Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
From:	Phillip Blanc, MD Medical Officer, Analytic Epidemiology Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Merck
Product:	RotaTeq® (rotavirus vaccine, live, oral, pentavalent)
STN:	125122/1589
Indication:	RotaTeq® is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by types G1, G2, G3, G4, and G9 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks. The first dose of RotaTeq® should be administered between 6 and 12 weeks of age.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2021

Contents

1 INTRODUCTION 3

1.1 Objective 3

1.2 Product Description 3

1.3 Regulatory History 3

2 MATERIALS REVIEWED 5

3 LABEL CHANGES IN REVIEW PERIOD 5

4 PRODUCT UTILIZATION DATA 5

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES 6

5.1 Pharmacovigilance Plan 6

5.2 Postmarketing Studies 7

6 ADVERSE EVENT REVIEW 7

6.1 Methods 7

6.2 Results 7

6.2.1 Deaths 8

6.2.2 Serious Non-Fatal Reports 14

6.2.3 Non-serious Reports 16

6.3 Data Mining 19

6.4 Periodic safety reports 22

7 LITERATURE REVIEW 22

8 CONCLUSION 27

9 RECOMMENDATIONS 27

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval, in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of BLA supplement 125122/1309 on February 23, 2017 for expansion of the indication to include prevention of rotavirus gastroenteritis caused by type G9 when administered as a 3-dose series to infants between the ages of 6 and 32 weeks.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

RotaTeq® is a live, oral pentavalent vaccine that contains 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts.

RotaTeq® is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by types G1, G2, G3, G4, and G9 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks. The first dose of RotaTeq® should be administered between 6 and 12 weeks of age.

Of note, the 2006 initial approval (STN 125122/0) was for the prevention of rotavirus gastroenteritis caused by the types G1, G2, G3, and G4. The assay used for the evaluation of type G9 had not been validated prior to the original licensure. Efficacy data for the 2017 approval (STN 125122/1309) to extend the indication for type G9 included post-hoc analysis of two efficacy studies previously conducted in support of the original US licensure. The product in the 2017 supplement had not changed from the original product approved in 2006.

1.3 Regulatory History

- February 3, 2006: FDA initial approval of STN 125122/0 for the prevention of rotavirus gastroenteritis in infants and children caused by types G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks.

- June 15, 2007: FDA approval of STN 125122/316 for changes to the label in the Adverse Reactions section regarding Kawasaki Disease.

- April 30, 2008: FDA approval of STN 125122/443 for changes to the label in the Postmarketing Experience section to include a postmarketing report of a death due to intussusception that occurred after vaccination with RotaTeq®.

- September 5, 2008: FDA approval of STN 125122/368 to include pertussis immune response data from the Rotavirus Efficacy and Safety Trial (REST) to support concomitant use of DTaP with RotaTeq®.

- December 23, 2009: FDA approval of STN 125122/636 to revise the Contraindications section to include infants with Severe Combined Immunodeficiency Disease (SCID) because of postmarketing reports describing severe gastroenteritis and vaccine viral shedding in these patients.

- September 7, 2010: FDA approval of STN 125122/731 to include changes to the package insert regarding transmission of vaccine virus strains to non-vaccinated contacts.

- April 8, 2011: FDA approval of STN 125122/685 to include changes to the label regarding results of a postmarketing safety study (Study 019). The sponsor had committed to conduct this study as part of the product's initial February 3, 2006 approval.

- July 8, 2011: FDA approval of STN 125122/845 to update the package insert to include a contraindication for "history of intussusception" and for a corresponding revision to the patient package insert to update the section "Who should not receive RotaTeq."

- December 21, 2012: FDA approval of STN 125122/1054 to include changes to the package insert and patient package insert to include postmarketing reports of anaphylaxis and angioedema.

- May 10, 2013: FDA issued a Safety Labeling Change Notification Letter under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), to require a safety labeling change to include new safety information on the risk of intussusception (STN 125122/1133). The increased risk of intussusception after the first dose of RotaTeq® was based on an evaluation of more than 1.2 million RotaTeq® vaccinations (507,000 of which were first doses) administered to infants 5 through 36 weeks of age in the FDA Postmarket Risk Identification and Analysis System for vaccines, through the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program. FDA approved the required changes to the label on June 13, 2013.

- February 23, 2017: FDA approval of STN 125122/1309 for expansion of the indication to include prevention of rotavirus gastroenteritis caused by type G9 when administered as a 3-dose series to infants between the ages of 6 and 32 weeks.
    - This approval is the trigger for the presentation to the 2021 PAC.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - Adverse event reports for RotaTeq® received and processed into VAERS during February 23, 2017 to March 15, 2021 (PAC review period)

- Manufacturer's Submissions
    - RotaTeq® U.S. package insert (USPI); updated August 2020
    - Applicant response to information request regarding distribution data, received April 21, 2021
    - Pharmacovigilance Plan, dated July 7, 2021
    - Periodic safety reports

- FDA Documents
    - STN 125122/1309 RotaTeq® Approval Letter, dated February 23, 2017

- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety-related labeling changes during February 23, 2017 to March 15, 2021 (PAC review period). The label changes implemented in 2007 to 2013 occurred prior to this review period (triggered by the 2017 new approval expanding the indication to include type G9 rotavirus). RotaTeq® has not been presented to the PAC prior to this review period, because this product's original approval was in 2006, pre-dating the 2007 Food and Drug Administration Amendments Act (FDAAA)-required procedure for presenting newly approved products to the PAC.

4 PRODUCT UTILIZATION DATA

As provided by Merck, distribution data[1] for the US and worldwide for time intervals March 1, 2017 to March 31, 2021 are summarized in **Table 1**.

[1] These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

Table 1. US and Worldwide RotaTeq® distribution, March 1, 2017 to March 31, 2021*

	US	Worldwide
Number of Doses Distributed (est.)	(b) (4)	
Number of Patients Vaccinated (est.)		

*Per Merck, estimates assume that all doses that were distributed were also administered and that three doses were administered to each patient. Also, per Merck: "All distribution data presented are assumed to reflect administration of RotaTeq™ in the pediatric age group (specifically, in the noted infant age group) in accordance with the label."

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's U.S. Risk Management Plan (RMP) Annex (version 1.0), dated July 7, 2021, was reviewed. As per the manufacturer, at this time, intussusception is an important identified risk.

