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ORIGINAL RESEARCH

Acute Gastroenteritis Morbidity and Mortality Trends Following Universal Rotavirus Vaccination in Children in Peru: Ecological Database Study with Time-Trend Analysis

Patricia Juliao · Adriana Guzman-Holst · Vinay Gupta · Claudia Velez · Veronica Petrozzi · Theresa J. Ochoa

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ABSTRACT

Introduction: Rotavirus (RV) infection is the leading cause of severe diarrhea in children worldwide. It is responsible for around 25% of gastroenteritis (GE) cases, 33% of hospitalized GE cases, and an annual mortality rate of 113.4/100,000 in children < 5 years of age in Peru. RV infant vaccination is recommended by the World Health Organization and provides the best public health strategy to manage the disease. Universal RV vaccination was introduced in Peru in 2009.

Methods: Trends in GE ambulatory visits, hospitalizations, and deaths in children < 5 years of age are described in the pre-vaccination (2004–2008) versus post-vaccination (2010–2018) periods. Time-trend analysis was performed (using generalized linear regression models) to assess the impact of vaccination nationwide and by region after adjusting for variables.

Results: Between 2009 and 2011, vaccination coverage increased to over 80% in Peru. In infants < 1 year of age, GE ambulatory cases, hospitalizations, and deaths decreased in the post-vaccination period by 40.3%, 46.2%, and 55.5%, respectively (and in children < 5 years of age, by 34.4%, 41.9%, and 54.3%, respectively) compared with the pre-vaccination period. Results of the multivariate time-trend analysis also found significant decreases in the post-vaccination period of 10.7% (GE ambulatory cases), 17.2% (GE hospitalizations), and 37.3% (GE mortality) in children < 5 years of age. Data analyzed by region varied, with Costa and Sierra regions generally in line with the national findings; however, some findings were less robust for Selva due to fewer available data.

Conclusion: After 9 years of RV vaccination in Peru, there appears to be a statistically significant positive impact of vaccination, in terms of reducing GE-related mortality, hospitalizations, and ambulatory visits in infants and young children. For policymakers to understand regional differences and future vaccination needs, continued improvement in surveillance is needed.

Graphical Abstract:

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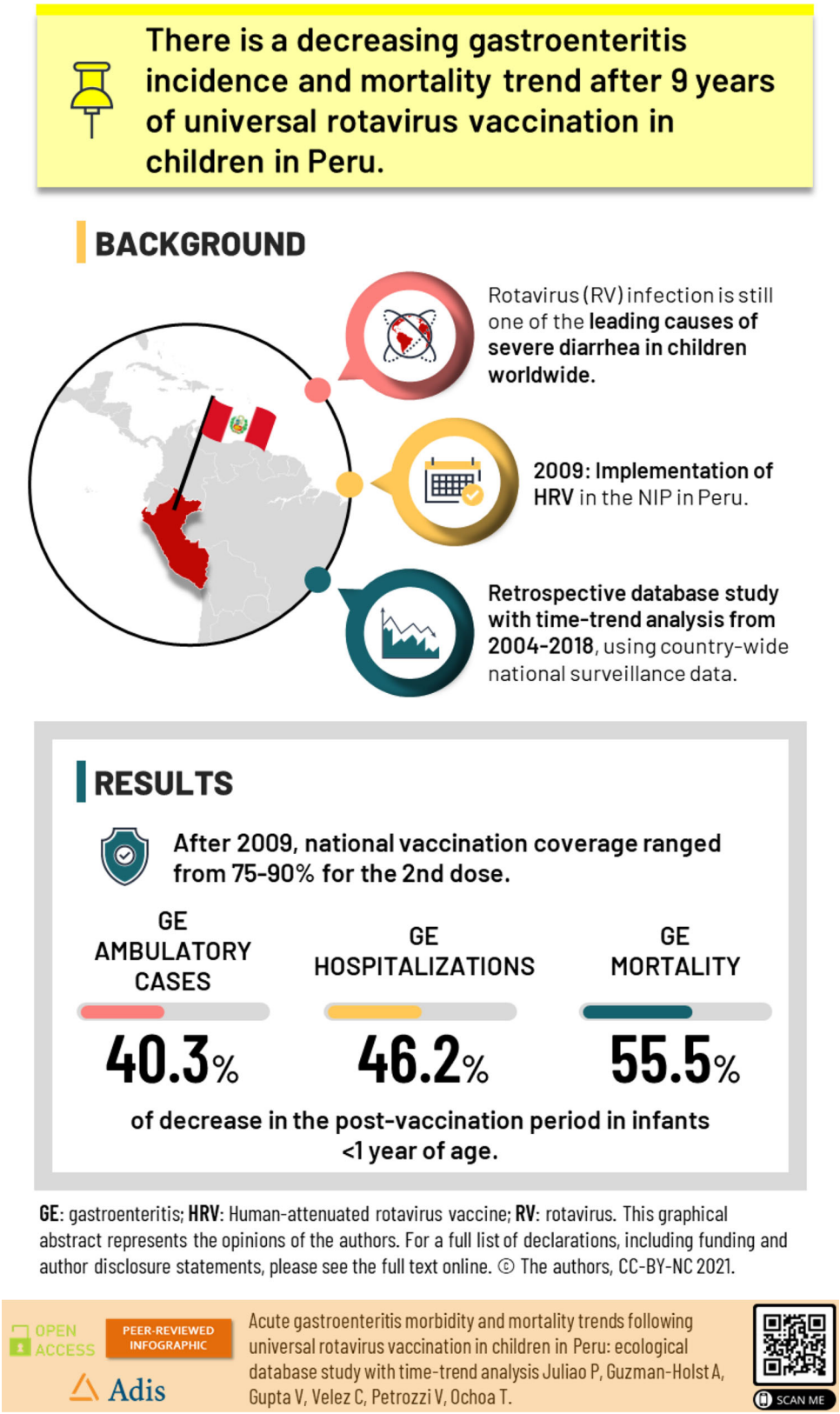
P. Juliao · A. Guzman-Holst (✉)
GSK, Ciudad del Saber Edificio 230, Panama City, Panama
e-mail: adriana.x.guzman@gsk.com

