The Texas Medical Center Library
DigitalCommons@TMC

Library Staff Publications | Texas Medical Center Library

5-12-2023

Viral Coinfections in Kawasaki Disease: A Meta-analysis.

Hannah C Neubauer

Michelle A Lopez

Heather A Haq

Lara Ouellette

Andrea A Ramirez

See next page for additional authors

Follow this and additional works at: https://digitalcommons.library.tmc.edu/library_docs

Recommended Citation
Citation Information:Neubauer, Hannah C; Lopez, Michelle A; Haq, Heather A; Ouellette, Lara; Ramirez, Andrea A; and Wallace, Sowdhamini S, "Viral Coinfections in Kawasaki Disease: A Meta-analysis." (2023).
DigitalCommons@TMC, Texas Medical Center Library, *Library Staff Publications.* Paper 62.
https://digitalcommons.library.tmc.edu/library_docs/62

This Article is brought to you for free and open access by the Texas Medical Center Library at DigitalCommons@TMC. It has been accepted for inclusion in Library Staff Publications by an authorized administrator of DigitalCommons@TMC. For more information, please contact digcommons@library.tmc.edu.

Authors

Hannah C Neubauer, Michelle A Lopez, Heather A Haq, Lara Ouellette, Andrea A Ramirez, and Sowdhamini S Wallace

This article is available at DigitalCommons@TMC: https://digitalcommons.library.tmc.edu/library_docs/62

REVIEW ARTICLE

Viral Coinfections in Kawasaki Disease: A Meta-analysis

Hannah C. Neubauer, MD,[a] Michelle A. Lopez, MD, MPH,[b,c] Heather A. Haq, MD, MHS,[b,c] Lara Ouellette, MLS,[d] Andrea A. Ramirez, MD,[c,e] Sowdhamini S. Wallace, MD, MS[b,c]

ABSTRACT

CONTEXT: Viral infections are suspected triggers in Kawasaki disease (KD); however, a specific viral trigger has not been identified.

OBJECTIVES: In children with KD, to identify (1) overall prevalence of viral infections; (2) prevalence of specific viruses; and (3) whether viral positivity was associated with coronary artery aneurysms (CAAs) or refractoriness to intravenous immunoglobin (IVIG).

DATA SOURCES: We searched Embase, Medline, and Cochrane databases and gray literature.

STUDY SELECTION: Eligible studies were conducted between 1999 and 2019, and included children diagnosed with KD who underwent viral testing.

DATA EXTRACTION: Two investigators independently reviewed full-text articles to confirm eligibility, extract data, appraise for bias, and assess evidence quality for outcomes using the Grading of Recommendations Assessment Development and Evaluation criteria. We defined viral positivity as number of children with a positive viral test divided by total tested. Secondary outcomes were CAA (z score ≥2.5) and IVIG refractoriness (fever ≥36 hours after IVIG).

RESULTS: Of 3189 unique articles identified, 54 full-text articles were reviewed, and 18 observational studies were included. Viral positivity weighted mean prevalence was 30% (95% confidence interval [CI], 14–51) and varied from 5% to 66%, with significant between-study heterogeneity. Individual virus positivity was highest for rhinovirus (19%), adenovirus (10%), and coronavirus (7%). Odds of CAA (odds ratio, 1.08; 95% CI, 0.75–1.56) or IVIG refractoriness (odds ratio, 0.88; 95% CI, 0.58–1.35) did not differ on the basis of viral status.

LIMITATIONS: Low or very low evidence quality.

CONCLUSIONS: Viral infection was common with KD but without a predominant virus. Viral positivity was not associated with CAAs or IVIG refractoriness.

[a]*Department of Pediatrics, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, Colorado;* [b]*Divisions of Pediatric Hospital Medicine and* [e]*Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas;* [c]*Texas Children's Hospital, Houston, Texas; and* [d]*Texas Medical Center Library, Houston, Texas*

www.hospitalpediatrics.org
DOI:https://doi.org/10.1542/hpeds.2023-007150
Copyright © 2023 by the American Academy of Pediatrics

Address correspondence to Sowdhamini S. Wallace, DO, MS, Division of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, 1102 Bates St, FC 1860, Houston, TX 77030. E-mail: sswallac@texaschildrens.org

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FUNDING: No external funding.

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated they have no conflicts of interest relevant to this article to disclose.

Dr Neubauer conceptualized and designed the study, determined study eligibility based on full text review, extracted data from studies, appraised for bias, and determined evidence quality for outcomes using Grading of Recommendations Assessment Development (Continued)

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

Kawasaki disease (KD) is a systemic vasculitis that most commonly affects young children and is the leading cause of acquired heart disease in the United States. The mainstay first-line treatments for KD, intravenous immunoglobulin (IVIG) and acetylsalicylic acid, are aimed at reducing risk for coronary artery aneurysms (CAAs) and decreasing systemic inflammation.

Additional targeted treatments for KD could be used if the etiology of the disease was better understood. The predominant theory believed by experts is that KD is triggered by infectious pathogens in a genetically susceptible host.[1,2] The seasonality of KD and clustering of cases within and external to families support the theory of an infectious trigger.[1–4] The investigators of the multicenter KD Comparative Effectiveness trial published an epidemiologic study where they found a decline in KD prevalence during the coronavirus disease 2019 (COVID-19) pandemic in 2020 compared with 2018 to 2019 coinciding with strict masking precautions.[5] The authors postulated that a respiratory trigger for KD is likely. However, the cause of KD has not been definitively identified. Various viral, bacterial, and environmental triggers have been suggested.[6,7] Features of the disease, including fever, rash, and mucous membrane changes, can overlap with those seen in some viral infections. Multiple studies have found viral coinfection in children diagnosed with KD.[6,8] The prevalence ranged from 7.5% to as high as 42%,[7,8] though patient populations, surveillance protocols, and detection methods differed across studies. Furthermore, some experts argue that bacterial pathogens are less likely because antibiotics are not helpful in KD.[3] Nakamura et al described the pathologic and immunologic features of KD to be consistent with viral pathogens.[1] Moreover, authors of the 2017 American Heart Association Clinical Practice Guideline for Diagnosis, Treatment, and Long-Term Management of KD describe a novel RNA virus with entry though the upper respiratory tract as potential mechanism for KD, citing reports that show a higher frequency of intracytoplasmic inclusion bodies in KD fatalities as compared with controls.[9] It is unclear, however, whether specific viruses may be more likely to occur as concomitant infections or recent past infections in children with KD. It is also unknown whether the presence of a viral infection may influence the disease course.

