Brief Report

Safety Signals Detected for Multiple Vaccines for Infants

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Safety Signals Detected for Multiple Vaccines for Infants

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Abstract

Introduction: Safety signals were detected for infants aged 0 for epilepsy, bradycardia, cardiac arrest, and gastrointestinal adverse events (AEs) for specific vaccines and coadministered vaccine combinations. From these observations, additional elevated infant age 0 AEs safety signals are suspected. This study examines additional AEs, examining elevated infant age 0 AEs safety signals to provide etiology insights. **Methods:** Herein, the Vaccine Adverse Events Reporting System (VAERS) was retrospectively examined for candidate AE safety signals for infants aged 0. **Results:** Additional safety signals were identified for multiple AEs affecting infants. Safety signals were detected for specific vaccines, specific concomitantly administered vaccines, and live attenuated vaccines. **Conclusions:** Specific vaccines (including live, attenuated viral vaccines) and specific concomitant vaccine combinations are resulting in elevated frequencies of multiple infant AEs. Elevated normalized frequencies of AEs for multiple concomitant vaccine combinations have additive normalized frequencies. Elevated normalized frequencies for multiple manufacturing lots are consistent with possible manufacturing contaminants (e.g., endotoxins) as causative components for multiple elevated AE frequencies.

Keywords.: death; sudden infant death syndrome; SIDS; hypotonic-hyporesponsive episode

Introduction

Vaccinating children against multiple diseases has dramatically decreased the incidence of these diseases in these children. Public health systems include database systems like the Vaccine Adverse Events Reporting System (VAERS) for passive identification of unknown safety signals through retrospective studies. Three recent studies have identified safety signals for infants associated with a set of vaccines and combinations of specific vaccines. In the first study, epilepsy adverse events (AEs) were detected with higher frequencies for infants less than one year of age compared to older children for specific vaccines [1]; statistically different frequencies were observed for the same vaccine from different manufacturers [1]. In the second study, bradycardia and cardiac arrest AEs were detected with higher frequencies for infants less than one year of age compared to infants aged 1 year for a similar set of vaccines and vaccine combinations [2]. In the third study, similar safety signals were identified associating specific vaccines with Kawasaki disease in infants [3].

Note that AEs and serious adverse events (SAEs) are referred to as AEs following immunization (AEFI) [4]. AEFIs are represented by a combination of background AEs and (when they occur) vaccine-associated AEs. A previous VAERS retrospective study identified an infant age and mortality linear relationship [5]. For infants less than one year of age, multiple AEs occur, including collapse (hypotonic-hyporesponsive episode – HHE), infantile spasms, and sudden infant death syndrome (SIDS) or sudden unexpected infant death (SUID). Observation of these AEs may represent background AEs with possible additional vaccine-associated AEs. The effect of age on the risk of collapse (HHE) has been observed for younger infants based on age at immunization for infants less than 1 year of age [6]. In a risk-benefit comparison, the risk of pertussis for infants is high compared to the risks of expected AEs and SAEs associated with immunizations. Overall, SIDS mortality is

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decreasing, and it is inversely related to immunization coverage [7,8]. A possible association of SIDS with bacterial toxins has been previously proposed [9]. This observation is supported by the observation that the incidence of SIDS decreased after the introduction of Haemophilus influenzae type b (Hib) vaccine to Hungarian infants [10]. In the United States, a retrospective study of VAERS reported no unexpected safety concerns for Hib vaccines [11]. Likewise, infantile spasms (onset 3 to 10 months) overlap with the timing of infant immunizations [12]. Evidence of coincidental temporal proximity does not establish causation of AEs and SAEs.

Additional AEs are observed in infants post-immunization. AEs reported post DTP-HB-Hib immunization included diarrhea (2.95%), vomiting (1.88%), and HHE (0.36%) [13]. A case of a 2-month-old infant developing myocarditis and HHE after immunization with pneumococcal + Haemophilus B conjugate + polio vaccine + DTP vaccine has been reported [14]. HHE has been reported following 13-valent pneumococcal conjugate vaccine (PCV13) [15] and hexavalent vaccine (DTP, hepatitis B, inactivated poliovirus, & Haemophilus influenzae type b conjugate vaccine) [16]. An infant developed a HHE AE after receipt of multiple vaccines: poliovirus, DTP, Haemophilus influenzae type b-hepatitis B virus, and pneumococcal vaccines [17]. Multiple AEs and SAEs can occur post-immunization with rare frequencies.

The risks associated with pathogen infections should be considered in the context of risks associated with vaccines in the risks versus benefits for patients. Patients and parents need to be fully informed of both pathogen risks versus risks associated with each vaccine in the principle of informed consent; while compulsory vaccines can increase population coverage [18], it is inconsistent with informed consent. In general, public health officials consider the disease risks to outweigh the risks of possible AEs and SAEs. Increasing public outreach and improving local supply chains can also improve population immunization coverage [19]. Monitoring AEs is important for maintaining the public trust in national vaccination programs [20]. The risks associated with different vaccines targeting the same pathogen(s) may be similar or different. Note that the background occurrences of any specific AE are related to the period of time examined, with no relationship to specific vaccines; any differences in AE frequencies for two vaccines examined for the same period of time will be due to random variations and vaccine-associated AE occurrences.

Herein, the VAERS database was retrospectively examined for multiple AEs for elevated normalized frequencies of AEFIs for infants less than a year of age. Multiple safety signals were observed; results support multiple causative factors, including live attenuated vaccines, unknown vaccine components or possible manufacturing contaminants, and concomitant administration of specific vaccines.

