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Single-dose varicella vaccine effectiveness in school settings in China☆

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Abstract

Background—Varicella vaccine has been available in the private sector in China for a decade as a single-dose regimen, but varicella vaccine effectiveness (VE) has not been fully examined in school settings yet.

Methods—A matched case–control study was carried out in elementary schools and daycares in Tai'an prefecture, Shandong province, China. Clinical diagnosis of varicella and breakthrough disease was used for this study. Four controls were randomly selected from classmates; two from classmates of the case and two from another class of the same grade without cases. Vaccination status, date of vaccination, and vaccine product received if vaccinated were collected from home and clinic immunization records. Vaccination status of all students in schools/daycares with varicella cases from home immunization records or parental recall was used to calculate vaccination coverage.

Results—The overall varicella VE was 83.4% (95% confidence interval 71.4–90.3%). Receipt of varicella vaccine five years or more years before the outbreak was significantly associated with breakthrough varicella (odds ratio = 4.7, $P < 0.001$), while age at vaccination (<15 vs. ≥15 months) was not (odds ratio = 1.5, $P = 0.62$). Varicella vaccination coverage was 41% with substantial variation across schools (range of 0–93.8%).

Conclusions—Single-dose varicella vaccine is highly effective in school settings. Maintaining limited vaccination coverage might shift varicella disease burden to older individuals, who are more prone to develop severe outcomes if varicella occurs.

Keywords

Chickenpox; Vaccine effectiveness; Vaccination coverage

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

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1. Introduction

Varicella (chickenpox) is a highly contagious disease caused by infection with varicella zoster virus (VZV), and is characterized by a generalized pruritic vesicular rash. Although varicella is usually self-limiting and resolves within a week, severe complications, including death, can occur [1].

Varicella vaccines are now widely available as the most effective measure for prevention and control of varicella. In China, varicella vaccine first became available in 1998. Five vaccines are currently licensed in China for single dose use in persons 12 months and older: Varilrix® (GlaxoSmithKline) and four domestic vaccines (Baike, Changsheng, Keygen, and Shanghai). The five varicella vaccines have similar concentrations of Oka strain VZV: >1995 plaque forming unit/dose (0.5 mL) in Varilrix, and >2000 plaque forming unit/dose (0.5 ml) in the domestic vaccines. The five vaccines have the same temperature requirement (2–8 °C) for cold-chain storage and transportation. Currently, varicella vaccines are only available for private purchase in China and vaccination coverage varies substantially by regional level of economic development [2–5]. Although their immunogenicity and safety have been assessed previously in randomized clinical trials [6–13], the effectiveness of these vaccines in China have not yet been fully examined in school settings, the most likely places for intense varicella exposure as a consequence of decreasing family sizes in China [14]. A matched case–control study was carried out in schools and daycares to examine the post-licensure effectiveness of varicella vaccines in school settings in Shandong Province, China.

2. Methods

2.1. Study population

The China Center for Disease Control and Prevention (CDC) and Tai'an CDC conducted a case–control study in schools and daycare centers in five counties of Tai'an prefecture, Shandong province, from 3/2010 to 6/2011. A case of varicella was defined as an acute generalized maculopapulovesicular rash without other apparent cause [15]. Breakthrough varicella was defined as a case that developed >42 days after vaccination [15]. Although varicella was not a notifiable disease in Tai'an prefecture during this period, 248 elementary schools and daycare centers in five counties of Tai'an prefecture agreed to report varicella cases to the local department of health, whose staff enrolled eligible case-patients and controls and interviewed parents/guardians. Informed consent for study participation was obtained from parents/guardians. For each enrolled case-patient from an elementary school, two classmates sitting directly around the case were randomly selected, and another two students from a class of same grade without any varicella cases were also randomly selected as controls. Each control group was analyzed separately with the cases to calculate vaccine effectiveness and finding no difference, the controls were grouped together. For each case from a daycare center, two controls were selected from the case-patient's classroom and another two controls were randomly selected from daycare attendees of the same age from a classroom without cases.

