

COMMUNICATION

Potential vagus nerve-related adverse events in rotavirus vaccination

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Abstract

Vagus nerve-related adverse events (AEs) can be triggered by gastrointestinal infections. This raises the question of whether AE data from live-attenuated virus vaccination can be leveraged to investigate potential vagus nerve involvement. In this study, data from the Vaccine AEs Reporting System were retrospectively analyzed for candidate vagus nerve-related AEs in infants aged 0 and 1. Live-attenuated rotavirus vaccinations were associated with elevated normalized frequencies across all 16 selected vagus nerve-related AEs in both age groups, with the majority showing higher normalized frequencies in infants aged 0 than in those aged 1. These findings suggest that oral, live-attenuated virus vaccination may provide valuable insights into vagus nerve-related AEs. Furthermore, the higher normalized frequencies of AEs observed in infants aged 0 could indicate that the administered dose or minimum infectious units may be excessive for a subset of younger infants.

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1. Introduction

The vagus nerve (also known as the 10th cranial nerve, cranial nerve X, or CN X) plays a central role in the parasympathetic control of the heart, lungs, and digestive tract. It carries both afferent and efferent fibers, serving as the primary communication pathway between the brain and the digestive system.¹ Vagus nerve-related adverse events (AEs) can be vague and non-specific, involving symptoms such as difficulty swallowing, altered appetite, changes in heart rate and respiration, gastric secretion abnormalities, impaired intestinal motility, coughing, nausea, vomiting (emesis), and vasovagal syncope (loss of consciousness). Notably, these vagus nerve-related AEs overlap with common AEs of rotavirus infection, including diarrhea, vomiting,² fever, nausea, malaise, headache, abdominal discomfort, myalgia (muscle pain), fatigue, chills, and loss of appetite.³

Rotavirus is a non-enveloped, double-stranded ribonucleic acid virus belonging to the Reoviridae family. It is highly contagious and affects infants, young children, and adults. Before the introduction of rotavirus vaccines, an estimated 2.7 million rotavirus infections occurred annually in the United States (US).⁴ The US Centers for Disease Control and Prevention (CDC) recommends rotavirus immunization for infants using either Rotarix (administered at 2 and 4 months of age) or RotaTeq (administered at

2, 4, and 6 months).⁵ In addition, three other rotavirus vaccines (Rotasiil, Rotavac, and Rotavin-M1) have been deployed in other countries.^{6,7} Rotavirus infections can cause gastroenteritis, which is characterized by severe diarrhea and vomiting. Nausea and vomiting are mediated through vagal afferent nerves.⁸ The rotavirus enterotoxin, non-structural protein 4, induces the release of serotonin (5-hydroxytryptamine [5-HT]) from enteroendocrine cells, thereby increasing intestinal motility and contributing to diarrhea.⁹ 5-HT binds to 5-HT₃ receptors present on the soma of vagal afferent neurons.¹⁰ In a mouse model, rotavirus infection downregulated tyrosine hydroxylase in the noradrenergic sympathetic nervous system of the ileum.¹¹ These findings indicate that the vagus nerve may play a role in certain gastrointestinal infections.

To investigate potential vagus nerve-related AEs following immunization, data from the Vaccine AEs Reporting System (VAERS) were retrospectively analyzed for candidate vagus nerve-related AEs in infants aged 0 and 1. VAERS is the US's early warning system for vaccine safety. It is a passive reporting system that collects a small fraction of AEs reported by vaccinees. These AE reports represent population samples for safety monitoring. The analysis revealed that majority of the examined AEs occurred at higher frequencies in infants aged 0 compared to those aged 1. This finding indicates that the dosage or minimum infectious units (IU) of rotavirus vaccines could be too high for a subset of younger infants.

2. Materials and methods

2.1. Retrospective study

The VAERS database¹² was retrospectively analyzed for the AEs designated by the following Medical Dictionary for Regulatory Activities (MedDRA) codes:¹³ convulsion and seizure, cough, decreased appetite, dyspnea (shortness of breath or discomfort in breathing), eating disorder, gastrointestinal disorder, gastrointestinal hypermotility, gastrointestinal hypomotility, gastroesophageal reflux disease, hypophagia, loss of consciousness and syncope, nausea, respiratory arrest, respiratory distress, and tachycardia. MedDRA is an international standardized medical terminology developed under the auspices of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. The downloaded VAERS data included all reported AEs from 1990 to December 27, 2024.