V. Gupta · C. Velez
JSS Research, Saint Laurent, QC, Canada

V. Petrozzi
GSK, Lima, Peru

T. J. Ochoa
Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru



GE: gastroenteritis; **HRV**: Human-attenuated rotavirus vaccine; **RV**: rotavirus. This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online.

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Keywords: Diarrhea; Mortality; Morbidity; Peru; Rotavirus; Trends; Vaccination

Key Summary Points

Why carry out this study?

Rotavirus (RV) causes severe gastroenteritis (GE) leading to morbidity and mortality in young children.

This study assessed the impact, in the first 9 years of universal RV vaccination in Peru, on GE mortality, hospitalizations, and ambulatory visits.

What was learned from the study?

There was a significant decrease in GE mortality, hospitalizations, and ambulatory visits in the post-vaccination period compared with the pre-vaccination period, in both observed data and the time-trend analysis after controlling for secular trends.

Regional differences in data availability highlight the need for improved surveillance.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.15172764.

INTRODUCTION

Diarrhea is the second leading cause of mortality worldwide in children < 5 years of age [1], and rotavirus (RV) infection is the primary cause of severe diarrhea in children, responsible for around 40% of diarrhea hospitalizations [2]. RV gastroenteritis (RVGE) is common, affecting nearly every child by the age of 5 years, for which 1 in 65 will require hospitalization and 1 in 293 will die [3]. In 2008, 37% of childhood diarrheal deaths were attributed to RV, 95% of which were in the poorest countries [4]. The burden of RV in Latin America between 1977 and 2009 was also considerable, with 24.3% of gastroenteritis (GE) cases and 29.7% of hospitalized GE cases caused by RV (25.1% and 32.6% in Peru, respectively), and an annual mortality rate in children < 5 years of age of 88.2/100,000 (113.4 in Peru) [5]. RV is a highly contagious and common pathogen, and, with no specific antiviral treatment available, prevention through vaccination is the most effective public health strategy to reduce the burden of RVGE.

Two effective RV vaccines with an acceptable safety profile are currently licensed in infants: 2-dose *Rotarix* (GSK, Belgium), a human attenuated vaccine (HRV) [6, 7] and 3-dose *RotaTeq* (MSD, USA), a bovine-human reassortant vaccine (BHRV) [8, 9]. Both vaccines protect against major circulating RV serotypes.

The World Health Organization recommended infant RV vaccination in Europe and the Americas in 2007, and worldwide in 2009, in particular in high child mortality countries [10]. The aim was to help achieve the target of a two-thirds reduction in childhood mortality (the fourth Millennium Development Goal) [10–12]. Since 2006, RV vaccination has been successfully implemented achieving high coverage in several Latin American countries, and producing important reductions in childhood diarrhea incidence and mortality [10]. In Peru, a country with high child mortality [4], RV vaccination was recommended in 2007, implemented in the most vulnerable and at-risk parts of the country by 2008, and universal infant RV vaccination was introduced in the National Immunization Program (NIP) in 2009. Following the introduction of RV sentinel surveillance in 2009, available data from 2010 to 2013 showed a sustained decrease in observed RV cases, with RV vaccination coverage reaching 85% in 2013 [13]. However, after this initial analysis, there is no further information available on the overall long-term impact of RV vaccination or data by region in Peru.

