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Single-dose varicella vaccine effectiveness in Brazil: A case-control study

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ABSTRACT

Background: Varicella vaccine was introduced into the Brazilian Immunization Program in October 2013, as a single-dose schedule administered at 15 months of age. Its effectiveness had not yet been assessed in the country.

Methods: A matched case-control study was carried out in São Paulo and Goiânia (Southeast and Midwest regions, respectively), Brazil. Suspected cases, were identified through a prospective surveillance established in the study sites. All cases had specimens from skin lesion collected for molecular laboratory testing. Cases were confirmed by either clinical or PCR of skin lesions and classified as mild, moderate, and severe disease.

Methods: Two neighborhood controls were selected for each case. Cases and controls were aged 15–32 months and interviewed at home. Evidence of prior vaccination was obtained from vaccination cards. Univariate and multivariate logistic regression models were used, and odds ratio and its respective 95% confidence intervals were estimated. Vaccine effectiveness was estimated by comparing de odds of having received varicella vaccine among cases and controls.

Results: A total of 168 cases and 301 controls were enrolled. Moderate and severe illness, was found in 33.3% and 9.9% of the cases. Effectiveness of a single dose varicella vaccine was 86% (95%CI 72–92%) against disease of any severity and 93% (95%CI 82–97%) against moderate and severe disease. Out of 168 cases, 81.8% had positive PCR results for wild-type strains, and 22.0% were breakthrough varicella cases. Breakthrough cases were milder compared to non-breakthrough cases ($p < .001$).

Conclusions: Effectiveness of single dose varicella vaccine in Brazil is comparable to that in other countries where breakthrough varicella cases have also been found to occur. The goal of the varicella vaccination program, along with disease burden and affordability should be taken into consideration when considering the adoption of a second dose of varicella vaccine into national immunization programs.

1. Introduction

Varicella is a highly infectious disease caused by the varicella-zoster virus (VZV). Transmission occurs by either direct contact with contagious skin lesions or by airborne spread from respiratory secretions or infected lesions. Although symptoms are generally mild in children, severe complications may follow, such as secondary bacterial infections, pneumonia, encephalitis, and even death [1,2]. Among vaccinated individuals, varicella can emerge as a modified disease, known as breakthrough varicella [3,4]. This infection may present a diagnostic challenge, due to its atypical and milder presentation [5,6].

Varicella surveillance is not mandatory in Brazil. However, since 2000 varicella outbreaks in daycare centers, preschools, schools, and in the community, are to be reported to the National Notifiable Diseases Surveillance System. Furthermore, in addition to out-

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breaks, severe cases or varicella-related deaths are to be reported since 2014 [7].

In October 2013 varicella vaccine was introduced into the routine public Brazilian National Immunization Program (NIP) to prevent moderate and severe disease among the target population, including varicella-related deaths. A combined tetravalent vaccine containing measles, mumps, rubella, and varicella antigens (MMRV), manufactured by GlaxoSmithKline® was introduced. Despite surveillance evidence indicating varicella community outbreaks, Brazil opted for a one dose schedule, administered at the age of 15 months [8]. Decision on the adoption of a 2-dose schedule was deferred for later, once evaluation of the vaccine effectiveness was available.

Prior to 2013, the vaccine was available only for high-risk groups such as susceptible individuals who had contact with a varicella case, particularly in outbreak control settings. Coverage was thus very low, reported at 3% in children aged 1–4 years old [9]. In the private healthcare setting, varicella vaccine is available since 1996.

Post-licensure studies are crucial to evaluate vaccination effectiveness and impact [10]. The impact of single dose varicella vaccination is still unknown in Brazil. Worldwide, information is scarce to what extent one-dose schedule prevents cases of breakthrough infection soon after vaccine introduction. We evaluated the effectiveness of varicella vaccine in a case-control study conducted within the first two years of its introduction into the NIP.

2. Methods

2.1. Study population and setting

From November/2013 to December/2015, a prospective matched case-control methodology on varicella [11] was conducted in two Brazilian State Capital cities, São Paulo (Southeast region) and Goiânia (Midwest region). Varicella vaccination coverage rates reached 83% and 60% in Goiânia and 69% and 66% in São Paulo, respectively, during 2014 and 2015 [12]. Children targeted for vaccination (aged $\geq$ 15 months) born from June 2012 onwards, and residing in any of the two study municipalities included in the study, were eligible. Children without vaccination cards to confirm vaccination history; children with contraindications for varicella vaccination; and children who received varicella vaccine within the prior 42 days were excluded.