The Ruby program `vaers_slice4.rb`¹⁴ was used for retrospective analysis of the VAERS data files VAERSDATA, VAERSSYMPTOMS, and VAERSVAX, covering the years 1990 – 2024, as well as the NonDomestic file. The `vaers_slice4.rb` program tallies AEs by vaccine, day of onset, year,

and age. It accepts a list of one or more MedDRA terms (used by VAERS) as input. Microsoft Excel was used to prepare figures.

2.2. Statistical analysis

To facilitate standardized comparisons across datasets, AE frequencies were normalized relative to 100,000 VAERS reports for each vaccine. For a given vaccine (V) and specific AE type (X), the normalized frequency was calculated as the fraction of reports of X among all AEs reported for that vaccine, scaled to 100,000 reports. In this context, the population (P) is represented as 100,000 reports submitted to VAERS for vaccine V , rather than a true epidemiological population. The normalized frequency is calculated using Equation 1.

$$AE(V | X, P = 100,000) = \frac{AE(V | X, P)}{\sum_i AE(V | i, P)} \times 100,000 \quad (1)$$

3. Results

3.1. Vomiting

Compared to other infant vaccines, both Rotarix and RotaTeq exhibited the highest normalized frequency of vomiting AEs among infants aged 0 and 1 (Figure 1). Notably, a decreasing yearly trend in vomiting AEs was observed for oral poliovirus vaccine (Orimune) and all three rotavirus vaccines (i.e., Rotashield, Rotarix, and RotaTeq) (Figure 2). The estimated normalized frequency of vomiting AEs for the Rotarix vaccine was 23,922/100,000 reports (23.9%), which is comparable to the reported incidence of 17.8% (range: 17 – 18.6%) in a previous study.¹⁵ It should be noted that the calculated normalized frequencies do not include asymptomatic vaccinees. The estimated normalized frequency of vomiting for the RotaTeq vaccine was 7,838/100,000 reports (7.8%) overall and 13,506 (13.5%) for infants aged 0, compared to the reported incidence of 10.4% in a previous study.¹⁶

3.2. Potential vagus nerve-related AEs

Both Rotarix and RotaTeq are live-attenuated rotavirus vaccines. For both of them, the normalized frequencies of multiple AEs were higher in infants aged 0 than in those aged 1 (Figure 3). For infants aged 2, VAERS reports were limited, with $n = 32$ for Rotarix and $n = 52$ for RotaTeq, including one AE report each for nausea (Rotarix), convulsion (RotaTeq), and respiratory distress (RotaTeq), while no reports were made for all other AE types. Among infants aged 0, the normalized frequencies for Rotarix were higher than those for RotaTeq, with a mean of 3.6 times and a median of 2.3 times. Importantly, the majority of vaccinated infants did not experience these AEs, as the

