



## Impact of varicella vaccination in Argentina: Seroprevalence in children and adults in a pediatric hospital



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### ABSTRACT

**Background:** Varicella is the primary infection caused by varicella-zoster virus (VZV). In Argentina, the varicella vaccine was introduced in the National Immunization Programme in 2015 as a single dose scheduled at 15 months of age.

**Objectives:** To estimate VZV seroprevalence in a healthy hospital based population before and after vaccine introduction to the NIP.

**Material y Methods:** Cross-sectional, observational, analytic study. Healthy subjects 1–40 years of age were included between June and December 2019 and tested for VZV-antibodies. Results were compared to data from a similar prevaccination study.

**Results:** Out of 599 samples, 11 indeterminate results were excluded, 424 were positive; overall seroprevalence rate was 72.1% (95 %CI = 68,3–75,8%). No differences were observed between pre and post vaccination studies for overall prevalence or between age groups, except for vaccinated children aged 11–15 (p = 0,005). Rates increased in both periods in subjects aged 6 years or older. Primary vaccine failures were 21%; in subjects <5 years 83% seropositive cases had been vaccinated, in >5 year-olds >90% seropositive cases were associated with a history of infection (OR: 10,4; IC95%: 6,4–16,8; p < 0,001) or household contact (OR:4,8; IC95%: 3,1–7,6; p < 0,001). Vaccination protected against disease (OR: 0.25; 95 %CI: 0.09–0.68; p = 0.004).

**Conclusion:** seroprevalence was high in all age groups except in unvaccinated 12 to 15-month infants. Seropositivity was due to vaccination in 15 months to 5 year-old children and to infection in older children.

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### Introduction

Varicella is an acute, self-limited infection caused by varicella zoster virus (VZV) [1]. The disease is globally distributed with seasonal fluctuations in temperate climate countries such as Argentina, peak incidence occurring in spring with outbreaks every 2–5 years [2]. Before vaccination, over 90% of cases occurred in young or school-aged children and severe cases were seen in immunocompromised patients, adolescents and adults [3].

A live attenuated Oka-strain vaccine has been available for over 40 years and was progressively introduced into National Immunization Programmes (NIPs) in different countries to reduce vari-

cella morbidity and mortality and provide indirect protection to unvaccinated population [4].

WHO recommended introducing the vaccine into NIPs in 1998. Argentina incorporated the vaccine in 2015, free of charge, in children aged 15 months [5].

Few studies have been published to date regarding the impact of vaccination in Latin American countries. We think it is important to generate local epidemiological models that will allow us to measure the impact of this intervention; seroprevalence studies are useful tools to assess the situation.

### Objectives

To estimate the seroprevalence of VZV in a healthy hospital based population. To compare the global prevalence and by age group of VZV IgG antibodies before and after the introduction of

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varicella vaccine in the NIP. To describe the causes of positivity in both time periods and determine the factors associated with seropositive results.

## Materials y methods

### Study design

A cross-sectional, observational and analytic study.

### Population

Healthy individuals aged 12 months to 40 years attending the Ricardo Gutiérrez Children's Hospital between June to December 2019.

Subjects included comprised children aged over 12 months old attending the outpatient laboratory for blood assays, and adults donating blood at the hemotherapy service, assisting for control parasitology tests and parents or guardians of outpatients and inpatients. Only one person was selected per family group or household.

Sample size for this study was estimated to be 590 based on expected seroprevalence rates stratified by age calculated from data obtained by Gentile et al. in a seroprevalence study carried out in 1996 [6].

### Data collection

Participants aged 18 years or older and parents or tutors of children 12 months to 18 years old were invited to participate and asked to sign the informed consent form. Participants completed a survey reporting demographic data. Blood samples drawn were kept at room temperature until centrifuged at 2500 rpm for 10 min after which 3–5 ml of serum was separated into two separate sterile tubes and stored at  $-20^{\circ}\text{C}$ . Serologic testing for VZV IgG antibodies was performed using the fluorescent-antibody-to-membrane-antigen (FAMA) test, and titers  $\geq 1:4$  considered positive [7]. With regard to this study, standardized imprints containing the viral antigen of VZV, from the MBL BION brand, were used.

### Statistical analysis

Median, interquartile range and rates and 95% confidence intervals (95 %CI) were estimated for categorical variables. Seroprevalence was calculated overall and for 9 age categories: 12–14 months, 15–23 months, 2–5 years, 6–11, 12–15, 16–20, 21–25, 26–30 and 31–40 years. The first two age groups were selected based on the varicella vaccine recommendation of administration at 15 months.

We compared results to those of a similar study by Gentile et al. performed in 1996 before varicella vaccine introduction to the NIP [6].

