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Etiology Model of Kawasaki Disease and Multisystem Inflammatory Syndromes: Mast Cell Activation

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Highlights

Kawasaki's disease and multisystem inflammatory syndrome adverse events in VAERS findings:

- Consistent with candidate manufacturing contaminant(s) (e.g., endotoxins trigger).
- Kawasaki's disease, MIS-C, MIS-A, MIS-N, and MIS-V are consistent with activation of mast cells associated disease symptoms

What are the implications of the main findings?

- Reduction or elimination of causative components will reduce or eliminate Kawasaki's disease and MIS-V cases post immunization.
- Proposed two different models for activation of mast cells provide insights into IVIG non-responders and future directions for candidate adjunctive treatments to evaluate.

Abstract

Background/Objectives: Kawasaki's disease (KD) is a leading cause of heart disease in children. The multisystem inflammatory syndrome (MIS) associated with the SARS-CoV-2 virus is similar to KD. The etiologies of KD and MIS are unknown. Both diseases are associated with pathogens and immunizations. **Methods:** The Vaccine Adverse Event Reporting System (VAERS) was retrospectively examined for etiology insights into both KD and MIS. **Results:** Immediate-onset KD-associated safety signals were detected for specific vaccines and coadministered combinations of these vaccines for young infants; a subset of these associations have a male sex bias, whereas others appear to be sex neutral. These specific vaccines may contain manufacturing contaminants (e.g., endotoxins) that are activating mast cells via Toll-like receptors. MIS-V cases were enriched in children of all ages. **Conclusions:** Both KD and MIS appear to involve two activation pathways. The first pathway involves high titers of immune complexes that activate Fc receptors on mast cells, platelets, and other immune cells. Immune complex titers higher than primary immune response levels are predicted to be required to activate low-affinity IgG FcγR2α receptors on immune cells and platelets. IVIG treatment is predicted to directly compete with immune complex binding to FcγR2α receptors. The second pathway appears to directly activate mast cells and other immune cells without involving immune complexes or Fc receptors. Cardiac adverse events, coronary artery aneurysms (CAAs), myocarditis, transient left ventricular dysfunction, and acquired heart disease are predicted to result from pressure induced lesions indirectly caused by cardiac capillary vasoconstrictions. Second, mast cell activation (e.g., endotoxin contaminants) or persistent infections are likely causes of IVIG nonresponders for KD and MIS. MIS appears to be KD associated with the SARS-CoV-2 virus or the COVID-19 spike protein (MIS-V).

Keywords: Kawasaki disease; multisystem inflammatory syndrome; MIS; vasculitis disease; mast cells; histamine; vaccines; immunization; manufacturing contaminant; endotoxin

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1. Introduction

Kawasaki disease (KD) (also known as mucocutaneous lymph node syndrome) is a form of vasculitis in which medium-sized blood vessels become inflamed throughout the body. KD primarily affects children under 5 years of age. Symptoms include fever, rash, conjunctivitis (red eye), oral changes (red, dry, cracked, or fissured lips, "strawberry tongue", and inflamed oral mucosa), palmar and plantar erythema (redness of hands and feet), cervical adenopathy (enlarged lymph nodes of the neck), coronary artery aneurysms (CAAs) or lesions (CALs) (~25%), and peripheral artery aneurysms [1]. KD fever typically lasts for more than five days and is unresponsive to paracetamol (acetaminophen) or ibuprofen. KD is the leading cause of acquired heart disease (including myocarditis and CAA) in children. The skin from the hands and feet may peel after patient recovery. The etiology of KD is currently unknown. Atypical (or incomplete) KD patients do not fulfill the complete diagnostic criteria for KD but are also at risk for developing coronary artery abnormalities [2]; treatment of KD patients and atypical KD patients with intravenous immunoglobulin (IVIG) and aspirin greatly reduces the incidence of CALs in patients (overview [2]). Notably, aspirin is normally contraindicated for children because of the possible risk of Reye's syndrome [3]. Up to 20% of IVIG-treated patients develop recurrent or persistent fever (IVIG-resistant) (overview [2]). Kawasaki disease shock/toxic-shock syndrome (KDSS) is an acute phase of KD [4].

Associations between KD and multiple viruses [5–26] and bacterial pathogens [14,27–32] have been reported. KD cases can frequently occur several weeks after pathogen outbreaks [22,33,34]. Pyroptosis is a form of inflammatory, programmed, and lytic cell death triggered by infections or other signals were cells rupture and release some proinflammatory molecules. Infection triggered pyroptosis [35] and endothelial cell pyroptosis may play a role in some KD patients [36]. Seasonal exposure patterns are associated with some KD patients aged 3 years or older but not younger [37]. During the COVID-19 pandemic, the incidence of KD cases decreased and remained low during the period of masking and school closures for older children more than for infants [38,39]. KD has also been reported as a rare adverse event associated with individual vaccines and concomitant vaccine combinations [40–54]. Patients with KD can also have altered gastrointestinal microbiota [55,56]. KD cases also temporally cluster [57]. Environmental exposures may be triggering some KD cases [58]. Cumulative prenatal and postnatal air pollution exposure to carbon monoxide (CO), nitric oxide (NO), nitric dioxide (NO_2), and nitrogen oxide (NOx) but not ozone (O_3) exposure has a dose-dependent effect on increasing KD incidence [59]. O_3, but not CO, NO_2, particulate matter with an aerodynamic diameter < 10 μm (PM_{10}), and SO_2 were not found to be associated with each other in a different study [60]. A study of CO, NO_2, SO_2, O_3, $PM_{2.5}$, and PM_{10} reported positive associations for only SO_2 and $PM_{2.5}$ for KD [61]. An exposure dosage relationship between $PM_{2.5}$ and KD has been reported [62]. Additionally, increases in the monthly mean temperature and dry season were associated with increased KD in the Philippines [63]. $PM_{2.5}$, PM_{10}, SO_2 (warm season), and temperature associations have been detected [64]. A meta-analysis revealed both prenatal and postnatal associations between ambient air pollution and KD [65]. KD associations include pathogens, vaccines, air pollution, and increased temperature.

Individuals with COVID-19 can develop multisystem inflammatory syndrome (MIS) in children (MIS-C), adults (MIS-A) [66], and neonates (MIS-N), with significant similarities to KD or KD toxic-shock syndrome [67]. MIS-C has also been named Pediatric Inflammatory Syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) [68]. MIS is thought to be distinct from KD because of differences in patient age; gastrointestinal and cardiovascular system involvement (including myocarditis, transient left ventricular dysfunction, and depressed cardiac output); and laboratory findings [67–71]. Elevated troponin and elevated B-type natriuretic peptide are key laboratory findings of MIS compared with KD [72]. KD and KDSS are associated with coronary artery pathologic changes and long-term cardiovascular sequelae [73–75]. KD and MIS symptoms overlap with those of mast cell activation syndromes (MCAS) [76]. Note that temperature changes and air pollution are known to trigger MCAS.

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Hypothesis 1: Multisystem inflammatory syndrome is Kawasaki disease associated with the SARS-CoV-2 pathogen, with differences associated with specific infectious pathogen (e.g., SARS-CoV-2). Similarly, MIS-V is KD-V [77] associated with a COVID-19 (spike protein) vaccine. The differences between KD and MIS are likely due to the SARS-CoV-2 virus associated symptoms (MIS-C, MIS-A, and MIS-N).