Material and Methods

The VAERS database [21] was retrospectively examined for all AEs with the Ruby program vaers_tally_age [22] for infants aged 0. The spelling of AEs matches the Medical Dictionary for Regulatory Activities (MedDRA) codes [23] 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 January 2, 2026. Microsoft Excel was used to prepare figures. An online calculator for the Chi-square test 2 × 2 contingency table was used [24].

Adverse Events Modeling

For adverse event (X), vaccine (V), possible associated safety signal (S), age group population (P_{age}), and background adverse events (B^X_{age}) can be modeled with **equation I** [2].

(I) $AE(V|X, P_{age}) = (S^X_{V,age} + B^X_{age}) \times P_{age}$

When there is no associated safety signal (S) for adverse event (X), then **equation I** reduces to **equation II** [2].

(II) $AE(V|X, P_{age}) = B^X_{age} \times P_{age}$

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For each AE in VAERS, normalized AE frequencies per P=100,000 VAERS reports for all AEs can be calculated with **equation III** for each age group [2].

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

Vaccines and Adverse Events Selection

Vaccines were selected when $\sum_i AE(V|i,P) \geq 100$, with V representing 38 singly and 62 coadministered vaccines. Normalized frequencies of AEs were averaged across these vaccines and sorted by decreasing average of normalized frequencies. Normalized frequencies for 65 AEs are summarized in Supplemental Table S1.

Results

Death and Sudden Infant Death Syndrome (SIDS)

For infants aged 0 year, multiple vaccines were observed with death and SIDS AEs normalized frequencies of zero: COVID-19 (Moderna bivalent), DTaP+IPV (Kinrix), Hep A (Havrix), Hep A (Vaqta), Hib + Hep B (Comvax), HPV (Gardasil 9), Influenza seasonal (Flulaval quadrivalent), Influenza seasonal (Fluvirin), Measles+Mumps+Rubella+Varicella (Proquad), and Polio virus, inact. (Ipol) (Figure 1A). For singly administered vaccines, the highest normalized frequencies for the death AE were observed for the Polio virus, inact. (Poliovax)=13,089 per 100,000 VAERS reports, Pneumo (Prevnar13)=5,543, Hib (Hiberix)=3,378, Pneumo (Prevnar)=2,339, Hep B (Engerix-B)=2,285, Hib (Acthib)=2,021, and DTaP+IPV+Hib (Infanrix quinta)=1,941 (Figure 1A). The infants aged 0 year normalized frequency for AE Death for Pneumo (Prevnar20)=3,121. For infants aged 0, AE Meningitis pneumococcal was observed for Pneumo (Prevnar13)=7,249 and Pneumo (Prevnar)=3,143. For children aged 1, the AE Death normalized frequencies for Pneumo (Prevnar)=1,714 and Pneumo (Prevnar13)=3,274. In contrast to IPol at 0 death reports for 322 total VAERS reports, polio virus, inact. (Poliovax) had 25 death AE reports for 191 total Poliovax VAERS reports with a normalized frequency of 13,089 (chi-square χ^2 2x2 $p<0.00001$). The highest normalized frequencies for SIDS AE were observed for Hep B (Engerix-B)=4,461, Hep B (Recombivax HB)=2,648, Polio virus, inact. (Poliovax)=2,094, DTP (Tri-Immunol)=1,464, DTAP+IPV+HIB (Infanrix quinta)=1,456, Hib (Hibtiter)=1,287, and Pneumo (Prevnar)=950 (Figure 1A).

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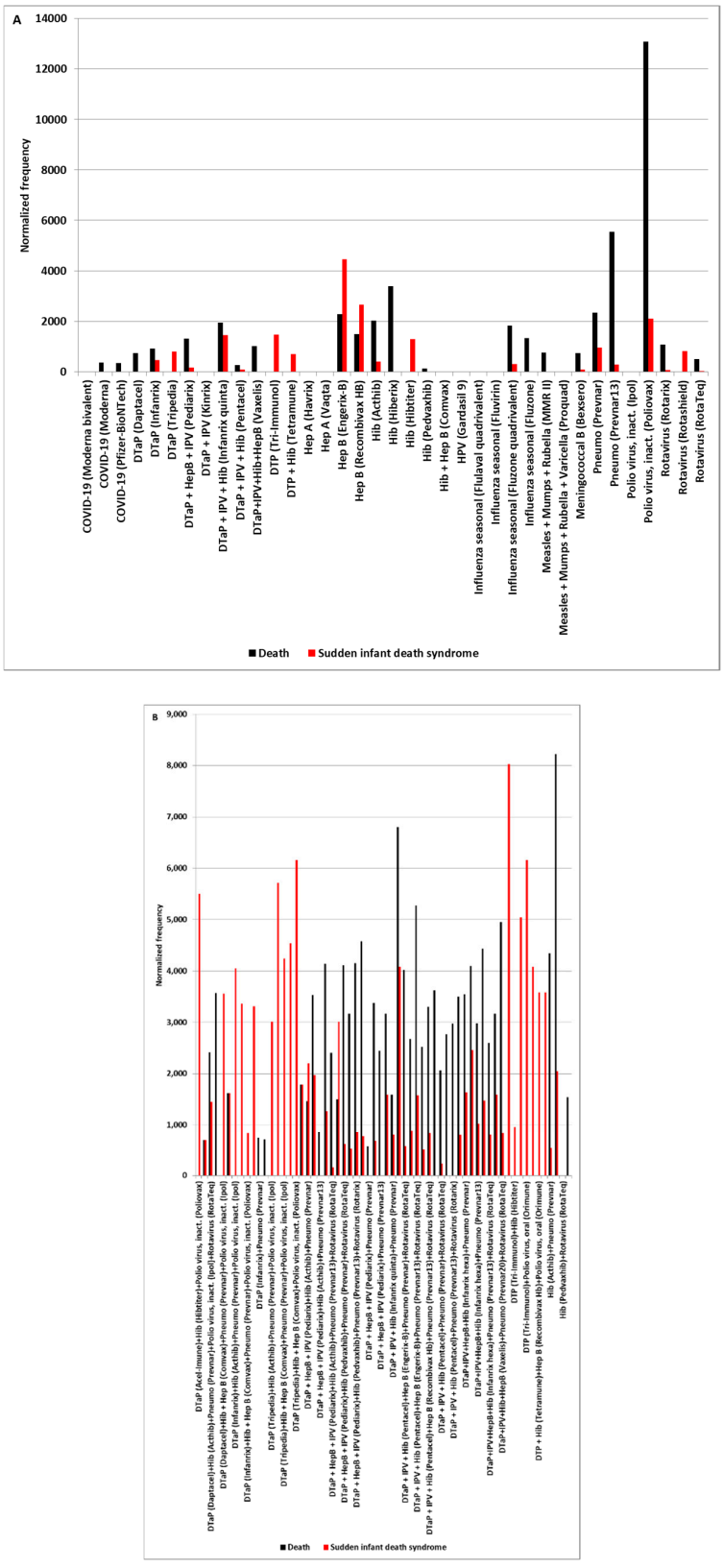

