# Calculating the fraction of Kawasaki disease potentially attributable to seasonal pathogens: a time series analysis

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## Summary

**Background** Kawasaki disease is an acute, febrile, systemic vasculitis of children that primarily affects medium-sized blood vessels with a tropism for the coronary arteries. Although the etiological factors remain unknown, infections have been suggested as the trigger of Kawasaki disease. We sought to calculate the fraction of Kawasaki disease potentially attributable to seasonal infections.

**Methods** This cohort study used a population-based time series analysis from the French hospitalisation database (Programme de Médicalisation des Systèmes d'Information), which includes all inpatients admitted to any public or private hospital in France. We included all children aged 0–17 years hospitalised for Kawasaki disease in France over 13 years. The monthly incidence of Kawasaki disease per 10,000 children over time was analysed by a quasi-Poisson regression model. The model accounted for seasonality by using harmonic terms (a pair of sines and cosines with 12-month periods). The circulation of eight common seasonal pathogens (adenovirus, influenza, metapneumovirus, *Mycoplasma pneumoniae*, norovirus, rhinovirus, rotavirus, respiratory syncytial virus, and *Streptococcus pneumonia*) over the same period was included in the model to analyse the fraction of Kawasaki disease potentially attributable to each pathogen. Infections were identified on the basis of polymerase chain reaction or rapid antigen testing in hospital laboratories.

**Findings** Between Jan 1, 2007, and Dec 31, 2019, we included 10,337 children with Kawasaki disease and 442,762 children with the selected infectious diseases. In the Kawasaki disease cohort, the median age [IQR] was 2 [0–4] years, 6164 [59.6%] were boys. Adenovirus infection was potentially responsible for 24.4% [21.5–27.8] ($p < 0.001$) of Kawasaki diseases, Norovirus for 6.7% [1.3–11.2] ($p = 0.002$), and RSV 4.6% [1.2–7.8] ($p = 0.022$). Sensitivity analyses found similar results.

**Interpretation** This cohort study of data from a comprehensive national hospitalisation database indicated that approximately 35% of Kawasaki diseases was potentially attributable to seasonal infections.

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## Research in context

### Evidence before this study

The pathophysiology of Kawasaki disease remains unclear, although current data indicate that environmental factors, particularly infections, appear to be involved. Similar to what has been observed in post-SARS-Cov 2 associated multisystemic inflammatory syndrome in children, we can hypothesise that infections may contribute to the development of Kawasaki disease with some time lag. Using correlation analysis, a recent study showed that in South Korea, outbreaks of several viral infections precede Kawasaki disease outbreaks. Studies on the temporal association between seasonal infections and Kawasaki disease in the epidemiological context outside of Asia are currently lacking, and data to assess the fraction of Kawasaki disease potentially attributable to seasonal infections are not available. We aimed to address this knowledge gap.

### Added value of this study

In this cohort study from the national French hospitalisation national database, we included 10,337 children with Kawasaki disease and 445,528 with 8 selected seasonal infectious diseases over 13 years. Using a population-based time series analysis, we demonstrate that approximately one third of Kawasaki disease cases are potentially attributable to seasonal infection. The association with adenovirus was the strongest, followed by norovirus and respiratory syncytial virus.

### Implications of all the available evidence

Our results suggest that at least one third of Kawasaki diseases could be attributed to viral infections in Europe and support the role of an infectious trigger in the pathophysiology of Kawasaki disease. Close monitoring of infectious diseases may, to some extent, announce Kawasaki disease outbreaks.

