



HAL
open science

Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis

Naim Ouldali, Marie Pouletty, Patricia Mariani, Constance Beyler, Audrey Blachier, Stephane Bonacorsi, Kostas Danis, Maryline Chomton, Laure Maurice, Fleur Le Bourgeois, et al.

► To cite this version:

Naim Ouldali, Marie Pouletty, Patricia Mariani, Constance Beyler, Audrey Blachier, et al.. Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis. *The Lancet Child & Adolescent Health*, 2020, 4, pp.662 - 668. 10.1016/S2352-4642(20)30175-9 . hal-03492277

HAL Id: hal-03492277

<https://hal.science/hal-03492277>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Emergence of Kawasaki disease related to SARS-CoV-2 infection in children, a time-**
2 **series analysis**

3
4 Naim Ouldali, MD, PhD^{1,2,3,4}; Marie Pouletty, MD^{1,4}; Patricia Mariani, MD^{4,5}; Constance
5 Beyler, MD⁶; Audrey Blachier, MD⁷; Stephane Bonacorsi MD, PhD^{4,5,8}; Kostas Danis, PhD⁹;
6 Maryline Chomton, MD¹⁰; Laure Maurice, MD¹⁰; Fleur Le Bourgeois, MD¹⁰; Marion Caseris
7 MD^{1,5}; Jean Gaschignard, MD, PhD^{1,4,8}; Julie Poline, MD^{1,11}; Robert Cohen, MD⁴; Luigi
8 Titomanlio, MD, PhD^{4,12}; Albert Faye MD, PhD^{1,2,4}; Isabelle Melki, MD, PhD^{1,13,14}; Ulrich
9 Meinzer MD, PhD^{1,4,11,15}

10
11 **Authors affiliations:**

12 ¹ Department of General Pediatrics, Pediatric Internal Medicine, Rheumatology and
13 Infectious Diseases, National Referee Centre for Rare Pediatric Inflammatory Rheumatisms
14 and Systemic Auto-immune diseases RAISE, Robert Debré University Hospital, Assistance
15 Publique-Hôpitaux de Paris, Paris, France

16 ² Université de Paris, INSERM UMR 1123, ECEVE, Paris, France

17 ³ ACTIV, Association Clinique et Thérapeutique Infantile du Val-de-Marne, Créteil, France

18 ⁴ Université de Paris, UFR de Médecine Paris Nord, 75010 Paris, France

19 ⁵ Department of Microbiology, Robert Debré University Hospital, Assistance Publique-
20 Hôpitaux de Paris, Paris, France

21 ⁶ Department of Pediatric Cardiology, Robert Debré University Hospital, Assistance Publique-
22 Hôpitaux de Paris, Paris, France

23 ⁷ Department of Medical Information, Robert Debré University Hospital, Assistance Publique-
24 Hôpitaux de Paris, Paris, France

25 ⁸ Université de Paris, IAME, INSERM UMR1137, Paris, France.

26 ⁹ Santé publique France, French national public health agency, Saint Maurice, France

27 ¹⁰ Pediatric intensive care unit, Robert Debré University Hospital, Assistance Publique-
28 Hôpitaux de Paris, Paris, France

29 ¹¹ Center for Research on Inflammation, INSERM, UMR1149, Paris, France.

30 ¹² Department of Pediatric Emergency Care, Assistance Publique Hôpitaux (APHP) Hospital
31 Robert Debré, Paris, France

32 ¹³ Laboratory of Neurogenetics and Neuroinflammation, Imagine Institute, Paris, France

33 ¹⁴ Pediatric Hematology-Immunology and Rheumatology Department, Hôpital Necker-Enfants
34 Malades, AP-HP, Paris, France, Referee center for Rheumatic, AutoImmune and Systemic
35 diseases in children (RAISE)

36 ¹⁵ Biology and Genetics of Bacterial Cell Wall Unit, Pasteur Institute, Paris, France

37

38

39 **Emails of authors:** naim.ouldali@aphp.fr; marie.pouletty@aphp.fr;
40 partricia.mariani@aphp.fr; constance.beyler@aphp.fr; audrey.blachier@aphp.fr;
41 stephane.boncarsi@aphp.fr; daniscostas@gmail.com; maryline.chomton@aphp.fr;
42 laure.maurice@aphp.fr; fleur.lebourgeois@aphp.fr; marion.caseris@aphp.fr;
43 jean.gaschignard@aphp.fr; juliepoline@gmail.com; robert.cohen@wanadoo.fr;
44 luigi.titomanlio@aphp.fr; albert.faye@aphp.fr; isabelle.melki@aphp.fr;
45 ulrich.meinzer@aphp.fr;

46

47 **Corresponding author:** Ulrich Meinzer, MD, PhD, Department of General Pediatrics,
48 Pediatric Internal Medicine, Rheumatology and Infectious Diseases, Reference Centre for
49 Rare Pediatric Inflammatory Rheumatism and Systemic Auto-immune diseases RAISE,
50 Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, F-75019 Paris,
51 France Tel.: xx-33-1-40.03.20.48; Fax: xx-33-1-40.03.20.43; Email: ulrich.meinzer@aphp.fr

52

53 **Contributors:** UM and NO designed the study. NO, MP, PM, CB, AB, SB, KD, MC, LM, FLB,
54 MC, JG, JP, RC, LT, AF, IM and UM analysed and interpreted the data and drafted the
55 article. NO and MP performed the statistical analysis. SB and PM performed the
56 microbiological analysis. All authors revised and approved the manuscript.

57

58 **Funding:** French National Research Agency ANR-16-CE17-0009 to U.M.

59

60 **Declaration of interests:** All authors: none to declare.

61

62 **Acknowledgement:** None

63

64

65

66

67 **Panel: Research in context**

68 **Evidence before this study**

69 The rapid spread of COVID-19 caused by SARS-CoV-2 has led to a global pandemic. In
70 recent weeks physicians from several countries had the impression the number of children
71 with multi system inflammatory symptoms, including Kawasaki disease (KD) were increasing.
72 This led to alerts by several health authorities in Europe and North America.