Intussusception

As described in the USPI, intussusception has been observed in RotaTeq® clinical trial *(Adverse Reactions [6.1])* and postmarketing *(Warnings and Precautions [5.3], Adverse Reactions [6.2])* experiences. RotaTeq® is contraindicated in infants with a history of intussusception *(Contraindications [4.3])*. An increased intussusception risk was noted in relation to administration of a formerly licensed live rhesus rotavirus reassortant vaccine *(Warnings and Precautions [5.3]).*

There are no other risks or missing information listed in the RMP. It is the manufacturer's assessment that the safety profile for RotaTeq® has been well characterized, and that most safety risks have been well researched and are appropriately managed. The manufacturer is not planning to conduct investigation or evaluation via additional pharmacovigilance and/or risk minimization activities for RotaTeq® at this time. The manufacturer will continue monitoring postmarketing safety for RotaTeq® through routine pharmacovigilance.

Routine safety surveillance for RotaTeq® includes review of adverse event reports submitted to FDA, manufacturer-submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for RotaTeq®. There are no outstanding postmarketing commitment (PMC) safety-related studies for RotaTeq® (Section 5.2).

5.2 Postmarketing Studies

In 2009, the sponsor submitted a final study report (STN 125122/674) to satisfy the postmarketing commitment (listed in the 2006 initial approval letter STN 125122/0) for an observational postmarketing study of the incidence of intussusception, Kawasaki Disease, and other safety parameters in recipients of RotaTeq®. The study was conducted using a large US medical claims database and the study population included 85,150 infants receiving one or more doses of RotaTeq®. No new safety concerns were identified by this study. On April 8, 2011, FDA approved labeling changes (STN 125122/685) to include these study results which are described in Section 6.2 *(Postmarketing Experience)*.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following RotaTeq® use between February 23, 2017 to March 15, 2021. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for RotaTeq® during the PAC review period are listed in **Table 2** below. There were 4,540 US and 1,559 foreign reports.

Table 2. VAERS Reports for RotaTeq® during February 23, 2017 to March 15, 2021

Age	Serious Non-Fatal, US	Serious Non-Fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	374	1046	70	43	2046	9	2490	1098
≥18 years	0	0	0	0	5*	0	5	0
Unknown^	23	441	1	16	2021	4	2045	461
All ages	397	1487	71	59	4072	13	4540	1559

*Involved adult health care workers inadvertently exposed to RotaTeq® (please see section 6.2.3 for details).
^Further review of the case narratives identified the age in some of these reports.
NOTE: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions (OMIC).

6.2.1 Deaths

A query for fatal reports during the PAC review period yielded 130 fatal reports. All fatal cases were pediatric except for four cases, for which age was not reported. The reports with unknown age are assumed to be pediatric since RotaTeq® is approved in children in the US. Individual review of all death reports revealed 15 duplicate cases and four cases indicating that RotaTeq® was not administered. Excluding these cases resulted in 111 unique death reports (n=68 [US]; n=43 [Foreign]). Overall, deaths reported to VAERS during the reporting period occurred between zero days and over two years after vaccination. Female sex accounted for 40 (36.0%) death cases and male sex for 67 (60.4%) death cases. In most death cases, children had received multiple vaccinations on the day of RotaTeq® administration. While causes of death in US reports are obtained through follow-up information—either from autopsy reports or death certificates—the cause of death for foreign reports is often unverified. **Table 3** shows the primary cause of death, as listed in the autopsy reports or death certificates for US reports.

Table 3. Cause of death as listed in autopsy reports or death certificates in US reports

Cause of Death (Autopsy or Death Certificate)	Number of US Cases
Sudden Unexpected Infant Death (SUID)/ Sudden Infant Death Syndrome (SIDS)	13
Suffocation/Asphyxia	9
Other*	4
Infection/Sepsis	5
Congenital or Genetic Anomaly	2
Necrotizing Enterocolitis or Complication of Intussusception	1
Complication of Prematurity	1
Undetermined	22
Autopsy results not available	11

*Discussed in narrative below.

US Death Cases

In 2018, the US infant mortality rate was 5.7 deaths per 1,000 live births.[1] The above causes of death reflect some of the most common causes of infant mortality in the US, which, as of 2018, included: 1. Birth defects; 2. Preterm birth and low birth weight; 3. Maternal pregnancy complications; 4. Sudden infant death syndrome (SIDS); and 5. Injuries (including suffocation).[1] Given an estimated (b) (4) individuals were vaccinated with RotaTeq® in the US from March 1, 2017 to March 31, 2021 and 68 unique US death cases were reported to VAERS during most of this period[2], the reporting rate over this period (approximately (b) (4) deaths reported per 1,000 vaccinees) is far below the background rate (5.7 deaths per 1,000 live births). Additionally, the proportion of all AE reports for RotaTeq® to VAERS that involve deaths (approximately 0.01 deaths per 1,000 reports) is also below this background rate of deaths in infants; (note: because each VAERS report is a surrogate for a RotaTeq® vaccination, this proportion assesses the frequency of death while limiting the effect of under-reporting).

Sudden Unexpected Infant Death (SUID)/Sudden Infant Death Syndrome (SIDS)

[2] The PAC reporting period (February 23, 2017 to March 15, 2021) did not align exactly with the sponsor's exposure data cut dates (March 1, 2017 to March 30, 2021).

Sudden unexpected infant death (SUID), also known as sudden unexpected death in infancy (SUDI), is a term used to describe any sudden and unexpected death occurring during infancy, whether explained or unexplained (including SIDS and ill-defined deaths). Approximately 3,500 infants die annually in the US from sleep-related infant deaths, including SIDS, ill-defined deaths, and accidental suffocation and strangulation in bed.[2] SIDS is the sudden unexpected death of an apparently healthy infant younger than age 12 months whose cause of death remains unknown, despite a death scene investigation, a review of the clinical history, and an autopsy.[3] SIDS is the leading cause of death among babies one month to one year of age in the US[4], overlapping with the age interval recommended for RotaTeq® administration in the US: 2, 4, and 6 months of age. Thus, some cases of SIDS would be expected to occur among infants receiving RotaTeq®. Identified risk factors associated with SIDS include male sex, prematurity, low birth weight, prone sleeping position, unsafe sleep environments (e.g., bed-sharing, loose bedding materials), and brain abnormalities.[5] The Institute of Medicine has reviewed the topic of SIDS and concluded, "The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS."[6] Given an estimated (b) (4) individuals were vaccinated with RotaTeq® in the US from March 1, 2017 to March 31, 2021, and 13 US death cases related to SIDS were reported during most of this period, the approximate reporting rate over this period (approximately (b) (4) deaths per 1,000 reports) does not exceed the background US SIDS rate (40 deaths per 100,000 live births in 2013[2]).

