RAPID RISK ASSESSMENT

Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children

14 May 2020

Summary

Recently, in countries with large outbreaks of coronavirus disease 2019 (COVID-19), both in Europe and in the United States, there have been reports of cases of children hospitalised in intensive care due to rare paediatric inflammatory multisystem syndromes (PIMS). Presenting signs and symptoms are a mix of the ones known for Kawasaki disease (KD) and toxic shock syndrome (TSS), i.e., fever, abdominal pain and cardiac involvement are prominent. In total, about 150 suspected PIMS cases have been reported in EU/EEA countries and the UK in 2020, including one fatality, and are under further investigation.

A possible temporal association with SARS-COV-2 infection has been hypothesised as some of the children that were tested for SARS-CoV-2 infection were either polymerase chain reaction (PCR) (+) or serology (+) for SARS-CoV-2.

So far, epidemiological studies have shown that children have been among the least affected by COVID-19, with only 2.1% of all laboratory confirmed COVID-19 cases reported to The European Surveillance System (TESSy) in the age group 0-14 years old.

To date, the association between SARS-CoV-2 infection and this new clinical entity of multisystem inflammation is not yet established, although it appears plausible.

In the current situation, the assessment of the risk is that:

- The overall risk of COVID-19 in children in the EU/EEA and UK is currently considered **low**, based on a **low** probability of COVID-19 in children and a **moderate** impact of such disease;
- The overall risk of paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 infection (PIMS-TS) in children in the EU/EEA and the UK is considered **low**, based on a **very low** probability of PIMS-TS in children and a **high** impact of such disease.

While the clinical management of these children is the absolute priority, data collection from across EU/EEA Member States and the UK would strengthen the body of knowledge on this rare condition and allow for more power in the analysis of these cases. Analysis of surveillance data should clarify the incidence of KD and of PIMS, and identify the most affected age groups and risk factors for both conditions. ECDC has agreed with EU/EAA Member States and the UK to include PIMS as a possible complication to be reported in the EU-level COVID-19 surveillance. Research efforts should aim at determining the role of SARS-CoV-2 in the pathogenesis of PIMS and answering other significant remaining questions.

Risk communication is needed to raise awareness in the medical community about PIMS and inform parents and caregivers about signs and symptoms, as well as the importance of timely contact with a healthcare

Suggested citation: European Centre for Disease Prevention and Control. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children – 14 May 2020. ECDC: Stockholm; 2020.

worker. Risk communication should stress that PIMS is a rare condition and that its potential link with COVID-19 is neither established nor yet well understood.

Event background

On 31 December 2019, a cluster of pneumonia cases of unknown aetiology was reported in Wuhan, Hubei Province, China. On 9 January 2020, China CDC reported a novel coronavirus as the causative agent of this outbreak SARS-CoV-2. Since 31 December 2019 and as of 13 May 2020, 1 268 603 cases of COVID-19 were reported by EU/EEA countries and the UK, including 150 327 deaths [1]. Detailed information on the COVID-19 cases reported so far are available in the dedicated ECDC webpage [2].

On 27 April 2020, health authorities in the United Kingdom (UK) reported a number of seriously ill children presenting with signs of circulatory shock and hyperinflammatory state with features consistent with toxic shock or Kawasaki Disease (KD) (Table 1). Some of the tested children also were positive for SARS-CoV-2 infection. A case of classic KD with concurrent COVID-19 had already been reported **on 7 April 2020** in the United States (US) [3].

On 1 May 2020, the Royal College of Paediatrics and Child Health (RCPCH) published guidance on clinical management of children with a presentation of paediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) and proposed a case definition [4].

On 4 May 2020, the department of health of New York City in the US also issued an alert to identify children with PIMS-TS in New York City hospitals and **as of 10 May**, at least 85 children in New York City have been reported as presenting such inflammatory syndromes and are under investigation. Three have died due a toxic shock syndrome with links to SARS-CoV-2 infection, with a further two deaths under investigation [5].

France and Italy also observed an unusually high number of children in paediatric intensive care with shock syndrome that shared some of the features of KD; some of those children also tested positive for SARS-COV-2 [6,7]. Austria, Denmark, Greece and Sweden reported not seeing an overall increase in cases of KD (Table 1). No increase was observed in Asian countries, where KD is much more prevalent than in Europe, such as Japan and South Korea (communication from the WHO COVID-19 Clinical Network Knowledge Exchange).

In France, **as of 5 May 2020** approximately 40 cases of KD were reported to be under investigation [6]. In the province of Bergamo in Italy, approximately 20 PIMS-TS cases have been recorded up to 6 May [7]. **On 6 May 2020**, the demographics, clinical findings, imaging findings, treatment, and outcome from eight British children presenting paediatric multi-system inflammatory syndromes were published. Of the eight children, three were SARS-CoV-2 RT-PCR negative; three were RT-PCR negative but had a possible exposure to SARS-CoV-2; two were SARS-CoV-2 positive [8]. Austria, Germany, Ireland, Italy and Portugal reported in the EWRS PIMS-TS cases testing positive for SARS-CoV-2, while the Netherlands and Slovenia reported paediatric KD cases testing negative for SARS-CoV-2 (Table 1).

Few additional PIMS cases have been reported through media reports from Canada (n=12) and Switzerland (n=3) (Table 1) [9,10].

Table 1. Distribution and characteristics of reported PIMS cases in EU/EEA countries in 2020, as of 12 May 2020

Country	Date of reporting in 2020	Reported cases	Median age in years (range)	SARS-CoV-2 infection status	Other associated pathogens	Clinical manifestations	Fatalities	Sources (references)
Austria	29 April 2020	1	11 years	COVID-19 PCR positive before deterioration of symptoms, positive IgG 2 weeks later	Group A streptococci	Hyper inflammatory state with abdominal symptoms, high fever, circulatory shock, DIC and elevated inflammatory parameters	0	EWRS
Canada	3 May 2020	12	NS	NS	NS	Atypical KD	NS	Media [9]
Denmark	8 May 2020	0						EWRS
France	8 May 2020	34	9.5 (3-17)	PCR positive for SARS-CoV-2 or positive serological test or possible links with COVID-19	NS	Fever, abdominal pain, vomiting, rash, cardiac and circulatory failure	0	Media: [11,12]
Germany	11 May 2020	5	8 (3-14)	Positive	None	Hyperinflammatory state with features consistent with toxic shock or Kawasaki Disease	NS	EWRS
Greece	11 May 2020	1	NS	Negative	NS	NS	NS	Official: (personal communication)
Ireland	28 April 2020	1	NS	Positive	NS	Some features consistent with KD	NS	EWRS