Platelet activation plays an important role in KD pathogenesis [78]; monocyte–platelet aggregates (MPAs) (markers of platelet activation) are significantly elevated in the acute stages of KD [78]. Platelet count and plateletcrit (PCT) were found to be diagnostic markers for KD [79]. Thrombocytopenia has been reported in a KD patient [80]. Thrombocytopenia or thrombocytosis can be associated with KD [81]. In a murine model of KD vasculitis, platelets exacerbated cardiovascular inflammation [82]. A KD etiology model in which activated mast cells and platelets are important KD pathogenic characteristics has been proposed [83]. In KD, platelets and activated monocytes can result in Kawasaki disease complicated with macrophage activation syndrome (KD-MAS) [84].

In this study, the Vaccine Adverse Event Reporting System (VAERS) was retrospectively examined to obtain additional insights into both KD pathogenesis and MIS pathogenesis. Previously proposed KD and MIS etiology models are refined, linking pathogen infections, immunization, and environmental triggers with activated mast cells. Candidate manufacturing contaminants were identified as likely causative agents triggering KD and MIS post immunization.

2. Methods

This is a retrospective analysis of the VAERS database [85] from January 1, 1990, until January 30, 2026. VAERS was used to search for Kawasaki's disease, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, and Death AEs. The Ruby program vaers_slice5.rb [86] was used for retrospective analysis of the VAERS data files VAERSDATA, VAERSSYMPTOMS, and VAERSVAX for the years 1990--2026 and NonDomestic.

For the vaccine (V_{name}) and each adverse event (X) in VAERS, normalized AE frequencies per P=100,000 VAERS reports per category of AEs can be calculated with Equation (1).

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

3. Results

In VAERS, KD is nonrandomly associated with multiple specific vaccines with different normalization frequencies for children aged 0, 1, and 2 years (Figure 1); a subset of these vaccines are associated with elevated normalized frequencies for Infants aged 0 year (Figure 2A). Associations of KD with immunization (Figure 1) may account for the lack of seasonal exposure patterns for some KD patients aged younger than 3 years [37]. The frequency of vaccine names in Figure 2A is plotted in Figure 2B; these same vaccines have similar patterns of normalized frequencies for AE death, Pearson r=0.66 (Figure 2C). The vaccines and concurrent vaccine combinations with higher normalized frequencies (Figures 1 & 2) are predicted to contain unknown manufacturing contaminant(s), most likely endotoxins. Endotoxin exposure activates mast cells [87]. The normalized frequencies for MIS-V associated with the COVID-19 Pfizer-BioNTech vaccine are shown in Figure 3. The four vaccine lots with the most MIS reports include lot FK5127 with a normalized frequency of 696 (24 of 3,448 VAERS reports), FK5618 at 782 (20 of 2,255), FL00007 at 1,173 (21 of 1,790), and FN4072 at 1,775 (6 of 338) (Figure 4). While adverse events reported to VAERS are subject to reporting bias with fewer reports with increased time since immunization, the highest reports for KD and MIS are 1--2 days, with possible small increases associated with antibody immune responses (Figure 5). Note that the day of onset patterns post immunization for KD and MIS correlate with Pearson r=0.90 (Figure 5). An increased male sex bias is known for KD; normalized frequencies for AE KD by sex in VAERS are illustrated in Figure 6. Only four vaccines have imbalances between normalized frequencies for males versus females: DTaP+IPV+Hib (Infanrix quinta), DTaP+IPV+HepB+Hib

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(Infanrix hexa), Measles+Mumps+Rubella (Priorix), and Meningococcal B (Bexsero) (Figure 6), whereas the other vaccines have roughly equivalent normalized frequencies (Figure 6). Note that Measles+Mumps+Rubella (MMR II) has low normalized frequencies similar to Measles+Mumps+Rubella+Varicella (Proquad) but discordant from Measles+Mumps+Rubella (Priorix) with higher normalized frequencies for females and much higher normalized frequencies for males (Figure 6). Surprisingly, there are specific immunization doses associated with KD reports (Figure 7). For MIS, the majority of the reports are associated with the second COVID-19 shot. For COVID-19 Pfizer-BioNTech, the normalized frequency is higher for the second shot (169 reports) versus the first shot (155 reports). The symptoms reported in the VAERS for KD and MIS patients are summarized in Table S1.

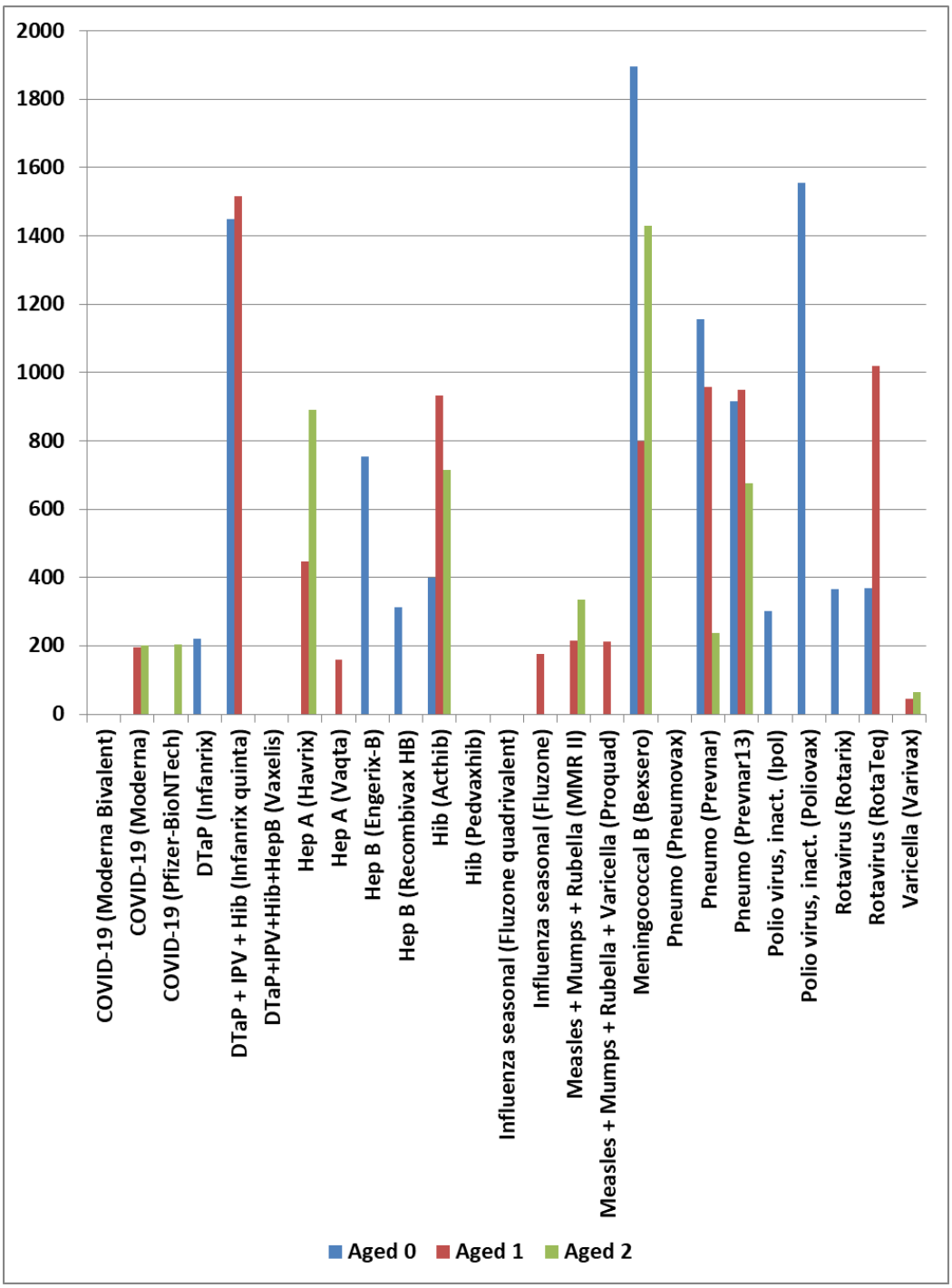

Figure 1. Kawasaki disease normalized frequency by year of age 0, 1, and 2.

