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Impact of single-dose varicella vaccination in Argentina, by province: a time series study

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ABSTRACT

Introduction. Argentina implemented the varicella vaccine in 2015. This study aimed to evaluate the impact of vaccine implementation in each province of Argentina.

Materials and methods. An observational, ecological analytic study using secondary data sources. We performed a time series description of varicella cases and built generalized additive models using a negative binomial distribution. We modeled the behavior of varicella in the period 2005-2014 and made a forecast of the most likely behavior until 2019. We assessed the impact by comparing expected and observed incidence rates. We studied whether 2015 was a turning point in the incidence trend in each jurisdiction. We used R and Joinpoint software.

Results. Between 2005 and 2019, Argentina had an incidence rate of varicella of 5.93 cases/100,000 population. At the national level, the incidence rate significantly decreased after 2015. In Argentina in general and in 6 provinces, 2015 was a breakpoint, whereas in the rest of the provinces, it occurred before (n = 2) or after (n = 1), or there was none in the time series analyzed (n = 15).

Conclusions. The work demonstrates the impact of vaccine implementation in each of Argentina's provinces and highlights the importance of evaluating national policies at the provincial level.

Keywords: *varicella; time series studies; varicella vaccine; public policy; epidemiology.*

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INTRODUCTION

Varicella-zoster virus (VZV) is a human herpesvirus whose primary infection causes chickenpox, during which the virus becomes latent in ganglion neurons. As cell-mediated immunity to VZV declines with age or in immunocompromised individuals, VZV reactivates and causes herpes zoster.[1-3] VZV is airborne, highly transmissible, and distributed worldwide. According to World Health Organization (WHO) estimates, it causes 4 200 000 serious complications requiring hospitalization and 4200 deaths per year worldwide. According to a systematic review, the single-dose vaccine had a mean efficacy of 83% (range 20-100%) in children aged 9 months to 12 years, 95% to prevent moderate to moderate or severe disease, and 100% to prevent severe disease.[4] The vaccine was beneficial in susceptible healthy adults, although it is less immunogenic than in children, requiring two doses to achieve gp-ELISA ≥90% of antibodies within a few years of the vaccination.[5]

In Argentina, as in temperate countries, all young adult individuals have been infected, and the highest incidence is observed in children under 14. It also shows a characteristic seasonal pattern with two incidence peaks: a lower one in winter and a higher one in spring.[6,7] In 2015, the National Ministry of Health (Ministerial Resolution 1029/2014) incorporated free, universal, and compulsory vaccination against chickenpox for children aged 15 months in single doses in all Argentine provinces.[8] Since that year, the OKA/Merck strain vaccine has been used in single doses, obtained from human diploid cell cultures WI-38 and MRC5.[9] In the pre-vaccine era (2005-2014), on average, the following were reported 146 130 cases per year in Argentina (incidence rate of 6.95 per 100 000 inhabitants), and after one year of implementation of vaccination decreased to 51 814 cases.[6] Despite suboptimal vaccination coverage (<80%) with one dose, varicella incidence rates in older children and adults were below those recorded before vaccination.[10]

A critical factor for the success of national vaccination programs is to achieve high coverage rates, which, according to WHO, should be above 80%. In 2015, Argentina's percentage of coverage, on average, was 44.80%, while in 2016-2019, it reached 78.60%. The degree of effectiveness of a national policy is sometimes different in the different jurisdictions of the country, and this depends on each province's infrastructure and health budget. In this context, of the 24 jurisdictions in Argentina, 4 provinces registered coverage below 75% in 2016-2019, and 4 provinces had coverage above 90%. The rest of the country's jurisdictions present 75% and 85% vaccination percentages.[11]

Currently, in Argentina, there is a lack of disaggregated information and studies that analyze the variability of the impact of the vaccine at the provincial level. This situation hinders a possible restructuring of strategies to achieve the objectives of the vaccination program at the national level. In this sense, for each of the 24 jurisdictions in Argentina (23 provinces and the Autonomous City of Buenos Aires), it is proposed:

1) to evaluate the effect of varicella vaccine implementation on the incidence of the disease, and 2) to test whether the year of implementation of the mandatory and free vaccine (2015) works as a breakpoint in the trend of varicella.