2.2. Data collection

Parents/guardians of the participants were interviewed using a standard questionnaire to collect information on sociodemographics, underlying diseases, prior varicella history, and recent possible VZV exposure. Case and control candidates with prior varicella history were excluded. For enrolled cases and controls, vaccination status, date of vaccination, and vaccine product received if vaccinated were collected from immunization records at home or in the immunization clinics. Date of rash onset and prior varicella history were collected from parents or clinic records. For evaluation of vaccine coverage in the schools and daycare centers under study, the vaccination status and prior varicella history were collected from immunization records at home or parental recall and vaccination coverage was calculated after the outbreak was over and excluded those with prior disease history.

2.3. Statistical analyses

We defined varicella VE as [1 − odds ratio (OR)] × 100%, where OR was calculated from conditional logistic regression for the matched case–control study. Vaccine product-specific VEs could only be calculated for the Baike and Changsheng vaccines due to the small number of participants who had received the other vaccine products. We used previously described methods to assess VE changes with time since vaccination [16]. For pairs in which either or both the case and the controls had received varicella vaccine, we defined the time since vaccination as the time interval between the date(s) of vaccination and the rash onset date of the matched case. For assessing vaccination status of controls, we used the date of rash onset in the case as the reference date. Thus, controls who received varicella vaccine after the disease onset date of the matched case were defined as unvaccinated. We performed all analyses with SAS version 9.2 (SAS Inc., Cary, NC).

China CDC Ethics Committee reviewed and approved this protocol.

3. Results

3.1. Characteristics of the study participants

There were a total of 180 cases reported from 44 schools and day cares and 679 controls enrolled. Half (434, 50.5%) of the 859 participants were female. The majority of participants were elementary school students (589, 68.6%) with a mean age of 7.3 years (range: 1.3–12.4). Five participants reported having underlying medical conditions of asthma and eczema. More than half of the cases (97/180) reported a VZV exposure, 93 (95.9%) of which were at school. Of the 250 (29.1%) vaccinated cases and controls, 135 (54.0%) received Changsheng vaccine and 83 (33.2%) received Baike vaccine (Table 1). There were no differences between cases and controls by sex, age, age at vaccination, or type of vaccine product received. However, cases were less likely to be vaccinated than controls (10.0% vs. 34.5%, $P < 0.001$), and vaccinated cases had a longer time since vaccination compared to vaccinated controls (3.1 vs. 2.6 years, $P = 0.01$) (Table 1).

3.2. Varicella vaccine effectiveness

Overall varicella VE was 83.4% (95% confidence interval: 71.4–90.3), with age at vaccination (<15 months vs. ≥15 months) having little effect on varicella VE (88% vs.

82.4%, $P = 0.59$). Varicella VE did not vary significantly during the first five years after vaccination, ranging from 81.7% to 94.3% with average of 88.7%, but was significantly lower among those vaccinated more than five years before the outbreak (46.9%, $P < 0.001$) (Table 2, Fig. 1).

One dose VEs of Baike and Changsheng vaccines were 91.4% and 77.1% ($P < 0.001$ for both) respectively, with the difference between them statistically significant ($P = 0.008$). This difference in VE between the two vaccines remained significant even after addressing the differences in time since vaccination (25.2% among Changsheng recipients had been vaccinated ≥5 years prior to the outbreak vs. 0% among Baike recipients, $P < 0.001$). The VE for the Baike vaccine was greater than that of the Changsheng vaccine among those who had received vaccine within five years (91.4% vs. 84.5% for Baike and Changsheng, respectively, $P = 0.02$).

3.3. Varicella vaccination coverage

The overall vaccination coverage among the 19,488 students from the involved daycares ($n = 21$) and elementary schools ($n = 23$) was 41%, ranging from 0 to 93.8%. The vaccination status of the majority of vaccinated students (78.5%, 6261/7980) was verified with an immunization record from home with the rest based on parental recall. Elementary school students ($n = 12,430$) were more likely to be vaccinated than daycare attendees ($n = 7058$) (43.6% vs. 36.4%, $P < 0.001$) as were children of urban residency ($n = 7018$) compared to those from rural areas ($n = 12,470$) (44.2% vs. 39.1%, $P < 0.001$). These differences were largely driven by higher varicella vaccination coverage in urban compared to rural elementary schools (56.9% vs. 39.2%, $P < 0.001$) (Table 3).