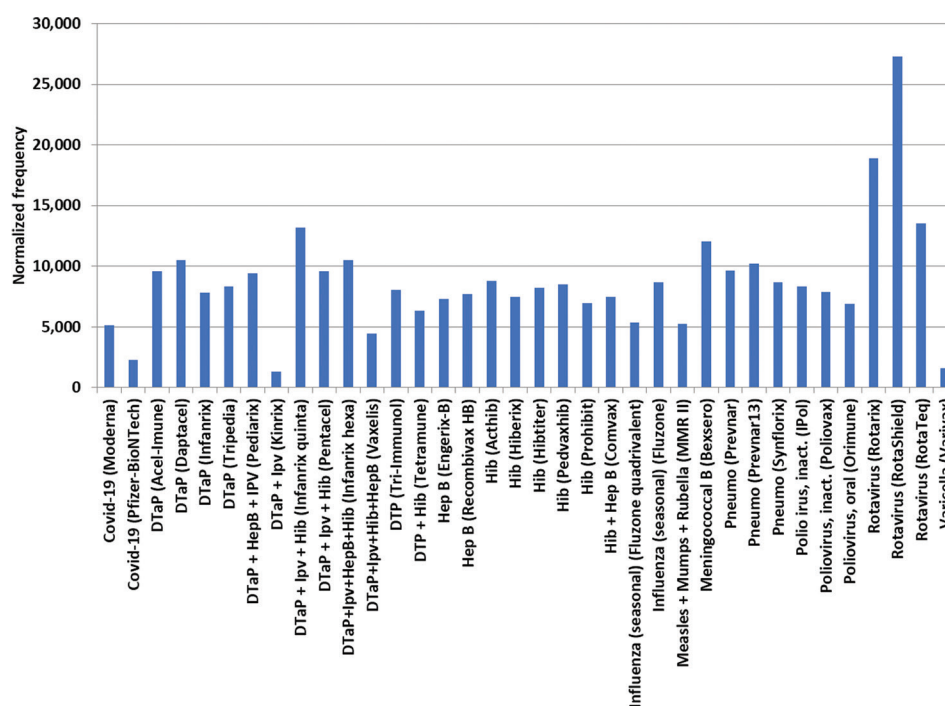


Figure 1. Comparison of vomiting adverse events in infants aged 0, with higher vagus nerve-associated vomiting in oral rotavirus vaccines. VAERS reports by vaccine, listed from left to right: $n = 510, 523, 264, 434, 130, 567, 207, 1,033, 484, 438, 906, 933, 688, 237, 754, 91, 114, 319, 633, 247, 1,264, 1,377, 1,389, 311, 186, 2,888,$ and $5,230$.

Abbreviations: COVID-19: Coronavirus disease 2019; DTaP: Diphtheria, tetanus, and acellular pertussis; Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; inact.: Inactive; IPV: Inactivated poliovirus; Pnemo: Pneumococcal; VAERS: Vaccine adverse events reporting system.

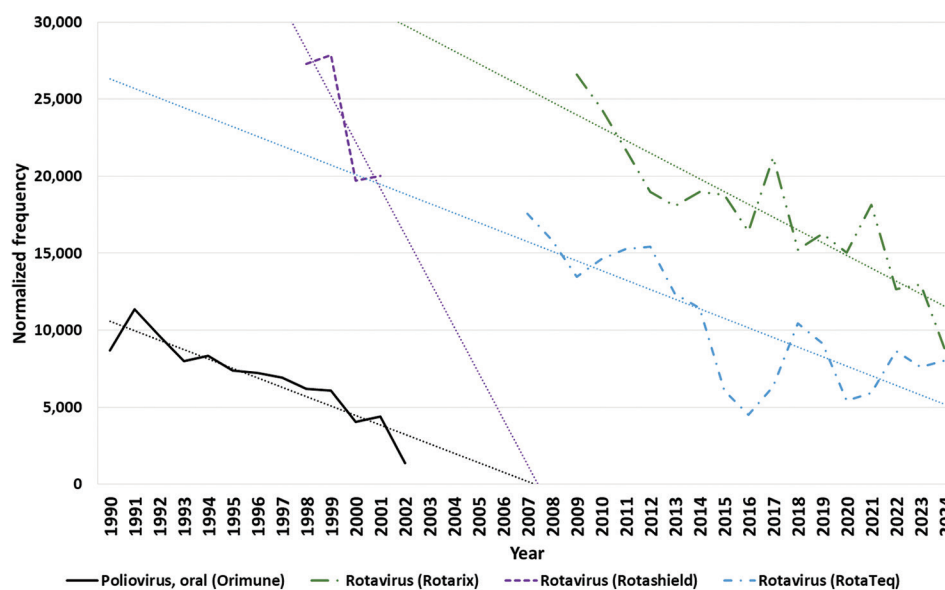


Figure 2. Normalized frequency of vomiting adverse events over the years. Decreasing yearly frequency trends have been observed for oral, live-attenuated virus vaccines. Yearly number of vaccine adverse events reporting system reports by vaccine: Orimune, in chronological order from 1990 to 2001, $n = 427, 3,118, 3,201, 2,859, 3,257, 2,922, 2,502, 1,645, 1,015, 984, 247,$ and 91 ; Rotarix, 2009 – 2024, $n = 436, 402, 437, 590, 653, 622, 979, 858, 1,041, 985, 903, 759, 595, 514, 655,$ and 811 ; RotaTeq, 2007 – 2024, $n = 1,871, 1,864, 1,040, 1,080, 1,120, 1,179, 1,084, 1,563, 2,482, 2,640, 1,917, 1,255, 1,390, 1,216, 928, 1,076, 984,$ and $1,245$; and Rotashield, 1998 – 2001, $n = 22, 481, 147,$ and 20 . The dotted lines indicate linear regressions