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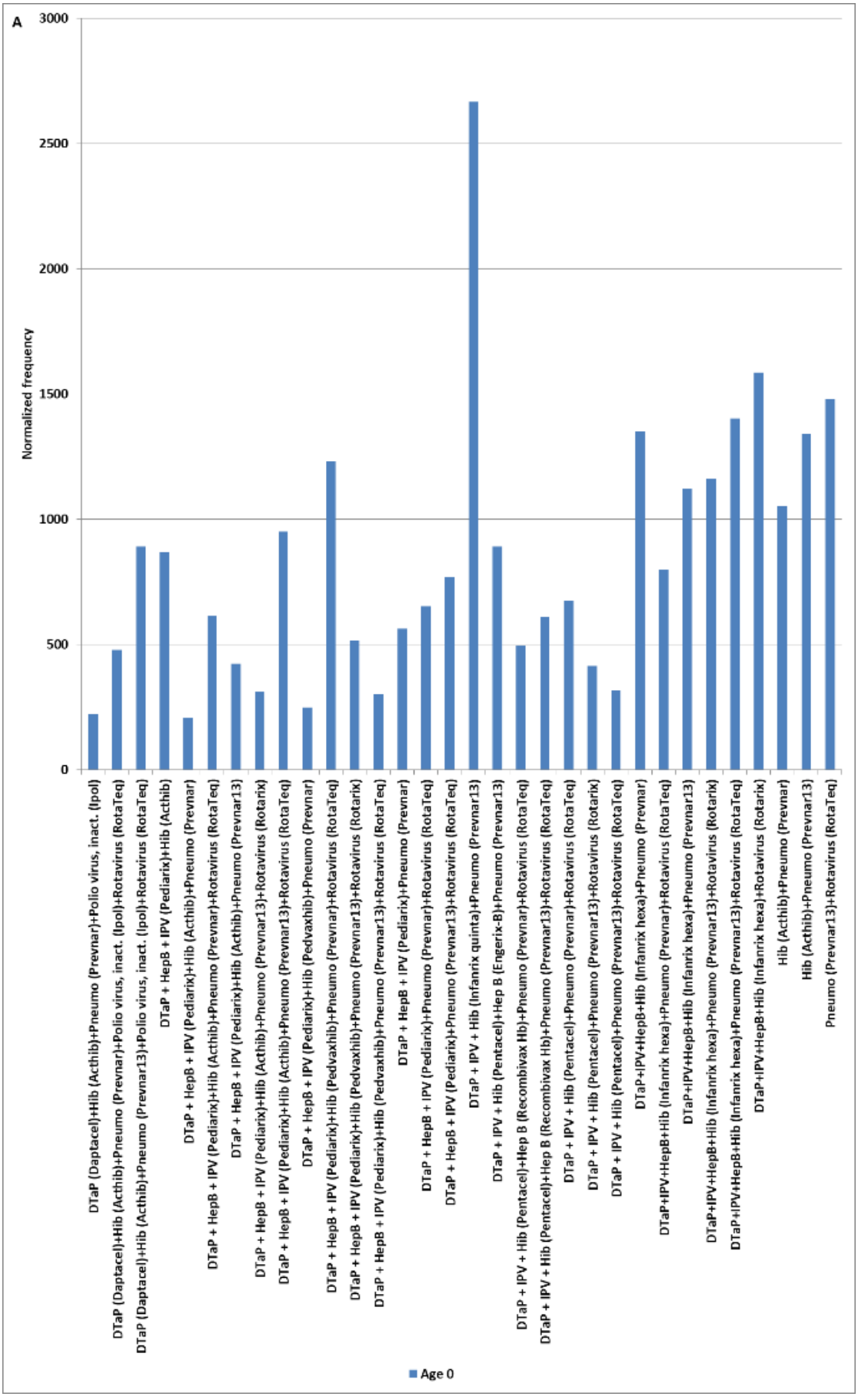

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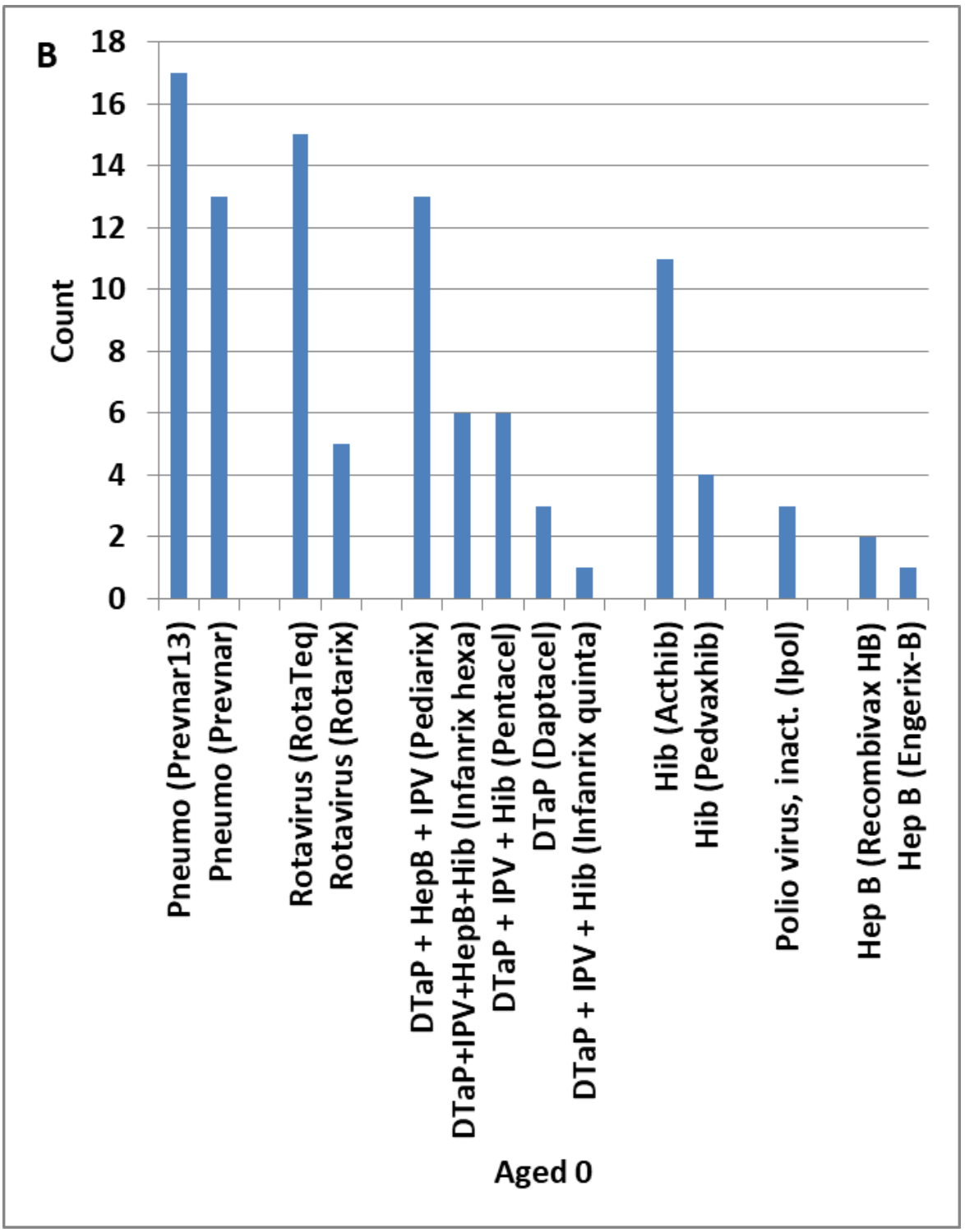