73 PubMed research for articles using the terms “Kawasaki disease” AND “coronavirus” OR
74 “COVID-19” OR “virus involvement” OR “SARS-CoV-2”, performed the 31st of May 2020,
75 identified scattered case reports and an observational cohort study from Italy.

76 Moreover, in the literature it has been suggested that viral infections could be the trigger of
77 KD. Thus, there is an urgent need for epidemiological studies to enlighten the potential link
78 between SARS-CoV-2 and the emergence of KD.

79 **Added value of this study**

80 We conducted a time series analysis based on a prospective surveillance of KD in a French
81 tertiary paediatric centre, located in an epicentre of the current COVID-19 outbreak, over the
82 past years. We found an important increase of Kawasaki disease during the COVID19
83 pandemic. During this period, the circulation of all other respiratory viruses experienced an
84 unprecedented drop since the national lockdown. Our observations strengthen the
85 persuasion that there is an association between SARS-CoV-2 infection and KD. Interestingly,
86 a second significant peak of KD was observed in December 2009, in the context of major
87 H1N1 pandemic. This study is novel from using a time series analysis of KD over a 15-year
88 period and the concurrent determination of other viral investigations during the COVID-19
89 pandemic period.

90

91 **Implications of all the available evidence**

92 The ongoing SARS-CoV-2 pandemic is followed by a rapid emergence of KD, shattering the
93 idea that children do not develop severe forms of COVID-19. This rise, mirrors with a second
94 peak of KD occurring after the H1N1 major pandemic, providing unique evidence of the role
95 of viral infections in triggering KD. Physicians should prepare to manage an increase of KD,
96 depending on the local COVID-19 outbreak magnitude.

97

98

99

100

101

102

103

104 **Abstract:**

105

106 **Background:** Kawasaki disease (KD) is an acute febrile systemic childhood vasculitis which
107 has been known to be triggered by respiratory viral infections. Here, we examined whether
108 the ongoing COVID-19 epidemic is associated with an increase of Kawasaki disease.

109 **Methods:** We conducted a quasi-experimental interrupted time series analysis over the last
110 15 years in a tertiary center in a French epicenter of COVID-19. The main outcome was the
111 number of KD cases over time, estimated by quasi-Poisson regression. In the same center,
112 we described the evolution (2005-2020) of hospital admissions from the emergency
113 department and the evolution of the respiratory pathogens identified by nasopharyngeal
114 multiplex PCR (2017-2020). These data were compared with the evolution of daily
115 admissions due to confirmed COVID-19 in the same region, recorded by Public Health
116 France.

117 **Findings:** We included 230 patients with KD. On April 2020, we identified a rapid emergence
118 of KD related to SARS-CoV-2 (+497% increase, 95% CI [+72; +1082], $p=0.0011$), starting
119 two weeks after the peak of the COVID-19 epidemic. SARS-CoV-2 was the only virus
120 circulating at high levels during this period, and was found in 80% (8/10, SARS-CoV-2
121 positive PCR or serology) of KD patients since April 15th. A second peak of KD
122 hospitalizations was observed in December 2009 (+365% increase, 95% CI [+31; +719],
123 $p=0.0053$), concomitant with the influenza A (H1N1) pandemic.

124 **Interpretation:** Health care providers should be prepared to manage an increased surge of
125 patients with severe KD, particularly in countries where the peak of COVID-19 has just been
126 reached.

127 **Funding:** French National Research Agency ANR-16-CE17-0009.

128

129 **Introduction:**

130

131 The rapid spread of Coronavirus disease 2019 (COVID-19) caused by Severe Acute
132 Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has led to a global pandemic.¹ The
133 pediatric population appears to be much less affected than adults with less than 3% of
134 reported cases under 20 years of age.¹ To a recent date available data suggested that
135 compared with adult patients, pediatric patients have milder symptoms and a better
136 prognosis.^{2,3}

137

138 In recent weeks, physicians from several countries had the impression that the numbers of
139 children with multi system inflammatory symptoms, including Kawasaki disease (KD) and
140 features of shock with intensive care unit admissions were increasing.⁴ This led to alerts by
141 several health authorities in Europe and North America.^{5,6} A link between Covid-19 and KD
142 has been suggested by scattered case reports⁷⁻⁹ and a very recent observational cohort
143 study reported an outbreak of severe Kawasaki-like disease at the Italian epicenter of the
144 SARS-CoV-2 epidemic.¹⁰ Acute heart failure in multisystem inflammatory syndrome in the
145 context of SARS-CoV-2 has also been reported in a multicenter cohort.¹¹ It is currently not
146 known whether these various manifestations should be considered as the clinical spectrum
147 of a novel disease or as an association of various suspected post infectious diseases
148 triggered by SARS-CoV-2. As this increase of KD related to COVID-19 needs to be
149 confirmed by epidemiological data and longitudinal analysis, we undertook a study focusing
150 on patients fulfilling the established diagnostic criteria of KD.

151

152 KD is an acute febrile systemic childhood vasculitis that affects medium and small-sized
153 blood vessels with a coronary artery tropism.^{12,13} It is one of the leading causes of acquired
154 heart disease in industrialized countries.^{12,13} There is no specific test to confirm the
155 diagnosis. The diagnosis of KD is based on internationally accepted clinical criteria^{14,15},
156 combining a fever lasting five days or more with at least four of the following clinical signs:

157 bilateral conjunctival injection, changes affecting the lips and oral cavity (inflammation of the
158 oral and pharyngeal mucosa), polymorphic exanthema, changes in the peripheral extremities
159 or perineal area, and cervical lymphadenopathy ≥ 15 mm. Patients who meet the case
160 definition based on principal clinical findings are said to have complete KD. Patients who do
161 not have sufficient principal clinical findings may be diagnosed with incomplete KD.

162

163 The cause of KD disease remains unknown.¹⁶ Regions of the extratropical northern
164 hemisphere experience two seasonal peaks in winter and spring and some outbreaks have
165 been observed in Japan, even if no clear cause has been underlined.¹⁷ A correlation
166 between this bimodal seasonality and viruses such as influenza, RSV in winter and
167 enterovirus in summer has been suggested.¹⁸⁻²⁰ This has led to the speculation that viral
168 infections could be the trigger of KD. To date, it is unknown whether SARS-CoV-2 can lead
169 to KD.