Qualitative variables were analysed using Chi-square test with Yates correction. The odds ratio (OR) with a 95% confidence interval (CI) was used as measure of association and  $p$  value  $< 0.05$  was considered statistically significant.

Statistical analysis was carried out using Epi Info version 7 (CDC, Atlanta).

### Ethical considerations

The study was approved by the Ethics Review Committee at the Ricardo Gutiérrez Children's Hospital and was done according to Good Clinical Practice guidelines.

## Results

In total, 599 participants were included in the study and blood samples were collected. Eleven serum specimens had indeterminate results and were excluded. Of the remaining 588 samples, 424 tested positive for VZV IgG antibodies, resulting in a global seroprevalence of 72.1%.

Of 186 children aged 15 months to 5 years eligible for varicella vaccine according to the NIP, only 126 (67.7%) had received the vaccine, 27 of these (21.4%) tested negative.

### Seropositive rates before and after the introduction of the vaccine to the NIP by age group

Overall seroprevalence was similar in both periods, namely prevaccination (PreV) 72.4% (95 %CI = 68.4–77%) and postvaccination (PostV) 72.1% (95 %CI = 68.3–75.8%,  $p = 0.85$ ), with the exception of the 11 to 15-year-old age group in which rates were significantly different ( $p = 0.005$ ). Seroprevalence rates for different age groups increased from age 6 onwards during both periods (Fig. 1).

In the PreV period, seropositivity corresponded solely to infection by wild type varicella virus. In the PostV period, seropositivity in children under the age of 5 was 83%, due mainly to vaccination, and 90% in subjects  $> 5$  due mainly to infection. (Fig. 2).

### Analysis of positivity rates in children 1–5 years according to age at vaccination and sources of seropositivity

Infants 12–15 months of age showed 12.2% seropositivity rate (secondary to infection in all cases) which increased to 53.6% in infants 15–23 months (92% due to vaccination) and 69.7% in children 2–5 years of age (82.3% due to vaccination). Table 1

Of 126 children aged 15 months to 5 years who received one dose of varicella vaccine, 27 (21.4%) showed no detectable VZV antibodies. Primary vaccine failure was similar in 15–23 months and 2–5 years' age groups. Fig. 3.

### Univariate analysis of factors associated with seropositive rates

Positive VZV IgG result was associated with a history of varicella infection (OR: 10.4; 95% CI: 6.4–16.8;  $P < 0.001$ ) and household contact of a varicella case (OR:4.8; 95% CI: 3.1–7.6);  $p < 0.001$ ). Vaccination protected against disease in children under 5 year-olds (OR: 0.25; CI 95%: 0.09–0.68;  $p = 0.004$ ).

## Discussion

Universal vaccination programmes are prevention strategies that have dramatically reduced morbidity and mortality due to severe infectious diseases averting millions of complications and deaths worldwide [8]. In Argentina, the Ministry of Health introduced the varicella vaccine to the NIP in 2015, in a single dose schedule at 15 months of age. Vaccine coverage rates have increased from 44.7% since the beginning of the prevention strategy to 77.7% in 2019 [9]. Several countries have incorporated routine immunization in different schedules. In 2015, only 9 countries in Latin America and the Caribbean region had included varicella vaccine to their NIP: Brazil, Costa Rica (since 2007), Ecuador, Panama, Paraguay, Puerto Rico, Argentina, Colombia and Uruguay. Of these, Uruguay (since 2015), Panama, Puerto Rico (since 1997) and Colombia use a 2 dose schedule (at 1 and 5 years) [10]. Currently, in the America's region the number of countries has increased to 20 (Argentina, Antigua and Barbuda, Brazil, Chile, Peru, Colombia, Ecuador, Bahamas, Santa Lucia, Barbados, Guyana,