The objectives of this study were: (1) to describe trends in the incidence of GE

ambulatory and hospital cases and GE mortality in children < 5 years of age in Peru between 2004 and 2018, as well as vaccine coverage since 2009, from pre- to post-vaccine periods, and (2) use time-trend analysis to assess the impact of vaccination after adjusting for other variables. These findings will assist policymakers in evaluating the impact of RV vaccination in Peru.

METHODS

Study Design and Population

A retrospective ecological database study was conducted to assess GE morbidity (incidence of ambulatory cases and hospitalizations) and mortality trends in children, before and after the introduction of RV vaccination (January 2009) in Peru. The broader International Classification of Diseases and Related Health Problems (ICD-10) diagnosis codes for GE were used (codes A0–A09) as a proxy for RVGE burden (which includes RVGE code A08), as most cases are related to RV, but in many cases RVGE is not confirmed due to under-reporting and case definition limitations. A pre-vaccination period (January 2004–December 2008) and post-vaccination period (January 2010–December 2018) was defined as well as a transition period for the year of vaccine introduction (Fig. 1). Vaccine coverage was also assessed over the study period.

Outcomes were assessed in children < 5 years of age and in infants (defined as < 1 year of age), who have the highest disease burden. Outcomes were evaluated at the national level, as well as in three regions, as follows: Costa (Coast) (Tumbes, Piura, Lambayeque, La Libertad, Ancash, Lima, Callao, Ica, Arequipa, Moquegua, Tacna, and Lima province), Sierra (Highlands) (Cajamarca, Huánuco, Pasco, Junín, Huancavelica, Ayacucho, Apurímac, Cusco, and Puno), and Selva (Jungle) (Amazonas, Loreto, Ucayali, Madre de Dios, and San Martin).

The CNEPCE [Centro Nacional de Epidemiología, Prevención y Control de Enfermedades (Center for Disease Control, Epidemiology and Prevention)] database was searched for GE cases and deaths (using International Classification of Diseases ICD-10/ICD-9 codes), the INEI (Instituto Nacional de Estadística e Informática [National Statistics and Informatics Institute]) was searched for population statistics, and the Dirección General de Intervenciones Estratégicas en Salud Pública (DGIESP; MINSA; Department of Health) for vaccine coverage data (Supplementary Table 1).

Descriptive Analysis and Time-Trends Analysis

For the descriptive analysis, outcome data were tabulated by month and year, age group, region, and vaccination period. Mortality was calculated as: number of deaths in a year (and/or month)/ total population) × 100,000. Incidence was calculated as: number of cases in a year (and/or month)/ total population) × 1000. The total population (denominator) refers to the total national population of children < 5 years of age.

The percent change in the post- versus pre-vaccination period was computed using the formula: [(pre-vaccination period mortality or incidence – post-vaccination period mortality or incidence)/pre-vaccination period mortality or incidence] × 100. The 95% confidence intervals (95% CI) were calculated using the Delta method [14].

Vaccine coverage data were summarized per calendar year since NIP introduction, using frequency and percentage, with population projections for the correct age group per dose used as the denominator to calculate the percentage.

For the time-trend analysis, the percent change in incidence and mortality post-vaccination (with 95% CI) was explored using several generalized linear regression models [Poisson and negative binomial regression models (NBR)]. The Poisson model was the best fit for the data [using: log (Number of cases or deaths) = log (population projections + intercept + β1 year or month)]. Vaccination period was a dummy/indicator variable, with 0 denoting the pre-vaccination period, 1 denoting the transition period, and 2 denoting the post-vaccination period. The model included year/-month for the effects of secular trends and