Figure 1. Normalized frequencies for VAERS adverse events autism, death, and sudden infant death syndrome for vaccines with a minimum of 100 VAERS reports for (A) singly administrated vaccines (any combination replacing Hiberix=3,378, Poliovax=13,089, Prevnar13=5,543) and (B) concomitantly administered vaccines.

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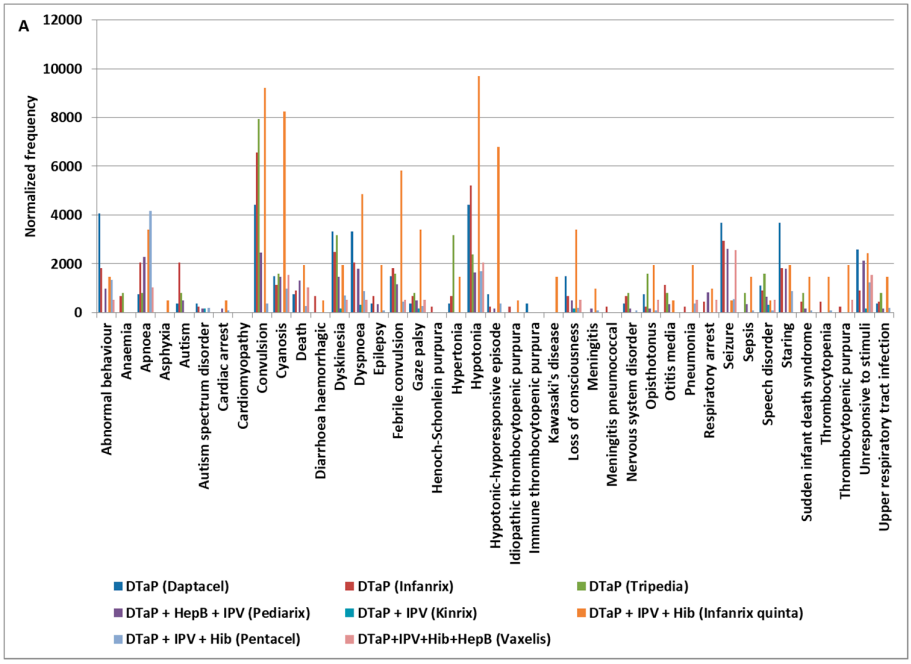
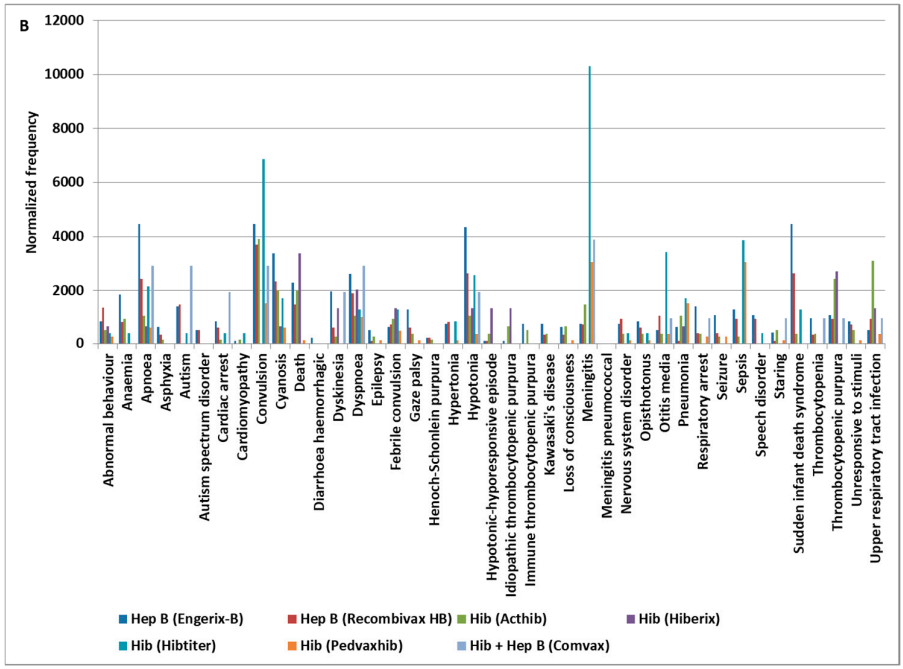
When individual vaccines were coadministered, approximate additive normalized frequencies were observed (Figure 1). For example, Hib (Acthib)=2,021 plus Pneumo (Prevnar13)=5,543 coadministered increased the observed normalized death AE normalized frequency to 8,219, and DTaP+IPV+Hib (Infanrix quinta)=1,941 plus Pneumo (Prevnar13)=5,543 coadministered increased the observed death AE normalized frequency to 6,802 (Figure 1). For the highest 20 normalized frequencies for SIDS AE ranging from 2,189 to 8,029 (Figure 2), 15 included DTaP and the other 5 DTP, 19 included Hib, 16 included a polio virus vaccine, 12 included Hep B, and 10 included Pneumo vaccine (Figure 1B). Given the disparity between identified vaccines, candidate causative components include adjuvants, excipients, and possible manufacturing contaminants.