MATERIALS AND METHODS

An ecological analytical observational study was conducted using secondary data sources.

Data sources

Argentina comprises 23 provinces and the Autonomous City of Buenos Aires (CABA), representing the 24 jurisdictions. It has 40 117 096 inhabitants with a relatively young population profile, with a median age of 32.[12] In Argentina, varicella is a notifiable disease; that is, in each province, there are homogeneously distributed notification nodes. The national health surveillance system, which belongs to the National Ministry of Health of Argentina, reported the varicella cases. They were grouped by epidemiological week (EW) for each province.[13] This makes it possible to standardize

The time scale is used to obtain homogeneous information between provinces. To evaluate the burden of varicella in each province and compare them, incidence rates were constructed using the national censuses of 2001 and 2010 and the inter-census projections of the population of the National Institute of Statistics and Census of the Argentine Republic (INDEC, by its Spanish acronym).

Data analysis

Statistical analyses were performed using the "mgcv" package of the R software, both for time series and for constructing generalized additive models (GAM).[14] A description of the time series of cases for Argentina was made. GAM models

were constructed using a negative binomial distribution to verify the impact in each Argentine province. In addition, the epidemiological week (SE) from which the risk increased in each province was determined.

The period 2005 to 2014 was considered to verify the vaccine's impact, and a GAM model was built to predict the most likely pathology behavior in subsequent years (2015 to 2019) based on the behavior in previous years. The year 2015 was considered the cut-off point because it was the year the vaccine was implemented and supplied to the population. Subsequently, the impact was evaluated by comparing the rates and confidence intervals between the expected and observed values. This made it possible to compare the confidence intervals of the incidence rate (95%CI) between the expected behavior if the vaccine had not been implemented and the behavior observed in the years following the vaccine implementation in each province.

We used the Joinpoint Regression Program 4.7.0.0 software to verify whether the year of vaccine implementation resulted in a breakthrough point for the varicella incidence trend in each of the units of analysis.[15] First, we calculated the crude annual incidence rates for each unit. Then, we analyzed the temporal trends in incidence rates and identified the breakthrough points at which significant changes in the trend occurred. We tested for at least one breakthrough point in the annual incidence series and then estimated the APC (annual percentage change) to characterize trends in varicella incidence rates over time. In addition, AAPC (average annual percentage change) was calculated and defined as a summary measure of the trend over a fixed pre-specified interval.[16]

Ethical considerations

The present observational study did not involve interventions or direct patient contact. National Law 25326 on Personal Data Protection respected data confidentiality at all stages of the study.[17] The study was evaluated and approved by the Ethics and Methodology Committee of the Ministry of Public Health of Tucumán.

RESULTS

During 2005-2019, 1 904 565 cases were reported in 24 jurisdictions (23 provinces and CABA), with an incidence rate of 5.93 per 100 000 inhabitants. There was seasonality at the national and provincial levels, with peak incidence in spring (EW 44 on average). The northern provinces had a smaller temporal window than those in the south. In Argentina, the average number of cases reported per year before the implementation of the vaccine (2005-2014) was 145 396 cases (rate: 6.95 per 100 000 inhab.). After vaccine implementation (2015-2019), it decreased to 88 652.5 cases/year (rate: 3.89 per 100 000 inhab.). The magnitude of the decrease in incidence rate varied between jurisdictions (*Table 1*).

A significant negative trend has been observed recently at the national level, and 2015 was a breakpoint (*Table 2*, *Figure 1*). At the provincial level, 9 jurisdictions presented breakpoints (*Table2, Figure 1*). The breakpoint occurred in 2015 in 6 provinces, whereas in the rest of the provinces, it occurred earlier (CABA and San Luis) or later (Tucumán) (*Table 2*, *Figure 1*). The varicella incidence rate's AAPC was negative for the 24 jurisdictions and significant in 21/24 (*Table 3*).