Our objectives in this systematic review and meta-analysis were to:

1. describe the overall prevalence of concomitant viral infections in children with KD
2. describe the prevalence of specific viruses in children with KD; and
3. determine whether viral positivity is associated with CAA or failure to respond to IVIG treatment.

These objectives have important implications for better understanding the role of viruses as triggers and their impact on KD outcomes.

METHODS

We conducted a systematic review and meta-analysis of published and unpublished literature of children with KD.

Search Strategy, Screening, and Study Selection

A literature search was conducted independently by a medical librarian (L.O.) and 2 investigators (M.L. and H.H.). Published and unpublished medical articles were searched using MeSH terms and natural language keywords for KD, viruses, and diagnostic techniques. Medline Ovid, Embase, and Cochrane Library databases were used, in addition to review of abstracts from national conference proceedings and contacting experts in the field regarding unpublished studies. Articles were limited to studies published in English from 1999 to 2019 to capture more recent epidemiologic data and diagnostic tools for viral detection. Case reports, nonsystematic review articles, studies based on survey data, and duplicate publications of the same data set were excluded. Duplicate articles were identified and removed using EndNote software. The final search strategies can be found in Supplemental Table 2. The last search was conducted in February 2019.

Three investigators (M.L., H.H., and L.O.) screened titles and abstracts for eligible studies. Full-text articles were subsequently independently reviewed by 2 investigators (S.W. and H.N.) to confirm eligibility according to inclusion and exclusion criteria. Reference lists from full-text articles were also reviewed to identify further articles.

To be eligible for inclusion, studies had to include a population of children aged 0 to 18 years admitted to the hospital with a diagnosis of KD made by the American Heart Association (AHA) criteria[9] and receipt of a viral test. AHA criteria was required for complete KD and incomplete KD. Studies that included children with both complete and incomplete KD but only used AHA criteria for complete KD had data for incomplete KD excluded from the analysis. Viral tests could be of any type, including polymerase chain reaction (PCR), direct antigen test, or viral culture. Studies that did not include the raw number of children who were positive for the viral test or the total number tested were excluded.

Data Variables and Extraction

Two investigators (H.N. and S.W.) independently conducted data extraction of each final article and met to compare findings from data extraction. Any discrepancies in findings were mediated by rereview of the study findings and then consensus among the 2 investigators. When needed, authors were contacted to help address investigators' questions on reporting of results or availability of any outcomes not reported within studies.

Covariates collected from studies included the following: demographics of the population in the study (age, ethnicities/races, sex), setting (country, inpatient versus outpatient), type of KD (complete, incomplete), clinical features of KD (lymphadenopathy, rash, extremity

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

changes, conjunctivitis, oral changes), number of febrile days before viral test, type of viral test performed (PCR, direct florescence antigen, serology), sensitivity and specificity of test(s), respiratory signs on exam (eg, tachypnea, cough, congestion, rhinorrhea, wheezing, rales), and gastrointestinal symptoms (vomiting, diarrhea).

Dependent variables included the proportion of children with KD with any viral positivity (number of children with any positive test divided by total tested), viral positivity for specific viruses, coronary artery changes (defined as coronary lesions with z score ≥2.5), and IVIG-refractoriness (defined as persistence or recrudescence of fever >36 hours but <7 days after completion of IVIG). Data from studies where CAAs were reported but not defined via z scores were excluded from the analysis. Attempts were made to contact authors for clarifications if the definition for CAAs was unclear.

Risk of Bias Assessment for Individual Studies

Two investigators independently assessed the selected full-text articles for bias using the 13-item risk of bias assessment tool for observational studies from the Agency of Healthcare Research and Quality.[10] The tool assesses for biases in the study design, recruitment of subjects, intervention, comparison, measurement of results, and subject retention, with a final assessment of overall quality and believability of the results. More specifically, the tool probes users to consider factors within the methodology of a study that could cause confounding bias, selection bias, performance bias, detection bias, attrition bias, and reporting bias. The questions in the tool were designed to apply to case series, case-control, cohort, and cross-sectional designs. As recommended by the creators of the tool, the specific instructions to the users of the tool were adapted to include additional information relevant to appraisal of studies of KD, such as examples of confounding variables or how other biases could occur.

Quality of the Body Evidence by Outcome

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to examine the overall quality of evidence for each outcome.[11] The body of evidence for each outcome was assessed by 2 investigators (H.N. and S.W.) independently and the final determination of the quality level was determined through discussion and consensus. While utilizing GRADE, the initial quality of the evidence was determined by the study design and then downgraded and/or upgraded according to the set criteria. The final quality of evidence for each outcome was classified as either high, moderate, low, or very low.

Statistical Analysis

We performed random effects analysis of single proportions using the inverse variance method to calculate the overall viral positivity. Logit transformation of proportions was performed to allow appropriate weighting of studies with extreme values of positivity close to 0 or 1. Without transformation, the studies with 0% prevalence would have had overestimations of their weight because the variance would be close to 0.[12,13] Additionally, a continuity correction of 0.5 was applied for study proportions of 0. The Clopper-Pearson interval method was used to produce 95% confidence intervals (CIs). Sensitivity analysis was performed by removing studies with potential selection bias because of <80% of participants being tested. Additionally, subgroup analysis was performed for Asian countries and non-Asian countries. The effect of country on heterogeneity was also explored through meta-regression analysis. Random effects analysis was also performed for individual viruses using the inverse variance method. We performed random effects analysis using the Mantel-Haenszel test, which generated odds ratios (ORs) while stratifying across studies, to evaluate for associations between viral positivity and patient outcomes (coronary aneurysms and IVIG refractoriness). R version 4.0.0 (2020) and RevMan 5.3 were used for the analysis.