## Introduction

Kawasaki disease is an acute febrile systemic childhood vasculitis that mainly affects medium-sized blood vessels with a tropism for the coronary arteries.[1] It is the leading cause of acquired paediatric cardiopathy in industrialised countries.[2] Though infectious, environmental, and genetic factors are thought to be involved, the pathophysiology and triggers of Kawasaki disease are not clearly understood.[2,3]

In the extra-tropical regions of the northern hemisphere, two seasonal peaks of Kawasaki disease have been observed, a larger one in winter and a smaller one in spring, and a few outbreaks have been observed in Japan, without clear cause.[4] A correlation between this bimodal seasonality and respiratory viruses has led to the speculation that viral infections may be the trigger for Kawasaki disease.[5–8] The co-occurrence of infection and Kawasaki disease is also well described, particularly for viral respiratory tract infection,[8] but no unique infectious trigger has been identified. The role of viral infections in the Kawasaki disease acute phase remains unclear[9] as patients with Kawasaki disease do not exhibit serological evidence of exposure to known viruses in comparison to match controls.[10]

During the COVID-19 pandemic, many cases of multisystemic inflammatory syndrome in children (MIS-C) following SARS-Cov-2 infection were reported in various countries.[11,12] This may provide important insights into the inflammatory process also observed in Kawasaki disease, suggesting that an infectious trigger may contribute to the pathogenesis of Kawasaki disease. Thus, establishing the link between viral infections and Kawasaki disease requires epidemiological studies using methodological approaches that remain sensitive when the two events occur with some time lag. Using time series analysis with a univariate model, a recent study showed that in South Korea, epidemics of several viral infections precede epidemics of Kawasaki disease.[13] However, studies assessing the temporal association between seasonal infections and Kawasaki disease outside Asia are currently lacking, and there is no data to assess the potentially attributable fraction of seasonal infections on Kawasaki disease.

We aimed to assess the evolution of Kawasaki disease incidence over time and to analyse the respective role of a range of pathogens in Kawasaki disease epidemiology.

## Methods

### Study design

We conducted a quasi-experimental, population-based, time-series analysis of patient data from a hospital-based French national surveillance system over 13 years (January 1, 2007–December 31, 2019). The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed to report this study.[14] Access to the database was requested from and approved by the National Commission on Information and Liberty. This study was conducted as part of an ongoing continuous mission of public health using anonymous aggregated data for public health

purposes. Therefore, our study did not require ethical committee approval or written informed consent based on guidelines in French law from the 2021 National Data Protection Act.

### Data sources

Data were extracted from the French National Hospitals Database (Programme de Médicalisation des Systèmes d'Information), which is a comprehensive national medico-administrative database which includes all inpatients admitted to any public or private hospital in France. The information recorded are anonymous and include demographic data, diagnoses related to the hospital stay, geographical location, and death. Diagnoses regarding the hospital stays are recorded according to the International Classification of Diseases, Tenth Revision (ICD-10).

### Study data and settings

We included all children aged 17 years or younger hospitalised for Kawasaki disease between January 1st, 2007, and December 31st, 2019. Kawasaki disease was defined as the ICD-10 discharge diagnosis code M303. All children aged 17 years or younger hospitalised for adenovirus, influenza, metapneumovirus, *Mycoplasma pneumoniae*, norovirus, rhinovirus, rotavirus, respiratory syncytial virus (RSV), and *Streptococcus pneumoniae* infection were also recorded. Infections were identified based on PCR or rapid antigen testing in hospital laboratories. During the study period, there were no changes of national guidelines for pathogens detection.

The details of ICD-10 diagnosis codes are presented in Supplementary Table S1. The following data were extracted for each inpatient stay: age, sex, date, and length of hospital stay, hospital ZIP code, and death. Data were aggregated to a monthly level and the age-specific French population demographics, obtained from the National Institute of Statistics and Economic Studies (INSEE), were used as the denominator to calculate the monthly incidence of Kawasaki disease and selected pathogens per 10,000 children.

### Outcomes

The main outcome was the monthly incidence of Kawasaki disease per 10,000 children aged 17 years or younger in France and the estimated fraction of Kawasaki disease attributable to the selected seasonal pathogens. The term "potentially attributable fraction" is an epidemiological term reflecting a temporal association between Kawasaki disease incidence and the pathogen epidemiology. The secondary outcomes were the monthly incidence of Kawasaki disease by age group (0–4 years, and 5–17 years).