DISCUSSION

We evaluated the varicella vaccine's impact in each of Argentina's jurisdictions. We analyzed varicella incidences and identified points of change in the incidence rate around the year of vaccine implementation (2015). A clear seasonality was observed in each jurisdiction, with the peak incidence in spring. At the national level, 2015 was a turning point. At the provincial level, this behavior was evidenced in 6 jurisdictions, while in 3 jurisdictions, the breakpoints occurred before or after 2015.

In Argentina, after five years of its implementation (2015-2019), the overall incidence rate of varicella decreased by more than 50%, with national vaccination coverage below 80%. A marked reduction in case notification and incidence rates for all age groups was evident in 2020. The most significant decreases in disease incidence are recorded in groups of 12-23 months and 2-4 years. However, cases and rates also decreased in all age groups. This suggests considerable herd protection that extends the benefit of vaccination beyond the population directly benefited by the strategy. According to WHO, single-dose schedules are primarily intended to reduce severe morbidity and mortality from varicella. However, they cannot limit virus circulation and prevent outbreaks even in vaccinated children. The two-dose schedules showed that the number of cases and possible

Table 1. Estimated and observed incidence of varicella per 100 000 population in each of the 23 Argentine provinces and the Autonomous City of Buenos Aires during the preceding period (2005-2014) and subsequent (2015-2019) to vaccine implementation