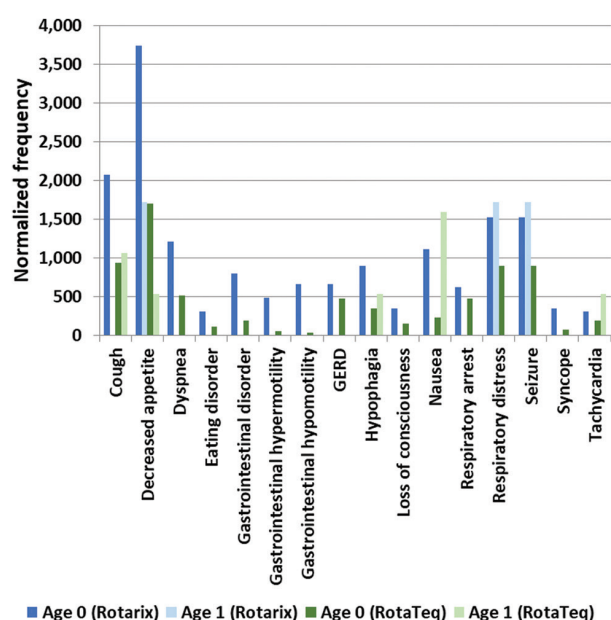


Figure 3. Normalized frequencies of candidate vagus nerve-related adverse events in Rotarix- or RotaTeq-vaccinated infants aged 0 and 1. Number of vaccine adverse events reporting system reports for Rotarix, $n = 2,888$ for age 0 and $n = 58$ for age 1; for RotaTeq, $n = 5,230$ for age 0 and $n = 188$ for age 1.

normalized frequencies would have been substantially higher if these AEs were common. For the Rotarix vaccine, 14 out of 15 AE types (93%) had higher normalized frequencies in infants aged 0 than in those aged 1. For the RotaTeq vaccine, 11 out of 15 AE types (73%) showed the same pattern.

4. Discussion

This retrospective study examined multiple candidate AEs potentially involving the vagus nerve in association with rotavirus vaccinations, in comparison to other infant vaccinations (Figure 1 and 3). The vomiting AE (Figure 1) is thought to be mediated through vagus nerve signaling.^{8,9} Interestingly, the normalized frequencies of AEs for four live virus vaccines (three for rotavirus and one for oral poliovirus) showed decreasing trends over multiple years (Figure 2). The significance of this observation is currently unclear, despite the decreasing trends for two of the rotavirus vaccines spanning at least a decade.

Among the candidate AEs examined, the Rotarix vaccine was associated with 16 AEs (100%) having normalized frequencies of at least 300/100,000 VAERS reports (Figure 3). Several of these AEs are known to be associated with the vagus nerve, including decreased appetite/hypophagia, cough, dyspnea, nausea, gastrointestinal symptoms, and vasovagal syncope.

In a subset of infants immunized with a rotavirus vaccine, multiple AEs were observed (Figure 3), with the majority of normalized AE frequencies higher in infants aged 0 than in those aged 1. The most frequent AE was vomiting (Figure 1), followed by decreased appetite (Figure 3). This suggests that, for infants with these AEs, the minimum IU delivered by rotavirus vaccines may be too high, potentially due to the lack of dose adjustment based on infant body size or weight. In addition, the higher AE frequencies in infants aged 0 may be associated with differences in immune system development (e.g., reduced immunocompetence) or pre-existing conditions (e.g., prematurity or congenital immunodeficiencies). The US CDC recommends that the RotaTeq vaccine be administered in three doses at ages 2, 4, and 6 months, and the Rotarix vaccine in two doses at ages 2 and 4 months.⁵ The body size and weight of infants at 2 and 4 months are typically smaller than children aged 1. Similar patterns in post-vaccination AEs associated with infant age have been reported for epilepsy,¹⁷ bradycardia (slow heart rate),¹⁸ cardiac arrest,¹⁸ and Kawasaki disease.¹⁹ With a goal of minimizing known rare serious AEs, efforts are underway to develop alternative, non-live rotavirus vaccines.²⁰

4.1. Study limitations

This exploratory study investigated potential vagus nerve-related AEs associated with live-attenuated rotavirus vaccination. However, it does not establish a causal relationship or confirm whether the observed AEs directly involve the vagus nerve, or if the association is coincidental.

5. Conclusion

Live-attenuated virus vaccines can provide insights into candidate vagus nerve-related AEs. The observed higher normalized frequencies of AEs in infants aged 0 than in those aged 1 may indicate that the administered dosage or minimum IU is too high for a subset of infants. Among the AEs examined in infants aged 0, Rotarix was associated with higher normalized frequencies than RotaTeq. These findings highlight the need for further investigation into age-related differences in vaccine response and the potential role of the vagus nerve in post-vaccination AEs.

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Conflict of interest

The author declares no conflicts of interest.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The original data supporting this study have been uploaded to the Harvard Dataverse (<https://doi.org/10.7910/DVN/PFN1ZR>).

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