

Measurement in the Generated Impact by One Dose of Varicella Vaccine in Paraguay

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Abstract

Introduction: In the group of infectious exanthematic diseases of childhood we find the presence of Varicella or Chickenpox, which can be prevented by vaccination in its most serious forms that generate complications and hospital admissions. This pathology has a worldwide distribution [1,2] seasonal trend, predominated in winter and spring. It is a predominantly childhood infection, 90% of cases occur before 9 and 13 years of age [1,2].

The vaccine that prevents it began to be recommended in Paraguay (PRY) in February 2013 at the age of 15 months. Being used the MAV chicken pox, which entered the country with high safety standards by the PAHO Revolving Fund.

Objective: Measure the impact of vaccination in Paraguay, analyzing a period of 8 years (2009 - 2017).

Materials and Methods: Descriptive and analytical study of cases and hospital admissions for Varicella reported to the national system, before (2009 - 2012) and after (2014 - 2017) of the introduction of the vaccine, adding active surveillance data reported in the period 2016 - 2018.

Results: They were found seasonal circulation of the virus in the two periods analyzed (pre- and post-vaccine) [epidemiological week (EW) incidence peaks 36 to 42], although a smoothing of cases in the post-vaccine was confirmed, the behavior It was bi-annual cyclic. There was a 38% -50% decrease in the total incidence of varicella during the post-vaccination period, in relation to the 2009 - 2012 period (OR: 0.03 [95% CI: 0.01 - 0.04]) ($p < 0.05$). A higher incidence of cases in children aged 1 - 5 years in the pre-vaccination period, as well as a displacement of cases at unvaccinated ages against the heterogeneity of coverage achieved (vaccination coverage oscillation: 62% - 86%) and its consequent greater involvement of children with aged over 6 years in the post vaccine period (2014 - 2017). Hospitalized cases decreased at all ages in the post-vaccination period, being the same 97% (OR: 0.06 [95% CI: 0.03 - 0.14]) ($p < 0.05$) in the cohort of vaccinated. There were self-limited cases of varicella (less than 50 vesicles) vaccinated children (3%), none required hospitalization.

Conclusion: One dose of vaccine at 15 months of age generated a significant decrease in incidence and hospital discharges for varicella, as well as in mortality from the same cause in all age groups and more importantly in the cohort of vaccinated, demonstrating the efficacy (direct effect) and effectiveness of the vaccine, by recording the ability to produce herd immunity. The heterogeneous oscillation of vaccine coverage against varicella generated a displacement of affectation rates at unvaccinated ages, the need to maintain homogeneous and ideal coverages being indisputable, as well as the assessment of adding a second dose of the vaccine in the national vaccination scheme to achieve the cutting of the virus circulation.

Keywords: Varicella; Chickenpox; Efficacy; Effectiveness; Vaccination Coverage; Immunization; Vaccinated Cohort

Introduction

Varicella (chickenpox), is a feverish and eruptive disease caused by the Varicella Zoster Virus. Highly contagious infection spread by air-borne transmission or contact with vesicle fluid from skin lesions, with secondary attack rates, even higher than 90% [3]. Varicella is often more severe in immunocompromised [4].

The reports confirm annual incidence rates of 300 - 1291 per 100,000 inhabitants in Europe [5]; and between 500 to 700 per 100,000 in the pre-vaccine era [6,7], in Latin America. During 2014, the World Health Organization (WHO) estimated an approximate annual 4.2 million hospitalizations due to serious complications and 4200 deaths due to the disease, generating an even greater impact on public health at only the incidence rate or its complications [8].

In Paraguay, the vaccine that prevents this disease was recommended by the National Immunization Committee (NIC) in February 2013, following one-dose varicella vaccine has been recommended for all children aged 15 months, concomitant with one-dose hepatitis A vaccine.

In the compliance of the National Vaccines Law No 4621, Paraguay acquires exclusively vaccines and supplies related to vaccination through the Revolving Fund (FR) of the Pan American Health Organization (PAHO), ensuring the country, a transparent mechanism of purchases through economy of scale, as well as, the efficacy, effectiveness and certified safety of the same, taking into account the high and strict standards of measurement and quality control managed by the FR and finally, avoiding the conflict of interests with vaccine producing laboratories. In faithful compliance with the above, the varicella vaccine (live attenuated viruses) with MAV strain of the GCC® laboratory (Green Cross Corporation- Korea), was entered into the national scheme in 2013 [9], being the same continuously administered throughout the country until the current date.