Jurisdictions	Incidence	Vaccine impact						
	Prevaccine period (2005-2014)	Estimated incidence		Observed incidence				
		2015	2016-2019	2015	2016	2017	2018	2019
CABA	**4.81**	5.23 [5.13-5.34]	4.78 [4.70-4.90]	4.96 [4.81-5.01]	2.50 [2.45-2.56]	2.02 [1.98-2.06]	1.00 [0.98-1.02]	0.88 [0.87-0.90]
Buenos Aires	**6.46**	7.01 [6.87-7.15]	6.43 [6.31-6.56]	5.61 [5.48-5.73]	3.37 [3.32-3.42]	3.18 [3.12-3.23]	1.65 [1.63-1.67]	1.66 [1.63-1.68]
Catamarca	**8.38**	9.25 [9.03-9.47]	8.35 [8.16-8.54]	5.44 [5.26-5.61]	6.20 [6.05-6.36]	4.98 [4.84-5.11]	2.91 [2.84-2.98]	3.47 [3.39-3.55]
Chaco	**7.11**	7.84 [7.64-8.04]	7.09 [6.93-7.26]	5.40 [5.27-5.52]	7.51 [7.29-7.72]	3.06 [3.00-3.12]	2.79 [2.73-2.85]	3.45 [3.37-3.52]
Chubut	**11.36**	12.23 [12.01-12.44]	11.30 [11.11-11.49]	13.58 [13.27-13.88]	8.00 [7.81-8.19]	3.33 [3.27-3.39]	2.18 [2.13-2.22]	1.63 [1.59-1.69]
Córdoba	**6.44**	7.10 [6.92-7.29]	6.43 [6.28-6.59]	6.88 [6.68-7.07]	3.21 [3.13-3.29]	2.87 [2.81-2.94]	1.63 [1.60-1.65]	1.82 [1.78-1.85]
Corrientes	**4.44**	4.86 [4.74-4.98]	4.41 [4.32-4.52]	4.81 [4.68-4.94]	4.58 [4.45-4.71]	2.02 [1.99-2.06]	2.08 [2.04-2.12]	2.81 [2.76-2.86]
Entre Rios	**7.75**	8.33 [8.18-8.49]	7.71 [7.57-7.84]	6.96 [6.81-7.10]	4.92 [4.82-5.02]	4.91 [4.81-5.02]	3.03 [2.98-3.08]	3.69 [3.63-3.74]
Formosa	**5.48**	5.98 [5.84-6.12]	5.46 [5.35-5.58]	4.89 [4.74-5.04]	4.71 [4.62-4.80]	2.59 [2.53-2.64]	3.26 [3.18-3.34]	1.66 [1.62-1.69]
Jujuy	**8.60**	9.28 [9.06-9.51]	8.60 [8.41-8.79]	7.55 [7.36-7.75]	7.63 [7.39-7.86]	4.88 [4.76-5.00]	3.58 [3.52-3.65]	3.31 [3.26-3.36]
La Pampa	**9.36**	10.41 [10.17-10.65]	9.34 [9.13-9.56]	11.18 [10.91-11.45]	5.10 [5.00-5.20]	10.8 [10.44-11.16]	6.36 [6.20-6.53]	3.81 [3.73-3.90]
La Rioja	**7.61**	8.39 [8.17-8.60]	7.56 [7.37-7.74]	3.13 [3.06-3.20]	4.31 [4.19-4.42]	6.68 [6.45-6.90]	6.05 [5.93-6.17]	3.44 [3.34-3.53]
Misiones	**4.71**	5.10 [5.00-5.21]	4.70 [4.60 4.80]	4.31 [4.21-4.41]	4.57 [4.44-4.70]	3.23 [3.15-3.31]	1.95 [1.91-1.98]	1.72 [1.68-1.75]
Neuquén	**11.05**	11.98 [11.76-12.20]	11.00 [10.80-11.20]	13.81 [13.48-14.15]	5.34 [5.25-5.43]	5.81 [5.70-5.94]	3.85 [3.77-3.93]	4.31 [4.22-4.39]
Río Negro	**10.11**	10.98 [10.77-11.20]	10.07 [9.90-10.25]	9.37 [9.14-9.61]	4.51 [4.44-4.60]	4.39 [4.30-4.48]	4.42 [4.33-4.50]	4.00 [3.90-4.10]
Salta	**11.32**	12.41 [12.09-12.72]	11.27 [11.00-11.53]	7.97 [7.73-8.20]	5.05 [4.92-5.18]	2.93 [2.87-3.00]	2.17 [2.13-2.21]	2.16 [2.11-2.22]
San Juan	**8.88**	9.60 [9.35-9.78]	8.88 [8.69-9.06]	7.51 [7.38-7.65]	4.37 [4.30-4.45]	4.91 [4.77-5.05]	3.14 [3.01-3.19]	4.32 [4.22-4.42]
San Luis	**11.58**	12.68 [12.39-12.98]	11.50 [11.25-11.76]	8.34 [8.13-8.55]	4.47 [4.32-4.61]	4.48 [4.39-4.57]	2.35 [2.30-2.40]	3.63 [3.53-3.72]
Santa Cruz	**13.02**	14.15 [13.92-14.38]	12.95 [12.74-13.16]	8.02 [7.82-8.21]	4.13 [4.04-4.21]	2.94 [2.83-3.06]	3.63 [3.53-3.74]	6.24 [6.05-6.43]
Santa Fe	**5.77**	6.36 [6.21-6.50]	5.74 [5.61-5.86]	2.74 [2.68-2.81]	1.98 [1.93-2.03]	1.55 [1.52-1.58]	0.99 [0.97-1.01]	0.62 [0.61-0.64]
Santiago del Estero	**5.58**	6.22 [6.05-6.39]	5.58 [5.43-5.72]	4.52 [4.40-4.64]	6.81 [6.64-7.00]	3.75 [3.68-3.82]	3.16 [3.10-3.22]	3.59 [3.50-3.70]
Tierra del Fuego	**14.25**	15.38 [14.98-15.77]	14.07 [13.74-14.40]	7.95 [7.68-8.23]	18.33 [17.65-19.01]	5.23 [5.07-5.39]	5.36 [5.20-5.52]	4.14 [4.00 4.28]
Tucumán	**8.34**	9.12 [8.86-9.39]	8.35 [8.13-8.57]	8.45 [8.25-8.65]	7.62 [7.43-7.82]	5.58 [5.43-5.72]	3.46 [3.39-3.53]	4.31 [3.26-3.37]
Argentina	**6.95**	7.57 [7.40-7.73]	6.93 [6.79-7.07]	6.16 [6.02-6.29]	4.24 [4.16-4.32]	3.50 [3.43-3.56]	2.24 [2.21-2.28]	2.22 [2.19-2.25]

CABA: City of Buenos Aires.

