HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2088215 (8 pages)
https://doi.org/10.1080/21645515.2022.2088215

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Kawasaki disease following immunization reported to the Canadian Immunization Monitoring Program ACTive (IMPACT) from 2013 to 2018

Khaled Alsager[a], Nirma Khatri Vadlamudi[b,c], Taj Jadavji[a], Julie A. Bettinger[b,c], Cora Constantinescu[a], Wendry Vaudry[d], Ben Tan[e], Laura Sauvé[b,c], Manish Sadarangani[b,c], Scott A. Halperin[f], and Karina A. Top[f*] for the IMPACT Investigators

[a]Division of Infectious Diseases, Department of Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada; [b]Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada; [c]Division of Infectious Diseases, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, BC, Canada; [d]Division of Infectious Diseases, Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, AB, Canada; [e]Division of Infectious Diseases, Department of Pediatrics, Jim Pattison Children's Hospital, Saskatoon, SK, Canada; [f]Department of Pediatrics, Dalhousie University, and Canadian Center for Vaccinology, IWK Health, Halifax, NS, Canada

ABSTRACT

Kawasaki disease (KD) is an acute systemic vasculitis primarily affecting children younger than 5 y of age that has been reported as an adverse event following immunization (AEFI). The Canadian Immunization Monitoring Program ACTive (IMPACT) conducts active surveillance for KD following immunization across Canada. We characterized KD cases reported to IMPACT between 2013 and 2018. Cases admitted to an IMPACT hospital with a physician diagnosis of complete or incomplete KD with onset 0–42 d following vaccination were reviewed. Cases meeting the Brighton Collaboration case definition (BCCD) levels of diagnostic certainty levels 1 a/b, 2a/b or 3a-e were defined as KD cases. Demographic and vaccination characteristics were compared between KD cases and non-cases. Of 84 cases reviewed, 58 met the BCCD: 47 (81%) cases met level 1a (Complete KD), 8 (14%) met level 1b (Incomplete KD), 2 (3%) met level 2a, and 1 (2%) met level 2c (Probable KD). Median age at admission was 13 months (interquartile range 7–26 months). A median of 9.5 cases were reported per year (range 4–14). Thirty-one (53%) KD cases were temporally associated with diphtheria-tetanus acellular pertussis containing vaccinations, followed by 21 (36%) cases with pneumococcal conjugate vaccines. Symptom onset was 0–14 d after vaccination in 32 (55%) cases. Echocardiogram results were available for 43 (74%) cases with 22 reported as abnormal. Age, sex, interval to symptom onset, and vaccines received were similar between KD cases and non-cases. No safety signals were detected in these data.

ARTICLE HISTORY
Received 21 October 2021
Revised 27 May 2022
Accepted 8 June 2022

KEYWORDS
Adverse events; immunization; pediatrics; vasculitis; vaccination; vaccine safety

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis primarily of infancy and childhood.[1] KD has been reported worldwide, with highest rates reported in Japan, Korea and Taiwan.[2,3] The annual incidence of KD in Canada is 19.6, 6.4, and 1.3 cases per 100,000 children younger than 5 y, 5–9 y, and 10–14 y old, respectively, with coronary artery (CA) aneurysms affecting 3–25% of all patients.[3,4]

Though the cause of KD remains unknown, an infectious or inflammatory trigger has been postulated to lead to the development of KD in genetically predisposed individuals.[3,5,6] For this reason, vaccines have been evaluated as a possible trigger for KD.[7] Temporal associations have been reported between certain vaccines (diphtheria-pertussis-tetanus [DPT], influenza, rotavirus [RV], and Bacille Calmette–Guérin [BCG]) and onset of vasculitis in general, and KD specifically.[8–10] Among post-vaccination cases reported to passive surveillance, symptom onset was within 30 d of vaccination in 91% of cases,[10] with analytical studies generally using risk intervals for KD onset of 0–28 to 0–42 d post-vaccination.[7,11] No vaccines have been causally linked to KD to date, but KD remains an adverse event following immunization (AEFI) of special interest for vaccine safety surveillance.[9] To support the evaluation of AEFIs, the Brighton Collaboration developed a standardized KD case definition with multiple levels of diagnostic certainty (complete, incomplete, possible, probable, not KD and insufficient evidence, Table 1).[12]

Since 2013, the Canadian Immunization Monitoring Program ACTive (IMPACT) has been conducting active surveillance for KD occurring within 42 d after immunization at 12 pediatric tertiary care centers in 8 of 10 Canadian provinces, representing 90% of pediatric tertiary care beds in Canada.[13,14] The objective of this study was to characterize hospitalized KD cases following immunization in

CONTACT Karina A. Top karina.top@dal.ca IWK Health Centre, 5850/5980 University Ave, Halifax, NS B3K 6R8, Canada

*Investigators and centers participating in this IMPACT project included: N. Bridger MD, Cheryl Foo MD, Janeway Children's Health & Rehabilitation Center, St. John's, NL; S.A. Halperin MD, K.A. Top MD, IWK Health Center, Halifax, NS; P. Déry MD, R. Thibeault MD, Center Mère-Enfant de Québec, CHUL, Quebec City, PQ ; D. Moore MD, J. Papenburg MD, The Montreal Children's Hospital, Montreal, PQ; M. Lebel MD, CHU Ste-Justine, Montreal, PQ; N. Le Saux MD, Children's Hospital of Eastern Ontario, Ottawa, ON; D. Tran MD, S. Morris MD, The Hospital for Sick Children, Toronto, ON; J. Embree MD, Winnipeg Children's Hospital, Winnipeg, MB; B. Tan MD, Athena McConnell MD, Jim Pattison Children's Hospital, Saskatoon, SK; T. Jadavji MD, C. Constantinescu MD, Alberta Children's Hospital, Calgary, AB; W. Vaudry MD, Stollery Children's Hospital, Edmonton, AB; D. Scheifele MD, M. Sadarangani BM BCh DPhil, J. Bettinger PhD, L. Sauvé MD, BC Children's Hospital, Vancouver, BC