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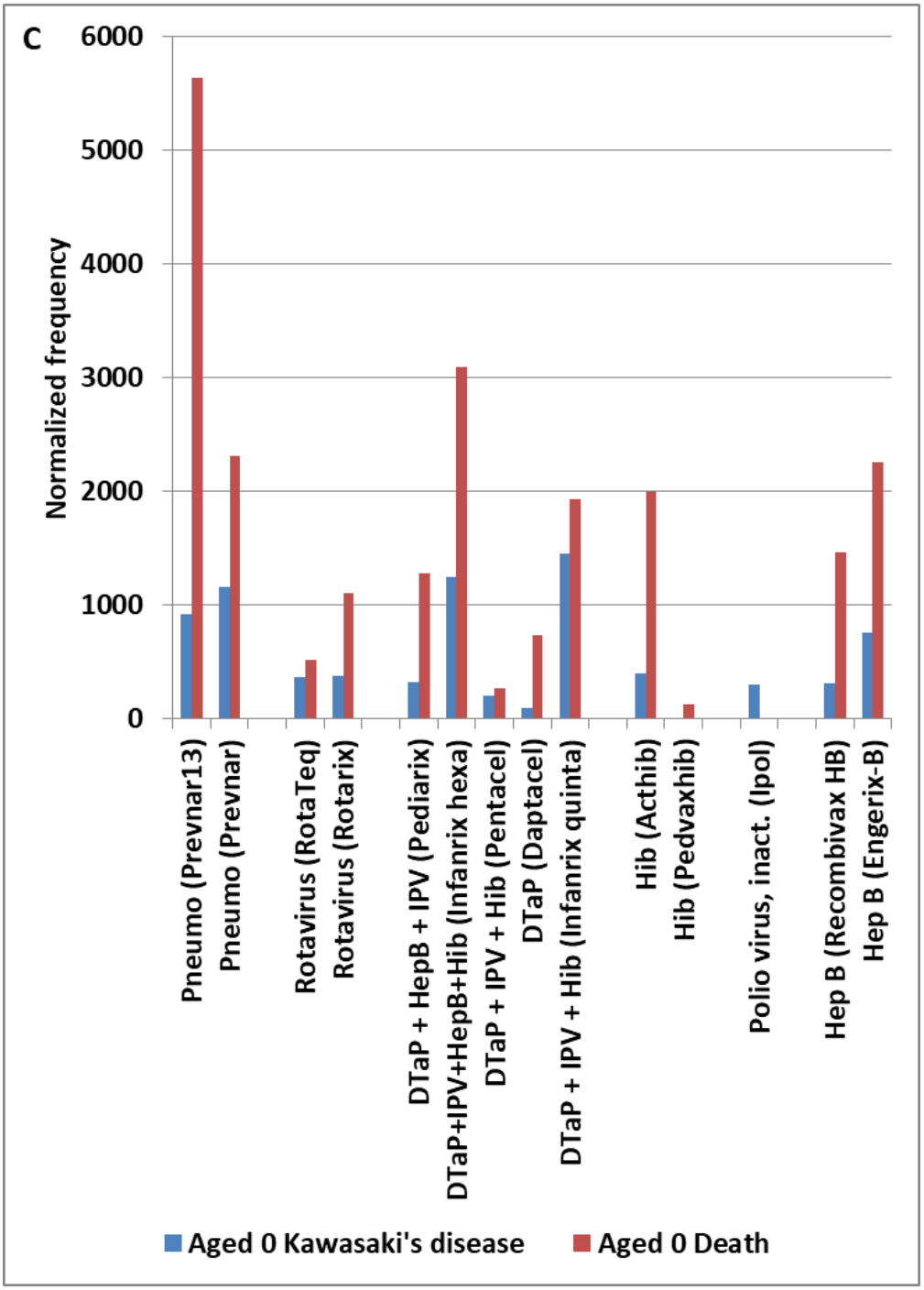

Figure 2. Kawasaki disease normalized frequency for infants aged 0 (A) concomitantly administered vaccines, (B) number of occurrences in concomitantly administered vaccines, and (C) with AE death (Pearson r=0.66).

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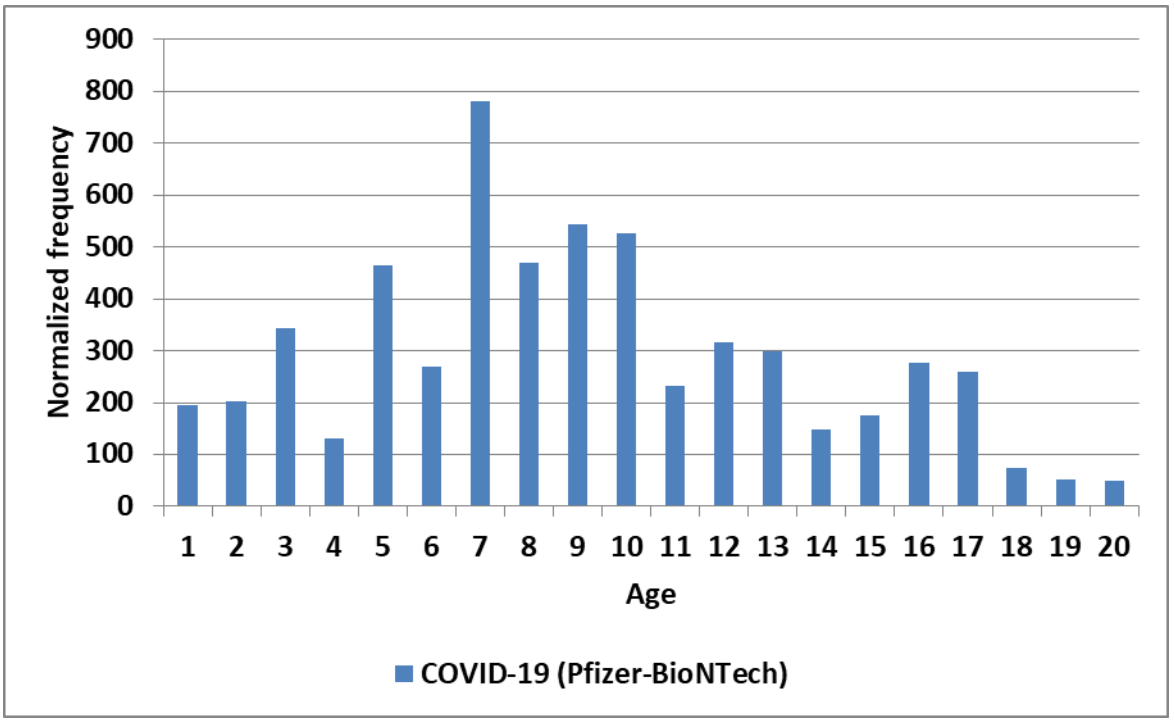

Figure 3. MIS normalized frequency by age for COVID-19 (Pfizer-BioNTech).