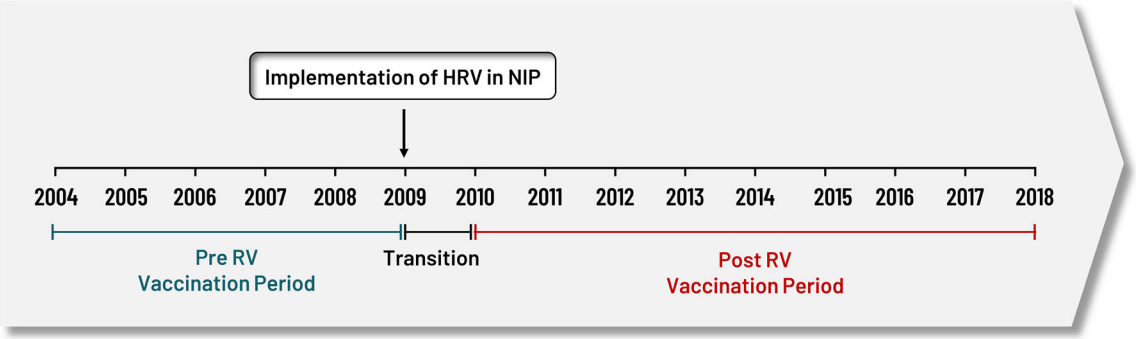

Fig. 1 Pre-vaccination, transition, and post-vaccination periods studied for RV, showing the pre-vaccination study period, the transition period when universal rotavirus (RV) vaccination was introduced in Peru, and the post-vaccination study period. Human rotavirus vaccine (HRV) was administered in a 2-dose schedule given at 2 and 4 months. *NIP* National Immunization Program

could include other relevant covariates (e.g., age group and region), if found to be significantly associated with the outcome in initial univariate analyses, and if they did not add an interaction effect.

All descriptive analysis and time-trends analysis were conducted in SAS v.9.4 and R 3.6.3.

Compliance with Ethics Guidelines

This study used anonymized aggregated database data with no personally identifiable information which can be linked to a patient. It was therefore considered out of scope for ethics review based on Peru's law on Transparency and Access to Information (Law 27806).

RESULTS

RV Vaccination Coverage

After universal RV vaccination was introduced in 2009, national vaccine coverage of the 2nd dose was, by 2011, above 80% in most regions and around 70% in Sierra (Fig. 2).

Incidence of GE ambulatory cases

In infants (< 1 year of age), 3,517,332 GE ambulatory cases were reported over the study period (2004–2018), with the highest number of cases seen in the Costa (1,945,065) and Sierra (837,542) regions followed by Selva (734,725) region. The GE ambulatory case rate in the pre-vaccination period was 528.83/1000 (nationwide). Post-vaccination, the national incidence decreased by 40.3% (95% CI 40.3, 40.4), with comparable significant decreases in each region (Table 1; Supplementary Fig. 1). Among all children < 5 years of age, 9,543,462 GE ambulatory cases were reported for 2004–2018 and incidence rates were lower (i.e., 275.30/1000 nationwide) than for infants. There were comparable regional trends in incidence and slightly lower post-vaccination incidence reductions [i.e., 34.4% (34.4, 34.5) nationwide] compared to the infants (Table 1; Supplementary Fig. 1).

For GE ambulatory cases (for children < 5 years of age), univariate analyses demonstrated significant decreases nationally [e.g., Poisson: − 32.3% (− 32.5, − 32.0)] and by region [Costa − 34.6% (− 34.9, − 34.3), Sierra − 34.4% (− 35.2, − 33.5) and Selva − 14.6% (− 15.4, − 13.7)]. After adjusting for secular trends in multivariate analyses, decreases in GE ambulatory incidence post- versus pre-vaccination remained statistically significant nationwide and in each region [e.g., Poisson: − 10.7% (− 11.4, − 10.1) nationwide] (Supplementary Table 2).

