Intussusception Adverse Events Post Vaccination and Etiology Model

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Article

Intussusception Adverse Events Post Vaccination and Etiology Model

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Abstract: Aim: Intussusception is a rare serious adverse event (SAE) that occurs following immunization (AEFI) and viral infections. The etiology of intussusception is currently unknown. This study analyzes infant intussusception AEFIs. **Methods:** The Vaccine Adverse Event Reporting System (VAERS) database is retrospectively examined for intussusception AEFIs in young children. **Results:** Intussusception AEFIs are associated with all rotavirus vaccines. The risk level is higher for infants age 0 than age 1 and also for specific other concomitant vaccine combinations. **Conclusions:** An etiology model of vaccine induced hyperplasia of Peyer's Patches disrupting the tissue support of enclosed intestinal segment results in enfolding of this segment into the subsequent segment is proposed. To reduce risk levels, it is recommended to avoid concomitant administration of rotavirus vaccine with other vaccines (i.e., reducing the risk of hyperplasia in Peyer's Patches). These results support the development and evaluation of rotavirus vaccines with improved safety profiles.

Keywords: intussusception; vaccines; diarrhea haemorrhagic; feces discolored; hematochezia; mucous stools

Introduction

Diarrheal diseases are one of the leading causes of illness and death in young children with rotavirus being the major pathogen [1]. Rotavirus vaccines have lowered the incidence of severe rotavirus gastroenteritis (RVGE) for immunized children [2]. The first licensed rotavirus vaccine, RotaShield, was withdrawn by its manufacturer due to an increased risk of intussusception (in which a small segment of the intestine enters into the adjacent part of the intestine) following immunization. Currently licensed rotavirus vaccines, RotaTeq® (RV5) and Rotatix™ (RV1) are generally considered to not be associated with increased risk of intussusception [2–7].

Intussusception occurs during viral infections or rarely after immunization. Intussusception has been reported associated with abnormal proliferation of intestinal Peyer's patches in two infants after measles, mumps, and rubella (MMR) vaccination [8]. One study in Mexico and Brazil found a short-term risk of intussusception of 1 in 51,000 to 68,000 RV1 immunizations [9]. In clinical trial, NCT00090233 with 34,035 infants in the vaccine group and 34,003 infants in the control group, 6 infants in the RV5 treatment group and 5 infants in the control group were associated with intussusception after adjudication (out of 115 potential cases of intussusception reported) [10]. The etiology of intussusception is currently unknown.

Herein, the Vaccine Adverse Event Reporting System (VAERS) is retrospectively examined for intussusception and associated adverse events (AEs). A consistent pattern of intussusception AEFIs appear for all live attenuated rotavirus vaccines. An etiology model of intussusception following hyperplasia of Peyer's patches is proposed.

Materials and Methods

The VAERS database [11] was retrospectively examined for the AEs designated by the following Medical Dictionary for Regulatory Activities (MedDRA) codes [12]: Diarrhoea haemorrhagic, Faeces

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discoloured, Haematochezia, Intussusception, and Mucous stools. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The downloaded VAERS data includes all AEs reported from 1990 to November 29, 2024.

The Ruby program vaers_slice4.rb [13] was used for retrospective analysis of the VAERS data files VAERSDATA, VAERSSYMPTOMS, and VAERSVAX for the years 1990 to 2024 and NonDomestic. The vaers_slice4.rb program tallies vaccine AEs by vaccine, day of onset, age, and concomitant vaccines. The vaers_slice4.rb program takes a list of one or more MedDRA names (used by VAERS) as input. Microsoft Excel was used to prepare figures.

Adverse Events Modeling

Adverse events reported after immunization can be either associated with the vaccine (V_{name}) or unrelated background population events (BG_X). The observed number of adverse events (AE) for any adverse event (X), vaccine (V_{name}), and age group population (P_{age}) can be modeled with **equation I** including expected background population adverse events (BG_X) (modified from [14]).

$$(I)\ AE\left(V_{name}\middle|X, P_{age}\right) = (V_{name} + BG_X) \times P_{age}$$

For concomitant administration of more than one vaccine, V_{name} in **equation I** can also represent a list of vaccine names. Note that the expected number of background population events, BG_X, for adverse event X is the same for all vaccines with expected random sampling variation. If $AE(V_{name} | X, P_{age}) = 0$ is observed for a vaccine, then $V_{name} = 0$ and $BG_X = 0$; hence $BG_X = 0$ for all vaccines for adverse event X.