Supplemental data for this article can be accessed on the publisher's website at https://doi.org/10.1080/21645515.2022.2088215

Table 1. Brighton collaboration case definition for all levels of evidence of Kawasaki disease.[12]

Level of evidence	Definition
Level 1a	≥4 d of fever, AND ≥4 principal features, AND no echo abnormalities or insufficient to meet criteria.
Level 1b	≥4 d of fever or incomplete documentation of duration of fever, AND 2–3 principal features, AND definitive coronary artery aneurysm*.
Level 2a	≥4 d of fever, AND 2–3 principal features, AND BCG site or perineal changes or transitory echo changes§, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria(A).
Level 2b	Incomplete documentation of duration of fever, AND ≥4 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 2c	IVIG before day 4 of fever, AND 3 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 3a	Infant <6 months of age with ≥7 d of fever, 1–3 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 3b	≥4 d of fever, AND 2 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 3c	Incomplete documentation of duration of fever, 2–3 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 3d	IVIG before day 4 of fever, AND 2 principal features, AND no echo abnormalities or insufficient to meet criteria, AND CRP ≥30 mg/L or ESR ≥40 mm/hr, AND ≥3 Supplementary laboratory criteria.
Level 3e	≥4 d of fever with presentation after acute illness (>10 d following onset of fever), 2–3 principal features, AND no echo abnormalities or insufficient to meet criteria, AND did not have blood test and did not receive treatment with IVIG.
Insufficient evidence	If the evidence available for an event is insufficient because information is missing, such an event should be categorized as "Reported KD with insufficient evidence to meet the case definition".
Not a case of KD	If investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis, such an event should be rejected and classified as "Not a case of KD", e.g. fever duration less than 4 d and no treatment with IVIG OR no principal features OR one principal feature and age greater than 6 months.§

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IVIG: Intravenous immunoglobulin, KD: Kawasaki disease.

A. Supplementary laboratory criteria: albumin <30 g/L, anemia for age, elevation of alanine aminotransferase (ALT) OR aspartate aminotransferase (AST), platelets >450,000/mm >7 d after onset of fever, WBC count >15,000/mm^3, or urine >10 WBC/high powered field (HPF.

* Z-score of left anterior descending artery (LAD) or right coronary artery (RCA) 2.5 or more OR coronary artery features meet Japanese Ministry of Health age-related criteria for aneurysm.

§ One of the following transitory echocardiogram changes: coronary artery dilatation with z-scores of 2–2.5, decreased left ventricular (LV) function, mitral regurgitation, OR pericardial effusion

Canada that were reported to IMPACT from 2013 to 2018 and met the Brighton Collaboration case definition (BCCD).

Patients and methods

Study design and population

This was a retrospective review of cases of KD reported to IMPACT from 2013 to 2018. Cases were identified via prospective, active surveillance by IMPACT nurse monitors at 12 hospitals across Canada.[13]

Nurse monitors screened daily hospital admissions lists for KD and related terms (e.g., fever) and reviewed medical records and immunization records to identify reportable cases of KD. To ensure complete case ascertainment, hospital discharge databases were searched using the International Classification of Diseases, 10th revision (ICD-10-CA) diagnostic code for KD (M30.3). Cases were eligible for reporting if they were admitted to an IMPACT hospital with a physician diagnosis of KD and had symptom onset within 42 d of vaccine administration. The reporting interval of 42 d was based on standard, national Canadian AEFI reporting guidelines.[15] Data were collected on the national AEFI reporting form, capturing age at vaccination, admission, interval from vaccination to symptom onset, vaccination history, symptoms, investigations, treatment, and outcome at discharge ("fully recovered" [resolution of all signs and symptoms], "not yet recovered" [residual signs or symptoms remain], "permanent disability" [expected impairment to perform normal activities for remainder of their life], death).[15,16] Forms were submitted to the Canadian AEFI Surveillance System (CAEFISS) where the data were coded using MedDRA terms and entered into the CAEFISS database. Data were extracted from the CAEFISS database, downloaded into MS Excel and transmitted to the IMPACT Data Center in Vancouver, BC for analysis. Additional data was requested from the IMPACT sites for all cases missing information regarding principal features, echocardiogram results and laboratory values needed to apply the BCCD.

Ethics statement: Ethics and/or hospital approvals were obtained at each participating site: IWK Health Center Research Ethics Board (REB): # 1002978; Comité d'éthique de la recherche du CHU de Québec-Université Laval: 47.05.02; The SickKids REB: #0019900593; Winnipeg Health REB: #HS15505; University of British Columbia Children's & Women's REB: H15-00782; Children's Hospital of Eastern Ontario REB: # 10001163; Conjoint Health REB: #REB15-1989_REN4; Montreal Children's Hospital: Approved by the Director of Professional Services for surveillance; Health REB for Eastern Health (St John's, NL): #1208.000; Comité d'éthique de la recherché du CHU Sainte-Justine: #1994-15, 108; Health REB for University of Alberta: #Pro00000929; Biomedical REB for University of Saskatoon: #99-125. IMPACT operates with a waiver of consent.