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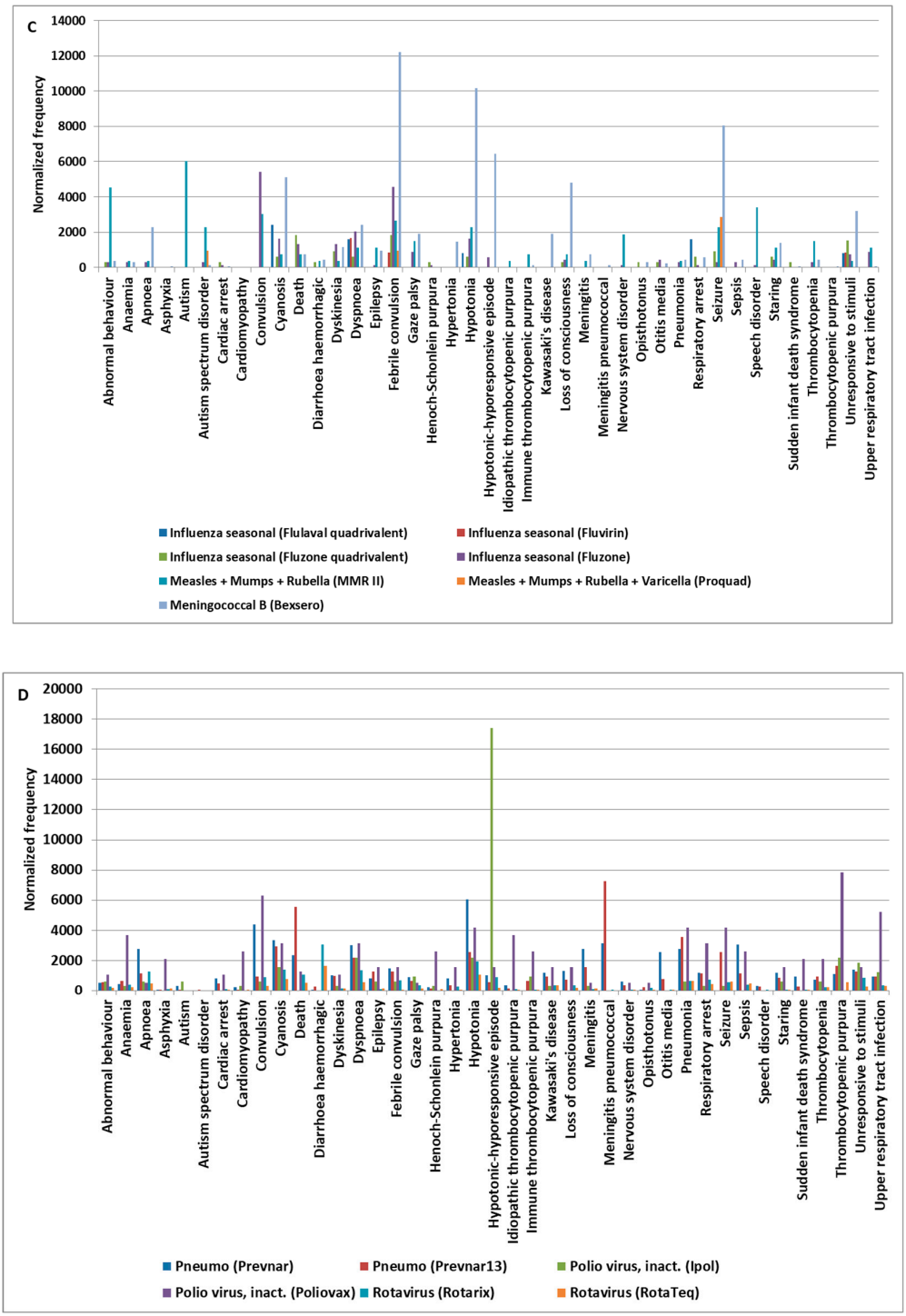

Figure 2. Selected normalized frequencies for VAERS adverse events for singly administered vaccines with a minimum of 100 VAERS reports (A) DTaP (Daptacel), DTaP (Infanrix), DTaP (Tripedia), DTaP + HepB + IPV (Pediarix), DTaP + IPV (Kinrix), DTaP + IPV + Hib (Infanrix quinta), DTaP + IPV + Hib (Pentacel), and DTaP+IPV+Hib+HepB (Vaxelis), (B) Hep B (Engerix-B), Hep B (Recombivax HB), Hib (Acthib), Hib (Hiberix), Hib (Hibtiter), Hib (Pedvaxhib), and Hib + Hep B (Comvax), (C) Influenza seasonal (Flulaval quadrivalent), Influenza seasonal (Fluvirin), Influenza seasonal (Fluzone quadrivalent), Influenza seasonal (Fluzone), Measles + Mumps + Rubella (MMR II), Measles + Mumps + Rubella + Varicella (Proquad), and Meningococcal B (Bexsero) , and (D) Pneumo (Prevnar), Pneumo (Prevnar13), Polio virus, inact. (Ipol), Polio virus, inact. (Poliovax), Rotavirus (Rotarix), and Rotavirus (RotaTeq).