The fraction of adverse events for a vaccine is calculated by dividing the number of adverse events for X by the total of all adverse events for that vaccine $\frac{AE(V|X,P)}{\sum_i AE(V|i,P)}$. This fraction can be scaled to a standard number of VAERS reports by multiplying by a common constant; herein, 100,000 VAERS reports is adopted for comparisons; these normalized frequencies are standard data normalization calculations. For each AE in VAERS, normalized AE frequencies per P=100,000 VAERS reports for all AEs for P_{age} can be calculated with **equation II**.

$$(II) AE\left(V|X, P_{age}\right)\ normalized\ frequency = \frac{AE(V|X,P)}{\sum_i AE(V|i,P)} \times P_{100,000}$$

Results

Intussusception AEFIs for infants age 0 are shown in **Figure 1** for no concomitant vaccines. Rotavirus vaccines represent 95.9% of the Intussusception AEFIs reported to VAERS from 1990 until November 29, 2024 (**Figure 1**) with no concomitant vaccines for infants age 0. With $AE(V_{name} | Intussusception, P_0)$=0 for V_{name}=COVID19 (MODERNA), V_{name}=COVID19 (PFIZER-BIONTECH), V_{name}=HEP A (VAQTA), V_{name}=MEASLES + MUMPS + RUBELLA (MMR II), and V_{name}=VARICELLA (VARIVAX), then $BG_{Intussusception} = 0$ for infants age 0 after immunization; hence, all VAERS Intussusception AEFIs are vaccine-associated AEs with likely no or few background events. For infants age 1 with $AE(V_{rotavirus} | Intussusception, P_1) = 2{,}128$ for ROTATEQ and 1,724 for ROTARIX are 9.5-times and 3.4-times lower than infant age 0 normalized frequencies. Per the United States Center for Disease Control (CDC) recommended vaccine schedule [15], the majority of the children immunized with rotavirus vaccines are less than one year of age. There appears to be a consistent association pattern of intussusception AEFIs with all three rotavirus vaccines (**Figure 2**). Diarrhoea haemorrhagic, faeces discolored, haematochezia, and mucous stools AEFIs for infants age 0 are shown in **Figure 3**; RV1 and RV5 rotavirus vaccines represent 82.0% of these additional gastrointestinal AEFIs (**Figure 3**). Like Intussusception AEs, the $BG_X = 0$ for these AEFI and these VAERS AEs are all vaccine-associated with no or few background events. Multiple infant vaccines

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are frequently concomitantly administered together in the United States in accordance with the recommended CDC vaccine schedule [15]; concomitant administration of rotavirus vaccine with other vaccines can increase the risk of intussusception AEFIs, see **Table 1**. The normalized frequencies for some vaccine combinations exhibit synergy (higher than simply additive) safety signals (**Table 1**) for *AE*[HIB (ACTHIB)+PNEUMO (PREVNAR13)+ROTAVIRUS (ROTARIX)] = 32,258, *AE*[DTAP (DAPTACEL)+HIB (ACTHIB)+PNEUMO (PREVNAR)+ROTAVIRUS (ROTATEQ)] = 25,714, *AE*[DTAP (DAPTACEL)+PNEUMO (PREVNAR)+POLIO VIRUS, INACT. (IPOL)+ROTAVIRUS (ROTATEQ)] = 23,077 normalized frequency for 100,000 VAERS reports for these concomitant vaccines (**Table 1**). Intussusception adverse events by rotavirus vaccine dose reported to VAERS is summarized in **Table 2**; note that Rotarix is a two dose vaccine and Rotateq is a three dose vaccine.