Data analysis

This was a descriptive analysis of clinical characteristics and temporally associated vaccines among patients with KD following immunization that met the BCCD levels of diagnostic certainty. We applied the BCCD for KD to classify cases accordingly as definite complete KD (level 1a), definite incomplete KD (level 1b), probable KD (level 2a, b or c), possible KD (level 3a, b, c, d or e), reported KD with insufficient evidence to

meet the case definition, or not a case of KD (Table 1).[12] Cases meeting levels 1a/b, 2a-c, 3a-e were defined as KD cases in the analysis and cases with insufficient evidence or not a case were defined as non-cases.

Patient demographic and clinical characteristics were reported by BCCD level of diagnostic certainty in a descriptive analysis. Interval from vaccination to symptom onset was reported by vaccine type(s) based on the routine childhood immunization schedules in Canada (Supplemental Table S1),[17] according to 6 overlapping groups: diphtheria, tetanus, and acellular pertussis (DTaP) containing; measles, mumps, and rubella (MMR) containing; pneumococcal conjugate vaccine (PCV); influenza; RV; and other vaccines. Categorical variables were presented as counts and proportions, with continuous variables reported as medians and range or interquartile range. To assess whether meeting the BCCD was associated with differences in demographic characteristics or vaccination history, we conducted bivariate analyses comparing KD cases and non-cases using chi-square tests. Regression analyses were not conducted due to small cell size. The analysis was conducted using SAS® version 9.4 (Cary, NC).

Results

Patient characteristics

A total of 703 adverse events were reported to IMPACT centers from 2013 to 2018. Of these, 84 cases of physician diagnosed KD with onset within 42 d following immunization were admitted to IMPACT centers from 2013 to 2018 (Supplemental Figure S1). Fifty-eight (69%) cases met the Brighton Collaboration definition for KD and were considered KD cases: 47 cases (81%) were classified as level 1a (Complete KD); 8 (14%) as level 1b (Incomplete KD); 2 (3%) as level 2a and 1 (2%) as level 2c (Probable KD); and no cases were classified as level 3. Of the remaining 26 cases, 5 (19%) were classified as not a KD case based on confirmation of less than 2 principal features of KD, and 21 (81%) had insufficient evidence to classify them (Supplemental Table S2).

The median number of KD cases reported yearly from 2013 to 2018 was 9.5 (range 4 to 14) (Figure 1). The median age at admission was 13 months (IQR 7–26 months) (Table 2). The majority of cases (37/58; 64%) were males.

Clinical features, treatment, and outcomes of KD cases are shown in Table 2. Fifty-six of 58 KD cases had ≥4 d of fever while 2 cases (both level 1b) had unknown fever duration; both cases had >2 principal features and abnormal echocardiogram. All cases except one were given intravenous immunoglobulin for treatment. At the time of discharge, 45 (78%) cases had fully recovered.

Vaccines temporally associated with KD and time to onset

Vaccination combinations temporally associated with KD are shown in Table 3. Patients received a median of two vaccines concurrently (IQR 1–3). The most common vaccine combinations included DTaP-containing vaccine (received by 53% of cases), followed by PCV (received by 36% of cases), and influenza vaccination (received by 29%).

The overall median time from vaccination to onset was 10.5 d, IQR (4–24.5 d). Median onset ranged from 8 d (IQR 4–20 d) for cases receiving MMR-containing vaccines with or without other vaccines to 20 d (IQR 7–28 d) for cases receiving DTaP vaccines with or without other vaccines. IQRs were wide and overlapped for all vaccine combinations.

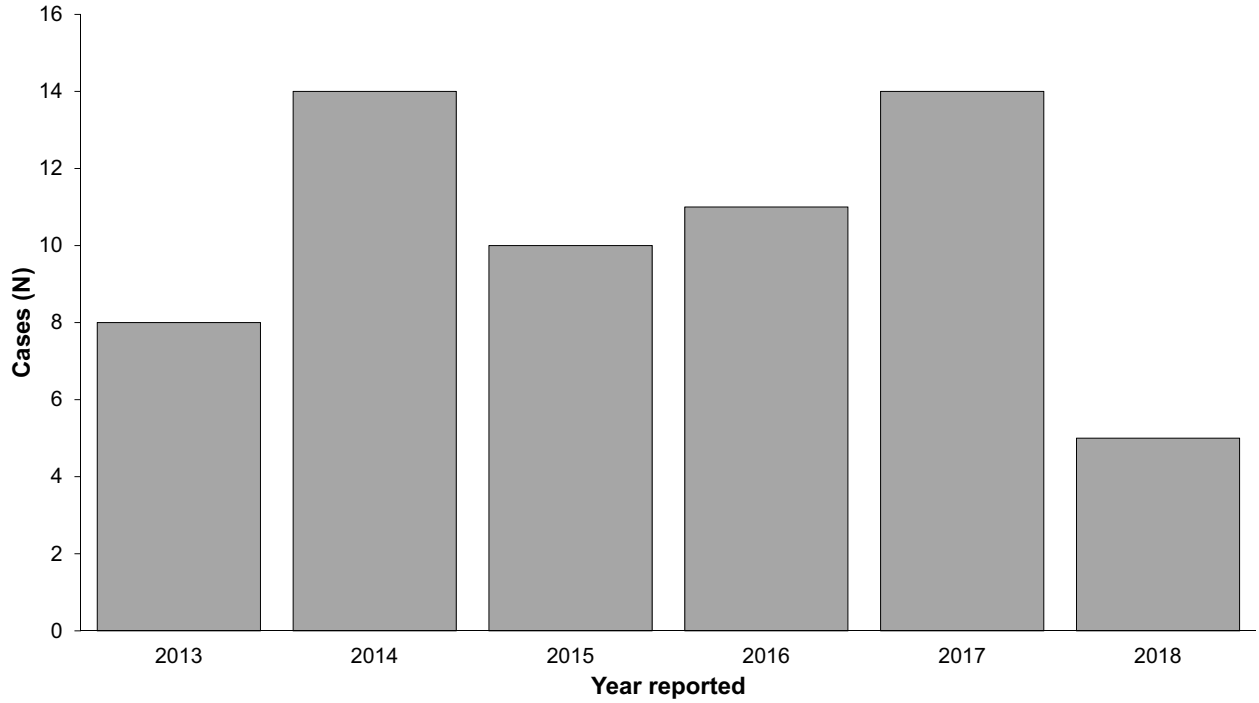

Figure 1. Number of confirmed Kawasaki disease cases reported to IMPACT per year with onset 0–42 d after vaccination.

