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Safety Profile of ROTAVAC: An Observational Prospective Study

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Abstract: **The research seeks to assess the safety profile of ROTAVAC®, a rotavirus vaccine, utilizing an observational prospective methodology. The findings are likely to contribute valuable insights to the field of vaccine safety. Rotavirus vaccination (ROTAVAC®) was incorporated into the Universal Immunisation Program (UIP) of Punjab, India, in 2019. This research constitutes a single-centre observational prospective study conducted in a Government Civil Hospital in Punjab, India.**

Methods:

This study comprises two endpoints: primary, to detect and investigate the adverse events (AE) arising subsequent to ROTAVAC® vaccine administration to infants; and secondary, to generate awareness and facilitate the reporting of adverse events following immunisation (AEFI) by Health Care Practitioners (HCPs).

Results:

In this study, 47% of the subjects receiving ROTAVAC® vaccine experienced AEFIs. Most of the AEFIs were consistent with the established safety profile of ROTAVAC® vaccine. No statistically significant difference was observed between the various demographics and AEFI incidence. All 30 HCPs interviewed demonstrated limited knowledge regarding AEFI reporting and had infrequently reported any AEFI. The mean score prior to the provision of health education was 4.07±1.17, and the score following education increased to 7.27±1.05, indicating a statistically significant difference ($W=465.000$, $p<0.005$).

Conclusion:

The ROTAVAC® vaccine demonstrated safety in Punjab, India, following its recent implementation. No novel clinically significant safety concerns with medical implications were identified for ROTAVAC®. Furthermore, this investigation underscores the significance of conducting knowledge dissemination sessions for healthcare professionals (HCPs) at immunisation clinics to enhance adverse event detection and reporting.

Keywords: **Rotavirus, ROTAVAC®, adverse events, adverse events following immunisation, safety profile.**

I. INTRODUCTION

Rotavirus is a highly infectious viral pathogen that primarily affects infants and young children, causing acute gastroenteritis characterized by severe diarrhea, emesis, pyrexia, and abdominal discomfort. It is globally recognised as the predominant etiological agent of severe dehydrating diarrhoea in children under 5 years of age [1]. The virus exhibits high environmental stability and is transmitted via the faecal-oral route, with an incubation period of 1-3 days and symptomatic phase lasting 3-8 days [2]. Severe cases can precipitate rapid dehydration, electrolyte disturbances, and mortality, if left untreated. While rotavirus infections occur throughout the year, their incidence peaks during the winter months in temperate regions. Prophylaxis through immunisation is crucial, as rotavirus is responsible for over 200,000 annual fatalities in children under 5, predominantly in developing nations [3]. Therapeutic interventions primarily focus on prevention and management of dehydration through oral rehydration therapy or intravenous fluid administration in severe cases. The global impact of rotavirus extends beyond its immediate health consequences, affecting socioeconomic factors and healthcare systems. In low- and middle-income countries, the burden of rotavirus infections places significant strain on already limited healthcare resources. The economic impact is multifaceted, encompassing direct medical costs, lost caregiver productivity, and long-term consequences on child development and education.

The pathogenesis of rotavirus infections involves several mechanisms. Upon ingestion, the virus targets the mature enterocytes at the tip of the small intestinal villi. Viral replication leads to cell lysis and villous atrophy, resulting in malabsorption and secretory diarrhea [4]. Additionally, rotavirus infection activates the enteric nervous system, stimulating intestinal secretion and motility. The virus also produces the enterotoxin NSP4, which further contributes to diarrhoea by altering intestinal permeability and calcium homeostasis [5].

Recent research has highlighted the potential long-term consequences of rotavirus infection, particularly in early childhood. Some studies have suggested a link between severe rotavirus gastroenteritis and the subsequent development of celiac disease and type 1 diabetes, although more research is needed to establish causal relationships [5]. Efforts to improve rotavirus vaccines continue, with research focusing on developing next-generation vaccines that offer broader protection, improved efficacy in low-income settings, and alternative delivery methods. The oral administration of current vaccines can be challenging in regions with a high enteric disease burden, prompting the exploration of parenteral vaccine formulations.

