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Safety of pentavalent vaccine against rotavirus in Mexico during 2011-2017: surveillance reports

Seguridad de la vacuna pentavalente contra el rotavirus en México durante 2011-2017: Informes de vigilancia

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ABSTRACT

Diarrhoeal rotavirus diseases among children under one year old represent one of the main causes of medical care. Rotavirus vaccines have demonstrated impact on reducing diarrhoea morbidity and mortality worldwide. Thus, the World Health Organization (WHO) recommends to be considered within national immunization programs. In Mexico, the pentavalent rotavirus vaccine is currently used in children under 8 months of age. As part of the surveillance program, monitoring adverse events has improved in the last years, specially focused on the identification of intestinal invagination. The objective of the study was to identify and determine the causality of adverse events given by the pentavalent rotavirus vaccine considering the notifications made in the national system. An observational, descriptive and retrospective study was carried out to evaluate the notifications of adverse events related to vaccination during 2011-2017 in Mexico. During the follow-up period, 20,852,313 dose of pentavalent rotavirus vaccines were applied. Intestinal invagination was reported at a rate of 0.94 per 100,000 dose applied. The pentavalent rotavirus vaccine was shown in Mexico to be safe.

Keywords: Rotavirus vaccine, intestinal invagination, safety, Mexico.

RESUMEN

Las enfermedades diarreicas por rotavirus en niños menores de un año representan una de las principales causas de atención médica. Las vacunas contra el rotavirus han demostrado un impacto en la reducción de la morbilidad y mortalidad por diarrea en todo el mundo. Por ello, la Organización Mundial de la Salud (OMS) las recomienda dentro de los programas nacionales de inmunización. En la actualidad, en México, se utiliza la vacuna pentavalente contra rotavirus en niños menores de ocho meses de edad. Como parte del programa de vigilancia, el monitoreo de eventos adversos ha mejorado en los últimos años, con especial interés en la identificación de la invaginación intestinal. El objetivo del estudio fue identificar y determinar la causalidad de eventos adversos dados por la vacuna pentavalente para rotavirus considerando las notificaciones realizadas en el sistema de vigilancia nacional. Para ello, se llevó a cabo un estudio observacional, descriptivo y retrospectivo para la evaluación de las notificaciones de eventos adversos relacionados a la vacunación (VR5) durante el periodo 2011-2017 en México. Durante el periodo de seguimiento se aplicaron 20,852,313 dosis de vacunas pentavalentes contra rotavirus. Se reportó invaginación intestinal con una tasa de 0.93 por cada 100,000 dosis aplicadas. La vacuna pentavalente contra rotavirus se demostró que es segura en México.

Palabras clave: *Vacuna contra el rotavirus, invaginación intestinal, seguridad, México.*

INTRODUCTION

Immunization through vaccination has been considered one of the most efficient ways to avoid diseases, disabilities and deaths due to preventable diseases, such as diarrheal diseases caused by rotavirus, which remains as the most common cause of severe diarrhoea or severe gastroenteritis among

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young children worldwide.[1,2] By the end of 2018, the rotavirus vaccine had been introduced in 98 countries[1] as part of their phased, regional or national basis, with an estimated global coverage of 25%.[3]

Rotaviruses are double-stranded (ds) RNA viruses and are transmitted primarily via faecal-oral route, generating symptoms within the first two days after infection, where the first episode results in the most severe disease outcome and subsequent ones are associated with milder disease or appear to be asymptomatic.[4,5] In this sense, specific prevention for rotavirus not only reduces diarrhoea disease in pediatric age but also has an impact on mortality rate of children under five years[6] and contributes to economic growth and increases life expectancy.[4] Thus, the World Health Organization (WHO) recommends that rotavirus vaccines should be included in all national immunization programs for prevention and treatment-oriented interventions to reduce diarrhoea morbidity and mortality[2] and reiterates its recommendation that the first dose of monovalent or pentavalent vaccine should be administered after 6 weeks of age.