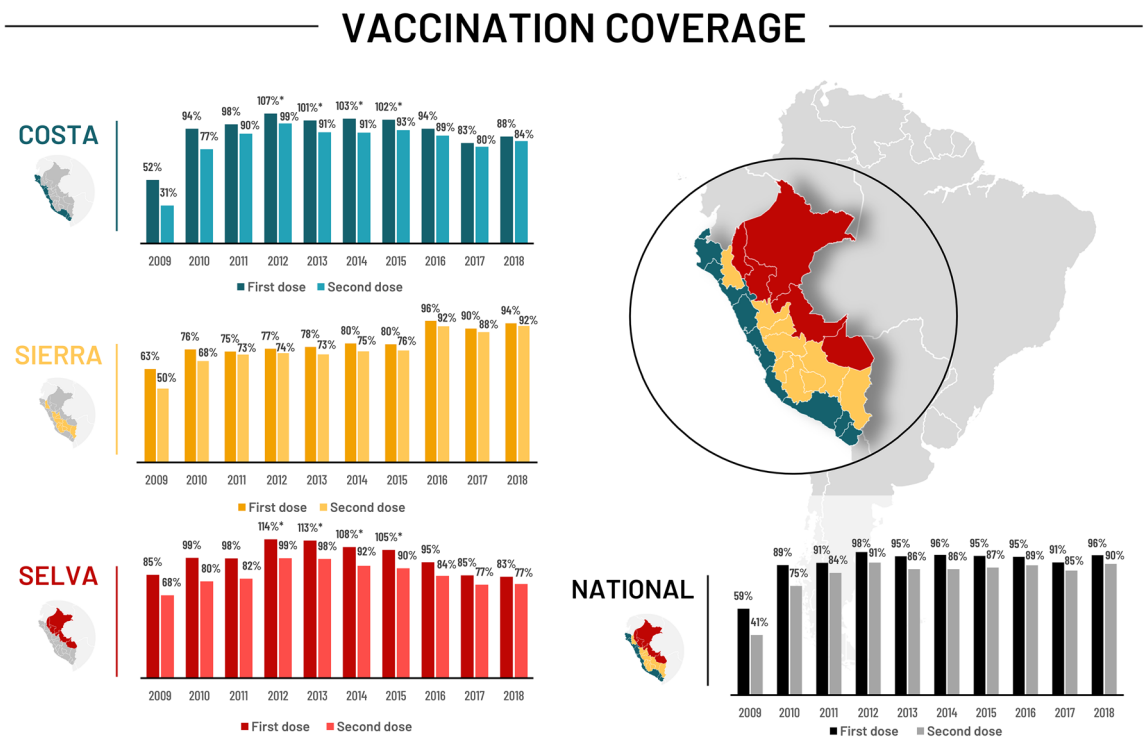

Fig. 2 RV vaccine coverage data for Peru. *Coverage levels > 100% are occasionally reported in national administrative databases as a result of systematic error in the numerator or denominator, such as the inclusion of children outside the target age group in the numerator. The population of infants < 1 year old was used as the denominator. Annual vaccination coverage levels are reported for the first and second dose in Costa, Sierra, Selva, and National level

Incidence of GE Hospitalization

In infants, 38,482 GE hospital cases were reported over the study period (2004–2018), with the highest number of cases seen in the Costa (21,537) and Sierra (11,221) regions followed by Selva (5,724) region. The GE hospitalization rate in the pre-vaccination period was 6.13/1000 nationwide. Post-vaccination, national incidence decreased by 46.2% (45.2, 47.2), with significant decreases of 43.0–54.2% also seen in each region (Table 1; Fig. 3a). Among children < 5 years of age, 93,580 GE hospitalizations were reported for 2004–2018 and incidence rates were lower than for infants (i.e., 2.88/1000 nationwide). Regional incidence trends and post-vaccination incidence reductions [i.e., 41.9% (41.3, 42.4) nationwide], however, were similar to the younger age group (Table 1; Fig. 3a; Supplementary Fig. 1).

For GE hospitalization (for children < 5 years of age), univariate analyses demonstrated significant decreases nationally [e.g., Poisson: − 37.6% (− 39.8, − 35.4)] and by region [Costa − 34.4% (− 37.0, − 31.8), Sierra − 41.7% (− 48.7, − 33.8) and Selva − 52.7% (− 57.1, − 47.8)]. After adjusting for secular trends in multivariate analyses, decreases in GE hospitalization incidence post- versus pre-vaccination remained statistically significant nationwide and in Costa [e.g., Poisson: − 17.2% (− 23.1, − 10.8) nationwide] (Supplementary Table 2).

GE Mortality

In 2004–2018, there were 709 GE deaths in infants (1,485 in children < 5 years of age). The highest number of deaths were in the Sierra (388) and Costa (198) regions and the lowest in Selva (123). Prior to vaccination, GE mortality

Table 1 Percent reduction in GE morbidity and mortality estimates after RV vaccination in children < 1 year of age and < 5 years of age in Peru (descriptive analysis)