4. Discussion

Our study showed that single-dose varicella vaccination in China was highly effective in preventing varicella in school settings. With varicella vaccine currently only available in China in the private sector, we found moderate varicella vaccination coverage had been achieved, although there was substantial variation across schools. Our study is the first to examine the effectiveness of two varicella vaccines (Baike and Changsheng) that are produced in China., which appear to offer comparable protection to Varilrix® and two other varicella vaccines from China (Shanghai and Changchun, now called Keygen) [13,17–19]. Though our study showed higher vaccine effectiveness for one of the vaccines, additional studies are needed to confirm or refute this finding. In our study, single-dose varicella vaccine-induced immunity appears to decrease 5 years after vaccination. This is similar to findings from an ecological study from the U.S. which reported that vaccine recipients were more than twice as likely to develop moderate/severe breakthrough varicella ≥5 years after vaccination compared to those who had been vaccinated more recently [20]. A retrospective cohort study in Turkey where varicella vaccine was also available only in private section found receipt of vaccination ≥5 years was associated with a more than three-fold likelihood of breakthrough varicella compared to more recent vaccination [21]. In contrast, a study of varicella VE changes after vaccination in Guangzhou China [13] did not find any statistically significant differences in VE during the seven years after vaccination. More data are needed to better understand the duration of protection in children after one dose varicella

vaccination, although this is increasingly challenging to investigate as disease circulation declines rapidly in many settings after introduction of varicella vaccination.

Because the effectiveness of single-dose varicella vaccination is approximately 85% against all varicella regardless of manufacturer [13,17,19,22], about 15% of vaccinated single-dose recipients may be incompletely protected against varicella. Over time, this proportion of vaccinated single-dose varicella recipients, which would increase along with increases in single-dose vaccine coverage [23], may become the driving force for school outbreaks [22,24,25]. Since two-dose varicella vaccination induces higher immunity and protection against varicella [26–28], some counties have implemented a 2-dose vaccine program among children to further reduce varicella disease burden and outbreaks [29–31]. Similar to the Varivax® and Varilrix®, several varicella vaccines manufactured in China, have been shown previously to have higher effectiveness against moderate/severe varicella than against all varicella [17,19,22]. Though not examined in this study, because they have been shown to offer similar protection against varicella of any severity as Varivax® and Varilrix®, it is likely that the two vaccines from China examined here (Baike and Changsheng) will have similar effect against moderate/severe varicella and in preventing varicella hospitalizations and deaths.

Moderate levels of varicella vaccination coverage have been achieved in selected areas in China. Given that varicella vaccine in China is currently only available in the private sector and currently priced at more than 25 US dollars for domestic varicella vaccine and 50 US dollars for imported varicella vaccine, the coverage levels achieved thus far suggest that varicella vaccination is well accepted in China among those who can afford it [3–5]. Achieving universal childhood varicella vaccination coverage while varicella vaccine availability is limited to the private sectors appears unlikely. Including varicella vaccine in the national or local immunization program could be a durable choice to achieve and maintain high vaccine coverage [2]. A potential disadvantage of achieving and maintaining only moderate levels of vaccination coverage is a decreased risk of varicella exposure for unvaccinated individuals during childhood which, over the long term, might cause a shift in the epidemiology of varicella that would result in an increase in the numbers of cases among older individuals who are more likely to develop severe outcomes if varicella occurs. For this reason, the World Health Organization recommends high (85–90%) and sustained routine vaccination coverage levels as a prerequisite for the introduction of a varicella vaccination program [32]. If fully implemented, in addition to reducing varicella among children, a routine childhood varicella vaccination program has the potential to reduce VZV exposure in infants who are too young to be eligible for vaccination, and adults, as well as those for whom vaccination is contraindicated but who remain at high risk of severe disease.