Current rotavirus vaccines approved by the *Food and Drug Administration are RotaTeq*® a pentavalent rotavirus vaccine (RV5) and *Rotarix*® (RV1)[7] and both are considered safe and well tolerated and the results of some published studies confirm the high efficacy of both vaccines against severe diarrhoea caused by rotavirus.[8-10] However, there is one consideration with oral rotavirus vaccines, as there is a lack of information regarding the absence of evidence of their potential increased risk of a rare but serious cause of bowel obstruction, as a result of an intussusception, in which one portion of the intestine invaginates into another portion.[9]

In Mexico, diarrhoea remains a public health problem; within the first five main causes of morbidity and mortality in children under five years, with devastating economic consequences for the family economy with a sick child with rotavirus. However, some studies have suggested that seasonality does not affect rotavirus, specifically during winter, as in the case of diarrhoea caused by another etiology.[10] During the 1990's, mortality and morbidity rates due to this disease decreased significantly due to oral hydration therapy, improvements in environmental sanitation and the implementation of other taken measures to control cholera.[10]

Vaccination to vulnerable groups began in 2006 in Mexico, with a monovalent vaccine and in 2007 got universalized in children under seven months 29 days of age. In 2011, it was changed from the monovalent to the pentavalent vaccine.[11] The currently used vaccination scheme for children under eight months of age was approved by the National Vaccination Council in 2011, for a pentavalent rotavirus vaccine (RV5) which is an attenuated vaccine containing five reassortant rotaviruses derived from human and bovine parent strains that express human outer capsid proteins of common circulating strains (G1, G2, G3, G4 and P).[12] The vaccination schedule consists of three oral dose of 2 mL each at 2, 4 and 6 months of age; considering that no child should receive first, second or third dose after seven months with 29 days of age[13,14] or children with a history of a chronic disease of the intestines, including any malformation, or subjects with any or severe combined inmunodeficiency.[15]

The safety and efficacy of allowed vaccines for the prevention of severe rotavirus gastroenteritis among infants have been assessed in several settings performing randomized controlled trials worldwide.[5,16] In Mexico, the National Pharmacovigilance System is aimed to generate information on the safety of medicines, including vaccines, through notification of Events Allegedly Attributed to Vaccination or Immunization (ESAVI) in a national database in order to facilitate their surveillance and to evaluate the causal relationship between vaccine with the ESAVI to elaborate recommendations for the prevention of the events supposedly attributable to vaccination or inmunization.[17]

Adverse events related to pentavalent rotavirus vaccine have been monitored, the most frequently reported are fever $\geq$ 38.1 °C (20.9%), diarrhoea (17.6%) and vomiting (10.1%), among others. On the other hand, those considered as serious events that can occur, such as anaphylaxis and intussusception, with an overall frequency of 0.1%.[17] Special attention has been focused on intussusception, considering, before vaccination rates of intussusception was reported in 68 per 10,000 infants and until December 2008, 1,118 deaths were considered to be related to diarrhoea in children under five years of age.[18]

In some studies, conducted in other countries, it was observed that the relative risk of intussusception among the vaccinated children, compared with those who received placebo, was 1.6 (95%CI; 0.4-6.4) during the period of 42 days after any dose, suggesting an acceptable safety profile for this vaccine. Meanwhile, other reports have described an increased risk of intussusception after the first

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dose of pentavalent vaccine, during the first week of vaccination but not in the second or third dose.[19] This study aimed to provide a brief summary of the safety of the current use of pentavalent rotavirus vaccines regarding the notifications of events allegedly attributed to vaccination or immunization among Mexican infants during a period of seven years (2011-2017).

MATERIAL AND METHODS

A descriptive and retrospective study was performed, considering published data from the National Database during the period of 2011 to 2017, and concentrated by the national surveillance system; ESAVI; which is structured in 4 different levels: local, jurisdictional, state and federal and is based on the health personnel information and which includes patients of the main national public institutions of the national health system; Ministry of health, Mexican Institute of Social Security (IMSS), IMSS Prospera and Institute of Security and Social Services for Workers of the State (ISSSTE). Sample size calculation was not required since total reported cases were considered in this analysis.

