Rotavirus Vaccine Impact since Its Introduction in the National Immunization Program of Argentina

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ABSTRACT

Introduction: Rotavirus (RV) is the most common cause of childhood diarrhea. Argentina introduced RV vaccination in the National Immunization Program in January 2015. This study evaluates the impact of RV vaccine implementation on the burden of acute diarrheal disease (ADD) and RV positive cases, and hospitalizations among children in Argentina.
Methods: A counterfactual time-series analysis was performed. Data on ADD (2013–2018) and RV diarrhea (2012–2018) cases in children aged < 5 years were collected from the National Healthcare Surveillance System (clinical and laboratory data). Data on hospital discharges following ADD and RV diarrhea (2011–2017) were retrieved from the Health Statistics and Information Office. All data were classified by the age groups < 1 year, < 2 years, 2–5 years. Vaccine impact was defined as the difference between the predicted time trend (simulated using 2012–2014 data) and the actual post-vaccination data (2015–2018).
Results: A significant reduction of 22.1% of notified ADD cases and 15.4% of hospital discharges following ADD among children < 2 years was observed in the 3 years after RV vaccine implementation. Data also showed a significant decline of 54.0% and 59.4% of notified RV cases in children < 2 and < 1 years, respectively, and a reduction of 39.3% and 40.8% in RV hospital discharges for the same age groups.
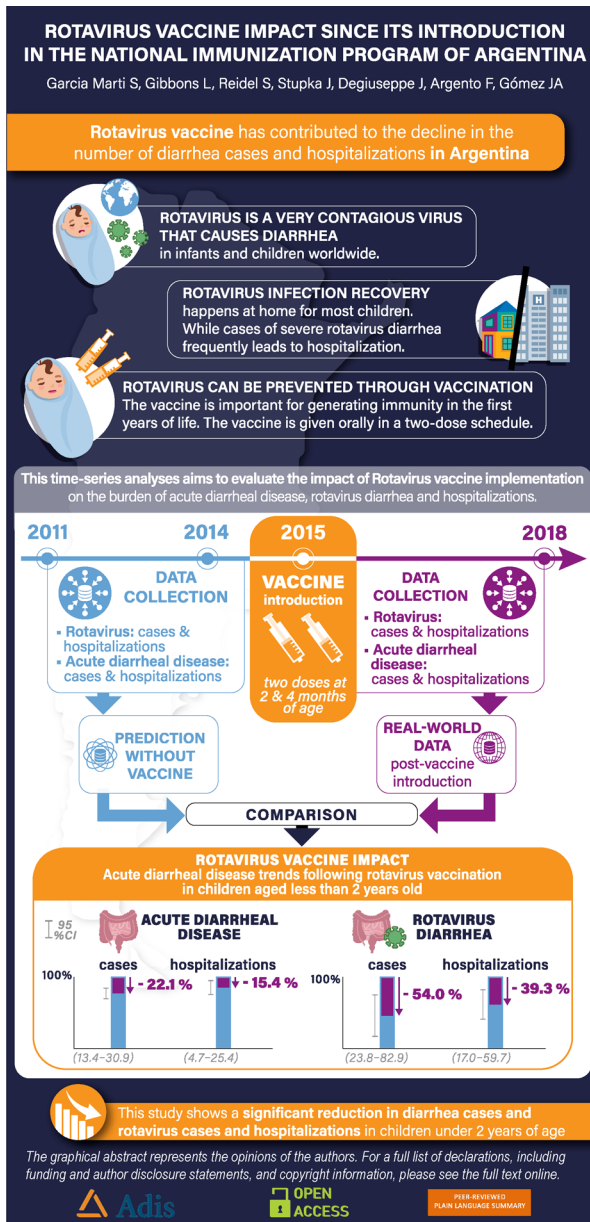***Conclusion***: This study shows a significant reduction in notified ADD cases and RV cases and hospital discharges following ADD and RV cases in children < 2 years after RV vaccine introduction in Argentina in 2015.

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Graphical abstract:

Keywords: Argentina; Children; Rotavirus; Vaccine

Key Summary Points

Why carry out this study?

Rotavirus (RV) is the most common cause of diarrhea among children, and the leading cause of childhood mortality in Latin America before rotavirus vaccination.

This study evaluated the impact of RV vaccine implementation on the burden of acute diarrheal disease (ADD) and RV positive cases.

The study also evaluated the impact of RV vaccination on hospitalizations among ADD and RV positive cases.

What was learned from the study?

Significant decrease in notified ADD cases and RV cases in children < 2 years after RV vaccine introduction in Argentina in 2015.

Hospital discharges due to ADD and RV infection reduced in children < 2 years after RV vaccine introduction.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate the understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.21221468.

INTRODUCTION

Rotavirus (RV) infection is the most common cause of diarrhea among children aged 5 years or less worldwide [1]. Globally, between 2013 and 2017, RV was the leading etiology of nearly 122,000–215,000 RV-related diarrhea deaths among children under the age of 5 years [2–4]. In Latin America and the Caribbean, RV is the

leading cause of childhood mortality, and it was estimated to cause 8000 annual deaths prior to the introduction of RV vaccination [5, 6].

RV vaccination is recommended to prevent RV disease; about nine out of ten children who receive the vaccine are protected from its severe form [7]. In 2009, the World Health Organization (WHO) recommended its use among infants to reduce associated fatality rates, especially in countries with childhood mortality rates > 10% [8]. Currently, four WHO-approved RV vaccines are available for infant vaccination: *RotaTeq* (Merck & Co. Inc., Whitehouse Station, NJ, USA), *Rotarix* (GSK, Rixensart, Belgium), *Rotavac* (Bharat Biotech International Ltd, India), and ROTASIIL (Serum Institute of India, India) [9]. While 114 countries have introduced RV vaccines in their National Immunization Programs (NIPs), approximately 59 million children still lack access to RV vaccines [10]. Seven Latin American countries that had introduced the RV vaccines in their NIPs notified vaccine coverage rates ranging from 39% to 91.8% in 2007 [11]. As of January 2011, 14 Latin American countries have included RV vaccines in their NIP's [6]. According to the 2021 estimates from the Pan American Health Organization, RV vaccine coverage in Latin America ranged from 56% in Paraguay to 100% in Nicaragua [12]. Argentina incorporated the RV vaccine (*Rotarix*, GSK, Belgium) in its NIP in 2015 [13]. This monovalent vaccine, made from the human viral strain G1P [8], is administered orally as a two-dose regimen to infants aged 2 and 4 months [14, 15]. After introduction of the vaccine, the vaccine coverage rates in Argentina were notified to be 61% [16]. The latest data from the WHO (2021) estimates an increased vaccination coverage rate of 74% [17].