RESULTS

We identified 3189 unique articles, and after screening, 71 articles remained and underwent full-text review for eligibility. Ultimately, 18 articles were included in the meta-analysis, all of which were prospective and retrospective observational designs (Fig 1). Characteristics of included studies are presented in Table 1. All of the included studies were observational designs, either cohort or case-control designs, and half were prospective. Fifteen studies included children with both complete and incomplete KD; however, the data for children with incomplete KD were excluded from 3 studies where AHA criteria were not used to define incomplete KD. Study sample size ranged from small ($N = 10$) to large ($N = 1053$). Six studies were based in East Asian countries and the remaining 12 were from Western countries. The median or mean age of the population was reported for 12 of 18 studies, with median age ranging from 2.0 to 3.6 years and mean age ranging from 2.0 to 4.5 years across studies. Five studies reported estimates of overall upper respiratory infection symptom prevalence within the study population, and it ranged from 32% to 78% across study populations. Three other studies reported specific viral symptom prevalence with the following symptom ranges across studies: rhinorrhea, 44% to 72%; cough, 32% to 75%; and diarrhea, 15% to 72%.

Primary Outcome: Viral Positivity

Of the 8 studies that used broad testing for respiratory viruses, the weighted mean prevalence was 30% (95% CI, 14%–51%), with significant between-study heterogeneity ($I^2 = 98\%$, $P < .01$) (Fig 2). The prevalence reported by individual studies ranged from 5% to 66%. A sensitivity analysis was performed including only studies that tested ≥80% of their population, and of these 5 studies, the weighted mean prevalence was 42% (95% CI, 34%–50%), with improvement in between-study heterogeneity ($I^2 = 74\%$, $P < .02$) (Fig 2). Subgroup analysis was performed on Asian and non-Asian

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

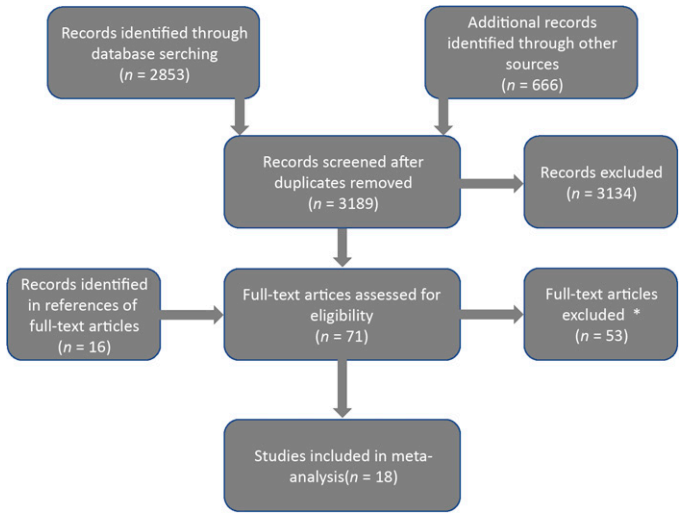

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection. *Fifty-three studies were excluded for the following reasons: did not test for viruses or report number tested ($n = 24$), unclear definition for complete KD ($n = 15$), not an original research article ($n = 7$), duplicate ($n = 6$), or not available in English ($n = 1$).

countries. Five of 8 studies were in Asia and mean weighted prevalence of viruses was 34% (95% CI, 12%–66%). For the 3 studies in a non-Asian country, the weighted mean prevalence of viruses was similar at 24% (95% CI, 6%–61%). Overall, the country of the study, whether Asian or non-Asian, did not contribute to the heterogeneity seen in the overall pooled viral prevalence ($R^2 = 0\%$, $P = .44$).

Secondary Outcome: Viral Pathogens Identified

When evaluating the prevalence of individual viruses across studies, individual viral prevalence ranged from 3% to 19%. Rhinovirus had the highest prevalence (19%; 95% CI, 13%–28%), followed by adenovirus (10%; 95% CI, 5%–18%); coronavirus (7%; 95% CI, 3%–15%); respiratory syncytial virus (5%; 95% CI, 3%–8%); influenza A and B (4%; 95% CI, 2%–8%); parainfluenza 1, 2, and 3 (4%; 95% CI, 2%–8%); bocavirus (4%; 95% CI, 1%–23%); enterovirus (3%; 95% CI, 0%–30%); and human metapneumovirus (3%; 95% CI, 2%–5%) (Fig 3).

Patient Outcomes

Six studies were available to compare the outcomes of CAAs and IVIG refractoriness among viral and nonviral KD. The odds of having CAAs did not differ on the basis of viral status (OR, 1.08; 95% CI, 0.75–1.56) (Fig 4). The odds of IVIG refractoriness also did not differ on the basis of viral status (OR, 0.88; 95% CI, 0.58–1.35) (Fig 4).

Risk of Bias of Individual Studies

Sources of bias were identified in many studies included in this review (Supplemental Table 3). The predominant sources of potential bias in individual studies were detection bias because of the lack of blinding, and selective outcome reporting bias because of the lack of reporting of important outcomes. Fifteen of the 18 studies did not incorporate blinding. The lack of blinding of viral status, however, is unlikely to have influenced the outcomes of CAAs or IVIG refractoriness. Important data variables that were frequently not reported included sensitivity and specificity of the viral test, and the timing of testing in relation to fever and longitudinal echocardiogram results. Sensitivity and specificity were only reported in 3 studies,[14–16] and the timing of testing was reported in 11 of 18 studies. Two studies, Chang et al and Kim et al, mention long-term follow-up for CAAs in the manuscript, but the data are not reported.[6,7]

Population definitions in relation to patient selection did not vary greatly, but some concern for selection bias for viral testing exists in several studies. All studies included in this systematic review used the AHA criteria to define complete KD. Twelve studies included incomplete KD in their study population, and of these, 4 studies did not use the AHA criteria to define incomplete KD. Selection bias in which patients received viral testing is possible in 5 of 18 studies because a large proportion of children with KD did not receive viral testing. In these studies, viral testing was performed at the discretion of the treating physician or, for Lee et al, testing was performed for patients with respiratory symptoms only.