Prevention strategies extend beyond vaccination. Improved sanitation, access to clean water, and the promotion of handwashing practices play crucial roles in reducing rotavirus transmission. Educational programs targeting caregivers and healthcare providers are essential for the early recognition of symptoms and prompt initiation of appropriate management. The impact of climate change on rotavirus epidemiology is an emerging area of research. Alterations in temperature and precipitation patterns may affect the survival of the virus in the environment and influence transmission dynamics, potentially leading to shifts in seasonal patterns and the geographical distribution of infections[6].

Rotavirus vaccines have demonstrated high efficacy in preventing severe rotavirus gastroenteritis in high-income countries, with effectiveness ranging from 85% to 98%[7]. However, their performance in low- and middle-income countries has been less optimal, with effectiveness ranging from 40% to 60%[5]. Several factors contribute to reduced vaccine efficacy in resource-limited settings, including malnutrition, concurrent enteric infections, high levels of maternal antibodies, and differences in gut microbiome composition.

Rotavac is an oral rotavirus vaccine developed in India to prevent severe rotavirus gastroenteritis in infants and young children. The key aspects of the Rotavac are as follows.

1. Development: Rotavac was developed through a collaborative public-private partnership involving the Indian government, Bharat Biotech, and various research institutions [8][9].

3. Efficacy: Clinical trials have demonstrated the effectiveness of Rotavac in preventing severe rotavirus gastroenteritis, with an efficacy rate of approximately 56% against severe rotavirus diarrhoea.

4. Dosage: The vaccine is administered orally in three doses, typically at 6, 10, and 14 weeks of age.

5. Advantages: Rotavac exhibits heat stability, making it suitable for use in resource-limited settings with unreliable cold chain infrastructure.

6. Cost-effectiveness: As an indigenously developed vaccine, Rotavac offers a more affordable alternative compared to other rotavirus vaccines, thereby increasing accessibility to a broader population in developing countries.

7. WHO prequalification: In 2018, Rotavac received the World Health Organization (WHO) prequalification, enabling its use in global immunisation programs [10].

In India, ROTAVAC® was launched in a phased manner in the Universal Immunisation Program (UIP) by the Government of India (GOI). It was launched in four states in 2016, and later expanded to seven more states. Thus, 11 states were covered by the end of 2018. Since then, 17 more states have been covered under India's immunisation program [11]. It was launched in the state of Punjab in August 2019.

To detect rare Adverse Events following immunisation (AEFI), such as intussusception, it is imperative to monitor the safety profile of rotavirus vaccines. ROTAVAC® was introduced in India in 2016, following a trial involving approximately 4500 infants, prior to the introduction of RotaTeq®, a trial of 70,000 subjects was conducted across 11 countries. Consequently, rare AEFIs, such as intussusception, cannot be definitively excluded in the Indian population using ROTAVAC®[12]. Furthermore, monitoring the safety profile of a vaccine is an ongoing process; however, to date, only a limited number of studies, such as Kar et al., have evaluated its safety profile in select Indian state. Given that ROTAVAC® was recently introduced in Punjab, it is crucial to ascertain the safety profile of the vaccine in this region. To the best of our knowledge, no such study has been conducted in the Punjab region thus far. Therefore, this study aimed to identify various AEFI occurring after the administration of ROTAVAC®.

Collection and evaluation of AEFI through solicited and unsolicited methods facilitates the examination of a drug's safety profile. This aspect constitutes a component of pharmacovigilance (PV) or drug safety. The Pharmacovigilance Program of India (PvPI) was initiated by the Government of India in 2010 [13]. Subsequently, a hierarchical structure of centres was established to implement a robust ADR monitoring system. However, practical knowledge of PV among HCPs remains relatively limited. This limited understanding of PV among healthcare professionals can lead to underreporting of adverse events and incomplete safety profiles for medications. To address this gap, comprehensive training programs and awareness campaigns are essential to improve PV knowledge and practices among HCPs. Additionally, implementing user-friendly reporting systems and providing regular feedback on reported adverse events can encourage active participation in pharmacovigilance activities. Therefore, this study also aimed to educate healthcare professionals regarding the importance of AEFI reporting.

II. METHODOLOGY

A. Study design: This is a single centre observational prospective study conducted in a Government Civil Hospital in Punjab, India.

B. Study population Inclusion criteria:

- Infants attending the immunisation clinic for routine vaccination for 1st, 2nd or 3rd dose.
- Male or Female
- Age: 6 weeks to 8 months
- Parents willing to provide informed consent and to participate in the study were selected on a first-come, first-serve basis.

