenomenon called "breakthrough varicella" emerged after the introduction of the varicella UMV. Breakthrough was defined as varicella disease in a child who had been vaccinated 42 d or more before the onset of a rash.[2,3] Although 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 transmission from the breakthrough rash.[4] Breakthrough varicella outbreaks in close settings, such as healthcare centers, were described.[5] Previous studies showed a breakthrough varicella infection rates from 4 to 68%[6] and the annual rate of breakthrough seemed to increase with the time after vaccination.[5]

Several risk factors have been proposed to explain the increase of varicella vaccine failure and have been debated in the literature, including history of eczema, asthma, chronic disease.[7]

In Italy, immunization strategies for varicella have provided two doses at 12 mo and 5–6 y; other countries have adopted a short schedule, with the second dose administered 4 wk after the first dose in the second year of life.[8] In 2006, the Puglia Region (Italy) introduced UMV against varicella disease. The strategy involved the administration of just a single dose of vaccine to children aged 2–24 mo. Since 2010 a two-dose strategy has been adopted with the first dose administered at 13–15 mo of age, and the second at 5–6 y of age. There is also a catch-up strategy for susceptible adolescents.

It has yet to be established whether the second dose should be administered as close as possible to the first dose (within 4–6 wk) in order to provide for more complete protection from (partially) primary vaccine failure, or at the age of 5 or 6 y, for more effective long-term protection.[8]

Because the breakthrough varicella infection rate has a great influence on vaccine effectiveness, knowledge about the determinants of breakthrough would influence decision-making between the two schedules (long or short).

This study aims to evaluate the determinants of breakthrough infection after one dose of varicella vaccine.

Results

We enrolled 45 cases and 135 controls. The response rate was 100%. **Table 1** shows the characteristics of cases and controls. The distribution per gender did not differ between the two groups (chi-square = 0.18; *P* = 0.67). Average age at the vaccination was 3.3+/-2.4 y (range 1–13), without differences between cases (3.2+/-2.6) and controls (3.2+/-2.6; t = 0.05; *P* = 0.48).

*Correspondence to: Silvio Tafuri; Email: silvio.tafuri@uniba.it
Submitted: 09/27/2013; Revised: 11/21/2013; Accepted: 11/30/2013
http://dx.doi.org/10.4161/hv.27382

©2014 Landes Bioscience. Do not distribute.

Table 1. Proportion (%) of interviewed subjects who reported asthma, allergies, chronic disease, hospital admission in the previous 12 mo, between cases and controls groups

	Cases (n. 45)			Controls (n. 135)			*P*
	n	%	95% CI	n	%	95% CI	
Male	20	44.4	29.9–59.0	65	48.1	39.7–56.6	0.67
Average age at vaccination	3.2+/-2.6			3.2+/-2.4			0.48
Subjects with at least one risk factor	18	40	25.4–54.6	71	39	30.9–47.6	0.93
Asthma	2	4.4	–1.6–10.5	1	0.7	–0.7–2.2	0.093
Allergies	12	26.7	13.7–39.6	27	20	13.2–26.7	0.347
Chronic disease	3	6.7	–0.6–13.9	-			0.002
Hospital admissions in the previous 12 mo	9	20	8.3–31.7	35	26.7	18.5–33.3	0.409
Time from vaccination (days)	797+/–445			638+/–439			0.018

40% of cases (n = 18; 95% CI = 25.4–54.6) reported at least one risk factor; this proportion was 39% (n = 71; 95% CI = 30.9–47.6) among the controls (chi-square = 0.0078; *P* = 0.93).

There were no differences in the proportion of cases and controls who reported history of allergies or asthma or hospital admission in the previous 12 mo. The proportion of people reporting chronic disease was higher among cases than among controls (*P* = 0.002). Time from vaccination and virus exposure was longer among cases (797+/–445 d) than among controls (638+/–439 d; t = -2.11; *P* = 0.018). **Table 2** shows the determinants of breakthrough infection in a multiple logistic regression model. Breakthrough disease was associated with the time (in months) from vaccination to varicella virus exposure (OR: 1.02 CI 95%: 1.001–1.04; *P* = 0.04).

Discussion

Our study showed that time from varicella vaccination was the most important risk factor for varicella breakthrough.

We detected a higher proportion of subjects with chronic diseases in breakthrough cases than in those who had received the vaccine and had been exposed to the virus without developing symptoms. The difference between the groups with respect to time since vaccination (797 d vs. 637 d) is less than one year.

Our results suggest that most of the failures occurred in the 5–6 y age group and then the immunity provided by varicella vaccines wanes over time.

The strength of this paper is the analysis of the association between varicella breakthrough and some risk factors such as asthma, allergies, and chronic diseases. Another strength is the high response rate and this could be related to the cooperation with the school and GPs.

