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SHORT REPORT

Background rates of disease in Latin American children from a rotavirus vaccine study

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ABSTRACT

Background: Knowledge of background rates of adverse events is crucial to assess vaccine safety concerns. We used data from a rotavirus vaccine study (Ruiz-Palacios et al., NEJM, 2006) including 63,225 infants from 11 Latin American countries to investigate reporting rates of serious adverse events (SAEs) among these infants, and describe rates by country, gender, age, and season.

Methods: For this randomized, double-blind, placebo-controlled, phase 3 trial, investigators from Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela recruited 6-to-13-week-old healthy infants. The infants received 2 oral doses of vaccine or placebo. The study population was followed 100 d for the assessment of adverse events. SAEs were captured by an active surveillance system.

Results: Strong differences in event rates could be observed between countries (min. 48.1/10,000 person-years in Dominican Republic/Peru; max. 296.2/10,000 person-years in Brazil) and between genders: gastroenteritis, pneumonia, bronchiolitis and bronchitis occurred significantly more frequently in males. In addition, infections and infestations, and most disorders, including immune system and cardiac disorders, were more frequent at earlier ages. Finally, looking at seasonality we noted higher rates of SAEs in the second half of the year in all countries except Mexico.

Discussion: Significant differences in reporting rates of SAEs between countries, gender and calendar months illustrate the importance of knowing the local epidemiology when interpreting SAEs. Data from clinical trials can be used to better understand background rates of diseases that may be perceived as potential adverse events following immunization.

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Introduction

Vaccines are among the most effective tools available for preventing infectious diseases. High immunization coverage has resulted in drastic declines in vaccine-preventable diseases. The burden of these diseases is largest in countries outside the EU and US, and consequently, many clinical trials for new vaccines are performed on other continents, including Latin America.

Public concern about real or perceived adverse events associated with vaccines is a barrier to vaccination.[1] For adequate assessment of possible vaccine safety concerns knowledge of the background rates of a disease is crucial to distinguish events that are temporarily associated with, but not caused by, vaccination from those caused by vaccination.[2] Background rates of selected medical events, stratified by age, sex, and seasonal distribution, could strengthen vaccine safety assessment, and provide an evidence-based focus for discussing the incremental risk of vaccines.[2]

An important source to estimate baseline rates are clinical trials. GSK has expressed the intention to make anonymized patient-level data available for all the trials it has performed since 2007,[3, 4] after review of the request for access by an independent expert panel (https://clinicalstudydatarequest.com, last accessed 15 February 2016). Astellas, Bayer, Boehringer Ingelheim, Daichi-Sankyo, Eisai, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare have subsequently joined this initiative.

Of particular interest to our objective is a study in which a rotavirus vaccine was investigated, because of its study population size powered to test a potentially increased risk of intussusception, a very rare condition where the bowel telescopes into itself. In this study, a total of 63,225 healthy infants from 11 Latin American countries and Finland, divided over a study arm (receiving 2 oral doses of the human rotavirus vaccine (Rotarix, GSK), 31,673 infants) and a control arm (receiving 2 doses of placebo, 31,552 infants) were followed-up to investigate the safety, of which 20,169 infants (10,159 vaccinees and 10,010 placebo recipients) had a prolonged follow-up to evaluate the efficacy of the vaccine.[5] We have used the data from this study to investigate the overall reporting rate of any SAEs among Latin American infants, overall and by country, gender, age, and season.

Results

A total of, 61,167 infants from 11 Latin American countries were studied for an average follow-up period of 8.3 months (Table 1). Follow-up time differed between countries, based on the absence or presence of an efficacy cohort in the country.

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Supplemental data for this article can be accessed on the publisher's website.

Table 1. Number of subjects and average follow-up time (in months) by country.