Exclusion criteria:

- Evidence of any underlying illness in the infant
- Parents unwilling to provide informed consent
- Parents unwilling to follow up for the study

C. Study treatment: ROTAVAC®, a live attenuated monovalent vaccine, is currently administered as a rotavirus vaccine in the EPI schedule in India. It is administered orally in three dose series at 6, 10, and 14 weeks of age.

D. Study endpoints:

- Primary endpoint: Safety and tolerability of ROTAVAC® vaccine.
- Secondary endpoint: Increasing awareness of AEFI identification and reporting among HCPs at the study site.

E. Study Conduct and Patient Safety: The study was conducted from 01 January 2020 to 31 March 2020 in the immunisation clinic of the Government Civil Hospital, Mohali, Punjab. Informed consent was obtained from the parents/caregivers of the infants attending the vaccination clinic. Informed consent was also obtained from healthcare professionals at the vaccination clinic for participation in the study.

A pre-designed structured questionnaire was prepared to solicit sociodemographic and relevant clinical information. The questionnaire was administered telephonically on the day of vaccination at the study site and on days 0, 1, 7, 14, and 30.

In the case of an AEFI, parents/caregivers were counselled and, if required, referred to appropriate health care facilities for their management.

A second pre-designed structured questionnaire was used to collect information from healthcare professionals working in these clinics regarding their level of awareness of AEFI reporting. After an initial assessment, a knowledge-sharing session was conducted for the HCPs to instruct them regarding pharmacovigilance and the importance of reporting such events. The questionnaire was then re-administered to the HCPs on a different date to measure the difference in awareness after the knowledge-sharing session.

F. Statistical analysis: Data is presented using appropriate descriptive statistics. Chi square/Fisher's exact test was used to explore the association across categorical variables. The difference in HCP scores before and after imparting knowledge was assessed using the paired samples T Wilcoxon signed-rank test. The data was analyzed using IBM® SPSS® v20.0.0. The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 was used for coding of AE. Medical

judgement, where applicable, was used for grading AEFI. Causality assessment of AEFIs was performed using the WHO's new causality assessment algorithm by checking eligibility and using the checklist and algorithm. Finally, the AEFIs were categorised according to the causality assessment classification. A p value of <0.05 was considered statistically significant for the purpose of this study.

G. Ethical considerations: Written consent was obtained from the parents of the infants and HCPs. No intervention was performed for infants or HCPs.

The study was conducted after obtaining ethical approval from the University of Siena, Italy, and informed consent from the parents/caregivers. The study was conducted according to the Declaration of Helsinki (2013).

All patients attending the immunization clinic of Civil Hospital, Mohali, India from 1st January, 2020 to 31st January, 2020, were screened for this study. A total of 308 parents came to the immunisation clinic and 56 refused to provide informed consent. Hence, 252 infants aged 6 to 14 weeks were enrolled in the study and followed up for a period of one month.

III. RESULTS

AEFI

In total, 139 AEFIs were observed in 133 infants. Verbatim of the subjects' complaints was coded using MedDRA v23.0. The five most common PTs were as follows: pyrexia, 21.8%, crying, 7.5%, injection site erythema 4.7%, irritability, 4.3% and vomiting, 4.3%.

Seriousness of AEFI

Out of 252 infants, only two (approximately 1%) had a serious AEFI. One had diarrhoea which occurred on the third day post-vaccination, and the second had vomiting which occurred on the same day and lasted for a few hours. Both recovered after appropriate medical intervention.131 (approx. 52%) infants had a non-serious AEFI and 119 (approx. 47.2%) did not have any AEFI.

Severity of AEFI

126 (90.6 %) AEFIs were mild, 11 (7.9%) were of moderate severity and 2 (0.7%) were severe in nature.

AEFI on 30th day post vaccination

On 30th day after rotavirus vaccine administration, 12 infants (5.0%) reported an AEFI, while the rest (n=240, 95.0%) were healthy and did not have any AEFI.

Causality Assessment

93 (67%) of the events had consistent causal association,46 (33%) AEFIs had an inconsistent causal association, and no case had indeterminate association to ROTAVAC® immunisation. None of the reactions were unclassifiable (Table 1).