Several limitations should be considered in interpreting our findings. We employed a clinical case definition that did not require lab confirmation. Though medical practitioners in the study site were likely experienced in diagnosing varicella, their expertise with recognizing the milder clinical presentations of breakthrough varicella is unknown, therefore under-reporting of varicella in vaccinated persons may have occurred. If under-ascertainment of cases in vaccinated children occurred, our VE estimate would an overestimation. The vaccination status was assessed at the end of school outbreaks, therefore

the vaccine coverage might be overestimated in that some children counted as vaccinated may have gotten vaccinated during the outbreaks. Moreover, using parental recall on vaccination status could have led to over- or under-estimation of true vaccine coverage.

In summary, single-dose varicella vaccine is highly effective in preventing varicella disease in school settings in China. Optimally, higher varicella vaccination coverage in China should be achieved and maintained during childhood to maximize the benefit of the varicella vaccine program in decreasing severe varicella morbidity and mortality for all age groups and to prevent epidemiology shift to adolescents and adults who are prone to develop severe outcomes if varicella occurs.

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References

1. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev. 1996; 9(3):361–81. [PubMed: 8809466]
2. Xu A, Xu Q, Fang X, Bialek S, Wang C. Varicella vaccine uptake in Shandong province, China. Hum Vaccin Immunother. 2012; 8(9):1213–7. [PubMed: 22894966]
3. Huang Y, He Y. Analysis on varicella vaccination among children and its impact factors in Xixiang Community, Baoan District. Prev Med Trib. 2010; 16(12):1155–7.
4. Tian Z. Investigation on 8 types of extra EPI vaccines in vaccination clinic in Henan oil-field center for disease control and prevention. Mod Prev Med. 2008; 35(2):327–30.
5. Shen H. Analysis on the vaccine coverages in the children from a local community. Mod Med J China. 2007; 9(10):106–7.
6. Lu X, Zhou W, Gu K, Zhu F. Evaluation on safety and immunogenicity of Changshengkeji frozen-dried live attenuated varicella vaccine. J Southeast Univ. 2008; 27(3):5.
7. Chiu SS, Lau YL. Review of the Varilrix varicella vaccine. Expert Rev Vaccines. 2005; 4(5):629–43. [PubMed: 16221065]
8. Wang L, Liu Y, Li L, Li Z, Li Y, Ha X, et al. Observation on the immunity efficacy of domestic freeze-dried live attenuated varicella vaccine. South China J Prev Med. 2003; 2(29)
9. Wang S, Li C, Li Y, Yuan J, Tao H, Wang Z, et al. Study on safety and immunogenicity of lyophilized live attenuated domestic varicella vaccine. Chin J Vaccines Immunization. 2000; 6(6):4.
10. Ndumbe PM, Cradock-Watson JE, Heath RB, Levinsky RJ. Live varicella immunization in healthy non-immune nurses. Postgrad Med J. 1985; 61(Suppl 4):133–5. [PubMed: 3014470]
11. Kappagoda C, Shaw P, Burgess M, Botham S, Cramer L. Varicella vaccine in non-immune household contacts of children with cancer or leukaemia. J Paediatr Child Health. 1999; 35(4): 341–5. [PubMed: 10457288]
12. Arvin AM. Varlirix (GlaxoSmithKline). Curr Opin Investig Drugs. 2002; 3(7):996–9.
13. Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. Pediatr Infect Dis J. 2010; 29(8):690–3. [PubMed: 20216242]
14. Jin L, Feng F. Analysis of the epidemic situation of chicken pox from 2005 to 2006 in China. Disease Surveill. 2007; 22(4):251–3.
15. Council of State and Territorial Epidemiologists and Position Statement Number: 09-ID-68. Public Health Reporting and National Notification for Varicella.
16. Niccolai LM, Ogden LG, Muehlenbein CE, Dziura JD, Vazquez M, Shapiro ED, et al. Methodological issues in design and analysis of a matched case–control study of a vaccine's effectiveness. J Clin Epidemiol. 2007; 60(11):1127–31. [PubMed: 17938054]

