RAPID RISK ASSESSMENT

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

15 May 2020

Summary

Several countries affected by the coronavirus disease (COVID-19) pandemic recently reported cases of children that were hospitalised in intensive care due to a rare paediatric inflammatory multisystem syndrome (PIMS). The presenting signs and symptoms are a mix of the ones for Kawasaki disease (KD) and toxic shock syndrome (TSS) and are characterised, among others, by fever, abdominal pain and cardiac involvement. A possible temporal association with SARS-COV-2 infection has been hypothesised because some of the children that were tested for SARS-CoV-2 infection were either positive by polymerase chain reaction (PCR) or serology.

In total, about 230 suspected cases of this new paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) have been reported in EU/EEA countries and the UK in 2020, including two fatalities, one in the UK and one in France. These cases are being further investigated. So far, epidemiological studies have shown that children appear to be less affected by COVID-19. Only 2.1% of all laboratory-confirmed COVID-19 cases reported to The European Surveillance System (TESSy) were in the age group between 0 and 14 years of age.

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

At current, the risk is assessed as follows:

- 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 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 has absolute priority, data collection from EU/EEA Member States and the UK would strengthen the body of knowledge for this rare condition and allow for a better analysis of these cases. An analysis of surveillance data could clarify the incidence of KD/PIMS and identify the most affected age groups and risk factors for both conditions.

ECDC has agreed with the EU/EAA Member States and the UK to include PIMS as a possible complication to be reported for EU-level COVID-19 surveillance. Research efforts should aim at a) determining the role of SARS-CoV-2 in the pathogenesis of PIMS-TS and b) answering other significant remaining questions.

Risk communication is needed to raise awareness in the medical community about PIMS-TS and inform parents and caregivers about signs and symptoms. The importance of timely contact with a healthcare worker should be stressed. Risk communication should emphasise that PIMS-TS is a rare condition and that its potential link with COVID-19 is neither established nor well understood.

Suggested citation: European Centre for Disease Prevention and Control. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children – 15 May 2020. ECDC: Stockholm; 2020.

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 (now called SARS-CoV-2) as the causative agent of this outbreak. Since 31 December 2019 and as of 15 May 2020, 1 286 952 cases of COVID-19 were reported by EU/EEA countries and the UK, including 153 361 deaths [1]. Detailed information on the COVID-19 cases reported so far are available on a dedicated ECDC webpage [2].

On **27 April 2020**, health authorities in the United Kingdom reported a number of seriously ill children presenting with signs of circulatory shock and hyperinflammatory state, with features consistent with toxic shock or 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** in the United States [3].

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

On **4 May**, the New York City Department of Health and Mental Hygiene issued an alert to identify children with PIMS-TS in New York City hospitals [68], and **as of 10 May** at least 85 children in New York City have been reported as presenting with inflammatory syndrome. Three have died due to TSS with links to SARS-CoV-2 infection, and another two deaths are under investigation [5].

On **6 May**, 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 [6].

France and Italy observed an unusually high number of children with TSS (with some features reminiscent of KD) in paediatric intensive care; some of those children also tested positive for SARS-COV-2 [7,8]. In France, **as of 12 May**, 125 suspected cases were reported, 65 of which were considered PIMS-TS and an additional 15 have probable links to COVID-19 [7,9]. In the province of Bergamo in Italy, approximately 10 suspected Kawasaki-like disease cases have been recorded since 1 January 2020, eight of which were reclassified as PIMS-TS [8,10].

Austria, 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 (personal communication from the WHO COVID-19 Clinical Network Knowledge Exchange). Using the EU's Early Warning and Response System (EWRS), Austria, Germany and Portugal reported PIMS-TS cases testing positive 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) [11,12].