Suffocation/Asphyxia

Individual review of the above suffocation/asphyxia cases revealed that most cases suggested instances of accidental suffocation—particularly in the setting of dangerous sleep-related circumstances (e.g., lying prone, sleeping in an adult bed and/or co-sleeping with an adult, circumstances to which there is no plausible direct relationship to vaccination).

Infection/Sepsis

Deaths associated with an infection or sepsis included: *H. influenzae* suspected in a meningitis case; *S. Pneumo* for which a blood culture was positive in another case; and an infant who experienced severe dehydration associated with adenovirus enteritis. These cases were likely related to progression of an infectious etiology and do not indicate a directly causal relationship with RotaTeq®.

Other Causes of Death

Cases categorized as "Other" included two cases in which the infant experienced an anaphylactoid reaction. Signs and symptoms of anaphylactoid reactions are similar to anaphylaxis, which is currently labeled for RotaTeq®. Both patients

received multiple concomitant vaccines. Time between vaccination and death in both cases was within 24 hours. While one patient (a 4-month-old female) was born full-term without a significant medical history noted, the second patient (a 2-month-old male) was delivered at 36 weeks with a twin sister and had a history of poor weight gain.

The remaining cases categorized as “Other” involved one infant who experienced myocarditis and another infant who experienced cerebellitis. While it was unknown if the myocarditis was related to vaccination (per the autopsy report, “Post-vaccination myocarditis is very rare.”), the cerebillitis was considered possibly related to vaccination. The patient with cerebillitis was a 16-month-old male with a past medical history of MRSA abscess who received RotaTeq®, Fluarix Quadrivalent, Havrix, PedvaxHIB, and ProQuad on 09-Oct-2019 and expired on (b) (6) due to “anoxic encephalopathy secondary to bilateral acute cerebellitis, possibly related to vaccination.” Subsequent to vaccination, the patient developed encephalopathy, seizures, and respiratory failure, possibly related to an infectious cause (the patient had experienced rhinorrhea the week prior, in addition to MRI findings of acute cerebellitis). An acute viral infection was not confirmed, and the forensic pathologist attributed the acute cerebellitis to a possible vaccine reaction, given: 1. anecdotal reports suggesting a temporal relationship between vaccination and development of [acute cerebellitis] symptoms, and 2. due to the patient having been vaccinated with MMRV (the pathologist explains that varicella vaccine is more commonly associated with post-immunization reactions, compared to other vaccines). The time interval between vaccination and the onset of the patient’s symptoms was unclear, partly limiting assessment of the role of vaccination in this case.

Reviewer Comment: Assessing the role of vaccines in the last case above is limited by the unclear history, and by confounding by the administration of multiple vaccines on the same day as RotaTeq® administration. Though the role of vaccination, including RotaTeq®, cannot be ruled out, infection could also have led to the acute cerebellitis and fatal outcome.

Autopsy Results Not Available

Of the 11 cases in which autopsy results were not available, two cases included a non-autopsy-confirmed cause of death: one death was attributed to “lactic acidosis, metabolic acidosis, and cardiorespiratory failure”, and one identified seizure as the cause of death. Among the remaining cases, the FDA reviewer assessed deaths as likely related to: Seizure of Unclear Etiology (n=2), SUID/SIDS vs. Asphyxia/Suffocation (n=2), Cardiopulmonary Arrest of Unclear Etiology (n=1), Complication of Intussusception (n=1), and an Underlying Medical Condition (n=1). In the two remaining cases, limited information precluded a meaningful assessment of the cause of death.

Reviewer Comment: The case involving "complication of intussusception" described a 7-month-old female with no reported chronic illnesses who received RotaTeq® on 17-Jul-2018 and died due to an unspecified cause on (b) (6) . Twelve days after RotaTeq® administration, the patient was hospitalized for seizures (possibly hyponatremia-related) and bloody stool. After diagnosis of intussusception via ultrasound, the patient underwent an exploratory laparotomy, during which necrotic bowel was discovered and resected; during the procedure the patient experienced cardiac arrest. The patient's clinical course thereafter was consistent with septic shock and the patient died after support was withdrawn. Though no clear cause of death was noted on the submitted pathology report, the report attributes the necrotic small bowel "to intussusception, possibly related to lymphoid hyperplasia due to a viral infection." Findings from the lung and liver also supported a diagnosis of shock. The FDA reviewer concludes that the patient likely died due to septic shock due to necrotic bowel due to intussusception, however, the etiology of the intussusception is unclear. RotaTeq® is the only vaccine mentioned in the initial VAERS report (completed by the patient's caregiver), however, the route is reported as "Needle and Syringe (not specified further) – SYR"; it is unclear if this route was reported in error. Intussusception is a labeled event for RotaTeq® (Sections 4.3 "Contraindications", 5.3 "Warnings and Precautions" and 6 "Adverse Reactions"). Thus, the role of RotaTeq® in possibly leading to intussusception in this case cannot be ruled out. However, a viral illness (with a natural pathogen) may also be a plausible alternate cause (especially because family members were reported to have also experienced diarrhea). Stool or other testing (to confirm rotavirus or other infectious illness) was not identified in medical records for this case.

Foreign Death Cases

Of the 43 foreign death cases, autopsy-confirmed causes of death were reported in ten (23.3%) cases. Deaths in these cases were attributed to infections (n=2; including acute enterocolitis and meningococcal encephalitis), an "immunisation reaction" (n=1), an intracardiac mass (n=1), diffuse vasculitis (n=1), sudden infant death syndrome (n=1), and multiple organ failure due to acute intestinal obstruction (no intussusception noted) complicated by metabolic acidosis and electrolyte disturbance (n=1). In two death cases, structural cardiac disease appeared to have compromised the infant's ability to fight an infection. One cause of death was considered inconclusive.