170

171 Here, we examined whether the outbreak of COVID-19 is associated with an increase of KD
172 in a tertiary hospital in the French epicenter of COVID-19.

173

174

175 **Methods:**

176

177 We conducted a quasi-experimental interrupted time series analysis based on data
178 prospectively collected of all KD patients admitted over the past 15 years to a tertiary center,
179 Robert Debré University Hospital, in Paris, France. This center is a pediatric hospital that
180 mainly receives patients from the north and north-eastern part of Paris and its region, which
181 has been one of the epicenters of COVID-19 epidemic in France
182 (www.santepubliquefrance.fr). Robert Debré Hospital provides pediatric care support and
183 retrieval to approximately 2 million inhabitants and the proportion of children remained stable
184 over the study period (www.insee.fr). Referring hospitals and patient orientation to Robert
185 Debré Hospital remained unchanged during the observation period and during the COVID-19
186 epidemic.

187

188 We recorded the number of patients diagnosed with KD using the validated diagnostic
189 criteria¹⁵ from 2005 to 2020. Patients for whom another diagnosis was confirmed during the
190 follow-up were excluded. For each patient, demographic and clinical data were recorded. All
191 collected data was anonymous. This study followed national ethic guidelines and has been
192 approved by French data protection authorities (CNIL/No.2014908 & No1980120).
193 Furthermore, we recorded the number of hospital admissions of pediatric patients from the
194 emergency department in the same center between January 2017 and April 2020. The
195 results of the respiratory pathogens identified by multiplex nasopharyngeal PCR over the
196 period between January 2017 and April 2020 were also filed. These time-series were
197 compared with the evolution of daily admissions due to confirmed COVID-19 in the same
198 region, recorded by Public Health France (www.santepubliquefrance.fr).

199

200 The main outcome was the monthly number of KD cases over the study period. Secondary
201 outcomes were the number of hospital admissions following pediatric emergency department
202 visits, and the proportion of positive nasopharyngeal multiplex PCR over time. We also

203 analyzed the evolution of monthly KD rate per 100 hospital admissions following pediatric
204 emergency department visits over time. The multiplex PCR, FilmArray® Respiratory Panel 2
205 plus (Biomérieux), tested the following respiratory pathogens: Adenovirus, Coronavirus
206 229E, Coronavirus HKU, Coronavirus NL63, Coronavirus OC43, Metapneumovirus,
207 Rhinovirus/Enterovirus, Influenza A, Influenza B, Parainfluenza I, Parainfluenza II,
208 Parainfluenza III, Parainfluenza IV, VRS, *Bordetella parapertussis*, *Bordetella pertussis*,
209 *Chlamydomphila pneumoniae* and *Mycoplasma pneumoniae*. Furthermore, all KD cases
210 diagnosed since April 1st 2020 were tested with SARS-CoV-2 nasopharyngeal PCR using the
211 Xpert® Xpress SARS-CoV-2 (Cepheid).

212

213 The outcomes were analyzed by quasi-Poisson regression, accounting for seasonality,
214 secular trends, and overdispersion of data.^{21–23} Seasonality was taken into account by
215 including harmonic terms (sines and cosines) with 12-months and 6-months periods.²¹ To
216 provide optimal precision to the model the chosen time unit was one month.²³ As a delay
217 between respiratory viral infection and KD is expected, we hypothesized that the COVID-19
218 outbreak would have an impact a month (i.e., one time unit) after the peak. Thus, the COVID-
219 19 impact assessment involved a dummy variable in the model estimating the immediate
220 post-outbreak change in April 2020. The only previous major respiratory virus pandemic
221 identified over the study period was the influenza A (H1N1) pandemic in winter 2009. Thus,
222 another dummy variable was included in the model to allow for the immediate effect of
223 influenza A (H1N1) on Kawasaki occurrence in December 2009. The validity of the quasi-
224 Poisson regression model was assessed by visual inspection of the correlograms (Auto
225 Correlation and Partial Auto Correlation Functions) and analysis of the residuals. All
226 statistical tests were two-sided, and we considered a result as “significant” when the p-value
227 was <0.05. All statistical analysis was performed using R v3.6.1 (<http://www.R-project.org>).

228

229 Role of the funding source

230 The French National Research Agency had no role in the study design, data collection,
231 analysis, data interpretation, and writing of the report. The first author had full access to all
232 data and final responsibility for the decision to submit for publication.

233

234 **Results**

235

236 During the 2005-2020 period, 230 patients were hospitalized with KD. The median number of
237 KD hospitalizations estimated by the quasi-Poisson model was 1.2 per month (interquartile
238 [1.1; 1.3]).

239

240 In April 2020, we observed a significant increase of KD (+497% increase, 95% CI [+72;
241 +1082], $p=0.0011$, quasi-Poisson regression model). Similar results were obtained when
242 analyzing KD rate per 100 hospitalizations over time (Figure 1 and appendix Table 1) with an
243 occurrence between April 15th and May 15th. Thus, the increase of KD hospitalizations
244 started two weeks after the first peak of the COVID-19 epidemic in the Paris region, which
245 occurred around March 31st-April 1st 2020 (Figure 2).

246

247 The increase in KD observed in April 2020 was not related to an increase in overall hospital
248 admissions, which on the contrary significantly dropped since March 2020 (-31% decrease,
249 95%CI [-42; -18], appendix figure 1B) due to the lockdown. Furthermore, this increase
250 coincided with an unprecedented decrease of other respiratory viruses in our population
251 since March 2020 (Figure 3), probably as a consequence of the reduction of social contacts
252 after the lockdown. The only virus circulating at high levels during this period was the SARS-
253 CoV-2 (Figure 2), reinforcing the link between this virus and the KD increase.

254

255 The characteristics of patients with KD during the SARS-CoV-2 epidemic are shown in Table
256 1. Among the ten children presenting with KD from April 15th to May 20th 2020, 8 had a

257 positive nasopharyngeal SARS-CoV-2 PCR and or a positive SARS-CoV-2 serology (Table
258 1). One patient had a prolonged exposure with a confirmed COVID-19 individual but had
259 negative SARS-CoV-2 PCR and serological testings. Among these patients, five had a
260 complete KD and 5 patients had fever with only 3 other KD criteria. The age of KD patients
261 ranged from 18 months to 15.8 years. Six children (60%) had cardiac abnormalities,
262 including one major coronary aneurysm (Z score: 12) and five myocarditis. Six patients
263 (60%) required intensive care and five had inotrope treatment (50%). None required
264 mechanical ventilation, and no fatal outcome was observed.