Table 1. Distribution and characteristics of reported PIMS cases in EU/EEA countries in 2020, as of 12 3 May 2020

Country	Date of report-ing in 2020	Number of 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 positive by PCR before deterioration of symptoms, positive IgG two weeks later	Group A streptococci	Hyperinflammatory 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 [11]
France	14 May 2020	125	(<1- ≥ 15 years)-	Positive by PCR and serological test (65) 19possible links with COVID-19 29 pending testing results 16 unknown status	NS	Hyperinflammatory state with features consistent with TSS or KD	1	Official [9]
Germany	11 May 2020	5	8 (3-14)	Positive	None	Hyperinflammatory state with features consistent with TSS or KD	NS	EWRS
Greece	11 May 2020	1	NS	Negative	NS	NS	NS	Official: (personal communication)

Country	Date of report-ing in 2020	Number of reported cases	Median age in years (range)	SARS-CoV-2 infection status	Other associated pathogens	Clinical manifestations	Fatalities	Sources (references)
Italy	13 May 2020	10	7.5	Positive by serology (8), of which two were positive by PCR too One was tested right after a high dose of IVIG; test was inconclusive	NS	Classical KD (5) including non-exudative conjunctivitis, hand and feet anomalies (i.e. erythema or firm induration, or both), and polymorphic rash, changes of the lips or oral cavity, laterocervical lymphadenopathy, diarrhoea Incomplete KD (5) including bulbar non-exudative conjunctivitis; changes of the lips or oral cavity, or both; and polymorphic rash, coronary aneurysm pericardial effusion, diarrhoea	0	Publication: [8]
Luxembourg	30 April 2020	5	NS	One positive serology test for SARS-CoV-2 Two negative but with signs of infection Two negative	NS	Atypical KD	NS	EWRS
Portugal	4 May 2020	1	13	Positive by serology test for SARS-CoV (IgG antibodies positive) and negative by RT-PCR	NS	High fever >39 °C, 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 KD TSS: skin lesions were biopsied; results are pending. Chest X-ray – severe COVID-19 pneumonia	0	EWRS
Spain	10 May 2020	22 (including KD)	6.6 (6–13 months)	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	KLD	0	EWRS
Switzerland	1 May 2020	3	NS	NS	NS	NS	NS	Media: [12]
UK	27 April 2020	NS	NS	NS	NS	Signs of circulatory shock and hyperinflammatory state with features consistent with TSS or KD	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: [6]
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)

Country	Date of reporting in 2020	Number of reported cases	Median age in years (range)	SARS-CoV-2 infection status	Other associated pathogens	Clinical manifestations	Fatalities	Sources (references)
US	7 Apr 2020	1	6 months	Positive	NS	Fever, persistent erythematous, seemingly non-pruritic, blotchy rash, sinus tachycardia (200 beats/minute), tachypnea with an oxygen saturation of 100%, irritability, limbic-sparing conjunctivitis, 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]

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; KLD: Kawasaki-like 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 KD and concurrent COVID-19 was published in the United States 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 who tested positive for COVID-19 by RT-PCR [3]. Since this first report, countries with outbreaks of SARS-CoV-2 have reported further cases of PIMS-TS (Table 1 above). PIMS-TS, according to initial reports, shares a number of clinical features with KD in children (e.g. persistent fever, cardiac involvement) but also displays significant differences, e.g. in the affected age groups (mostly children >5 years of age, as compared to classical KD). According to media reports, scientific publications and official reports, more than 300 suspected classical KD or PIMS-TS cases are currently under investigation in Europe and 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

KD is a self-limited vasculitis of childhood [13]. 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 [14].

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 pathogens, which causes an immune-mediated response resulting in KD in genetically predisposed children [18]. 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, and Epstein–Barr virus [13]. To date, a causal association with SARS-CoV-2 has not been established.

Incidence of KD

Although the leading cause of childhood-acquired heart disease in industrialised nations, KD is a rare condition [19]. 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 is 10–30 times higher than in the US or Europe [25].

Clinical management of Kawasaki disease 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; 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 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 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, male–female ratio 1.1:1.0), and less likely among those aged 15 years and above (male–female 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. It is possible that the small proportion of cases reported among children reflects a lower risk of children developing COVID-19 symptoms or the fact that children generally experience milder symptoms, which explains that children are not prioritised when it comes to testing.

Pooled and country-specific TESSy data are available in an online report series, published weekly on the ECDC website: https://covid19-surveillance-report.ecdc.europa.eu/.