Table 2. Characteristics of Kawasaki disease cases meeting the Brighton Collaboration case definition levels 1–3 for Kawasaki Disease (n = 58).

Level of diagnostic certainty		1a (%)	1b (%)	2a (%)	2c (%)	Total
Total cases		47 (81)	8 (14)	2 (3)	1 (2)	58
Age at admission	Median in months (IQR)	15 (7–33)	8.5 (3.5–11.5)	13 (7–19)	3 (3–3)	13 (7–26)
	<12 months, n (%)	16 (34)	6 (75)	1 (50)	1 (100)	24 (41)
	12–23 months, n (%)	17 (36)	1 (12.5)	1 (50)	0	19 (33)
	24–71 months, n (%)	12 (25)	1 (12.5)	0	0	13 (22)
	7–16 years, n (%)	2 (4)	0	0	0	2 (3)
Sex	Male	32 (68)	4 (50)	1 (50)	0	37 (64)
	Female	13 (28)	3 (37.5)	1 (50)	1 (100)	18 (31)
	Unknown	2 (4)	1 (12.5)	0	0	3 (5)
Echocardiogram	Normal	18 (38)	0	2 (100)	1 (100)	21 (36)
	Abnormal	14 (30)	8 (57)	0	0	22 (38)
	Unknown	15 (32)	0	0	0	15 (26)
Principal features of KD*	2	0	3 (37.5)	0	0	3 (5)
	3	0	4 (50)	2 (100)	1 (100)	7 (12)
	4	35 (75)	1 (12.5)	0	0	36 (62)
	5	12 (25)	0	0	0	12 (21)
Interval from vaccination to symptom onset	<24 hours	3 (6)	1 (12.5)	0	0	4 (7)
	24 h—7 d	15 (32)	2 (25)	0	1 (100)	18 (31)
	8–14 d	9 (19)	0	1 (50)	0 (0)	10 (17)
	15–30 d	16 (34)	4(50)	0	0	20 (35)
	31–42 d	2 (4)	1 (12.5)	1 (50)	0	4 (7)
	Unknown	2 (4)	0	0	0	2 (3)
Outcome at discharge	Fully recovered	37 (79)	5 (62.5)	2 (100)	1 (100)	45 (78)
	Not fully resolved	8 (17)	2 (25)	0	0	10 (17)
	Unknown	2 (4)	1 (12.5)	0	0	3 (5)

*Principal features: bilateral bulbar conjunctival injection without exudate, changes in extremities, polymorphous exanthem, changes in the lips and/or oral cavity, cervical lymphadenopathy.

Table 3. Number of Kawasaki disease cases reported with each vaccination group and median of interval from vaccination to onset of symptoms (n = 58).:

Vaccine Given	n	Interval from vaccination to onset of symptoms in days, median (IQR)*
DTaP Containing Vaccines (**n = 31, 53%**)		20 (7–28)
DTaP-HB-IPV-Hib	2	
DTaP-HB-IPV-Hib, MMRV	2	
DTaP-HB-IPV-Hib, PCV	2	
DTaP-HB-IPV-Hib, PCV, RV1	7	
DTaP-HB-IPV-Hib, PCV, RV1, Men-C-C	1	
DTaP-IPV-Hib	7	
DTaP-IPV-Hib, Influenza	1	
DTaP-IPV-Hib, Men-B	1	
DTaP-IPV-Hib, MMRV	1	
DTaP-IPV-Hib, PCV-13, RV1	3	
DTaP-IPV-Hib, PCV-13, RV5	1	
Tdap-IPV, MMRV	2	
Tdap-IPV, HAHB	1	
MMR Containing Vaccines (**n = 13, 22%** including 5 cases listed above who also received DTaP vaccines, list below excludes those listed above)		8 (4–20)
MMRV	2	
MMRV, Men-C-C	2	
MMRV, Men-C-C, PCV	4	
MMRV, Men-C-C, PCV, Influenza	1	
PCV Containing Vaccines (**n = 21, 36%** including 14 cases who also received DTaP vaccines, and 5 cases who also received MMRV vaccines, list below excludes those listed above)		9.5 (4–20)
PCV-13, Men-C-C	1	
PCV-13, Influenza	1	
Influenza Containing Vaccines (**n = 17, 29%** including 1 cases who also received DTaP vaccines, 1 case who also received MMRV vaccines, 1 case who also received PCV-13, list below excludes those listed above)		9 (3–20)
Influenza alone	13	
Influenza, Men-C-C	1	
Rotavirus Containing Vaccines (**n = 12, 21%** and all the 12 cases also received DTaP vaccines	12	8 (4–25)
Other vaccines (**n = 4, 7%, including 1 case who also received Tdap**)		10.5 (0.5–23)
HAHB	1	
HA	1	
HA, Typhoid Vaccine	1	

DTaP= diphtheria, acellular pertussis, tetanus, HB= hepatitis B vaccine, IPV= inactivated polio vaccine, Hib= *Haemophilus influenzae* b, MMRV= measles mumps rubella, varicella, Men-B= Meningococcal B vaccine, PCV-13= Pneumococcal 13-valent, RV1= Monovalent rotavirus vaccine, RV5= Pentavalent rotavirus vaccine, Tdap= tetanus, acellular pertussis, reduced dose diphtheria, HAHB= combined hepatitis A & B vaccine, Men-C-C= Meningococcal C conjugate, HPV-4= quadrivalent human papillomavirus vaccine.