### Statistical analysis

To quantify the temporal association between Kawasaki disease and the seasonal pathogens of interest, we calculated the potentially attributable fraction (PAF) of Kawasaki disease to each pathogen, by using a seasonally adjusted quasi-Poisson regression model.[15,16]

This model accounted for seasonality by using harmonic terms (a pair of sines and cosines with 12-month periods). Autocorrelation was accounted for using Newey–West's heteroscedasticity and autocorrelation consistent (HAC) covariance matrix estimators with appropriate lag. To account for possible long-term linear trends, we fitted time as a continuous variable with the number of months since the start of the study as the unit of measurement. The time unit set was 1 month.

We first modelled the Kawasaki disease incidence using the quasi-Poisson model including all pathogens as explanatory variables (adenovirus, influenza, metapneumovirus, *M. pneumoniae*, norovirus, rhinovirus, rotavirus, RSV, and *Streptococcus pneumonia*). Then, we estimated the expected incidence of Kawasaki disease if each pathogen was not present during the study period by using the same equation and set each pathogen term equal to zero. The PAF of Kawasaki disease to each pathogen (i.e., estimated amount of Kawasaki disease which can be attributed to each pathogen) was calculated as the percentage change between Kawasaki disease incidence fitted by the model and the predicted Kawasaki disease incidence with each pathogen set to zero, for each time point of the study period. The 95% confidence intervals (CI) were calculated using seasonal block bootstraps with 10,000 replicates.

We performed four sensitivity analyses to assess the robustness of the study findings: (1) a negative-binomial regression model instead of the quasi-Poisson model; (2) an auto-regressive Integrated Moving Average (ARIMA) model; (3) a quasi-Poisson regression model without the harmonic parameter; and (4) a trigonometric quasi-Poisson regression with the monthly counts of the outcomes of interest instead of the incidences.

All analyses were performed using R language (4.0.2 version) in RStudio Desktop (1.3.1093 version).

### Role of the funding source

No funding was received for this work.

## Results

Between Jan 1, 2007, and Dec 31, 2019, we included 10,337 children with Kawasaki disease. Median age [IQR] was 2 [0–4] years, with 6164 [59.6%] boys. The Median [IQR] length of stay was 5 [3–7] days. Among patients with Kawasaki disease, 4 (0.04%) children died. The characteristics of children hospitalised for Kawasaki disease are detailed in Table 1. Kawasaki disease course showed a seasonal pattern with a higher incidence from December to March (Supplementary Figure S1). During the same period, 445,528 children with the selected infectious diseases were included. The respective infection rates of each infection are detailed in Table 2. The

| | Participants (n = 10,337) |
|---|---|
| Sex, n | |
| Male | 6164 (59.6%) |
| Female | 4173 (40.4%) |
| Age, years | |
| Median [Q1-Q3] | 2 [0–4] |
| Min-max range | 0–17 |
| Age subgroups, n | |
| 0–4 years old | 8411 (81.4%) |
| 5–17 years old | 1926 (18.6%) |
| Length of stay, days | |
| Median [Q1-Q3] | 5 [3–7] |
| Mean [SD] | 5.3 (4.1) |
| Min-max range | 0–139 |
| Deaths, n | 4 (0.04%) |

Data are n (%) unless otherwise stated. Abbreviations: Q1-Q3, first and third quartiles. SD, standard deviation.

***Table 1:*** **Baseline characteristics of children hospitalised with Kawasaki disease over the study period (Jan 2007 to Dec 2022).**

evolution of Kawasaki disease and the selected pathogens incidence over the study period is illustrated in Supplementary Figure S2.

Using the seasonally adjusted quasi-Poisson multivariate regression model, the fraction of Kawasaki diseases potentially attributable to adenovirus was 24.4% (95% CI 21.5–27.8; $p < 0.001$), to norovirus 6.7% (95% CI 1.3–11.2; $p = 0.002$), and to RSV 4.6% (95% CI 1.2–7.8; $p = 0.02$) (Fig. 1, Table 3). No association was found for rhinovirus, influenza, metapneumovirus, and *S. pneumoniae* (Table 3). Due to multicollinearity, *M. pneumoniae* was not included in the multivariate model. The four sensitivity analyses showed similar results (Supplementary Table S2).