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Manufacturing lots with at least 4 death AEs include DTaP+HepB+IPV (Pediarix) lots AC21B142AA, AC21B127AA, 74FN7, D93B4, and AC21B129AA and Pneumo (Prevnar13) lots EJ4512, 915192, W33490, DK2843, J11488, and W11304 (Table S2). Manufacturing lots with at least 4 SIDS AEs include Hib (Hibtiter) lots M155JA, M585JD, M460JP, M570HJ, M130HA, M180HH, M110KA, M605JD, M640FN, M600JA, M490JK, M180HB, M150JA, M680HE, M695HL, M195JF, M105JJ, and M210HK (Table S3).

DTaP Vaccines

Two DTaP vaccines, DTaP (Daptacel) and DTaP (Infanrix), have higher normalized frequencies for AEs: Abnormal behavior, Dyspnoea, Staring, and Unresponsive to stimuli that are not observed for DTaP (Tripedia) and DTaP+IPV (Kinrix) (Figure 2A). The vaccine DTaP + IPV + Hib (Infanrix quinta) has multiple AEs with higher normalized frequencies, including Hypotonia=9,708, Convulsion=9,223, Cyanosis=8,252, Hypotonic-hyporesponsive episode=6,796, and Febrile convulsion=5,825 (Figure 2A). Also, elevated normalized frequencies were observed for AE Hypertonia for DTap (Tripedia) and AE Hypotonia for DTaP (Infanrix)=5,203 and DTaP (Daptacel)=4,428. Three DTaP vaccines have the highest normalized frequencies for AE Dyskinesia (difficulty in performing or controlling voluntary movements) with Daptacel=3,321, Tripedia=3,174, and Infanrix=2,488. The highest normalized frequencies for AE Opisthotonus (severe, involuntary movement disorder characterized by dramatic backward arching of the head, neck, and spine, caused by intense muscle spasms) were observed for DTaP+IPV+Hib (Infarix quinta)=1,941 and DTaP (Tripedia)=1,587. The DTaP+IPV+Hib (Infanrix quinta) vaccine has elevated normalized frequencies for Cyanosis=8,252, Dyspnoea=4,854, Epilepsy=1,941, Febrile convulsion=5,825, Gaze palsy=3,398, Hypertonia=1,456, Hypotonia=9,708, Hypotonic-hyporesponsive episode=6,796.

Hepatitis B and Hib Vaccines

The Hepatitis B (Engerix-B) highest AEs normalized frequencies include Apnoea=4,461, Convulsion=4,461, SIDS=4,461, Hypotonia=4,352, Cyanosis=3,373, Dyspnoea=2,611, Death=2,285, and Gaze palsy=1,305; similar normalized frequencies were also observed for Hepatitis B (Recombivax HB) (Figure 2B).

The highest normalized frequencies for Hib vaccines were observed to be discordant. The highest AEs normalized frequencies for Hib (Hibtiter) observed were Meningitis=10,300, Convulsion=6,866, Sepsis=3,862, and Otitis media=3,433 were not reported for Hib (Hiberix) (Figure 2B). The highest normalized frequency for the AE Cardiac arrest was observed for Hib+Hep B (Comvax)=1,941. Comvax also had an elevated normalized frequency for AE Dyspnoea=2,912.

Influenza Vaccines

The AEs normalized frequencies for Influenza seasonal (Fluzone) include Febrile convulsion=4,552 and Death=1,321, and Influenza seasonal (Fluzone quadrivalent) Febrile convulsion=1,829 and Death=1,829, Influenza seasonal (Fluvirin) Febrile convulsion=833 and Death=0, and Influenza seasonal (Flulaval quadrivalent) Febrile convulsion=0 and Death=0 (Figure 2C).

Measles, Mumps, and Rubella Vaccines

The highest AEs normalized frequencies for Measles+Mumps+Rubella (MMR II) include Autism=6,037, Abnormal behavior=4,528, Speech disorder=3,396, Convulsion=3,018, Febrile convulsion=2,641, Autism spectrum disorder=2,264, and Gaze palsy=1,509 (Figure 2C). For the Measles+Mumps+Rubella+Varicella (Proquad) vaccine these normalized frequencies were Autism=0, Abnormal behaviour=0, Speech disorder=0, Convulsion=0, Febrile convulsion=952, and Autism spectrum disorder=952 (Figure 2C). MMR II had the highest normalized frequency for Nervous system disorder=1,886.

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Meningococcal B Vaccine

The highest AEs normalized frequencies for Meningococcal B (Bexsero) include Febrile convulsion=12,198, Hypotonia=10,153, Seizure=8,035, Hypotonic-hyporesponsive episode=6,428, Cyanosis=5,113, Loss of consciousness=4,821, and Unresponsive to stimuli=3,214 (Figure 2C). Bexsero also has elevated normalized frequencies for Cyanosis=5,113, Febrile convulsion=12,198, Gaze palsy=1,899, Hypertonia=1,460, Hypotonia=10,153, and Hypotonic-hyporesponsive episode=6,428.

Pneumo Vaccines

The highest AEs normalized frequencies for Pneumo (Prevnar13) include Meningitis pneumococcal=7,249, Death=5,543, Pneumonia=3,553, Cyanosis=2,914, Hypotonia=2,558, Epilepsy=1,279 (Figure 2D). The elevated Pneumo (Prevnar) normalized frequencies were observed for AEs: Cyanosis=3,362, Dyspnoea=2,997, Hypotonia=6,067, and Meningitis=3,143.