Country	Date of reporting in 2020	Reported cases	Median age in years (range)	SARS-CoV-2 infection status	Other associated pathogens	Clinical manifestations	Fatalities	Sources (references)
Italy	28 April 2020	20	NS	NS	NS	consistent with KD	NS	Media: [7,13]
Luxembourg	30 April 2020	5	NS	One positive serology test for SARS-CoV-2 2 negative but with signs of infection 2 negative	NS	Atypical KD	NS	EWRS
Netherlands	29 April 2020	2	NS	Negative	None	Similar clinical presentation as KD	NS	EWRS
Portugal	4 May 2020	1	13	Serology test for SARS-CoV positive (IgG antibodies positive) and RT-PCR negative	NS	High fever >39ºC, bilateral conjunctivitis, chest and abdominal pain, low procalcitonin and IL-6: 365 pg/mL; C-reactive protein (CRP): 400mg/dl, Troponin levels 4000 ng/ml , myocarditis without ischemia or ECG changes, Characteristics of Kawasaki Disease and Toxic Shock Syndrome: Skin lesions that were biopsied; pending results. Chest x-Ray - severe COVID-19 pneumonia	0	EWRS
Slovenia	29 April 2020	6	5 children and one teenager	Negative	NS	NS	NS	EWRS
Spain	10 May 2020	22 (including KD)	6.6 (6 months – 13)	71% positive by RT-PCR or serology test for SARS-CoV-2	hMPV (2), Staph. epidermidis (2), Rhinovirus (1)	Myocardial dysfunction, fever, rash, conjunctivitis, digestive symptoms, need of oxygen, inflammatory markers. Only 35% of these patients fulfil criteria for complete or incomplete KD		Official: (personal communication)
Sweden	12 May 2020	3	< 12 years	One positive by RT-PCR and one positive serology test for SARS-CoV-2, One negative by RT-PRC	NS	Kawasaki-like syndromes	0	EWRS
Switzerland	1 May 2020	3	NS	NS	NS	NS	NS	Media: [10]
UK	27 April 2020	NS	NS	NS	NS	Signs of circulatory shock and hyperinflammatory state with features consistent with toxic shock or Kawasaki Disease	NS	EWRS
UK	6 May 2020	8	8 (4-14)	3 SARS-CoV-2 negative and 3 negative but with possible exposure 2 SARS-CoV-2 confirmed positive	Adenovirus and HERV (1)	Fever, diarrhoea, abdominal pain, headaches, conjunctivitis, rash, vomiting, odynophagia, mechanical ventilation	1	Publication: [8]
UK	8 May 2020	40	11 (range 11 months to 17 years)	12/37 PCR positive, 17/20 IgG positive, 54% had evidence of Sars-CoV-2 infection	EBV viraemia	NS	1	Publication: *in press* (personal communication)
US	7 Apr 2020	1	6 months	Positive	NS	Fever, persistent erythematous, seemingly non-pruritic, blotchy rash, sinus tachycardia (200 beats/minute), and tachypnea with an oxygen saturation of 100%, irritability, limbic-sparing conjunctivitis, and dry cracked lips, hyponatremia and hypoalbuminemia		Publication: [3]
US (New York State)	10 May 2020	85	(2-15)	A proportion tested positive for COVID-19	NS	NS	3 (2 additional deaths under investigation)	Official: [5]

Note: *DIC: disseminated intravascular coagulation; EBV: Epstein-Barr virus; EU/EEA: European Union and European Economic Area; HERV: human endogenous retrovirus; hMVP: human metapneumovirus; KD: Kawasaki disease; NS: not specified; UK: United Kingdom; US: United States of America. EWRS: early warning and response system.*

Disease background

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS)

The first case report of a child with Kawasaki Disease (KD) and concurrent COVID-19 was published in the US on 7 April 2020. This case was a 6-month-old female infant admitted with persistent fever and minimal respiratory symptoms, diagnosed with classic KD and tested positive for COVID-19 by RT-PCR [3]. Since this first report, countries with large outbreaks of SARS-CoV-2, both in Europe and in the US, have reported further cases in paediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) (Table 1). This newly identified PIMS-TS, according to first reports shares a number of clinical features with KD in children (e.g. some of the presenting symptoms like persistent fever and the cardiac involvement), although it presents also significant differences, such as the difference in affected age groups (mostly children >5 years old, as compared to the classical KD). From media, scientific publications and official reports, more than 200 suspected classical KD or PIMS-TS cases are currently under investigation both in Europe and in north America (Table 1).

Below we outline scientific evidence on classical KD, COVID-19 and PIMS-TS in children, as well as available clinical information from the PIMS-TS cases identified and reported until 13 May 2020.

Kawasaki disease

Disease characteristics

Kawasaki disease (KD) is a self-limited vasculitis of childhood [14]. The most important complication of KD is artery abnormalities (aneurysms of mid-sized arteries, giant coronary artery aneurysms, pericarditis and carditis). A small percent of children can present with KD shock syndrome [15].

There are no diagnostic tests for KD. The diagnosis is based on prolonged fever (≥ 5 days) and at least four of the following criteria: bilateral conjunctivitis, changes of lips or the oral mucosa (strawberry tongue), skin rash, changes in the hands or feet (erythema, oedema, induration, desquamation), and, cervical lymphadenopathy with at least one node ≥ 1.5cm diameter [16-18].

KD aetiology remains unknown, but the hypothesis includes infection with common pathogen(s), which causes an immune-mediated response resulting in KD in genetically predisposed children [19]. It has been reported in association with a variety of infectious agents, including bacteria (mostly Group A Streptococci), fungi and viruses, including enteroviruses, adenovirus, human coronaviruses, parainfluenza virus, Epstein-Barr virus [14]. To date a causal association with SARS-CoV-2 has not yet been established.

Incidence of KD

Although the leading cause of childhood acquired heart disease in industrialised nations, KD is a rare condition [11]. In Europe KD is reported on average in 5-15/100 000 children under 5 years of age annually: England (5–8/100 000), Germany (7.2/100,000), Denmark (4.9/100 000), Finland (7.2/100 000), France (9.0/100 000), Italy (14.7/100 000), Ireland (15.2/100 000) and Sweden (6.2/100 000) [20-23]. In the US, 19 per 100,000 children younger than five years are hospitalised with KD annually [24]. The incidence of KD in north-east Asian countries such as Japan, South Korea, China, and Taiwan are 10–30 times higher than that in the US or Europe [25].

Clinical management of KD and treatment

Children suspected or diagnosed with KD usually require hospital admission for evaluation, observation and treatment. High dose intravenous immunoglobulin (IVIG) (2g/kg) is considered the first-line treatment for KD, and it is effective in reducing the risk of coronary artery disease, when administered within 10 days of the onset of fever. In addition to IVIG, acetylsalicylic acid, glucocorticoids and anti-TNF monoclonal antibodies have been used to combat the inflammation [26].

Rapid diagnosis of KD and treatment with IVIG prevent coronary artery abnormalities (CAA). Without timely treatment, CAAs and in particular aneurysms, could occur in up to 25% of children with KD [26,27]. Some children, however present resistance to IVIG treatment [27]. Up to 10–20% of children may not respond to IVIG, and they are usually considered high risk for CAA [26,27]. Giant coronary artery aneurysms in particular are considered predictive for long-term complications [20,26].

COVID-19 in children

As of 13 May 2020, children make up a very small proportion of the 576 024 laboratory confirmed COVID-19 cases reported to TESSy as case-based data with known age (0-4 years (n = 3 782, 0.7%), 5-9 years (n = 3 360, 0.6%), 10–14 years (n = 4 983, 0.9%)). Cases were slightly more likely to be male than female in children and adolescents (15 years or below, M:F ratio 1.1:1.0), and less likely among those aged 15 years and above (M:F ratio 0.8:1.0) [28]. The age distribution observed in the EU/EEA and the UK reflects testing policies and case definitions, which usually include the presence of symptoms. Therefore, it is possible that the small proportion of cases reported among children reflects a lower risk of children developing COVID-19 symptoms or children having milder symptoms in general, which do not lead to prioritisation for testing.