Published data [10,11], questioned the efficacy of the vaccine containing live attenuated viruses based on the MAV strain, in contra position other paper published [12]. All this, activated our alert, therefore it is the objective the present study, analyze the period 2009 to 2017, for evaluating the behavior of the varicella disease in the Paraguayan population, measuring the impact generated by vaccination.

Materials and Methods

We performed a matched observational and descriptive study of varicella, notified to the National System (Mandatory Notifiable Disease data weekly count by payroll CIE10 B01 2009 to 2017), hospitalizations and deaths due to the same cause. In addition, the active surveillance data carried out from Epidemiology Week (WE) 41/2016 to (WE) 8/2018 were added).

Any person with an acute (sudden onset) febrile (moderate fever) and eruptive disease with the appearance of superficial papules turned into vesicles that starts on the face, scalp or trunk, accompanied by pruritus, was included by case definition [13]. And, if the disease was presented in vaccinated person, it was included if the disease started after 42 days' post vaccination. This because, by definition, these cases occur more than 42 days after vaccination, are usually caused by wild type virus. Rashes occurring less than 14 days after vaccination are typically due to previously incubating wild-type disease [14-18] and rashes occurring 14 to 42 days after vaccination may be attributable to either strain and can be classified only by molecular typing [19,20].

The annual incidence rates per 100 thousand inhabitants were measured, taking the official reference population, published by the General Direction of Survey and Census Statistics (DGEEC) and the Ministry of Health. The rates of hospitalization, complications and mortality were analyzed, as well as the behavior of the disease according to the cohort of vaccinates. The comparison and analysis were established by contrasting two moments [pre-vaccine (years 2009 to 2012) and post-vaccine (years 2014 to SE 8 2018)]; the year 2013 was not assessed because it was the year of inclusion of the varicella vaccine in Paraguay. The impact of vaccination on the age groups under this preventive measure (individual effect of vaccination), as well as the indirect impact on age ranges not subject to such measure,

was evaluated. Variables such as epidemiological notification week, age, gender, hospitalization, complications, mortality and in the post-vaccination period, the vaccination status against varicella and the time elapsed between administration of the vaccine and the appearance of the disease were analyzed. The periods mentioned were compared by means of the incidences ratio (OR), with a 95% confidence level. All P values was analyzed, being statistically significant level of $p < 0.05$. Data were analyzed with SPSS version 25, adhering the χ^2 test for statistical comparisons.

Results

Data were analyzed between WE 1/2009 to WE 8 /2018 and the presence of varicella cases, was verified during the 52 WE annually, with increases, from WE 26 and peaks between WE 36 to 46, then gradually descending. This seasonality was maintained in both periods analyzed (pre and post-vaccine), differentiating, in the smoothing of cases in the second stage (post-vaccine 2014 to 2018). An apparent pattern of biannual cyclic behavior of the virus in national territory was also verified (See figure 1).