Similar results were retrieved in the subgroup of children younger than 5 years (Table 4), while no significant temporal association was found between Kawasaki disease incidence and any pathogen in the subgroup of patients aged 5–17 years (Table 4).

Finally, we performed the analysis with two lag options, 1 month and 2 months. The parameters of the model were similar for a lag of 0 (QAIC 673.61), 1 month (QAIC 668.27) and 2 months (QAIC 666.95).

| | Number of cases (n = 445,528) |
|---|---|
| RSV bronchiolitis and pneumopathy | 214,751 (48.2%) |
| Rotavirus gastroenteritis | 162,753 (36.5%) |
| Adenovirus gastroenteritis and pneumopathy | 17,818 (4.0%) |
| Influenza infection | 16,531 (3.7%) |
| *Streptococcus pneumoniae* pneumopathy | 14,294 (3.2%) |
| *Mycoplasma pneumoniae* pneumopathy | 12,288 (2.8%) |
| Metapneumovirus bronchiolitis | 2860 (0.6%) |
| Rhinovirus acute bronchitis | 2285 (0.5%) |
| Norovirus gastroenteritis | 1948 (0.4%) |

Data are n (%). Abbreviations: RSV, respiratory syncytial virus.

***Table 2:*** **Infectious diseases cohort: number of cases in 0–17 years old children, during the overall period.**

## Discussion

Our study demonstrated a temporal association between epidemics of adenovirus, norovirus, and RSV, with the occurrence of Kawasaki disease, suggesting that the onset of approximately one third of Kawasaki disease cases may be attributable to one of these viruses. To our knowledge, this is the first time-series analysis investigating the temporal association between infections and Kawasaki disease in Europe and establishing their respective potentially attributable fractions.

To date, very few studies have assessed the temporal relationship between Kawasaki disease and infections. Two pioneering studies were recently conducted in South Korea.[13,17] Similarly to our study, the authors used a national database to conduct a time-series analysis of correlation between viral infections and Kawasaki disease. The authors showed that the onset of Kawasaki disease was correlated with various infections that preceded the onset of Kawasaki disease with a lag of 1–3 months. In the article by Kang et al., calculating the Pearson correlation of 14 pathogens and Kawasaki disease, significant strong correlations were identified for varicella ($r = 0.7$; $p < 0.001$), RSV ($r = 0.5$, $p < 0.001$), adenovirus ($r = 0.5$; $p < 0.001$), coronavirus ($r = 0.5$; $p < 0.001$), norovirus ($r = 0.5$; $p < 0.001$), and lower correlations regarding influenza virus ($r = 0.4$; $p < 0.004$), scarlet fever (0.4; $p < 0.01$), parainfluenza virus ($r = 0.3$; $p < 0.02$), rhinovirus ($r = 0.3$; $p < 0.01$), and mumps ($r = 0.3$; $p < 0.01$). The statistical approaches differ between this study and ours. The first performed a univariate correlation analysis, whereas we used a multivariate time-series model, allowing for a stricter association and estimating the potentially attributable fraction of respective infections. However, it should be noted that the infectious agents identified in our study in France, namely adenovirus, norovirus, and RSV, were also in the highly correlated group in the South Korean study. Thus, despite epidemiologic and geographic disparities, these two studies together provide evidence of the crucial role of pathogens in the development of Kawasaki disease.

The strongest association with Kawasaki disease was found for adenovirus infection, with a 24.4% estimated PAF. This finding is compatible with the important role, although debated,[18] of adenovirus for the development of Kawasaki disease found in the literature.[18,19] Indeed, adenovirus has been detected in 8% of patients presenting with Kawasaki disease in a cohort study from Taiwan.[20] Fukuda et al. described simultaneous complete Kawasaki disease in the immediate aftermaths of