Table 2. Annual percentage change (APC) in the incidence rate of varicella with their respective 95% confidence intervals in Argentina and in each of the provinces

Jurisdictions**	Year	Segment	Lower final point	Higher final point	APC	95%CI	95%CI
CABA	2013	1	2005	2013	6.5	-4.2	18.4
		2	2014	2019	-26.4*	-37.6	-13.3
Buenos Aires	2015	1	2005	2015	-2.8	-9.4	4.2
		2	2016	2019	-27.4*	-45.4	-3.4
Chubut	2015	1	2005	2015	-3.1	-8.4	2.6
		2	2016	2019	-37.0*	-49.9	-20.7
Córdoba	2015	1	2005	2015	-2.9	-7.9	2.4
		2	2016	2019	-27.6*	-41.6	-10.2
Jujuy	2015	1	2005	2015	-3.0	-7.4	1.7
		2	2016	2019	-24.2	-46.6	7.4
Salta	2015	1	2005	2015	-5.9	-13.1	1.9
		2	2016	2019	-30.8*	-49.9	-4.4
San Luis	2014	1	2005	2014	-5.5	-11.0	0.4
		2	2015	2019	-21.2*	-32.0	-8.8
Santa Fe	2015	1	2005	2015	-10.8*	-16.6	-4.5
		2	2016	2019	-29.9*	-46.8	-7.7
Tucumán	2016	1	2005	2016	-1.6	-5.8	2.9
		2	2017	2019	-26.2	-46.9	2.5
Argentina	2015	1	2005	2015	-3.0	-8.1	2.4
		2	2016	2019	-23.2	-38.3	-4.3