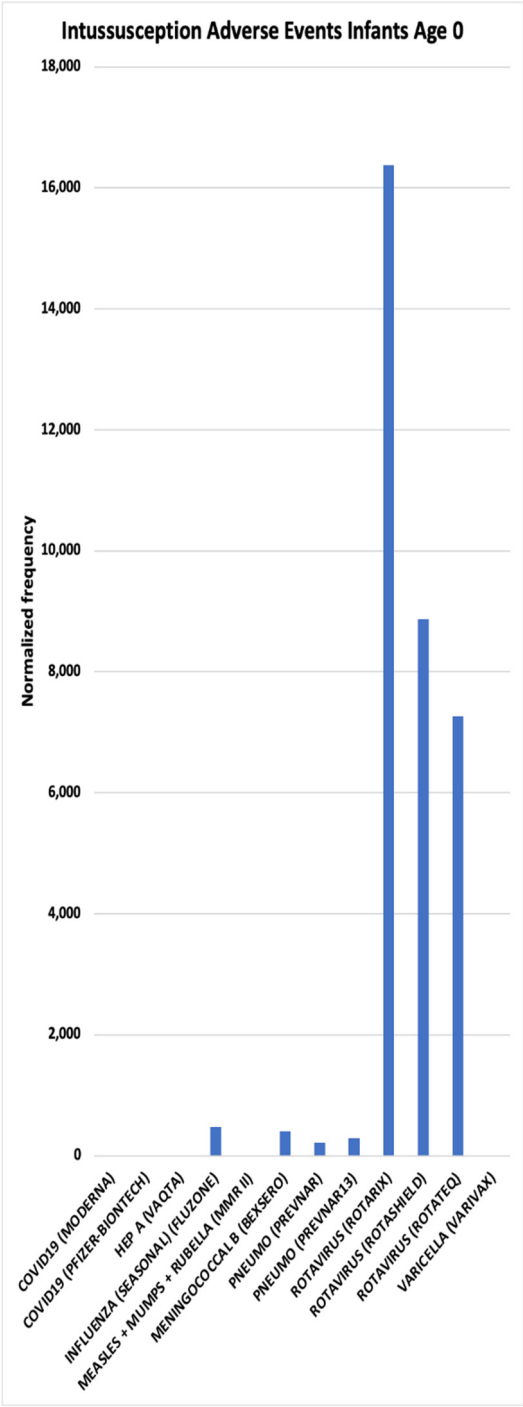

Figure 1. Infants Age 0 Intussusception adverse events per 100,000 VAERS reports with no concomitant vaccines.

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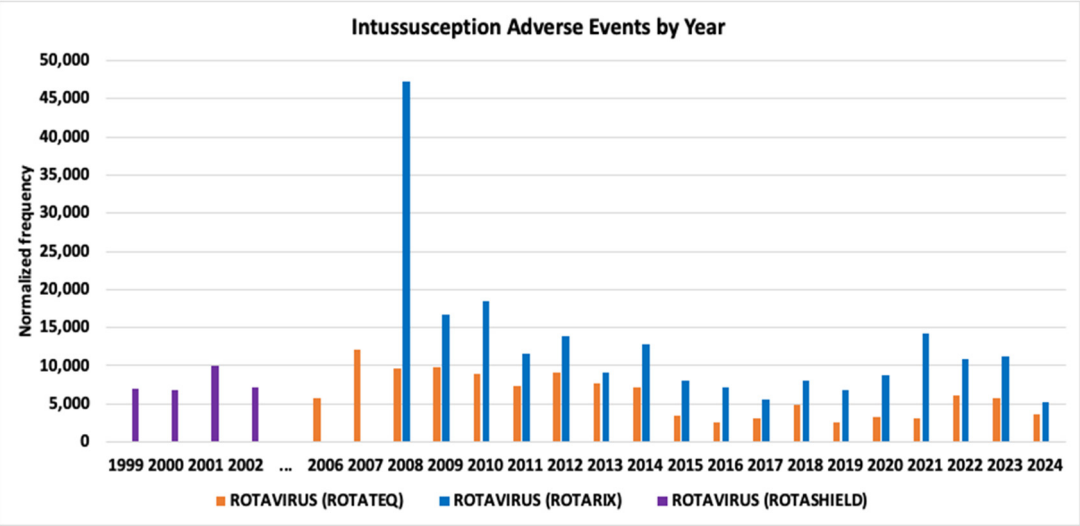

Figure 2. Intussusception adverse events by year per 100,000 VAERS reports.

