Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process

*Rachel Harwood, Benjamin Allin, Christine E Jones, Elizabeth Whittaker, Padmanabhan Ramnarayan, Athimalaipet V Ramanan, Musa Kaleem, Robert Tulloh, Mark J Peters, Sarah Almond, Peter J Davis, Michael Levin, Andrew Tometzki, Saul N Faust, Marian Knight, Simon Kenny, on behalf of the PIMS-TS National Consensus Management Study Group**

Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) is a novel condition that was first reported in April, 2020. We aimed to develop a national consensus management pathway for the UK to provide guidance for clinicians caring for children with PIMS-TS. A three-phase online Delphi process and virtual consensus meeting sought consensus over the investigation, management, and research priorities from multidisciplinary clinicians caring for children with PIMS-TS. We used 140 consensus statements to derive a consensus management pathway that describes the initial investigation of children with suspected PIMS-TS, including blood markers to help determine the severity of disease, an echocardiogram, and a viral and septic screen to exclude other infectious causes of illness. The importance of a multidisciplinary team in decision making for children with PIMS-TS is highlighted throughout the guidance, along with the recommended treatment options, including supportive care, intravenous immunoglobulin, methylprednisolone, and biological therapies. These include IL-1 antagonists (eg, anakinra), IL-6 receptor blockers (eg, tocilizumab), and anti-TNF agents (eg, infliximab) for children with Kawasaki disease-like phenotype and non-specific presentations. Use of a rapid online Delphi process has made it possible to generate a national consensus pathway in a timely and cost-efficient manner in the middle of a global pandemic. The consensus statements represent the views of UK clinicians and are applicable to children in the UK suspected of having PIMS-TS. Future evidence will inform updates to this guidance, which in the interim provides a solid framework to support clinicians caring for children with PIMS-TS. This process has directly informed new PIMS-TS specific treatment groups as part of the adaptive UK RECOVERY trial protocol, which is the first formal randomised controlled trial of therapies for PIMS-TS globally.

Lancet Child Adolesc Health **2021; 5: 133–41**

Published **Online** September 18, 2020 https://doi.org/10.1016/S2352-4642(20)30304-7

This online publication has been corrected. The corrected version first appeared at thelancet.com on January 20, 2021

*Listed at the end of this Review

Department of Paediatric Surgery (R Harwood MRCS, S Almond FRCS, S Kenny FRCS) **and Department of Paediatric Radiology** (M Kaleem FRCR), **Alder Hey Children's Hospital, Liverpool, UK; School of Life Sciences, University of Liverpool, Liverpool, UK** (R Harwood, S Almond, S Kenny); **National Perinatal Epidemiology Unit, Nuffield Department of Health, University of Oxford, Oxford, UK** (B Allin DPhil, M Knight DPhil); **Department of Paediatric Surgery, Ozxford Children's Hospital, Oxford, UK** (B Allin); **NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton Foundation NHS Trust and Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK** (C E Jones PhD, S N Faust FRCPCH); **Department of Paediatrics, Imperial College Healthcare NHS Trust, London, UK** (E Whittaker PhD, M Levin PhD); **Section of Paediatric Infectious Disease, Department of Infectious Disease, Imperial College London, London, UK** (E Whittaker, M Levin); **Children's Acute Transport Service, Great Ormond Street Hospital for Children, London, UK** (P Ramnarayan MD); **Department of Paediatric Rheumatology** (A V Ramanan FRCP),

Introduction

Since the first reports from London, UK, in late April, 2020, many countries have reported children presenting severely unwell with features of substantial inflammation temporally related to the COVID-19 pandemic, including the USA,[1] France,[2,3] Italy,[4] and the UK.[5,6] Subsequently, parallels have been drawn between the presenting features of this syndrome and other known conditions, including complete, incomplete, and atypical Kawasaki disease (with or without coronary artery dilatation), toxic shock syndrome, viral sepsis, and, less commonly, macrophage activation syndrome or haemophagocytic lymphohistiocytosis.[5] Preliminary case definitions of this novel inflammatory condition have been published by the UK Royal College of Paediatrics and Child Health (RCPCH),[7] the US Center for Disease Control and Prevention (CDC),[8] and WHO;[9] the CDC and WHO have both named the condition multisystem inflammatory syndrome in children (MIS-C). Variation in the definitions exists due to the novelty of this condition, the relatively small number of children described, and unconfirmed association with current or previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For the purposes of this Review, which focuses on the opinions of UK clinicians, we have used the RCPCH definition of the condition: paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS).

The many clinical uncertainties regarding this new disease syndrome rapidly became apparent after initial identification of the condition. These uncertainties include the prevalence, apparent differing clinical phenotypes, variable severity, clinical course, and optimal management. To provide clarity to UK clinicians, National Health Service (NHS) England led a process to develop national clinical management guidance through a rapid consensus exercise. The process also explored where equipoise exists for the planning of formal research trials that include children with PIMS-TS. Given the status of PIMS-TS as a new syndrome, clinical consensus combined with experience in treating the initial cases was the starting point in the process of constructing a clinical guideline and defining key areas of research. The UK Randomised Evaluation of COVID-19 (RECOVERY) trial Steering Committee opened the trial protocol (including anti-inflammatory drugs) to enrolment of children with COVID-19 and related inflammation before NHS England initiated the consensus process. Therefore, enrolment in the RECOVERY trial, and future studies, were included within the scope of the consensus process.