17. Sheffer R, Segal D, Rahamani S, Dalal I, Linhart Y, Stein M, 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(5):434–7. [PubMed: 15876943]
18. Passwell JH, Hemo B, Levi Y, Ramon R, Friedman N, Lerner-Geva L. Use of a computerized database to study the effectiveness of an attenuated varicella vaccine. Pediatr Infect Dis J. 2004; 23(3):221–6. [PubMed: 15014296]
19. Seward JF, Marin M, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. J Infect Dis. 2008; 197(Suppl 2):S82–9. [PubMed: 18419415]
20. Chaves SS, Gargiullo P, Zhang JX, Civen R, Guris D, Mascola L, et al. Loss of vaccine-induced immunity to varicella over time. N Engl J Med. 2007; 356(11):1121–9. [PubMed: 17360990]
21. Kurugol Z, Halicioglu O, Koc F, Koturoglu G, Aksit S. Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey. Int J Infect Dis. 2011; 15(7):e475–80. [PubMed: 21592838]
22. Lu L, Suo L, Li J, Zhai L, Zheng Q, Pang X, et al. A varicella outbreak in a school with high one-dose vaccination coverage, Beijing, China. Vaccine. 2012; 30(34):5094–8. [PubMed: 22687763]
23. Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, et al. Changing varicella epidemiology in active surveillance sites – United States, 1995–2005. J Infect Dis. 2008; 197(Suppl 2):S71–5. [PubMed: 18419413]
24. Civen R, Lopez AS, Zhang J, Garcia-Herrera J, Schmid DS, Chaves SS, et al. Varicella outbreak epidemiology in an active surveillance site, 1995–2005. J Infect Dis. 2008; 197(Suppl 2):S114–9. [PubMed: 18419383]
25. Lai CC, Chen SC, Jiang DD. An outbreak of varicella among schoolchildren in Taipei. BMC Public Health. 2011; 11:226. [PubMed: 21486458]
26. Watson B. Humoral and cell-mediated immune responses in children and adults after 1 and 2 doses of varicella vaccine. J Infect Dis. 2008; 197(Suppl 2):S143–6. [PubMed: 18419388]
27. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J. 2004; 23(2):132–7. [PubMed: 14872179]
28. Shapiro ED, Vazquez M, Esposito D, Holabird N, Steinberg SP, Dziura J, et al. Effectiveness of 2 doses of varicella vaccine in children. J Infect Dis. 2011; 203(3):312–5. [PubMed: 21208922]
29. 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(RR-4):1–40. [PubMed: 17585291]
30. Wiese-Posselt M, Hellenbrand W. Changes to the varicella and pertussis immunisation schedule in Germany 2009: background, rationale and implementation. Euro Surveill. 2010; 15(16)
31. Salvadori M. Preventing varicella: recommendations for routine two-dose varicella immunization in children. Paediatr Child Health. 2011; 16(7):415–6. [PubMed: 22851897]
32. Varicella vaccines. WHO position paper. Wkly Epidemiol Rec. 1998; 73(32):241–8. [PubMed: 9715106]

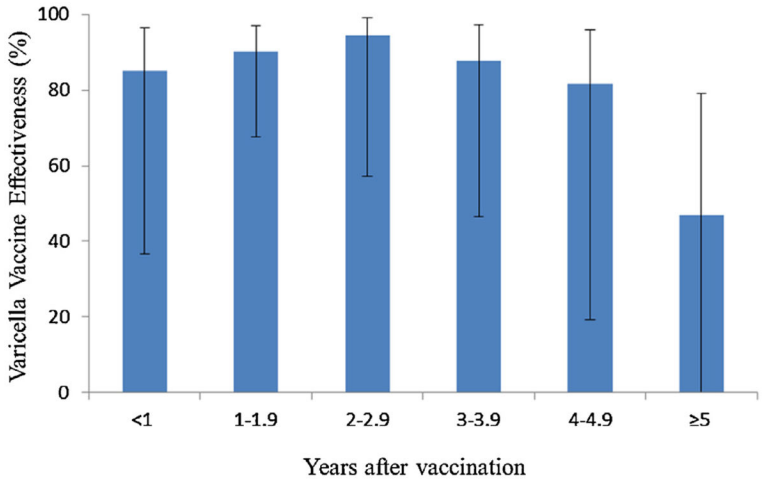

Fig. 1.
Varicella vaccine effectiveness changes by time since vaccination.