Symptoms

Similar to SARS and MERS, it appears that COVID-19 is less frequently observed in children and they tend to present with milder symptoms than adults [29-33]. The most commonly reported symptoms include fever and cough [34,35]. It appears that worldwide, children are also less likely to be tested due to the mild presentation of disease [31]. In a large nationwide case series from China, comprising 2 135 paediatric cases, only 34.1% of the cases were laboratory confirmed, and 4.4% of these were asymptomatic [36]. According to a systematic review of 12 case series from China with 6 to 2 143 children infected with SARS-CoV-2, a high number of pauci-symptomatic and asymptomatic children with SARS-CoV-2 infection were detected [32]. The five largest studies included in the systematic review reported 4 to 28% of asymptomatic patients [32]. In a cohort of 100 Italian children with SARS-CoV-2 infection assessed between March 3 and March 27, 21% were asymptomatic [34], while a multicentre Italian study of 168 children aged 1 day to 17 years with SARS-CoV-2 infection found 2.5% asymptomatic cases [33].

Among cases in TESSy with available data on clinical symptoms, there was a U-shaped pattern in the age distribution of the proportion of asymptomatic cases. The proportion of asymptomatic cases was higher among those aged under five years of age, 5-9 years and 10-14 years and 80 years and above, accounting for 15% (103/679 cases), 19% (116/603) and 17% (159/940) and 12% (800/6606) of cases, respectively. In contrast, the proportion asymptomatic was lower among those aged 15-44 years and 45-79 years, accounting for 8% (2173/28059) and 6% (2301/35637) of cases in these age groups, respectively. These figures will not represent the proportion asymptomatic by age in the population, given that testing case definitions for testing usually require symptoms to be present, and as they are based on available data submitted to TESSy from nine countries, they cannot be assumed to represent the EU/EEA and UK as a whole [28].

Severity

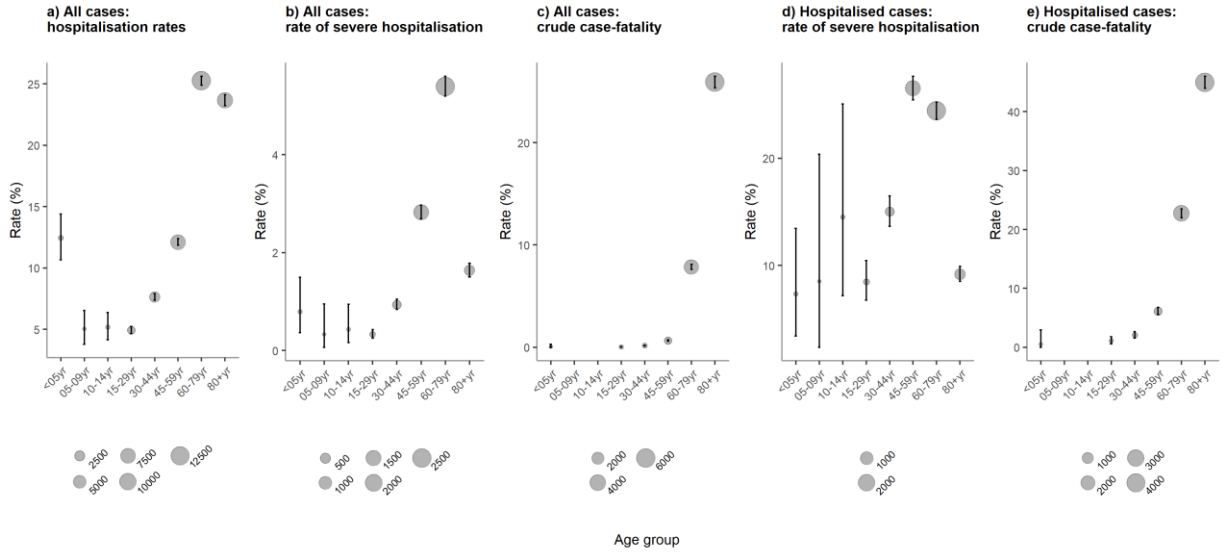
Different studies indicate mild disease in 10-60% of children, predominantly as a febrile upper respiratory tract disease. Although the course of disease in children tends to be milder, shorter and with respiratory or gastrointestinal symptoms, severe disease has also been reported [31].

A systematic review of 12 case series from China supported that moderate course of disease with mild pneumonia was most common and found in 39–82% of patients, while up to 8% of the hospitalized children showed a severe or very severe course, including fatalities [32]. Critically ill children accounted for less than 1% of all reported cases in China in early analyses [37,38]. Recent data from the US showed that 5.7%–20% of paediatric cases were hospitalised, a majority of them were infants [39]. A recent study from Italy involving 11 exclusively paediatric hospitals and 51 paediatric units across Italy, showed that hospital admission was inversely related to age ($p < 0.01$; Fisher exact test) [33], as also described for the TESSy data [28].

Data in TESSy show an elevated rate of hospitalisation among children under five years (12.5%; 95% confidence interval (CI): 10.7-14.4%) compared to persons aged 5-29 years, before increasing sharply with age among the older age groups. This pattern is present in most countries with available data for this outcome and is likely to reflect a lower threshold for hospitalisation for young children. Severe hospitalisation (requiring admission to ICU and/or respiratory support) was no more likely among children under five years (Figure 2) and children have a relatively shorter time from onset to hospitalisation and from hospitalisation to discharge than older groups [28]. Among cases aged under 15 years with information available on underlying health conditions, those who were hospitalised were more likely to have an underlying condition than those that were not (Table 2).

As of 13 May 2020, deaths among cases aged under 15 years were extremely uncommon; only four deaths among this age group out of a total of 44 695 (0.009%) had been reported to TESSy. This corresponds to a crude case-fatality of 0.06% among those aged under 15 years, compared to 16.9% among those age 15 years and above, driven largely by deaths in cases aged 60 years and above (Figure 2) [28].

Figure 2: Age-specific rates of severe outcome, TESSy, EU/EEA and UK, 13 May 2020



Note: y-axis scales differ for each plot; error bars are 95% confidence intervals; severe hospitalisation: hospitalised in ICU and/or requiring respiratory support; Crude case-fatality: proportion of deaths among total cases reported. Sources: Data are from a sub-set of countries reporting to TESSy that have sufficient data on the severe outcome. a) Austria, Croatia, Cyprus, Estonia, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Slovakia and United Kingdom; b) Cyprus, Estonia, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal and Slovakia; c) Austria, Croatia, Cyprus, Estonia, Germany, Greece, Iceland, Ireland, Latvia, Lithuania, Malta, Poland and Slovakia; d) Cyprus, Czechia, Estonia, Finland, Ireland, Italy, Latvia, Malta, Poland, Portugal and Slovakia; e) Austria, Cyprus, Czechia, Estonia, Finland, Germany, Ireland, Latvia, Lithuania, Malta, Norway, Poland, Slovakia and Sweden.

Table 2: Proportion of cases aged under 15 years with reported underlying health conditions by level of severity (TESSy data up to 13 May 2020)

Underlying health condition	Distribution, n (%)			
	Non-hospitalised cases	Hospitalised mild cases	Hospitalised severe cases	Fatal cases
None	720 (94%)	215 (85%)	5 (71%)	
Chronic lung disease, excluding asthma	25 (3%)	8 (3%)		
Asthma	9 (1%)	2 (1%)		
Cancer, malignancy	4 (1%)	3 (1%)	1 (14%)	
Cardiac disorder, excluding hypertension	4 (1%)	5 (2%)		
Neuromuscular disorder, chronic neurological	2 (<1%)	9 (4%)	1 (14%)	
Diabetes	1 (<1%)	1 (<1%)		
HIV / other immune deficiency	1 (<1%)	2 (1%)		
Liver-related condition, liver disease	1 (<1%)			
Haematological disorders	1 (<1%)	2 (1%)		
Total number of underlying conditions reported	**768 (100%)**	**247 (100%)**	**7 (100%)**	**0**

Hospitalised mild cases: hospitalised, not in ICU or requiring respiratory support; hospitalised severe cases: hospitalised in ICU and/or requiring respiratory support.

