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Kawasaki disease and immunisation: A systematic review

Linny Kimly Phuong [a,b], Caterina Bonetto [c], Jim Buttery [a,d,e], Yolanda Brauchli Pernus [f], Rebecca Chandler [g], Patrizia Felicetti [c], Karen L. Goldenthal [h], Merita Kucuku [i], Giuseppe Monaco [j], Barbara Pahud [k], Stanford T. Shulman [l], Karina A. Top [m], Francesco Trotta [c], Rolando Ulloa-Gutierrez [n], Frederick Varricchio [o], Sarah de Ferranti [p], Jane W. Newburger [p], Nagib Dahdah [q], Surjit Singh [r], Jan Bonhoeffer [f,s,*], David Burgner [a,d,e,t], The Brighton Collaboration Kawasaki Disease (KD) Working Group [1]

[a] Monash Children's Hospital, Clayton, Melbourne, Australia
[b] Royal Children's Hospital, Parkville, Victoria, Australia
[c] Italian Medicines Agency (AIFA), Rome, Italy
[d] Murdoch Childrens Research Institute, Parkville, Victoria, Australia
[e] Department of Paediatrics, Monash University, Clayton, Victoria, Australia
[f] The Brighton Collaboration Foundation, Basel, Switzerland
[g] Uppsala Monitoring Centre, Uppsala, Sweden
[h] Independent Consultant, Bethesda, MD, USA
[i] Department of Vaccines Control, National Agency for Medicines and Medical Devices, Tirana, Albania
[j] Pharmacovigilance Regional Centre of Lombardy, Italy
[k] Children's Mercy Hospital, Kansas City, MO, USA
[l] Ann & Robert H. Lurie Children's Hospital of Chicago, USA
[m] Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada
[n] Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera, San José, Costa Rica
[o] Independent Consultant Vaccinologist, Wakefield, RI, USA
[p] Boston Children's Hospital, Boston, USA
[q] CHU Sainte-Justine, Montreal, Canada
[r] Post Graduate Institute of Medical Education and Research (PGIMER)- Chandigarh, India
[s] University of Basel Children's Hospital, Basel, Switzerland
[t] Department of Paediatrics, Melbourne University, Parkville, Victoria, Australia

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ABSTRACT

Background: Kawasaki disease is a complex and potentially serious condition. It has been observed in temporal relation to immunisation.
Methods: We conducted a systematic literature review using various reference sources to review the available evidence published in the literature.
Results: We identified twenty seven publications reporting a temporal association between immunisation and Kawasaki disease. We present a systematic review of data drawn from randomised controlled trials, observational studies, case series and reports, and reviews. Overall there was a lack of standardised case definitions, making data interpretation and comparability challenging.
Conclusions: Although a temporal relationship between immunisation and Kawasaki disease is suggested, evidence for an increased risk or a causal association is lacking. Implementation of a standardised Kawasaki disease case definition would increase confidence in the findings and add value to future studies of pre- or post-licensure vaccine safety studies.

1. Background

Kawasaki disease (KD) is a systemic vasculitis predominantly of infancy and childhood affecting medium-sized muscular arteries [1]. Initially described by Tomisaku Kawasaki, a Japanese paediatrician, in 1967 [2] and subsequently in the English literature in 1971

* Corresponding author at: The Brighton Collaboration Foundation, Basel, Switzerland.
E-mail address: contact@brightoncollaboration.org (J. Bonhoeffer).
[1] Brighton Collaboration homepage: http://www.brightoncollaboration.org.

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[3], KD was initially believed to be a self-limiting illness, but was subsequently recognised to result in potentially fatal changes to the coronary arteries in some children. It is also referred to as "mucocutaneous lymph node syndrome" or "Kawasaki syndrome" in the scientific literature [4].

Kawasaki disease has been reported in almost all populations. It is especially common in North East Asia; Japan, Korea and Taiwan have the highest incidence worldwide, which in contrast to the US, Europe and Australia, continues to increase [5,6]. It is estimated that more than 1 in 100 Japanese have had KD by 12 years of age [7]. Kawasaki disease is primarily an illness of the pre-school child, with an estimated 65–80% of cases occurring between 6 months and before 5 years of age [6,8,9]. The median age of onset is approximately 13 months in Asian populations and 24 months in predominantly European-Caucasian populations [10]. In India, a significant proportion of patients are older than 5 years [11]. Kawasaki disease in neonates and infants is relatively rare and more challenging to diagnose. However, numerous cases have been described [12–14]. Rarely cases are reported in adults, particularly in the setting of human immunodeficiency virus (HIV) infection [15].