Events Allegedly Attributed to Vaccination or Immunization (ESAVI) are defined as: clinical manifestations or medical event that occurs after vaccination and is supposedly attributed to vaccination or immunization. The timing will depend on each of the vaccines, in the case of rotavirus up to 42 days after application. The classification by type of ESAVI is in two categories: non-serious and serious consequences. Non-serious outcomes include all events that do not meet the criteria of a serious one, a serious ESAVI is considered as any important clinical manifestation that meets one or more of the following criteria: They cause either endanger patient's life at the time they occur, make hospitalization necessary or prolong hospital stay, are related to alterations or malformations in the newborn, cause persistent or significant disability or disability or the death of the patient.[18]

Following way

Doctors, nurses and health personnel:

- That they provide vaccination services.
- From health centers, hospitals or others health units serving patients arriving with an ESAVI.
- From nurseries and schools where carry out vaccination work

To assume that the association between two events is of a causal nature, that is, that an independent variable has an effect or modifies the dependent variable. The independent variable corresponds to the cause or risk factor under study, in this case vaccination. While the dependent variable corresponds to the effect or outcome under investigation; any ESAVI related to the rotavirus vaccine. Some of these causality criteria were considered: 1) the statistical association between the independent variable and the dependent variable; 2) the temporal sequence between the variables (whether the independent precede the dependent or not, respectively); 3) the experimentation (whether the dependent variable is modified or not if the researcher exposes it to the independent variable), and 4) the dose-response relationship (the greater the independent variable, the greater the dependent change). The first two criteria, the statistical association and the temporal sequence, are necessary to establish the causal relationship, so that without these two conditions it is assumed that the independent event is not the cause of the dependent event. On the other hand, experimental evidence is, by itself, the best evidence of the causal relationship between two phenomena. And to assume that an event is coincident, it is the association that exists between two events that occur after vaccination but are not caused by the vaccine administered. The administration of most vaccines coincides with the period of greatest vulnerability of children to acquire diseases or manifest health problems (congenital neurological diseases, sudden death syndrome, among others).

Notifications corresponding to the period of 2011-2017 of the events supposedly attributable to the vaccination or immunization by pentavalent rotavirus vaccine (RV5) from the 32 federal entities of Mexico were retrieved. Likewise, records of the patients who were notified as serious were included, in order to carry out the investigation and conclude the causality considering whether the pentavalent rotavirus vaccine was the cause of the adverse events presented. Data are described and ESAVI presentation rates were calculated considering the number of cases per 100,000 doses applied. Analyzes were performed using the statistical package SPSS® version 25.0. For all the analyses a

Table 1: Rates of severe ESAVI for RV5 vaccine at national level during the period 2011-2017.

Year	Applied dose	Total number of notified ESAVIs*	Classification		Serious ESAVI rate‡
			Serious*	Not serious*	
2011	1,970,688	18	14	4	0.71
2012	3,069,940	11	9	2	0.29
2013	2,985,066	11	7	4	0.23
2014	3,250,364	43	30	13	0.92
2015	3,264,468	77	50	27	1.53
2016	3,182,690	60	40	20	1.26
2017	3,129,097	98	68	30	2.17

ETAV/ESAVI Database, CENSIA 2011-2017.
* Data presented as frequency (n).
‡ Reported rate per 100,000 applied doses.
Expected intestinal invagination rate 6 per 100,000 dose applied.[20]

statistical significance was considered from a value of $p < 0.05$.

In the case of serious ESAVI notified by RV5 vaccine, these were determined by the researchers with collaboration of the National Expert Committee on ESAVI, constituted by a group of specialists in the different branches of medicine, who meet in order to identify the data of the vaccine administered and determine the time between the administration of the vaccine and the appearance of signs and symptoms, according to the Manual of Events supposedly attributable to the vaccination or immunization, as well as investigate the ESAVI cases notified by any type of vaccine, through the analysis of clinical records, complementary examinations and results of necropsy in the two deaths presented, the risk factors, who contributed to explain the nature of ESAVI.

RESULTS

According to the information obtained from the Database of ESAVI, fed by the notifications at national level during the period 2011 to 2017; 20,852,313 pentavalent rotavirus vaccines were applied to children between two and eight months of age, there were no statistically significant differences according to the year of application ($p < 0.05$).

Adverse events were recorded during the next 35 days after vaccination and a total of 318 ESAVI related to RV5 vaccine were notified, corresponding to a rate of 1.53 cases per 100,000 applied doses, from them 68.6% (n = 218 cases; representing a rate of 1.05 per 100,000 applied dose) were considered serious, and 31.4% non-serious (n = 100; rate 0.48 × 100,000 doses applied). 61.0% (n = 194 cases); rate 0.93 × 100,000 doses applied) of all cases were due to intussusception. According to historical data, 1,251 cases of intussusception were expected during the mentioned period, corresponding to an expected rate of 6 per 100,000 doses applied.