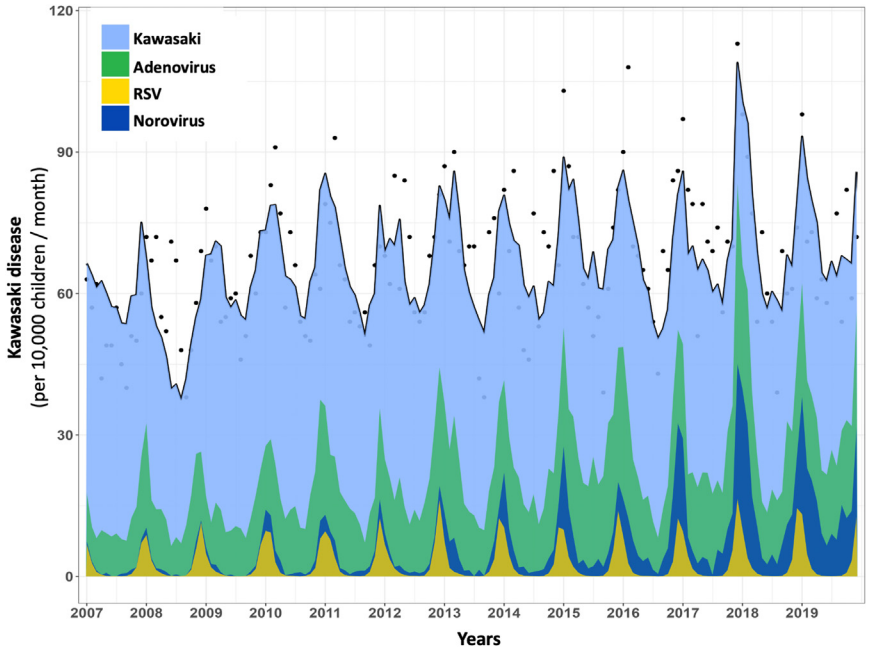


***Fig. 1:*** Temporal association of the monthly incidence of Kawasaki disease per 10,000 Children aged <18 years with the circulation of adenovirus, RSV, and norovirus in France (Jan 2007–Dec 2019). The black dots represent the observed data. The light blue curve indicates the estimated monthly incidence of Kawasaki disease per 10,000 children aged under 18 years over time using the seasonally adjusted quasi-Poisson regression model. The potentially attributable fractions (expressed in percentage) of Kawasaki diseases to adenovirus (green), RSV (yellow), and norovirus (dark blue), adjusted by the monthly incidence of each pathogen for each time point of study period (to account for variability of pathogen circulation), were calculated using the same quasi-Poisson regression model. Abbreviations: RSV, respiratory syncytial virus.

documented infection in two monozygotic twins, suggesting a genetic susceptibility to this microorganism.[21] As adenovirus is well known to mimic Kawasaki disease,[22] the conclusion of current studies have often been limited by the fact that, although clinical, biological criteria and even gene transcripts could be used to distinguish the two entities, differentiation between adenovirus infection and Kawasaki disease or concomitant diseases can be difficult.[23–25] The temporal association of adenovirus with Kawasaki disease has been recently reported[13] but the optimal lag and its imputability in the pathophysiology of Kawasaki disease are not well established. Our findings are in line with the temporal association between adenovirus and Kawasaki disease that has recently been suggested in a population-based cohort study in Taiwan, which estimated the Kawasaki disease incidence 5 times higher after adenovirus exposure compared to other infections.[26] Overall, the data from our study and from the literature corroborate a crucial triggering role of adenovirus infection in the pathophysiology of Kawasaki disease.

To a lesser extent, norovirus and RSV potentially explain 6.7% and 4.6% of Kawasaki disease, respectively. Publications on these associations are scarce and have been carried out mainly in Korea. Lim et al. found that norovirus infection could be associated with Kawasaki disease incidence, 1-to-2-months later,[17] whereas the study by Kang et al. found a positive correlation between norovirus and Kawasaki disease, but did not identify a clear time lag.[13] Both studies found an association between preceding RSV infection and Kawasaki disease.[13,17] Thus, the current data support the hypothesis that RSV and norovirus may be triggers of Kawasaki disease, which appears reasonably robust, as evidenced by geographically and ethnically different populations.