	Pre-Vx 2004–2008	Transition 2009	Post-Vx 2010–2018	% Reduction (95% CI)
GE ambulatory visit				
< 1 year of age				
National	528.83	492.91	315.63	40.3 (40.3, 40.4)
Costa	515.43	449.61	298.37	42.1 (42.0, 42.2)
Sierra	406.75	365.68	234.63	42.3 (42.2, 42.5)
Selva	962.00	1098.13	655.34	31.9 (31.8, 31.9)
< 5 years of age				
National	275.30	254.37	180.50	34.4 (34.4, 34.5)
Costa	266.92	234.33	169.64	36.4 (36.4, 36.5)
Sierra	241.77	217.13	150.61	37.7 (37.6, 37.8)
Selva	419.43	470.13	329.78	21.4 (21.3, 21.4)
GE hospitalization				
< 1 year of age				
National	6.13	5.05	3.30	46.2 (45.2, 47.2)
Costa	5.78	4.72	3.29	43.0 (41.9, 44.2)
Sierra	5.66	5.31	2.97	47.5 (45.7, 49.3)
Selva	9.36	5.99	4.29	54.2 (51.3, 57.2)
< 5 years of age				
National	2.88	2.38	1.68	41.9 (41.3, 42.4)
Costa	2.55	2.19	1.65	35.5 (34.9, 36.1)
Sierra	2.70	2.48	1.51	43.9 (42.8, 45.0)
Selva	5.21	3.15	2.33	55.3 (53.5, 57.2)
GE mortality				
< 1 year of age				
National	12.19	10.40	5.42	55.5 (47.5, 64.8)
Costa	6.98	5.25	1.98	71.7 (52.6, 97.7)
Sierra	22.29	15.32	9.01	59.6 (48.3, 73.6)
Selva	9.88	23.32	14.12	30.0 (19.9, 45.4)[a]
< 5 years of age				
National	5.05	4.45	2.31	54.3 (48.8, 60.4)

Table 1 continued

	Pre-Vx 2004–2008	Transition 2009	Post-Vx 2010–2018	% Reduction (95% CI)
Costa	2.62	1.87	0.83	68.3 (54.9, 85.0)
Sierra	9.38	6.60	3.66	60.9 (52.6, 70.6)
Selva	5.25	11.85	6.59	20.4 (15.7, 26.4)[a]

GE gastroenteritis, *RV* rotavirus, *Vx* vaccination

[a] % increase; percent change in post versus pre-vaccination period computed using: [(pre-vaccination period mortality or incidence – post-vaccination period mortality or incidence)/ pre-vaccination period mortality or incidence] × 100; The 95% confidence intervals (95% CI) were calculated using the Delta method; morbidity refers to incidence (ambulatory cases and hospitalized cases)

rates were 12.19/100,000 nationwide, with the highest rate in Sierra (22.29) and the lowest in Costa (6.98) region. In the post-vaccination period, GE mortality significantly declined by 55.5% (47.5, 64.8) nationwide, and in Costa and Sierra regions by 71.7% and 59.6%, respectively, but increased by 30.0% in Selva region (Table 1; Fig. 3b). Among children < 5 years of age, GE mortality rates were lower (i.e., 5.05/100,000 nationwide) than in infants, however, regional trends and significant post-vaccination reductions in GE mortality [i.e., 54.3% (48.8, 60.4) nationwide] were comparable to those observed in infants (Table 1; Fig. 3b; Supplementary Fig. 1).

There were significant decreases in mortality in children < 5 years of age in the post- versus pre-vaccination period at the national level (e.g., Poisson: − 54.9% (− 56.4, − 53.3]) as well in Costa and Sierra regions [e.g., Poisson: Costa − 68.0% (− 69.4, − 66.4), Sierra − 60.6% (− 63.5, − 57.5)] with a statistically significant increase in Selva region [Poisson: 22.8% (13.6, 32.7)]. After adjusting for secular trends in the multivariate analysis, there were statistically significant decreases in post-vaccination mortality nationwide [− 37.3% (− 41.7, − 32.5)] and in Costa and Sierra regions. Due to the low number of deaths in Selva region the multivariate model yielded very different results to the univariate analysis [i.e., 152.4% increase (118.7, 191.2) versus 22.8% in univariate analysis] (Supplementary Table 2).

DISCUSSION

The highest burden of GE is seen in infants. Over the 14-year study period in Peru, infants with GE had more than 3.5 million ambulatory care visits and over 38,000 hospitalizations (despite a downward trend in GE hospitalizations observed from before vaccination implementation), and there were around 700 deaths. After RV vaccination was introduced in 2009, with a national coverage of around 80%, there was a statistically significant drop of 40% in ambulatory cases, 46% in hospital cases, and 56% in GE deaths in Peru. After adjusting for secular trends, the post-vaccination decline remained significant for ambulatory incidence (11% decline), hospital incidence (17% decline), and GE mortality (37% decline) at the national level. There were differences for some regions and endpoints, e.g., in Selva, which had the lowest vaccination coverage of the regions, there were wide fluctuations over time in observed GE deaths and the smaller number of deaths resulted in inconsistent multivariate results in this region. This region is known to have poorer access to healthcare, limitations in the surveillance system management, and lower vaccination awareness.