A Delphi process is a well established method for achieving consensus from multiple groups of stakeholders,[10] and has been used in health care for many purposes, including development of core outcome sets and identification of measures for monitoring quality of care.[11–15] Broadly, a Delphi process involves asking

Department of Paediatric Cardiology (R Tulloh FRCPCH, A Tometzki FRCPCH)**, and Paediatric Intensive Care Unit** (P J Davis FRCPCH)**, Bristol Royal Hospital for Children, Bristol, UK; Royal National Hospital for Rheumatic Diseases, Bath, UK** (A V Ramanan)**; University of Bristol, Bristol, UK** (A V Ramanan, R Tulloh)**; University College London Great Ormond Street Institute of Child Health and Great Ormond Street Hospital NHS Trust, NIHR Biomedical Research Centre, London, UK** (M J Peters PhD)**; and NHS England/Improvement, Redditch, UK** (S Kenny)

Correspondence to: Miss Rachel Harwood, Department of Paediatric Surgery, Alder Hey Children's Hospital, Liverpool, L12 2AP, UK **Rachel.Harwood@liverpool.ac.uk**

See **Online** for appendix

For the **RECOVERY trial** see https://www.recoverytrial.net

Key messages

- PIMS-TS is a novel condition that has emerged during the COVID-19 pandemic; ongoing research into its cause, disease course, and therapies that improve the outcomes of children with the condition is essential and should be supported by recruitment to relevant studies including RECOVERY, ISARIC-4C, DIAMONDS, and British Paediatric Surveillance Unit surveillance in the UK
- Children suspected of having PIMS-TS should undergo first-line blood tests to determine if they meet the diagnostic criteria; subsequent tests to determine the severity of disease, exclude important differential diagnoses, and screen for cardiac involvement are recommended
- A multidisciplinary team is an essential facet in the care of children with PIMS-TS and every child with suspected PIMS-TS should be discussed with a multidisciplinary team within 24 h of suspected diagnosis and when considering biological therapy
- Therapeutic choices for PIMS-TS are dependent on the presenting phenotype (Kawasaki disease-like or non-specific presentation) and high-risk features or severity of disease; a step-wise pathway of intravenous immunoglobulin, followed by methylprednisolone and biological therapy is recommended for children not recruited to a trial
- This management pathway is based primarily on expert opinion and should be updated as new evidence emerges.

PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with COVID-19.

respondents to complete sequential questionnaires with group opinion relayed to individual participants between completion of the questionnaires. Children with PIMS-TS require the expertise of clinicians who specialise in immunology, infectious diseases, respiratory medicine, rheumatology, cardiology, intensive care, general paediatrics, haematology, and, in some cases, surgery, radiology, and neurology. Therefore, we aimed to seek consensus from participants in these key stakeholder groups regarding the diagnosis and management of children with suspected PIMS-TS, to identify areas where equipoise existed to inform subsequent research, and to explore whether consensus existed on how children with PIMS-TS could be enrolled in the RECOVERY trial.

Methods

Study design

In summary, we used a three-phase online Delphi process to identify statements where a national multidisciplinary panel agreed that consensus existed regarding the investigation and management of children with suspected PIMS-TS (appendix p 1). A consensus meeting was held via a web-based platform (Zoom Video Communications, version 5.1.0) to review statements where consensus had not been achieved during the Delphi process. A face-to-face consensus meeting was not held because of COVID-19-related physical distancing restrictions.

This work was considered to be a quality improvement project by the Health Research Authority, and therefore approval from an ethical review board was not required.

The consensus processes centred on the definition of PIMS-TS, published by the RCPCH, which is as follows: a child presenting with persistent fever, inflammation (neutrophilia, increased C-reactive protein, and lymphopenia) and evidence of single-organ or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with additional features, which might include children fulfilling full or incomplete criteria for Kawasaki disease; exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, and infections associated with myocarditis such as enterovirus; and positive or negative SARS-CoV-2 PCR test.

All participants were clinicians who were specifically selected to cover the range of multidisciplinary clinical and research expertise needed to diagnose and manage children with PIMS-TS, and were invited personally by the study group via email or telephone to participate in the process through subspeciality groups and personal contacts. Clinicians were selected because of their expertise in their respective fields, their clinical experience of caring for children with PIMS-TS, or their involvement in research into PIMS-TS. Those who agreed to participate were divided into three panels to facilitate feedback throughout the Delphi process. Panel one comprised experts in paediatric infectious diseases and immunology, paediatric rheumatology, paediatric respiratory medicine, and pharmacists with specialist expertise in biological therapy; panel two comprised experts in paediatric cardiology, paediatric intensive care and transport, and paediatric haematology; and panel three comprised general paediatricians, paediatric radiologists, and paediatric surgeons.

Representation in all three panels was sought, but experience in management of children with PIMS-TS, and the need to rapidly conclude the consensus process were prioritised over seeking wider engagement of clinicians or achieving numerical balance between the panels.

Although in most health-care-related Delphi processes the involvement of patients or the public as key stakeholders has been appropriate, we felt that the clinical expertise required to assess the statements around which consensus was required for development of this clinical management pathway precluded inclusion of these groups. Therefore, patients and the public were not involved in either the design or conduct of this study.

The Delphi process

Statements for assessment in phase one of the Delphi process were derived by the study management group (RH, BA, MKn, SK) from reviews of the existing literature and expert opinion, including drafts of local guidelines.

Participants in the Delphi process were asked in phase one and phase two to propose additional statements that they considered necessary for assessment. These additional statements were reviewed by the study management group (RH, BA, CEJ MKn, SNF, AVR, SK), and if they were within the scope of the study they were included for assessment in the subsequent phase. A three-phase Delphi process was done online concurrently for the three panels. Results of the Delphi process were discussed in a virtual, online, consensus meeting attended by a representative sample of experts from each panel. The consensus meeting was chaired by an independent, non-voting, non-paediatric clinical academic who was experienced in Delphi methodology (MKn).