To date, several studies have evaluated the burden of RV disease in Latin American countries after the inclusion of the vaccine in their NIPs. Data showed a significant reduction in mortality associated with acute diarrheal disease (ADD) in the post-vaccination period (22–54%), in both infants aged less than 1 year and children aged less than 5 years [18–22]. The same trend was observed in the number of hospitalizations due to ADD, which decreased by 17–52%, and specifically for RV cases, by 59–81% [19, 22–29].

In the province of San Luis, Argentina, RV vaccination was implemented 2 years earlier than in the rest of the country [30]. A study conducted in this province to evaluate the use of the vaccine showed a reduction of 20–25% in ADD cases and 55–60% in hospitalizations in children younger than 5 years [30]. However, to date, a similar analysis has not been performed for the rest of the country [31, 32]. The objective of this study, therefore, is to evaluate how the introduction of RV vaccination in the Argentinian NIP affected the number of notified ADD cases, RV cases, ADD hospitalizations, and RV hospitalizations (in different datasets of the Ministry of Health) in children aged less than 5 years.

METHODS

A counterfactual time-series analysis was performed to study the impact of RV vaccination on the number of notified ADD cases (January 2013–May 2018), notified RV cases (January 2012–December 2018), ADD hospital discharges (January 2011–December 2017), and RV hospital discharges (January 2011–December 2017) in children aged less than 5 years in Argentina. Data were collected prior to (2012/2013–2014) and post (2015–2017/2018) RV vaccine introduction in the Argentinian NIP on 1 January 2015. Vaccine impact was measured estimating the difference between a predicted time trend (simulated using 2011/2013–2014 data) and the actual post-vaccination data (2015–2017/2018). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Database Description

ADD is a mandatory notifiable disease in Argentina. The National Healthcare Surveillance System (SNVS, Sistema Nacional de Vigilancia de la Salud) gathers all the data relating to the ADD cases. The SNVS constitutes two units: clinical and laboratory.

The clinical surveillance unit (C2) of the SNVS notifies ADD cases from all "medical consultations," making no distinction between inpatients and outpatient visits, and etiology [33, 34]. Data were collected from January 2013 to May 2018 by epidemiological week and were classified by age group: < 1 year, < 2 years, 2–5 years.

The laboratory surveillance unit (SIVILA, Sistema Nacional de Vigilancia por Laboratorios) of the SNVS gathers information from several sentinel hospital laboratories to report the number of tested cases and their etiology (e.g., RV) [34, 35]. Data were collected from January 2012 to December 2018 by epidemiological week and were classified by age group: < 1 year, < 2 years, 2–5 years.

Moreover, all notified RV cases were also regularly analyzed by the National Administration of Laboratories and Health Institutes (ANLIS, Administración Nacional de Laboratorios e Institutos de Salud) [36].

Hospital discharge data (due to ADD and RV) were retrieved from the Health Statistics and Information Office (DEIS, Dirección de Estadística e Información en Salud) [37]. Data were collected monthly from January 2011 to December 2017 and were classified by age group: < 1 year, < 2 years, 2–5 years. Hospital discharge cases were classified based on the International Classification of Diseases 10th revision (ICD-10) codes A08 "viral and other specified intestinal infections" and A09 "other gastroenteritis and colitis of infectious and unspecified origin" [38]. Hospital discharge data were missing for several provinces, and thus not included in the analysis (Table S1).

Samples were gathered from all regions of Argentina, except the province of San Luis, which was excluded from the analysis because vaccination was implemented in 2013.

Detailed information about the databases can be found in the Supplementary Material, Table S1.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Statistical Analysis

A counterfactual Bayesian time-series analysis was performed to assess the impact of the vaccine on the number of notified ADD and RV cases and hospital discharges [39]. A predicted scenario in which the vaccine was not introduced was modeled using data prior to the introduction of the RV vaccine in the NIP. The effect of vaccination was derived from the difference between the model-predicted scenario and the actual data.

A validation analysis of the model was performed as indicated in the Supplementary Material, Table S2.

Outcomes

Four outcomes were defined:

The first outcome was to assess the impact of the vaccine on the number of notified ADD cases in the age groups < 1 year, < 2 years, and 2–5 years.

The second outcome was to assess the impact of the vaccine on the number of notified RV cases in the sentinel hospitals for the age groups < 1 year, < 2 years, and 2–5 years.

The third outcome was to assess the impact of the vaccine on the number of hospital discharges following ADD in the age groups < 1 year, < 2 years, and 2–5 years.

The fourth outcome was to assess the impact of the vaccine on the number of hospital discharges following RV in the age groups < 1 year, < 2 years, and 2–5 years.

RESULTS

Overall results are presented in Table 1. Since vaccine introduction in January 2015, a decrease in the number of cases and hospital discharges per month was observed for both ADD and RV cases.