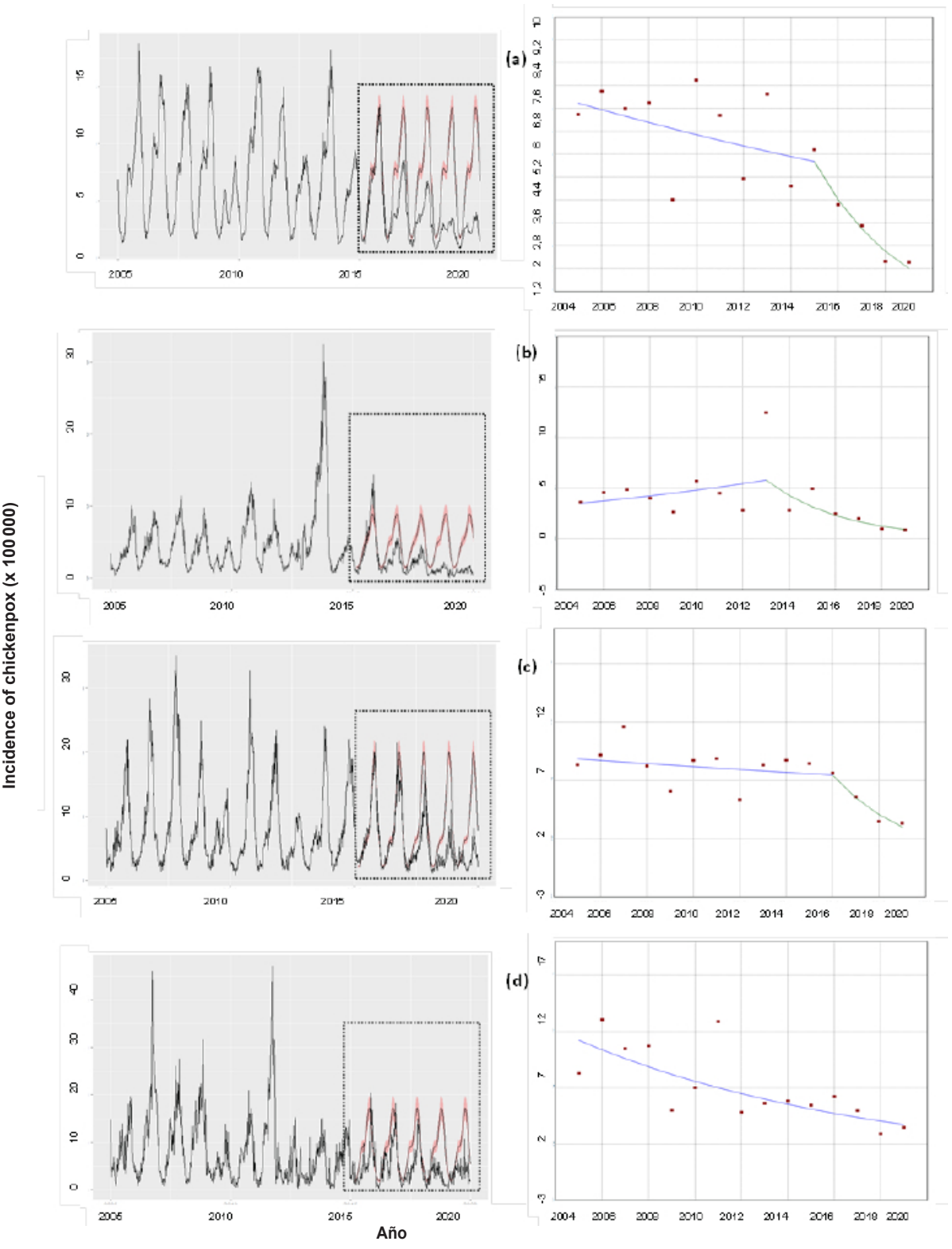
** Indicates that APC is significant and differs from zero (alpha = 0.05).*
*** The provinces not shown in the table did not present breakpoints in their trend: Catamarca. Chaco. Corrientes, Entre Ríos, Formosa, La Pampa, La Rioja, Mendoza, Misiones, Neuquén, Río Negro, San Juan, Santa Cruz, Santiago del Estero, Tierra del Fuego.*
**** AAPC (average annual percentage change) is a summary measure of the trend over a pre-specified fixed interval. It allows us to use a single number to describe the average APC over a period of several years. Each segment's APC is presented with its respective 95%CI to assess whether it is different from zero.*
CABA: City of Buenos Aires.

epidemics in vaccinated populations can be further reduced. The risk of varicella in children immunized with 2-dose schedules was 3.3 times lower during the first 10 years post-vaccination compared to the risk with single-dose schedules.[10]

Argentina has a homogeneous surveillance system with mandatory reporting uses the exact case definition throughout.[13] Central and Eastern European regions need a standardized case definition, have heterogeneity in their surveillance systems, or reporting is optional, leading to underestimation of varicella as a public health problem.[18] The United States, the country with the most years of experience, reported a 90% decrease in varicella incidence after five years of vaccine introduction in the United States. The United States, the country with the most years of experience, reported a 90% decrease in varicella incidence after five years of vaccine introduction in 1995.[19,20] During the two-dose program, the decrease was 97% over the 25 years of the program. Italy and Spain analyze the impact of the vaccine at the subnational level, in certain regions, or in a proportion that does not reach 100% of the provinces.[21-23] In Canada, the single-dose vaccine was implemented free of charge nationwide, in different years depending on the province, and reports a decrease in hospitalizations in children aged 1 to 4 years that varied from 65% to 94% between provinces.[24]

In Argentina, although all 24 jurisdictions implemented the one-dose vaccine, in 2015, San Luis and Jujuy had coverage above 80%. On average, 25% of the jurisdictions report vaccination percentages below 80%. In 79.17% of the jurisdictions in Argentina, the impact of the implementation of the vaccine was evidenced in the same year of its implementation. The pre-vaccination period and the efficiency of vaccination coverage are critical factors in the dynamics of varicella incidence. Thus, for example, La Pampa is one of the provinces with the highest incidence in the pre-vaccination period, and in 2015, vaccination coverage was

Figure 1. Time series of varicella incidence rate



On the left, the comparison between the observed behavior (continuous black line) and the expected behavior generated through a GAM model is shown with its respective 95%CI (red). On the right, the observed annual incidences (red dots) and the breakpoints in the trend are shown: (a) Argentina, (b) City of Buenos Aires, (c) Tucumán, and (d) Catamarca.