Limesurvey was used as the data collection platform for the three phases of the Delphi Process. A specific program developed by Limesurvey Consultancy and the National Perinatal Epidemiology Unit enabled participants to be invited by email, all statements to be reviewed and scored online, creation of the histograms used in phases 2 and 3, which were also checked manually, and data extraction for each phase. In phase one of the Delphi process, participants were asked to score statements from 1–9 on the basis of how much they agreed with the statements. Scores of 1, 2, and 3 were "disagree with statement"; 4, 5, and 6 were "agree with statement"; and 7, 8, and 9 were "strongly agree with statement". A further option of "Don't know" was given and participants were asked to score a statement as such if they did not consider themselves to have expertise in that area. In phase two, participants were shown graphical and numerical representations of how their panel overall had scored each statement and were asked to re-score the statements taking that information into account. Some statements were re-worded or were clarified with additional words between phase one and phase two in response to respondent's comments. In phase three, participants were shown graphical and numerical representations of how all three panels had scored each statement and asked to re-score the statements taking that information into account.

Each phase had a 72 h window for response, and participants were sent a reminder email if they had not completed the phase with 24 h remaining. Participants who did not complete a phase by the deadline were deemed to have withdrawn from the study and were not invited to take part in subsequent phases.

We used the COMET method for determining consensus.[16] Consensus agreement was defined as at least 70% of participants scoring a statement 7–9 (ie, strongly agree), and fewer than 15% of participants scoring a statement 1–3 (ie, disagree) in all three individual panels. Consensus disagreement was defined as at least 70% of participants scoring a statement 1–3, and fewer than 15% of participants scoring a statement 7–9 in all three individual panels. After phases two and three, if statements met consensus agreement or consensus disagreement, they were excluded from the next stage of assessment.

Statements for which consensus had been achieved in two of three panels at the end of phase three were discussed in the consensus meeting. Statements discussed at the consensus meeting were assessed using a simple binary vote of agree or disagree. Those statements for which more than 70% of participants either agreed or disagreed with the statement were deemed to have met consensus. If consensus was not met after the initial vote, in-depth discussions were held to understand why disagreement existed and were followed up with a second vote. In situations where participants felt agreement could be achieved with minor modifications to the statements, these modifications were made. The final guidance was constructed from the statements that met consensus agreement or that met consensus disagreement after phase two, phase three, or the consensus meeting.

The consensus statements are applicable to children in the UK suspected of having PIMS-TS. They might also be applicable in other high-income countries, although the views described here only represent those of UK clinicians. The statements are less likely to be applicable in countries where infrastructure and access to health care and treatments are substantially different to in the UK.

Findings

98 participants were invited to contribute to the Delphi process, 72 agreed and completed phase one (May 25–30, 2020), 56 completed phase two (June 2–6, 2020), and 46 (64%) completed phase 3 (June 9–13, 2020; table). Throughout the Delphi process the full range of specialities were represented, apart from haematology, for which no participants with expertise in this area continued to phase three (appendix p 1–2). Ten participants attended the consensus meeting (table). 217 statements were assessed in phase one, 35 statements were added for assessment in phase two, and three statements were added for assessment in phase three (figure). Details of the consensus process and all assessed statements and their final consensus decisions determined either in phase two or phase three are in the appendix (pp 2–75). The final guidance was formed from the 140 statements for which consensus was met throughout the consensus process (figure).

Consensus statements

Panels 1, 2, and 3 show the full consensus guidance and integration with clinical research developed during this process. Investigation of children suspected of having PIMS-TS is recommended to take place making use of a clinical multidisciplinary team and stepwise clinical management. To diagnose PIMS-TS, the first step after clinical history and examination is to obtain blood tests, specifically full blood count; C-reactive protein; urea, creatinine, and electrolytes; and liver function. If results from these tests support a diagnosis of PIMS-TS then

	Completed phase one	Completed phase two	Completed phase three	Attended consensus meeting
Panel one	40/51 (78%)	32/40 (80%)	25/32 (78%)	3/7 (43%)
Panel two	17/22 (77%)	11/17 (65%)	11/11 (100%)	5/5 (100%)
Panel three	15/25 (60%)	13/15 (87%)	10/13 (77%)	2/5 (40%)
Overall	72/98 (73%)	56/72 (78%)	46/56 (82%)	10/17 (59%)

Data are n/N (%), where n is the number of participants and N is number invited. Panel one comprised experts in paediatric infectious diseases and immunology, paediatric rheumatology, paediatric respiratory medicine, and pharmacists with specialist expertise in biological therapy; panel two comprised experts in paediatric cardiology, paediatric intensive care and transport, and paediatric haematology; and panel three comprised general paediatricians, paediatric radiologists, and paediatric surgeons.