*The median/IQR is provided for all in the group containing each vaccine and not those in the sub list only.

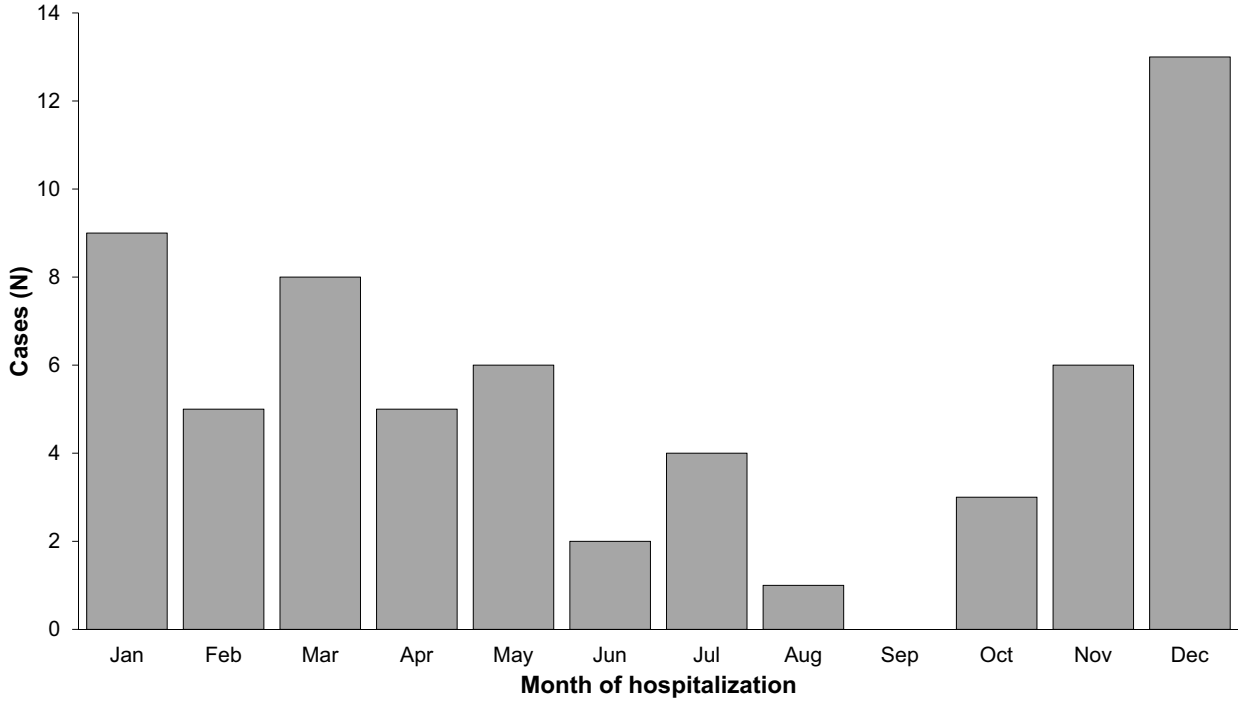

Figure 2. Onset of Kawasaki disease symptoms by month (n = 58).

Onset of KD by month (Figure 2)

The highest number of cases (33, 57%) presented during Winter (Dec–Mar), with the fewest cases (4, 7%) presenting in late Summer and early Fall (Aug–Oct).

Echocardiography results

Fifteen (32%) cases had no information on the echocardiogram result; all were level 1a (complete KD) based on clinical criteria (Table 2). Twenty-two cases had an abnormal echocardiogram including three with ectasia of the coronaries, eight with dilatation of the coronaries, four with aneurysm of the coronaries, three with aneurysm and dilatation, and one with ectasia and dilatation. In three cases no details of the abnormality were reported and it is not known if the findings were specific for KD or an unrelated incidental finding. Z-scores were not reported.

Supplementary laboratory results

Twenty-three (40%) cases had no supplementary laboratory results (such as albumin, anemia, pyuria, elevation of ALT or AST, increased platelets or leukocytosis) reported. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) results were reported in 25 (43%) and 40 (69%) cases, respectively, and were elevated in most cases where they were reported (Table 4).

Table 4. Laboratory results in confirmed KD cases (n = 58).

Brighton level of diagnostic certainty		1a (%) N=47	1b (%) N=8	2a (%) N=2	2a (%) N=1	Total (%) N=58
CRP >30 mg/L	Yes	30 (64)	5 (62)	2 (100)	1 (100)	38 (66)
	No	2 (4)	0	0	0	2 (3)
	Unknown	15 (32)	3 (38)	0	0	18 (31)
ESR >40 mm/h	Yes	18 (38)	3 (38)	0	1 (100)	22 (38)
	No	3 (6)	0	0	0	3 (5)
	Unknown	26 (55)	5 (62)	2 (100)	0	33 (57)
Albumin <30 g/L	Yes	7 (15)	2 (25)	2 (100)	1 (100)	12 (21)
	No	7 (15)	0	0	0	7 (12)
	Unknown	33 (70)	6 (75)	0	0	39 (67)
Anemia for age	Yes	11 (23)	1 (12)	1 (50)	1 (100)	14 (24)
	No	10 (21)	1 (12)	1 (50)	0	12 (21)
	Unknown	26 (55)	6 (76)	0	0	32 (55)
Platelets >450,000/mm^3	Yes	12 (26)	3 (38)	1 (50)	1 (100)	17 (29)
	No	8 (17)	0	1 (50)	0	9 (16)
	Unknown	27 (57)	5 (62)	0	0	32 (55)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Cases not meeting the Brighton Collaboration case definition