Infection and transmission

Data from population-based and cross-sectional studies indicate that children are unlikely to be primary source cases. In two cross sectional studies from Vo' (Italy) and a population-based screening programme in Iceland none of the 234 (Italy) and 848 (Iceland) children ≤10 years of age tested positive for SARS-CoV-2 [40,41]. In a targeted testing of symptomatic people or high-risk contacts in Iceland, 38 (6.7%) children under the age of 10 tested positive, in comparison to 13.7% of those who were 10 years or older [40]. In the Stockholm Region (Sweden), a cross-sectional study including 707 participants (147 were children <15 years of age) reported an overall positivity rate of 2.5% and a rate of 2.8% among children [42].

Children most likely contract COVID-19 in their households or through contact with infected family members, particularly in countries where school closures and strict physical distancing has been implemented [31,33,43,44]. In a recent publication from Italy, exposure to SARS-CoV-2 from an unknown source or from a source outside the child's family accounted for 55% of the cases of infection [34], while in another Italian cohort contact with a SARS-CoV-2 infected person outside the family was rarely reported and 67.3% (113/168) of children had at least one

parent who tested positive for SARS-CoV-2 infection [33]. Two studies on household transmission estimated the household secondary attack rate (SAR) to be 16.3% [45] and 13.8%, respectively [46].

Child-to-adult transmission appears to be uncommon. In the investigation of the first outbreak in France, an infected child did not transmit the disease despite close interactions with other children and teachers [47]. There are few case reports, with poorly documented data, describing a paediatric case as potential source of infection for adults [48,49].

Recent, yet not peer-reviewed, data from Switzerland show that initial SARS-CoV-2 viral loads at diagnosis in symptomatic children are comparable to those in adults [50], and that symptomatic children of all ages shed infectious virus in early acute illness [51]. In this study, also infectious virus isolation success was comparable to that of adults. The youngest patient from whom SARS-CoV-2 was isolated from, was a 7-day old neonate [51]. In another pre-print, it was also shown that there is no significant difference between viral loads in persons 1-20 years of age in comparison to adults 21-100 years of age [52].

Treatment of paediatric COVID-19

As mentioned above, the majority of paediatric COVID-19 cases detected have been mild and self-limited with few hospitalisations. Supportive care and oxygenation as required can be enough for mild and moderate cases. The management of severe cases presenting with severe respiratory distress and/or shock involves mechanical ventilation (usually of shorter duration than in adults) and use of IVIG. Thromboembolic episodes are not as frequent as in adults, although cases of myocarditis have been described [27]. For ethical reasons, children are usually not recruited to participate in clinical trials of the new antiviral and monoclonal antibody treatments for severe COVID-19.

PIMS-TS in children

PIMS-TS Symptoms

PIMS-TS cases presented with signs and symptoms similar to atypical KD and toxic shock Syndrome (TSS). All children had prolonged fever, abdominal pain and other gastrointestinal symptoms (50-60%) as well as conjunctivitis, rash, irritability and in some cases, shock, usually of myocardial origin. However, some respiratory symptoms could be present and dyspnoea was usually correlated with concurrent shock.

Some children were SARS-CoV-2 PCR (+), while others were IgG antibodies-positive. COVID-19 history or COVID-19-compatible symptoms could be either elicited in the history of the child or a household member. Markers of inflammation were elevated: neutrophilia with lymphopenia, significantly increased C-reactive protein (CRP), D-Dimer, IL-6 and ferritin levels, hypoalbuminaemia.

Coinfection with other pathogens has been investigated and in a few cases, human metapneumovirus (hMPV) or other pathogens have been detected (Communication from the WHO COVID-19 Clinical Network Knowledge Exchange, Table 1) [8,53].

Preliminary UK case definition

On 1 May 2020, the royal college of paediatrics and child health (RCPCH) published a guidance document on clinical management of the children presenting with PIMS-TS and proposed the following case definition [4]:

- A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other additional clinical, laboratory or imagining and ECG features. Children fulfilling full or partial criteria for Kawasaki disease may be included.
- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
- SARS-CoV-2 PCR testing positive or negative.

This case definition has also been disseminated to the International Network of Paediatric Surveillance Units (INoPSU [54]) as a suggestion for the development of an international case definition.

EU case definition

Currently, there is no agreed EU case definition, although it would be important to have a specific diagnostic code for follow-up surveys. Several EU Member States (e.g. Spain and France) are developing national case definitions to identify and monitor children presenting PIMS-TS.

Immune response and immunity

Immune response in KD and PIMS-TS

Although the aetiology for KD remains unknown, available evidence supports the hypothesis that the pathogenesis is closely associated with dysregulation of immune responses to an infectious agent [55-59]. The extent of the inflammatory reaction is also influenced by the genetic backgrounds of the individuals, resulting in a limited number of children developing KD in response to infectious stimuli [18]. As regards the PIMS-TS, no concrete working hypothesis for its pathogenesis has yet been put forward.

Differences in immune response in children and adults in SARS-CoV-2 infection

SARS-CoV, MERS, SARS-CoV-2 cause milder disease in children than in adults. This may be explained by differences in immune responses to the virus. In SARS-CoV-2 infection, CD8+ T cells and IL-6, a key cytokine, contributing to host defence through the stimulation of acute phase responses, hematopoiesis and immune reactions, play a vital role in virus clearance. The average level of IL-6 in paediatric cases was shown to be lower than in adults and significantly higher level of total T cells was observed in children, which may be partially responsible for the less severe symptoms in paediatric patients [60].

Immune response to SARS-CoV-2 involves both cell-mediated immunity and antibody production [61-63]. As for adults, the protection by antibodies and possibility of re-infection in children still remain to be studied. It is also too early to know how long the protective immune response against SARS-CoV-2 could last, as this will require longitudinal serological studies that follow patients' immunity over an extended period of time [64].

One possible mechanism to cause KD or PIMS-TS in children could be through antibody-dependent enhancement (ADE). The presence of antibodies can be detrimental when antibody levels are too low to provide protection but high enough that the antibodies enable the virus to spread [65]. ADE has been demonstrated in SARS-CoV where antibodies to the spike protein improve the ability of novel strains of the virus to enter cells in vitro [66].

Association between SARS-CoV-2 infection and PIMS

To examine causality between exposure to SARS-CoV-2 and PIMS-TS, the nine Bradford Hill causality criteria were applied (Table 3) to the relevant and limited available evidence identified from the literature and from the available data [67]. Based on the amount of information available, sample size of the studies and the certainty of the findings, each criterion was qualitatively assessed for supporting evidence and assigned a score, as follows: 3+ (the criterion is fully met); 2+ (the criterion is partially met); 1+ (the criterion is minimally met, with some aspects being consistent) and – (the criterion is not met) or "+/-" (conflicting evidence).