It was observed that there was an increase in the rate of severe ESAVI due to rotavirus, from 0.71 to 2.17 per 100,000 applied doses. After analysis made by a group of experts 70% of the ESAVI were considered causative events and 30% coinciding with the vaccination *(Table 1)*.

From all the serious ESAVI related to RV5 vaccine during the monitoring period, 89.0% (n = 194) were due to intussusception, other causes (11.0%; n = 24) includes coincident events (6.4%; n = 14) such as (convulsive seizures, lower respiratory tract infections, nosological entities), dehydration (0.92%; n=2), hypovolemic shock (0.92%; n = 2), bronchitis (0.46%; n = 1), acute abdomen (0.46%; n = 1), pneumonia (0.46%; n = 1), septic shock (0.46%; n = 1), iron deficiency anemia (0.46%; n = 1), and aspiration syndrome of gastric content (0.46%; n = 1). During this period and from all ESAVI, just two cases were reported as death and were considered not related to the vaccine and were evaluated as coincident with the vaccination, as one of them corresponding to 2011, which a previous diagnostic as bronchopneumonia and septic shock and the other one reported in 2015, diagnosed as intussusception

Table 2: Intestinal invagination rate for severe ESAVI reported at the national level during the period 2011-2017.

Year	Serious notifications (ESAVI)*	Intestinal Invagination*	Invagination rate‡
2011	14	13	0.66
2012	9	9	0.29
2013	7	6	0.20
2014	30	30	0.92
2015	50	38	1.16
2016	40	35	1.10
2017	68	63	2.01

ETAV/ESAVI Database, CENSIA 2011-2017.
* Data presented as frequency (n).
‡ Reported rate per 100,000 applied doses.
Expected intestinal invagination rate 6 per 100,000 dose applied.[20]

Table 3: Total cases reported by intestinal invagination according to the dose applied, during the period 2011-2017 in Mexico.

Year	Intestinal invagination cases*	Dose		
		First dose*	Second dose*	Third dose*
2011	13	4	6	3
2012	9	3	3	3
2013	6	1	3	2
2014	30	11	11	8
2015	38	11	12	15
2016	35	17	12	6
2017	63	13	30	20

ETAV/ESAVI Database, CENSIA 2011-2017.
* Data presented as frequency (n).
‡ Reported rate per 100,000 applied doses.
Expected intestinal invagination rate 6 per 100,000 dose applied.[20]

(corresponding to the second dose of the vaccine) in a five month-old patient, with bleeding of the digestive tract and vomiting of gastrobiliary content at 13 days after the vaccine application, the patients died within two hours after been admitted to the hospital with a diagnosis of broncho-aspiration.

The highest Intussusception rate during the analyzed period was observed in 2017 with an rate of 2.01 per 100,000 applied dose, which is below the expected rate 6 per 100,000 dose applied *(Table 2)*. Also, of the 63 serious ESAVI given by intussusception; 47.6% (n = 30) were presented with the second vaccine application, meanwhile 31.7% (n = 20) after the third one and 20.6% (n = 13) with the first doses *(Table 3)*.

The most frequent events presented as non-severe ESAVI due to RV5 were vomiting, diarrhoeal evacuations, fever and abdominal pain, within the severe ESAVIs the most frequent diagnosis was intussusception. It was observed that the main signs and symptoms presented in patients immunized with rotavirus vaccine were intussusception with a rate of 0.93; diarrhoea with a rate of 0.86; vomit with a rate of 0.80; hematochezia with a rate of 0.77 per 100,000 doses applied *(Table 4)*.

DISCUSSION

In this analysis including reports of ESAVI related to pentavalent rotavirus vaccine during the 2011-2017 period in Mexico, it was observed that the cases reported due to intussusception were associated and coincidental to vaccination with RV5 and it was observed an increase in the rate of severe ESAVI due to rotavirus. However, this is an expected situation, derived from the fact that in 2014 the situation of previous years, identifying the need to reinforce the training, in order to improve the vigilance, also a closer follow-up was carried out by the federal entity, and supervisory visits were made in all those states where there was minimal notification or epidemiological silence, achieving increase the identification of ESAVI cases and their timely notification.

It is not possible to foresee the appearance of an ESAVI, except for those caused by technical errors or by the quality of the vaccine, so it is important that the health worker has enough technical knowledge to apply the prevention measures and to inform to the population about the most frequent events and provide the corresponding treatment.