Table 1 Impact of RV vaccination on the number of notified ADD and RV cases, and the number of ADD and RV hospital discharges per month by age group

Age group	2011/2013–2014 Mean number of cases per month (n)	2015–2018 Mean number of cases per month—with vaccine in NIP (n)	Mean prediction per month—without vaccine in NIP, n (95% CI)	Mean cases averted per month, n (95% CI)	Cumulative cases averted since vaccine implementation, n (95% CI)	Reduction [a]% (95% CI)	p-Value
Impact on number of notified cases							
ADD <1 y	9949	7304	9909 (9029, 10,872)	2605 (1725, 3568)	114,613 (75,895, 157,000)	26.3 (17.4, 36.0)	0.001
<2 y	24,047	18,690	24,007 (21,899, 26,101)	5317 (3209, 7411)	233,947 (141,183, 326,068)	22.1 (13.4, 30.9)	0.001
2–5 y	16,582	14,484	16,638 (15,376, 18,062)	2154 (892, 3577)	94,764 (39,235, 157,403)	12.9 (5.4, 21.5)	0.001
RV <1 y	71	30	73 (50, 94)	43 (21, 65)	2071 (997, 3101)	59.4 (28.6, 88.9)	0.002
<2 y	124	59	128 (89, 165)	69 (30, 106)	3323 (1463, 5102)	54.0 (23.8, 82.9)	0.002
2–5 y	22	19	23 (17, 29)	4 (−2, 10)	180 (−117, 462)	16.4 (−10.7, 42.1)	0.115
Impact on number of hospital discharges							
ADD <1 y	632	518	639 (573, 705)	122 (55, 187)	4377 (1981, 6737)	19.0 (8.6, 29.3)	0.002
<2 y	761	651	770 (688, 847)	118 (36, 196)	4263 (1305, 7040)	15.4 (4.7, 25.4)	0.003
2–5 y	162	177	163 (151, 175)	−14 (−25, −1)	−502 (−912, −51)	− 8.6 (−15.6, −0.9)	0.015
RV <1 y	30	17	29 (23, 36)	12 (6, 18)	433 (214, 653)	40.8 (20.2, 61.6)	0.001
<2 y	34	21	34 (26, 41)	13 (6, 20)	479 (208, 728)	39.3 (17.0, 59.7)	0.002
2–5 y	5	5	5 (3, 6)	0 (−1, 1)	2 (−47, 48)	0.9 (−29.0, 30.0)	0.467

ADD acute diarrheal disease, *CI* confidence interval, *n* number, *RV* rotavirus, *y* years

[a]% = (number of cases averted/prediction × 100)

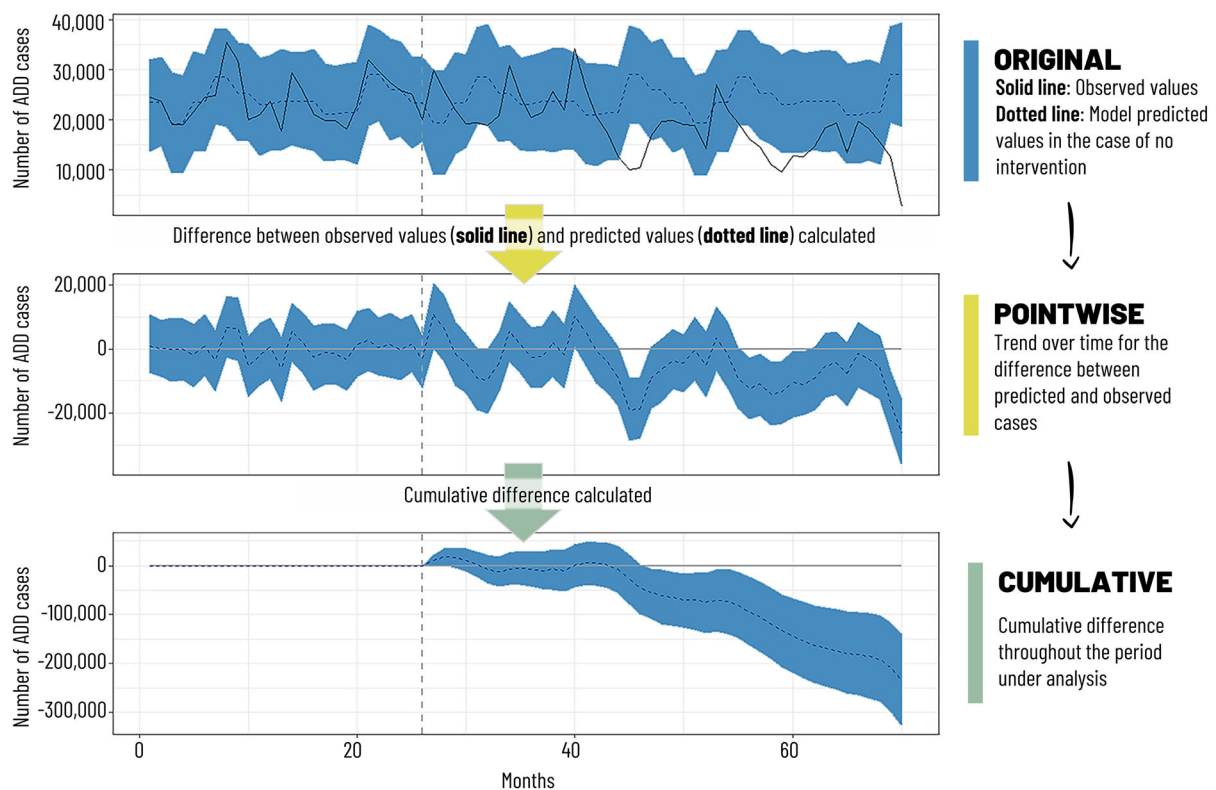## Impact of RV Vaccination on the Number of Notified ADD Cases

A statistically significant ADD case reduction was observed in Argentina's surveillance system for all age groups analyzed, being lowest in the age group least exposed to the vaccine (i.e., 2–5 years). Percentages of cases averted per month due to vaccination by outcome and age group varied between 12.9% and 26.3% (see Table 1).

The cumulative reduction in the number of notified ADD cases per year was greater for the age group < 2 years (Fig. 1). A total of 233,947 ADD cases were averted after vaccine introduction in this age group (Table 1 and Fig. 1). Similarly, in both age groups of < 1 year and 2–5 years of age, a reduction in notified ADD cases after vaccine incorporation was found (Figs. S1, S2). The cumulative reduction is more pronounced in the < 1 year age group than in the 2–5 year age group (Fig. S2).