265

266 A second peak of KD hospitalizations was detected by the model in December 2009 (+365%
267 increase, 95% CI [+31; +719], $p=0.0053$), concomitant with the influenza A (H1N1)
268 outbreak,²⁷ peaking in November-December 2009 in France (Figure 1A and appendix Table
269 1). The increase of KD hospitalizations occurred approximately 1 to 3 weeks after the peak of
270 the influenza A (H1N1) epidemic in the Paris region.

271

272 A comparison between patients with KD hospitalized in our center during the SARS-CoV-2
273 epidemic, during the H1N1 epidemics and out of these major epidemics is shown in Table 2.
274 Furthermore, we compared these patient groups to patients from a recent publication that
275 were hospitalized during the SARS-CoV-2 epidemic in Bergamo, Italy¹⁰ (Table 2). The
276 characteristics from KD patients hospitalized during the SARS-CoV-2 epidemic in our center
277 were similar to patients hospitalized during the SARS-CoV-2 epidemic in Bergamo with a
278 high proportion of severe KD with cardiac involvement and the need for a second line of
279 treatment. In contrast, the characteristics of KD patients during SARS-COV-2 epidemics
280 appeared to be different from those diagnosed during the H1N1 epidemics, (median age 11.8
281 vs 2.1 years, $p=0.034$; median CRP 23.6 vs 8.4 mg/dL, $p=0.042$; median lymphocytes count
282 1042 vs 3410×10^9 per L, $p=0.028$, respectively).

283

284

285 **Discussion**

286

287 Our study linked an emergence of KD to the ongoing COVID-19 pandemic. Several findings
288 support this association. First, we observed that the unexpected high emergence of KD
289 occurred 2 to 4 weeks after the peak of the COVID epidemic, in line with the previously
290 reported post-infection mechanism of KD.¹⁵ Second, following the nationwide lockdown in
291 March 2020, SARS-CoV-2 was the only respiratory virus with intense circulation in the weeks
292 before the emergence of KD, as confirmed by our results from respiratory multiplex PCR.
293 Third, almost all patients with KD in April 2020 had a positive nasopharyngeal SARS-CoV-2
294 PCR or exposure to a confirmed COVID-19 individual.

295

296 The only other peak in KD observed during the 15-year observation period occurred during
297 the context of the H1N1 influenza A pandemic, suggesting that SARS-CoV-2 is not the only
298 virus capable of triggering such an emergence of KD. These findings are in line with
299 observations in the literature, reporting seasonality and outbreaks of KD, especially in Japan,
300 where nationwide epidemics were observed in 1979, 1982 and 1986.^{12,17,28} Seasonal
301 patterns of KD have also been observed in many other countries, including European
302 countries and North America. This has led to the speculation that viral infections may
303 underline KD pathogenesis. However, large outbreaks of KD seem to be a rare event. The
304 significant surges of KD following two different major epidemic outbreaks, observed in our
305 study, provide a unique, quasi-experimental condition, confirming the crucial role of viral
306 infections in the trigger of KD in susceptible patients.

307

308 In both observed epidemic peaks the increase was very sudden. Further studies will be
309 necessary to understand the immunological reasons leading to this strong and sudden
310 increase in the context of SARS-CoV-2 and H1N1 epidemics when compared to seasonal
311 viral infections. One could speculate that the sudden exposure to totally new antigens may
312 trigger a particular uncontrolled immune response in susceptible children. In contrast,

313 frequent seasonal viruses are encountered by children with "trained" immune systems, after
314 exposures to similar antigens during precedent seasons, and therefore only a minority of
315 them develop KD. Although our article shows an emergence of KD associated with COVID-
316 19, it is important to insist that even in the current epidemic context this strong inflammatory
317 disease is very rare.

318

319 The strength of our study was that it was performed over a large period of time (15 years) on
320 a stable population of multiethnic origins, living in a defined area, with stable medical
321 orientation to our tertiary center. This allowed us to observe a substantial stability of the KD
322 patients flow over time, enabling the detection of outbreaks. Our study also had some
323 limitations. Although the sample size was sufficient to reach a high statistical significance,
324 our study is limited by its monocenter nature and a relatively small number of patients.
325 However, we performed our analysis in a tertiary center localized in an epicenter of COVID-
326 19 in order to increase the sensitivity of SARS-CoV-2 associated KD. This approach may
327 have led to an over evaluation of the increased risk for KD (+497% increase). Our study
328 design allowed to provide a "proof of concept" of the link between COVID-19 pandemic and
329 KD. Larger population-based studies are required to evaluate the exact additional risk of KD
330 associated to SARS-CoV-2 infections.

331

332 The clinical spectrum of pediatric multi-system inflammatory diseases observed recently in
333 the COVID-19 context is believed to include features of KD (complete or incomplete), and/or
334 toxic shock syndrome and/or myocarditis.^{4,11,29} Pediatric and scientific societies in several
335 countries are currently gathering information to provide a detailed clinical description. In
336 order to reduce bias due to heterogenous clinical presentations, we decided to only focus on
337 patients with clinical presentation of KD according to established criteria.²⁹ Further studies
338 will be necessary to understand whether these patients should be classified as SARS-CoV-2
339 infection with a KD phenotype or SARS-CoV-2 triggered KD.

340

341 Our observations may have practical implications for clinicians and health care providers.
342 Indeed, the clinical characteristics of KD patients hospitalized during the COVID-19 epidemic
343 in our center in France resembled those of patients hospitalized in an epicenter of COVID-19
344 in Italy¹⁰ with a relatively high proportion of severe KD with cardiac involvement (abnormal
345 echocardiography, coronary aneurysm, myocarditis), ICU admissions, inotrope requirement
346 and need for additional treatments after a first IVIG. In contrast, KD occurring during the only
347 other observed KD peak in the context of H1N1 epidemic resembled that of classical KD
348 cohorts.^{15,30,31} These observations suggest that in the context of SARS-CoV-2 circulation a
349 higher proportion of KD patients may present a severe phenotype. Furthermore, these
350 observations indicate that in such a pandemic, healthcare systems should be prepared to
351 manage an increased influx of patients with KD and potential severe cardiac involvement,
352 particularly in countries where the peak of COVID-19 has just been reached.

