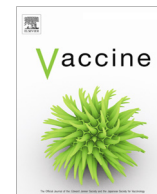




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## Early impact of universal varicella vaccination on childhood varicella and herpes zoster hospitalizations in Brazil <sup>☆</sup>

Marcelo Comerlato Scotta <sup>\*</sup>, Rolando Paternina-de la Ossa, Magali Santos Lumertz, Marcus Herbert Jones, Rita Mattiello, Leonardo Araújo Pinto

Centro Infantil, Department of Pediatrics, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Avenida Ipiranga 6690, 2nd floor, ZIP-Code: 90610-000, Porto Alegre, Rio Grande do Sul State, Brazil

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### ABSTRACT

**Introduction:** The Brazilian childhood National Immunization Program (NIP) introduced live and attenuated varicella vaccination in a single dose, combined as tetraviral vaccine, at 15 months of age in the whole country, during September to December of 2013. The aim of this study was to report trends in incidence of childhood hospital admissions related to varicella and zoster in Brazil from 2003 to 2016, including the first three years after vaccine introduction.

**Methods:** The number and incidence of hospital admission in patients aged less than 20 years in Brazilian public health system with an admission diagnosis of varicella and zoster from 2003 to 2016 were analyzed and pre (2003–2013) and post-vaccination periods (2014–2016) were compared. The data were obtained from DATASUS, a Brazilian government's open-access public health database system, and analyzed adjusting for secular trend and seasonality if a statistically significant change was found.

**Results:** During the study period, 69,791 admissions due to varicella and herpes zoster occurred in the children younger than 20 years. After adjusting for seasonality, the incidence of hospitalizations decreased from 27.33 to 14.33 per 100,000 per year, which corresponds to a reduction of 47.6% (95% confidence interval 18.19–77.04%,  $p < 0.001$ ) in the vaccinated age group (1–4 years) in 2014–2016 compared to pre-vaccination period. The changes were not significant in the unvaccinated age groups.

**Conclusion:** The hospitalizations due to varicella and herpes zoster were decreased by half early after the introduction of a single dose of tetraviral vaccine in NIP in the vaccinated children. Further studies may assess duration and intensity of this effect, as well as the indirect effect in the unvaccinated age groups.

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### 1. Introduction

Primary infection due to varicella-zoster virus (VZV), also known as chickenpox, is very common in children. It is a highly contagious illness, spreading through direct contact and aerosols, with a secondary attack index higher than 70% in unvaccinated

groups [1]. Although it usually manifests as a mild and self-limited disease, complications such as pneumonitis, encephalitis, secondary bacterial infections and deaths can occur [2]. Morbimortality is higher among adults, as well as in immunocompromised patients. During childhood, those aged less than four years have a higher incidence of hospitalizations and death [3]. The incidence of varicella peaks in November in Brazil. The reported estimates show a mortality rate of 0.88/100,000/year in infants younger than 12 months and 0.40/100,000/year in children aged 1–4 years [3,4].

The introduction of live, attenuated vaccination against varicella is a preventive strategy adopted in several countries. The schedules are variable regarding the number of doses (one or two), the combination with other vaccines and age of immunization [5]. The overall effectiveness of single dose varicella vaccine in preventing infection and severe disease is estimated to be 81 and 98%, respectively [6]. In a two doses schedule, the effectiveness against all forms of disease increases to more than 90%, with most

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<sup>\*</sup> Corresponding author.

E-mail addresses: [marcelo.scotta@pucrs.br](mailto:marcelo.scotta@pucrs.br) (M.C. Scotta), [rolapater@gmail.com](mailto:rolapater@gmail.com) (R. Paternina-de la Ossa), [magali.lumertz@pucrs.br](mailto:magali.lumertz@pucrs.br) (M.S. Lumertz), [mhjones@pucrs.br](mailto:mhjones@pucrs.br) (M.H. Jones), [rita.mattiello@pucrs.br](mailto:rita.mattiello@pucrs.br) (R. Mattiello), [leonardo.pinto@pucrs.br](mailto:leonardo.pinto@pucrs.br) (L.A. Pinto).

of the data obtained from high-income countries, as United States of America, Australia, Germany, Italy, Spain and Canada [6–12].

In 2013, a tetraviral combined live and attenuated vaccine including measles, mumps, rubella and varicella (MMRV) was introduced in the Brazilian National Immunization Program (NIP), including all Brazilian states. The introduction occurred from September to December in children in a single dose regimen, at 15 months of age. The first dose of MMR (measles, mumps, and rubella) at one year of age, which was previously part of Brazilian NIP schedule, was also maintained. Both MMR and MMRV are being manufactured in Brazil, at Institute of Technology in Immunobiologicals (Bio-Manguinhos/Fiocruz), after a technology transfer from GlaxoSmithKline (GSK) [3,5]. The estimated coverage of MMRV vaccination according to the Brazilian Ministry of Health from 2014 to 2016 was 60% [13]. Previously, varicella or MMRV vaccines were available only in private health system to a small subset of the Brazilian population and in a few municipalities [14].

The primary aim of this study was to assess the direct and indirect impacts of tetraviral vaccine by comparing the incidence of varicella and herpes zoster admissions in children before (2003–2013) and after (2014–2016) MMRV introduction. The description of deaths and costs due to VZV-related admission during the same period were the secondary aims.