Most studies were not designed to compare patient outcomes on the basis of viral positivity in children with KD. Many studies also varied in their definition of CAAs, which we defined per AHA criteria as a coronary arterial z score of ≥2.5. Some studies used other z score cutoffs, absolute measurements, or did not provide a definition of how aneurysms were measured. Of those study designs with a comparison group, the group was selected appropriately in all but 1 study (Lee, 2015), and techniques like matching were used to reduce confounding. Of the 8 studies that included such comparisons, 3 had potential confounding bias because of lack of reporting of the timing of administration of IVIG and other adjunctive treatments received which could affect the risk of CAAs. One study (Kim, 2018) compared outcomes in children with KD on the basis of viral positivity and did not report baseline characteristics to assess for potential confounders.[6] Three studies (Huang, 2015; Jordan-Villegas, Esper) controlled for potential confounding via matching patients in groups by key patient characteristics like age and date of hospitalization.[18–20]

Overall, despite the limitations of individual studies, the primary outcome of viral positivity was believable after completion of the risk of bias assessment (Supplemental Table 3). For several studies evaluating patient outcomes in association with viral

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

TABLE 1 Characteristics of Included Studies of Hospitalized Children with KD

Source	Design	Time Period and Geographical Location	Sample Size	Type of Viruses and Tests Performed
Kim et al, 2018[6]	Retrospective cohort study	2012–2016 (Seoul, Korea)	Total KD: $N = 129$; complete KD and incomplete KD: $n =$ unknown	Influenza A/B, adenovirus, parainfluenza virus types 1–4, RSV A/B, bocavirus types 1–4, coronavirus NL 63, OC 43 and 229E, enterovirus, HMPV, and rhinovirus A/B/C: respiratory virus PCR
Chang et al, 2014[7]	Prospective case-control study	2004–2010 (Taipei, Taiwan)	Total KD: $N = 226$ (all complete KD)	Enterovirus, adenovirus, influenza A/B, parainfluenza type 3, rhinovirus, HMPV, coronavirus: viral culture, viral PCR
Turnier et al, 2015[8]	Retrospective cohort study	2009–2013 (Colorado, United States)	Total KD: $N = 222$; complete KD = 138 of 192; incomplete KD = 54 of 192	Adenovirus, coronavirus, HMPV, influenza A/B, parainfluenza, RSV, rhinovirus, enterovirus: viral respiratory PCR
Barone et al, 2000[14]	Retrospective cohort study	1996–1998 (New York, United States)	Total KD: $N = 36$; typical KD: $n = 23$; atypical KD[a]: $n = 13$	Adenovirus rapid DFA assay from nasopharyngeal secretions
Song et al, 2016[15]	Retrospective cohort study	2011–2012 (Columbus, Ohio, United States)	Total KD: $N = 68$; complete KD and incomplete KD: $n =$ unknown	Respiratory real-time PCR assays for adenovirus; influenza A/B; RSV; HMPV; parainfluenza viruses 1, 2, and 3; and rhinovirus/ enterovirus
Jaggi et al, 2016[16]	Prospective cohort study	2009–2011 (Ohio, United States)	Total $N = 57$; complete and incomplete KD: $n =$ unknown	Adenovirus: RT-PCR of throat or nasal swabs
Chang et al, 2006[17]	Prospective cohort study	2004–2005 (Taipei, Taiwan)	Total KD: $N = 53$; complete KD: 52; incomplete KD[a]: 1	Human coronavirus NL63 and New Haven strains RT-PCR of throat, nare, blood, and rectal specimens
Esper et al, 2005[18]	Retrospective case-control study	2001–2004 (Connecticut, United States)	Total KD: $N = 53$; complete KD: 10 of 11; incomplete KD[a]: 1 of 11	New Haven coronavirus RT-PCR
Huang et al, 2015[19]	Retrospective cohort study	2011–2013 (Guangzhou, China)	Total KD: $N = 1053$; comparisons made on $N = 45$ between viral KD and nonviral KD; complete KD and incomplete KD: $n =$ unknown	IgM serology for mycoplasma, *Chlamydia*, influenza A/B, adenovirus, RSV, EBV; IFA and pharyngeal PCR swab for influenza, adenovirus, RSV, enteric viruses; if diarrhea, rotavirus by RT-PCR and *Shigella* coagglutination assay
Jordan-Villegas et al, 2010[20]	Retrospective cohort study	1999–2008 (Texas, United States)	Total KD: $N = 394$; data reported on $N = 66$ (22 with viral KD matched with 44 nonviral KD); complete KD and incomplete KD: $n =$ unknown	RSV; parainfluenza types 1, 2 and 3; influenza A and B; adenovirus DFA and, if negative, viral culture sent
Lee et al, 2015[23]	Prospective cohort study	2010–2013 (Seoul, Korea)	Total KD: $N = 138$; complete KD and incomplete KD[b]: $n =$ unknown	Coronavirus; parainfluenza virus 1, 2, and 3; influenza A and B; RSV A and B; rhinovirus A/ B/C; HMPV; adenovirus; bocavirus: multiplex RT-PCR for respiratory viruses from nasopharyngeal secretions