2.2. Case definition

Suspected cases were defined as children aged 15–32 months with rash and either suspected as having varicella by an attending physician or being a contact to a confirmed varicella case. Cases were confirmed by either clinical or laboratory criteria. Clinically confirmed cases were those with a clinical diagnosis given by the physician. Laboratory confirmation was by means of identification of DNA varicella-zoster virus by real-time PCR (RT-PCR) from a skin lesions, as further described below.

Cases were further classified by severity of disease based on number of skin lesions, being either: (1) Mild – fewer than 50 lesions; (2) Mild/moderate – between 50 and 249 lesions; (3) Moderate – between 250 and 499 lesions; and (4) Severe – 500 lesions or more, having been hospitalized or having any complication.

Cases of varicella in vaccinated children 42 days or more before the onset of a rash was defined as breakthrough cases [13,14].

2.3. Case ascertainment

Suspected varicella cases were identified through active prospective surveillance in selected primary health services (PHS) and day-care centers integrating the study network, which were contacted twice weekly. Whenever a case of varicella was detected, cases and their legal guardians were asked periodically, during a three-week period after rash onset, if they knew about another suspected varicella case within the age group of the study, following a snowball sampling rationale. By so doing, our aim was to find the younger home and neighborhood contacts that did not attend day-care centers, as well as the mild cases that did not seek healthcare.

The study network was comprised of 104 PHS in Goiânia located throughout all regions in the city. In São Paulo, cases were ascertained in 5 PHS located in the Western (4 services) and in the Southeast (1 service) regions of the city.

When a varicella suspected case was identified, the PHS pediatrician or infectious disease physician was responsible for clinical confirmation and ascertainment of disease severity.

2.4. Control definition and selection

For each case of varicella two neighborhood controls were selected, matched by age (15–32 months). Controls were defined as children residing in the neighborhood of the case, in which no history of varicella or outpatient clinics visits due to skin lesion was reported. To identify controls, houses nearby the cases were visited following a systematic sampling procedure.

2.5. Data collection

Study data collectors were trained prior to study start on standardized case definitions; and processes for requesting verbal consent, filling out the case reporting form (CRF), and collection of clinical samples. Parents or legal guardians of case and controls were interviewed at their respective homes. For cases, interviews took place up to 5 days after the case's disease onset. Controls were interviewed within up to 2 weeks of the corresponding case disease onset date. The data collection form captured data on child's name, date of birth, gender, varicella history, vaccine receipt and number of doses, types and dates of MMRV and MMR vaccines, underlying and chronic diseases, use of corticosteroids; day care attendance of other children living in the same household; and mother's name, age, education and address. For cases, additional information was collected: date of symptom onset, date of swab collection of the lesion, and number of lesions.

Clinical samples were collected from all children with a clinical diagnosis of varicella and sent for PCR testing to either the Virology Laboratories of the Federal University of Goiás, or the Adolfo Lutz Institute. All samples were processed using PCR detection assay and Real Time PCR, as described by Watzinger et al. [15]. The use of restriction reactions made it possible to differentiate the wild-type varicella-zoster (WT-VZV) from the vaccine strain (Oka strain), as described by Loparev et al. [16].

Evidence of prior vaccination was obtained from vaccine cards. For the purpose of this analysis, children were considered as immunized if they received vaccine at least 42 days before the rash onset (cases) or study interview (controls). All other cases and controls were considered as non-immunized. Cases who received varicella vaccine within 42 days of rash onset (for cases) or date of the interview (for controls) were not eligible for participation.

2.6. Statistical considerations

Assuming that the odds of becoming ill is 60% lower in vaccinated children when compared to non-vaccinated children, vaccine coverage of 90%, and 90% power and a two-sided significance level of 5%, a sample size of 167 cases and 334 controls (1:2 ratio) was estimated. Enrollment of 175 cases and 350 was

planned, to compensate for an estimated 5% of children from whom it would be impossible to collect timely lesion samples in addition to screen failure or refusal.

Analysis of vaccine effectiveness considered all clinically-confirmed varicella cases, regardless of laboratory confirmation by PCR. Descriptive analysis of cases and controls was performed. We also conducted a descriptive analysis of clinical and demographic characteristics contrasting immunized and non-immunized study subjects, including all cases and controls. Categorical variables were compared by Pearson chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared by Wilcoxon rank-sum test. Breakthrough and non-breakthrough cases were compared according to clinical and socio-demographic characteristics using a chi-square test and *t*-test when appropriate. Matched odds ratios (OR) of having been immunized among cases and controls, and its respective 95% confidence interval (CI), were calculated considering all cases and also stratified by severity of illness. Multiple conditional logistic regression models were used to adjust for potential confounding. The backward selection was used to build the final model.