In the strategies proposed by the different health instances, both national and international, the implementation of surveillance systems is recommended in order to define risk profiles and as a complementary instrument to others to create a progressive culture of safety. So that in Mexico, the inter-institutional working group formed by the Directorate General of Epidemiology (DGE), Federal Commission for Protection against Health Risks (COFEPRIS) and National Center for Child and Adolescent Health (CENSIA) are working on a

Table 4: Rate of signs and symptoms presented in patients notified during the 2011-2017 period in Mexico.

Sign or symptom	Rate*	Sign or symptom	Rate*
Intestinal invagination	0.93	Fever	0.26
Diarrhoea	0.86	General discomfort	0.13
Vomiting	0.80	Erythema‡	0.13
Hematochezia	0.77	Hyporexia	0.10
Irritability	0.38	Food intolerance	0.10
Abdominal pain	0.26	Cough‡	0.10

ETAV/ESAVI Database, CENSIA 2011-2017.
* Rate per 100,000 dose applied.
‡ Symptomatology that does not correspond as an event related to the application of a pentavalent rotavirus vaccine according to the literature.

National platform, which allows us to have timely, reliable information and that provides data for the construction of process indicators, opportunity, that allow us to perform evaluations in the federative entities, as well as contributing to the decision-making regarding vaccination.

Some of the first reports regarding RV5 vaccine were published in the last years and have showed higher efficacy in the first year against severe rotavirus diarrhoea and have not identified any concerns.[21,22]

It is interesting to compare the results of the reported by Reyna-Figueroa and collaborators of the events associated with vaccination for rotavirus with the monovalent vaccine in 2008 and 2009, using the ETAV (passive type registration) reporting system, to estimate the risk of events associated with vaccination, with which they evaluated 7,691,757 doses of vaccine, and concluded that the estimated risk of an associated event was 2.9 per one million doses.[18] In the present study that includes from 2011 to 2017 with 20,852,313 doses of vaccines against pentavalent rotavirus in children between 2 and 8 months of age and recorded adverse events during the following 35 days; 318 adverse events were found (rate 1.53 × 100,000 doses), 100 non-serious (rate 0.48 × 100,000 doses), 218 serious (rate 1.05 × 100,000 doses), and 194 cases of intussusception (rate 0.94 × 100,000 doses), very much below the expected rate of 6 per 100,000 doses.[20]

While it is true that different vaccines were used and also different methodology, it is important to note that both the vaccination of a period with monovalent vaccine, and that of this other period with pentavalent vaccine, were very safe, as shown in other reports.[23] Also, vaccination does not seem to impact on the risk of intussusception or any serious adverse events, as the incidence rate for intussusception before this immunization strategy remains in 68 cases per 10,000 infants,[18] as reported by Cochrane review.[5]

These findings are consistent with the literature referenced by WHO, and although all vaccines against rotavirus have a small risk of intussusception after the first or second dose, the benefit / risk ratio strongly favors the use of these vaccines, both in developed and developing countries.[24,25] Also, our study is important in refining the understanding of the effects of rotavirus vaccine in a «real world» context, where a low observed rates of ESAVI found in this analysis suggest that rotavirus vaccination in Mexico was most protective than related to adverse events.

Therefore, the pertinent recommendations were issued to those responsible for each of the states that notified ESAVI for RV5 vaccine, in order to carry out the exchange of information with the person in charge of the universal vaccination program and this in turn with the corresponding levels, in order that these recommendations and the final result of the ruling of the ESAVI investigation, reach the local level where the ESAVI was presented and the result is notified to the patient's relatives, as well as generate strategies and Solution alternatives in the corresponding medical unit.

CONCLUSIONS

Vaccination against rotavirus is safe and according to data obtained from 20,852,313 dose applied in Mexico. It was observed that the frequency of ESAVI, including intussusception, is low compared with reported data or rates before the implementation of the vaccine as a national strategy.

The analysis of the information obtained from the ESAVI Surveillance System allowed us to have reliable and comparable statistics, suggesting that pentavalent vaccine against RV5 has a high safety margin, since intussusception rates are very low. Vaccination against rotavirus has a greater benefit than risks because it prevents diarrhoea, complications and deaths, thus should be considered as an effective and safe prevention measure.

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