TABLE I: Causality assessment of ROTAVAC® AEFI with Preferred Terms.

Type	Causality assessment, n	Preferred Term (PT) (%)
I. Cases with adequate information	139 (100%)	
Consistent with causal association to immunization	93 (67.0%)	**Pyrexia 44, Crying 16, Vomiting 8, Rash 7, Infantile spitting up 6, Irritability 5, Diarrhea 4, Cough 3**
Indeterminate	0	
Inconsistent with causal association to immunization (coincidental)	46 (33.0%)	**Injection site erythema 12, Pyrexia 11, Irritability 6, Diarrhea 5, Crying 3, Rhinorrhea 3, Vomiting 3, Cough 2,**
II. Cases without adequate information	**0**	

Association of AEFI with different socio-demographic and clinical variables

The association of various socio-demographic and clinical variables such as birth weight, gender, place of delivery etc. with incidence of AEFI is presented in Table 2. None of the variables showed a statistically significant association with the presence of AEFI (p>0.05).

TABLE II: Association of AEFI with variables

Variables	No. of infants with AEFI			P value
		Yes (n=133)	No(n=119)	
Birth Weight	LBW	20	11	0.16*
	Normal Weight	113	108	
Gender	Male	66	68	0.23*
	Female	67	51	
Mother's working status	Working	19	23	0.28*
	Homemaker	114	96	
Place of Birth	Tertiary hospital	116	104	0.97*
	Home	17	15	
Type of Birth	Normal	75	81	0.06*
	Caesarian	58	38	
Place of residence	Rural	24	17	0.42*
	Urban	109	102	
Breastfed	Yes	116	105	0.81*
	No	17	14	
Gestational age	Normal	126	106	0.10*
	Preterm	7	13	
Literacy of father	Literate	130	114	0.48**
	Illiterate	3	5	
Literacy of mother	Literate	120	110	0.54*
	Illiterate	13	9	
Religion	Hindu	78	63	0.65**
	Sikh	50	51	
	Christian	0	1	
Socio-economic Class	Lower	0	2	0.07**
	Upper Lower	34	31	
	Lower Middle	93	72	
	Upper Middle	6	12	
	Upper	0	2	

*Chi-square test, **Fischer's exact

Pharmacovigilance education to HCPs

Thirty HCPs associated with the immunisation clinic agreed to participate in a knowledge sharing session for pharmacovigilance with pre- and post-session assessments.

Health care professionals were administered a questionnaire prior to and after PV education. The mean score prior to imparting health education was 4.07±1.17, with a median (IQR) score of 4 (2), and the score after education increased to 7.27±1.05, with the median (IQR) score increasing to 7(1).

The difference in the median related pair of scores was explored using Related Samples Wilcoxon Signed Rank test which depicted a statistically significant difference. (W=465.000, p<0.005). The graph below depicts the scores achieved by the Healthcare professionals before and after imparting knowledge about pharmacovigilance (Figure 1).

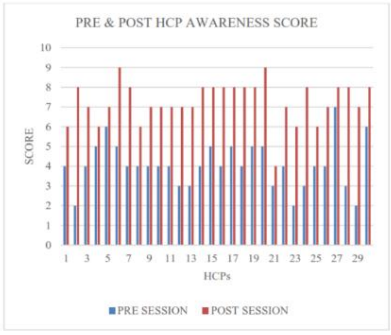

Fig. 1: Pre and post pharmacovigilance session score of HCPs (Maximum score=9).

IV. DISCUSSION

The WHO recommends monitoring for any significant AEFI of unexplained causes occurring within 30 days after vaccination [14][15].

Causality assessment plays a crucial role in evaluating the safety profile of vaccines and in addressing potential concerns. This systematic approach involves analysing adverse events reported after vaccination to determine whether a causal relationship exists between the vaccine and the observed effects. By conducting thorough causality assessments, regulatory authorities and healthcare professionals can make informed decisions about the continued use of a vaccine and

implement appropriate risk-mitigation strategies [16]. In this study, causality assessment of AEFIs was performed for association with the ROTAVAC® vaccine. 93 (67%) AEFI showed a consistent causal association, 46 (33%) had an inconsistent causal association, and no AEFI had an indeterminate causal association with ROTAVAC®. Most of the consistent events are also known to be caused by the administration of concomitant vaccines (OPV, IPV, PCV, and Pentavac); however, the role of the ROTAVAC® vaccine cannot be ruled out. Infantile spitting up was considered consistent, as the event was caused by oral administration of ROTAVAC®, whereas injection site erythema was considered inconsistent, as it was caused by the administration of concomitant injectable vaccines. To our knowledge, the causal association between ROTAVAC® and AEFI has not been reported in any previous study.