Table: **Participants in the Delphi process**

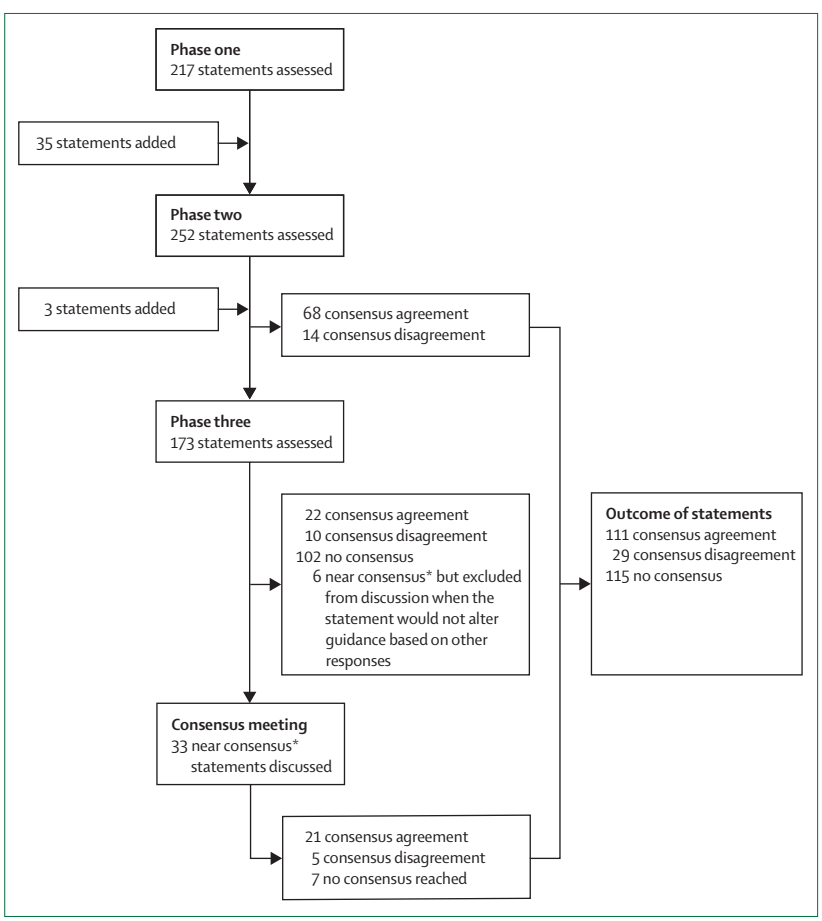

Figure: **Flow of statements through consensus process**
*Near consensus meaning ≥70% agreement in two of three panels.

additional investigations are recommended to determine the diagnosis and severity of disease and look for complications of PIMS-TS (panel 1).

The consensus process determined that patients with PIMS-TS should be primarily categorised according to the phenotype of disease (Kawasaki disease-like or non-specific) but that severity assessment for both phenotypes is recommended to support clinicians in determining a patient's location of care (panel 2). Kawasaki disease-like phenotype is defined using the criteria for the diagnosis of Kawasaki disease published by the American Heart Association,[17] and the distinction between phenotypes is based on expert opinion rather than a proven biological difference. The consensus process did not determine that children who present with shock should be cared for in a level 2 paediatric High Dependency Unit or a level 3 Paediatric Intensive Care Unit with availability of extracorporeal membrane oxygenation (ECMO) on site. However, substantial discrepancy existed between the views of the intensive care panel (ie, panel two), who felt the ability to deliver ECMO is important, and the clinical infectious diseases and immunology panel (ie, panel one), among whom most agreed that ECMO availability was not necessary. This discrepancy in opinion might be due to many centres specialising in infectious diseases and immunology not being co-located with ECMO services and shows the importance of the input of a multidisciplinary team in the management of children with PIMS-TS. Panel 2 describes the core and additional members of the multidisciplinary team, as determined through the consensus process.

All children with PIMS-TS should be treated for presumed sepsis until the microbiological culture results are available. The Delphi process has provided the consensus for the adaptation of the UK RECOVERY randomised, controlled, platform trial to open for specific groups of children with PIMS-TS of all phenotypes and we recommend that all children who meet criteria for inclusion in the trial are offered the opportunity to enrol. If the patient is not enrolled in the RECOVERY trial, specific management varies according to phenotype and severity. Intravenous immunoglobulin is recommended for all children with Kawasaki disease-like phenotype but is not recommended for each and every child with a non-specific presentation, for whom no treatment might be required (panel 3). Methylprednisolone is recommended as the second-line therapy for both phenotypes and is advised to be given at the same time as intravenous immunoglobulin for high-risk children with Kawasaki disease-like phenotype (panel 3). The dose of methylprednisolone was not asked about in the Delphi process, but dosing of 10 –30 mg/kg per day for 3 days is typically recommended. Biological therapy is recommended as the third-line therapy for all children with PIMS-TS. A consensus was met that infliximab is the biological therapy of choice for Kawasaki disease-like phenotype but equipoise exists between anakinra, infliximab, and tocilizumab for children with a non-specific presentation of PIMS-TS.

Consensus was gained in the consensus meeting for children with both phenotypes of PIMS-TS to receive either intravenous immunoglobulin or methylprednisolone as a first-line therapy in a clinical trial setting and this decision has been incorporated into the first stage

Panel 1: Investigation of children with suspected PIMS-TS

Initial investigation

Children presenting to hospital with fever*, abdominal pain, gastrointestinal, respiratory, or neurological symptoms who are stable and have no other clear cause for their symptoms should have the following initial blood tests done to help to identify whether they have PIMS-TS: full blood count†; C-reactive protein†; urea, creatinine, and electrolytes†; and liver function† If the diagnostic criteria for PIMS-TS are met and it remains a differential diagnosis, the following investigations are recommended

Second-line investigations

(1) In addition to the initial investigations, children presenting with features that meet the criteria for PIMS-TS should have measurement of the following blood tests‡: blood gas and lactate§, fibrinogen†, ferritin†, D-dimer†, troponin†, N-terminal pro-B-type natriuretic peptide§, lactate dehydrogenase¶

(2) SARS-CoV-2 RT-PCR test on an appropriate respiratory tract sample and SARS-CoV-2 serology†‡

(3) Septic and viral screen† (lumbar puncture only if specifically indicated§)‡

(4) 12-lead electrocardiogram†‡

(5) Chest radiograph†‡

(6) Echocardiogram†‡

(7) In children with abdominal pain who meet the criteria for PIMS-TS and require imaging, abdominal ultrasound scan should be the first-line investigation to rule out alternative diagnoses (eg, appendicitis)§

(8) Echocardiogram is not routinely recommended for children presenting with symptoms that do not meet the criteria for PIMS-TS§

(9) Children who are physiologically unstable should have a daily echocardiogram†

(10) No consensus exists about the frequency of subsequent echocardiograms for physiologically stable children with PIMS-TS; we recommend that frequency is determined by a paediatric cardiologist on the basis of previous echocardiography findings, the clinical status of the patient, and change in blood markers of inflammation