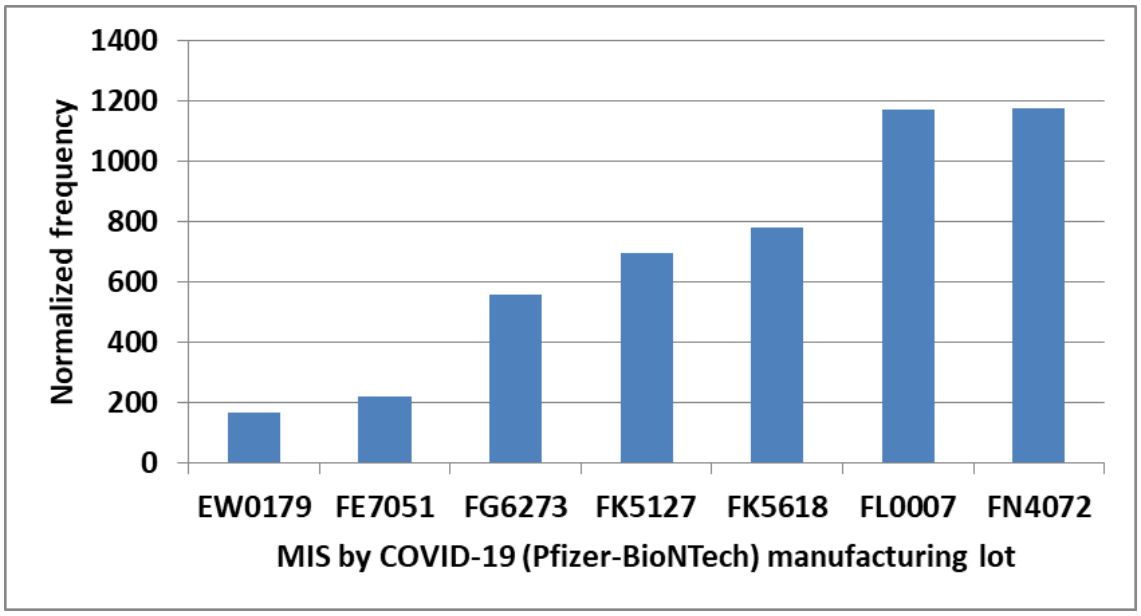

Figure 4. MIS normalized frequency by COVID-19 (Pfizer-BioNTech) manufacturing lot.

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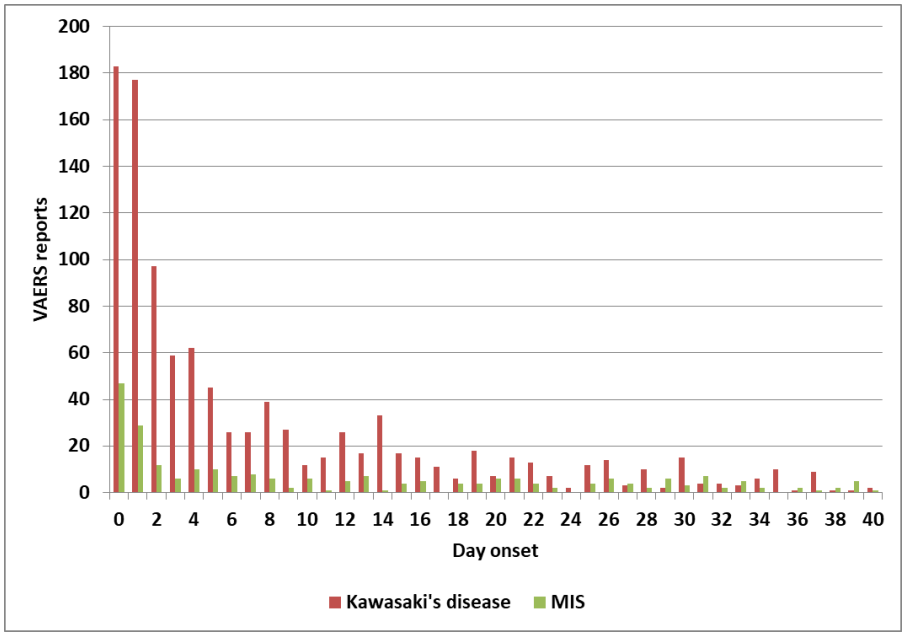

Figure 5. Kawasaki disease and MIS onset day (Pearson r=0.90).

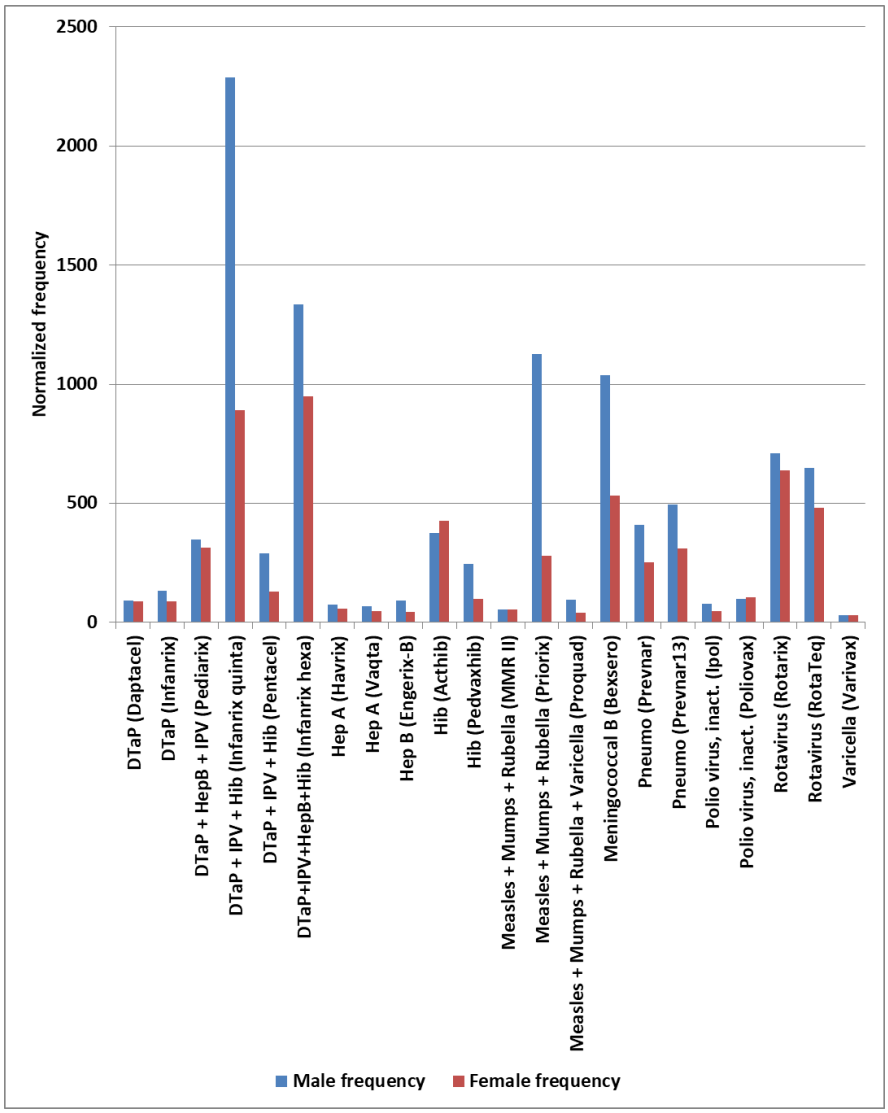

Figure 6. Kawasaki disease normalized frequency by gender.