Vaccine effectiveness was estimated as the percent reduction in the varicella disease odds $(1 - \mathrm{OR}) \times 100$. All p-values are two-sided, with significance levels of .05.

2.7. Ethical approval

This study was approved by the Research Ethics Committee of the Federal University of Goiás, Goiania (#162.53, #751.383 and #979.713), and by the Secretary of Health of São Paulo municipality (#800.776).

3. Results

3.1. Case and control subject characteristics

During the study period, a total of 168 cases and 301 controls were enrolled. All cases had 2 controls, except for 35 cases that had only one control. Characteristics of cases and controls are presented in Table 1. Demographic characteristics were generally similar among cases and controls, except for cases were older than controls, and proportion of cases having siblings attending day-care centers was higher (63.1% vs.13.0%). Chronic pulmonary conditions were more frequent among cases. Varicella vaccination was significantly lower for cases when compared to controls (22.0 vs 57.1%). Prior MMR vaccination was similar for cases and controls.

Table 2 describes vaccination characteristics among vaccinated children, comparing the 37 vaccinated cases and 172 vaccinated controls. Cases had received the vaccine at an older age than controls. Time since vaccination was longer for cases than controls.

3.2. Breakthrough varicella case characteristics

Among 168 varicella cases, thirty-seven (22.0%) were breakthrough cases. Breakthrough and non-breakthrough cases were statistically different only in terms of number of varicella lesions. Mild (<100 lesions), moderate (100–499 lesions) and severe (≥500 lesions) illness, were found in 53.4%, 36.6% and 9.9% of non-breakthrough cases; and 5.4%, 21.6% and 0% of breakthrough cases respectively. All children presenting ≥500 lesions were non-breakthrough cases (Table 3).

3.3. Vaccine effectiveness

In the unadjusted model having received a valid dose of varicella vaccine (OR = 0.19; 95%CI 0.11–0.31; p = .000), having previous respiratory disease or asthma (OR = 4.62; 95%CI 1.45–14.74; p = .010), and having older sibling attending day-care center (OR = 14.51; 95%CI 8.06–29.83; p = .000), were associated with varicella cases of any severity. After adjusting for these variables and for age, vaccine effectiveness was 86% (95%CI 72–92%), considering cases of any severity and their matched controls, and 93% (95%CI 82–97%) considering moderate/severe cases, as shown in Table 4.

Having an older sibling attending day-care center (OR = 16.31; 95%CI 6.41–41.49; p = .000) was found to be independently associated with moderate/severe cases, and respiratory disease or asthma did not remain independently associated to varicella cases. As expected, MMR vaccination had no effect in preventing the occurrence of varicella cases of any severity (VE = 37%; 95%CI; 121–82, p-value .475).

4. Discussion

This is the first study to assess the effectiveness of varicella vaccine in Brazil. We found that the VE of single dose of varicella

Table 1
Demographic, clinical, and vaccination characterization of varicella cases and controls. Brazil, 2013–2015.

Characteristics	Cases N = 168[a]	Controls N = 301[a]	p-value
Age in months	28 (21–32)	23 (19–28)	<.001
Males	90 (53.6)	151 (50.2)	.479
Number of children under 5 years of age living at same home	1 (1–2)	1 (1–2)	.930
Number of people (children or adults) sleeping at same room	2 (1–3)	2 (1–3)	.818
Race/skin color			.827
White	68 (40.5)	131 (43.5)	
Black	9 (5.4)	15 (5.0)	
Brown	91 (54.2)	155 (51.5)	
Education of mother			.543
Illiterate	0 (0.0)	2 (0.7)	
Middle-school	69 (41.1)	122 (40.5)	
High-school	88 (52.4)	148 (49.2)	
College	11 (6.5)	29 (9.6)	
Family Health Program enrollment	117 (69.6)	210 (69.8)	1.000
Day-care attendance of household contact	106 (63.1)	39 (13.0)	<.001
Respiratory disease or asthma	17 (10.1)	10 (3.3)	.003
Use of corticosteroids[c]	6 (3.6)	8 (2.7)	.569
Varicella vaccination	37 (22.0)	172 (57.1)	<.001
MMR[b] vaccination	159 (94.6)	283 (94.0)	.781

[a] All continuous variables summarized by their median and inter-quartile range. All categorical variables presented as numbers and percentages.
[b] MMR: measles, mumps and rubella vaccine.
[c] 1 control = missing.