Country	N subjects			Average follow-up time (in months)
	Total	Females	Males	
Argentina	4,671	2,320	2,351	8.3
Brazil	3,218	1,573	1,645	7.4
Chile	3,458	1,709	1,749	5.7
Colombia	3,910	1,944	1,966	11.1
Dominican Republic	4,056	1,965	2,091	8.4
Honduras	4,195	2,033	2,162	10.4
Mexico	13,246	6,484	6,762	9.5
Nicaragua	4,057	1,993	2,064	11.4
Panama	4,062	1,957	2,105	8.2
Peru	12,044	5,907	6,137	4.6
Venezuela	4,250	2,082	2,168	9.8
Overall	*61,167*	*29,967*	*31,200*	*8.3*

During this follow-up period, the SAE rates (expressed as number per 10,000 person-years) were calculated per country. The data for preferred terms occurring more than 1/10,000 person-years are shown in Table 2. The table including 95% confidence intervals (CIs) is shown in Supplementary file S1. There are strong differences in the overall SAE reporting rates, ranging from 48.1 per 10,000 person-years in the Dominican Republic to 296.2 per 10,000 person-years in Brazil, as well as the rates of particular SAEs per country.

The data for preferred terms occurring more than 1/10,000 person-years are shown by gender in Table 3. These show significantly higher rates of SAEs overall in males. All 3 most common SAEs (gastroenteritis, pneumonia, and bronchiolitis) occurred significantly more frequently in males than in females, while a few less common SAEs occurred more frequently in females, e.g. urinary tract infection. All 387 different SAEs are shown in Supplementary file S2, by preferred term (PT) code.

In addition, the rates were calculated per system organ class (SOC) by age, Table 4. The rates including the 95% CIs are shown Supplementary file S3. As expected, most SAEs, in particular infections and infestations, immune system disorders, and cardiac disorders, occurred more frequently at early age, although the number of participants in the youngest and oldest age groups was limited, resulting in wide CIs.

Finally, we looked at seasonality of the occurrence of SAEs. The monthly SAE rates show large differences between countries, ranging from a mean of 2.74 per 10,000 person-months in Mexico to 19.25 in Brazil. In general, the rates are higher in the second half of the year, except in Mexico where the peak starts later and continues until February (figures for the separate countries are shown in Supplementary file S4).

Discussion

We report background incidences of several health conditions that may occur after vaccination. It should be noted that we are reporting events that are temporally related to vaccination, meaning only that they occur after vaccination and not necessarily because of vaccination. As data were collected from all children, irrespective of whether they received the rotavirus vaccine or not, our estimates are similar to what would be considered population observations, not necessarily implying any link to causation by vaccination. Inference of a causal link with vaccination would imply further assumptions.

Knowledge of the baseline rates of events provides an appropriate context to interpret adverse events as even rare health conditions are expected to occur coincidentally after vaccination. The observed rates of such events can be used to estimate the number of events that will occur after vaccination for a prespecified number of individuals. This approach has been used previously in New Zealand, where during a mass campaign against meningococcus type B, background rates were used to calculate observed versus expected ratios for adverse events as the vaccine campaign progressed.[6] Similarly, background rates of potential adverse events following immunization were determined before the expansion of the human papillomavirus vaccination program.[7-9]

We estimated an overall rate of SAEs of 1.05% in all Latin American countries combined. This rate was low compared with studies of the same vaccine in other regions of the world. In a European study of Rotarix, 5.5% (95% CI: 4.6–6.4) of the 2,646 infants in the study arm and 7.0% (95% CI: 5.7–8.5) of the 1,348 infants in the placebo arm had at least one SAE reported.[10] In a study performed in South Africa and Malawi, at least one SAE occurred in 319 of the 3,298 infants in the study arm (9.7%; 95% CI: 8.7–10.7) and in 189 of the 1,641 infants in the placebo arm (11.5%; 95% CI: 10.0–13.2).[11]

Table 2. Overall SAE rates and rates of most common (> 1/10.000 person years) SAEs by country.