In our study, subpopulation analyses showed that the association between infections and Kawasaki disease

| | PAF | 95% CI | p value |
|---|---|---|---|
| Adenovirus | 0.244 | [0.215–0.278] | **<0.001** |
| Influenza | 0.011 | [−0.025 to 0.045] | 0.372 |
| Metapneumovirus | −0.005 | [−0.043 to 0.031] | 0.805 |
| Norovirus | 0.067 | [0.013–0.112] | **0.002** |
| *S. pneumoniae* | 0.056 | [0.021–0.092] | 0.080 |
| Rhinovirus | −0.038 | [0.077–0.001] | 0.286 |
| Rotavirus | 0.046 | [0.012–0.082] | 0.126 |
| RSV | 0.046 | [0.012–0.078] | **0.022** |

Abbreviations: PAF, potentially attributable fraction; RSV, respiratory syncytial virus.

***Table 3:*** **Estimated fractions of Kawasaki disease potentially attributable to pathogens, analysed by a trigonometric quasi-Poisson multivariate model.**

| | 0–4 years | | | 5–17 years | | |
|---|---|---|---|---|---|---|
| | PAF | 95% CI | p value | PAF | 95% CI | p value |
| Adenovirus | 0.161 | [0.119–0.204] | **0.009** | −0.035 | [−0.088 to 0.014] | 0.557 |
| Influenza | 0.001 | [−0.063 to 0.060] | 0.952 | 0.011 | [−0.035 to 0.057] | 0.539 |
| Metapneumovirus | −0.010 | [−0.078 to 0.051] | 0.607 | 0.012 | [−0.033 to 0.055] | 0.243 |
| Norovirus | 0.055 | [0.005–0.097] | **0.011** | −0.029 | [−0.087 to 0.031] | 0.310 |
| *S pneumoniae* | 0.018 | [−0.048 to 0.080] | 0.575 | 0.000 | [−0.049 to 0.047] | 0.999 |
| Rhinovirus | −0.052 | [−0.128 to 0.019] | 0.121 | 0.012 | [−0.034 to 0.056] | 0.670 |
| Rotavirus | 0.010 | [−0.053 to 0.069] | 0.744 | −0.033 | [−0.087 to 0.018] | 0.594 |
| RSV | 0.040 | [−0.016 to 0.094] | **0.048** | −0.042 | [−0.092 to 0.009] | 0.082 |

For the 0–4 years group: n = 8411 for Kawasaki disease, n = 420,385 for infections. For the 5–17 years group: n = 1926 for Kawasaki disease, n = 25,143 for infections. Abbreviations: PAF, potentially attributable fraction; RSV, respiratory syncytial virus.

***Table 4:*** **Estimation of each infection potentially attributable fraction on Kawasaki disease occurrence, by age sub-groups (0–4 years and 5–17 years, inclusive) using the trigonometric multivariate quasi-Poisson model.**

was higher in children aged younger than 5 years, whereas no association was found in children aged 5 years or older. These results are consistent with observations from the study by Lim et al.[17] which used the Granger causality test between time series of Kawasaki disease diagnosis and the time points of positive virus detection rates, which also found a temporal association of viruses (RSV, rhinovirus, norovirus, and rotavirus) in patients up to 5 years of age. No association was found in children aged 5 years and older. Additionally, in the Hang et al. study, the increased Kawasaki disease risk was associated with previous adenovirus infection, especially in children aged 3–5 years.[26] These results need to be taken with some caution due to the reduced statistical power due to small sample sizes in the group of patients with Kawasaki disease over 5 years of age in both ours (n = 1926) and in the Korean study (n = 1105),[13] compared to the groups of patients aged 4 years and under (n = 8411 and n = 15,635, respectively). Nevertheless, these findings highlight the possibility that viral infections may be a valid mechanism for triggering Kawasaki disease, especially in young children, who had no contact with the triggering virus yet or have developed little immune education to specific viruses during their lives.