The majority (n=33, 76.7%) of foreign death cases did not include an autopsy-confirmed cause of death. Among these 33 cases, 19 included a cause of death (non-autopsy-confirmed) or identified AEs experienced by the patient as fatal, and 14 cases did not include a cause of death. The FDA reviewer classified the 19 cases for which a non-autopsy-confirmed cause of death was provided (or for which AEs were considered fatal) into the following categories: Anaphylaxis (n=1), Cardiopulmonary arrest (n=1), Complication of intussusception (n=2), Multifactorial (without a single clear etiology) (n=4), Sepsis/Infection (n=2), SIDS (n=5), Suffocation (n=1), and Undetermined (n=3).

The FDA reviewer classified the 14 cases for which no cause of death was reported into the following categories: Complication of intussusception (n=3), Limited information (n=5), Recent injury/Illness/Hospitalization (n=3), Seizure of unclear etiology (n=1), and Significant medical history (n=2).

Reviewer Comment: *Intussusception—for which RotaTeq® is labeled—was described in six foreign death cases that did not include an autopsy-confirmed cause of death. Summaries for these cases are provided below:*

> *6-month-old female described as "a healthy twin, vaccinated with normal development" received RotaTeq®, Infanrix, and Prevnar on 22-Nov-2016 and died due to unspecified cause on* (b) (6) *. Patient experienced intussusception on 27-Dec-2016 and was referred for surgery in setting of vomiting and apparent hemodynamic compromise. However, prior to surgery, patient required continued resuscitation which was ultimately unsuccessful. Postmortem CT was consistent with intussusception, cardiac ventricular disorder, and collapse of lung.*
>
> *8-month-old female subject in a clinical trial ("A Study of the Effectiveness and Safety of a New Formulation of RotaTeq® in Routine Use in a Developing World Setting") received RotaTeq® on 19-Sep-2016, 19-Oct-2016, and 22-Nov-2016 and died due to unspecified cause on* (b) (6) *. Patient experienced symptoms including inconsolable crying, vomiting, and hematochezia on 09-Apr-2017, after which surgery on* (b) (6) *revealed intussusception without necrosis. Anesthesia was difficult to reverse and patient experienced convulsions and loss of consciousness on 17-Apr-2017.*
>
> *6-month-old female enrolled in postmarketing active surveillance died on* (b) (6) *, approximately 4 months after the second dose of* RotaTeq®*, due to septic shock. Patient had experienced intussusception with symptom onset on 30-Jun-2015, as well as inflamed appendix noted on surgery performed on* (b) (6) *. Unspecified if autopsy performed.*
>
> *4-month-old male subject in a clinical trial ("A Study of the Effectiveness and Safety of a New Formulation of RotaTeq® in Routine Use in a Developing World Setting") experienced intussusception approximately 5 weeks after the second dose of RotaTeq® (V260) and underwent surgery. A necrotic appendix was noted and an appendectomy was performed. Anesthesia was difficult to reverse and patient experienced two cardiac arrest episodes and died. Unspecified if autopsy performed.*
>
> *6-month-old female received RotaTeq® on 31-May-2016, 30-Jun-2016, and 01-Aug-2016 and expired due to unspecified cause on* (b) (6) *. Patient experienced pyrexia and vomiting on 07-Oct-2016. Intussusception was identified on ultrasound and during surgery performed on* (b) (6) *.*

Patient developed pyrexia and respiratory distress on 18-Oct-2016 and was diagnosed with pneumonia and abdominal obstruction before developing cardio-respiratory arrest on (b) (6) *. Unknown if autopsy performed.*

8-month-old male received RotaTeq® on 16-Aug-2016, 20-Sep-2016, and 25-Oct-2016 and died on (b) (6) *due to unspecified cause. Patient experienced inconsolable crying, pyrexia, and hematochezia on 15-Feb-2017. Intussusception without necrosis was identified during surgery on* (b) (6) *. Unspecified if autopsy performed.*

The background rate of US intussusception hospitalizations among infants prior to RotaTeq® licensing has been estimated at 35 cases per 100,000 infants.[7] Intussusception is labeled (as "Intussusception (including death)") in Section 6.2 (Postmarketing Experience) of the USPI, which also includes a description of results from postmarketing observational safety surveillance studies evaluating this risk. Given this known risk, a causal relationship between RotaTeq® and intussusception in the above cases cannot be completely ruled out. However, given the postmarket study results described in the USPI indicate a risk window of 21 days from the first RotaTeq dose (with clustering observed within the first seven days)[3], a causal relationship between RotaTeq® and intussusception appears less likely in the above cases since intussusception was observed beyond 21 days after RotaTeq® administration in all of the above cases.

In summary, there was one US death and six foreign deaths involving intussusception. After review of the above deaths, most occurred beyond the 21-day risk window. No new safety concerns were identified from review of these deaths. The risk of intussusception has been characterized by postmarketing studies, and described in the label. While attribution of some cases of intussusception, including deaths, to vaccination cannot be ruled out, these cases are consistent with the known risk of intussusception described in the USPI. As described in the USPI, intussusception has been observed in RotaTeq® clinical trial *(Adverse Reactions [6.1])* and postmarketing experiences *(Warnings and Precautions [5.3], Adverse Reactions [6.2])*. RotaTeq® is contraindicated in infants with a history of intussusception *(Contraindications [4.3])*.

6.2.2 Serious Non-Fatal Reports

The PAC review period yielded 1,884 serious non-fatal reports, of which, 1,420 (75.4%) involved pediatric patients. Age was unknown for the remaining 464 (24.6%) serious non-fatal reports.

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[3] Based on study results, approximately 1 to 1.5 excess cases of intussusception occur per 100,000 vaccinated US infants within 21 days following the first dose of RotaTeq®. Another postmarketing observational cohort study, conducted using a large US medical claims database, evaluated data post-dose 1 and post any dose, in both 7-day and 30-day risk windows; and a statistically significant increased risk of intussusception after RotaTeq® vaccination was not observed.

The 20 most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) are displayed in **Table 4**. Of note, a single report can include multiple PTs.