The use of clinical-case definition (without laboratory diagnosis) could be a weakness of our protocol. In fact, the force of infection and the different virulence of varicella virus could have a important role for the vaccine failure.[9] Because subjects who developed breakthrough some years ago has been enrolled, the predictive value of the reported information could be not high.

These results are according to Chaves et al. who, in a 10-y control study, reported that children who had been vaccinated for more than 5 y were at 2.6 times the risk of acquiring moderate-to-severe varicella than those who had been vaccinated less than that time.[10] Also Zhang et al., in 2012, showed that contact history, time since vaccination, age at vaccination and combined vaccination were associated with the occurrence of breakthrough varicella.[11]

Cenoz et al. reported that a single dose of varicella vaccine was 93% effective in the first year, which declined to 61% after the third year, and concluded that "varicella vaccine is highly effective in preventing confirmed cases, although this effect declines over time since the first dose"[12].

Only a few studies, such as Baxter et al., indicated that varicella vaccine protection does not wane over time,[13] but the case definition of breakthrough seem to differ from other surveys, and this could explain these differences.

Breakthrough varicella rates ranged from 0% to 42%, which appeared to have no association with vaccination coverage.[7] Michalik et al. report that primary vaccine failure (as defined by FAMA) occurs in almost one-quarter of vaccines.[14]

Breakthrough varicella cases in household settings were half as contagious as unvaccinated persons with varicella, although contagiousness varied with numbers of lesions[15]; in close settings, such as school, the breakthrough cases are contagious and could contribute to the spread of an outbreak and to the chain of infection. The parents also perceived a breakthrough case as a vaccine failure, and this could determine concerns about the vaccine effectiveness.

However, the current recommendations for Italy[1] are that primary vaccination be given at 12–15 mo of age and that a second vaccine be delivered at 4–6 y of age, when school exposure occurs.

Prevention of breakthrough varicella should be a public health priority, and the immunization strategies should support this objective. According to this and other studies, a 'short schedule', with a second dose of varicella vaccine administered during the second year of life, should be adopted. CDC criteria for vaccine schedules already suggest that primary vaccination at an older age (>13) should be followed by a second vaccination 1–2 mo later.

Future research is necessary in order to analyze other questions concerning this option (pharmaco-economic evaluation, costs of an ad hoc access to vaccination services, acceptance of parents and health care workers).

©2014 Landes Bioscience. Do not distribute.

Table 2. Determinants of breakthrough infection in a multiple logistic regression model

Condition	OR	95% CI	*P*
Asthma	5.492	0.44–68.79	0.19
Allergies	1.129	0.25–5.14	0.87
Chronic disease	0.596	0.14–2.57	0.49
Hospital admissions in the previous 12 mo	1.263	0.22–7.09	0.79
Time (months) from vaccination and rash onset	1.020	1.001–1.040	0.04

Patients and Methods

We designed a retrospective case-control study to evaluate the determinants of varicella vaccine failure after one dose of the vaccine. The survey was performed in September–November 2012.

The case definition was based only on the clinical diagnosis and the cases were not laboratory-confirmed.

The Puglian breakthrough cases during 2006–2011 were detected from the Regional Infectious Disease Database (SIMI). The vaccination status of cases and controls were obtained from the Immunization Services Database.

We identified the General Practitioner (GP) of each case using the Health Regional Data-warehouse in order to explain to them the protocol of the study and to request the address of each case.

We sent a letter to all cases to explain the protocol of the study, and we contacted them by phone for an interview. Using a standardized questionnaire, we requested information about their history of allergies, asthma or chronic diseases or hospital admissions during the previous 12 mo. We also requested them to indicate the school and the class they attended during the onset of breakthrough.

The positive predictive value of the memory of varicella was set at 100%.[16]

The cases included children, aged 1–15, who developed varicella symptoms ≥42 d after the first dose of varicella vaccine (breakthrough varicella). Controls were children, aged 1–15 y, who attended the same class (in a school or in a kindergarten) as cases in the same year of breakthrough onset; they had received a dose of varicella vaccine ≥42 d before the rash onset, and they did not develop varicella symptoms.

For each case, we selected three controls. Information was obtained using the same process as with cases. To increase the statistical power, we enrolled subjects who developed breakthrough some years ago.

Questionnaires were computerized in a database built by FileMaker pro 10 software; statistical analysis was performed using STATA MP11 software.

We calculated the proportion of interviewees who reported a history of allergies or asthma or chronic diseases or hospital admission during the previous 12 mo, both among cases and controls; the proportions were compared using a chi-square test.

We calculated, for each control, the time since vaccination and the rash onset of the paired case as a proxy of time from vaccination and virus exposure; we verified the normality of the data, to use parametric tests. The mean time in each group was compared using a *t* test for unpaired samples.

A regression logistic model was designed to assess the association of the risk factors for vaccine failure. A P value < 0.05 was considered significant.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethical Disclosure

The procedures are in accordance with the Helsinki Declaration of 1975; Ethics Committee of Human Experimentation approval is not required, because of data were collected for public health purpose and according to privacy law.