Table 3. Available evidence on causality of association between SARS-CoV-2 infection and PIMS

Criterion	Description	Qualitative evaluation of the Bradford Hill criteria (a)	Evidence	References
Strength	Whether those **with the exposure are at a higher risk of developing disease** and if so, how much more risk? This criterion suggests that a larger association increases the likelihood of causality.	+	• Countries with large outbreaks of SARS-CoV-2, both in Europe (France, Italy, Spain, UK) and in the US, have seen the occurrence of cases of PIMS in the late stages of the first wave of the COVID-19 pandemic. These countries, however have large populations.	See event background and Table 1
Consistency	The credibility of findings increases with **repetition of findings**, including consistency of study findings across **different populations** and **geographical locations**.	++	Several countries (France, Italy, Spain, Slovenia, UK and the US) observed increase of number of cases of PIMS-TS in children while others did not	See Table 1
Specificity	Causality is **more likely if the exposure causes only one specific disease** or syndrome, or if a specific location or population are being affected.	-	SARS-CoV-2 causes different kinds of symptoms	See disease background
Temporality	This criterion requires that the **exposure must occur before the disease**, and not	++	• PIMS-TS cases have been observed in children negative by PCR but	See Table 1 and [8,53,68]

Criterion	Description	Qualitative evaluation of the Bradford Hill criteria (a)	Evidence	References
	after a latency period that is too long. This criterion must always be fulfilled for causality to be concluded.		positive by serology suggesting prior exposure to SARS-CoV-2 between one to up to 14 days. • In addition, some children had confirmed and plausible COVID-19 exposure in their household or through contact with infected family members • PIMS_TS are reported relatively late during the waning tail of the first epidemic curve	
Biological gradient	The argument for causality is stronger in the presence of a **dose–response relationship**, where higher or longer exposure leads to an increased risk of disease.	-	Unknown whether higher or longer exposure leads to an increased risk of disease. But children most likely contract COVID-19 in their households or through contact with infected family members	Absence of evidence
Plausibility	A **conceivable mechanism** for causation between disease and exposure should exist for there to be a causal relationship.	+	The cause of KD remains unknown, but some evidence suggests that it could be triggered by an infection, which, in this case, would be consistent with SARS-CoV-2 infection. Putative mechanisms include induction of: • Immunoglobulin A (IgA)-producing plasma cells • RNA virus-like inclusion bodies • Up-regulation of type I interferon (IFN)-induced genes • Increased plasma level of C-X-C motif chemokine ligand 10 • A representative IFN-alpha2a/gamma-inducible protein • superantigens (SAgs) and pathogen/ microbe-associated molecular patterns (PAMPs/MAMPs)	[55-59]
Coherence	The current association should **not contradict any previous knowledge** available about the disease and/or exposure.	+	The current hypothesis on SARS-CoV-2 triggers hyperinflammation in the PIMS-TS cases, consistent with previous knowledge	
Experiment	This criterion can **involve scientific experiments** and addresses the association of exposure with disease. However, 'experiment' relates to the decrease in disease risk when the exposure is removed and often involves animal models.	-	Animal models have been produced for KD but do not accurately reproduce the pathologic features of KD (no data with SARS-CoV-2 yet).	[69-71]
Analogy	This criterion uses previous evidence of **an association between a similar exposure** and disease outcome to strengthen the current argument for causation.	+/-	Seasonal coronavirus (HCoV-NL63) and other viruses suggested to have an association e.g. Epstein-Barr virus, but also conflicting data presented for that; alternative hypotheses suggest that bacterial or fungal infection or exposure could cause KD	[72,73]

(a) A score: 3+ (the criterion is fully met); 2+ (the criterion is partially met); 1+ (the criterion is minimally met, with some aspects being consistent), – (the criterion is not met) and or "+/-" (conflicting evidence).

Overall, evidence that was assessed as limited to substantial was identified that support only 5/9 of the criteria for a causal relationship between SARS-CoV-2 infection and the development of PIMS-TS. Further clinical, epidemiological and experimental studies may elucidate the biological determinants of this syndrome and further assess the evidence supporting these causality criteria.

Disease surveillance for Kawasaki disease and COVID-19 disease in the EU/EAA and in the UK

While COVID-19 is under EU-level surveillance since the 26 January 2020, KD is not. A limited number of countries in the EU/EEA, however maintain surveillance systems or registries for KD.

Surveillance for COVID-19 in the EU/EEA and UK collects daily the number of laboratory-confirmed cases of COVID-19 within 24 hours after identification through the Early Warning and Response System (EWRS) and more comprehensive case-based and aggregated data in TESSy.

EWRS has been used to report and exchange the first information about these KLD cases in the EU/EEA and in the UK (Table 1).

Risk assessment questions

- What is the overall risk of COVID-19 in children in the EU/EEA and UK?
- What is the overall risk of PIMS-TS in children in the EU/EEA and the UK?

ECDC risk assessment for the EU/EEA

This assessment is based on information available to ECDC at the time of publication and unless otherwise stated, the assessment of risk refers to the risk that existed at the time of writing. It follows the ECDC rapid risk assessment methodology, with relevant adaptations. The overall risk is determined by a combination of risk of the probability of an event occurring and of its consequences (impact) to individuals or the population [74].

Risk of CoVID-19 in children in the EU/EEA and UK: In recent months, SARS-CoV-2 has been circulating and spreading in the EU/EEA and the UK through human-to-human transmission. SARS-CoV-2 proved to be highly transmissible amongst a virtually fully susceptible population. However, children were reported in relatively low number and with mostly asymptomatic or mild infection. There is not yet consensus whether the low proportion of cases reported in children is due to a low probability of infection or a low probability of developing severe symptoms, and therefore being less likely to be tested.

SARS-CoV-2 does not appear to be highly transmissible amongst children, particularly in younger children, as school outbreaks or school transmission instances have been rarely reported [6]. However, due to mild symptoms and the fact that school closure was one of the first physical distancing measures implemented by most countries, outbreaks may have remained undetected.

After reaching a peak in the end of March or in April, most EU/EEA countries have observed decreases in the daily number of newly reported cases in the last weeks. Consequently, although transmission persists, children are currently experiencing decreased opportunities for infections and, therefore, the likelihood of seeing large number of COVID-19 cases in children in the coming weeks is very small. For those countries where community transmission keeps occurring at high rate, opportunities for infection amongst children are similar to the previous months.

In summary, the probability of COVID-19 in children is currently assessed as "**low**". The impact of such disease is assessed as "**moderate**", therefore the overall risk of COVID-19 in children is assessed as **LOW.**

Risk of PIMS-TS in children in the EU/EEA and the UK: A causal association between SARS-CoV-2 infection and PIMS-TS has not yet been proven and several unknowns limit our ability to accurately assess this risk. However, it is hypothesised that PIMS-TS, seen as a dysregulation of the immune response to a pathogen, may occur as a late reaction to SARS-CoV-2 infection. The simultaneous occurrence of reported PIMS-TS cases and of children exposed to SARS-CoV-2 would support this hypothesis. It has to be noted, however, that only a relatively small number of children has been reported with PIMS-TS compared with those confirmed or suspected to have suffered SARS-CoV-2 infection.

The PIMS-TS paediatric cases detected until now are rather severe. It is possible that this relatively small number represents the more severe end of the spectrum of a post-infectious syndrome, as yet not fully recognised. As the onset of symptoms of PIMS-TS is estimated to be 2-4 weeks post COVID-19 infection [53], and as primary care services are going to start operating gradually in a more regular mode, more cases of PIMS-TS may be detected to provide us with a more complete picture of this phenomenon.

As of 11 May, four fatalities in PIMS-TS cases have been reported (1 in UK and 3 in USA) [8,53]. Long-term outcome and possible sequelae are overall unknown, however, since a number of children present with myocardial involvement (either myocarditis or coronary artery abnormalities), long-term follow up would be warranted.

In summary, the probability of PIMS-TS in children in the EU/EEA is currently assessed as **"very low**" and the impact of such disease is assessed as "**high**", therefore the overall risk of COVID-19-associated PIMS-TS in children is assessed as **LOW** risk.