Impact of RV Vaccination on the Number of Notified RV Cases

As presented in Table 1, the number of notified RV cases decreased in all age groups in the years after the implementation of the vaccine. Moreover, these estimations were higher than those

Fig. 1 Impact of RV vaccination on the number of notified ADD cases in children < 2 years. The graphic at the top shows the number of predicted and observed notified ADD cases over time. The dotted line shows the predicted values (January 2013–May 2018 without vaccination). The solid line represents the observed values (January 2013–December 2014 without vaccination and January 2015–May 2018 with vaccination). The graphic in the middle shows the trend over time for the difference between the predicted and observed ADD cases for the age group of < 2 years of age by month. The graphic at the bottom shows the cumulative difference between the predicted and observed data over time. Blue shades are confidence intervals. The vertical dotted line is the date of vaccine inclusion in the NIP (January 2015). *ADD* acute diarrheal disease, *RV* rotavirus

observed for notified ADD cases (the RV outcome is more specific to assess the vaccine's effects), being 54.0% in the age group < 2 years. A total of 3323 RV cases were averted in the selected sentinel hospitals after vaccine introduction in this age group (Table 1 and Fig. 2). A statistically significant difference in the number of notified RV cases attributable to vaccination was observed in the age groups < 1 year and < 2 years. No significant differences were observed for the age group of 2–5 years.

Again, the age group with the biggest reductions in the number of notified RV cases per year was the group < 2 years (Fig. 2, Fig. S3). A reduction in the number of RV cases is observed following vaccine introduction, together with a loss of seasonality over the study period for the age groups < 1 year and < 2 years (Fig. 2, Fig. S3).