Overall, most reported AEFIs were non-serious and resolved completely in less than a day. The AEFIs were consistent with the established safety profile of ROTAVAC® vaccine.

The evidence regarding the risk of intussusception associated with various rotavirus vaccines remains inconclusive [17]. Although this study did not demonstrate any risk of intussusception in infants receiving ROTAVAC® vaccine, the limited sample size precludes definitive conclusions regarding the absence of intussusception risk with ROTAVAC®. Further research with larger cohorts, statistically powered to detect rare events such as intussusception, is necessary to establish the safety profile of ROTAVAC® vaccine with respect to intussusception.

It is important to note that the WHO underlines the importance of rotavirus vaccination, inspite of the risk of intussusception, in its position paper, on Rotavirus vaccines published in January 2013 with the following statement:

"..... the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception [18]. "

30 HCPs were given the predesigned, structured questionnaire before and after imparting knowledge regarding AEFI reporting. The mean score prior to imparting pharmacovigilance education was 4.07±1.17, with maximum score of 9, and the score after educating them increased to 7.27±1.05. The difference in scores was statistically significant ($p<0.05$). This indicates the benefit of imparting appropriate pharmacovigilance education to HCPs. The HCPs recognised the significance of AEFI reporting; however, they perceived the process as challenging to implement due to time constraints.

Although there is a robust pharmacovigilance program in India (PvPI), this study highlights that there is a lack of knowledge regarding AEFI reporting among HCPs in Punjab. Therefore, wider efforts to educate and inform the HCPs regarding pharmacovigilance and AEFI reporting are required. To the best of our knowledge, this study represents the first endeavour to generate AEFI data following ROTAVAC® administration in children within the state of Punjab. The findings indicate that the vaccine demonstrates safety in the studied population, and no novel safety concerns regarding the vaccine were identified.

This study on the safety profile of ROTAVAC rotavirus vaccine presents several notable **limitations**:

1. Limited generalizability: The predominantly urban study population (73%) may not accurately represent the broader Indian population, particularly those in rural areas. Consequently, the findings may not be applicable to rural settings.

2. Potential over-reporting of adverse events: The active solicitation of adverse events following immunization (AEFIs) may have resulted in higher reporting rates compared to typical passive surveillance methods.

3. Insufficient sample size: The enrolment of only 252 infants limited the study's statistical power to detect rare adverse events or evaluate associations between variables and AEFI incidence.

4. Difficulty in distinguishing vaccine effects: The concurrent administration of other vaccines (OPV, IPV, PCV, Pentavac) alongside ROTAVAC complicates the attribution of observed AEFIs specifically to ROTAVAC.

5. Absence of dose-specific data: The lack of information on AEFIs occurring after individual ROTAVAC doses restricts dose-related safety analysis.

6. Limited follow-up duration: The 30-day follow-up period may have failed to capture longer-term adverse events.

These limitations underscore the necessity for larger, multi-center studies with extended follow-up periods to more comprehensively evaluate the safety profile of ROTAVAC rotavirus vaccine.

Despite the aforementioned limitations, this study on the safety profile of ROTAVAC rotavirus vaccine exhibits several notable **strengths**:

1. Active surveillance: The study utilized active solicitation of adverse events following immunization (AEFIs), likely resulting in more comprehensive data collection compared to passive surveillance methods.

2. Diverse population: Although predominantly urban, the study included participants from various socioeconomic backgrounds, providing insights into vaccine safety across different demographic groups.

3. Real-world setting: The study was conducted in a routine immunization clinic, reflecting actual clinical conditions and enhancing the practical applicability of the findings.

4. Comprehensive AEFI assessment: The study evaluated a wide range of adverse events, including both common and rare occurrences, providing a thorough safety profile.

5. Timely follow-up: The utilization of multiple follow-up time points (24 hours, 72 hours, 7 days, and 30 days) facilitated the detection of both immediate and delayed adverse events.