(11) All children with coronary artery dilatation should be discussed with a paediatric cardiologist†

(12) Contrast-enhanced CT of the coronary vessels is not routinely recommended for children with PIMS-TS†

PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with COVID-19. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *The current definition for PIMS-TS includes persistent fever as a presenting complaint; as more cases are reported, this definition might change but currently most experts think that PIMS-TS should only be considered in febrile children—the ongoing study by the British Paediatric Surveillance Unit will provide further details around this definition. †Determined in phase two of the Delphi process. ‡To be done within 12 h of admission to hospital. §Determined in phase three of the Delphi process. ¶Determined during the consensus meeting.

of randomisation of the RECOVERY trial (panel 3). If a decision has been made by a multidisciplinary team to commence biological therapy, there was consensus that a child within the RECOVERY trial should be offered the opportunity to enter the second stage of randomisation to either tocilizumab or standard of care. There was support within the consensus group that a trial could consider supportive care only as an additional group, but this statement was not voted on because it was not asked within the first three phases of the Delphi process, and therefore not included in the consensus guidance.

Consensus was met to follow local protocols for anti-platelet therapy for children with Kawasaki disease-like phenotype and that all children with PIMS-TS should be given low-dose aspirin for a minimum of 6 weeks. There was agreement that, for a child who is otherwise well, stable cardiac function and no pyrexia for 24 h are criteria for discharge from hospital (panel 2).

Clinical follow-up is recommended at 1–2 weeks and 6 weeks after discharge with echocardiography being a key investigation during follow-up because coronary artery aneurysms have been seen even after mild disease courses.[5] Multi-disciplinary follow-up with paediatric infectious diseases and immunology consultants and paediatric cardiologists is recommended for children with coronary artery abnormalities or who have required organ support for PIMS-TS (panel 2).

There was strong support for ongoing research into PIMS-TS and consensus that children should be offered the opportunity to be included in studies including DIAMONDS, ISARIC-4C (ISRCTN66726260), and the national British Paediatric Surveillance Unit (BPSU) PIMS-TS registry.

Discussion

Use of an online Delphi process and virtual consensus meeting has enabled a national multidisciplinary panel to achieve consensus around 140 statements relating to the investigation and management of children with PIMS-TS, and participation of these children in studies including, but not limited to, DIAMONDS, ISARIC-4C, and the RECOVERY trial. Based on the results of this process, we have been able to develop a national consensus management pathway for the care of children with suspected PIMS-TS within 6 weeks of the need for such guidance becoming apparent. However, all participants recognise that this process has relied on clinical opinion based on the little evidence available. Until further evidence is available, this management pathway can provide a framework for managing children with suspected PIMS-TS in the UK.

The key strength of this work was the ability to achieve consensus relating to the management of a novel and complex condition on the basis of quantitative data from a relatively large number of participants from multiple geographical regions. The process was done over a short period of time (5 weeks), in the middle of a global pandemic, without the ability to hold face-to-face

For more on **DIAMONDS** see https://www.diamonds2020.eu

For more on **ISARIC-4C** see https://isaric4c.net

For **BPSU website** see https://www.rcpch.ac.uk/work-we-do/bpsu

For the **PIMS-TS registry** see https://www.rcpch.ac.uk/workwe- do/bpsu/study-multisysteminflammatory-syndromekawasaki- disease-toxic-shocksyndrome

Panel 2: Management processes for children with PIMS-TS

Classification of PIMS-TS

Primary classification of PIMS-TS should be based on the presenting phenotype*:

(A) Kawasaki disease-like: complete and incomplete, classified using the American Heart Association criteria[17]

(B) Non-specific: children presenting with shock or fever, or both, and symptoms that might include abdominal pain, gastrointestinal, respiratory, or neurological symptoms that do not meet the criteria for Kawasaki disease

Subsequent classification of severity is recommended*

Location of care and features of severity of PIMS-TS

(1) Location of care should be determined by the severity of disease and discussion in a multidisciplinary team will aid risk stratification

(2) Features of severe disease might be indicated by the presence of any of the following factors, particularly when present in combination:

- Physiological features of severe disease: extended capillary refill time†; persistent hypotension†; persistent tachycardia†; requirement for 40 mL/kg fluid bolus†; oxygen saturation <92% in room air†
- Haematological and biochemical features: clinically significant increase in C-reactive protein† (consensus reached for >300 mg/L but subsequent evidence suggests >150 mg/L); clinically significant increase or increasing troponin†; increasing NT-proBNP†; increased or increasing lactate†; clinically significant increase or increasing ferritin†; clinically significant increase or increasing D-dimer‡; increased or increasing lactate dehydrogenase‡; high or low fibrinogen‡; increased creatinine‡
- Cardiac features: abnormal electrocardiogram†; coronary artery aneurysms on echocardiogram†; left ventricular failure*

(3) Children with features of complete or incomplete Kawasaki disease-like phenotype can be cared for in a local hospital without a PICU if they meet the following criteria: they do not have single or multiple organ dysfunction or cardiac involvement and they can have an echocardiogram by a clinician with competency to assess for cardiac involvement including coronary artery abnormalities*

(4) Escalation to a PICU that has clinicians with cardiology expertise should be considered early for any child with single or multiple organ dysfunction†

(5) Children with any evidence of cardiac involvement (increased troponin, increased NT-proBNP, abnormal coronary arteries on echocardiogram or contrast-enhanced CT) should be cared for in a paediatric high dependency unit or PICU with clinicians who have cardiology expertise†

Multidisciplinary team

(1) Early discussion with the core multidisciplinary team should occur for children who are severely unwell

(2) Every child with suspected PIMS-TS should be discussed by a multidisciplinary team within 24 h of admission or identification of PIMS-TS if already an inpatient†