Preferred term	All	Argentina	Brazil	Chile	Colombia	Dom Rep	Honduras	Mexico	Nicaragua	Panama	Peru	Venezuela
Gastroenteritis	22	26.6	115	12.3	16.1	10.6	18.2	16.8	24.5	30.7	10.5	12.4
Pneumonia	17.9	14.2	80	10.7	21	15.3	10.3	1.9	50	7.8	19.7	15.1
Bronchiolitis	11.6	7.7	24	5.6	11.8	8.2	11.3	19.5	3.9	21.1	4.7	0.7
Bronchopneumonia	4.5	—	2.1	8.2	5.5	—	0.2	7.5	4.5	19.9	0.2	—
Bronchitis	2.8	10.6	6.3	24	1.8	—	0.2	0.2	0.6	5.7	0.4	0.5
Bronchospasm	2.8	0.3	0.4	—	0.9	—	0.5	0.2	—	—	23.9	—
Dehydration	2.8	2.8	11.4	2.6	—	0.6	0.9	1.9	0.4	5.1	6.7	2.4
Urinary tract infection	2.6	6.2	0.8	10.7	5.1	—	1.4	1.1	3	2.7	0.9	2.9
Head injury	1.9	11.9	0.4	—	1.6	0.3	0.9	1.3	1.9	1.5	0.5	1.2
Asthma	1.8	—	11	1.5	0.7	—	4.6	0.2	0.2	10.2	—	0.7
Febrile convulsion	1.8	3.6	1.7	0.5	2.3	0.9	3	1.5	2.4	1.8	0.5	1.4
Pertussis	1.6	0.8	1.3	2.6	0.7	—	0.2	0.2	—	0.3	8.9	2.9
Diarrhea	1.3	—	—	6.1	0.2	—	3	0.7	0.9	1.8	4	—
Convulsion	1.1	2.6	0.4	2	1.4	—	1.6	0.6	0.6	1.5	1.1	1.4
Any PT[*]	104.8	135.9	296.2	137.5	90.7	48.1	82	74.3	116.9	162.4	99.8	76.5

Dom. Rep. = Dominican Republic, PT = preferred term.
[*]including both common and uncommon SAEs.

Table 3. Rate of the most common (> 1/10.000 person years) SAEs by gender.

Preferred term	Rate per 10.000 [95% CI]		
	All	Girls	Boys
Gastroenteritis	22.0 [20.9;23.5]	18.7 [17.1;20.5]	25.5 [23.6;27.5]
Pneumonia	17.9 [16.8;19.2]	16.6 [15;18.3]	19.2 [17.6;21]
Bronchiolitis	11.6 [10.7;12.6]	8.5 [7.4;9.8]	14.6 [13.2;16.2]
Bronchopneumonia	4.5 [3.9;5.1]	4.1 [3.4;5]	4.9 [4.1;5.8]
Bronchitis	2.8 [2.3;3.3]	2 [1.5;2.7]	3.5 [2.8;4.3]
Bronchospasm	2.8 [2.4;3.3]	2.5 [1.9;3.2]	3.1 [2.4;3.9]
Dehydration	2.8 [2.3;3.2]	2.5 [1.9;3.2]	3 [2.4;3.8]
Urinary tract infection	2.6 [2.1;3]	3.3 [2.6;4.1]	1.9 [1.4;2.5]
Head injury	1.9 [1.6;2.3]	2.1 [1.6;2.8]	1.7 [1.3;2.3]
Asthma	1.8 [1.5;2.3]	1.7 [1.2;2.2]	2 [1.5;2.6]
Febrile convulsion	1.8 [1.4;2.2]	1.5 [1.1;2.1]	2.1 [1.5;2.7]
Pertussis	1.6 [1.3;2]	1.5 [1.1;2.1]	1.6 [1.2;2.2]
Diarrhea	1.3 [1;1.7]	1.1[0.7;1.5]	1.6 [1.1;2.2]
Convulsion	1.1 [0.8;1.4]	0.9 [0.6;1.4]	1.3 [0.9;1.8]
Any SAE[*]	104.9[102;107.7]	90 [86.3;93.8]	119.2 [115;123.4]

95%CI = 95% Poisson exact confidence interval.
[*]including both common and uncommon SAEs.

Despite differences in absolute frequency, the most frequent SAEs were essentially the same in Latin America and Africa: gastroenteritis, pneumonia, bronchopneumonia and bronchiolitis were among the most frequent SAEs on both continents.[11] The higher SAE rate in Africa is most likely related to higher morbidity whereas the slightly higher rate in Europe may be related to a higher health care seeking behavior. These differences underscore the importance of comparing reported rates to background rates from the same region.