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

TABLE 1 Continued

Source	Design	Time Period and Geographical Location	Sample Size	Type of Viruses and Tests Performed
Belay et al, 2005[24]	Retrospective case-control study	1999 (San Diego, California, United States)	Total KD: $N = 10$; all complete KD	Coronavirus New Haven and NL63 RT-PCR from pharyngeal swabs
Shike et al, 2005[25]	Prospective cohort study	2002–2004 (California, United States)	Total KD: $N = 70$; complete KD: $n = 52$; incomplete KD: $n = 18$	Adenovirus and adenovirus-associated viruses PCR from 2 specimens (throat, blood, urine), viral culture from nasopharynx, neutralization assay
Shimizu et al, 2005[26]	Prospective multicenter cohort study	2000–2005 (California, Illinois, United States; the Netherlands)	Total KD: $N = 48$; complete KD: $n =$ unknown; incomplete KD: $n =$ unknown	Coronavirus NL63 RT-PCR
Dominguez et al, 2006[27]	Retrospective case-control study	2004–2005 (Denver, Colorado, United States)	Total KD: $N = 30$; complete KD: 20 of 26; incomplete KD: 6 of 26	Coronavirus NL63 RT- PCR
Lehmann et al, 2009[28]	Prospective case-control study	2006–2008 (Southeastern Germany)	Total KD: $N = 21$; complete KD: $n = 12$; incomplete KD: $n = 9$	Coronavirus serology, bocavirus humoral responses by ELISA, bocavirus RT-PCR
Kim et al, 2012[29]	Prospective case-control study	2010–2011 (Seoul, Korea)	Total KD: $N = 55$; complete KD: $n = 48$; incomplete KD: $n = 7$	RSV A/B, adenovirus, rhinovirus, parainfluenza viruses 1 and 4, influenza A/B, HMPV, bocavirus, coronavirus, and enterovirus: RT-PCR of nasopharyngeal secretions
Bajolle et al, 2014[30]	Prospective cohort study	2006–2007 (Paris, France)	Total KD: $N = 32$ (all complete KD)	Bocavirus: PCR and viral load; adenovirus, RSV, influenza A and B, parainfluenza 1, 2, and 3: respiratory virus DFA

DFA, direct fluorescence antibody; ELISA, enzyme-linked immunosorbent assay; HMPV, human metapneumovirus; IFA, immunofluorescence assay; IgM, immunoglobulin M; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

[a] Diagnosis of incomplete KD was made by criteria other than AHA criteria (eg, expert opinion). These children were excluded from the qualitative and quantitative analysis.

positivity, it was uncertain whether the results were valid because of the small numbers of patients with the outcome in each group (viral versus nonviral) and the potential for unmeasured confounding factors.

Quality of Body of Evidence for Outcomes

We assessed the quality of the body of evidence for 4 outcomes: overall proportion of viral positivity, viral positivity for specific viruses, CAAs, and IVIG refractoriness (Supplemental Table 4). The starting level of the quality of evidence for all outcomes is low quality attributable to the body of evidence coming from observational studies. The outcome of overall viral positivity was downgraded by 1 point for risk of bias and upgraded by 1 point for the effect of plausible residual confounding. The risk of bias was because of testing not being performed on all study participants and potential for selection bias in who received a test. Additionally, many studies did not use broad viral panels, but rather focused on an individual virus, resulting in missing data for positivity of nontested viruses. We had attempted to mitigate this bias by only including studies with broad multiplex PCR panels in the analysis for overall viral prevalence. The effect of plausible residual confounding may be possible because tests were performed at the discretion of the physicians, and those who were tested might have had clinical symptoms consistent with the virus and those who not tested were less likely to be positive. If this is true, then the positivity prevalence of viruses could be higher in populations where there was selective testing than what would be seen if all children were tested. For the outcome of viral positivity for specific viruses, the quality of evidence was downgraded by 1 point for risk of bias for the same reasons as described for overall viral positivity. The final quality of evidence was very low. CAAs and IVIG refractory outcomes were downgraded by 1 point because of risk of bias from unmeasured confounding factors, such as initial adjunctive therapies received and characteristics of participants (eg, age), in several studies.

DISCUSSION

In this meta-analysis of viral coinfections in children with KD, we synthesized a large body of literature that included children with KD who were tested for viral pathogens. We found significant rates of viral positivity affecting approximately

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

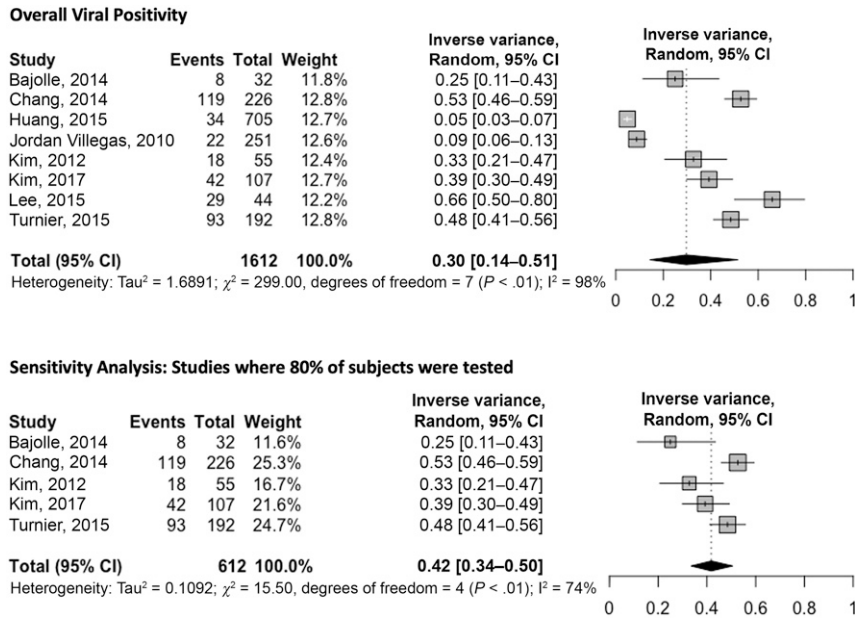

FIGURE 2 Overall viral positivity and sensitivity analysis. Studies were included if they utilized broad viral testing or a multiplex PCR test. Studies with <80% of patients tested were excluded in the sensitivity analysis. Estimates of positivity were calculated with a random effects analysis using an inverse variance method. IV, inverse variance.

one-third of children, though specific viral pathogens varied. From this data, we are unable to identify 1 predominant viral pathogen associated with KD. Further, we found that viral positivity is not associated with the proportion of children with CAAs or refractoriness to IVIG treatment, which may indicate that viral positivity has limited prognostic value in KD.