## 2. Materials and methods

This observational study was based on the analysis of data on admissions and deaths due to varicella and herpes zoster. The data were obtained from the Department of Informatics of Brazilian Public Health System (DATASUS) through the Health Information section (<http://www2.datasus.gov.br/DATASUS/index.php?area=0203>, last accessed in September, 10th, 2017). The DATASUS database provides a universal coverage of Brazilian population. Further information about DATASUS is described elsewhere [15]. The absolute numbers of hospitalizations and deaths in public system were obtained according to International Classification of Diseases (ICD), version 10, considering the main diagnosis at admission. Data from period studied are included in DATASUS since 2003. The codes of “varicella and zoster” were used to search the main study outcome (grouped together in DATASUS as ICD B01 and B02) from 2003 to 2016. As VZV infection is not a notifiable disease, data from outpatients were not available [5]. The costs of VZV-related admissions were also obtained from DATASUS. The children aged less than 20 years were included, in order to assess both direct VZV immunization effect and herd immunity. The data obtained from DATASUS were divided into five age groups: children aged less than 12 months, from 12 months to 4 years, from 5 to 9 years, from 10 to 14 year and from 15 to 19 years. The data from age groups are provided as a whole group, without other possible cut-offs of age. Two independent researchers using the same methods collected the data and a third researcher checked the quality.

Monthly and annual incidences of admission per 100,000 children were calculated by dividing the number of hospitalizations by the estimated population of the age groups without health insurance, obtained from the Brazilian Census of 2010 for all studied months and years and multiplying the result by 100,000 [16]. The average cost for both periods was also described. Brazilian National Health Agency provides the percentage of population which has health insurance each year. This percentage rose gradually during the study period from 17.5% in 2003 to 24.7% in 2016 and the same percentage of the population was excluded from the denominator [17].

The relative decrease in admissions was calculated in all age groups from pre- vs. post-vaccination time-periods, as the average yearly admission rate in 2014–2016 minus the average yearly

admission rate in 2003–2013, multiplied by 100. For statistical analysis, averages values were compared through *t* test for independent samples and a decrease was considered if  $p < 0.05$ . If a statistical change was found, the monthly incidences of VZV-related admissions, from 2003 to 2016, were taken into account to adjust for seasonality and secular trend. Thus the time series data included pre-vaccination (2003–2013) and post-vaccination periods (2014–2016). The Dickey–Fuller test was used for the secular-trend analysis, where  $p < 0.05$  indicated that the series are stationary and secular trend is not present. Fischer’s G test was performed to determine the seasonality. Dynamic Linear Model was used to test the association between the predictors (PRIORIX-TETRA® introduction) and outcome (incidence of varicella and herpes zoster admissions). All variables that were statistically significant were included in the multivariate model. For statistical analysis, the cut-off for null hypothesis rejection was less than 5% ( $p < 0.05$ ). All statistical analyses were performed using the R software ([www.r-project.org/](http://www.r-project.org/)). Since DATASUS has no individual data, this study did not require approval by the institutional ethics review board of Pontifícia Universidade Católica do Rio Grande do Sul.

## 3. Results

From 2003 to 2016, a total of 69,791 admissions due to VZV were identified in patients aged less than 20 years. Comparing pre and post-vaccination periods, the incidence of hospitalizations in the vaccinated group (1–4 years) significantly decreased from 27.33 to 14.33 per 100,000 per year, a reduction of 47.60% (95% confidence interval (CI) 18.19–77.04%,  $p < 0.001$ ), as shown in Fig. 1. The changes were not significant in other age groups. The percentage change in admissions was (mean and CI95%) – 26.8 (95% CI 8.47 to –62.1%), –21.4 (95%CI 12.9 to –55.8%), –12.2 (95%CI 20.3 to –44.7%) and +7.4% (95% CI 16.5% to –1.8%) in patients aged less than 1 year, 5 to 9 years, 10 to 14 years and 15 to 19 years, respectively.

In the vaccinated group, seasonality was detected ( $p < 0.001$ ) with the yearly peak of VZV-associated incidence between September and November. A secular trend was not found ( $p < 0.05$ ). The decrease in the incidence of VZV admissions was statistically significant in the vaccinated group, even after adjusting for seasonality ( $p < 0.001$ ).

The direct costs of VZV related admissions decreased 37.91% after vaccine introduction, as shown in Table 1. This corresponds approximately to yearly costs of 300,000 US dollars. The absolute number of deaths related to VZV is shown in Table 2. No statistical analysis was performed due to the low number of deaths.

## 4. Discussion

This is the first study showing an early nationwide impact of a universal single dose of varicella vaccine on VZV-related hospitalizations in a large, middle-income country as Brazil. Although previous evidences about VZV vaccination effectiveness are available, the nationwide data on the impact of universal VZV immunizations on hospitalizations are derived mostly from high-income countries such as USA, Germany, Canada and Australia, with few data from Latin America [7,9,10,12,18,19].

Many countries and parts of some countries have introduced varicella vaccine in their national programs. The vaccine schedules include one or two doses, and the efficacy in decreasing hospitalization is around 80%, as well as decrease in complications [5,20–22]. However, as mentioned above, many studies are regional or cohort and case-controls with few considering the nationwide data of a populous country [7,8,11,18,23–35]. A recent meta-analysis

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