Other studies have also reported positive findings with RV vaccination in Peru. In 2013, 3 years after HRV implementation, data also showed a sustained decrease in observed RV cases, with RV vaccination coverage reaching 85% [13]. Early signs of RV vaccine impact were seen in a peri-urban community of Lima in the

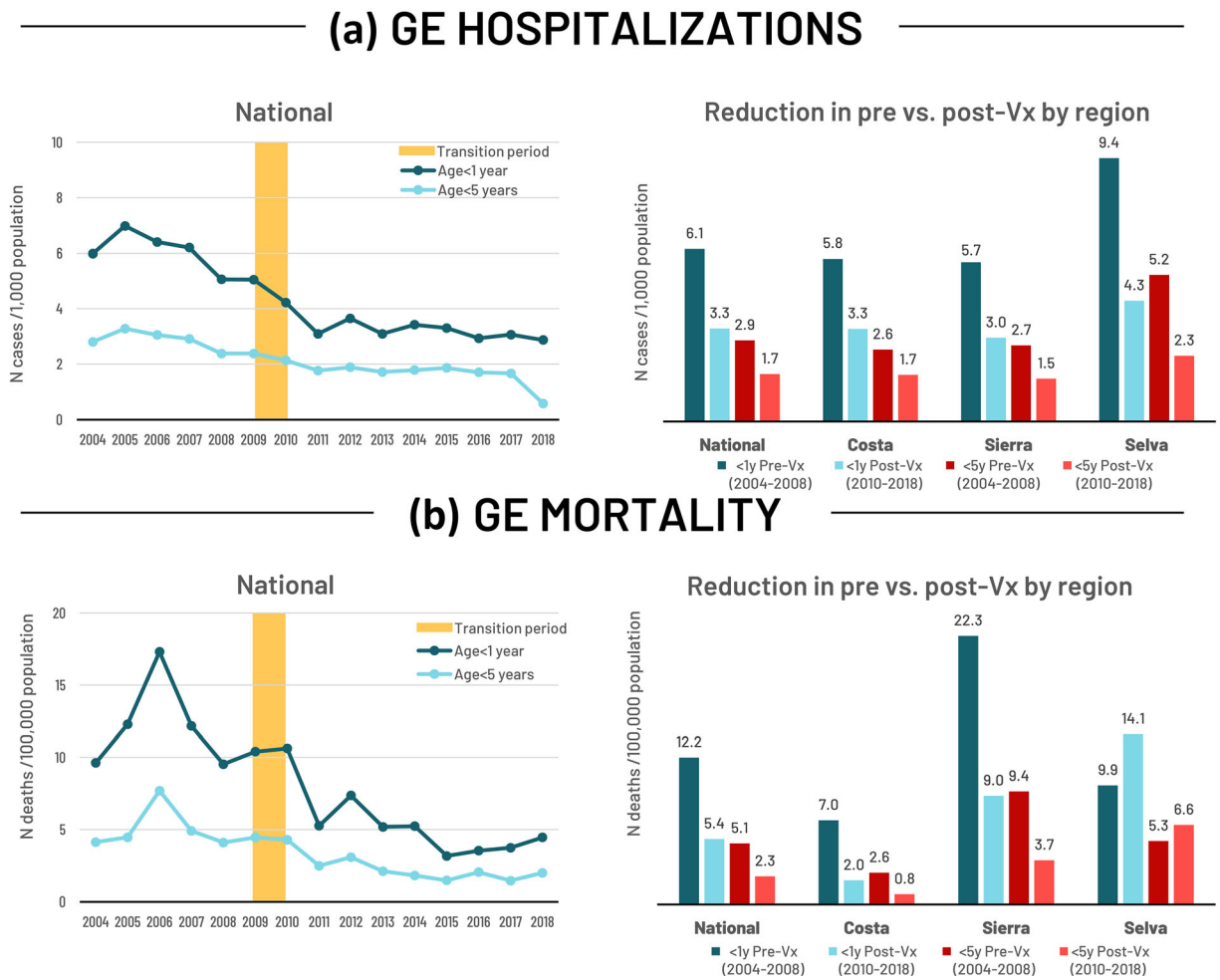

Fig. 3 National GE **a** hospitalization (/1000) and **b** mortality (/100,000) yearly trends (descriptive analysis). *GE* gastroenteritis, *N* number, *Vx* Vaccination, *y* year. Transition period period during when the rotavirus vaccination was introduced in Peru. **a** presents national GE hospitalization trends by year and in the pre- and post-vaccination periods (national and by region). **b** presents national GE mortality trends by year and in the pre- and post-vaccination periods (national and by region)

first two years after vaccine introduction. Data from a randomized trial on prevention of diarrhea were reanalyzed to estimate the annual RV prevalence among 1235 diarrhea episodes in children 1–2 years old. The study findings show a marked decrease in RV cases of diarrhea from 2008 to 2010 (from prevalence of 8.2% in 2008 to 2.4% in 2010) [15].