Although we cannot make causal claims on the basis of the observational data in this meta-analysis, our data could possibly be congruent with the hypothesis of many experts that viruses may serve as a trigger for KD in certain hosts given the substantial proportion of children with KD that tested positive. Given the absence of a predominant virus in our study, it is possible that multiple viruses may trigger KD. The question of whether multiple or single pathogens trigger KD is debated among experts. The argument to support a single pathogen mainly resides in the low recurrence rate of KD, which may be attributed to acquired immunity against the trigger in the host.[2] With the theory of a single pathogen, the varying presentations of KD are thought to be because of genetic variation in hosts. In fact, multisystem inflammatory syndrome in children lends credence to this theory because the inflammatory response to past severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection tends to vary among children despite the presence of a single causative pathogen.[21] However, on the flip side of the debate, the heterogeneity in KD presentations may be because of varying, multiple infectious triggers. The occurrence of KD in both hot and cold climates lends support to varying infectious triggers.[1] Our data, which represents 20 years of studies focused on identifying viral triggers for KD, also support the likelihood of multiple viruses being associated with KD.

More research is needed to identify whether a causal link is present between identified viruses and KD. One may question whether the identification of a concomitant virus is because of chance alone in children with 2 separate conditions, a viral infection and KD, at times of high community spread. A few case-control studies included in our meta-analysis compared viral positivity, using broad viral panel testing, in children with KD to controls without KD and found mixed results. Chang et al compared viral isolation via indirect fluorescent antibody testing and PCR for multiple viruses in children with KD and age-matched healthy controls with upper respiratory tract infection symptoms, and found that children with KD had higher positivity by both viral isolation (7.5% vs 2.2%) and by PCR (50% vs 16%).[7] Kim et al also looked at age-matched, healthy controls and viral positivity on the basis of a broad reverse transcription-PCR panel and found similar viral positivity in both groups (32% in KD and 30% in controls), with no significant difference between groups for any individual viruses.[22] Lee et al compared viral detection by PCR for children with KD and a febrile control group with respiratory symptoms and found a similar prevalence of viral detection (72% KD and 78% control), but positivity was higher for adenovirus in KD patients than controls. Controls had higher positivity for parainfluenza virus. No significant difference existed for viral detection of other viruses like coronavirus, respiratory syncytial virus, rhinovirus, metapneumovirus, and bocavirus.[23] Further large prospective studies are needed to examine the causal link between detected viruses and KD, and perhaps with use of blood and tissue samples, to retrieve evidence of the mechanistic link between detected viral infections and KD in children.

Although we did not find an association between viral positivity and the outcomes of CAAs or IVIG refractoriness, further studies are needed to determine whether specific viruses may mount a specific, more severe immune and inflammatory response that may be associated with severe KD, CAAs, and IVIG refractoriness. Researchers have recently identified heterogeneity in host immune responses in KD and postulate that 1 explanation may be that varying infectious triggers may cause different immune responses in hosts.[23] The immune response in KD has some overlap to response seen in viral and