Polio Virus Vaccines

The highest AEs normalized frequencies for Polio virus, inact. (Poliovax) include Death=13,089, Thrombocytopenia purpura=7,853, Convulsion=6,282, and Upper respiratory tract infection=5,235 and for Polio virus, inact. (IPol) Hypotonic-hyporesponsive episode=17,391, Thrombocytopenic purpura=2,173, Hypertonia=1,570, Hypotonia=4,188, Dyspnoea=3,141, Cyanosis=3,141, Epilepsy=1,570, and Death=0 (Figure 2D); note that the normalized frequency for Poliovax, in any administration, of 1,252 was plotted. Poliovax has the highest normalized frequency for Anaemia=3,664, Asphyxia=2,094, Cardiomyopathy=2,617, Henoch-Schonlein purpura=2,617, Idiopathic thrombocytopenic purpura=3,664, Immune thrombocytopenic purpura=2,617, Respiratory arrest=3,141, Thrombocytopenia=2,094, Thrombocytopenic purpura=7,853, and Upper respiratory tract infection=5,235.

Rotavirus Vaccines

AEs normalized frequencies for attenuated live rotavirus vaccines are illustrated in Figures 2D and 3. The AEs in Figure 3 are likely associated with vaccine strain rotavirus infections (e.g., Gastroenteritis rotavirus, Gastroenteritis, Intussusception, Haematochezia, Mucous stools, Faeces discoloured, Diarrhoea haemorrhagic, Surgery, and Intensive care).

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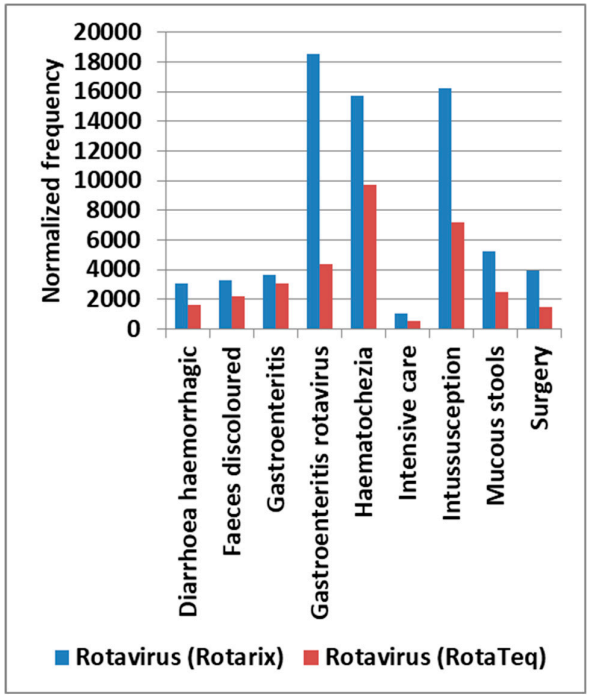

Figure 3. Selected normalized frequencies for VAERS adverse events for singly administered live attenuated rotavirus vaccines Rotavirus (Rotarix), and Rotavirus (RotaTeq).

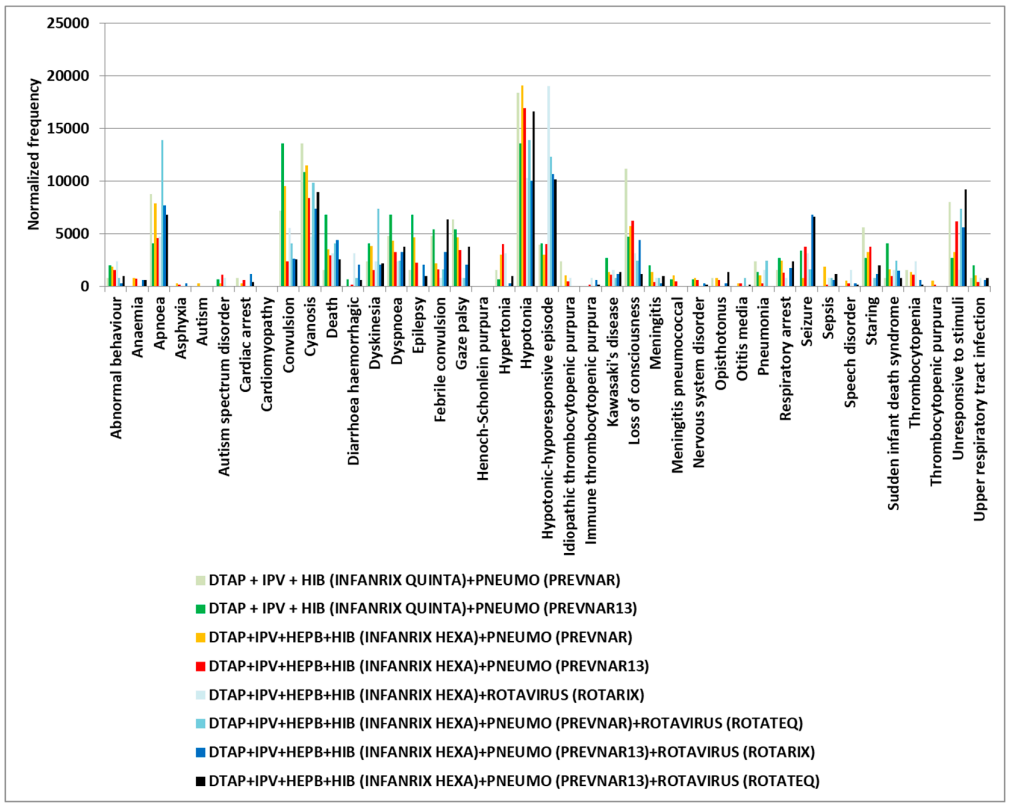

Figure 4. Selected normalized frequencies for VAERS adverse events for concomitantly administered vaccines including either DTaP + IPV + Hib (Infanrix quinta) or DTaP+IPV+HepB+Hib (Infanrix hexa).