Impact of RV Vaccination on the Number of Hospital Discharges Following ADD

After implementation of the RV vaccination, a decrease in hospital discharges following ADD was observed for the age groups < 1 year and < 2 years (Table 1, Fig. 3, Figs. S4, S5). These reductions varied between 19.0% and 15.4% in children < 1 years old and < 2 years old, respectively (Table 1). A total estimate of 4263
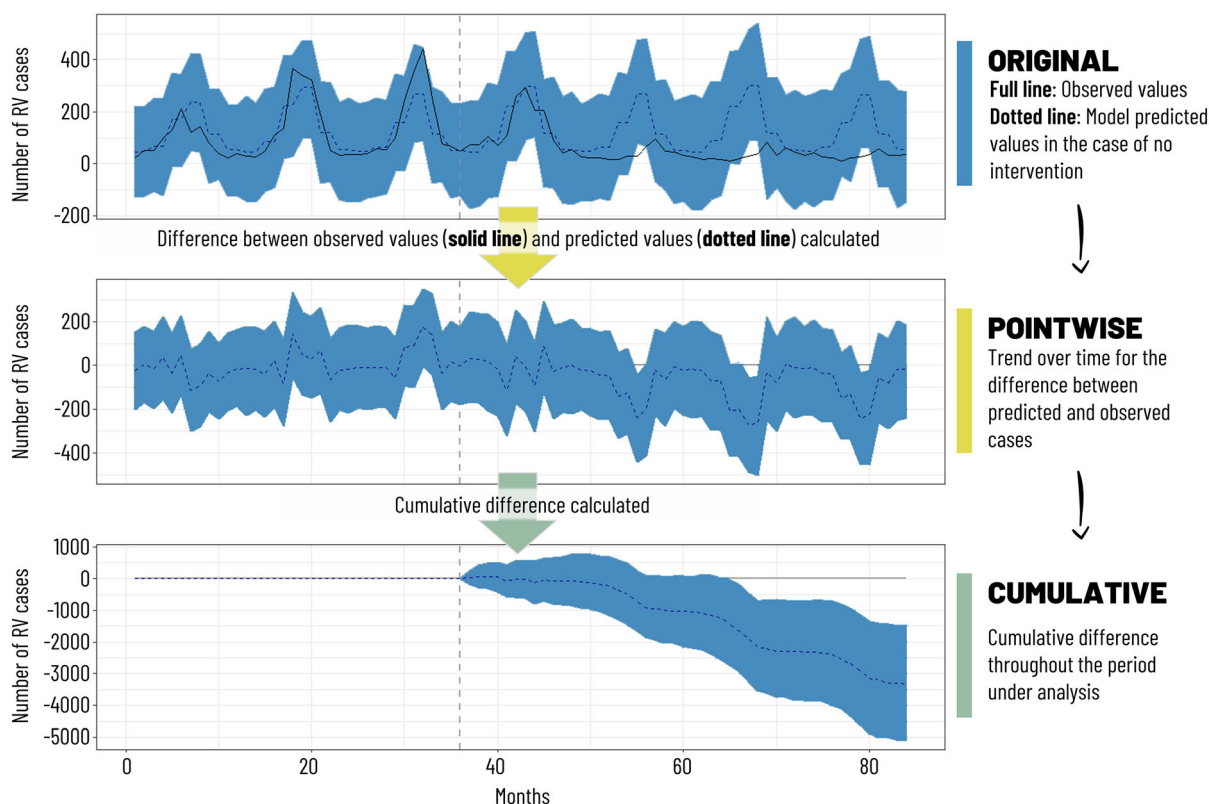
Fig. 2 Impact of RV vaccination on the number of notified RV cases in children < 2 years. The graphic at the top shows the number of predicted and observed notified RV cases over time. The dotted line shows the predicted values (January 2012–December 2018 without vaccination). The solid line represents the observed values (January 2012–December 2014 without vaccination and January 2015–December 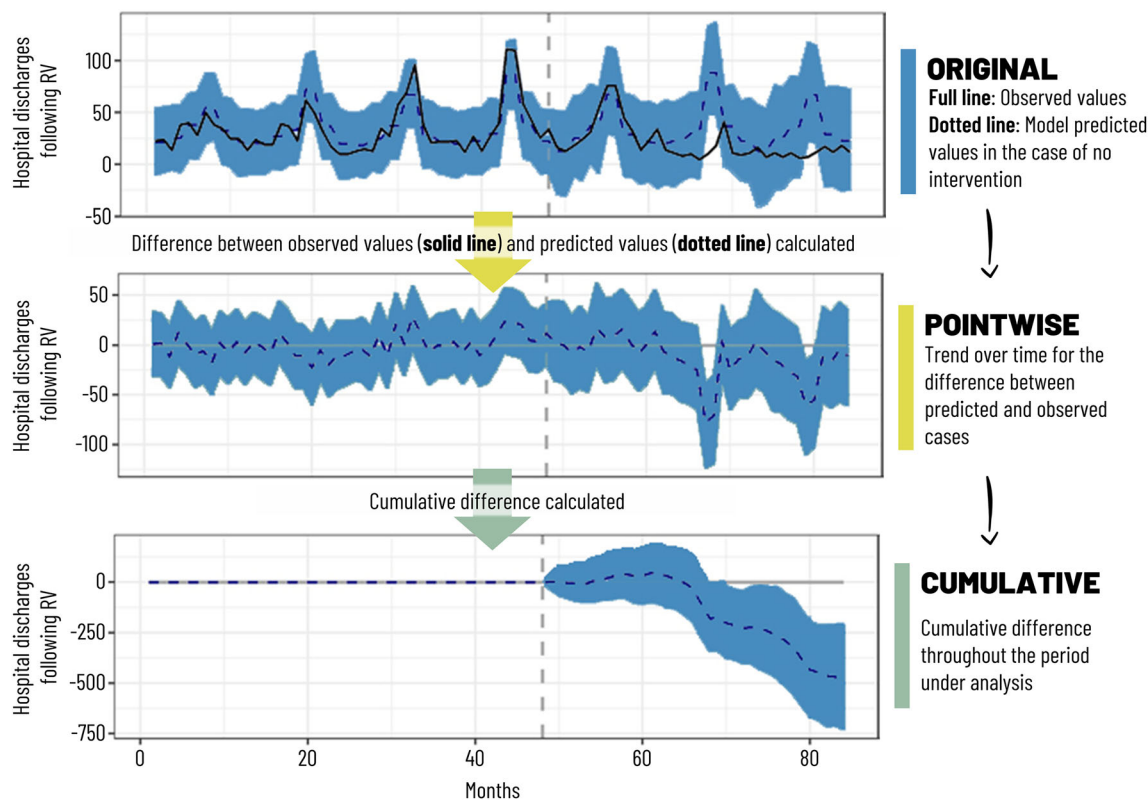2018 with vaccination). The graphic in the middle shows the trend over time for the difference between the predicted and observed notified RV cases for the age group < 2 years of age by month. The graphic at the bottom shows the cumulative difference between the predicted and observed data over time. Blue shades are confidence intervals. The vertical dotted line is the date of vaccine inclusion in the NIP (January 2015). *ADD* acute diarrheal disease, *RV* rotavirus
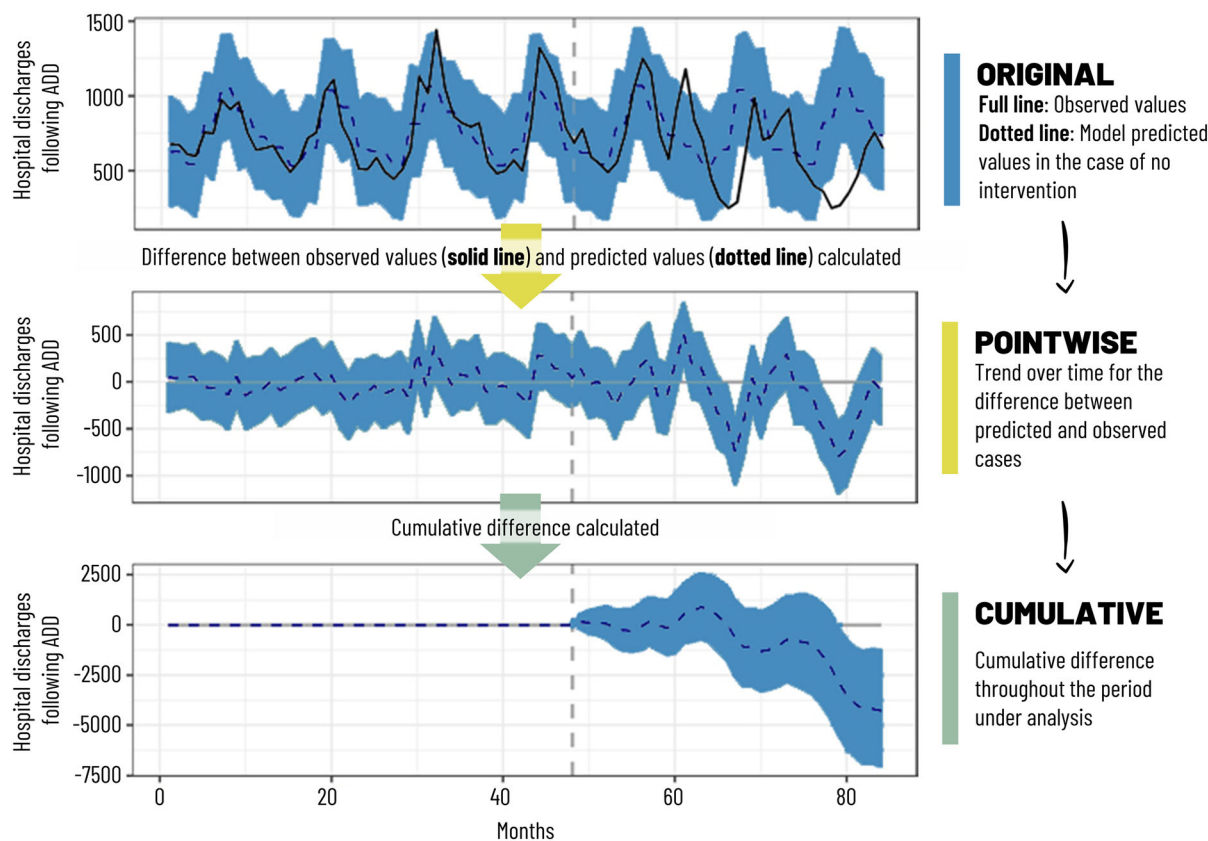
Fig. 3 Impact of RV vaccination on the number of hospital discharges following ADD in children < 2 years. The graphic at the top shows the number of predicted and observed ADD hospital discharges over time. The dotted line shows the predicted values (January 2011–December 2017 without vaccination). The solid line represents the observed values (January 2011–December 2014 without vaccination and January 2015–December 2017 with vaccination). The graphic in the middle shows the trend over time for the difference between the predicted and observed ADD hospital discharges for the age group < 2 years of age by month. The graphic at the bottom shows the cumulative difference between the predicted and observed data over time. Blue shades are confidence intervals. The vertical dotted line is the date of vaccine inclusion in the NIP (January 2015). *ADD* acute diarrheal disease, *RV* rotavirus