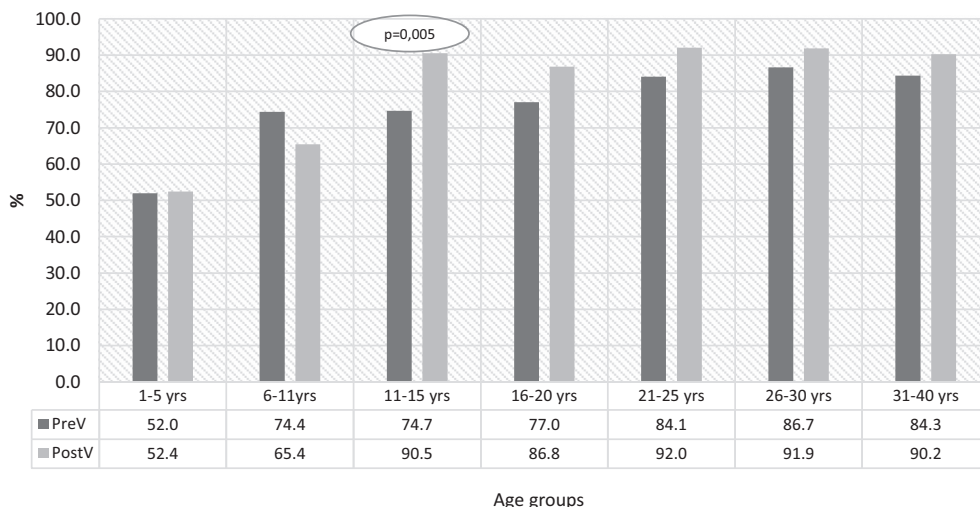


Fig. 1. Seroprevalence by age group comparing pre and post vaccination periods. PreV: prevaccination period. PostV: postvaccination period.

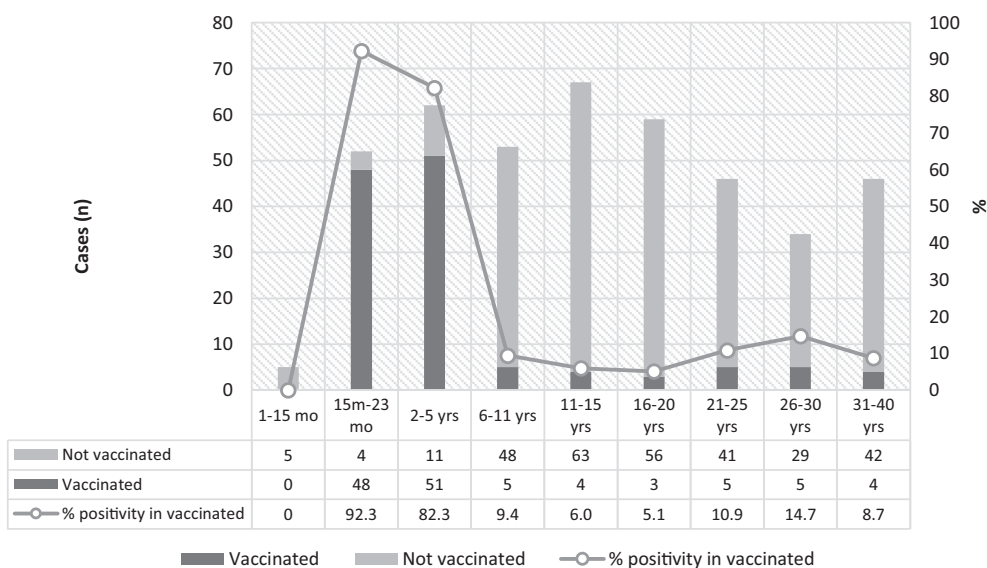


Fig. 2. Positive seroprevalence: sources and percentage of vaccine-positives cases in the PostV period.

Table 1 Seroprevalence according to age in children <5 years.

Seroprevalence	12–15 months	%	15–23 months	%	2–5 years	%
Positive	5	12,2	52	53,6	62	69,7
Negative	36	87,8	45	46,4	27	30,3
Total	41	100,0	97	100,0	89	100,0

Costa Rica, Granada, Canada, United States, Trinidad and Tobago, Mexico, Panama, Paraguay and Uruguay) [11].

Four years after the introduction of the vaccine in Argentina, we observed high seroprevalence rate (72.1%) in all age groups, except in infants 12–15 months old who had not yet been vaccinated or contracted the infection. In children 15 months to 6 years of age, seropositivity was related to vaccination, while in older children and adults to history of disease. A prior multicentre study carried out by Gentile et al. in 1996 before vaccine introduction, showed an overall seroprevalence of 72.4% [6].

In Spain, 2 years after the vaccine was introduced as a single dose at 15 months of age, estimated seroprevalence reached

95.3% in individuals 2–60 years of age, and over 90% of children > 10 years had detectable antibodies [12]. Seroprevalence rates exceeded 90% in the first study year decreasing to 82.6% the following year. Antibodies elicited by vaccination have shorter duration than natural infection antibodies as shown by Duncan et al [13].

In our study, 21.4% (27/126) of children aged 15 months to 5 years who had received one dose of varicella vaccine were seronegative. Efficacy of a single dose against all cases of varicella is 82% in the literature and 100% against severe cases, while two doses provide 92% protection (88–98%) against all forms of disease [14–16].