Symptoms

It appears that COVID-19, just like SARS and MERS, is less frequently observed in children, and children tend to present with milder symptoms than adults [28-32]. The most commonly reported symptoms include fever and cough [33,34]. Due to the mild presentation of the disease in children, it appears that children are also less likely to be tested [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% asymptomatic patients [32]. In a cohort of 100 Italian children with SARS-CoV-2 infection assessed between 3 and 27 March, 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 the following age groups; under five years of age, 5–9 years, 10–14 years and 80 years and above, accounting for 15% (103/679 cases), 19% (116/603), 17% (159/940) and 12% (800/6 606) of cases, respectively. By contrast, the proportion of asymptomatic cases was lower among those aged 15–44 years and 45–79 years, accounting for 8% (2 173/28 059) and 6% (2 301/35 637) of cases in these age groups, respectively. These numbers do not accurately reflect the actual proportion of asymptomatic cases in each age group. This is due to the fact that in order to get tested, certain criteria must me be met, usually the presence of symptoms. Numbers are also in no way representative of the actual situation because so far only nine countries have submitted data to TESSy [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 in children [31].

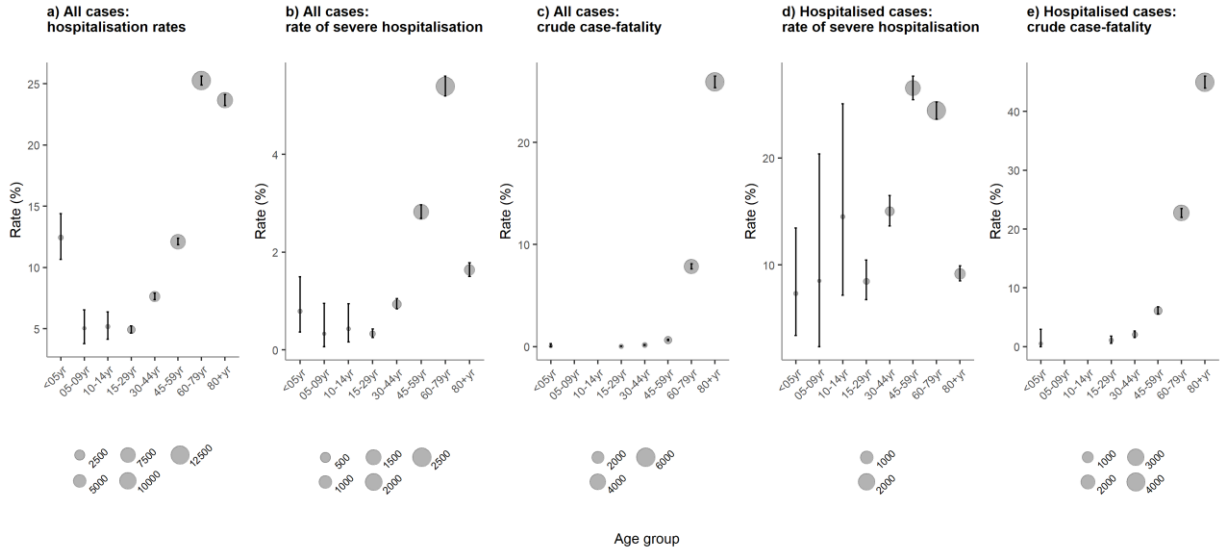
A systematic review of 12 case series from China found that moderate courses of disease with mild pneumonia were most commonly found in 39–82% of patients, while up to 8% of the hospitalised children showed a severe or very severe course, including fatalities [32]. Critically ill children accounted for less than 1% of all reported cases in China in early analyses [36,37]. Recent data from the US showed that 5.7%–20% of paediatric cases were hospitalised, a majority of them 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 by 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. 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 however no more likely among children under five years compared to other children aged 5–14 years (Figure 2). Children also have a relatively shorter time from onset to hospitalisation and from hospitalisation to discharge than older groups [28]. Among cases aged under 15 years of age and with information 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%) have 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 aged 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 subset 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 [39,40]. 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 [39]. 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 have been implemented [30,32,42,43]. 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 infections [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 to be 16.3% [45] and 13.8%, respectively [46].

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

Recent, not yet 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, infectious virus isolation success was comparable to that in adults. The youngest patient from whom SARS-CoV-2 was isolated, was a 7-day old neonate [51]. In another pre-print, it was shown that there was no significant difference between viral loads in the age group 1–20 years and the adult age group 21–100 years of age [52].