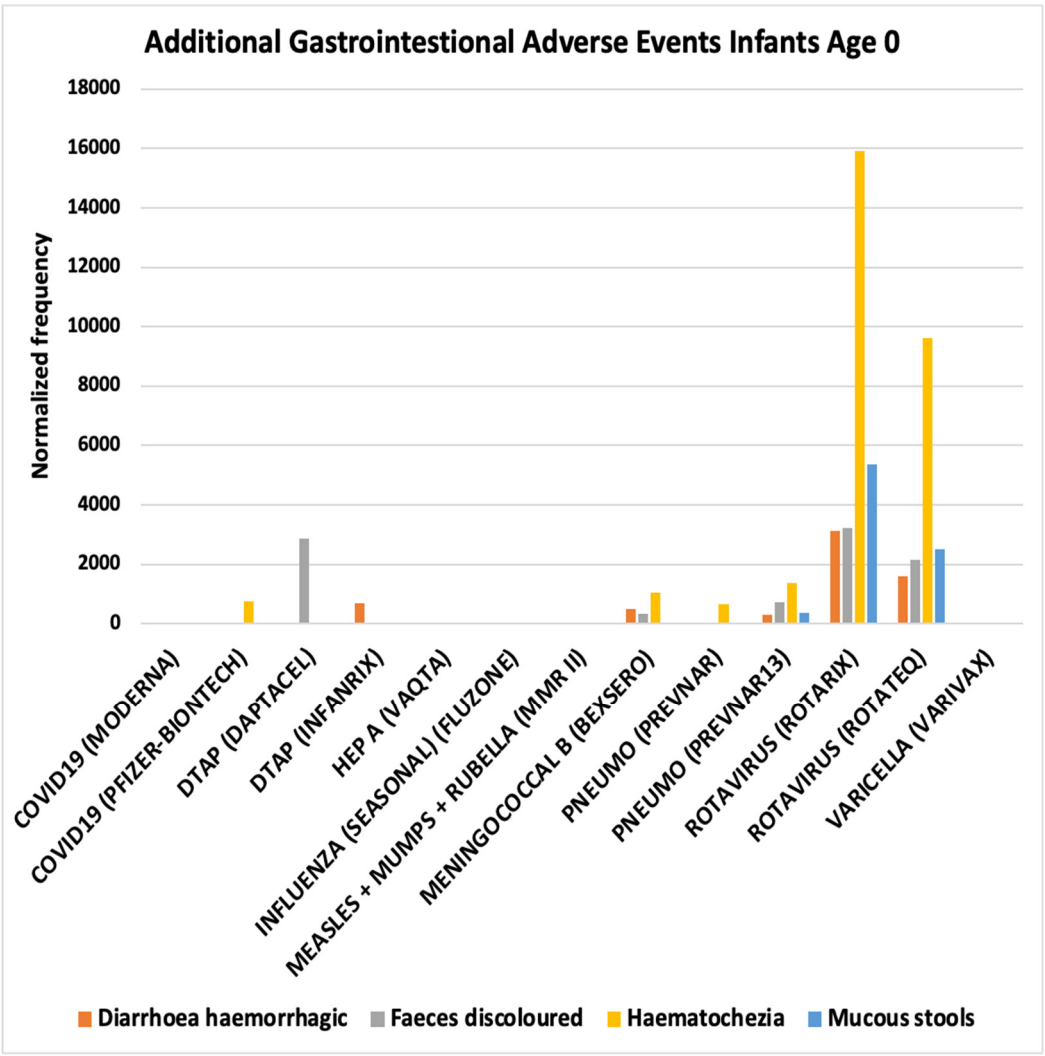

Figure 3. Infants age 0 additional gastrointestinal adverse events per 100,000 VAERS reports.