The post-vaccination period coincided with major improvements in sanitation and poverty levels in some regions of Peru, which may have resulted in differences in vaccine impact. One study in Loreto (Selva region), for example, reported good vaccine protection in infants but not in older children aged 1–2 years [16]. Therefore, the impact of universal RV vaccination in Peru was assessed between 2005 and 2015 in a study analyzing long-term trends and controlling for factors, such as access to piped water and sewerage and poverty, that can affect rates of diarrhea [16]. The results of this study are in line with our findings; after adjusting for long-term trends, the post-vaccination period had significantly fewer diarrhea clinic visits in children < 5 years of age nationwide. Areas with higher access to water and sanitation had

reductions in diarrhea visits, while this was not evident in areas with the poorest access [16].

A meta-analysis of recent data up to 2018 in Latin American countries that implemented RV vaccination reported a positive impact on acute gastroenteritis (AGE) hospitalizations and mortality, with benefits observed in both low- and high-mortality countries. In high-mortality countries (similar to Peru), in children < 1 year, RV hospitalizations declined by 51% and AGE hospitalizations by 20% compared to the pre-vaccination period, while AGE mortality declined by 45% [17]. Another study in six Latin American countries using sentinel RV surveillance networks found an overall 16% reduction in RV-associated diarrhea hospitalizations, with large country variations and a shift in seasonal peak to later in the year in high-mortality countries. The lower reduction estimated versus other studies may be due to differences in case definitions and methods used across studies in the region; however, all studies have reported a positive impact of RV vaccination on prevalence of RV and hospitalizations, as found in our study [18].

While it is possible to determine the impact of vaccination from ecological database studies, the results are strongly dependent on the quality of data reported in the databases. Over such a long timeframe, there are many changes that could have affected the data and which are difficult to control for; for example, a similar study assessing outpatient and hospital trends (following pneumococcal conjugate vaccination) in Peru from 2006 to end 2012 reported that improved access to healthcare over this time period may have resulted in increased reporting of cases [19]. In our study, we observed an increase in mortality in the Selva (jungle) region, despite good vaccination coverage, which could reflect improved health statistics and better reporting of cases and deaths in recent years (post-vaccination).

In addition to the limitations of data quality from passive surveillance systems, there were differences in data by region and over time, and it was not possible to adjust the models for the impact of seasonal trends in RV. Regions with poorer access to healthcare may have under-reporting of cases. Another limitation is the lack of data on ICD-10-coded RV gastroenteritis versus overall gastroenteritis. In many Latin American countries, studies must often rely on limited passive surveillance data, yet it is useful for evaluating population level trends and the impact of RV vaccination as well as seasonal changes.

CONCLUSIONS

Data from the first 9 years of RV vaccination in Peru are promising, showing a significant reduction in GE ambulatory and hospital cases and in GE deaths among young children and infants. Improvements in data reporting in all regions of the country will help policymakers to gain a better understanding of the impact and needs of vaccination at the regional level.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. CV, PJ and TO were involved in the conception and/or the design of the study. CV, PJ and AGH participated in the data collection/generation of the study data. AGH, PJ, VG, CV and VP were involved in the interpretation of the data. All authors reviewed and approved the final manuscript.

Disclosures. AGH and PJ are employed by the GSK group of companies. PJ holds shares in the GSK group of companies. VP was previously an employee of Merck Sharp & Dohme and is now an employee of the GSK group of companies. AGH, PJ and VP declare no other financial and non-financial relationships and activities. TO and VG declare no financial and non-financial relationships and activities and no conflicts of interest.

Compliance with Ethics Guidelines. This study used anonymized aggregated database data with no personally identifiable information which can be linked to a patient. It was therefore considered out of scope for ethics review based on Peru's law on Transparency and Access to Information (Law 27,806).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets were formally solicited from the main data sources outlined in Supplementary Table 1.

Trademark. Rotarix is a trademark owned by or licensed to the GSK group of companies. RotaTeq is a trademark owned by or licensed to Merck Sharp & Dohme Corp.

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