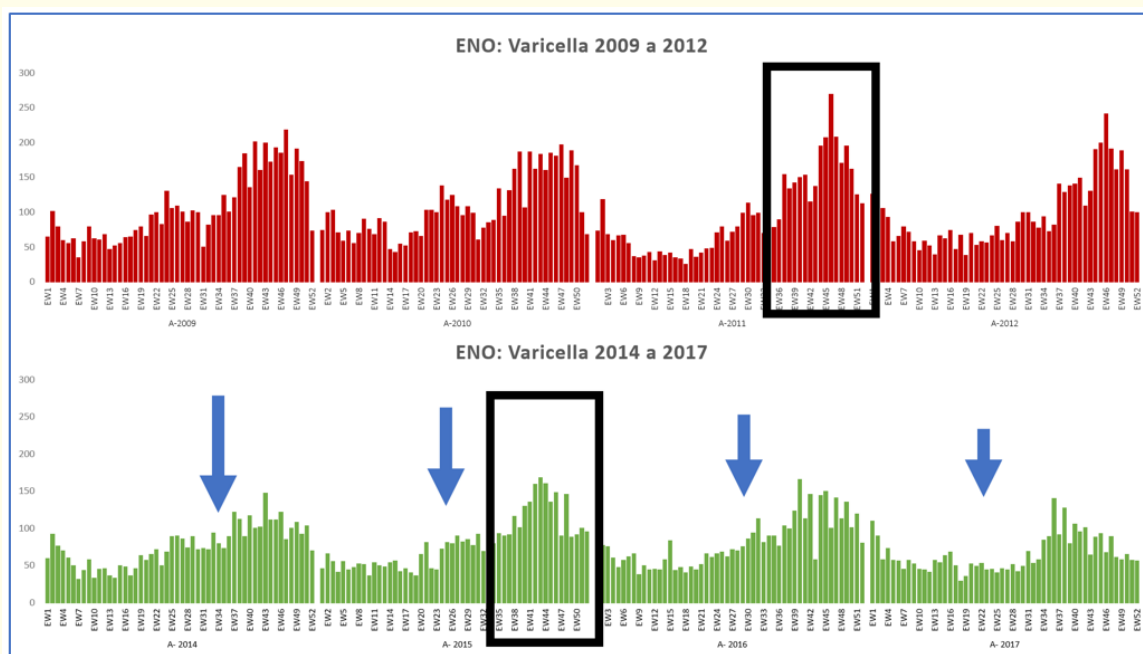


Figure 1: Reported cases of varicella (chickenpox) pre-vaccine period 2009 to 2012 compared to cases reported in post-vaccine period 2014 to 2017.

Observation: The figure shows varicella cases with the annual distribution by epidemiological week (EW). Note the reduction of chickenpox cases in the post-vaccination period, seasonality and biannual peaks of cases.

Analyzing the post-vaccination period (Table 1), a decrease in disease incidence rates was observed in the general population, ranging from 38% - 50%. However, when performing this same analysis in the cohort of children who should be vaccinated (population 1 to 5 years old), the decrease in cases was greater, reaching levels of 85%, being statistically significant, being corroborated by the incidence rate the vaccination protective factor $OR = 0.03$ (95% CI 0 to 0.03) in the same period of time, where vaccination coverage averaged 74% (range 62% - 86%)

Biannual	Varicella cases	total	Average population	inc. rate/100.00	Reduction	Vaccinated	Invaccinated	% vaccinated	OR	IC 95%
2009 - 2010	10941	20950	6213317	176,0895187	38 a 50% in general poblacion	8329	268247	3	0,01	(0,00 - 0,04)
2011 - 2012	10017		6412459	156,2115251		8919	269089	3	0,01	(0,00 - 0,03)
2014 a 2015	7016		6706494	104,6150194		190852	82511	71	0,03	(0,02 - 0,03)
2016 a 2017	6015		6904091	87,12225838		217363	62666	78	0,00002	0

Table1: Incidence rates for varicella in the general population and its comparison according to vaccinated population: pre vaccine period (2009 to 2012) and pos vaccine period (2014 to 2017).

Observation: note the reduction of up to 50% in incidence rates of varicella in the general population, associated with the important protective factor of vaccination in the post-vaccine period (OR < 1).

It was verified that vaccination coverage did not reach 95% in any of the vaccinated cohorts, this value being as high as 86% and as low as 62%. An important verifiable fact was that as vaccination coverage increased, the number of cases of the disease decreased, this situation being reversed with the decrease in vaccine coverage (Figure 2). There were no significant differences in affectation, when comparing gender, the ratio F/M: 1/1 and although the highest concentration of cases of the disease occurred in children under 10 years in both periods of time, an important increase of cases was confirmed in children over 5 years (45% a 61%) in the post-vaccination period, generating a displacement of those affected to unvaccinated cohorts, this finding being statistically significant (Table 2).

Aged Group	% Varicella Cases Distribution				Hospital Expenses Vari-cella		OR		
	A: 20958	%Distribution	B: 13031	% Distribution	2009 - 2012	2014 - 2017	A-B	IC 95%	P value
0	2300	10,97432961	1469	11,27311795	69	77	1,8	(1,30 - 2,49)	p > 0,05
1 - 4	6987	33,33810478	2998	23,00667639	160	6	0,06	(0,03 - 0,14)	p < 0,05
5 - 9	3809	18,17444413	3800	29,16123091	56	25	0,72	(0,45 - 1,15)	p > 0,05
10 - 14	2514	11,99541941	2118	16,25354923	22	7	0,51	0,22 - 1,20	p > 0,05
15 - 19	1914	9,132550816	1141	8,756043281	15	10	1,07	(0,48 - 2,39)	p > 0,05
20 - 24	1134	5,410821643	544	4,174660425	12	4	0,54	(0,17 - 1,66)	p > 0,05
25 - 29	839	4,003244584	361	2,770316937	1	5	8,04	(0,94 - 68,86)	p > 0,05
30 and more	1461	6,971085027	600	4,604404881	27	13	0,77	(0,40 - 1,5)	p > 0,05
Total	20958	100	13031	100	362	147	0,65	(0,54 - 0,79)	p < 0,05