Options for response

The COVID-19 epidemiological situation in the EU/EEA and the UK varies by region and country. To date, most countries in the EU/EEA and the UK are still experiencing sustained transmission, even if, following large-scale community-level measures, a few countries are transitioning to or have reached a situation where transmission is reduced to localised clusters. PIMS-TS cases appeared or were recognised in several EU/EEA countries and the UK in this decreasing phase of the epidemic. It is possible, as more countries enter this phase and more publicity is given to this syndrome, that more cases will be recognised.

Clinical management

Based on information from the reporting countries, management of the PIMS-TS cases identified until now has been mostly supportive as they are at the severe end of the spectrum. As KD was in the differential diagnosis, treatment with IVIG has been the mainstream management option, and antibiotics, corticosteroids (methyl-prednisolone), heparin, and anti-inflammatory agents (e.g. tocilizumab) have also been used. A few of the PIMS-TS cases have required critical care support with vasopressors and mechanical ventilation, and rarely extra corporeal membrane oxygenation (ECMO).

In the event of a suspect case, efforts should be made to test for a variety of infectious agents including, besides COVID-19 (both PCR and serology, if available): bacteria (like *Staphylococcus* and Group A *Streptococcus*), enteroviruses, Epstein-Barr virus, other respiratory viruses, etc. In addition, the household members should also be investigated for COVID-19.

Surveillance

There is a need for additional data on the incidence of PIMS-TS among children as well as defining the most affected age-groups and risk factors for this complication. In addition, the relevant conditions for identifying and reporting PIMS-TS need to be specified, along with the time-period between infection and onset of PIMS-TS and the confirmation of previous or current COVID-19 disease in the affected children. Although research studies are best placed to answer these questions, surveillance can provide initial supporting data. ECDC has discussed with Member States and will be including PIMS-TS as a possible complication to be reported in COVID-19 surveillance. Considering this syndrome appears to be rare, collation of data from across EU/EEA Member States and the UK would allow for more statistical power in the analysis describing these cases.

An important surveillance constraint is the challenge to link clinical presentation of PIMS-TS, and COVID- infection status. This is complex due to a) the non-specific symptoms associated with clinical presentation (see case definition) and b) the fact that the COVID-19 disease status of the presenting patient is often unknown. Asymptomatic infection may be more common in children and in many cases PIMS-TS presentation appears 2-4 weeks after infectious disease symptoms have subsided. Hence non-infectious disease clinicians who typically lead diagnosis and treatment of KD must be made aware of the potential link to COVID-19, and, even in the absence of COVID-like symptoms, ensure testing of presenting paediatric patients and their contacts to support case ascertainment.

PIMS-TS as defined in the case definition above should be reported in TESSy using the variable Complication = "PIMS". If data on previously diagnosed cases are available, these can also be reported in TESSy. In addition, WHO is considering adding information in the eCRF for COVID-19 surveillance to include PIMS-TS.

Risk communication

Risk communication messages to parents and caregivers should focus on what is known about this condition, while also adding that since it has only recently been reported in the context of COVID-19 disease, much about it remains unknown. Clear information about signs and symptoms should be provided, as well as simple explanation of what we know, and the importance of seeking treatment if there are concerns. It should be highlighted that the condition appears to be very rare, and that research is ongoing to find out more about the potential link of this syndrome with COVID-19 disease.

Messages should emphasise:

- Serious COVID-19-related illness and associated mortality among children is rare, and this newly reported condition appears to comprise only a very small proportion of these already rare, serious paediatric cases. On the other hand, it is well-known that children may develop inflammatory conditions in response to various infections.

- The potential association of this new condition with COVID-19 disease is still under investigation. There is still much that remains unknown about it.
- Early diagnosis of the inflammatory illness is important in order to ensure early treatment and reduce the risk of long-term complications. Therefore:
- Clear information should be given about signs and symptoms that parents/caregivers should 'watch out for' in order to seek immediate treatment.
- Information should indicate who to contact for further advice and referral, as per the national/local advice (e.g. hotline, paediatric services).
- Reassurance should be given about the availability of treatment for the inflammatory illness, but it should also be clarified that this condition can be severe and some patients may require intensive care for cardiac and respiratory support.
- Reminders of the importance of all households maintaining high standards of hand hygiene, respiratory etiquette and implementation of any necessary physical distancing and other preventive measures in the context of the COVID-19 pandemic, as per the public health advice in their country, in order to protect themselves and others.
- Interest in this topic may be substantial due to its novelty and because it is being reported in a population group that has been continuously referred to as having very low risk of severe disease from COVID-19 until now. Health authorities should therefore consider providing information about current knowledge regarding this illness in their information platforms (e.g. websites, FAQ sections). The information should be updated accordingly as more evidence becomes available.

Communication efforts should also target healthcare workers in order to:

- Inform via the dedicated communication channels for general practitioners and paediatricians about the recent reports, whilst including reassurance that it is not common.
- Inform about recommended course of action, treatment and any reporting requirements.
- Highlight the importance of early diagnosis and treatment.
- Provide links for further information.

Research needs/gaps

Several unknowns still exist as regards SARS-CoV-2 that have significant implications in understanding this new syndrome. Quality transmissibility studies are missing to clarify the role of children. There are also needs to understand the SARS-CoV-2 induced humoral and cellular immune responses in more detail and for how long those immune responses last as well as how those may relate to PIMS-TS.

To improve our understanding about the possible association between SARS-CoV-2 infection and PIMS-TS, children suspected of this condition could be considered for recruitment in research and surveillance studies, respecting ethical principles of involvement of children in such studies. In addition to descriptive observational studies to further understand the basic clinical, epidemiological and genetic parameters associated with this emerging condition, focus should also be given to aetiological studies, such as those using a case/control design, to assist in verifying a causal link between COVID-19 and PIMS-TS. In addition, animal models on KD and PIMS-TS would help to understand the dose-response and association of SARS-CoV-2 with PIMS-TS as well as the immune response pathways associated with PIMS-TS pathogenesis.

As regards the management of PIMS-TS, it remains unclear; most cases have been treated as atypical KD with additional supportive care as needed. It would be important, considering the rarity of the syndrome, to coordinate (e.g. by a learned society) a clinical expert group at the EU level for providing diagnosis, treatment and follow-up guidance.

There are currently few interventional clinical trials for COVID-19 open to patients younger than 18 years of age [75,76]; however, there are a number of EU-led research actions that may provide an opportunity to further knowledge. For example, within the connect4children network funded under the IMI initiative, one UK-led study specifically focuses on KD, and may offer opportunities for enhanced understanding and possible options for therapeutic intervention [76]. The International Network of Paediatric Surveillance Units (INoPSU) used to lead research studies on KD, and could reactivate and promote surveillance studies on KD and PIMS-TS [54].

In the UK, the EU Horizon2020 project DIAMONDS is recruiting children with infectious and inflammatory disorders for the development of a molecular test for the rapid diagnosis of serious infectious and inflammatory diseases using personalised gene signatures [77]. A British Paediatric Surveillance Unit study has started on 12 May 2020 this week to gather information on this inflammatory syndrome.

From the COVID-19 perspective, the RECOVER project has already well-established hospital networks to support understanding of clinical presentation of COVID-19, and could be used to increase understanding of the emerging condition [78]. Moreover, the European Medicines Agency has announced accelerated regulatory procedures for the development and marketing authorisation of therapeutics and vaccines, which include a rapid agreement of paediatric investigation plans (PIPs) and rapid compliance [79].