hospital discharges following ADD were averted after vaccine introduction in the group < 2 years of age (Table 1 and Fig. 3). In the 2–5 years age group, the trend observed was the opposite, with a slight nonsignificant increase (Table 1, Fig. 3, and Fig. S5).

Impact of RV Vaccination on the Number of Hospital Discharges Following RV

A statistically significant reduction in hospital discharges following RV was observed for the age groups < 1 year and < 2 years, where the

percentages of cases averted per month were about 40% (40.8% and 39.3%, respectively) (Table 1). The cumulative number of prevented RV hospital discharges after vaccine introduction was greater for the age group < 2 years, with an estimated 479 cases of RV averted in the analyzed dataset (Table 1, Fig. 4, Fig. S6).

DISCUSSION

To our knowledge, this is the first time series analysis that evaluates the impact of RV

Fig. 4 Impact of RV vaccination on the number of hospital discharges following RV in children < 2 years. The graphic at the top shows the number of predicted and observed RV hospital discharges over time. The dotted line shown the predicted values (January 2011–December 2017 without vaccination). The solid line represents the observed values (January 2011–December 2014 without vaccination and January 2015–December 2017 with vaccination). The graphic in the middle shows the trend over time for the difference between the predicted and observed RV hospital discharges for the age group < 2 years of age by month. The graphic at the bottom shows the cumulative difference between the predicted and observed data over time. Blue shades are confidence intervals. The vertical dotted line is the date of vaccine inclusion in the NIP (January 2015). *RV* rotavirus

vaccination on the number of notified ADD and RV cases and hospital discharges, following its introduction in the Argentinian NIP. During the period analyzed, a decreasing trend was observed, being more pronounced for the age groups < 1 year and < 2 years than for the age group 2–5 years. The impact was in all cases greater for RV disease than for ADD. For the age groups < 1 year and < 2 years, the reduction in the number of notified ADD cases was in line with the number of ADD hospital discharges; the same effect was observed for notified RV cases and hospital discharges.

A statistically significant reduction in notified ADD cases was also observed in the

2–5 years age group. This age group may include a proportion of children who were not eligible to be vaccinated based on age. This may suggest indirect community-based protection or herd immunity as a consequence of infant RV vaccination. A similar observation has been notified in El Salvador, where a significant reduction in RV-related hospitalizations was observed in children ineligible for the vaccine [28]. Indirect community-based protection was also observed in Europe [40, 41] and the USA [42].

In contrast, RV vaccination did not show any noticeable impact on the number of notified RV cases and hospital discharges in the 2–5 years age group. It is possible that no significant

reduction was seen due to the overall low number of RV cases notified.

This study also reports a loss of seasonal rotavirus epidemic patterns after introduction of the RV vaccine. This is in line with a previous study that has shown that seasonal trends of RV were less pronounced after vaccine introduction [43]. Currently, in the USA, high RV vaccine coverage of 85% among infants resulted in annual RV epidemic patterns [44].

The RV vaccine coverage rates have been steadily increasing in Argentina since the introduction of the vaccine. Coverage rates have risen from 61% in 2015 to 75%, 78%, and 80% in 2016, 2017, and 2018, respectively [10, 16]. An increase in vaccine coverage rates may have contributed to the decreased incidence of ADD, as observed in the current study, and the previously performed analysis in the province of San Luis, Argentina [30]. Most recently, a vaccine impact of 25% and 23% in the number of ADD cases was estimated for children aged < 1 year and < 2 years, respectively, in line with our estimations (26.3% and 22.1%, respectively). However, the impact on the number of ADD hospitalizations was greater in the San Luis study (55–60% in the San Luis study and 15–19% in the current study) [30].

Another study in Argentina evaluated the early impact of RV vaccine implementation on the ADD burden. This observational study included post-vaccination data from 2016 and compared them with previous years (2011–2015). They found a decrease of 20.8% in ADD cases and 61.7% in RV cases in children < 5 years [32]. Our study showed lower vaccination impact, although the results are aligned. This difference may be explained by the number of years post-vaccination analyzed: this study only included the first year (2016), while our study evaluated three years (2016–2018). But it may also be explained by the different strategies used to calculate the impact of RV vaccination; Degiuseppe et al. compared 2016 data with the mean number of cases during the pre-vaccination period (2011–2014) [32], while in our study the impact was derived from the difference between the predicted (calculated through simulations) and the actual data (2015–2018).