Table 1

Characteristics of the cases and the controls by exposure status in 44 schools, Tai'an prefecture, China, 2010–2011.

	Cases, No. (%) (*n* = 180)	Controls, No. (%) (*n* = 679)	*P* value
Sex			0.15
Male	97 (53.9)	328 (48.31)	
Female	83 (46.1)	351 (51.69)	
Age in years: mean (SD)	7.4 (2.2)	7.3 (2.1)	0.66
Having any underlying disease			1.0
Yes	1 (0. 6)	5 (0.74)	
No	179 (99.4)	674 (99.26)	
Type of school			0.33
Elementary school	118 (65.6)	471 (69.37)	
Daycare	62 (34.4)	208 (30.63)	
Varicella vaccination status			<0.001
Vaccinated	18 (10.0)	232 (34.17)	
Unvaccinated	162 (90.0)	447 (65.83)	
Varicella vaccine product[a,b]			0.30
Baike	3 (16.7)	80 (34.637)	
Changsheng	12 (66.6)	123 (53.25)	
GlaxoSmithKline	0 (0.0)	1 (0.43)	
Keygen	1 (5.6)	15 (6.49)	
Shanghai	2 (11.1)	12 (5.19)	
Age at vaccination[a]			0.62
<15 months	3 (16.7)	37 (92.50)	
≥15 months	15 (83.3)	195 (92.86)	
Year since varicella vaccination:			
Mean (SD)[a]	4.1 (2.3)	2.9 (2.0)	0.01

[a] Single-dose varicella vaccine recipients only.

[b] One control with missing information on varicella vaccine product received.

Table 2

Varicella vaccine effectiveness in a matched case–control study in elementary schools and daycares, Tai'an prefecture, China, 2010–2011.

	Cases, No. (%) (*n* = 180)	Controls, No. (%) (*n* = 679)	Vaccine effectiveness (95% confidence interval)[a]	*P* value
Overall VE				
Vaccinated	18 (10.0)	232 (34.2)	83.4 (71.4–90.3)	<0.001
Unvaccinated	162 (90.0)	447 (65.8)	Reference	
VE by age at vaccination				
<15 months	3 (1.7)	37 (5.5)	88.0 (55.3–96.8)	0.002
≥15 months	15 (8.3)	195 (28.7)	82. (68.8–90.0)	<0.001
Unvaccinated	162 (90.0)	447 (65.8)	Reference	
VE by time since vaccination				
<5 years	10 (5.6)	194 (28.6)	88.7 (77.7–94.3)	<0.001
≥5 years	8 (4.4)	38 (5.6)	47.0 (0–79.2)	0.18
Unvaccinated	162 (90.0)	447 (65.8)	Reference	

[a] Vaccine effectiveness (VE) is defined as (1 − odds ratio) × 100.

Table 3

Varicella vaccination coverage in 44 elementary schools and daycares (number of students = 19,488), Tai'an prefecture, China, 2010–2011.

Residence	Type of school	Vaccinated students, No. (%) (*n* = 7980)	Unvaccinated students, No. (%) (*n* = 11,508)	*P* value
Urban	Elementary school (*n* = 3)	1781 (56.9)	1350 (43.1)	<0.001
	Daycare (*n* = 11)	1323 (34.0)	2564 (66.0)	
Rural	Elementary school (*n* = 20)	3633 (39.1)	5666 (60.9)	0.90
	Daycare (*n* = 10)	1243 (39.2)	1928 (60.8)	