Table 4. Most frequently reported PTs for serious non-fatal reports

Preferred Term (PT)	Number of Serious Non-Fatal Reports	Label Status*	Label Section(s)*
Vomiting	391	Labeled	Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Pyrexia	348	Labeled (as Fever)	Warnings and Precautions (5.6), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Diarrhoea	343	Labeled	Contraindications (4.2), Warnings and Precautions (5.4), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Rotavirus test positive	278	Labeled (as Antigen rotavirus positive, Rotavirus antigen-positive)	Warnings and Precautions (5.5), Clinical Studies (14.5)
Gastroenteritis rotavirus	236	Labeled	Indications and Usage (1), Clinical Pharmacology (12.1), Clinical Studies (14, 14.1-14.6)
Haematochezia	234	Labeled	Adverse Reactions (6.1, 6.2)
Crying	224	*Unlabeled*	N/A
Intussusception	202	Labeled	Contraindications (4.3), Warnings and Precautions (5.3), Adverse Reactions (6.1, 6.2), Patient Counseling Information (17)
Irritability	173	Labeled	Adverse Reactions (6.1)
Seizure	164	Labeled	Adverse Reactions (6.1)
Pallor	159	*Unlabeled*	N/A
Hypotonia	135	*Unlabeled*	N/A

Preferred Term (PT)	Number of Serious Non-Fatal Reports	Label Status*	Label Section(s)*
Gastroenteritis	124	Labeled	Indications and Usage (1), Contraindications (4.2), Adverse Reactions (6.1, 6.2), Clinical Pharmacology (12, 12.1), Clinical Studies (14, 14.1-14.6)
Rotavirus infection	120	Labeled	Patient Counseling Information (17)
Ultrasound abdomen abnormal	110	*Unlabeled*	N/A
Enema administration	107	Labeled	Patient Counseling Information (17)
Vaccination failure	107	*Unlabeled*	N/A
Lethargy	98	*Unlabeled*	N/A
Dehydration	96	*Labeled*	Patient Counseling Information (17)
Somnolence	96	*Unlabeled*	N/A

*Label (USPI) dated 08/2020

***Reviewer Comment*:** Most of the above PTs are currently labeled. Unlabeled PTs reflect AEs (e.g., Crying, Pallor, Hypotonia, Lethargy) labeled for commonly co-administered vaccines (e.g., Pediarix, Prevnar 13), as well as diagnostic (Ultrasound abdomen abnormal) and treatment (Enema administration) modalities for intussusception, a known and labeled risk for a RotaTeq®. Vaccination failure is a possible risk with all vaccines and is not unique to RotaTeq®; the efficacy of RotaTeq® is described in Section 14, "Clinical Studies" of the label.

PTs reported less commonly than the above serious non-fatal PTs (not displayed in the table above) similarly reflect AEs labeled for co-administered vaccines (e.g., Cyanosis, Hypotonic-hyporesponsive episode, Rash), as well as symptoms, tests, and treatments pertaining to gastrointestinal illness (e.g., Diarrhoea haemorrhagic, Haematocrit decreased, Gastrointestinal tube insertion).

6.2.3 Non-Serious Reports

The PAC reporting period yielded 4,085 non-serious reports, of which, 2,055 (50.3%) involved pediatric patients. **Table 5** lists the 20 most commonly reported PTs. Of note, a single report can include multiple PTs.

Table 5. Most frequently reported PTs in non-serious reports

Preferred Term (PT)	Number of Non-Serious Reports	Label Status*	Label Section(s)*
Product storage error	1949	*Unlabeled*	N/A
Incorrect product storage	424	*Unlabeled*	N/A
Pyrexia	272	Labeled (as Fever)	Warnings and Precautions (5.6), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Irritability	170	Labeled	Adverse Reactions (6.1)
Expired product administered	169	*Unlabeled*	N/A
Vomiting	163	Labeled	Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Diarrhoea	137	Labeled	Contraindications (4.2), Warnings and Precautions (5.4), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Crying	131	*Unlabeled*	N/A
Injection site erythema	97	*Unlabeled*	N/A
Rash	91	Labeled	Patient Counseling Information (17)
Product administered to patient of inappropriate age	83	*Unlabeled*	N/A
Haematochezia	81	Labeled	Adverse Reactions (6.1, 6.2)
Urticaria	72	Labeled	Adverse Reactions (6.2)
Injection site swelling	66	*Unlabeled*	N/A

Preferred Term (PT)	Number of Non-Serious Reports	Label Status*	Label Section(s)*
Product preparation issue	60	*Unlabeled*	N/A
Screaming	60	*Unlabeled*	N/A
Body temperature increased	54	Labeled (as Elevated temperature)	Adverse Reactions (6.1)
Extra dose administered	52	Subsumable under labeled event Overdosage	Overdosage (10)
Drug administered to patient of inappropriate age	46	*Unlabeled*	N/A
Inappropriate schedule of drug administration	45	*Unlabeled*	N/A
Inappropriate schedule of product administration	45	*Unlabeled*	N/A

*Label (USPI) dated 08/2020

***Reviewer Comment*:** Most of the above unlabeled PTs reflect product use issues and medication errors (Product storage error, Incorrect product storage, Expired product administered, Product or drug administered to patient of inappropriate age, Product preparation issue, Inappropriate schedule of drug or product administration) that are not associated with a clinical adverse event. Based on a separate query, the FDA reviewer was able to confirm that most non-serious reports from the PAC reporting period that included the aforementioned product use issue/medication errors PTs were also coded with a "No adverse event" PT, suggesting that most of these cases did not result in harm to the patients involved. The remaining unlabeled PTs reflect AEs (e.g., Crying, Injection site erythema, Injection site swelling, Screaming) that are labeled for commonly co-administered vaccines (e.g., Pediarix, Prevnar 13). Of note, the five non-serious adult cases in Table 2 (not captured in the table above) involved adult health care staff members who were inadvertently exposed to RotaTeq® (e.g., via eye contact, by a patient who received RotaTeq® and spat RotaTeq® into a nurse's eye; via skin contact in

a case involving a medical assistant exposed to RotaTeq® while handling a reportedly defective product container).

PTs reported less commonly than the above non-serious PTs (not displayed in the table above) also reflected AEs associated with medication errors (e.g., Incorrect dose administered), AEs labeled for co-administered vaccines (e.g., Cyanosis, Hypotonic-hyporesponsive episode, Rash), as well as symptoms, tests, and treatments pertaining to gastrointestinal illness (e.g., Abdominal pain, Ultrasound abdomen, Enema administration).