353

354

355 **Conclusion**

356 Our study provides evidence of a rapid emergence of KD in children related to SARS-CoV-2,
357 starting approximately two weeks after the peak of COVID-19 epidemic. Health care
358 providers and health authorities need to be prepared to manage a potential increased influx
359 of children with severe KD.

360

361

362

363 **Contributors**

364 UM and NO designed the study. NO, MP, PM, CB, AB, SB, KD, MC, LM, FLB, MC, JG, JP,
365 RC, LT, AF, IM and UM analysed and interpreted the data and drafted the article. NO and
366 MP performed the statistical analysis. SB and PM performed the microbiological analysis. All
367 authors revised and approved the manuscript.

368

369 **Declaration of interests**

370 The other authors declared no conflicts of interest.

371

372 **References**

373

- 374 1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the
375 Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of
376 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*
377 2020.
- 378 2. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in Pediatric Emergency
379 Departments in Italy. *New England Journal of Medicine* 2020
- 380 3. Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease
381 2019 (COVID-19) in Children in Madrid, Spain. *JAMA Pediatr* 2020.
- 382 4. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in
383 children during COVID-19 pandemic. *The Lancet* 2020:S0140673620310941.
- 384 5. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the
385 COVID-19 pandemic. *Lancet* 2020.
- 386 6. Loomba RS, Raskin A, Gudausky TM, et al. Role of the Egami Score in Predicting
387 Intravenous Immunoglobulin Resistance in Kawasaki Disease Among Different
388 Ethnicities. *Am J Ther* 2016;23:e1293–e1299.
- 389 7. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki Disease: Novel Virus
390 and Novel Case. *Hosp Pediatr*. 2020 Apr 7; hpeds.2020-0123.
- 391 8. Rivera-Figueroa EI, Santos R, Simpson S, et al. Incomplete Kawasaki Disease in a
392 Child with Covid-19. *Indian Pediatr* 2020.
- 393 9. Schroeder AR, Wilson KM, Ralston SL. COVID-19 and Kawasaki Disease: Finding
394 the Signal in the Noise. *Hospital Pediatrics* 2020.
- 395 10. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease
396 at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study.
397 *The Lancet* 2020:S014067362031103X.
- 398 11. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory
399 syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic.
400 *Circulation* 2020.
- 401 12. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease
402 in Japan: results from the nationwide survey in 2005-2006. *J Epidemiol* 2008;18:167–
403 172.
- 404 13. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome hospitalizations in the
405 United States, 1997 and 2000. *Pediatrics* 2003;112:495–501.
- 406 14. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for
407 the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936–941.
- 408 15. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-
409 Term Management of Kawasaki Disease: A Scientific Statement for Health
410 Professionals From the American Heart Association. *Circulation* 2017;135:e927–
411 e999.
- 412 16. Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol*
413 2016;67:1738–1749.
- 414 17. Burns JC, Herzog L, Fabri O, et al. Seasonality of Kawasaki disease: a global
415 perspective. *PLoS ONE* 2013;8:e74529.
- 416 18. Burns JC, Cayan DR, Tong G, et al. Seasonality and temporal clustering of Kawasaki
417 syndrome. *Epidemiology* 2005;16:220–225.
- 418 19. Gambacorta A, Buonsenso D, De Rosa G, et al. Resolution of Giant Coronary
419 Aneurysms in a Child With Refractory Kawasaki Disease Treated With Anakinra. *Front*
420 *Pediatr* 2020;8.
- 421 20. Rigante D, Andreozi L, Fastiggi M, et al. Critical Overview of the Risk Scoring
422 Systems to Predict Non-Responsiveness to Intravenous Immunoglobulin in Kawasaki
423 Syndrome. *Int J Mol Sci* 2016;17:278.
- 424 21. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the

- 425 evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;46:348–355.
426 22. Kontopantelis E, Doran T, Springate DA, et al. Regression based quasi-experimental
427 approach when randomisation is not an option: interrupted time series analysis. *BMJ*
428 2015;350:h2750.
- 429 23. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of
430 interrupted time series studies in medication use research. *J Clin Pharm Ther*
431 2002;27:299–309.
- 432 24. Kim GB, Park S, Kwon BS, et al. Evaluation of the Temporal Association between
433 Kawasaki Disease and Viral Infections in South Korea. *Korean Circ J* 2014;44:250.
- 434 25. Jordan-Villegas A, Chang ML, Ramilo O, et al. Concomitant Respiratory Viral
435 Infections in Children with Kawasaki Disease. *Pediatr Infect Dis J* 2010;29:770–772.
- 436 26. Turnier JL, Anderson MS, Heizer HR, et al. Concurrent Respiratory Viruses and
437 Kawasaki Disease. *Pediatrics* 2015;136:e609-614.
- 438 27. Dawood FS, Iuliano AD, Reed C, et al. Estimated global mortality associated with the
439 first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling
440 study. *Lancet Infect Dis* 2012;12:687–695.
- 441 28. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic Features of Kawasaki
442 Disease in Japan: Results of the 2009–2010 Nationwide Survey. *J Epidemiol*
443 2012;22:216–221.
- 444 29. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock
445 syndrome. *Pediatrics* 2009;123:e783-789.
- 446 30. Chbeir D, Gaschignard J, Bonnefoy R, et al. Kawasaki disease: abnormal initial
447 echocardiogram is associated with resistance to IV Ig and development of coronary
448 artery lesions. *Pediatr Rheumatol Online J* 2018;16:48.
- 449 31. Piram M, Darce Bello M, Tellier S, et al. Defining the risk of first intravenous
450 immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. *Sci*
451 *Rep* 2020;10:3125.
452
- 453
454
455
456
457

458 **Figure 1: Evolution of monthly Kawasaki disease rate per 100 admissions to hospital**
459 **over time.**

460 KD: N=230. Hospital admission following pediatric emergency department visits, N=110,824.
461 The black line depicts the observed data. The bold red line depicts the model estimates
462 based from the quasi-Poisson regression model. The vertical black arrows indicate the H1N1
463 and COVID-19 outbreak (respectively: November-December 2009 and March-April 2020).