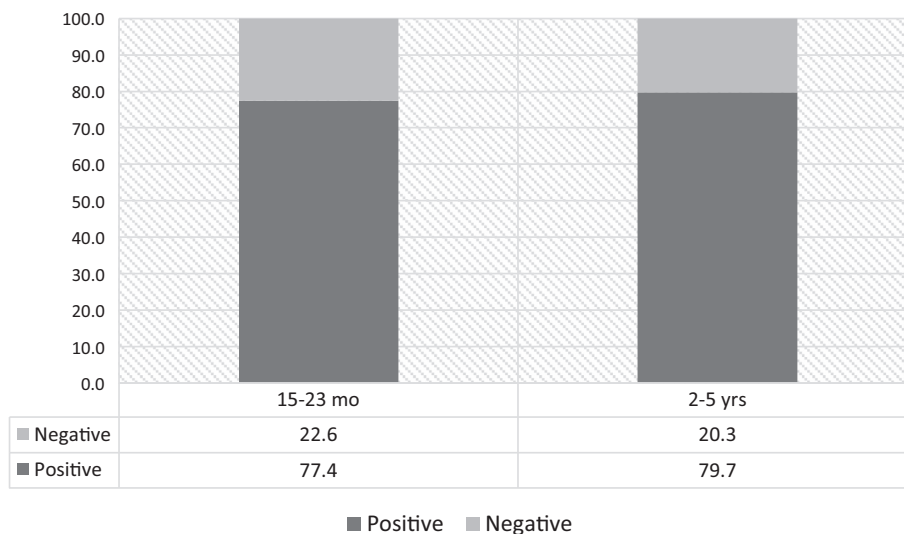


Fig. 3. Seroprevalence in vaccinated children aged 15 months to 5 years.

As a weakness, it is worth mentioning that the comparison between pre- and post-vaccination periods has been made based on data from a study carried out in 1996. To minimize selection bias we followed the same criteria selection in both studies as well both populations have similar characteristics except the exposure (vaccine introduction to NIP). In spite of this, results are not representative of the national epidemiology but shows the impact of vaccination on a hospital based population.

In Argentina, a study carried out by Marco del Pont et al in 2005 showed an overall efficacy of 82.7%, with 47.6% of varicella cases occurring in young children 1–2 years of age [17]. Vaccination prevented severe cases as 95.2% of cases were mild.

In another seroprevalence study conducted in Beijing, children aged 1–9 years receiving a single dose of varicella vaccine presented an overall seropositive rate of 61.8% (102/165), rates according to age categories were as follows: 61.5% (32/52) in 1 to 3-year-olds, 58.5% (38/65) in 4 to 6-year-olds and 66.7% (32/48) in 7 to 9-year-olds [18]. Seropositivity declined as the time between vaccination and blood testing increased, and 36% (216/603) of children with one dose remained seronegative.

In relation to the 21.4% primary vaccine failure we observed, it is important to point out that a FAMA test was used to measure VZV antibodies and may have been less sensitive than ELISA assay. Michalik et al. studied 148 healthy vaccinated children, 113 samples (76%) screened positive for VZV antibodies using FAMA test and showed lower results than the 86% to 96% seroconversion rates reported for other assays suggesting cases of varicella in immunized children are due probably to primary vaccine failure [19]. Assuming this relatively high rate of primary vaccine failure, a second dose would be useful to further reduce the burden of this disease. Different VZV vaccine schedules are currently recommended, however there is an increasing amount of evidence supporting use of two doses. Both Baxter et al. and Sheridan et al have reported that although one dose protects against severe varicella, two doses are needed to gain herd immunity and disease control [20,21].

In a review of 17 studies on vaccine effectiveness in the US, Seward et al found that one dose was 84.5% (range 44–100%) effective in preventing all cases and 100% in preventing severe varicella suggesting that although one dose provides excellent protection, two doses are needed to interrupt transmission and prevent outbreaks in high contact settings [22].

In addition, WHO has made clear recommendations regarding varicella vaccine policies: one dose is sufficient for reducing mor-

bidity and mortality, two doses are more effective and are recommended to reduce the number and size of outbreaks and limit virus circulation [2,23].

We found that factors associated with seropositivity were history of infection with wild type VZV or household contact with varicella case. Clinical manifestations of varicella are characteristic facilitating diagnosis. Higher seroprevalence rates were observed in subjects with a household contact than in those without. History of disease has a high positive predictive value to determine susceptibility and is therefore very useful in clinical practice [6,24]. Negative predictive value however is low, particularly in the elderly, since a significant number of adults do not remember having had varicella.

### Conclusion

VZV seroprevalence was high in all age groups except in infants 12–15 months of age who are below the age approved for vaccination in the Argentine NIP. Seropositivity in children aged 15 months to 5 years was mainly secondary to vaccination, whereas in children older than 5 years positive IgG VZV antibodies were associated with prior history of disease. In the future, seropositive rates secondary to vaccination will spread to older age groups as vaccinated cohorts increase.

Follow-up studies should be carried out to determine the duration of antibodies and the need of a second vaccine dose.

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### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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