6.3 Data Mining

Data mining was performed to evaluate whether any reported events following the use of RotaTeq® were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal Management with the US VAERS Vac Name run with a data lock date of April 30, 2021 identified 59 PTs with a disproportional reporting alert for RotaTeq® (EB05 >2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Most disproportionality alert scores with EB05 > 2.0 for RotaTeq® were for PTs related to Gastroenteritis and Intussusception, which are both labeled events. **Table 6** includes these PTs and excludes PTs reflecting diagnostic and treatment modalities (these are listed in **Appendix A**), as well as one PT (Eye irrigation[4]) that is unrelated to Gastroenteritis and Intussusception.

Table 6. RotaTeq® Data Mining Results: Preferred terms related to Gastroenteritis and Intussusception

Preferred Term (PT)	Label Status*	Label Section(s)*
Abdominal distension	*Unlabeled*	N/A
Abdominal mass	*Unlabeled*	N/A
Abdominal pain	Related to labeled event Stomach pain	Patient Counseling Information (17)
Abdominal rigidity	*Unlabeled*	N/A

[4] Eye irrigation (n = 9) referred to health care workers being inadvertently exposed to RotaTeq® in the process of administering RotaTeq®.

Preferred Term (PT)	Label Status*	Label Section(s)*
Abdominal tenderness	Related to labeled event Stomach pain	Patient Counseling Information (17)
Abnormal faeces	*Unlabeled*	N/A
Dehydration	Labeled	Patient Counseling Information (17)
Diarrhoea	Labeled	Contraindications (4.2), Warnings and Precautions (5.4), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Diarrhoea haemorrhagic	Related to labeled event Hematochezia	Adverse Reactions (6.1, 6.2)
Faeces discoloured	*Unlabeled*	N/A
Flatulence	*Unlabeled*	N/A
Fontanelle depressed	*Unlabeled*	N/A
Frequent bowel movements	Related to labeled event Diarrhea	Contraindications (4.2), Warnings and Precautions (5.4), Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)
Gastroenteritis	Labeled	Indications and Usage (1), Contraindications (4.2), Adverse Reactions (6.1, 6.2), Clinical Pharmacology (12, 12.1), Clinical Studies (14, 14.1-14.6)
Gastroenteritis rotavirus	Labeled	Indications and Usage (1), Clinical Pharmacology (12.1), Clinical Studies (14, 14.1-14.6)
Gastrointestinal necrosis	*Unlabeled*	N/A
Gastrointestinal sounds abnormal	*Unlabeled*	N/A
Haematemesis	*Unlabeled*	N/A

Preferred Term (PT)	Label Status*	Label Section(s)*
Haematochezia	Labeled	Adverse Reactions (6.1, 6.2)
Infantile spitting up	Labeled (as Infant spits)	Dosage and Administration (2.2)
Intussusception	Labeled	Contraindications (4.3), Warnings and Precautions (5.3), Adverse Reactions (6.1, 6.2), Patient Counseling Information (17)
Mucous stools	*Unlabeled*	N/A
Platelet count increased	*Unlabeled*	N/A
Rectal haemorrhage	*Unlabeled*	N/A
Regurgitation	Labeled	Dosage and Administration (2.2), Overdosage (10)
Rotavirus infection	Labeled	Patient Counseling Information (17)
Small intestinal obstruction	Related to labeled event Blockage of the intestines	Patient Counseling Information (17)
Urine output decreased	*Unlabeled*	N/A
Vomiting projectile	Related to labeled event Vomiting	Adverse Reactions (6.1), Clinical Studies (14, 14.1, 14.2), Patient Counseling Information (17)

*Label (USPI) dated 08/2020

Unlabeled PTs that reflect clinical signs or symptoms of gastroenteritis or intussusception include: *Mucous stools*, *Faeces discoloured*, *Abnormal faeces*, *Flatulence*, *Abdominal mass*, *Abdominal distension*, *Gastrointestinal sounds abnormal*, *Abdominal rigidity*, *Gastrointestinal necrosis Haematemesis*, and *Rectal haemorrhage.*

Similarly, unlabeled PTs that may be related to dehydration, a sequela of gastroenteritis or intussusception, include: *Urine output decreased*, *Platelet count increased*, and *Fontanelle depressed*.

6.4 Periodic Safety Reports

The manufacturer's postmarketing periodic safety reports for RotaTeq® were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified. The sponsor addressed the important identified risk, intussusception, in updates to its labeling; otherwise, no significant actions taken by the sponsor for safety reasons during the PAC review period were noted.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on April 30, 2021, for peer-reviewed literature, with the search terms "RotaTeq" and "Safety" limited by human species, and dates from February 23, 2017 (PAC trigger) to April 30, 2021 (date of search), retrieved 19 publications, of which 16 pertained to rotavirus vaccine safety. Abstracts discussing AEs that may not be typically considered linked to rotavirus vaccine exposure are presented in the first two rows of **Table 7** below. Given the mechanism of exposure described with regard to Eye irritation in the first article (e.g., irritation in the eyes of health care workers who have been inadvertently exposed to rotavirus vaccine), as well as the limitations of postmarketing data mining discussed in the second article (e.g., confounding by co-administered vaccines that have biologically plausible ties to the potential signal events and/or even acknowledge some of the events in their labels), neither these, nor the remaining articles retrieved in this literature search confirm a new safety concern.

Table 7. RotaTeq® safety literature search results, as of April 30, 2021

Publication	Authors' Safety Conclusion
[1]Haber P, Tate J, Marquez PL, Moro PL, Parashar U. Safety profile of rotavirus vaccines among individuals aged ≥8 months of age, United States, vaccine adverse event reporting system (VAERS), 2006-2019. Vaccine. 2021 Jan 22;39(4):746-750. doi: 10.1016/j.vaccine.2020.11.026. Epub 2020 Nov 29. PMID: 33267969.	No unexpected AEs noted. Given AEs pertaining to indirect exposure (e.g., Accidental exposure, Eye irritation), individuals (e.g., health care staff) are advised to take necessary precautions.
[2]Bonaldo G, Noseda R, Ceschi A, Vaccheri A, Motola D. Evaluation of the safety profile of rotavirus vaccines: a pharmacovigilance analysis on American and European data. Sci Rep. 2020 Aug 12;10(1):13601. doi:	Study authors analyzed VAERS and VigiBase data (2007-2017) to contribute to existing knowledge pertaining to the safety profiles of RotaTeq® and Rotarix®, from a postmarketing perspective. Similarities in reporting across the databases were observed, including the reporting odds ratio (RoR) exceeding 20 for the