The cause of KD is unknown. The widely accepted consensus is that it arises from an abnormal and exaggerated inflammatory response to one or more environmental triggers in genetically susceptible individuals [6,7,16,17]. Epidemiological features, including previous major epidemics, temporal and spatial clustering, relative rarity of recurrence, and the low incidence in very young infants, all suggest that the trigger(s) are likely to be of microbial origin and widely distributed in populations, although no consistent agent has been identified to date [18]. Kawasaki disease has been observed in temporal relation following immunisation and this systematic review summarises the published data.

2. Methods

Following the standard Brighton Collaboration Process [19], a systematic literature review was conducted using the following resources: Medline (1946- current, June 2016), EMBASE (1975-current, June 2016), PubMed, and Cochrane. The complete search strategy previously published in Bonetto et al. [20] has been updated to reflect further articles since publication of this original paper. We used the MeSH terms and keywords "mucocutaneous lymph node syndrome", "lymphatic diseases" and "Kawasaki disease" with relevant thesaurus terms. These terms were combined with "immunisation", "vaccines" and variations of adverse effects or adverse drug reactions. All duplicates were removed. The search was limited to humans and publications in English. All identified titles and abstracts were reviewed for relevance. Relevant articles were those which presented any potential association between Kawasaki disease and vaccination, regardless of the type of vaccine.

After removing duplicates, our database search yielded 854 articles from Medline, Embase, Pubmed and the Cochrane Library. Based on these titles and abstracts, 27 articles were identified. Four of these papers were case reports. Additional articles were identified by screening references of eligible papers. Where the papers were not freely available, such as in the case of abbreviated conference abstracts or abstracts ahead of print, we contacted the authors to retrieve the publication or further details. Given the paucity of published data, these abstracts were included if sufficient information was available. Further details regarding the search methodology are presented in Appendix 1.

Of note, a recent review by Esposito et al. entitled "Vaccines and Kawasaki disease" discussed putative immunological mechanisms that may play a role in KD. The authors concluded that there is currently no evidence to suggest an association between KD and vaccination [21].

3. Results

Twenty seven publications have considered a temporal association between immunisation and KD (Table 1A and B). Overall there is no evidence of a causal association. A case definition was applied in seven publications, but not explicitly discussed in any of the four case reports. The case definitions varied and included those derived from the current AHA Guidelines [8], the American Academy of Pediatrics Red Book [22], Centers for Disease Control and Prevention (CDC) [23] and a modified case definition [24].

The articles referred to vaccination against: diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b (DTP-IPV-Hib) (n = 1), *Haemophilus influenzae* type b (Hib) (n = 1), Japanese encephalitis (n = 1), measles, mumps, rubella (MMR) or measles, mumps, rubella, varicella (MMR-V) (n = 1), meningococcal B (n = 5), pneumococcal: 7-valent and 13-valent (n = 4), rotavirus (n = 7), and vaccinations in general (n = 3).

Four publications were case reports of single cases, and referred to DPT (diphtheria, pertussis, tetanus) (n = 1), hepatitis B (n = 1), influenza (n = 1) and yellow fever (n = 1) (Table 1B).

3.1. General vaccination

An observational study by Abrams et al. [25] investigated KD rates for 1,721,186 children aged 0–6 years from 1996 to 2006 in the Vaccine Safety Datalink (VSD) in the US. Cases were verified using medical records where available and stratified according to time post-vaccination. This study did not demonstrate an increase in KD incidence following vaccination, but an apparent protective effect. The conclusions were likely to be limited due to time-varying confounding. Of note, the authors also observed that there may have been an underestimation of effect due to rotavirus vaccines, as they were not commonly used during the study time period.

Hua et al. [24,26] reviewed all KD cases received by the US Vaccine Adverse Event Reporting System (VAERS) from 1990 to 2007. There were 97 cases including those classified as classic, "atypical" and possible KD. The reported timing of onset of KD was within 30 days of vaccination in 91% of reports. It was suggested that there were a greater than expected number of reports of possible KD following RotaTeq® (rotavirus), Pediarix® (DTP-hepatitis B-IPV) and Prevnar® (pneumococcal 7-valent polysaccharide) vaccinations. However, the authors concluded that overall there did not appear to be an increased risk for RotaTeq® or the other US-licensed vaccines. Moreover, a revision of the package insert for RotaTeq® during this time period may have contributed to greater reporting rates.

In a matched case-control study in Colorado during a KD outbreak [27], 37 patients met the CDC definition for KD, but there was no evidence of an association with vaccination; odds ratio for KD within 30 days following vaccination was 1.3 (95% CI: 0.4–4.3).

3.2. Diphtheria, tetanus, pertussis, inactivated polio, Haemophilus influenzae type b (DTP-IPV-Hib) vaccination

An inter-changeability study between two brands of DTP-IPV-Hib vaccines, Pentacel® and Infanrix®, by Halperin et al. [28] reported that, of the 433 enrolled participants, there was one reported case of KD occurring 21 days after Infanrix® vaccination. However, this event was assessed not to be vaccine-related.

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