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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.

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## 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

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