Table 2
Characteristics of varicella vaccination among cases and controls, only for children that had been vaccinated. Brazil, 2013–2015.

Vaccination characteristics[a]	Cases	Controls	p-value
	n = 37	n = 172	
Age at varicella vaccination in months[b]	25 (22–32)	23 (20–27)	.005
Interval between varicella vaccination and study interview in months[b]	9.8 (6.7–14.1)	7.3 (4.0–10.5)	.005
Type of varicella vaccine[b]			.529
Mono Glaxo/Varilrix	0 (0)	9 (5.2)	
Mono Merck/Varilrix	0 (0)	2 (1.2)	
Mono Biogenetech/Green Cross	1 (2.7)	0 (0)	
Tetraviral Glaxo	36 (97.3)	160 (93.6)	

[a] All continuous variables summarized by their median and inter-quartile range. All categorical variables presented as numbers and percentages.
[b] Missing data for one child: 1 control.

Table 3
Characteristics of breakthrough and non-breakthrough varicella cases. Brazil, 2013–2015.

Characteristics[a]	Breakthrough varicella		p-value
	Yes n = 37	No n = 131	
Age in months	25 (22–31)	29 (20–32)	.620
Number of children under 5 years of age living at same home	1 (1–2)	1 (1–2)	.987
Number of people (children or adults) living at same home	4 (3–4)	4 (3–5)	.979
Interval between onset of rash and study interview in days	6 (4–8)	6 (3–8)	.563
Prematurity, <37 weeks gestational age	4 (10.8)	12 (9.2)	.763
Female sex	18 (48.6)	60 (45.8)	.759
Race/skin color			1.000
White	15 (40.5)	53 (40.5)	
Brown	20 (54.1)	71 (54.2)	
Black	2 (6.4)	7 (5.3)	
Education of mother			.196
Middle-school	11 (35.5)	58 (44.3)	
High-school	22 (59.5)	66 (50.4)	
College	4 (10.8)	7 (5.3)	
Child registered in Family Health Program	29 (78.4)	88 (67.2)	.259
Day-care attendance of household contact	28 (75.7)	78 (59.5)	.084
Pulmonary disease or asthma	5 (13.5)	12 (9.2)	.624
Use of corticosteroids[b]	3 (8.1)	3 (2.3)	.307
Previous history of varicella	0 (0.0)	3 (2.3)	.353
Exposure to varicella or zoster in prior 3 weeks[c]	28 (77.8)	97 (74.6)	.697
Estimated number of varicella lesions			<.001
<50	23 (62.2)	26 (19.8)	
50–99	6 (16.2)	44 (33.6)	
100–249	6 (16.2)	27 (20.6)	
250–499	2 (5.4)	21 (16.0)	
≥500	0 (0.0)	13 (9.9)	
Fever two days prior to rash[c]	13 (36.1)	58 (44.6)	.361
Abdominal pain two days prior to rash[d]	5 (13.5)	27 (20.9)	.313
Anorexia two days prior to rash	12 (32.4)	52 (39.7)	.422
Malaise two days prior to rash	18 (48.6)	79 (60.3)	.205

[a] All continuous variables summarized by their median and inter-quartile range. All categorical variables presented as numbers and percentages.
[b] Missing data: 1 breakthrough case.
[c] Missing data: 1 breakthrough case and 1 non-breakthrough case.
[d] Missing data: 2 non-breakthrough cases.

vaccine administered at 15 months of age and measured in children aged up to 32 months was 86% (95%CI 72–92%) against all grades of disease severity, and 93% (95%CI 82–97%) against moderate and severe disease. These results are comparable to those of a recent meta-analysis of 42 studies of varicella VE assessment conducted within the first decade after vaccine introduction in which pooled VE was 81% against all cases, and 98% against moderate and severe cases [10].

Only nine (35%) Latin American countries had introduced universal vaccination against varicella by 2015. To date, the impact of varicella vaccination had only been assessed in the first two countries in the region to introduce varicella vaccine into their NIPs – Uruguay and Costa Rica. In Uruguay, where more than 90% coverage has been rapidly achieved with one dose and maintained since vaccine introduction in 1999, a study performed with data up to 2005 showed 81% reductions in varicella hospitalizations, and 86% reductions in outpatient visits in the age-groups eligible for vaccination, compared to the pre-vaccination period (1997–99) [17]. In Costa Rica, varicella vaccine was introduced in 2007 and coverage has increased from 76% in 2008 to 95% in 2015. A study conducted in 2005 with secondary national data showed 79.1% reduction in notified cases, and 87% reduction in hospitalization in children under 5 years of age [18].