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Adverse Events

Elevated normalized frequencies for were observed for AE Abnormal behaviour: Measles+Mumps+Rubella (MMR II)=4,528 and DTaP (Daptacel)=4,059, AE Apnoea: Hep B (Engerix-B)=4,461, DTaP+IPV+Hib (Pentacel)=4,155, and DTaP+IPV+Hib (Infanrix quinta)=3,398, AE Kawasaki's disease: Meningococcal B (Bexsero)=1,899, Polio virus, inact. (Poliovax)=1,570, and DTaP+IPV+Hib (Infanrix quinta)=1,456, AE Loss of consciousness: Meningococcal B (Bexsero)=4,821 and DTaP+IPV+Hib (Infanrix quinta)=3,398, AE Otitis media (an infection or inflammation of the middle ear): Hib (Hibtiter)=3,433 and Pneumo (Prevnar)=2,558, AE Pneumonia: Polio virus, inact. (Poliovax)=4,188, Pneumo (Prevnar13)=3,553, Pneumo (Prevnar)=2,777, and DTaP+IPV+Hib (Infanrix quinta)=1,941, and AE Sepsis: Hib (Hibtiter)=3,862, Pneumo (Prevnar)=3,070, Hib (Pedvaxhib)=3,045, and Polio virus, inact. (Poliovax)=2,617.

Coadministered Vaccines

Elevated AE normalized frequencies for coadministered vaccines are illustrated in Table 1; these normalized frequency values are higher than all observed singly administered vaccines (Figure 2). Vaccine names occurring more than once in Table 1 include Pneumo (Prevnar13) 20 times, Pneumo (Prevnar) 15 times, DTaP+IPV+HepB+Hib (Infanrix hexa) 16 times, DTaP+IPV+Hib (Infanrix quinta) 11 times, Rotavirus (RotaTeq) 13 times, Rotavirus (Rotarix) 3 times, Hib (Acthib) 3 times, DTaP+HepB+IPV (Pediarix) 3 times, Hib (Hibtiter) 2 times, and DTaP (Infanrix) 2 times.

Table 1. Candidate additive elevated normalized frequencies for multiple adverse events.

Adverse event	Coadministered vaccines	Normalized frequency
Gaze palsy	DTaP (Acel-Imune)+Hib (Hibtiter)+Polio virus, inact. (Poliovax)	6,422
Unresponsive to stimuli	DTaP (Daptacel)+Hib (Acthib)+Pneumo (Prevnar)+Polio virus, inact. (Ipol)	6,178
Apnoea	DTaP (Infanrix)+Pneumo (Prevnar13)	10,563
Epilepsy	DTaP (Infanrix)+Pneumo (Prevnar13)	4,225
Dyskinesia	DTaP + HepB + IPV (Pediarix)+Hib (Acthib)	5,357
Surgery	DTaP + HepB + IPV (Pediarix)+Pneumo (Prevnar)+Rotavirus (RotaTeq)	8,783
Seizure	DTaP + HepB + IPV (Pediarix)+Pneumo (Prevnar13)+Rotavirus (RotaTeq)	7,142
Cyanosis	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	13,600
Depressed level of consciousness	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	18,400
Gaze palsy	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	6,400
Hypotonia	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	18,400
Loss of consciousness	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	11,200
Unresponsive to stimuli	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar)	8,000
Cyanosis	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar13)	10,884

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Depressed level of consciousness	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar13)	25,170
Dyspnoea	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar13)	6,802
Epilepsy	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar13)	6,802
Gaze palsy	DTaP + IPV + Hib (Infanrix quinta)+Pneumo (Prevnar13)	5,442
Cyanosis	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)	11,475
Epilepsy	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)	4,644
Hypotonia	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)	19,125
Apnoea	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)+Rotavirus (RotaTeq)	13,934
Dyskinesia	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)+Rotavirus (RotaTeq)	7,377
Hypotonic-hyporesponsive episode	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)+Rotavirus (RotaTeq)	12,295
Unresponsive to stimuli	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar)+Rotavirus (RotaTeq)	7,377
Hypotonia	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)	16,957
Unresponsive to stimuli	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)	6,166
Hypotonic-hyporesponsive episode	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (Rotarix)	10,650
Seizure	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (Rotarix)	6,804
Hypotonia	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (RotaTeq)	16,600
Hypotonic-hyporesponsive episode	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (RotaTeq)	10,200
Seizure	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (RotaTeq)	6,600
Unresponsive to stimuli	DTaP+IPV+HepB+Hib (Infanrix hexa)+Pneumo (Prevnar13)+Rotavirus (RotaTeq)	9,200
Hypotonic-hyporesponsive episode	DTaP+IPV+HepB+Hib (Infanrix hexa)+Rotavirus (Rotarix)	19,047
Otitis media	Dtp (Tri-Immunol)+Hib (Hibtiter)	5,600
Respiratory arrest	Hib (Acthib)+Pneumo (Prevnar13)	5,479
Pneumonia	Pneumo (Prevnar13)+Rotavirus (RotaTeq)	5,384

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Thrombocytopenic purpura	Pneumo (Prevnar13)+Rotavirus (RotaTeq)	9,230
Upper respiratory tract infection	Pneumo (Prevnar13)+Rotavirus (RotaTeq)	5,384

Discussion

Current vaccines are protecting children against multiple diseases with well-established efficacy. The results observed in this study identify patterns of safety signals with associations for specific vaccines and specific concomitantly administered vaccines. Identification of these observed safety signals may enable possible adjustments to further improve safety profiles for these vaccines while reducing AEs and SAEs in vaccinated children.