Five cases with confirmation of 0 or 1 principal KD features and age over 6 months were determined to be "not a KD case" (Table S2). Among the 21 cases with insufficient evidence to be classified according to the BCCD criteria, duration of fever was unknown in 11 (52%) cases, echo results were unknown in 14 (67%), and supplementary labs and inflammatory markers were also unknown in a majority of cases.

We did not find differences between KD cases and non-cases by age group ($p = 0.69$), sex ($p = 0.14$), interval from vaccination to symptom onset ($p = 0.43$), or vaccines received (Tables S3 and S4).

Discussion

This study identified 58 reports of post-immunization KD that met the Brighton Collaboration case definition over a 6-y period at Canadian pediatric tertiary care centers. The median age at symptom onset was younger than the overall KD population in Canada reported by Manlhiot et al.[4] ($p = 0.04$) (Supplemental Table S3). Hua et al. reported a similar finding when they looked at Vaccine Adverse Event Reporting System (VAERS) in the USA in the period 1990 to 2007 where approximately 40% of the 97 cases of KD were less than 6 months of age.[10] The gender distribution was approximately 2:1 Male: Female, consistent with what has been reported previously in the overall KD population in Canada and other countries.[4,18,19]

One third of cases from this study had documented abnormalities of the coronary arteries (ectasia, dilation, aneurysm), slightly higher than previously reported (3–25%).[3,4,19] However, this frequency is similar to some reports in younger patients. In a study of KD in Spain over 5 y (2011–2016), coronary aneurysms were seen in 21/103 (20%) infants under 12 months of age.[18] This may also reflect a bias as normal echocardiogram results may not have been reported consistently on the AEFI form or coded in the national database. Though missing information was requested from study sites, additional information was not available on all cases.

Most patients had received multiple vaccines prior to KD onset, which complicates assessment of temporal associations between KD and specific vaccines. In addition, vaccination schedules vary between Canadian provinces,[17] which may have accounted for the wide range of vaccine combinations received prior to KD onset in this study. DTaP vaccines were most frequently reported prior to KD onset, followed by PCV. DTaP is the vaccine combination most frequently administered in this age group, with four doses recommended before 2 y of age. The onset of KD was in the first two weeks post-vaccination in more than half of KD cases and was similar to non-cases. Time to onset was similar among those who received a live vaccine versus those who received inactivated vaccines only.

Cases of KD have been reported temporally following DTaP-Inactivated Poliovirus-*Haemophilus influenzae* type b-Hepatitis B vaccine (DTaP-IPV-Hib-HepB), PCV7, PCV13, meningococcal B vaccine, influenza, RV, and Hib vaccination but no clear causal relationships have been identified.[11–31] Phuong and colleagues published a systematic review of KD and immunization and found 27 publications that considered a temporal association between immunization and KD. Overall there was no evidence of a causal association between KD and immunization.[9] Huang et al. studied KD after RV vaccination in Taiwanese infants and found that the risk of KD was higher during the third week after the second dose of RV5, and during the fourth week after the first dose of RV1. In our study, RV was always given in combination with DTaP vaccination and the onset of symptoms after vaccination was earlier than Huang et al reported.[31]

Seasonality of KD was assessed in a 2013 study which included data from 25 countries (including Canada) over 42 y.[32] In the Northern hemisphere, case numbers were highest in winter months (January through March) and lowest from August through October (late summer to fall). We noted a similar seasonal trend with highest case numbers in December to March and lowest from August to October.

The cases with insufficient evidence to meet the Brighton Collaboration case definition, comprising 25% of physician-diagnosed KD cases reported to IMPACT, lacked information for a range of key diagnostic criteria, most frequently echocardiogram results and duration of fever. This information is expected to be part the workup for any suspected KD case. Therefore, it is possible that these investigations were performed but the results either were not available in the hospital chart, not reported on the AEFI form, or were not coded when data were entered into the CAEFISS database. The national AEFI form used to report KD following immunization is not designed to capture KD and nurse monitors enter most of the case details in a free text field which may lead to inconsistencies or incompleteness in the data collected.[16] Our literature search did not identify other studies that applied the Brighton collaboration standardized KD definition to surveillance data.

A limitation of this study is that IMPACT could not influence the diagnostic work-up for KD nor the exclusion of other potential triggers for KD and therefore the investigations were not standardized across the network. In addition, diagnostic investigations to exclude other causes are not collected in a standardized fashion on the national AEFI form and therefore may not have been captured, or if captured, may not have been coded in the national database. We tried to mitigate this limitation by requesting additional case data from sites to enable application of the Brighton level of certainty; however, some required information was not available in the medical record. Another limitation is that we did not have details on coronary artery z-scores to confirm whether those with coronary dilation/ectasia actually met the Brighton Collaboration definitions for these abnormalities. The study also highlights the limitations of using a passive surveillance AEFI reporting form for a complex case definition and relying on details entered in free text fields to capture key data elements. Specific reporting forms for each case definition that could be mapped to fields in the national AEFI database may improve the quality of data collected and the ability to apply standard case definitions via hospital-based sentinel surveillance.