Treatment of paediatric COVID-19

As mentioned above, the majority of paediatric COVID-19 cases have been mild and self-limited with few hospitalisations. Supportive care and oxygenation as required may be sufficient for mild and moderate cases. The management of 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.

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection in children

PIMS-TS symptoms

PIMS-TS cases presented with signs and symptoms similar to atypical KD and 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 positive for SARS-CoV-2 by PCR, while others were positive for IgG antibodies. 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, D-dimer, IL-6 and ferritin levels, and hypoalbuminaemia.

Coinfection with other pathogens has been investigated, and in a few cases, human metapneumovirus (hMPV) or other pathogens have been detected (personal communication from the WHO COVID-19 Clinical Network Knowledge Exchange, see also Table 1) [6,53].

Preliminary UK case definition

On 1 May 2020, the Royal College of Paediatrics and Child Health published a guidance document on the clinical management of 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 with 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 [53-57]. 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 [17]. 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 and 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, while a significantly higher level of total T cells was observed in children, which may be partially responsible for the less severe symptoms in paediatric patients [58].

Immune response to SARS-CoV-2 involves both cell-mediated immunity and antibody production [57-59]. As for adults, the protection by antibodies and the 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 that causes KD or PIMS-TS in children could be via 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, in vitro, antibodies to the spike protein improve the ability of novel strains of the virus to enter cells [64].

Association between SARS-CoV-2 infection and PIMS

In order 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 evidence identified from literature and 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: 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); or +/– (conflicting evidence).

Table 3. Available evidence on causality of association between SARS-CoV-2 infection and PIMS, according to Bradford Hill [67]

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 (France, Italy, Spain, UK, 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, also have large populations.	See event background and Table 1

Criterion*	Description*	Qualitative evaluation of the Bradford Hill criteria (a)	Evidence	References
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, US) observed an increase of case numbers 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 is 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 after a latency period that is too long. This criterion must always be fulfilled for causality to be concluded.	++	PIMS-TS cases have been observed in children negative by PCR but 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 is reported relatively late during the waning tail of the first epidemic curve	See Table 1 and [8,52,66]
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)	[53-57]
Coherence	The current association should **not contradict any previous knowledge** available about the disease and/or exposure.	+	The current hypothesis holds that SARS-CoV-2 triggers hyperinflammation in the PIMS-TS cases, which is consistent with previous knowledge	

Criterion*	Description*	Qualitative evaluation of the Bradford Hill criteria (a)	Evidence	References
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 for SARS-CoV-2 as of yet).	[66-68]
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 were suggested to have an association, e.g. Epstein–Barr virus; but there are also conflicting data for this association; alternative hypotheses suggest that bacterial or fungal infection or exposure could cause KD	[70,71]

**: Criteria and description are based on Hill's criteria for causation [67]*
Scores: 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).

After assessing the evidence and rating it (limited to substantial), only five out of nine criteria would support a causal relationship between SARS-CoV-2 infection and the development of PIMS-TS. Future clinical, epidemiological and experimental studies may elucidate the biological determinants of this syndrome and further explore the evidence supporting these causality criteria.

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

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

Surveillance systems for COVID-19 in the EU/EEA and UK collect every day the number of laboratory-confirmed cases of COVID-19 within 24 hours after identification through the Early Warning and Response System (EWRS); in addition, more comprehensive case-based and aggregated data are collected in TESSy.

The EWRS was 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 among a virtually fully susceptible population. However, children were reported in relatively low numbers and with mostly asymptomatic or mild infection. There is no consensus yet 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 (which makes getting tested for the disease less likely).

SARS-CoV-2 does not appear to be highly transmissible in children, particularly in younger children, and school outbreaks or school transmission instances have been rarely reported [7]. However, due to mild symptoms and the fact that school closures were among the first physical distancing measures implemented in most countries, outbreaks may have remained undetected.

After reaching a peak at 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 infection and, therefore, the likelihood of seeing large number of COVID-19 cases in children in the coming weeks is very small. In countries where community transmission keeps occurring at high rate, opportunities for infection in 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 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 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 the large overall number of children with confirmed or suspected SARS-CoV-2 infection.