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

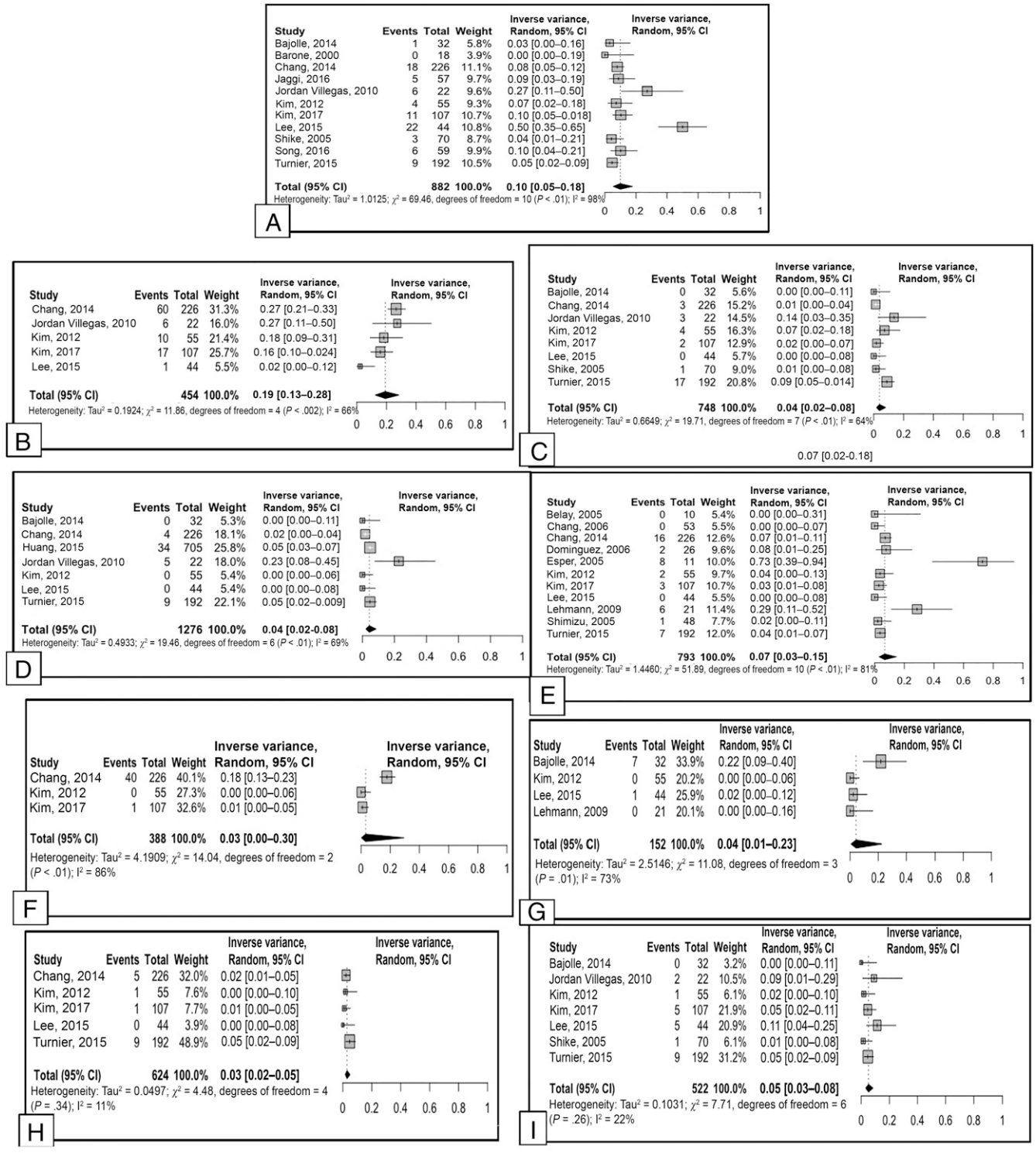

FIGURE 3 Combined estimates of viral positivity for specific viruses. All studies that tested for a particular virus had data for that virus included in the analysis.

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

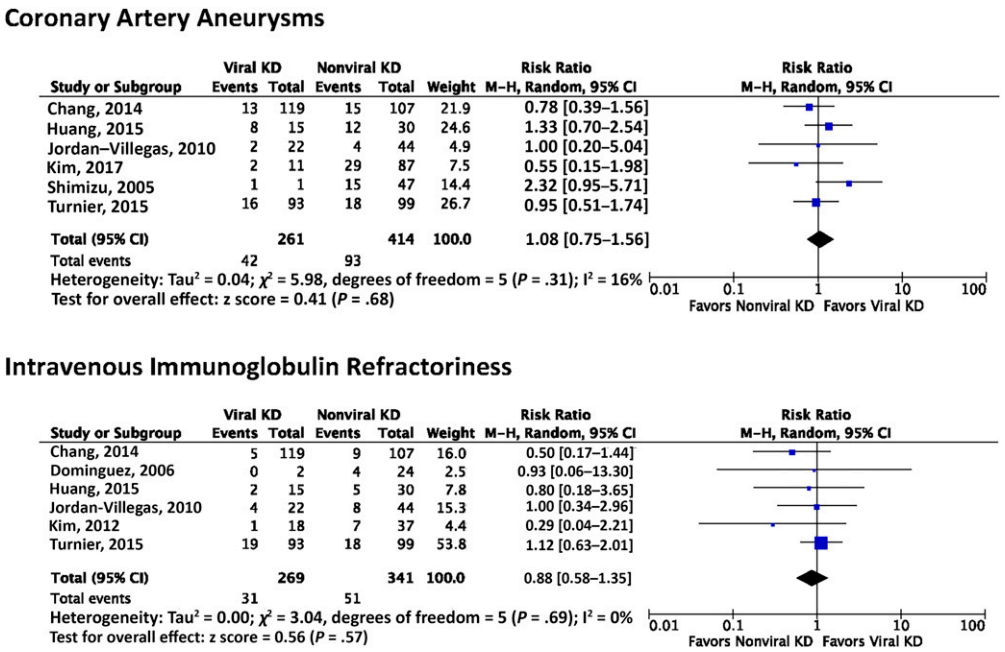

FIGURE 4 Viral positivity and patient outcomes of CAAs and IVIG refractoriness.

bacterial infections, but overall has several unique features. Identifying the viral trigger and specific inflammatory and immune responses associated with poor outcomes may aid in development and utilization of additional therapeutics for KD.

This meta-analysis has several strengths and limitations. As a strength, we designed the eligibility criteria for studies to overcome diagnostic ambiguity related to the diagnosis of KD in children by using the AHA criteria for complete KD as inclusion criteria. Additionally, in the analysis of the primary outcome, overall viral prevalence, we used studies with broad viral panels using multiplex PCR and performed a sensitivity analysis to address selection bias that could occur in selective viral testing. Nevertheless, PCR tests do come with limitations. The PCR viral panels may not be inclusive of all viruses, and especially novel viruses. Viral positivity rates for specific viruses were also quite variable (eg, ranging from 0% in 1 study to 50% in another study for adenovirus), which could be explained by seasonality, geographical location, and differences in populations tested. Additionally, positivity of a PCR could represent current or past infection because viral DNA can be detected even after resolution of the infection. Further, the meta-analysis was limited overall by the availability of low- or very low-quality evidence. However, the lower evidence quality ratings were primarily driven by a lower starting evidence quality level as determined with GRADE because of the observational study design of included studies, which are designs for examining viral prevalence. Furthermore, our findings for the overall prevalence of concomitant viral infections in children with KD and the prevalence of specific viruses is believable. Greater limitations reside in the outcomes of CAAs and IVIG refractoriness, which were measured in fewer studies and with variable definitions precluding inclusion of data from all studies where these outcomes were reported. Future prospectively designed studies may be helpful to further examine risk for CAAs on the basis of viral positivity. Last, this meta-analysis was completed before the onset of the COVID-19 pandemic, and therefore did not consider SARS-CoV-2 as a potential viral trigger nor how population behaviors and viral transmission during the pandemic impacted KD. Future studies on SARS-CoV-2 and multisystem inflammatory syndrome in children associated with COVID-19 may provide additional insight into what drives KD.

