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Kawasaki disease and immunisation: Standardised case definition & guidelines for data collection, analysis

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Abbreviations: ADR, adverse drug reaction; AHA, American Heart Association; ALT, alanine transaminase; AST, aspartate transaminase; BCG, Bacillus Calmette, Guérin (vaccine); CAAs, coronary artery aneurysms; CMRA, cardiac magnetic resonance angiography; CRP, C-reactive protein; DTP, *diphtheria, tetanus, p*ertussis; DTaP,, diphtheriatetanus, acellular pertussis; EBV, Epstein Barr Virus; ESR, erythrocyte sedimentation rate; GGT, gamma glutamyl transferase; HHV, human herpes virus; Hib, *Haemophilus influenza* type b; HPF, high powered field; HSP, heat shock protein; IVIG, intravenous gamma globulin; JMoH, Japanese Ministry of Health; KD, Kawasaki disease; LAD, left anterior descending; LV, left ventricular; MRI, magnetic resonance imaging; MSCT, multi, slice computed tomography; PAN, polyarteritis nodosa; PCV, pneumococcal conjugate vaccine; PCR, polymerase chain reaction; RCA, right coronary artery; RMSF, Rocky Mountain Spotted Fever; RTPE,, recurrent toxin, mediated perineal erythema; sJIA, systemic juvenile idiopathic arthritis; SPECT, single photon emission computed tomography; TSS, toxic shock syndrome; TST, tuberculin skin test; WBC, white blood cells.

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1. Preamble

1.1. The need for a case definition

Kawasaki disease (KD), is a systemic vasculitis of infancy and childhood affecting medium-sized muscular arteries [1]. It causes potentially life-threatening changes in the coronary arteries of some children and is the most common cause of paediatric-acquired heart disease in high income countries [2,3].

The systematic review "Kawasaki disease and Immunisation" in the same volume of this journal summarises the published data on KD as a possible adverse event following immunisation (AEFI) [4]. Although a temporal relationship is observed, evidence for an increased risk or causal association is lacking. Harmonised and active surveillance using a widely applicable case definition is important to address whether new or current vaccines are associated with increased KD activity.

The literature review further highlighted that there is no uniformly accepted case definition of KD, nor is there a single unifying definition broadly applicable across surveillance, epidemiological, genetic, clinical or intervention studies [4].

A standardised case definition allowing for different levels of diagnostic certainty in different settings would add value to individual studies by facilitating data interpretation and comparability and promoting the scientific understanding of potential AEFI. Harmonised and active surveillance for possible KD in relation to established and new immunisations is most valuable in the paediatric population for several reasons. First, the age of KD peak incidence in children is less than 6 years of age. This is the age when many routine childhood immunisations are administered [5,6]. Second, many infectious diseases may present with clinical features similar to KD, so that misclassification is possible [7–13]. Third, KD is a comparatively rare disease with an incidence rate (in children less than 5 years of age) ranging from approximately 5–20 in many settings such as the UK, US and Europe, to 80–200 per 100,000 in Japan, Korea and Taiwan [5,14]. Thus, robust risk estimates require large population-based observational studies, or the ability to perform meaningful meta-analysis of multiple smaller studies.

1.2. Methods for the development of the case definition

Following the standard process described in the overview paper [15] as well as on the Brighton Collaboration Website (https://brightoncollaboration.org), the Brighton Collaboration *Kawasaki Disease Working Group* was formed in 2014 and included members with academic, clinical, public health, and industry backgrounds.

For decision-making regarding the case definition and guidelines, a literature search was performed using PubMed (Medline) and EMBASE. We applied the same search strategy as in our systematic literature review of any form of vasculitis following immunisation [16] to identify papers from 1994 to June 2014 that included both any form of vasculitis (all terms included in the Chapel Hill Consensus Conference 2012 [1]) and any term relating to immunisation. Articles relating to KD were extracted. Using this systematic search we found seven articles reporting on a temporal association with KD following immunisation.

We also performed a systematic literature search [16] for previous published consensus case definitions using a Pubmed search keyword 'vasculitis', 'Kawasaki', 'definition', with the filters 'humans', 'English', and extracted articles relating to KD. The search method is detailed in Paper 1 Appendix 1. We modified existing case definitions [16] based on recent evidence and the purpose of the definition in the context of globally harmonised disease and vaccine safety monitoring.

1.3. Rationale for selected decisions about the case definition of Kawasaki disease as an adverse event following immunisation

Kawasaki Disease is also referred to in the scientific literature as mucocutaneous lymph node syndrome or Kawasaki syndrome [17]. The Working Group agreed to employ the most commonly used term "Kawasaki Disease".

We have formulated a standardised KD case definition using the Brighton Collaboration template [18] that provides varying degrees of diagnostic certainty and is aimed to be applicable across various settings, populations and data sources. It should be emphasised that the proposed definition levels reflect the diagnostic certainty of an observed event rather than its clinical severity or any degree of causal association of the event with immunisation. The KD case definition is not intended as a tool for diagnosis or management in the clinical setting.

The number of symptoms and/or signs that will be documented for each case may vary considerably. The case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. Detailed information about the severity of the event should additionally be recorded, as specified by the data collection guidelines. In the following sections, we provide the rationale relating to individual criteria used in the KD case definition.

1.3.1. Fever

The Japanese Ministry of Health (JMoH) criteria allow fever of four days, or less if early intravenous immunoglobulin (IVIG) is given, as almost a third of Japanese patients receive IVIG on or before the fourth day of fever [19].

Prolonged fever is the strongest predictor of coronary artery lesions [20–23] even following IVIG treatment [24]. Although there have been occasional reports of children diagnosed with KD in the apparent absence of fever [25–27], this is (at best) an extremely rare occurrence. Therefore the presence of fever is considered a *sine qua non* for the diagnosis of KD in the proposed case definition.

In contrast to the current American Heart Association (AHA) definition requiring $\geqslant$5 days of fever, the KD working group agreed on $\geqslant$4 days of fever, as in many settings with a high incidence and where clinicians are familiar with KD, the diagnosis is often made before day 5 and treatment may be commenced. Therefore the child may defervesce prior to day 5.

1.3.2. Perineal or perianal changes

Perineal or perianal changes have been reported as early non-specific signs of KD, in contrast to the desquamation of the peripheries, which typically occurs in the sub-acute phase (days 10–14) [12,28–35]. Perineal changes are described as a rash of erythematous macules or papules, which then desquamate over these regions. In one study, this finding occurred in 67% of patients within the first week of onset of illness [34]. Importantly, differential diagnoses such as scarlet fever, staphylococcal or streptococcal toxic shock syndrome, and recurrent toxin-mediated perineal erythema [36,37] should be excluded.

1.3.3. BCG vaccination site changes

The significance of the finding of BCG site changes is acknowledged in the Diagnostic Guidelines for Kawasaki Disease (5th

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