REF A: Pre Vaccine Period 2009 a 2012; B: Post Vaccine Period 2014 - 2017

Table 2: Varicella cases distribution and hospital expenses pre and post vaccine introduction in Paraguay.

Observation: Note the increase cases unvaccinated population (cases displacement) and very important decrease expenses for varicella in vaccinated cohort. Data: Department bio statistical - DIGIES- MSP y BS.

It was also verified that in a total of 59 vaccinated children whose average age was 29 months, presented a moderate varicella disease (cases self-limited with less than 50 vesicles on the skin). All of them had received a dose of varicella vaccine, the average time elapsed being about 19 months (limit 6 to 36 months). All evolved favorably and none were hospitalized or complications occurred. In addition, opportunities lost to vaccinate were confirmed in the 17 health regions and country capital. A large number were not vaccinated (between 26 - 40%), corroborating fluctuations in vaccination coverage according to departmental constituent districts and within these for each micro territory. At the same time an insignificant percentage of cases occurred in children between 12 to 14 months of age, who despite having resorted to health centers before, did not receive the vaccine because it should be applied at 15 months of age according to the technical an administrative guideline in the varicella vaccine.

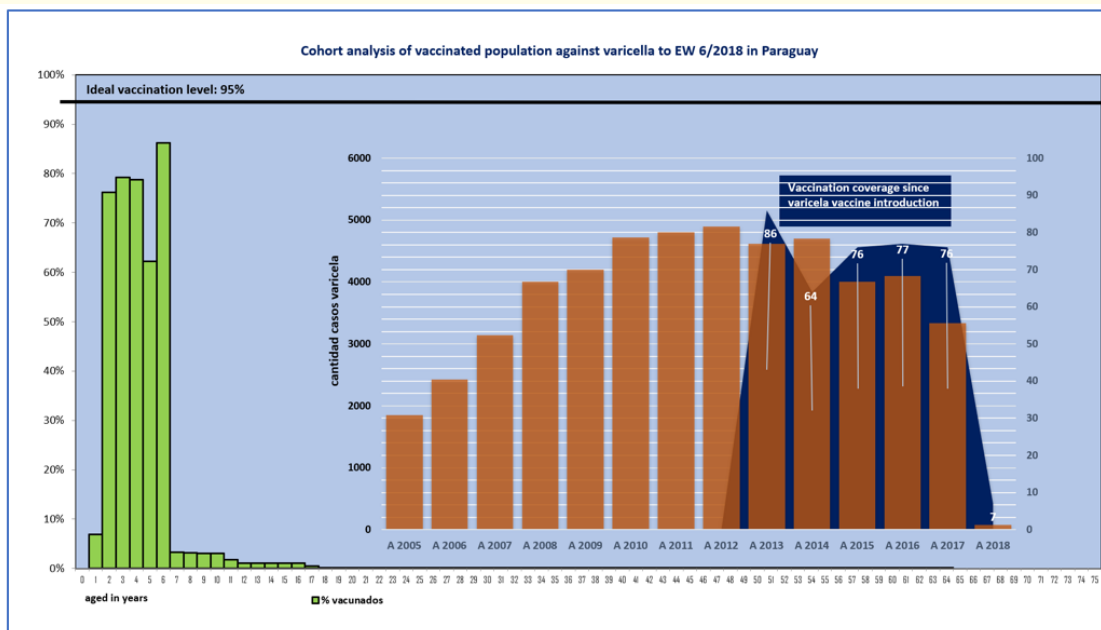


Figure 2: Cohort analysis of vaccinated population against varicella in Paraguay, since vaccine introduction in national scheme of immunization.