As in Uruguay, in Brazil the uptake of a new children's vaccination program is commonly high from the start [19], even though in one of the cities of the study it remained less than 70% in the first year after vaccination start. At a population level, if the country is able to keep a high coverage, we expect that the beneficial effect of the vaccine will rise as new cohorts of children are vaccinated and herd protection expands, as documented in other studies [17,20–22]. But the 22% of breakthrough cases in our study may be an indication that sporadic cases and outbreaks of varicella among vaccinated individuals will continue to happen in Brazil as they did in other countries, despite the milder disease of breakthrough cases [6,14,23]. Breakthrough cases in our study can be attributed to primary vaccine failure, as data collection took place in the first two years after vaccine introduction, and cases had on average been vaccinated only 9 months before [24]. Waning of vaccine-induced immunity may also increase varicella susceptibility many years after vaccination, even though there is conflicting evidence on this topic [4,25].

Discussions on varicella vaccine schedule change, in particular adding a second vaccine dose, have already started in the Brazil. In other countries, second dose introduction has been justified by the need for an even higher degree of protection to prevent outbreaks in settings with high contact rates and to reduce severe breakthrough disease [25–27]. Local evidence provided by surveillance data, in particular regarding the occurrence of outbreaks and severe cases among highly vaccinated individuals is important to characterize the remaining disease burden, despite known data quality issues in varicella surveillance data [3,4,28].

This case-control study has strengths and limitations. While we cannot be certain that all cases in our study age group have been identified by the active surveillance that was put in place in the study areas, PCR positivity was over 80%, which suggests that the clinical diagnosis by the physicians had high specificity, minimizing misclassifications for both cases and controls. It is also possible that they had a lower risk of developing varicella disease once infected given their lower age and rates chronic respiratory disease rates, including asthma. Although the association of asthma and increased risk for breakthrough varicella has been suggested in a

Table 4
Varicella vaccine effectiveness, according to disease severity. Brazil, 2013–2015.

Disease severity	Unadjusted		Adjusted		
	OR (95%CI)	% VE (95%CI)	OR (95%CI)	% VE (95%CI)	P-value
Any severity of disease (1)	0.19 (0.11–0.31)	81 (69–89)	0.14 (0.07–0.28)	86 (72–92)	<.001
Moderate/severe cases, ≥50 lesions (2)	0.09 (0.04–0.19)	91 (81–96)	0.07 (0.03–0.18)	93 (82–97)	<.001

Number of observations in each model: (1) unadjusted = 469, adjusted = 469 (2) unadjusted = 333, adjusted = 333.
Adjusted for confounders: age in months, day-care attendance and pulmonary diseases.

recent study [29], our findings showed that asthma did not remain independently associated with varicella cases in the adjusted model. While these differences indicate that our controls were not fully representative of the population from which cases arose, it is of note that the adjustment for these three variables (age, day-care attendance and presence of chronic respiratory disease rates), in our multiple conditional regression analysis did not change by much the observed estimates. The fact that we did not find any significant association of MMR vaccine on varicella cases, as expected, is also an indication that selection bias was likely not an important issue [30]. Neighborhood matching has likely helped us to control for some confounding and to improve the precision of our estimates [11]. We also believe that we have avoided information bias on vaccination exposure by interviewing parents and guardians in their homes, which allowed us easy access to vaccination cards. Another issue is that the diagnosis of the number of lesions was performed in only one evaluation, at the time of the interview (we did not follow the patient). Thus, it is not possible to be sure if the number of lesions increased or not in the subsequent days of the interview, which could lead to bias in the number of lesions in varicella breakthrough. Finally, the study areas were limited to the city of Goiânia and some regions of the city of São Paulo, so that representativeness of the country as a whole is not guaranteed.

In conclusion, this study showed that the effectiveness of the one-dose varicella vaccine schedule introduced into the Brazilian NIP is comparable to that found in other countries, where breakthrough cases have also been found to occur. The goal of the varicella vaccination program, along with disease burden and affordability should be taken into consideration when considering the adoption of a second dose of varicella vaccine into national immunization programs.

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Conflict of interests

ALA has received research grant from GSK and also grants from Pfizer and GSK for participation at meetings. RM has received grants from GSK for participation at meetings. All other authors declare having no conflicts of interest.

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