7. Consideration of concomitant vaccines: By documenting the concurrent administration of other vaccines, the study provides valuable information on the safety of ROTAVAC in the context of routine immunization schedules.

8. Identification of risk factors: The study analysed potential associations between demographic factors and AEFI incidence, contributing to a better understanding of at-risk populations.

V. CONCLUSION

ROTAVAC® vaccine was found to be safe in a small study sample in Punjab, India where the vaccine was launched recently. There were no new safety concerns identified with ROTAVAC®. However, since the vaccine is relatively new in the region, the HCPs have to be vigilant in identifying and reporting any rare safety concerns with the vaccine. To this effect, the study evaluated and educated the HCPs in the tertiary level hospital, to strengthen AEFI reporting from the study site. This will help in monitoring the safety profile of newer vaccines being launched in the region.

VI. RECOMMENDATIONS

Larger multicentric studies should be conducted in the region to confirm the safety of ROTAVAC® vaccine, demonstrated in this study. This will generate more confidence in use of ROTAVAC® vaccine and help in reducing the rotavirus induced diarrheal burden which would then reflect in a decreased infant mortality rate in the country. HCPs at all healthcare levels including primary healthcare centers should be educated and encouraged to report AEFIs. Pharmacovigilance workshops and knowledge sharing sessions for HCPs will be helpful to emphasize the importance of AEFI reporting. Proper infrastructure, support and knowledge of pharmacovigilance centers should be provided to facilitate smooth reporting of AEFIs. Parents of infants should be counselled appropriately regarding detection and reporting of AEFIs. This will ensure timely detection of AEFI and help in appropriate management of the infants.

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REFERENCES

[1] E. Elliott, "Acute gastroenteritis in children".

[2] M. M. Alam et al., "Viral Etiologies of Acute Dehydrating Gastroenteritis in Pakistani Children: Confounding Role of Parechoviruses".

[3] S. M. Cook, R. I. Glass, C. W. LeBaron and M. Ho, "Global seasonality of rotavirus infections.".

[4] O. Lundgren and L. Svensson, "Pathogenesis of diarrhea".

[5] U. D. Parashar, E. A. S. Nelson and G. Kang, "Diagnosis, management, and prevention of rotavirus gastroenteritis in children".

[6] P. A. Barril et al., "Rotavirus seasonality in urban sewage from Argentina: Effect of meteorological variables on the viral load and the genetic diversity".

[7] A. Chandran, "Prevention of rotavirus gastroenteritis in infants and children: rotavirus vaccine safety, efficacy, and potential impact of vaccines".

[8] K. N. Sindhu, S. Babji and S. K. Ganesan, "Impact of rotavirus vaccines in low and middle-income countries".

[9] "Indigenously-developed rotavirus vaccine: a case-study of ROTAVAC in India".

[10] R. Ella, S. Babji, M. Ciarlet, W. C. Blackwelder and K. M. Vadrevu, "A randomized, open-labelled, non-inferiority phase 4 clinical trial to evaluate the immunogenicity and safety of the live, attenuated, oral rotavirus vaccine, ROTAVAC® in comparison with a licensed rotavirus vaccine in healthy infants".

[11] "Routine Immunization Program in India".

[12] R. Ella, R. Bobba, S. Muralidhar, S. Babji, K. M. Vadrevu and M. K. Bhan, "A Phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India".

[13] N. Mittal, R. Mittal and M. Gupta, "An overview of the pharmacovigilance system in India".

[14] "Monitoring vaccine safety and adverse events following immunization", who.int, (Accessed: 19 Oct. 2024).

[15] A. E. Tozzi, E. J. Asturias, M. R. Balakrishnan, N. A. Halsey, B. Law and P. Zuber, "Assessment of causality of individual adverse events following immunization (AEFI): A WHO tool for global use".

[16] K. Stratton, A. Ford, E. Rusch and E. W. Clayton, "Adverse Effects of Vaccines: Evidence and Causality".

[17] B. Rha et al., "Intussusception following rotavirus vaccination: an updated review of the available evidence".

[18] U. D. Parashar, M. M. Cortese, D. C. Payne, B. Lopman, C. Yen and J. E. Tate, "Value of post-licensure data on benefits and risks of vaccination to inform vaccine policy: The example of rotavirus vaccines".