In this study, KD appeared to be a rare adverse event following immunization with only 58 cases meeting the Brighton Collaboration definition reported over 6 y across 12

Canadian tertiary care centers. Sex and seasonal distribution of KD cases was similar to the published literature, while distribution of age and vaccines temporally associated with KD reflected the routine childhood immunization schedule for children <5 y of age. Therefore, we did not find evidence of a safety signal between vaccination and KD. Ongoing surveillance for this serious AEFI and analysis for evidence of associations with vaccination remains important to maintain confidence in the safety of immunization programs.

Acknowledgements

The authors gratefully acknowledge the expert assistance of the Monitor Liaisons (Heather Samson, Annick Audet), IMPACT nurse monitors, staff of the IMPACT Data Center (Kim Marty, Jennifer Mark) and Melanie Laffin (Canadian Paediatric Society).

Disclosure statement

KAT has received grants from GlaxoSmithKline outside the submitted work. SAH has received grants and consulting fees from Pfizer and GlaxoSmithKline outside the submitted work. MS is supported via salary awards from the BC Children's Hospital Foundation, the Canadian Child Health Clinician Scientist Program and the Michael Smith Foundation for Health Research. MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments. NKV has recently received stipend from a Pfizer grant outside the submitted work. The other authors have no disclosures.

Funding

The Canadian Immunization Monitoring Program Active (IMPACT) is a national surveillance initiative managed by the Canadian Paediatric Society and conducted by the IMPACT network of pediatric investigators on behalf of the Public Health Agency of Canada's Centre for Immunization and Respiratory Infectious Diseases.

ORCID

Julie A. Bettinger http://orcid.org/0000-0002-2118-4174
Manish Sadarangani http://orcid.org/0000-0002-9985-6452
Scott A. Halperin http://orcid.org/0000-0003-0525-589X
Karina A. Top http://orcid.org/0000-0002-9981-368X

References

1. Jennette JC. Overview of the 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. Clin Exp Nephrol. 2013;17(5):603–606. doi:10.1007/s10157-013-0869-6.
2. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Arch Dis Child. 2015;100(11):1084–1088. doi:10.1136/archdischild-2014-307536.
3. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol. 2016;67(14):1738–1749. doi:10.1016/j.jacc.2015.12.073.
4. Manlhiot C, O'-Shea S, Bernknopf B, LaBelle M, Chahal N, Dillenburg RF, Lai LS, Bock D, Lew B, Masood S, et al. Epidemiology of Kawasaki disease in Canada 2004 to 2014: comparison of surveillance using administrative data vs periodic medical record review. Can J Cardiol. 2018;34(3):303–309. doi:10.1016/j.cjca.2017.12.009.
5. Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? Int J Infect Dis. 2005;9(4):185–194. doi:10.1016/j.ijid.2005.03.002.
6. Masood S, Manlhiot C, Chahal N, Yeung R, McCrindle B. Environmental exposures and Kawasaki disease: the infectious trigger hypothesis. Pediatr Int. 2012;54:64. doi:10.1111/j.1442.200X.2012.03535.x.
7. Abrams JY, Weintraub ES, Baggs JM, McCarthy NL, Schonberger LB, Lee GM, Klein NP, Belongia EA, Jackson ML, Naleway AL, et al. Childhood vaccines and Kawasaki disease, Vaccine safety datalink, 1996-2006. Vaccine. 2015;33:382–387. doi:10.1016/j.vaccine.2014.10.044.
8. Bonetto C, Trotta F, Felicetti P, Alarcón GS, Santuccio C, Bachtiar NS, Brauchli Pernus Y, Chandler R, Girolomoni G, Hadden RD, et al. Vasculitis as an adverse event following immunization – systematic literature review. Vaccine. 2016;34(51):6641–6651. doi:10.1016/j.vaccine.2015.09.026.
9. Phuong LK, Bonetto C, Buttery J, Pernus YB, Chandler R, Felicetti P, Goldenthal KL, Kucuku M, Monaco G, Pahud B, et al. Kawasaki disease and immunisation: a systematic review. Vaccine. 2017;35(14):1770–1779. doi:10.1016/j.vaccine.2016.09.033.
10. Hua W, Izurieta HS, Slade B, Belay ED, Haber P, Tiernan R, Woo EJ, Iskander J, Braun MM, Ball R. Kawasaki disease after vaccination: reports to the vaccine adverse event reporting system 1990-2007. Pediatr Infect Dis J. 2009;28(11):943–947. doi:10.1097/INF.0b013e3181a66471.
11. Stowe J, Andrews NJ, Turner PJ, Miller E. The risk of Kawasaki disease after pneumococcal conjugate & meningococcal B vaccine in England: a self-controlled case-series analysis. Vaccine. 2020;38(32):4935–4939. doi:10.1016/j.vaccine.2020.05.089.
12. Phuong LK, Bonetto C, Buttery J, Pernus YB, Chandler R, Goldenthal KL, Kucuku M, Monaco G, Pahud B, Shulman ST, et al. Kawasaki disease and immunisation: standardised case definition & guidelines for data collection, analysis. Vaccine. 2016;34(51):6582–6596. doi:10.1016/j.vaccine.2016.09.025.
13. Bettinger JA, Halperin SA, Vaudry W, Law BJ, Scheifele DW. The Canadian Immunization Monitoring Program, ACTive (IMPACT): active surveillance for vaccine adverse events and vaccine-preventable diseases. Can Commun Dis Rep. 2014;40(S3):41–44. doi:10.14745/ccdr.v40is3a06.
14. Top KA, Macartney K, Bettinger JA, Tan B, Blyth CC, Marshall HS, Vaudry W, Halperin SA, McIntyre P. Active surveillance of acute paediatric hospitalisations demonstrates the impact of vaccination programmes and informs vaccine policy in Canada and Australia. Euro Surveill. 2020;25(25). doi:10.2807/1560-7917.Es.2020.25.25.1900562.
15. Public Health Agency of Canada. Reporting adverse events following immunization (AEFI) in Canada: user guide to completion and submission of the AEFI reports. Ottawa (ON): Government of Canada; 2022 Jan 21 [accessed 2022 Jan 22]. https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/user-guide-completion-submission-aefi-reports.html.
16. Public Health Agency of Canada. Report of adverse events following immunization (AEFI). Ottawa (ON): Government of Canada; Sep 2016 [accessed 2022 Jan 22]. https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/adverse-events-following-immunization-reporting-declaration-manifestations-cliniques-inhabituelles-suite-immunisation-eng.pdf.
17. Public Health Agency of Canada. Canada's provincial and territorial routine (and catch-up) vaccination programs for infants and children. Ottawa (ON): Government of Canada; 2021 Dec 10 [accessed 2022 Jan 22]. https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/provincial-territorial-routine-vaccination-programs-infants-children.html.
18. Fernandez-Cooke E, Barrios Tascón A, Sánchez-Manubens J, Antón J, Grasa Lozano CD, Aracil Santos J, Villalobos Pinto E, Clemente Garulo D, Mercader Rodríguez B, Bustillo Alonso M, et al. Epidemiological and clinical features of Kawasaki disease in Spain over 5 years and risk factors for aneurysm development. (2011-2016): KAWA-RACE study group. PLoS One. 2019;14(5):e0215665. doi:10.1371/journal.pone.0215665.