Publication	Authors' Safety Conclusion
10.1038/s41598-020-70653-3. PMID: 32788620; PMCID: PMC7423960.	rotavirus (RV) vaccine-intussusception pair. Across databases, labeled events (diarrhea and vomiting) were the most frequently reported Adverse Events Following Immunization (AEFIs). The authors identified some AEs as potential signals, including: fontanelle bulging, hypotonic-hyporesponsive episode, livedo reticularis, infantile spasms, opisthotonos and seizure like phenomena. Though most of the AEFIs observed are currently labeled (i.e., in the Summary of Product Characteristics (SPCs)), for the potential signals detected, the authors recommend further investigation to rule out the need for inclusion of these AEs into the products' labeling. The authors acknowledged several limitations inherent in depending on spontaneous reports while conducting pharmacovigilance research, including limited ability to an actual incidence rate, as well as the potential for inaccurate and/or under-reporting, or misattributing effects that could be due to co-administered vaccines.
[3]Benninghoff B, Pereira P, Willame C. Letter to the editor concerning the article 'Association between rotavirus vaccination and risk of intussusception among neonates and infants: a systematic review and meta-analysis' (JAMA Netw Open. 2019;2(10):e1912458). Hum Vaccin Immunother. 2020 Oct 2;16(10):2502-2503. doi: 10.1080/21645515.2020.1730119. Epub 2020 Mar 18. PMID: 32186946; PMCID: PMC7734962.	Despite a slightly increased intussusception risk associated with rotavirus (RV) vaccination, benefit-risk profile of RV vaccination remains favorable.
[4]Sartorio MUA, Folgori L, Zuccotti G, Mameli C. Rotavirus vaccines in clinical development: Current pipeline and state-of-the-art. Pediatr Allergy Immunol. 2020 Feb;31 Suppl 24:58-60. doi: 10.1111/pai.13167. PMID: 32017224.	Abstract suggests development of new rotavirus (RV) vaccines may help offset known safety risks of current RV vaccines, including intussusception, as well as the live-attenuated nature of the vaccine.

Publication	Authors' Safety Conclusion
[5]McIlhone KA, Best EJ, Petousis-Harris H, Howe AS. Impact of rotavirus vaccine on paediatric rotavirus hospitalisation and intussusception in New Zealand: A retrospective cohort study. Vaccine. 2020 Feb 11;38(7):1730-1739. doi: 10.1016/j.vaccine.2019.12.045. Epub 2019 Dec 27. PMID: 31889608.	Intussusception cases were observed after rotavirus (RV) vaccination in a national cohort study in New Zealand. However, no change in overall intussusception incidence (presumably, pre- vs. -post-RotaTeq® implementation in New Zealand since 2014) was noted.
[6]Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2019 Oct 28;2019(10):CD008521. doi: 10.1002/14651858.CD008521.pub5. PMID: 31684685; PMCID: PMC6816010.	In a meta-analysis of three rotavirus (RV) vaccines, intussusception was observed, however, no increased risk of serious adverse events (SAEs) was observed.
[7]Hemming-Harlo M, Lähdeaho ML, Mäki M, Vesikari T. Rotavirus Vaccination Does Not Increase Type 1 Diabetes and May Decrease Celiac Disease in Children and Adolescents. Pediatr Infect Dis J. 2019 May;38(5):539-541. doi: 10.1097/INF.0000000000002281. PMID: 30986791.	No significant difference in Type 1 diabetes mellitus occurrence among RotaTeq® vaccinated subjects compared to subjects who received placebo.
[8]Mwenda JM, Mandomando I, Jere KC, Cunliffe NA, Duncan Steele A. Evidence of reduction of rotavirus diarrheal disease after rotavirus vaccine introduction in national immunization programs in the African countries: Report of the 11th African rotavirus symposium held in Lilongwe, Malawi. Vaccine. 2019 May 21;37(23):2975-2981. doi: 10.1016/j.vaccine.2019.03.047. Epub 2019 Apr 24. PMID: 31029514.	Data—presumably showcased at the 11th African Rotavirus Symposium—supported the safety of RotaTeq® and Rotarix®.
[9]Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for	Appears to be an update to publication #6. As above, no increased serious adverse event (SAE) risk noted.

Publication	Authors' Safety Conclusion
preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2019 Mar 25;3(3):CD008521. doi: 10.1002/14651858.CD008521.pub4. Update in: Cochrane Database Syst Rev. 2019 Oct 28;2019(10): PMID: 30912133; PMCID: PMC6434239.	
[10]Ledent E, Arlegui H, Buyse H, Basile P, Karkada N, Praet N, Nachbaur G. Benefit Versus Risk Assessment of Rotavirus Vaccination in France: A Simulation and Modeling Analysis. BioDrugs. 2018 Apr;32(2):139-152. doi: 10.1007/s40259-018-0273-6. PMID: 29589230; PMCID: PMC5878204.	Despite known rotavirus (RV) vaccine-associated intussusception risk, Rotarix®'s benefit-risk profile in France is favorable.
[11]Saleh E, Eichner B, Clark DW, Gagliano ME, Troutman JM, Harrington L, McNeal M, Clements D. Open-Label Pilot Study to Compare the Safety and Immunogenicity of Pentavalent Rotavirus Vaccine (RV5) Administered on an Early Alternative Dosing Schedule with Those of RV5 Administered on the Recommended Standard Schedule. J Pediatric Infect Dis Soc. 2018 Feb 19;7(1):82-85. doi: 10.1093/jpids/pix005. PMID: 28340179; PMCID: PMC5907846.	Vomiting and diarrhea were more commonly reported for subjects administered RV5 on an alternative vaccination schedule (during the neonatal period) than those administered RV5 on a standard schedule. Though this was not a significant difference, vomiting was reported significantly more often among younger subjects *within* the alternative schedule group, compared to older subjects within this group (authors propose this may be due to increased vomiting/spitting up during the neonatal period). Authors concluded that RV5 is generally well tolerated in the neonatal period.
[12]Esposito S, Pugni L, Mosca F, Principi N. Rotarix® and RotaTeq® administration to preterm infants in the neonatal intensive care unit: Review of available evidence. Vaccine. 2018 Aug 28;36(36):5430-5434. doi: 10.1016/j.vaccine.2017.10.013. Epub 2017 Oct 14. PMID: 29037579.	Authors advocate to study the efficacy and safety of rotavirus (RV) vaccination among preterm (PT) infants, suggesting results from such studies may improve neonatologists' knowledge as to how RV vaccines should be administered among PT infants, particularly so that vaccine virus transmission to high-risk contacts can be avoided.