Since 2006, several Latin American countries have implemented RV vaccination in their NIPs. Brazil was one of the first to include this vaccine in 2006, altogether with El Salvador, Mexico, Nicaragua, Panama, and Venezuela [1]. Since then, several publications in Brazil have estimated 17–52.5% of ADD hospitalizations averted and a 42.2% reduction in RV samples [19, 23, 27, 29]. Panama followed the same trend, with a decrease of 22–37% in ADD hospitalizations among children < 5 years [18, 24]. Mexico, after vaccine implementation, saw a decline in ADD hospitalizations of 40–47%, with the greatest decline in infants < 1 year (52%) and children < 2 years old (43–49%) [25, 45]. In El Salvador, RV hospitalizations were reduced by 69–81%, again with the highest decline observed in infants < 1 year, although sizable reductions were also observed in children < 2 years [28]. After introduction of the vaccine in Bolivia, El Salvador, Honduras, and Venezuela, the reduction of diarrhea-related hospitalizations and deaths ranged from 15.7% to 56.8% and from 5.6% to 17.9% respectively [22]. Although estimates vary widely between these countries, partially influenced by vaccine uptake, they are consistent and in agreement with our results in estimating a decreasing trend in the number of cases and hospitalizations after RV vaccine implementation. Although the number of cases and hospitalizations followed an overall decreasing trend, this effect was statistically significant only for the age groups < 1 year and < 2 years. A small non-significant increase was observed in the number of ADD hospitalizations in the 2–5 years age group (8.6% increase), which may be attributed to inconsistencies in data registries. In addition, RV vaccination resulted in similar reduction rates for the number of notified ADD cases and ADD hospital discharges. For instance, in infants < 1 years, reductions of 26.3% [95% confidence interval (CI) 17.4–36.0%] and 19.0% (95% CI 8.6–29.3%) were observed in the number of notified ADD cases and ADD hospital discharges, respectively; and reductions of 59.4% (95% CI 28.6–88.9%) and 40.8% (95% CI 20.2–61.6%) were observed in the number of notified RV cases and RV hospital discharges.

This study has several limitations. First, the number of ADD cases is expected to be under-reported, even though ADD represents a mandatory notifiable event in Argentina. Under-notification occurs mainly because people do not seek medical care owing to the mildness and self-limited nature of the symptoms. Also, institutional commitment to national health information systems may vary between different institutions and regions in the country. RV data is only provided by certain sentinel hospitals participating in the laboratory surveillance system, and even in these institutions RV testing is limited to the demand of local physicians and is not a population-based surveillance strategy [32].

Second, complete hospital discharges datasets were not available for some Argentinian provinces (i.e., Catamarca, Corrientes, Entre Ríos, Formosa, Jujuy, La Pampa, La Rioja, Misiones, Rio Negro, San Juan, Santiago del Estero, and Tierra del Fuego). These provinces were thus excluded from the analysis to avoid inconsistency of the final results; however, this might have affected the observed effect of the RV vaccine. Previously, total numbers of RV hospitalizations per year in Argentina of around 18,000 and 24,000 were estimated [46, 47]. Although this dataset contains a very much reduced number of RV cases analyzed, we were able to demonstrate a significant impact observed after vaccine introduction, even when vaccine coverage was 61–80% during the studied period [17].

CONCLUSION

The introduction of the RV vaccine in the NIP of Argentina has contributed to the decline in the number of notified ADD and RV cases, especially among children < 2 years (22.1% and 54.0%, respectively). The reduction in the number of ADD and RV hospital discharges after vaccine implementation was in line with the reduction in the number of notified cases. This study paves the way for future studies to assess the effect of RV vaccination on the economic burden of RV and ADD in addition to gastroenteritis-related (GE) mortality. Beyond these limitations, this evaluation of the actual impact of the vaccine may complement clinical trials, providing important information for decision-making, as well as for the assessment of public health programs and interventions.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. GSK makes available the anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To request access to patient-level data and documents for this study, please submit an enquiry via www.clinicalstudydatarequest.com. Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

REFERENCES

1. Pan American Health Organization (PAHO) Rotavirus. Available from: https://www.paho.org/en/topics/rotavirus. Accessed on: 18 Nov 2021.

2. Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA Pediatr. 2018;172(10):958–65.

3. Tate JE, Burton AH, Boschi-Pinto C, et al. Global, regional, and national estimates of rotavirus mortality in children < 5 years of age, 2000–2013. Clin Infect Dis. 2016;62(suppl 2):S96–105.

4. Moraga P. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151–210.

5. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(2):136–41.

6. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Progress in the Introduction of Rotavirus Vaccine—Latin America and the Caribbean, 2006–2010. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6047a2.htm. Accessed on: 18 Nov 2021.

7. Centers for Disease Control and Prevention. Rotavirus vaccination Available from: https://www.cdc.gov/rotavirus/vaccination.html. Accessed on: 18 Nov 2021.

8. World Health Organization. Meeting of the immunization Strategic Advisory Group of Experts, April 2009–conclusions and recommendations. Wkly Epidemiol Rec. 2009;84(23):220–36.

9. World Health Organization. Rotavirus vaccines: WHO position paper—July 2021. Wkly Epidemiol Rec. 2021;96(28):219–301.

10. Rotavirus Organization of Technical Allies. Global Introduction Status. Available from: https://preventrotavirus.org/vaccine-introduction/global-introduction-status/. Accessed on: 12 Aug 2022.

11. Helena De Oliveira L, Danovaro-Holliday M, Matus C, Andrus J. Rotavirus vaccine introduction in the Americas: progress and lessons learned. Expert Rev Vac. 2008;7:345–53.

12. Pan American Health O. Vaccination Coverage. PAHO; Available from: http://ais.paho.org/imm/IM_JRF_COVERAGE.asp. Accessed on: 29 Aug 2022.

13. Ministerio de Salud de Argentina. Boletín Nacional. Resolución 1027/2014. Available from: https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-1027-2014-232068. Accessed on: 29 Nov 2021.

14. World Health Organisation. Weekly Epidemiological record. Rotavirus vaccines. WHO position paper—January 2013: Available from: http://apps.who.int/iris/bitstream/handle/10665/242024/WER8805_49-64.PDF?sequence=1&isAllowed=y. Accessed on: 29 Nov 2021.

15. Ministerio de Salud. Enfermedades inmunoprevenibles. Available from: https://www.argentina.gob.ar/salud/hospitalsommer/programas/vacunaci%C3%B3n. Accessed on: 29 Nov 2021.

16. World Health Organization. Global Health Observatory data repository-Rotavirus Immunization coverage estimates by country. Available from: https://apps.who.int/gho/data/node.main.ROTACn. Accessed on: 26 Aug 2022.

17. World Health Organization. Rotavirus vaccination coverage. Available from: https://immunizationdata.who.int/pages/coverage/ROTA.html?CODE=ARG&ANTIGEN=ROTAC&YEAR=. Accessed on: 23 Mar 2022.