Table 1. Intussusception AEFIs in infants age 0 for concomitant vaccines per 100,000 VAERS reports. VAERS vaccine codes: DTAP: diphtheria, tetanus, and acellular pertussis vaccine, HEP A: hepatitis A vaccine, HEP

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B/HEPB: hepatitis B vaccine, HIB: Haemophilus influenzae type b vaccine, IPV: inactivated polio virus vaccine, and PNEUMO: pneumococcal vaccine.

Concomitant Vaccines	Intussusception AEFIs Infants Age 0 normalized frequency
DTAP (ACEL-IMUNE)+HIB + HEP B (COMVAX) & POLIO VIRUS, INACT. (POLIOVAX) & ROTAVIRUS (ROTASHIELD)	9,375
DTAP (DAPTACEL) & HEP B (RECOMBIVAX HB) & HIB (ACTHIB) & PNEUMO (PREVNAR) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	14,706
DTAP (DAPTACEL) & HEP B (RECOMBIVAX HB) & HIB (ACTHIB) & PNEUMO (PREVNAR13) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	20,833
DTAP (DAPTACEL) & HIB (ACTHIB) & PNEUMO (PREVNAR) & POLIO VIRUS, INACT. (IPOL)	671
DTAP (DAPTACEL) & HIB (ACTHIB) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	25,714
DTAP (DAPTACEL) & HIB (ACTHIB) & PNEUMO (PREVNAR13) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	14,286
DTAP (DAPTACEL) & HIB (ACTHIB) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	14,286

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DTAP (DAPTACEL) & HIB (ACTHIB) & ROTAVIRUS (ROTATEQ)	12,500
DTAP (DAPTACEL) & HIB + HEP B (COMVAX) & PNEUMO (PREVNAR) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	12,397
DTAP (DAPTACEL) & PNEUMO (PREVNAR) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	23,077
DTAP (INFANRIX) & HIB (ACTHIB) & PNEUMO (PREVNAR13) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	18,182
DTAP (INFANRIX) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTARIX)	17,391
DTAP (INFANRIX) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	8,571
DTAP (TRIPEDIA) & HIB (ACTHIB) & PNEUMO (PREVNAR) & POLIO VIRUS, INACT. (IPOL) & ROTAVIRUS (ROTATEQ)	10,256
DTAP + HEPB + IPV (PEDIARIX) & HIB (ACTHIB) & INFLUENZA (SEASONAL) (FLUZONE) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	15,625
DTAP + HEPB + IPV (PEDIARIX) & HIB (ACTHIB) &	9,305

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PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	
DTAP + HEPB + IPV (PEDIARIX) & HIB (ACTHIB) & PNEUMO (PREVNAR13)	1,271
DTAP + HEPB + IPV (PEDIARIX) & HIB (ACTHIB) & ROTAVIRUS (ROTATEQ)	17,241
DTAP + HEPB + IPV (PEDIARIX) & HIB (PEDVAXHIB) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	10,062
DTAP + HEPB + IPV (PEDIARIX) & INFLUENZA (SEASONAL) (FLUZONE) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	16,667
DTAP + HEPB + IPV (PEDIARIX) & PNEUMO (PREVNAR)	1,695
DTAP + HEPB + IPV (PEDIARIX) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	19,608
DTAP + IPV + HIB (INFANRIX QUINTA) & PNEUMO (SYNFLORIX) & ROTAVIRUS (ROTATEQ)	17,500
DTAP + IPV + HIB (PENTACEL) & HEP B (RECOMBIVAX HB) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	7,613
DTAP + IPV + HIB (PENTACEL) & INFLUENZA (SEASONAL) (FLUZONE) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	10,204
DTAP + IPV + HIB (PENTACEL) & PNEUMO (PREVNAR) &	10,384

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ROTAVIRUS (ROTATEQ)	
DTAP + IPV + HIB (PENTACEL) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	9,264
DTAP+IPV+HEPB+HIB (INFANRIX HEXA) & PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	11,200
DTAP+IPV+HEPB+HIB (INFANRIX HEXA) & PNEUMO (PREVNAR13)	619
DTAP+IPV+HEPB+HIB (INFANRIX HEXA) & ROTAVIRUS (ROTATEQ)	10,000
DTAP+IPV+HIB+HEPB (VAXELIS) & PNEUMO (VAXNEUVANCE) & ROTAVIRUS (ROTATEQ)	8,108
HIB (ACTHIB) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTARIX)	32,258
HIB (ACTHIB) & PNEUMO (PREVNAR13) & ROTAVIRUS (ROTATEQ)	8,333
PNEUMO (PREVNAR) & ROTAVIRUS (ROTATEQ)	7,692

Table 2. Intussusception adverse events by vaccine dose.