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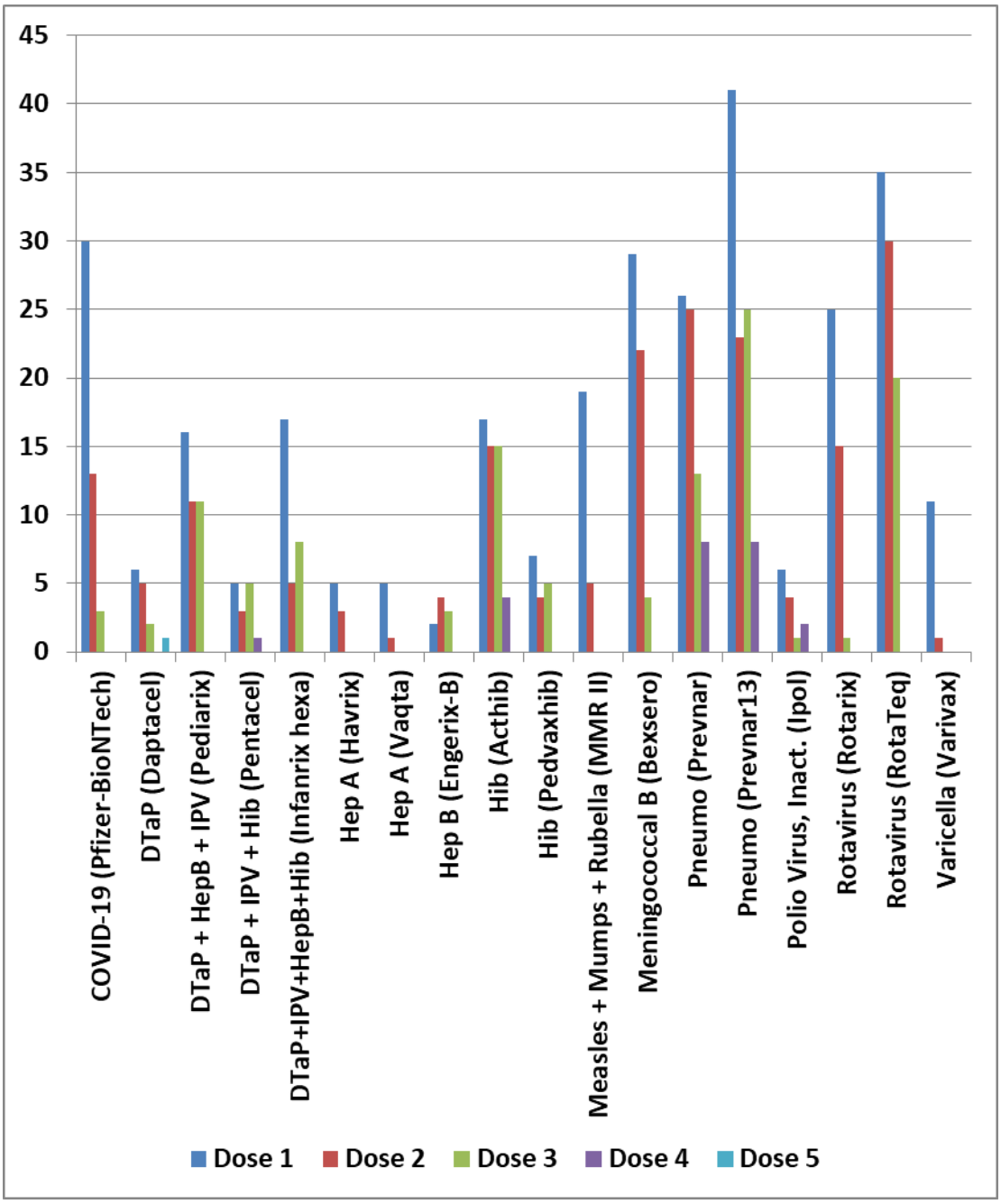

Figure 7. Kawasaki disease normalized frequency according to vaccine dose.

For Kawasaki's disease, five vaccines have manufacturing lots with three reported Kawasaki's disease cases: DTaP+HepB+IPV (Pediarix): AC21B248CA, Hib (Acthib): T1E12, Pneumo (Prevnar13): EG8873 and CS7258, Rotavirus (Rotarix): RT014 and RT018, and Rotavirus (RotaTeq): 0324X. For MIS, seven COVID-19 (Pfizer-BioNTech) manufacturing lots have four or more MIS cases: EW0179: 4 reports, FE7051: 4 reports, FG6273: 4 reports, FK5127: 24 reports, FK618: 20 reports, FL0007: 21 reports, and FN4072: 6 reports (Figure 4). The elevated MIS normalized frequencies for manufacturing lots are not associated with high-risk recipient groups (none are known) or background occurrences.

4. Discussion

The initial etiology model for KD and MIS is for high titers of IgG antibodies in immune complexes binding to low-affinity *FcγR2α* receptors activating mast cells, platelets, and other immune cells [83]. These retrospective VAERS results support expanding this etiology model to also include

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activation of mast cells from predicted manufacturing contaminant(s) (e.g., endotoxins, etc.) for specific vaccines (Figures 1, 2, and 4). The limulus amebocyte lysate (LAL)-based assays may miss endotoxins (e.g., low endotoxin recovery (LER)) due to a "masking effect" caused by chelators or detergents commonly used in buffer formulations [88]. Note that the SARS-CoV-2 spike protein bind to bacterial LPS (endotoxin) and boots proinflammatory activity [89,90]. By design, vaccines stimulate innate and humeral immune responses. The *Toll-like receptor (TLR4)* are activated by LPS (endotoxin) of Gram-negative bacteria [[91]]. TLRs recognize pathogen-associated molecular patterns (PAMPS). KD is associated with pathogen-associated molecular patterns (PAMPS) [92] and microbe-associated molecular patterns (MAMPS) [32]. The immediate onset of KD and MIS associated with immunization (Figure 5) are predicted to result from manufacturing contaminant(s) activating mast cells via TLR4. Increased TLR2 and TLR4 expression in peripheral neutrophils has been detected in some KD patients [93]. Some KD cases may be associated with endotoxins and elevated soluble CD14 (sCD14) [94,95]. Polyclonal expansion of TCRBV2- and TCRBV6-bearing T cells occurs in KD patients (likely associated with endotoxin exposure) [31]. Low-level endotoxin induces potent inflammatory activation of human blood vessels [96].

Multiple patients with KD or MIS also have associated gastrointestinal (GI) symptoms/intestinal involvement [97,98]; this may include intestinal dysbiosis and sometimes disruption of gut barrier [99]. Disruption of the gut barrier is likely associated with the presence of a superantigen (perhaps endotoxin) [100]**.** Elevated Vβ2 T cells expansion in some KD patients is consistent with the superantigen model [101]**.** KD patients with abdominal manifestations (symptoms) are more likely to be IVIG-resistant ($p<0.005$) and have CAA ($p=0.007$) [102].

4.1. KD and MIS Etiology Model

Etiology Model: KD and MIS are associated with activated mast cells and platelets.

Pathogen-associated reports are predicted to be associated with elevated immune complexes IgG antibody levels above primary immune response levels, activating low-affinity IgG *FcγR2α* receptors on platelets, mast cells, and additional immune cells (note the risk of persistent infections) (Table 1) [103,104]. Elevated histamine and likely serotonin levels are likely associated with most of the KD and MIS symptoms [83]. For KD and MIS patients with high IgG antibody titers, IVIG treatment is predicted to directly compete with immune complex binding to *FcγR2α* receptors, resulting in reduced activation of mast cells and platelets resulting in relief of associated symptoms. Immunization and environmental exposures can activate mast cells, immune cells, and likely platelets without (likely IVIG resistant) or sometimes with *FcγR2α* receptor binding (e.g., humeral responses post immunization) (Table 1). Gastrointestinal symptoms are reported in the majority of MIS-C patients [105–109]. A MIS-A patient with profound gastrointestinal symptoms have been reported [110]. SARS-CoV-2 virus or spike protein (COVID-19 vaccines) can induce additional gastrointestinal and cardiac symptoms in MIS and MIS-V patients, respectively. The spike protein also activates mast cells via *TLR4* and *angiotensin-converting enzyme 2* (*ACE2)* receptors [111]. For KD and MIS associated with onset within a few days of immunization, endotoxin manufacturing contaminant(s) (or Spike protein binding) is predicted to activate mast cells via TLR4; this activation pathway does not involve *FcγR2α* receptors and these patients are anticipated to be resistant to IVIG treatment (Table 1).