Kawasaki disease pathophysiology remains unclear as genetic, immune, and environmental factors are intricated.[2] Since the early description of Kawasaki disease, infectious stimuli have been studied[27] with the influence of seasonality and Covid-19 pandemic social distancing on disease onset has been observed.[4,5,13] At the individual level, the Kawasaki disease outbreak is preceded by an infectious episode in about 56–83% of cases,[28] and concomitant viral infections in Kawasaki disease have been detected in 7.5–50% of cases, depending on the identification technique.[8,20] Our study showed that approximately one third of Kawasaki disease cases can be attributed to the fraction of viruses studied. Although this already represents a significant fraction and the inclusion of other viruses may increase this fraction, it seems unlikely that all Kawasaki disease cases could be attributed to viral infections. It is therefore possible that in addition to viruses, some Kawasaki disease may be triggered by other unidentified factors, and that local epidemiology, several types of immunisation depending on the maturity of the immune system, and the genetic background of the host must be considered.[29,30]

The strengths and originality of our study are as follows. First, it focused on the viral epidemiology of northern Europe during an extended 13-year pre-pandemic period and considers a large and comprehensive dataset. Second, the calculation of the estimated PAF allowed us to determine that one third of Kawasaki diseases occurrences could be caused by seasonal infections. These results were reinforced by several sensitivity tests which supported the robustness of the results.

Our study also had several limitations. First, we used a hospital-based surveillance system to assess the circulation of pathogens in children over time, which may not be exhaustive. However, it has previously been shown that hospital admission rates for viral respiratory infections in children were correlated with data from ambulatory observatories and laboratory-based surveillance networks in France.[15,31]

Second, the analysis was based on a French nationwide surveillance dataset and is therefore limited to a single European country. Third, the term "potentially attributable fraction" is an epidemiological term reflecting a temporal association between Kawasaki disease incidence and the pathogen epidemiology but does not assert a definitive causal relationship. Fourth, in this study, we focused on frequent infectious agents with a seasonal pattern and selected the most likely candidate infections based on published data Kang et al.[13] and Lim et al.[17] We cannot exclude that other infectious agents may also contribute to the incidence of Kawasaki disease, which would lead to an underestimation of the fraction of Kawasaki diseases attributable

to infectious agents. Fifth, due to the wide confidence intervals, PAF estimations should be interpreted with caution. Lastly, the nature of our data did not allow us to distinguish between complete and incomplete forms of Kawasaki disease, neither to establish whether a specific clinical phenotype, particularly concerning coronary involvement or severity, could be associated to the identified infections compared to Kawasaki disease independent of them.

Our results pave the way for the possibility that close monitoring of infectious diseases may, to some extent, predict Kawasaki disease outbreaks. However, it should be noted that the results provided in our study reflect the attributable fractions of viral infections on Kawasaki disease during the pre-pandemic era of COVID-19. Since the onset of the pandemic, the decrease in respiratory infections and priming of the immune system in young children due to increased barrier measures may have affected immune susceptibility to viral infections, which could secondarily result in a change of the immune responses that lead to the development of Kawasaki disease in exposed susceptible individuals. It is therefore difficult to predict the future Kawasaki disease epidemiology and how the link between Kawasaki disease and seasonal pathogens will be influenced after the redesign by the legacy of the COVID-19 pandemic.

This time-series cohort study on Kawasaki disease and common epidemic infectious diseases established their strong temporal association in about one third of Kawasaki disease cases. Adenovirus was the strongest trigger. These results provide a deeper appreciation association between seasonal infectious and Kawasaki disease.

#### Contributors

ZV, NA, FK, and UM designed the study. ALU, NO, and UM wrote the initial version of the manuscript. ZV, PB, and NO performed the statistical analyses. ZV, ALU, NO, CB, PB, CD, AFe, AFa, IM, FK, and UM analysed and interpreted the data and drafted the article. ZV, NO and UM accessed and verified the underlying data. All authors revised and approved the manuscript.

#### Data sharing statement

Individual participant data required to reach aims in an approved proposal, after de-identification, will be made available to investigators whose proposed use of the data has been approved by the study's Executive Committee. Proposals may be submitted up to 36 months after article publication and should be directed to ulrich.meinzer@aphp.fr.

#### Declaration of interests

We declare no competing interests.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102078.

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