Limitations

There are many limitations in this rapid risk assessment:

- The true incidence of COVID-19 in children is unknown. The reasons behind the low proportion of children amongst all COVID-19 cases are not completely clear. One explanation could be that the milder symptoms they exhibit, possibly, do not lead to prioritisation for testing.
- Only few countries maintain surveillance systems for Kawasaki disease, therefore accurate incidence comparisons pre- and post- COVID-19 cannot be made with certainty.
- Currently, there is no agreed international nor EU case definition of the PIMS-TS; national case definitions are being developed, which may lead to difficulties to compare data from different countries. PIMS-TS is not reported yet at the EU level, therefore the impact of the new syndrome cannot be fully assessed.
- As was the case with COVID-19 at the beginning of the pandemic, we lack the full spectrum of disease and outcome data.
- Overall limited evidence was identified to support a causal relationship between SARS-CoV-2 infection and the development of PIMS-TS.

Source and date of request

ECDC internal decision, 11 May 2020.

Consulted experts

ECDC experts (in alphabetic order): Barbara Albiger, Leonidas Alexakis, Agoritsa Baka, Eeva Broberg, Sergio Brusin, Nick Bundle, Orlando Cenciarelli, Silvia Funke, John Kinsman, Csaba Ködmön, Favelle Lamb, Katrin Leitmeyer, Howard Needham, Taina Niskanen, Thomas Mollet, Andreea Salajan, Ettore Severi, Gianfranco Spiteri, Marc Struelens, Andrea Würz.

Consulted public health experts:

Austria: Werner Zenz (Medical University of Graz);
Germany: Felix Reichert (Robert Koch Institute - RKI), Jakob Armann (University Children's Hospital, Dresden);
Italy: Patrizia Parodi (Ministry of Health), Rolando Cimaz (University of Milan);
Netherlands: Aura Timen (Rijksinstituut voor Volksgezondheid en Milieu - RIVM);
Portugal: Maria Joao Brito (Hospital Dona Estefânia, Lisboa);
Spain: Alfredo Tagarro (Hospital Universitario Infanta Sofía, Madrid);
Sweden: Bernice Aronsson (the Public Health Agency of Sweden);
Switzerland: Mirjam Mäusezahl (Swiss Federal Office of Public Health);
United Kingdom: Elizabeth Whittaker (Imperial College Healthcare NHS Trust, London);
World Health Organization (WHO): Richard Pebody (European Regional Office).

All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

References

1. European Centre for Disease Prevention and Control (ECDC). Situation update worldwide. Stockholm: ECDC. Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases.
2. European Centre for Disease Prevention and Control (ECDC). COVID-19. Stockholm: ECDC; 2020 [cited 2020 12 May 2020]. Available from: https://www.ecdc.europa.eu/en/novel-coronavirus-china.
3. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Bradley Segal J, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hospital pediatrics. 2020.
4. Royal College of Paediatrics and Child Health, editor. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. UK: Royal College of Paediatrics and Child Health; 2020.
5. New York State Government. Amid Ongoing COVID-19 Pandemic, Governor Cuomo Announces New York is Notifying 49 Other States of COVID-Related Illness in Children 2020 [11/05/2020]. Available from: https://www.governor.ny.gov/news/amid-ongoing-covid-19-pandemic-governor-cuomo-announces-new-york-notifying-49-other-states.
6. Santé publique France. COVID-19 chez l'enfant : état des connaissances en amont de la réouverture des écoles Paris: Santé publique France; 2020 [10/05/2020]. Available from: https://www.santepubliquefrance.fr/les-actualites/2020/covid-19-chez-l-enfant-etat-des-connaissances-en-amont-de-la-reouverture-des-ecoles.
7. Osservatorio malattie rare. Malattia di Kawasaki e COVID-19: possibile un nesso tra le due patologie? Roma: OMAR; 2020 [10/05/2020]. Available from: https://www.osservatoriomalattierare.it/news/attualita/16038-malattia-di-kawasaki-e-covid-19-possibile-un-nesso-tra-le-due-patologie.
8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020.
9. Slaughter G, Favaro A, St Philip E. Canadian doctors investigate possible link between COVID-19 and rare children's disease Toronto: CTV News; 2020 [11/05/2020]. Available from: https://www.ctvnews.ca/health/coronavirus/canadian-doctors-investigate-possible-link-between-covid-19-and-rare-children-s-disease-1.4922856.
10. Welt.de. Fieber und Ausschlag – Uniklinik meldet mysteriöse Symptome bei Kindern: Welt.de; 2020 [11/05/2020]. Available from: https://www.welt.de/wissenschaft/article207653797/Zusammenhang-mit-Corona-Uniklinik-Dresden-meldet-mysterioese-Symptome-bei-Kindern.html.
11. Lecrubier A. COVID-19: How to Recognize and Manage Kawasaki-like Syndrome: Medscape; 2020 [10/05/2020]. Available from: https://www.medscape.com/viewarticle/930203.
12. Lecrubier A. Kawasaki : les 25 enfants d'Ile-de-France tous testés positifs au COVID-19: Medscape; 2020 [11/05/2020]. Available from: https://francais.medscape.com/voirarticle/3605952.
13. Marrone C. Sindrome di Kawasaki: colpisce i vasi sanguigni dei più piccoli (e potrebbe essere legata al coronavirus) Milan: Corriere della Sera; 2020 [13/05/2020]. Available from: https://www.corriere.it/salute/malattie-rare/20_aprile_28/coronavirus-l-infiammazione-vasi-sanguigni-che-colpisce-bambini-ac22ec24-895f-11ea-8073-abbb9eae2ee6.shtml.
14. Son MB, Sundel RP. Chapter 35 - Kawasaki Disease. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. Textbook of Pediatric Rheumatology (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 467-83.e6.
15. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123(5):e783-9.
16. 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.
17. Giray T, Bicer S, Kucuk O, Col D, Yalvac Z, Gurol Y, et al. Four cases with Kawasaki disease and viral infection: aetiology or association. Le infezioni in medicina. 2016;24(4):340-4.
18. Nakamura A, Ikeda K, Hamaoka K. Aetiological Significance of Infectious Stimuli in Kawasaki Disease. Frontiers in Pediatrics. 2019;7(244).
19. Rowley AH, Shulman ST. The Epidemiology and Pathogenesis of Kawasaki Disease. Frontiers in pediatrics. 2018;6:374-.
20. Dietz SM, van Stijn D, Burgner D, Levin M, Kuipers IM, Hutten BA, et al. Dissecting Kawasaki disease: a state-of-the-art review. European journal of pediatrics. 2017;176(8):995-1009.
21. Tulloh RMR, Mayon-White R, Harnden A, Ramanan AV, Tizard EJ, Shingadia D, et al. Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015. Archives of disease in childhood. 2019;104(7):640-6.
22. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, et al. Kawasaki Disease in Germany: A Prospective, Population-based Study Adjusted for Underreporting. Pediatr Infect Dis J. 2016;35(2):129-34.
23. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. Journal of epidemiology. 2012;22(2):79-85.
24. Saguil A, Fargo M, Grogan S. Diagnosis and management of kawasaki disease. American family physician. 2015;91(6):365-71.
25. Kim GB. Reality of Kawasaki disease epidemiology. Korean J Pediatr. 2019;62(8):292-6.
26. Kimberlin DW, Brady MT, Jackson MA, Long SS. Kawasaki Disease. Red Book 2018: American Academy of Pediatrics; 2018. p. 490-7.