Table 1. Kawasaki and MIS etiologsy model disease factors, mast cell activators, and predicted IVIG resistance.

Primary factor	Additional factor	Mast cell activator(s)	Likely IVIG resistance
neonate pathogen infection	maternally transferred antibodies (MatAbs)	high Ab titers	very low
pathogen infection	elevated Ab titers (ongoing, prior infections, …)	high Ab titers	very low
immunization	elevated Ab titers	high Ab titers	very low

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immunization	manufacturing contaminant(s)—endotoxin	endotoxin or bacterial components	high
immunization	live attenuated vaccine GI pathogen (e.g., rotavirus)—possible disruption of gut barrier	possible high Ab titers and/or bacterial components	variable depending upon mast cell activators
GI infection	disruption of gut barrier [99]	endotoxin or bacterial components	high
environmental exposures including increased temperature	genetic risk factor	direct mast cell activation	high

Notably, overall immune activation is increased in KD [112]. It is unknown whether histamine intolerance (HIT) plays a role in KD or MIS. Multiple factors can influence an individual's tolerance threshold for histamine; including drugs [113]; foods (cocoa, spinach, tomatoes, wine, beer, cheeses, yogurt, meat, soy, fermented foods, etc.) [113,114]; the gastrointestinal microbiome [113]; and the stage of the menstrual cycle [114].

4.2. Age-Related Risk Patterns

The proposed KD and MIS etiology model proposes the activation of mast cells, platelets, and immune cells by Fc receptor binding to immune complexes or via direct activation of immune cells. Maternally transferred antibodies (matAbs) may play a role in KD-N and MIS-N in neonates with neonate antibody responses combined with matAbs to reach the higher levels of IgG antibodies in immune complexes needed to trigger disease [115]. For the 0–5 year age group, it appears that specific vaccines predicted to be contain the endotoxin manufacturing contaminant(s) are associated with KD (KD-V) (Figure 1) and also MIS-V (Figure 3). The normalized frequencies observed for COVID-19 (Pfizer-BioNTech) may approximate MIS (both MIS-C and MIS-V) risk levels in children (Figure 3).

4.3. Cardiac Adverse Events and Acquired Heart Disease

This model also proposes that aneurysms are pressure induced by contracted cardiac capillary pericyte vasoconstrictions [104]; notably, serotonin released from activated platelets is also associated with vasoconstrictions [116,117]. Induced cardiac capillary pericyte contractions are predicted to be associated with anoxia and possibly pressure-induced CAA and peripheral artery aneurysms [104,118]. Untreated patients with ongoing ischemia are predicted to experience cardiac myocyte anoxia, which may account for KD-associated acquired heart disease; this also explains the vascular dysfunction in patients who do not have echocardiographic evidence of coronary artery abnormalities in the acute phase of KD. An increased proportion of KD patients with CAA also have the plasma fibrinogen (FG) alpha genotype Thr312Ala [119]. Sex differences in cardiac mast cells activation have also been observed [120]; this may be associated with the KD male sex bias for specific vaccines (Figure 6).

The differences between MIS-related cardiac symptoms and KD-related symptoms (myocarditis, transient left ventricular dysfunction, and depressed cardiac output) may be directly due to the SARS-CoV-2 virus or the SARS-CoV-2 vaccine spike protein. For COVID-19 mRNA vaccines, circulating spike proteins are observed in vaccinees with myocarditis [121], along with elevated cardiac troponin levels [122]. For COVID-19 vaccines, the Spike protein disrupts cardiac pericytes through *cluster of differentiation 147* (*CD147)* receptor-mediated signaling and another unknown mechanism [123]. The spike protein also activates mast cells via *TLR4* and *angiotensin-converting enzyme 2* (*ACE2)* receptors [111]. These spike protein interactions may account for the increased risk for myocarditis and transient left ventricular dysfunction observed in MIS compared with KD [124]. Note that the spike protein interactions cannot account for MIS normalized frequency disparities for COVID-19 Pfizer-BioNTech manufacturing lots (Figure 4).

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4.4. KD and MIS Delayed Onset

Clusters of KD and MIS (Figure S1) reports are frequently observed with delayed disease onset (approximately 1 month or more) following various pathogen [22,33,34] and SARS-CoV-2 outbreaks [125], respectively. For this delayed disease onset pattern, the proposed etiology model requires IgG antibody levels to be higher than primary immune response levels to trigger disease [115]. One scenario includes persistent infections (e.g., gastrointestinal infections), which may occur in some KD and MIS patients [115]. Elevated SARS-CoV-2 antibody titers [105,126–128], current SARS-CoV-2 infections, or prior SARS-CoV-2 infections or exposures [129–134] are observed in MIS patients. For MIS-C, sustained levels of inflammatory macrophage-activating, Fc receptor-binding antibodies are selectively maintained in severe disease [135]. MIS-C develops in some children with COVID-19 and persistent SARS-CoV-2 infections [136].

4.5. KD Genetics

Genetic variants are predicted to increase or decrease associated KD and MIS risks. Confirmed KD genetic variants include *inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)* (calcineurin, a nuclear factor of the activated T-cell pathway—calcium signaling pathway) [137,138], *caspase-3 (CASP3)* [138,139], toll like receptor 6 (TLR6) [140], and the low-affinity IgG receptor gene *FcγR2α* (encoding *FcγRIIa*) [141–144]. The *FcγR2α* rs1801274 C allele encodes arginine (R) (low binding to IgG2 and IgG3), and the T allele encodes histidine (H) (high binding to IgG2 and IgG3) [145]. The *FcγR2α* pHis167Arg is associated with KD risk in males [146]. Candidate KD associated genes are associated with immune system, calcium signaling, KD susceptibility, IVIG resistance, and aneurysm formation (reviewed [147,148]); identified gene variants include *B-cell lymphoid tyrosine kinase (BLK)* [143,149–151], *CD40 (tumor necrosis factor receptor superfamily member 5)* [149,150], *FcγRIIA*-131H variant [152], *FcγR2B* [153], *FcγR2C* gene copy number [154], *FcγR2C-ORF* [155], FcγR3B gene copy number [154], *FcγRIIIB neutrophil antigen 1* (*NA1*) variant overexpression in IVIG nonresponders [152], *immunoglobulin heavy variable gene (IGHV)* [156], *human leukocyte antigen (HLA)* [150], *calcium release-activated calcium modulator 1 (ORAI1)* (involved in calcium influx in immune cells) [157], *potassium calcium-activated channel subfamily N member 2 (KCNN2)* (associated with CAA) [158], *TGF-beta receptor II (TGFBR2)* [159,160], *Mothers against decapentaplegic homolog 3 (SMAD3)* (*TGF-beta* signaling pathway) [159], *Mothers against decapentaplegic homolog 5 (SMAD5)* (*TGF-beta* signaling pathway) [161]. Note that CASP3 is released by activated mast cells [162]. Mast cells express CD40 ligand (CD40L) that interacts with CD40 on B cells [163]. Differentially expressed candidate KD genes have also been characterized via transcriptome analysis [164,165]. Whole-exome sequencing revealed that KD candidates include myosin *heavy chain 14 (MYH14)* and *retinol-binding protein 3 (RBP3)* [166]. While no association with the *FcγR2α* rs1801274 polymorphism was found, MIS-C patients with the homozygous *FcγR2α* rs1801274 gene polymorphism developed severe cardiac dysfunction [167]. Individual genetics alter KD and MIS risks. Genetic variants in T helper cell pathways may contribute to immune dysregulation in KD [168]. Identified genetic variants associated with KD play roles in immune cells, including mast cells, activation or signaling.