(3) Core members of the team should include paediatric infectious diseases experts or immunologists† or paediatric rheumatologists†, or both, and paediatric cardiologists† and paediatric intensivists†

(4) Additional members of the multidisciplinary team should include general paediatricians caring for children in a local hospital with a PICU for children with multiple comorbidities*, a paediatric transport team for children who are severely unwell in a local hospital with a PICU at the time of discussion with the multidisciplinary team*, and paediatric haematologists for children with haemoglobinopathies, clotting disorders, coagulopathy, or thrombosis‡

Discharge criteria and follow-up

(1) To be discharged from hospital, children who are otherwise well should have stable cardiac function† and no pyrexia for 24 h‡

(2) Children with PIMS-TS should be followed up in the first 1–2 weeks after discharge* and have further follow-up 6 weeks after discharge†; echocardiography should form part of this follow-up for all children with PIMS-TS

(3) Multidisciplinary follow-up should be done for children with coronary artery abnormalities* or who have required organ support due to PIMS-TS*

(4) During follow-up, multidisciplinary clinicians should include paediatric cardiology† and paediatric infectious disease‡ experts

NT-proBNP=N-terminal pro-B-type natriuretic peptide. PICU=paediatric intensive care unit. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Determined in phase three of the Delphi process. †Determined in phase two of the Delphi process. ‡Determined during the consensus meeting

meetings, large round-table discussions, or focus groups. A similar process has been used in the USA for multisystem inflammatory syndrome in children;[19] however, the small number of participants and less diverse range of experts restrict the applicability of some of their findings, particularly around the choice of biological therapy when the equipoise that is found within the Delphi process described in this Review is not shown.

Our Delphi process had three key limitations. First, the output and recommendations from a Delphi process can only ever be as robust as the statements that are assessed within it. Because the statements assessed here were all developed on the basis of expert opinion (level 5 evidence), the guidance can only ever seek to summarise this expert opinion. Once higher levels of evidence become available and clinical experience increases, this evidence and experience should be incorporated into future guidance to

Panel 3: Clinical management of children with PIMS-TS

Management of children with PIMS-TS and features of Kawasaki disease-like (complete and incomplete) phenotype

(1) First-line therapy for all children is intravenous immunoglobulin at a dose of 2 g/kg, calculated using ideal bodyweight, which can be administered in a single or divided dose depending on the clinical picture and cardiac function*

- A second dose of intravenous immunoglobulin might be considered for children who have not responded or partially responded to the first dose†

(2) All children who meet the criteria for the RECOVERY trial should be invited to participate in the first stage of randomisation for the trial‡

(3) High-risk children include those younger than 12 months* and those with coronary artery changes*; these children should be given early intravenous methylprednisolone (10-30 mg/kg; alongside intravenous immunoglobulin)†

(4) If a child is recruited to the first randomisation step in the RECOVERY trial, they will be randomly assigned to either therapy or standard of care†

(5) Second-line therapy is intravenous methylprednisolone (10–30 mg/kg) and should be considered as the next treatment option for children who remain unwell 24 h after infusion of intravenous immunoglobulin, particularly if they have ongoing pyrexia*

(6) Gastric protection (eg, omeprazole) should be given to children on high-dose steroids*

(7) Biological therapy should be considered as a third-line option in children who do not respond to intravenous immunoglobulin and methylprednisolone;* the decision to commence a biological therapy should be made by a multidisciplinary team*

- If a child is recruited to the RECOVERY trial, they should be offered the opportunity to enter the second-stage intervention phase and be randomly assigned to either tocilizumab or standard of care; the first and second stage randomisations in the RECOVERY trial can occur at the same time†
- The preferred biological therapy for children not recruited to the RECOVERY trial who have a Kawasaki disease-like phenotype is infliximab‡

Management of children with PIMS-TS and non-specific presentation phenotype

(1) Indications for therapy include: evidence of coronary artery abnormality*; meeting the criteria for toxic shock syndrome*; evidence of progressive disease‡; extended duration of fever (>5 days)‡

(2) First-line therapy is intravenous immunoglobulin at a dose of 2 g/kg, calculated using ideal bodyweight, which can be administered in a single or divided dose depending on the clinical picture and cardiac function*

- A second dose of intravenous immunoglobulin might be considered for children who have not responded or partially responded to the first dose†

(3) All children who meet the criteria for the RECOVERY trial should be invited to participate in the first stage of randomisation of the trial‡

(4) If a child is recruited to the first randomisation step in the RECOVERY trial, they will be randomly assigned to either therapy or standard of care†

(5) Second-line therapy is intravenous methylprednisolone (10–30 mg/kg), and should be considered as the next treatment option for children who remain unwell 24 h after infusion of immunoglobulin, particularly if they have ongoing pyrexia‡

(6) Gastric protection (eg, omeprazole) should be given to children on high-dose steroids*

(7) Third-line therapy should be a biological therapy in children who do not respond to intravenous immunoglobulin and methylprednisolone*; the decision to commence a biological agent should be made by a multidisciplinary team*

- If a child is recruited to the RECOVERY trial, they should be offered the opportunity to enter the second-stage intervention phase and be randomly assigned to either tocilizumab or standard of care; first and second stage randomisations in the RECOVERY trial can happen at the same time
- Consensus was not reached on a preferred biological agent with equipoise shown for all tocilizumab, anakinra, and infliximab; for all patients, the choice of biological agent should be informed by the experience of the clinician†

(8) A small number of children in this phenotype have met the criteria for HLH; in these children, discussion with a specialist team and awareness of the HLH-2004 guidelines[18] is recommended†

Antiviral and antibiotic therapy

(1) Children with PIMS-TS who are SARS-CoV-2 positive on RT-PCR or antigen testing might be considered for antiviral therapy; remdesivir is the first-choice antiviral therapy for SARS-CoV-2†