464

465 **Figure 2. Evolution of the COVID-19 outbreak in the Ile-de-France region, Public health**
466 **France data, N=35,732.**

467 The black line depicts the daily number of new admissions in hospital for all-age confirmed
468 COVID-19 in Ile de France. Source: Santé publique France.

469

470 **Figure 3. Evolution of respiratory pathogens from 2017 to 2020, N=4,662.**

471 The black, red, blue, green, and orange lines depict observed data for Influenza, RSV,
472 Rhino-enterovirus, Metapneumovirus and Parainflunza. The bold black, red, blue, green, and
473 orange slope shows the model estimates from the final quasi-Poisson regression models.

474 Abbreviations: PEDs: Pediatric emergency departments. Rhino-ERV: rhino-enterovirus,
475 Metapneumo: metapneumovirus.

476

477 **Table 1. Characteristics of patients with Kawasaki disease who presented during**
478 **SARS-CoV-2 epidemic (April-May 2020).**

479

480 **Table 2. Comparison between patients with Kawasaki disease (KD) presenting during**
481 **the SARS-CoV-2 epidemic in Paris region, France, in Bergamo, Italy, during the H1N1**
482 **epidemics and out of major viral epidemics.**

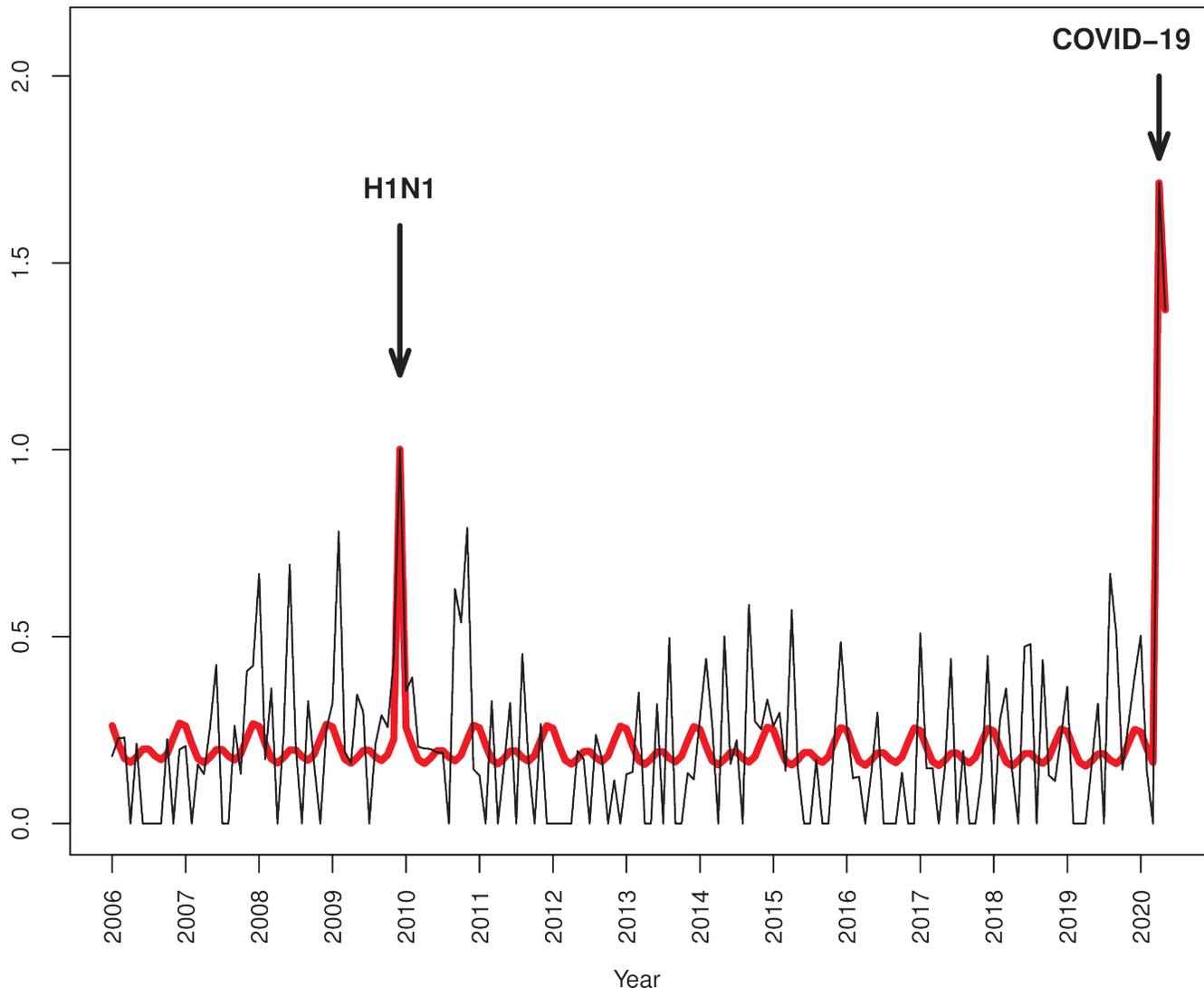
483

484

485

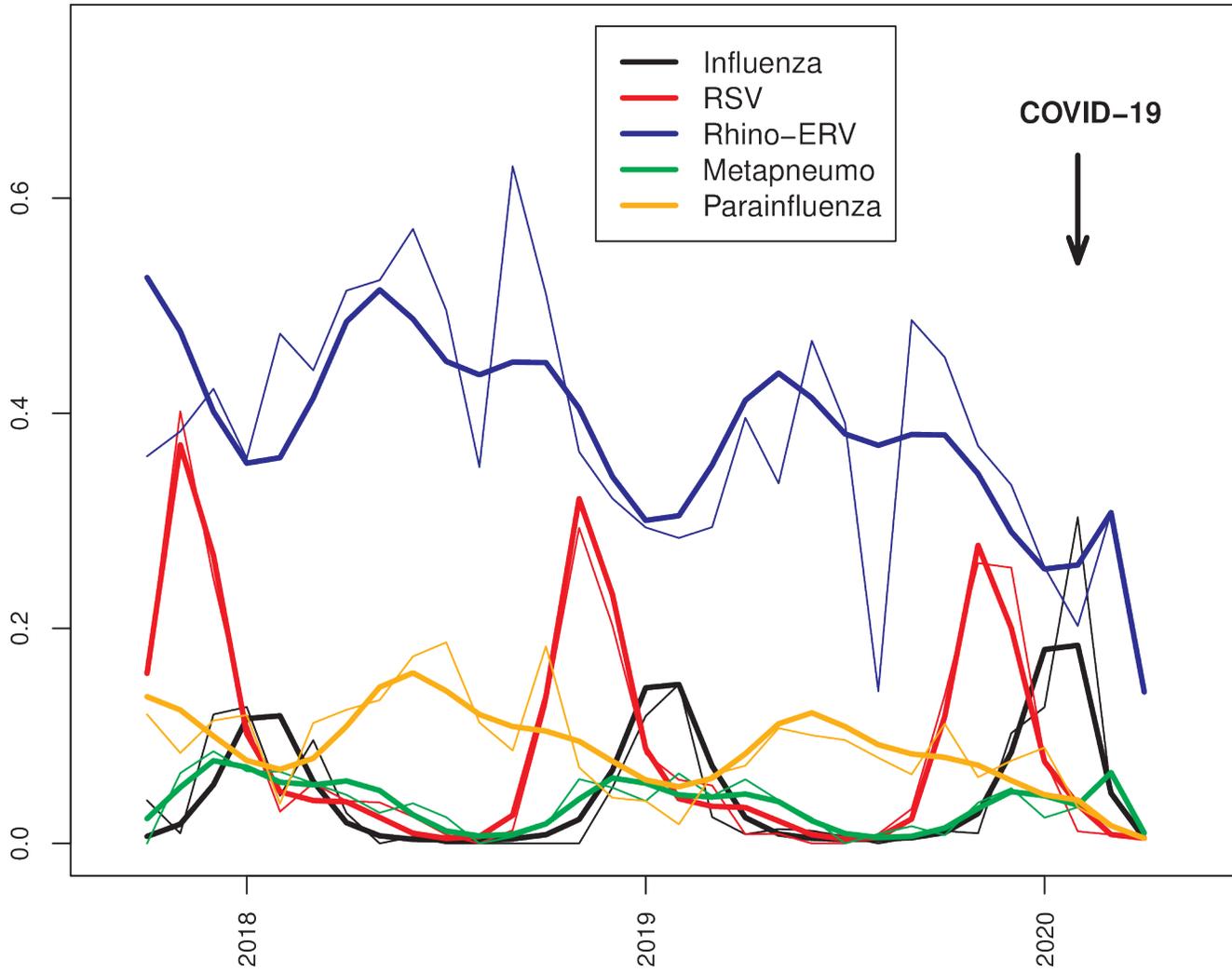
Kawasaki disease

Rate of Kawasaki diseases per 100 admissions



Evolution of respiratory pathogens

Proportion of positive respiratory pathogens



- Influenza
- RSV
- Rhino-ERV
- Metapneumo
- Parainfluenza

COVID-19
↓

Hospitalizations for COVID-19 in Ile De France

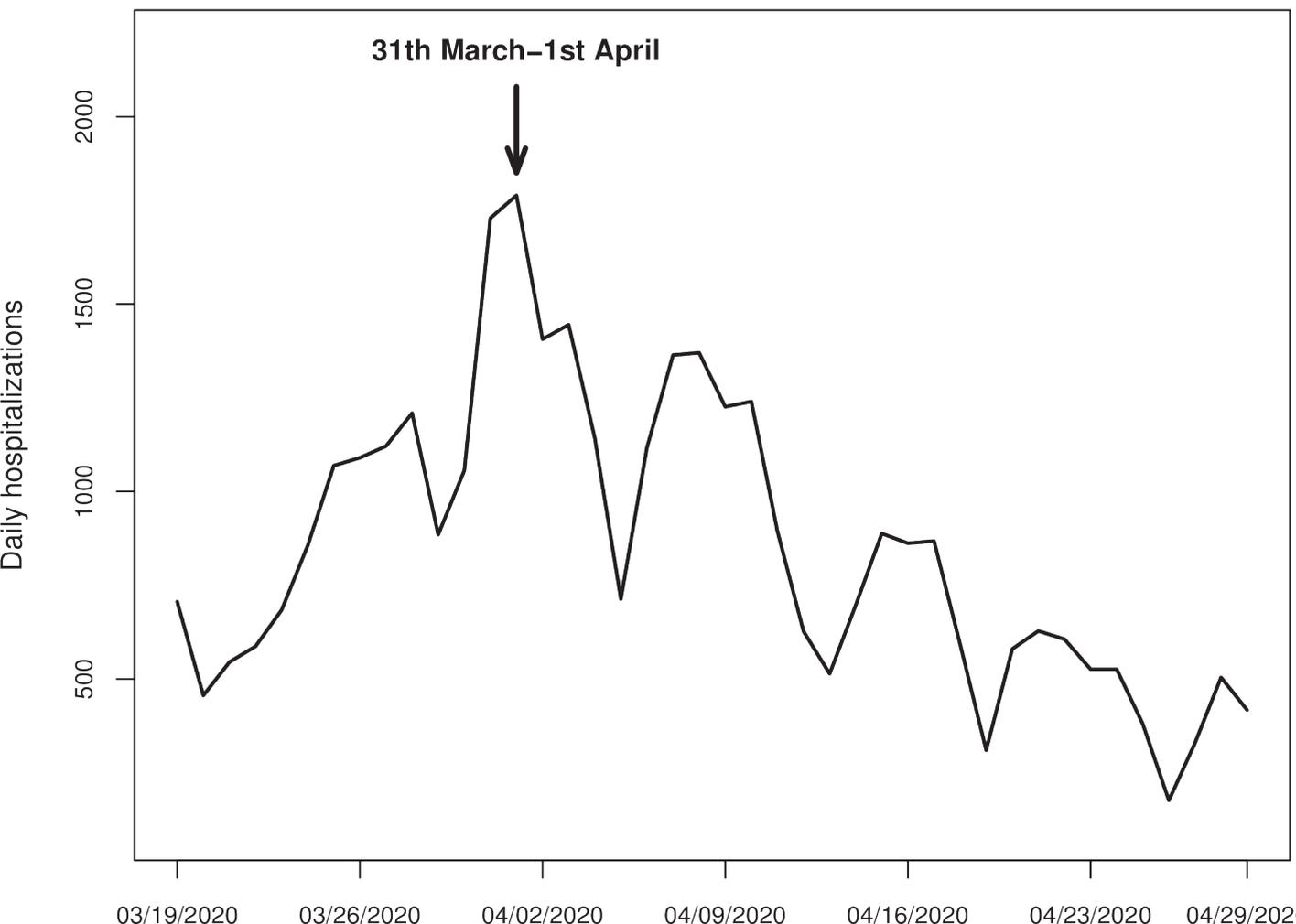


Table 1: Characteristics of patients with Kawasaki disease who presented during SARS-CoV-2 epidemic (April-May 2020)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age, years	12	1.8	11.5	1.5	15.5	13.5	9.8	14.5	15.8	6.3