For infants aged 0, multiple elevated AE normalized frequencies were observed for some singly administered vaccines and not others (Figures 1A, 2, & 3); for some coadministered vaccine combinations, additive patterns of normalized frequencies were observed (Figure 1B & Table 1). These AEs' normalized frequency patterns exclude Background events as significant contributors to the observed elevated AEs. Discordant patterns of normalized frequencies between different DTaP vaccines provide likely evidence that possible unintentional manufacturing contaminants may be candidate causative constituents (e.g., endotoxins). Possible unintended manufacturing contaminants are consistent with the overrepresentations of the pair Pneumo (Prevnar13) and Pneumo (Prevnar) plus the pair Infanrix hexa and Infanrix quinta in Table 1. The imbalanced pair of Rotavirus (RotaTeq) occurring 13 times and Rotavirus (Rotarix) 3 times in Table 1 is consistent with (1) possible unintended manufacturing contaminant(s) and/or (2) contributions from live attenuated rotavirus pathogen. By Occam's razor rationale, the AE illustrated in Figure 3 can be attributed to rotavirus infections from the live attenuated rotavirus vaccines.

Hypothesis 1: Some vaccines may be contaminated with manufacturing contaminants (e.g., endotoxins) that may be contributing to the observed AEFIs.

Candidate manufacturing lots have been identified associated with AE death for DTaP+HepB+IPV (Pediarix) and Pneumo (Prevnar13) (Table S2) and AE SIDS for Hib (Hibtiter) (Table S3). These lots can be examined for possible manufacturing contaminants with techniques like mass spectrometry and tests for identification of endotoxins, etc.

Hypothesis 2: Live attenuated rotavirus vaccines ($V_{rotavirus}$) are contributing to multiple AEFIs in some infants.

Death and Sudden Infant Death Syndrome (SIDS) Adverse Events

The high AE death normalized frequencies were observed for Polio virus, inact. (Poliovax)=13,089, Pneumo (Prevnar13)=5,543, Pneumo (Prevnar)=2,339, Hib (Hiberix)=3,378, Hep B (Engerix-B)=2,285, Hib (Acthib)=2,021, and DTaP+IPV+Hib (Infanrix quinta)=1,941. For the Polio virus, inact. (Poliovax), in any administration, the much lower normalized frequency of 1,252 was observed and used in Figures 1A and 2D. Multiple combinations of coadministered vaccines had higher normalized frequencies, consistent with additive risk patterns (Figure 1).

The risk for SIDS or sudden unexpected infant death (SUID) is highest for infants less than 1 year of age, with peak risk window overlapping the recommended timing of Diphtheria-tetanus toxoids-pertussis (DTP) immunization. While DTP vaccination associated with SIDS was observed [25], this observation is not supported by longitudinal evidence [26], and a case-control study [27] does not support an association between SIDS and vaccination. In contrast, a study of 70 SIDS cases found 2/3 had been immunized with DTP prior to death [28]. Association with diphtheria, tetanus, and whole-cell pertussis (DTwP) but not with acellular pertussis (DTaP) with SIDS was also reported [29]. It is suggested that DTP associations with SIDS are expected due to temporal proximity to receipt of DTP by simple chance [30]. Association of vaccine hexavalent vaccine and Infanrix hexa with SIDS has also been reported [31–33]. While discordant with their conclusions, increased numbers of SIDS

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and SUD cases were observed in the first five days following immunization with Infanrix hexa vaccine for infants less than 1 year of age [34]. The candidate association signal detected in Germany [33] was not reproduced in an Italian case series for hexavalent vaccines [35].

The estimated control background AE normalized frequency for SIDS AE is close to zero for infants aged 0 per 100,000 VAERS reports (Figure 1). Seven (1 post-marketing) FDA package insert documents include the SIDS AE, with two being single SIDS reports not thought to be associated with the vaccine. Published studies report a lower incidence of SIDS for vaccinated infants compared to unvaccinated infants [8,36]. In a study of 50 SIDS cases, seven (21.9%) had received immunization within 7 days of death [37]. A previous VAERS retrospective study of SIDS also detected safety signals ($p<0.00001$) [38]. Herein, elevated normalized frequencies for multiple singly administered vaccines for AE SIDS were observed (Figure 1A). Higher AE SIDS normalized frequencies were observed for specific combinations of coadministered vaccines (Figure 1B), consistent with additive risks. These observations are consistent with unknown causative vaccine component(s), likely possible manufacturing contaminant(s), associated with observed elevated SIDS AEs.

Study Limitations

The VAERS database collects only a small subset of AEs experienced by vaccinees; this data represents population samples. It is well known that reporting bias increases with elapsed time post-immunization. All reporting biases or exclusion of AEs would perturb the normalized frequencies presented herein. Aside from observed reporting bias in VAERS for Autism and ASD with the MMR II vaccine [39], the author is unaware of any biases for or against reporting other AEs by specific vaccine, vaccine type, or population age group.

Study Recommendations

Understanding the etiology of how these SAEs are developing in young infants will provide the foundation for the avoidance of these SAEs in current and future vaccines.

When infants are immunized with current rotavirus vaccines, it is recommended to avoid identified specific combinations with higher SAEs or considering avoiding concomitant administrations to minimize SAE risks.

Conclusions

The VAERS database was retrospectively examined for multiple AEs to provide insights into observed safety signals for infants aged 0. Candidate causative factors include unknown constituents of multiple vaccines consistent with possible manufacturing contaminants, live attenuated vaccines, and specific concomitant vaccine combinations. Additive increases in SAEs were observed for specific concomitant vaccine combinations. Only for specific vaccines identified herein that exhibit either elevated AE normalized frequencies or additive AE normalized frequencies, vaccine substitutions, alternate combinations, or single administration of these specific vaccines is strongly encouraged. Avoiding specific concomitant vaccine combinations with additive AEs, and identifying causative agents coupled and eliminating them from infant vaccines are strongly encouraged.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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