References

1. Alfonsi V, D'Ancona F, Giambi C, Nacca G, Rota MC; Regional Coordinators for Infectious Diseases and Vaccinations. Current immunization policies for pneumococcal, meningococcal C, varicella and rotavirus vaccinations in Italy. Health Policy 2011; 103:176-83; PMID:22030308; http://dx.doi.org/10.1016/j.healthpol.2011.10.002
2. White CJ, Kuter BJ, Ngai A, Hildebrand CS, Isganitis KL, Patterson CM, Capra A, Miller WJ, Krah DL, Provost PJ, et al. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. Pediatr Infect Dis J 1992; 11:19-23; PMID:1312704; http://dx.doi.org/10.1097/00006454-199201000-00006
3. Clements DA. Modified varicella-like syndrome. Infect Dis Clin North Am 1996; 10:617-29; PMID:8856356; http://dx.doi.org/10.1016/S0891-5520(05)70317-2
4. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA 2004; 292:704-8; PMID:15304467; http://dx.doi.org/10.1001/jama.292.6.704
5. Park CS, Kim DS, Kim KH. Varicella outbreak in the patients during group therapy: seroprevalence in a healthcare system during breakthrough varicella occurrence. Clin Exp Vaccine Res 2013; 2:140-3; PMID:23858406; http://dx.doi.org/10.7774/cevr.2013.2.2.140
6. Huang WC, Huang LM, Chang IS, Tsai FY, Chang LY. Varicella breakthrough infection and vaccine effectiveness in Taiwan. Vaccine 2011; 29:2756-60; PMID:21315697; http://dx.doi.org/10.1016/j.vaccine.2011.01.092
7. Bonanni P, Gershon A, Gershon M, Kulcsár A, Papaevangelou V, Rentier B, Sadzot-Delvaux C, Usonis V, Vesikari T, Weil-Olivier C, et al. Primary versus secondary failure after varicella vaccination: implications for interval between 2 doses. Pediatr Infect Dis J 2013; 32:e305-13; PMID:23838789; http://dx.doi.org/10.1097/INF.0b013e31828b7def
8. Spackova M, Wiese-Posselt M, Dehnert M, Matysiak-Klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. Vaccine 2010; 28:686-91; PMID:19874924; http://dx.doi.org/10.1016/j.vaccine.2009.10.086
9. Tafuri S, Martinelli D, Prato R, Germinario C. Vaccine effectiveness evaluation during a varicella outbreak among children of primary schools and day-care centers in a region which adopted UMV. Hum Vaccin Immunother 2013; 9:184-8; PMID:23108354; http://dx.doi.org/10.4161/hv.22373
10. Chaves SS, Gargiullo P, Zhang JX, Civen R, Guris D, Mascola L, Seward JF. Loss of vaccine-induced immunity to varicella over time. N Engl J Med 2007; 356:1121-9; PMID:17360990; http://dx.doi.org/10.1056/NEJMoa064040
11. Zhang X, Yan Y, Liu F, Luo Y, Zhang J, Peng X, Zhang Y, Han S, Zhao J, He Y. The epidemiology and risk factors for breakthrough varicella in Beijing Fengtai district. Vaccine 2012; 30:6186-9; PMID:22867721; http://dx.doi.org/10.1016/j.vaccine.2012.07.062

©2014 Landes Bioscience. Do not distribute.

12. Cenoz MG, Martínez-Artola V, Guevara M, Ezpeleta C, Barricarte A, Castilla J. Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain. Hum Vaccin Immunother 2013; 9:1172-6; PMID:23324571; http://dx.doi.org/10.4161/hv.23451
13. Baxter R, Ray P, Tran TN, Black S, Shinefield HR, Coplan PM, Lewis E, Fireman B, Saddier P. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. Pediatrics 2013; 131:e1389-96; PMID:23545380; http://dx.doi.org/10.1542/peds.2012-3303
14. Michalik DE, Steinberg SP, Larussa PS, Edwards KM, Wright PF, Arvin AM, Gans HA, Gershon AA. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. J Infect Dis 2008; 197:944-9; PMID:18419532; http://dx.doi.org/10.1086/529043
15. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA 2004; 292:704-8; PMID:15304467; http://dx.doi.org/10.1001/jama.292.6.704
16. Celikbas A, Ergonul O, Aksaray S, Tuygun N, Esener H, Tanir G, Eren S, Baykam N, Guvener E, Dokuzoguz B. Measles, rubella, mumps, and varicella seroprevalence among health care workers in Turkey: is prevaccination screening cost-effective? Am J Infect Control 2006; 34:583-7; PMID:17097453; http://dx.doi.org/10.1016/j.ajic.2006.04.213

©2014 Landes Bioscience. Do not distribute.