Publication	Authors' Safety Conclusion
[13]Mo Z, Mo Y, Li M, Tao J, Yang X, Kong J, Wei D, Fu B, Liao X, Chu J, Qiu Y, Hille DA, Nelson M, Kaplan SS. Efficacy and safety of a pentavalent live human-bovine reassortant rotavirus vaccine (RV5) in healthy Chinese infants: A randomized, double-blind, placebo-controlled trial. Vaccine. 2017 Oct 13;35(43):5897-5904. doi: 10.1016/j.vaccine.2017.08.081. Epub 2017 Sep 19. PMID:28935470.	Intussusception was noted among RV5 recipients (n=2), however, neither event was considered related to vaccine. AE and SAE reporting between RV5 and placebo groups appeared comparable. RV5 was considered well-tolerated among Chinese infants.
[14]Saluja T, Palkar S, Misra P, Gupta M, Venugopal P, Sood AK, Dhati RM, Shetty A, Dhaded SM, Agarkhedkar S, Choudhury A, Kumar R, Balasubramanian S, Babji S, Adhikary L, Dupuy M, Chadha SM, Desai F, Kukian D, Patnaik BN, Dhingra MS. Live attenuated tetravalent (G1-G4) bovine-human reassortant rotavirus vaccine (BRV-TV): Randomized, controlled phase III study in Indian infants. Vaccine. 2017 Jun 16;35(28):3575-3581. doi: 10.1016/j.vaccine.2017.05.019. Epub 2017 May 20. PMID:28536027.	When concomitantly administered with other vaccines, live attenuated tetravalent rotavirus (RV) vaccine (BRV-TV) demonstrated a similar safety profile as RV5.
[15]Martinón-Torres F, Greenberg D, Varman M, Killar JA, Hille D, Strable EL, Stek JE, Kaplan SS. Safety, Tolerability and Immunogenicity of Pentavalent Rotavirus Vaccine Manufactured by a Modified Process. Pediatr Infect Dis J. 2017 Apr;36(4):417-422. doi: 10.1097/INF.0000000000001511. PMID: 28141698.	Offering stability at higher temperatures—and potentially less burdensome refrigeration/storage requirements—modified RV5 (RV5mp) demonstrated a safety profile that was comparable to RV5.
[16]Tanaka Y, Yokokawa R, Rong HS, Kishino H, Stek JE, Nelson M, Lawrence J. Concomitant administration of diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine derived from Sabin strains (DTaP-sIPV) with	A lower incidence of systemic AEs was observed when RV5 and diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine derived from Sabin strains (DTaP-sIPV) were given concomitantly, compared to when they were given separately. When concomitantly

Publication	Authors' Safety Conclusion
pentavalent rotavirus vaccine in Japanese infants. Hum Vaccin Immunother. 2017 Jun 3;13(6):1-7. doi: 10.1080/21645515.2017.1279769. Epub 2017 Jan 31. PMID:28140752; PMCID: PMC5489296.	administered, RV5 and DTaP-sIPV demonstrated an acceptable safety profile.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the February 23, 2017 approval of sBLA 125122/1309 for expansion of the indication to include prevention of rotavirus gastroenteritis caused by type G9 when administered as a 3-dose series to infants between the ages of 6 and 32 weeks. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for RotaTeq® does not indicate any new safety concerns. Most adverse events are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of RotaTeq®.

REFERENCES

[1] Centers for Disease Control and Prevention (CDC). (n.d.). *Infant Mortality | Maternal and Infant Health | Reproductive Health | CDC*. Centers for Disease Control and Prevention (CDC), Reproductive Health. Retrieved May 5, 2021, from https://www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm

[2] Moon RY, Task Force on Sudden Infant Death Syndrome. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment. Pediatrics. 2016 Nov 1;138(5).

[3] Goldberg N, Rodriguez-Prado Y, Tillery R, Chua C. Sudden Infant Death Syndrome: A Review. Pediatr Ann. 2018 Mar 1;47(3):e118-e123.

[4] "Fast Facts about SIDS." https://Safetosleep.nichd.nih.gov/, National Institutes of Health, 2019, safetosleep.nichd.nih.gov/safesleepbasics/SIDS/fastfacts. Accessed 19 May 2021.

[5] Corwin MJ. Sudden infant death syndrome: Risk factors and risk reduction strategies. In: UpToDate, Hoppin AG (Ed), Mallory GB (Ed), Sanghamitra MM(Ed), UpToDate, Waltham, MA. (Accessed on August 03, 2021.)

[6] Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Stratton KR, Almario DA, Wizemann TM, and McCormick MC (eds). Washington, DC: National Academy Press, 2003

[7] Tate JE, Simonsen L, Viboud C, Steiner C, Patel MM, Curns AT, Parashar UD. Trends in intussusception hospitalizations among US infants, 1993-2004: implications for monitoring the safety of the new rotavirus vaccination program. Pediatrics. 2008 May;121(5):e1125-32. doi: 10.1542/peds.2007-1590. PMID: 18450856; PMCID: PMC2680116.

APPENDIX A: RotaTeq® Data Mining Findings (Non-AEs)

The following PTs resulting from RotaTeq® data mining are not AEs; rather, these PTs represent diagnostic and treatment modalities related to gastroenteritis or intussusception.

Preferred Term (PT)
Abdominal X-ray
Appendicectomy
Barium double contrast
Barium enema
Barium enema abnormal
Culture stool
Culture stool negative
Culture stool positive
Enema administration
Intestinal resection
Explorative laparotomy
Laparoscopic surgery
Laparotomy
Large intestinal obstruction reduction
Occult blood negative
Occult blood positive

Oral administration complication
Rotavirus test negative
Rotavirus test positive
Ultrasound abdomen
Ultrasound abdomen abnormal
Small intestinal intussusception reduction
Surgery
Preferred Term (PT)
Ultrasound abdomen normal
Ultrasound scan abnormal
Urinary system X-ray
X-ray abnormal
X-ray gastrointestinal tract normal
X-ray gastrointestinal tract abnormal