4.6. IVIG Treatment and IVIG Resistance

The model of high IgG antibody activation of *FcγR2α* receptor binding represents a novel form of antibody-dependent enhancement (ADE) for both KD and MIS [103]. IVIG treatment is predicted to compete with pathogen IgG antibodies for *FcγR2α* receptor binding with a possible increased risk for IVIG resistance; note that TLR4 (non-*FcγR2α* receptor) activated mast cells are likely IVIG resistant (due to different activation pathway). This model explains the unpredictable ineffectiveness of current therapy and the observed IVIG resistance in both KD and MIS patients.

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4.7. MIS Differences from KD

KD and MIS reports not associated with recent vaccinations may be associated with persistent (perhaps gastrointestinal in some reports) infections. The greater number of KDs at ages 0--5 may be associated with immunizations. Resilience against the development of pressure-induced CAA may reduce incidence rates as the age of patients increases. SARS-CoV-2 infection or spike protein interactions may account for cardiac differences between MIS and KD. Otherwise, MIS appears to be KD associated with SARS-CoV-2 virus or COVID-19 immunization (MIS-V).

4.8. Candidate Adjunctive Treatments

If the proposed KD and MIS etiology model is correct, then additional adjunctive treatments, including mast cell stabilizers, antihistamines, and possibly serotonin antagonists, may reduce symptoms; institutional review board (IRB)-approved targeted clinical studies (e.g., report series) are suggested (perhaps targeting IVIG nonresponders).

4.9. Study Limitations

The VAERS database includes only a small subset of adverse events experienced by vaccinees. Any reporting biases or exclusion of adverse events would perturb the accuracy of VAERS, which represents the population.

4.10. Study Recommendations

This study proposes that mast cell and platelet activation drive the etiology of both KD and MIS. Many of the disease symptoms are consistent with predicted elevated levels of histamine and/or serotonin. Evaluations of adjunctive treatments targeting elevated histamine or serotonin levels are candidates for evaluation in approved clinical studies. Early treatments may reduce the risk of CALs and acquired heart disease in KD patients and ventricular dysfunction and cardiac adverse events in MIS patients. KD and MIS reports not associated with immunizations may have undiagnosed persistent infections for which appropriate treatments should be considered. Elimination or reduction of predicted endotoxin manufacturing contamination level in identified vaccines with higher KD and MIS normalized frequencies is predicted to reduce AEs KD, MIS, and death in children.

5. Conclusions

The etiology of both KD and MIS are both likely novel MCAS. An etiology model is proposed that can account for the etiology of both KD and MIS. For pathogen-associated infections, high-titer immune complexes are required to activate low IgG -affinity *FcγR2α* receptors; this results in delayed disease onset clusters following pathogen outbreaks. Air pollution and increased temperature can also activate mast cells, triggering KD. Immediate onset KD and MIS post immunization is likely caused by predicted endotoxin manufacturing contaminants in specific vaccines activating mast cells directly via TLR4; these patients are predicted to be IVIG nonresponders. KD-related male sex bias may be partially due to specific vaccine associations and sex differences between cardiac mast cells. CAA, myocarditis, myocarditis, transient left ventricular dysfunction, and acquired heart disease are predicted to result from cardiac capillary vasoconstrictions, and aneurysms are predicted to be pressure induced. While appearing clinically distinct, MIS appears to be KD associated with the SARS-CoV-2 virus or COVID-19 spike protein (MIS-V).

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Abbreviations

The following abbreviations are used in this manuscript:

ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
AE	Adverse event
B-cell	Immune B lymphocyte
BLK	B-cell lymphoid tyrosine kinase
CAA	Coronary artery aneurysm
CALs	Coronary artery lesion
CASP3	Caspase 3
CD14	Cluster of differentiation 14
CD147	Cluster of differentiation 147, also known as EMMPRIN (Extracellular Matrix Metalloproteinase Inducer), or Basigin
CD40	Cluster of differentiation 40
CD40L	Cluster of differentiation 40 ligand
CO	Carbon monoxide
COVID-19	Coronavirus disease 2019
DTaP	Diphtheria, tetanus, and pertussis (whooping cough) vaccine
Fc	fragment crystallizable region of antibody
FcγR	Fc gamma receptor
FG	plasma fibrinogen
GI	gastrointestinal
Hep B	hepatitis B
Hib	*Haemophilus influenzae* type b vaccine
HIT	histamine intolerance
HLA	human leukocyte antigen
IgG	immunoglobulin G
IGHV	immunoglobulin heavy variable gene
IPV	inactivated poliovirus vaccine
ITPKC	inositol 1,4,5-trisphosphate 3-kinase C
IVIG	intravenous immunoglobulin
KCNN2	Potassium Calcium-Activated Channel Subfamily N Member 2
KD	Kawasaki's disease
KD-MAS	Kawasaki disease complicated with macrophage activation syndrome
KD-N	Kawasaki's disease in neonates
KDSS	Kawasaki disease shock/toxic-shock syndrome
KD-V	Kawasaki's disease associated with vaccination
LAL	Limulus Amebocyte Lysate
LER	Low endotoxin recovery
LPS	Lipopolysaccharide
MAMPS	Microbe-associated molecular patterns
matAbs	Maternally transferred antibodies
MCAS	Mast cell activation syndromes
MIS	Multisystem inflammatory syndrome
MIS-A	Multisystem inflammatory syndrome in adults
MIS-C	Multisystem inflammatory syndrome in children
MIS-N	Multisystem inflammatory syndrome in neonates

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MIS-V	Multisystem inflammatory syndrome after COVID-19 vaccination
MMR	Measles, mumps, and rubella vaccine
MPAs	Monocyte–platelet aggregates
mRNA	Messenger ribonucleic acid
MYH14	Myosin heavy chain 14
NA1	Neutrophil antigen 1
NO	Nitric oxide
NO2	Nitric dioxide
NOx	Nitrogen oxide
O3	Ozone
ORAI1	calcium release-activated calcium modulator 1
ORF	Open reading frame
PAMPS	pathogen-associated molecular patterns
PCT	Plateletcrit
PIMS-TS	Pediatric Inflammatory Syndrome temporally associated with SARS-CoV-2 infection
PM10	Inhalable particulate matter 10 micrometers or smaller
PM25	fine inhalable particles less than or equal to 2.5 micrometers in diameter
RBP3	retinol-binding protein 3
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sCD14	Soluble CD14 protein
SMAD3	Mothers against decapentaplegic homolog 3
SMAD5	Mothers against decapentaplegic homolog 5
SO2	Sulfur dioxide
T-cell	T lymphocyte
TCRBV2	T-cell receptor Beta-chain V2
TCRBV6	T-cell receptor Beta-chain V6
TGF-beta	Transforming growth factor-beta
TGFBR2	Transforming growth factor-beta receptor type 2
TLR	Toll-like receptor
VAERS	Vaccine Adverse Event Reporting System

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