(2) Intravenous antibiotics should be commenced in all patients; these should be focused or stopped on the basis of the clinical picture and culture results*

(3) Children who meet the criteria for toxic shock syndrome should be given clindamycin in addition to broad-spectrum antibiotics*

(4) The initial infection screen does not have to be negative for other pathogens before commencing high-dose steroids†

Antiplatelet and anticoagulation therapy for children with PIMS-TS

(1) All children older than 12 years should wear compression stockings‡

(2) The local Kawasaki disease guidelines for aspirin dosing should be followed for children with Kawasaki disease-like phenotype*

(3) Low-dose aspirin should be continued for a minimum of 6 weeks in all patients with PIMS-TS†

(4) Children who have a thrombotic event should follow the local protocol for management for this event*

(5) Children with abnormal coronary arteries should be discussed with a haematologist regarding long-term antiplatelet and anticoagulation therapy†

HLH=haemophagocytic lymphohistiocytosis. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with COVID-19. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
*Determined in phase two of the Delphi process. †Determined during the consensus meeting. ‡Determined in phase three of the Delphi process.

ensure that the management pathway remains relevant and up to date. Given the cost-efficient and timely nature of this Delphi process, we could feasibly re-run the process when clinically significant new data come to light, and to use the results of the process to inform development of the guidance. Second, a smaller number of participants were recruited from stakeholder groups than would normally be aimed for in a Delphi process, and the scope of the work precluded inclusion of parents, young people, and members of the public in the process. Despite this fact,

adequate representation was achieved across all panels, with multiple representatives from each stakeholder group participating in phases one, two, and three of the Delphi process. However, had time and the need to ensure clinical expertise of participants not been such pressing factors, seeking opinions from a larger number of stakeholders, and from parents, young people, and the public would have been preferable. Finally, the consensus meeting included only a few representatives of each stakeholder group because of the online format and need to ensure opinions from all stakeholder groups during the meeting. Parts of this guidance are only applicable to the UK, in particular determining where patients are cared for and the clinical trials that are available to them. However, consensus about the investigation and management of PIMS-TS when a child is not enrolled in a clinical trial is applicable internationally.

The management pathway created from this consensus process aligns well with the evidence base for PIMS-TS.[5,20,21] It builds on the RCPCH PIMS-TS definition,[7] which was developed with a much smaller working group than was used in this process and provided principles for management on the basis of the experience of managing the first cases of PIMS-TS in the UK, the majority of which were children with severe presentations. Awareness is increasing that patients with PIMS-TS have a spectrum of disease severity, and clinicians should consider a wide differential diagnosis in those presenting with persistent fever and evidence of inflammation, but without the other features of PIMS-TS that have been described. This management pathway is based on consensus from a wide group of clinicians and provides granular practical guidance for the management of children with PIMS-TS. Consensus was reached that identifying the phenotype should be the primary method of classifying children with PIMS-TS. The guidance focuses on the recognition of markers of severe disease and, in particular, cardiac disease, which has been described in both phenotypes of PIMS-TS.[3,5] This guidance includes a management pathway for Kawasaki disease-like phenotype that aligns with current guidance for the management of Kawasaki disease,[17] and might help to address the current variation in treatment regarding the indications for intravenous immunoglobulin and steroids.[3,21,22] Indicators of high-risk disease are extrapolated from the current understanding of Kawasaki disease and PIMS-TS but vigilance for cardiac complications of PIMS-TS is recommended in all patients, regardless of the severity of disease. Discussion and voting during the consensus meeting found equipoise for randomly assigning patients to intravenous immunoglobulin or methylprednisolone for both phenotypes of PIMS-TS. The distinction between phenotypes and treatment strategies is based on expert opinion because the biological mechanisms of PIMS-TS have not yet been elucidated. It was determined that equipoise exists between intravenous methylprednisolone and intravenous immunoglobulin as first-line therapy for both phenotypes of PIMS-TS, supporting a belief that clinical trials should compare the efficacy of these two therapies. This guidance has important implications internationally because access to intravenous immunoglobulin varies, and is often restricted in low-resource settings in particular, but methylprednisolone is readily and cheaply available.

Within the Delphi process, substantial discrepancy was noted between panel one (paediatric medical specialists with training in immunology and infectious diseases) and panel two (paediatric intensivists, cardiologists, and haematologists) with regards to whether children with PIMS-TS should be cared for in units with ECMO availability. 90% of panel two strongly agreed this should be the case, whereas 86% of panel one disagreed (appendix p 22). Data collected by the BPSU PIMS-TS surveillance study will help to provide underpinning research to resolve this discrepancy. Until such data are available, we would reinforce the need for important clinical decisions relating to the management of children with PIMS-TS to be done in a multidisciplinary setting, with adequate representation from all core members of the multidisciplinary team. Other areas where the need for future research have been highlighted by this Delphi process include the indications for, and identification of, the most appropriate immunomodulatory therapy for use in children with the non-specific PIMS-TS phenotype, and whether intravenous immunoglobulin or methylprednisolone should be first-line therapy for children with either phenotype of PIMS-TS.

As a direct result of this study, the RECOVERY trial has been amended (protocol version 8.0, which opened for recruitment in August, 2020). This amendment allows paediatric clinicians to select treatment groups to compare high-dose steroids (methylprednisolone) versus no additional treatment (in the presence and absence of intravenous immunoglobulin) and intravenous immunoglobulin versus no additional treatment (in the presence and absence of high-dose steroids) for the initial treatment of PIMS-TS.[23] This pragmatic design allows investigators to use no treatment, intravenous immunoglobulin, or high-dose steroids as standard of care if deemed necessary. The amendment allows the effects of high-dose steroids and intravenous immunoglobulin to be compared with no additional treatment separately (in the presence and absence of other drugs), and it will allow children with a wide spectrum of disease severity to be recruited. By using this Delphi study to inform the trial design, we hope that clinicians' willingness to recruit to the clinical trial will be maximised. The results will be important in the context of a global pandemic because of the high cost and poor availability of intravenous immunoglobulin in the UK and worldwide.