Significant differences in event rates could be observed, both between countries and between genders. The gender difference which we observed in SAE reporting seems to have been rarely observed for other vaccines before. Exceptions are a study of the Vaccine Adverse Event Reporting System, which found a higher rate of convulsions in boys vaccinated with acellular pertussis in a total of 913 reports over the years 1995–1998.[12] Another study saw a higher rate of adverse events following immunization in Omani boys in the national adverse events database.[13] Further studies are necessary to investigate whether this imbalance was also present in Rotarix studies on other continents, or whether the phenomenon might be related to gender differences in response to vaccine administration route/site.

The differences we observed between Latin American countries in overall rates may be due to several reasons. There may be differences in burden of disease as well as health care seeking behavior related to factors such as socio-economic status in the different countries. We can also not exclude difference in efforts made by investigators to capture and report all events (especially the milder ones), despite attempts by the sponsor to standardize these. Differences in seasonality are likely related to climatological differences across the Latin American continent, both within and between countries. For example, the high altitude regions in Colombia, Peru and Bolivia are completely different in climate from the low altitude regions. Similarly, in Brazil, the Amazonian region differs significantly from the southern states. This has an impact on diseases like respiratory infections, dengue and malaria. Seasonality was more or less as expected in the most Southern (Chile, Argentina) and Northern countries (Mexico), where the highest reporting rates were observed in their respective winter months. There were some less expected peaks in October in Peru and in October and November in the Dominican Republic. The Peruvian peak coincides with the start of the rain season. While the central and southern coastal parts, including Lima, have very little rainfall, most rainfall is noted in September.[14] The Dominican Republic has a tropical maritime climate, with little seasonal temperature variation, but with seasonal variation in rainfall.

Table 4. Rate of SAEs per specific organ class (SOC) by age, per 10.000 person-years.

SOC	All ages	Mo1-Mo2	Mo2-Mo3	Mo3-Mo4	Mo4-Mo5	Mo5-Mo6	Mo6-Mo12	Mo12-Mo18	Mo18-Mo24	Mo24-Mo30
Infections and infestations	75.5	117.5	75.2	88.2	83.1	84.4	72.9	45	38.2	117.5
Respiratory, thoracic and mediastinal disorders	8.4	15	13.6	9.1	9.6	8.1	9.9	5.6	11.4	15
Injury, poisoning and procedural complications	5.6	12.1	2.7	3.5	4.7	5.7	7.9	6.4	13.5	12.1
Gastrointestinal disorders	5	13	6.1	9	9.3	4.2	4.1	3.4	27	13
Nervous system disorders	4.2	5.8	3.4	4.7	5	3.9	4.7	6.2	7.1	5.8
Metabolism and nutrition disorders	4	4.6	4.5	6.2	5.5	6.3	3.9	1.9	10.6	4.6
General disorders and administration site conditions	1.7	15.4	7.8	4.2	5.1	1.8	1.6	2.5	—	15.4
Skin and subcutaneous tissue disorders	1.5	6.1	—	2.9	4.3	3.2	1.5	1.9	—	6.1
Blood and lymphatic system disorders	1.4	6.1	2.7	3.1	1.4	2.5	1.1	1.5	—	6.1
Congenital, familial and genetic disorders	0.9	9.9	2	2.7	1.7	1	0.8	1	17.1	9.9
Cardiac disorders	0.7	8.6	1.7	2.2	—	1	1.5	0.6	—	8.6
Immune system disorders	0.7	9.6	2.5	3.5	—	2.5	—	1.2	—	9.6
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0.6	—	2.1	3.2	—	0.7	—	1.3	—	—
Vascular disorders	0.6	—	0.8	—	3.1	1.2	0.4	1.3	4.8	—
Hepatobiliary disorders	0.5	—	—	3.2	—	—	—	1.7	—	—
Musculoskeletal and connective tissue disorders	0.5	3.7	—	4.4	—	0.3	—	1.4	—	3.7
Renal and urinary disorders	0.5	7.1	—	3.2	—	1	1.3	1.5	—	7.1
Investigations	0.4	—	—	2.9	—	—	—	1.3	—	—
Psychiatric disorders	0.4	—	—	1	4.7	1.2	0.4	—	—	—
Reproductive system and breast disorders	0.4	—	—	—	1.4	—	5.3	—	—	—
Social circumstances	0.4	—	—	—	—	—	—	1.2	—	—
Eye disorders	0.3	2.8	3.1	—	—	—	0.4	1.1	—	2.8
Surgical and medical procedures	0.2	—	—	1	—	1	—	—	—	—
Ear and labyrinth disorders	0.1	—	—	1	—	—	—	—	—	—