Observation: The figure shows cohort of vaccinated against varicella. Note that coverage vaccination and dynamics cases notified. At the same time, heterogeneous oscillating vaccination coverage, non-ideal levels $\geq 95\%$, in any age group.

In relation to hospitalization rates, in the pre vaccine period, national data indicate that 64% of hospitalized children were under 6 years of age, with hospital admissions due to complications of the disease of up to 15% of the total affected, associated with a 10% mortality rate. The analysis of hospitalization rates in the post-vaccination period, showed a decrease of 80%, in the general population from 0 to 15 years, being this decrease of 97% in children from 1 to 5 years (cohort of children who should be vaccinated) (Table 2 and Figure 3). However, after analyzing the data of active surveillance from 2016 to WE8 2018, only not vaccinated children were hospitalized for varicella or its complications and the mortality rate was less than 1%, in the unvaccinated population.

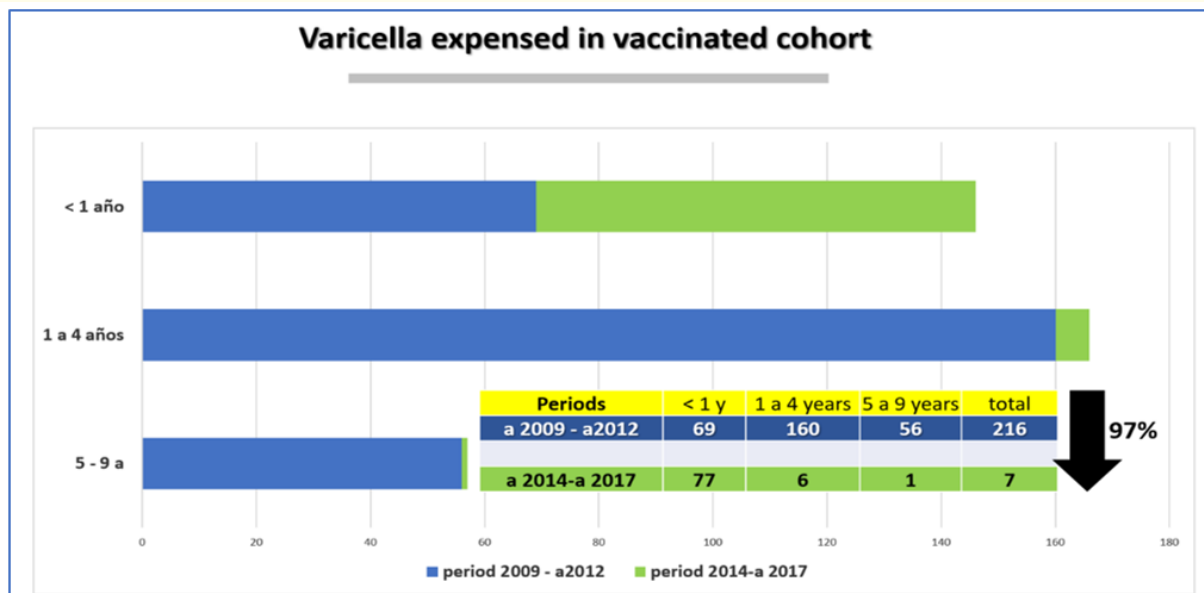


Figure 3: Varicella cases expensed in the post vaccine period. Surveillance active data comparison.

Discussion

From the inclusion of a dose of varicella vaccine MAV strain in the national immunization program (NIP), a decrease in incidence rates of this disease was verified in Paraguay. The impact on the cohort vaccinated being greater (children of 1 to 5 years to WE 8/2018). The finding of lower incidence rates in the general population demonstrates the ability of the vaccine to generate herd immunity [21-23], since the target population of vaccination in Paraguay are 15-month-old children. Our findings replicate data reported in the literature and the experiences published by several countries [24], since the effectiveness of a dose of varicella vaccine was moderate and highly effective (80% and 97%), according to the index of severity of the disease prevented and the measurement of this impact in the vaccinated cohort. However, although the results of the present study replicate the same results from several European and Latin countries, it is highlighted the fact that these bibliographic experiences were reported with a dose of the OKA strain vaccine [24] and in our country, the vaccine continuously applied from February 2013 to date, is the vaccine that contains MAV strain, at no time changed.