This consensus management pathway relating to the treatment of children with PIMS-TS is based on consensus expert opinion and is intended to act as a framework for the safe management of children with this condition. As

new, higher level evidence becomes available, the guidance will be updated.

Contributors

RH and BA designed and ran the Delphi process with SK, with additional input from SNF, CEJ, MKn and AVR. RH and BA wrote the manuscript with detailed input from SK, MKn, SNF, and CEJ. All authors were involved in study analysis and approved the final manuscript. SK (the lead author and the manuscript's guarantor)affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

The PIMS-TS National Consensus Management Study Group

R Agbeko, O Aragon, J Baird, A Bamford, M W Beresford, T Bharucha, P Brogan, K Butler, E D Carrol, K Cathie, A Chikermane, S Christie, M Clark, A Deri, C Doherty, S Drysdale, P Duong, S Durairaj, M Emonts, J Evans, J Fraser, S Hackett, R Hague, P Heath, J Herberg, M Ilina, N Jay, D Kelly, C Kerrison, J K Kraft, A Leahy, M Linney, H Lyall, L McCann, P McMaster, O Miller, S O'Riordan, S Owens, C Pain, S Patel, N Pathan, J Pauling, D Porter, A Prendergast, R Kumar, A Riordan, M Roderick, B R Schofield, M G Semple, E Sen, F Shackley, I Sinha, S Tibby, S Verganano, S B Welch, N Wilkinson, M Wood, I Yardley, R Harwood, B Allin, C E Jones, E Whittaker, P Ramnarayan, A V Ramanan, M Kaleem, R Tulloh, M J Peters, S Almond, P J Davis, M Levin, A Tometzki, S N Faust, M Knight, S Kenny.

Declaration of interests

AVR reports speaker fees and honoraria from Roche, SOBI, Eli Lilly, UCB, and Novartis outside of the submitted work. SNF reports personal fees and grants paid to his institution from Pfizer for being a symposium speaker; from AstraZeneca/Medimmune, Sanofi, Pfizer, Seqirus, Sandoz, and Merck for advisory board participation; and from Pfizer, Sanofi, GlaxoSmithKline, Johnson & Johnson, and Merck for being a clinical trial investigator outside of the submitted work. All other authors declare no competing interests.

Data sharing

Relevant raw data are provided in the appendix (pp 1–75).

Acknowledgments

We thank Marcel Minke and Gabriel Jenik for their support in developing the customised Limesurvey database that made conduct of the Delphi process possible within the required timeframe. We also thank Joseph Skelton whose organisational skills made this process possible and the RCPCH for their support for this project and guidance. The guidance presented in this manuscript is endorsed by the RCPCH and the British Paediatric Allergy, Immunity and Infection Group. NHS England funded the Limesurvey database that was required to collect responses. MKn and SNF are National Institute for Health Research (NIHR) Senior Investigators. BA is funded by an NIHR Doctoral Research Fellowship. RH holds a Kidney Research UK training fellowship. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. There was no involvement of patients or their families in this management pathway. We recognise their important role in the care of children with PIMS-TS and intend to consult them for future iterations of the pathway.

References

1 Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr* 2020; **10:** 537–40.

2 Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* 2020; **142:** 429–36.

3 Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 2020; **369:** m2094.

4 Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395:** 1771–78.

5 Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; **324:** 259.

6 Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395:** 1607–08.

7 Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Royal College of Paediatrics and Child Health, 2020. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20 syndrome-20200501.pdf (accessed Aug 26, 2020).

8 US Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Atlanta, GA: US Centers for Disease Control and Prevention, May 14, 2020. https://emergency.cdc.gov/han/2020/han00432.asp (accessed Aug 26, 2020).

9 WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, 15 May 2020. Geneva: World Health Organization, May 15, 2020. https://apps.who.int/iris/handle/10665/332095 (accessed Aug 26, 2020).

10 Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Inf Manage* 2004; **42:** 15–29.

11 Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS Med* 2011; **8:** e1000393.

12 Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. *Manage Sci* 1963; **9:** 458–67.

13 Bunch KJ, Allin B, Jolly M, Hardie T, Knight M. Developing a set of consensus indicators to support maternity service quality improvement: using Core Outcome Set methodology including a Delphi process. *BJOG* 2018; **125:** 1612–18.

14 Allin BSR, Bradnock T, Kenny S, Kurinczuk JJ, Walker G, Knight M. NETS[IHD] study: development of a Hirschsprung's disease core outcome set. *Arch Dis Child* 2017; **102:** 1143–51.

15 Allin BSR, Hall NJ, Ross AR, Marven SS, Kurinczuk JJ, Knight M. Development of a gastroschisis core outcome set. *Arch Dis Child Fetal Neonatal Ed* 2019; **104:** F76–82.

16 Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. *Trials* 2017; **18** (suppl 3)**:** 280.

17 McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135:** e927–99.

18 Henter J-I, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48:** 124–31.

19 Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. Version 1. *Arthritis Rheumatol* 2020; published online July 23. https://doi.org/10.1002/art.41454.

20 Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March–July 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 1074–80.

21 Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in the United Kingdom: prospective multicentre observational cohort study. *BMJ* 2020; **370:** m3249.

22 Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health* 2020; **4:** 669–77.

23 Hornby P. Randomised evaluation of COVID-19 therapy (protocol version 8, Recovery Trial. Aug 7, 2020. https://www.recoverytrial.net/files/recovery-protocol-v8-0-2020-07-08.pdf (accessed Sept 11, 2020).