27. World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected - Interim guidance. Geneva: World Health Organization (WHO), 2020 13/03/2020. Report No.: WHO/2019-nCoV/clinical/2020.4.
28. (ECDC) ECfDPaC. ECDC COVID-19 Surveillance Report, Week 19 2020 Stockholm: ECDC; 2020 [14/05/2020]. Available from: http://covid19-surveillance-report.ecdc.europa.eu.
29. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA pediatrics. 2020.
30. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta paediatrica (Oslo, Norway : 1992). 2020;109(6):1088-95.
31. Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. The Pediatric Infectious Disease Journal. 2020;39(5):355-68.
32. Streng A, Hartmann K, Armann J, Berner R, Liese JG. COVID-19 in hospitalized children and adolescents. Monatsschrift Kinderheilkunde : Organ der Deutschen Gesellschaft fur Kinderheilkunde. 2020:1-12.
33. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance. 2020;25(18):2000600.
34. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in Pediatric Emergency Departments in Italy. The New England journal of medicine. 2020.
35. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morbidity and mortality weekly report. 2020;69(14):422-6.
36. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020.
37. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: WHO; 2020 [1 March, 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.
38. Dong XC, Li JM, Bai JY, Liu ZQ, Zhou PH, Gao L, et al. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2020;41(2):145-51.
39. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 10;69(14):422-6. [23 April, 2020]. Available from: http://dx.doi.org/10.15585/mmwr.mm6914e4.
40. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. New England Journal of Medicine. 2020.
41. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. medRxiv. 2020. 2020.04.17.20053157]. Available from: https://www.medrxiv.org/content/medrxiv/early/2020/04/18/2020.04.17.20053157.full.pdf.
42. Folkhälsomyndigheten (FHM). Förekomsten av covid-19 i region Stockholm, 26 mars–3 april 2020. [cited 21 April, 2020]. Available from: https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/f/forekomsten-av-covid-19-i-region-stockholm-26-mars3-april-2020/.
43. Peng H, Gao P, Xu Q, Liu M, Peng J, Wang Y, et al. Coronavirus Disease 2019 in Children: Characteristics, Antimicrobial Treatment, and Outcomes. Journal of Clinical Virology. 2020:104425.
44. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020:S1473-3099(20)30198-5.
45. Li W, Zhang B, Lu J, Liu S, Chang Z, Cao P, et al. The characteristics of household transmission of COVID-19. Clinical Infectious Diseases. 2020.
46. Jing Q-L, Liu M-J, Yuan J, Zhang Z-B, Zhang A-R, Dean NE, et al. Household Secondary Attack Rate of COVID-19 and Associated Determinants. medRxiv. 2020:2020.04.11.20056010.
47. Danis K, Epaulard O, Bénet T, Gaymard A, Campoy S, Bothelo-Nevers E, et al. Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020. Clinical Infectious Diseases. 2020.
48. Cai J, Xu J, Lin D, Yang z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clinical Infectious Diseases. 2020.
49. See KC, Liew SM, Ng DCE, Chew EL, Khoo EM, Sam CH, et al. COVID-19: Four Paediatric Cases in Malaysia. International Journal of Infectious Diseases. 2020.
50. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020.
51. L'Huillier AG, Torriani G, Pigny F, Kaiser L, Eckerle I. Shedding of infectious SARS-CoV-2 in symptomatic neonates, children and adolescents. medRxiv. 2020:2020.04.27.20076778.
52. Jones TC, Mühlemann B, Veith T, Zuchowski M, Hofmann J, Stein A, et al. An analysis of SARS-CoV-2 viral load by patient age2020 10/05/2020]. Available from: https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf.
53. Morand A, Urbina D, Fabre A. COVID-19 and Kawasaki Like Disease: The Known-Known, the Unknown-Known and the Unknown-Unknown. Preprints. 2020.

54. International Network of Paediatric Surveillance Unit. Worldwide research on rare paediatric diseases 2020 [13/05/2020]. Available from: https://www.inopsu.com/.
55. Rowley AH, Baker SC, Orenstein JM, Shulman ST. Searching for the cause of Kawasaki disease--cytoplasmic inclusion bodies provide new insight. Nature reviews Microbiology. 2008;6(5):394-401.
56. Rowley AH, Baker SC, Shulman ST, Garcia FL, Fox LM, Kos IM, et al. RNA-containing cytoplasmic inclusion bodies in ciliated bronchial epithelium months to years after acute Kawasaki disease. PloS one. 2008;3(2):e1582.
57. Rowley AH, Shulman ST, Mask CA, Finn LS, Terai M, Baker SC, et al. IgA plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute Kawasaki disease. J Infect Dis. 2000;182(4):1183-91.
58. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. Journal of immunology (Baltimore, Md : 1950). 2001;166(2):1334-43.
59. Rowley AH, Wylie KM, Kim KY, Pink AJ, Yang A, Reindel R, et al. The transcriptional profile of coronary arteritis in Kawasaki disease. BMC genomics. 2015;16:1076.
60. Chen J, Zhang ZZ, Chen YK, Long QX, Tian WG, Deng HJ, et al. The clinical and immunological features of pediatric COVID-19 patients in China. Genes & diseases. 2020.
61. OKBA NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv. 2020:2020.03.18.20038059.
62. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. The Journal of Infectious Diseases. 2020.
63. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clinical Infectious Diseases. 2020.
64. Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. London: Imperial College London, 2020 9.
65. Gronvall G, Connell N, Kobokovich A, West R, Warmbrod KL, Shearer MP, et al. Developing a National Strategy for Serology (Antibody Testing) in the United States. Baltimore: 2020 22/04/2020. Report No.
66. Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. J Virol. 2020;94(5):e02015-19.
67. Hill AB. The environment and disease: Association or causation? Proceedings of the Royal Society of Medicine. 1965;58(5):295-300.
68. New York City Health Department. 2020 Health Alert #13: Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19. New York: New York City Health Department; 2020. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf.
69. Orenstein JM, Rowley AH. An evaluation of the validity of the animal models of Kawasaki disease vasculopathy. Ultrastructural pathology. 2014;38(4):245-7.
70. Wakita D, Kurashima Y, Crother TR, Noval Rivas M, Lee Y, Chen S, et al. Role of Interleukin-1 Signaling in a Mouse Model of Kawasaki Disease-Associated Abdominal Aortic Aneurysm. Arteriosclerosis, thrombosis, and vascular biology. 2016;36(5):886-97.
71. Yeung RS. Lessons learned from an animal model of Kawasaki disease. Clinical and experimental rheumatology. 2007;25(1 Suppl 44):S69-71.
72. Dominguez SR, Anderson MS, Glodé MP, Robinson CC, Holmes KV. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki syndrome. J Infect Dis. 2006;194(12):1697-701.
73. Chang LY, Chiang BL, Kao CL, Wu MH, Chen PJ, Berkhout B, et al. Lack of association between infection with a novel human coronavirus (HCoV), HCoV-NH, and Kawasaki disease in Taiwan. J Infect Dis. 2006;193(2):283-6.
74. European Centre for Disease Prevention and Control (ECDC). Operational tool on rapid risk assessment methodology. Stockholm: ECDC; 2019 [6 April, 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/operational-tool-rapid-risk-assessment-methodolgy-ecdc-2019.pdf.
75. Hwang TJ, Randolph AG, Bourgeois FT. Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19). JAMA pediatrics. 2020.
76. Conect4children. New conect4children Consortium Selects Inaugural Research Portfolio to Advance Development of Innovative Paediatric Medicines. 2019.
77. Diamonds2020. Diamonds – personalised molecular testing for serious illness 2020 [13/05/2020]. Available from: https://www.diamonds2020.eu/.
78. RECOVER. Rapid European COVID-19 Emergency Response research - A new EU-funded project to tackle COVID-19. 2020 [13/05/2020]. Available from: https://www.recover-europe.eu/.
79. European Medicines Agency (EMA). COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines. Amsterdam: EMA; 2020.