The cases of PIMS-TS detected so far have been rather severe. It is possible that this relatively small number of cases represents the more severe end of the spectrum of a post-infectious syndrome that has not been fully recognised. As the onset of symptoms of PIMS-TS is estimated to be 2-4 weeks post COVID-19 infection [9, 53], and as primary care services are gradually operating 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, five fatalities in PIMS-TS cases have been reported (one in France, one in the UK, three in the US) [6,53]. Long-term outcome and possible sequelae are overall unknown, but since a number of children present with myocardial involvement (either myocarditis or coronary artery abnormalities), long-term follow up is warranted.

In summary, the probability of PIMS-TS in children in the EU/EEA is currently assessed as **very low**, and the impact of PIMS-TS 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 that more cases will be recognised as more countries enter this phase and more publicity is given to this syndrome.

Clinical management

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

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

Surveillance

There is a need for additional data on the incidence of PIMS-TS among children. A better understanding of the most affected age groups and risk factors for this complication is required. In addition, the relevant conditions for identifying and reporting PIMS-TS need to be specified, along with the 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 suited to answer these questions, surveillance can provide initial supporting data. ECDC has discussed this with the Member States and will include PIMS-TS as a possible complication to its standard COVID-19 surveillance. Since this syndrome appears to be rare, collating data from across EU/EEA Member States and the UK would provide more statistical power for the analysis of these cases.

An important surveillance constraint is the challenge to link the clinical presentation of PIMS-TS with the 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 electronic case report form (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. It should also be mentioned that much about PIMS-TS remains unknown because it has only recently been reported in the context of COVID-19. Concise information about signs and symptoms should be provided, as well as clear explanations of what we know, and why it is important to seek 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 to COVID-19.

Messages should emphasise the following:

- 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 this 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 and respiratory etiquette; physical distancing and other preventive measures in the context of the COVID-19 pandemic should be observed, as per the public health advice in the patient's country.
- Interest in this topic may be substantial due to its novelty and because it is being reported in a population group that has been referred to as having a low risk of severe coronavirus disease. Health authorities should therefore consider providing information about the current knowledge regarding this illness on their online information platforms. The information should be updated as more evidence becomes available.

Communication efforts should target healthcare workers through dedicated communication channels for general practitioners and paediatricians in order to:

- inform about the most recent reports, while including reassurance that this is not a very common complication;
- inform about recommended courses of action, recommended treatment and requirements for reporting;
- highlight the importance of early diagnosis and treatment, and
- provide links for further information.

Research needs and gaps

Several unknowns still exist with regard to SARS-CoV-2. This has significant implications for the understanding of this new syndrome. Quality transmissibility studies that could clarify the role of children are missing. There is also a lack of understanding with regard to the SARS-CoV-2-induced humoral and cellular immune responses; more details are needed, especially on the duration of those immune responses and how they may relate to PIMS-TS.

In order 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 the ethical principles for 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 (case/control design) in order 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.

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

There are currently very few interventional clinical trials for COVID-19 open to patients younger than 18 years of age [67,68]; there are, however, several EU-led research actions. For example, one UK-led study specifically focuses on KD. The study is funded through the Innovative Medicines Initiative (IMI) and part of the 'connect4children' network and may provide 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 Horizon 2020 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 to gather information on this inflammatory syndrome [10].

From a COVID-19 perspective, the RECOVER project has already well-established hospital networks to improve the understanding of the clinical presentation of COVID-19. It could be used to increase our 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 several limitations in this rapid risk assessment:

- The true incidence of COVID-19 in children is unknown. The reasons behind the low proportion of children among all COVID-19 cases are not completely clear. One explanation could be that the milder symptoms that children display lead to a low testing rate.
- Only few countries maintain surveillance systems for KD, therefore accurate incidence comparisons pre- and post- COVID-19 cannot be made with certainty.
- Currently, there is no agreed international nor EU case definition for PIMS-TS; the national case definitions that are currently being developed may lead to difficulties when comparing data from different countries. PIMS-TS is not yet reported 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, only 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

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest. [34]

Disclaimer

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