CONCLUSIONS

The rate of viral positivity in children with KD varies, on average, from 30% to 42% across populations. No single predominant virus was associated with KD. In aggregate, viral positivity does not appear to be associated with CAAs or IVIG refractoriness outcomes, though data were of low quality. Further large, multicenter, prospective studies utilizing broad viral testing may be beneficial to evaluate whether specific pathogen viral positivity in children with KD is associated with increased disease severity and poorer outcomes.

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

and Evaluation; Drs Lopez and Haq assisted with conceptualizing the study, conducted the literature search, screened titles and abstracts for potentially eligible studies, and designed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram; Ms Ouellette assisted with study design of search methods and conducted the literature search; Dr Ramirez assisted with conceptualizing the study and interpretation of the results; Dr Wallace conceptualized the study and provided guidance with study design, determined study eligibility based on full text review, extracted data from studies, appraised for bias, determined evidence quality for outcomes using Grading of Recommendations Assessment Development and Evaluation, conducted the analysis, and generated the figures; and all authors edited the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

This study is registered at Prospero, #CRD42018116668.

REFERENCES

1. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis*. 2018;21(1):16–19
2. Rife E, Gedalia A. Kawasaki disease: an update. *Curr Rheumatol Rep*. 2020; 22(10):75
3. Rowley AH. Is Kawasaki disease an infectious disorder? *Int J Rheum Dis*. 2018;21(1):20–25
4. Kumrah R, Vignesh P, Rawat A, Singh S. Immunogenetics of Kawasaki disease. *Clin Rev Allergy Immunol*. 2020;59(1):122–139
5. Burney JA, Roberts SC, DeHaan LL, et al. KIDCARE Study Investigators. Epidemiological and clinical features of Kawasaki disease during the COVID-19 pandemic in the United States. *JAMA Netw Open*. 2022;5(6):e2217436
6. Kim JH, Kang HR, Kim SY, Ban JE. Discrimination of Kawasaki disease with concomitant adenoviral detection differentiating from isolated adenoviral infection. *Korean J Pediatr*. 2018; 61(2):43–48
7. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc*. 2014; 113(3):148–154
8. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glodé MP, Dominguez SR. Concurrent respiratory viruses and Kawasaki disease. *Pediatrics*. 2015; 136(3):e609–e614
9. McCrindle BW, Rowley AH, Newburger JW, et al. American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927–e999
10. Viswanathan M, Berkman ND, Dryden DM, Hartling L. Assessing risk of bias and confounding in observational studies of interventions or exposures: further development of the RTI item bank. *AHRQ Publication No. 13-EHC106-EF*. Rockville, MD: Agency for Healthcare Research and Quality; 2013
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; 336(7650):924–926
12. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97–111
13. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013; 67(11):974–978
14. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: use of clinical features and a rapid direct fluorescent antigen test. *Arch Pediatr Adolesc Med*. 2000;154(5):453–456
15. Song E, Kajon AE, Wang H, et al. Clinical and virologic characteristics may aid distinction of acute adenovirus disease from Kawasaki disease with incidental adenovirus detection. *J Pediatr*. 2016; 170:325–330
16. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clin Infect Dis*. 2013;56(1):58–64
17. Chang LY, Chiang BL, Kao CL, et al. Kawasaki Disease Research Group. Lack of association between infection with a novel human coronavirus (HCoV), HCoV-NH, and Kawasaki disease in Taiwan. *J Infect Dis*. 2006;193(2):283–286
18. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005; 191(4):499–502
19. Huang X, Huang P, Zhang L, et al. Influenza infection and Kawasaki disease. *Rev Soc Bras Med Trop*. 2015;48(3):243–248
20. Jordan-Villegas A, Chang ML, Ramilo O, Mejías A. Concomitant respiratory viral infections in children with Kawasaki disease. *Pediatr Infect Dis J*. 2010; 29(8):770–772
21. Jackson H, Menikou S, Hamilton S, et al. On Behalf Of The Perform Consortium. Kawasaki disease patient stratification and pathway analysis based on host

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user

transcriptomic and proteomic profiles. *Int J Mol Sci*. 2021;22(11):5655

22. Kim JH, Yu JJ, Lee J, et al. Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease. *Korean J Pediatr*. 2012;55(12):470–473
23. Lee SB, Choi HS, Son S, Hong YM. Cardiac function in Kawasaki disease patients with respiratory symptoms. *Korean Circ J*. 2015;45(4):317–324
24. Belay E, Erdman D, Anderson L, et al. Kawasaki disease and human coronavirus. *J Infect Dis*. 2005;192(2): 352–353
25. Shike H, Shimizu C, Kanegaye J, et al. Adenovirus, adeno-associated virus and Kawasaki disease. *Pediatr Infect Dis J*. 2005;24(11):1011–1014
26. Shimizu C, Shike H, Baker S, et al. Human coronavirus NL63 is not detected in the respiratory tracts of children with acute kawasaki disease. *J Infect Dis*. 2005;192(10):1767–1771
27. Dominguez S, Anderson M, Glode M, et al. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki syndrome. *J Infect Dis*. 2006;194(12):1697–1701
28. Lehmann C, Klar R, Lindner J, Lindner P, Wolf H, Gerling S. Kawasaki disease lacks association with human coronavirus NL63 and human bocavirus. *Pediatr Infect Dis J*. 2009;28(6):553–554
29. Kim J, Yu J, Lee J, Kim M, Ko H, Choi H, Kim Y, Ko J. Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease. *Korean J Pediatr*. 2012;55(12):470
30. Bajolle F, Meritet J, Rozenberg F, et al. Markers of a recent bocavirus infection in children with Kawasaki disease: "A year prospective study." *Pathologie Biologie*. 2014;62(6):365–368

Downloaded from http://publications.aap.org/hospitalpediatrics/article-pdf/13/6/e153/1483751/hpeds.2023-007150.pdf
by HAM-TMC Library user