Sex	Female	Female	Male	Male	Female	Female	Female	Female	Male	Male
SARS-CoV-2 nasopharyngeal PCR	Positive	NA	Positive	Negative	Positive	Positive	Negative	Positive	Negative	Negative
SARS-CoV-2 serology	NA	NA	IgG+	Negative	IgG+	NA	IgG+	NA	IgG+	IgG+
Contact with suspected or confirmed case	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Complete Kawasaki disease	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No
Kobayashi score ¹	8	1	4	0	4	8	7	6	8	6
KDSS ²	No	No	No	No	No	Yes	Yes	Yes	Yes	No
Cardiac involvement	Myocarditis	No	No	Coronary dilatation (Z=12)	No	Myocarditis	Myocarditis	Myocarditis, Pericarditis	Myocarditis	No
First line treatment	IVIG	IVIG	None	IVIG	IVIG	IVIG	IVIG	IVIG	IVIG	IVIG
Failure of first line treatment	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes
Second line treatment	IVIG+mPDN	No	No	IVIG+mPDN	No	Tocilizumab	IVIG+mPDN	No	IVIG+mPDN	IVIG+mPDN
Admission to PICU	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Inotropes treatment	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Lengths of hospital stay (days)	14	5	4	27	5	18	19	13	9	17

Abbreviations: mPDN: methylprednisolone. KDSS: Kawasaki disease shock syndrome. IVIG: intravenous immunoglobulin. PICU: paediatric intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. NA: not available

Table 2. Comparison between patients with Kawasaki disease (KD) presenting during the SARS-CoV-2 epidemic in Paris region, France, in Bergamo, Italy, during the H1N1 epidemics and out of major viral epidemics.

Symptom/clinical sign	SARS-CoV-2 epidemics in Robert Debré Hospital, France**	SARS-CoV-2 epidemics in Bergamo, Italy ¹⁰	H1N1 epidemics in Robert Debré Hospital, France	KD out of major viral epidemics in Robert Debré Hospital, France