Table 3. Annual percentage change (APC) of the incidence rate of varicella with their respective 95% confidence intervals in Argentina and each of the jurisdictions

Jurisdictions		Lower 95%CI	Upper 95%CI
CABA *	-9.1	-16.3	-1.4
Buenos Aires *	-10.6	-17.8	-2.7
Catamarca *	-7.6	-11.0	-4.0
Chaco *	-6.3	-10.1	-2.2
Chubut *	-14.3	-19.9	-8.3
Córdoba *	-10.7	-16.2	-4.8
Corrientes	-4.0	-8.0	0.2
Entre Ríos *	-5.5	-8.8	-2.2
Formosa *	-6.9	-10.3	-3.4
Jujuy *	-8.0	-14.5	-1.0
La Pampa	-3.7	-7.8	0.6
La Rioja	-3.9	-10.0	2.6
Mendoza *	-3.1	-5.7	-0.5
Misiones *	-6.1	-9.9	-2.1
Neuquén *	-7.2	-10.7	-3.6
Río Negro*	-6.7	-10.4	-2.9
Salta *	-13.8	-21.7	-5.2
San Juan *	-5.3	-9.4	-1.0
San Luis *	-11.4	-16.4	-6.2
Santa Cruz *	-9.4	-13.5	-5.2
Santa Fe *	-16.7	-23.2	-9.7
Santiago del Estero	-3.2	-6.6	0.3
Tierra del Fuego *	-8.8	-15.2	-1.9
Tucumán *	-7.5	-13.6	-0.8
Argentina *	-9.3	-14.9	-3.2

** Indicates that the annual percentage change differs significantly from zero at the alpha level = 0.05.*
CABA: City of Buenos Aires.

low (54.70%). However, the coverage in the following years exceeded 80%, reaching 91.20% in 2019. On the other hand, Corrientes had a low incidence in the pre-vaccination period. In 2015, coverage was also low (32.70%). However, unlike La Pampa, it maintained low levels of coverage in subsequent years, reaching 76.10% in 2019.[11] Studies in Italy showed that one- and two-dose routine vaccination strategies prevented a comparable number of varicella cases with complications.[25,26] Overall, a 20% increase in coverage resulted in a further 27-31% reduction in cases. A 10% increase in the efficacy of the first dose (from 65% to 75% efficacy) prevented between 2% and 5% more cases of chickenpox, suggesting that it is the least influential factor when considering routine vaccination against varicella. It is essential to analyze the situation at the subnational level to assess the correlation between vaccination coverage and the rate of hospitalization, mortality, and incidence of shingles, as evidenced in other parts of the world.[27-29]

This study provides empirical evidence of the trend in varicella incidence in Argentina and each of the 24 jurisdictions. It evaluates the significance and magnitude of changes in the trend between 2005 and 2019 and changes in the trend between shorter periods (segments) generated by the occurrence of breakpoints in the time series analyzed. The possible limitations of the work are that the secondary data source depends on the surveillance system, and the quality of the data reported at the national and provincial levels is mentioned. This study has an ecological design and evaluates the impact of implementing a public policy. For this reason, the level of resolution of the information allows us to identify patterns of disease behavior that help confirm or change specific policies' direction.

In conclusion, nationally and at the provincial level, there was a significant decrease in the incidence rate after 2015. In Argentina and 6 of the 24 jurisdictions, the year 2015 was a turning

point. In the others, none were identified or occurred after 2015. Evaluating policies implemented at the national and provincial levels with information generated by epidemiological surveillance systems supports the importance of having complete vaccination schedules. It contributes to providing the community with accurate, adequate, and reliable information to increase confidence in vaccination. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2025/10412_AO_Barrenechea_Anexo.pdf

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