Although there was a decrease in rates of disease involvement at the national level after vaccination, the fact of maintaining the seasonality of the virus, which, although softened by decreasing cases in the post-vaccine period (years 2014 to 2017), clearly demonstrates that a dose of varicella vaccine failed to cut the viral circulation, observing annual outbreaks. At the same time, its bi-annual cyclic behavior was confirmed. However, it is important to note that the vaccination coverage achieved against varicella, was not ideal ($\geq 95\%$) and despite achieving levels above 85%, these were not sustainable, reaching sub optimal coverage even 62%, same which oscillated heterogeneously in measurements for each micro territory nationwide. If we remember that, the cut of the seasonal pattern is described in immunopreventable diseases to the extent that vaccination coverage increases and is maintained in a homogeneous manner over time [13,25], this is a fact of consideration.

The decrease in hospitalization rates at all ages, as well as the mortality rates due to the disease, added the statistically significant demonstration of the protective value of the vaccine in the vaccinated cohort, demonstrates the efficacy of a dose of the MAV strain vaccine used, however, the shift in the number of cases to unvaccinated populations denotes poor coverage of vaccines to achieve a cut in the viral circulation, hailing the presentation of serious cases in older ages [13].

The presence of self-limited cases of varicella in the vaccinated population, as well as the absence of complications and hospitalizations in this group, translates the published effectiveness data of the varicella vaccine, being highly effective in preventing serious cases of the disease and with an effectiveness minor to avoid infection by the virus [26]. The increase in vaccination coverage sustainably is a non-negotiable premise, more experience shows, even in developed countries that for many years used a single dose of the vaccine [27-30] that a scheme that includes two doses of the vaccine against varicella, will ensure the strategy of elimination of the circulation of the virus, which would be achieving that the vaccinated population does not present cases and at the same time it could be achieving a decrease in the incidence of herpes Zoster in the adult population major [31], that although we know the determinant of this reactivation of the virus is the low immunocellular, the decrease in the presentation of herpes zoster in vaccinated people, would guide us to that the exposure to the virus plays an important role in it.

Recent reports [10,11] showed the lack of efficacy of the MAV vaccine against varicella, with sub-seroconversion levels being optimal in the vaccinated population or, the decline in antibody title after even the year of administration of the vaccine, denoting levels deficient seroprotection (even from scratch) (refract). These publications alerted our attention because on a continuous basis from February 2013 to the current date, in Paraguay we use the vaccine varicella MAV strain of GCC[®], acquired through the purchase mechanism required by the National Vaccine Law 4621: which is the Revolving Fund (RF) of the PAHO, where our country, apart from ensuring a transparent purchasing mechanism of economy of scale, avoids the conflict of interest with the producing laboratories, also ensures effectiveness; effectiveness and safety of the vaccines entered into the national calendar due to the control mechanisms and the high standards used by this RF regarding their quality control. Although these publications speak of serious limitations in their studies, such as the small population

number compared, the lack of precision regarding the concomitance or not that the population analyzed, has received other live attenuated vaccines or that have not clinically reviewed the patient with varicella, data were obtained through phone calls to family members for example, we also consulted those responsible for publications, if in Korea they continue to use the MAV strain, the answer was yes. And, in response to our question about what could have been the influence to reach this finding, they explained that they did not have a certain answer but perhaps the sustainability of the cold chain could have been involved in the loss of efficacy of the vaccine, since they had not ensured the maintenance of the cold chain of the lots of vaccines involved, as they stated [32]. We also raise the consultation to PAHO, an agency that ratified in writing the quality, safety, effectiveness and efficacy of the varicella vaccine acquired for the country [33].

Conclusion

We have verified that one dose of the varicella vaccine MAV strain, applied to children 15 months of age has generated a significant decrease in rates of incidence, complications and deaths for varicella in Paraguay, which argues the effectiveness (direct effect of the vaccine) and its effectiveness due to herd immunity. It is elementary that, vaccination coverage be high, optimal and homogeneous throughout the national territory and that ultimately a second dose administered as reinforcement to all children before school entry, would grant that added value for the realization of the strategy of the virus circulation cut, situation that the country must analyze since the sustainability of vaccination schemes are irrefutable. Likewise, active varicella surveillance should be strengthened just as Herpes Zoster surveillance should be activated, thus completing the safety of an intervention with a great impact on Paraguayan public health.

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