Mo = month

For the most densely populated area, the peak in SAEs coincided with the end of the rain season.[15] These findings illustrate the importance of knowing the local climate and epidemiology, especially of infectious diseases, when interpreting adverse event rates in small children.

Our study has strengths and limitations. As a first strength, serious adverse events were actively captured in this study, reducing under-reporting of events. Secondly, the number of infants vaccinated and the exact person-time was known, allowing us to estimate incidence rates unlike spontaneous reporting systems. The availability of data spanning at least an entire year allowed us to assess seasonal variations in SAE reporting. The population included in clinical trials such as the one we analyzed is likely to be healthier than the average general population, thereby resulting in relatively low rates of SAEs compared with the general population. Whereas this may hinder the use of these data for interpretation of rates observed in non-interventional trials, it is likely to be more representative than general population data when interpreting rates in other interventional trials. Adverse events are reported using a standard coding system used globally in clinical trials (MEDDRA). This coding system has limitation for epidemiological purposes as some events may be clinically comparable or even overlapping.

In conclusion, the availability of clinical trial data offers a great potential in assessing background rates of diseases that may be perceived as potential adverse events following immunization, keeping in mind that reported rates should be compared with background rates from the same region.

Materials and methods

Obtaining clinical trial data

A research proposal for the use of the clinical trial data from the GSK Rotarix study was submitted in October 2013. Upon review by the independent expert panel, the proposal was approved in March 2014. After signing the Data Sharing Agreement, access to the anonymized data set was provided by April 2014 through a password protected website.

GSK Rotarix clinical trial demographic data

For this randomized, double-blind, placebo-controlled, phase 3 trial,[5] investigators from Argentina, Brazil, Chile, Colombia, the Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela, and Finland recruited infants at public pediatric clinics or hospitals.

After a parent or guardian had provided written informed consent, 6-to-13-week-old healthy infants were enrolled. The infants were randomly assigned to receive 2 oral doses of either the human rotavirus vaccine or placebo — the first dose at visit 1 and the second at visit 2, one to 2 months later. The cohort was followed for a median duration of 100 d after the first dose for the assessment of any adverse events, including the occurrence of intussusception (the safety cohort), and a subgroup of infants was followed for 9 to 10 months for the assessment of efficacy (the efficacy cohort). An active surveillance system was established at hospital and medical facilities in the study areas. Parents were instructed to seek medical care at the nearest hospital or medical facility in case intussusception was suspected or if their child had severe gastroenteritis, and to contact the investigator. The study team visited or contacted the hospitals and medical facilities at least twice per week to identify study participants with intussusception, severe gastroenteritis, or any other event. Adverse events were considered serious if they resulted in death, were life-threatening, necessitated hospitalization or prolongation of existing hospitalization, or resulted in disability or incapacity. Outcomes were recaptured during the scheduled visits, if missed by the active-surveillance system. Parents who missed a follow-up visit were contacted by the study team. All adverse events were reported and classified into different categories by the investigators.

For the purpose of this study we included all Latin American countries, but excluded Finland from the final analyses. As we did not aim to assess causality of the reported events, data were collected from all children, irrespective of whether subjects were in the vaccine- or placebo arm.

Statistics

Rates (/10.000 person years) of SAEs (grouped by PT or SOC) were calculated by country, gender, age and season. The 95% CIs were calculated using the Poisson exact method.[16]

Disclosure of potential conflicts of interest

TV and KB have received consulting fees from GSK, unrelated to this work. The other authors declare no conflict of interest.

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