19. Saundankar J, Yim D, Itotoh B, Payne R, Maslin K, Jape G, Ramsay J, Kothari D, Cheng A, Burgner D. The epidemiology and clinical features of Kawasaki disease in Australia. Pediatrics. 2014;133(4):e1009–1014. doi:10.1542/peds.2013-2936.
20. Halperin SA, Tapiero B, Law B, Diaz-Mitoma F, Duval B, Langley JM, Elrick DB, Jacquet JM. Interchangeability of two diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, Haemophilus influenzae type b conjugate vaccines as a fourth dose in 15–20-month-old toddlers. Vaccine. 2006;24(18):4017–4023. doi:10.1016/j.vaccine.2005.11.012.
21. Liang H, Sakaguchi M. Quantitative vaccine safety signal detection techniques using vaccine adverse event reporting system (VAERS). Pharmacoepidemiol Drug Saf. 2013;22:238. doi:10.1002/pds.3512.
22. Tseng HF, Sy LS, Liu IL, Qian L, Marcy SM, Weintraub E, Yih K, Baxter R, Glanz JM, Donahue J, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine. 2013;31(22):2578–2583. doi:10.1016/j.vaccine.2013.03.040.
23. Shimada S, Watanabe T, Sato S. A patient with Kawasaki disease following influenza vaccinations. Pediatr Infect Dis J. 2015;34 (8):913. doi:10.1097/inf.0000000000000713.
24. Baker MA, Baer B, Kulldorff M, Zichittella L, Reindel R, DeLuccia S, Lipowicz H, Freitas K, Jin R, Yih WK. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: a self-controlled risk interval and cohort study with null results. PLoS Med. 2019;16(7):e1002844. doi:10.1371/journal.pmed.1002844.
25. Yung CF, Ma X, Cheung YB, Oh BK, Soh S, Thoon KC. Kawasaki disease following administration of 13-valent pneumococcal conjugate vaccine in young children. Sci Rep. 2019;9(1):14705. doi:10.1038/s41598-019-51137-5.
26. Center KJ, Hansen JR, Lewis E, Fireman BH, Hilton B. Lack of association of Kawasaki disease after immunization in a cohort of infants followed for multiple autoimmune diagnoses in a large, phase-4 observational database safety study of 7-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2009;28(5):438–440. doi:10.1097/INF.0b013e318196934a.
27. Huang K, Tao S, Zhou X, Mo J, Zhu B, Shen P, Lin H, Arena PJ, He N. Incidence rates of health outcomes of interest among Chinese children exposed to selected vaccines in Yinzhou electronic health records: a population-based retrospective cohort study. Vaccine. 2020;38(18):3422–3428. doi:10.1016/j.vaccine.2020.03.013.
28. Layton JB, Butler AM, Panozzo CA, Brookhart MA. Rotavirus vaccination and short-term risk of adverse events in US infants. Paediatr Perinat Epidemiol. 2018;32:448–457. doi:10.1111/ppe.12496.
29. Hoffman V, Abu-Elyazeed R, Enger C, Esposito DB, Doherty MC, Quinlan SC, Skerry K, Holick CN, Basile P, Friedland LR, et al. Safety study of live, oral human rotavirus vaccine: a cohort study in United States health insurance plans. Hum Vaccin Immunother. 2018;14(7):1782–1790. doi:10.1080/21645515.2018.1450123.
30. Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. Pediatr Infect Dis J. 2012;31(3):292–296. doi:10.1097/INF.0b013e3182421390.
31. Huang WT, Juan YC, Liu CH, Yang YY, Chan KA. Intussusception and Kawasaki disease after rotavirus vaccination in Taiwanese infants. Vaccine. 2020;38(40):6299–6303. doi:10.1016/j.vaccine.2020.07.038.
32. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, Burgner D, Bainto E, Pierce D, Tyree M, et al. Seasonality of Kawasaki disease: a global perspective. PLoS One. 2013;8(9): e74529. doi:10.1371/journal.pone.0074529.