18. Bayard V, DeAntonio R, Contreras R, et al. Impact of rotavirus vaccination on childhood gastroenteritis-related mortality and hospital discharges in Panama. Int J Infect Dis. 2012;16(2):e94–8.

19. do Carmo GM, Yen C, Cortes J, et al. Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med. 2011;8(4):e1001024.

20. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, et al. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med. 2010;362(4):299–305.

21. Lanzieri TM, Linhares AC, Costa I, et al. Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil. Int J Infect Dis. 2011;15(3):e206–10.

22. De Oliveira LH, Giglio N, Ciapponi A, et al. Temporal trends in diarrhea-related hospitalizations and deaths in children under age 5 before and after the introduction of the rotavirus vaccine in four Latin American countries. Vaccine. 2013;31(Suppl 3):C99-108.

23. Lanzieri TM, Costa I, Shafi FA, et al. Trends in hospitalizations from all-cause gastroenteritis in children younger than 5 years of age in Brazil before and after human rotavirus vaccine introduction, 1998–2007. Pediatr Infect Dis J. 2010;29(7):673–5.

24. Molto Y, Cortes JE, De Oliveira LH, et al. Reduction of diarrhea-associated hospitalizations among children aged < 5 years in Panama following the introduction of rotavirus vaccine. Pediatr Infect Dis J. 2011;30(1 Suppl):S16-20.

25. Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. Pediatr Infect Dis J. 2011;30(1 Suppl):S11–5.

26. de Palma O, Cruz L, Ramos H, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ. 2010;340:c2825.

27. Sáfadi MA, Berezin EN, Munford V, et al. Hospital-based surveillance to evaluate the impact of rotavirus vaccination in São Paulo Brazil. Pediatr Infect Dis J. 2010;29(11):1019–22.

28. Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J. 2011;30(1 Suppl):S6-s10.

29. De Jesus MCS, Santos VS, Storti-Melo LM, et al. Impact of a 12-year rotavirus vaccine program on acute diarrhea mortality and hospitalization in Brazil: 2006–2018. Expert Rev Vaccines. 2020;19(6):585–93.

30. García Martí S, Augustovski F, Gibbons L, et al. Impact assessment of the incorporation of the rotavirus vaccine in the province of San Luis—Argentina. Epidemiol Infect. 2019;147: e308.

31. Degiuseppe JI, Reale EA, Stupka JA, Network ARS. Rotavirus epidemiology and surveillance before vaccine introduction in Argentina, 2012–2014. J Med Virol. 2017;89(3):423–8.

32. Degiuseppe JI, Stupka JA. First assessment of all-cause acute diarrhoea and rotavirus-confirmed cases following massive vaccination in Argentina. Epidemiol Infect. 2018;146(15):1948–54.

33. Ministerio de Salud Argentina. Consolidado de eventos de notificación obligatoria - componente clínico (C2). Available from: https://bancos.salud.gob.ar/recurso/consolidado-de-eventos-de-notificacion-obligatoria-componente-clinico-c2. Accessed on: 8 Dec 2021.

34. Ministerio de Salud. Presidencia de la Nacion RA. Manual de normas y procedimientos de Vigilancia y Control de Enfermedades de Notificación Obligatoria. Available from: https://bancos.salud.gob.ar/sites/default/files/2019-10/2007_manual-normas-control-enfermedades-notificacion-obligatoria.pdf. Accessed on: 8 Dec 2021.

35. Buenos Aires Ciudad. Vigilancia de la salud y control de enfermedades. Vigilancia de Laboratorios (SIVILA). Available from: https://www.buenosaires.

gob.ar/salud/vigilancia-de-la-salud. Accessed on: 8 Dec 2021.

36. ANLIS Malbran. Ministerio de Salud Argentina. Mision, vision y objetivos. Available from: http://www.anlis.gov.ar/mision-vision-y-objetivos/. Accessed on: 29 Nov 2021.

37. Argentina DdEeIeSMdS. Reporte interactivo de estadísticas de salud. Available from: http://deis.msal.gov.ar/ReporteInteractivo/. Accessed on: 19 Jan 2022.

38. World Health Organization. ICD-10 Version: 2019 Available from: https://icd.who.int/browse10/2019/en#/A08.0. Accessed on: 9 Nov 2021.

39. Brodersen KH, Gallusser F, Koehler J, Remy N, Scott SL. Inferring causal impact using Bayesian structural time-series models. Ann Appl Stat. 2015;9(1): 247–74.

40. Atchison CJ, Stowe J, Andrews N, et al. Rapid declines in age group-specific rotavirus infection and acute gastroenteritis among vaccinated and unvaccinated individuals within 1 year of rotavirus vaccine introduction in England and Wales. J Infect Dis. 2016;213(2):243–9.

41. Paulke-Korinek M, Kundi M, Rendi-Wagner P, et al. Herd immunity after two years of the universal mass vaccination program against rotavirus gastroenteritis in Austria. Vaccine. 2011;29(15): 2791–6.

42. Payne DC, Staat MA, Edwards KM, et al. Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US Counties, 2006–2009. Clin Infect Dis. 2011;53(3):245–53.

43. Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. Pediatrics. 2009;124(2):465–71.

44. Ai CE, Steele M, Lopman B. Disease burden and seasonal impact of improving rotavirus vaccine coverage in the United States: a modeling study. PLoS ONE. 2020;15(2): e0228942.

45. Sánchez-Uribe E, Esparza-Aguilar M, Parashar UD, Richardson V. Sustained reduction of childhood diarrhea-related mortality and hospitalizations in Mexico after rotavirus vaccine universalization. Clin Infect Dis. 2016;62(Suppl 2):S133–9.

46. Gomez JA, Sordo ME, Gentile A. Epidemiologic patterns of diarrheal disease in Argentina: estimation of rotavirus disease burden. Pediatr Infect Dis J. 2002;21(9):843–50.

47. Martí SG, Alcaraz A, Valanzasca P, et al. Cost effectiveness evaluation of a rotavirus vaccination program in Argentina. Vaccine. 2015;33(42):5684–90.

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