Time of presentation	April-May 2020*	March-April 2020	December 2009	From 2005 to 2020
Number of patients	10	10	6	214
Incidence	6 per month	10 per month	6 per month	1 per month
Rate of KD per 100 hospitalizations	1.5	NA	1.0	0.2
Sex				
<i>Female</i>	4 (40%)	3 (30%)	5 (83%)	87 (41%)
<i>Male</i>	6 (60%)	7 (70%)	1 (17% ^o)	127 (59%)
Median age (years)	11.8 [7.4; 14.3]	7.2 [5.5; 8.1]	2.1 [1.7; 3.8]	2.1 [1.1; 3.7]
Complete Kawasaki disease	6/10 (60%)	5/10 (50%)	4/6 (67%)	138/214 (64%)
CRP, mg/dL	23.6 [13.2; 30.9]	24.1 [13.0; 29.5]	8.4 [5.1; 13.3]	14.4 [9.9; 19.8]
Lymphocytes, × 10 ⁹ per L	1042 [650; 1150]	832 [543; 960]	3410 [2010; 4590]	3044 [1855; 4770]
Platelets, × 10 ⁹ per L	274 [192; 715]	130 [120; 142]	613 [454; 715]	379 [285; 484]
Sodium, mEq/L	130 [129; 135]	131.5 [129; 133]	137.5 [136; 139]	135 [133.5; 137]
AST, U/L	35 [35; 53]	57 [35; 112]	30 [28; 37]	35 [28; 57]
ALT, U/L	33 [27; 38]	55 [34; 79]	20 [15; 28]	40 [19; 97]
Kobayashi score ≥5 ¹	7/10 (70%)	7/10 (70%)	0/6 (0%)	39/153 (25%, NA=61)
KDSS ²⁹	4/10 (40%)	5/10 (50%)	0/6 (0%)	NA
Abnormal echocardiography	6/10 (60%)	6/10 (60%)	3/6 (50%)	51/214 (24%)
Need for additional treatment to first dose of IVIG	6/10 (60%)	8/10 (80%)	1/6 (17%)	44/203 (22%, NA=9)
Admission to PICU	6/10 (60%)	NA	0/6 (0%)	14/160 (9%, NA=54)
Inotropes treatment	5/10 (50%)	2/10 (20%)	NA	NA

Quantitative data are presented as median [Q1–Q3] and categorical data as number (%). *: Data after May 20th not available. Abbreviations: KD: Kawasaki disease. CRP: C-reactive protein. ALT: alanine aminotransferase. AST: aspartate aminotransferase. KDSS: Kawasaki disease shock syndrome. IVIG: intravenous immunoglobulin. PICU: paediatric intensive care unit. NA: not available. **the total number of pediatric COVID19 patients that have been referred to our hospital was N=39.