Vaccine	Dose 1	Dose 2	Dose 3
ROTAVIRUS (ROTARIX)	56.1%	42.6%	1.2%
ROTAVIRUS (ROTASHIELD)	66.7%	19.4%	13.9%
ROTAVIRUS (ROTATEQ)	36.8%	36.0%	27.2%

Discussion

The VAERS intussusception AEFI reports are consistent with vaccine induced rotavirus infection in these children. The etiology of intussusception AEs is currently unknown. Intussusception AEFIs are consistently associated with all three rotavirus vaccines (Figures 1 & 2).

Intussusception Etiology Model: Hyperplasia of Peyer's patch[16] can destabilize the tissue structure supporting the enclosed small intestine segment causing it to prolapse into the following segment (enfolded/telescoped) causing intussusception.

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In clinical trial, NCT00090233, 115 potential cases of intussusception were adjudicated down to 27 cases [10]. Adjusting the calculated normalized frequencies for intussusception (Figure 1) for asymptomatic vaccinees, there remains a large unexplained difference between the clinical trial results and estimates from VAERS reports. Supporting the observed VAERS results, increased risk of intussusception was observed for both RV1 and RV5 in Australia [17].

Study Limitations

The VAERS database represents only a small population sample of AEs experienced by vaccinees. Any reporting biases or exclusion of AEs would perturb the calculated normalized frequencies presented herein.

Study Recommendations

These retrospective study results associated multiple SAEs, including intussusception, with current rotavirus vaccines in infants less than one year of age. In the United States, the CDC has a recommended vaccine schedule for the first rotavirus vaccine dose at 2 months, second dose at 4 months, and for RotaTeq® (RV5) the third dose at 6 months of age for infants [15]. Echoing Murphy et al. [18], these results support the development and evaluation of rotavirus vaccines with improved safety profiles. When infants are immunized with current live attenuated rotavirus vaccines, no concomitant vaccines are recommended to minimize AEs and SAEs risks.

Conclusions

This retrospective study detected intussusception AEFIs associated with all live attenuated rotavirus vaccines. The normalized frequencies for intussusception are higher for infants age 0 than infants age 1. The etiology model of hyperplasia of Peyer's Patches destabilizing the structural support of the enclosed intestinal segment resulting it enfolding into the following segment. Increasing the stimulation level of immune responses by concomitantly administering other vaccines with rotavirus vaccines can increase the risk level for intussusception to occur; it is recommended that concomitant administration of other vaccines with current rotavirus vaccines be avoided (i.e., reducing the risk of hyperplasia in Peyer's Patches).

Author contributions: OR: Conceptualization, Investigation, Formal analysis, Writing-original draft, Writing-review & editing. All authors read and approved the submitted version.

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Consent to participate: Not applicable.

Consent to publication: Not applicable.

Availability of data and materials: The datasets generated for this study from VAERS are available as open data in Harvard Dataverse [19].

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Abbreviations

AEFI: adverse event following immunization
CDC: Center for Disease Control
COVID19: coronavirus disease 2019 vaccine
DTAP: diphtheria, tetanus, and acellular pertussis vaccine
HEP A: hepatitis A vaccine
HEP B: hepatitis B vaccine
HIB: Haemophilus influenzae type b vaccine
ICH: International Council for Harmonisation
IPV: inactivated polio virus vaccine
MedDRA: Medical Dictionary for Regulatory Activities
MMR: measles, mumps, and rubella vaccine
PNEUMO: pneumococcal vaccine
RV1: Rotatix rotavirus vaccine
RV5: RotaTeq rotavirus vaccine
RVGE: rotavirus gastroenteritis
SAE: serious adverse event
VAERS: Vaccine Adverse Event Reporting System

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