

Joint ECDC-ESPID Webinar on Multisystem Inflammatory Syndrome in Children (MIS-C)

20 January 2022

Executive summary

The webinar enabled the sharing of experiences and epidemiological data on MIS-C between European researchers, with the aim of shaping future priorities for the condition across Europe.

Participants included members of ESPID, representatives from the World Health Organization (WHO), and focal points for the COVID-19 network at ECDC. Presentations from Sweden, United Kingdom, France, and Spain provided data in several areas of MIS-C.

The lack of a common standardised syndrome definition was highlighted. The webinar concluded that remaining challenges include the appropriate characteristics needed for a standardised case definition due to the lack of large case databases and the multiple phenotypes of children with MIS-C. Nevertheless, the prompt development of a WHO definition at the time the syndrome was first recognised has been an invaluable tool for clinicians and researchers. A collaborative approach involving public health specialists and expert groups is essential in responding to complex public health challenges as in the current COVID-19 pandemic.

Scope and purpose of the meeting

Background

Multisystem Inflammatory Syndrome in Children (MIS-C)

Following the initial wave of COVID-19 hospitalisations, a novel syndrome with hyperinflammatory response in children emerged, initially identified by physicians in the United Kingdom (UK) in April 2020. The Royal College of Paediatrics and Child Health in the UK defined it as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), while the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in the United States (US) refer to it as Multisystem inflammatory syndrome in children (MIS-C). There is currently no specific test available to diagnose this syndrome. Hence, the diagnosis of the syndrome is based on clinical signs and symptoms, as well as evidence of a previous SARS-CoV-2 infection or exposure. Children who develop the syndrome are generally previously healthy, and the primary infection with SARS-CoV-2 is usually mild or asymptomatic.

Most children with critical illness due to MIS-C have a favourable outcome and recover with intensive care support and appropriate treatment. Early recognition and prompt treatment of MIS-C cases is essential. As children often present with mild symptoms of COVID-19 and are less frequently tested than adults, the true proportion of cases that develop MIS-C remains unknown.

There is no comprehensive overview of MIS-C cases in the EU/EEA, although WHO has organised a platform and relevant forms for data collection at the global level.

Through surveillance data reported by EU/EEA countries to The European Surveillance System (TESSy), the European Centre for Disease Prevention and Control (ECDC) is able to describe the epidemiology of new SARS-CoV-2 diagnoses, including risk factors and severity outcomes by age. However, data on PIMS-TS/MIS-C are very rarely reported by Member States as this complication presents usually weeks after the time of COVID-19 diagnosis. The burden of this syndrome, its course and potential sequelae should also be estimated in a collaboration between clinical and public health experts.

Objectives of the webinar

The aim of this second joint ECDC-ESPID webinar was to facilitate the exchange of information between involved stakeholders from public health and clinical sectors to better understand the public health implications of MIS-C.

At the webinar, presentations included ongoing clinical research defining the clinical picture, pathophysiology, immunology, and management of MIS-C, and epidemiological research to quantify the occurrence of this syndrome among children and the impact of vaccination to its occurrence, as well as discussion of the possibilities for extended collaboration between ESPID, ECDC and research teams to better understand the impact of SARS-CoV-2 infection in children in the EU/EEA.

Summary of the webinar

Welcome and introductory remarks

Agoritsa Baka, Principal Expert Emergency Preparedness and Response, ECDC, welcomed participants to the webinar and gave an outline of the meeting.

Presentations

1. Immunology of MIS-C and related research in children. Overview of MIS-C in Sweden

Speaker: Peter Brodin, Garfield Weston chair, Professor of Pediatric Immunology, Department of Immunology and Inflammation, Imperial College London, UK, Professor of Pediatric Immunology, Karolinska Institutet, Stockholm, Sweden

Prof. Brodin presented epidemiological data on children with MIS-C in Sweden, including 306 recorded cases, of which 70 treated in ICU and no deaths between 2020 until January 2022. He also gave an overview on the immunology of SARS-CoV-2 infection and MIS-C in children. The role of nasal mucosa in children leading to faster virus clearance without developing systemic disease most of the times could be a possible explanation for the milder infection in children compared to adults. One of his studies compared healthy children with children who had developed: i) mild COVID-19, ii) Kawasaki disease, and iii) COVID-19 MIS-C. The group that developed MIS-C was observed to produce broadly reactive autoantibodies in comparison to other groups. Prof. Brodin also supported the idea that the location of superantigen is the key to answering why MIS-C appears several weeks after the primary mild infection. Children with acute COVID-19 present more frequently with gastrointestinal symptoms and this suggests that the higher viral load is in the intestine and there are indications of persistence of the virus in the intestine, which may lead to MIS-C.

2. MIS-C: Clinical characteristics, management, outcomes, and impact of different VOCs

Speaker: Elizabeth Whittaker, Paediatric Infectious Diseases Consultant at St Mary's Hospital, London, UK

Dr Whittaker presented data on the epidemiology of SARS-CoV-2 infection in children in the UK and also explained the most common clinical presentation of complications, such as MIS-C. She also shared evidence on the advances in diagnostics and treatment. She confirmed that hospital admissions of children are increasing during the Omicron wave, but both ICU admissions and deaths do not follow a similar trend. Dr Whittaker pointed out that the clinical picture of MIS-C shares signs and symptoms with several other diseases and therefore is difficult to diagnose it, particularly in settings with limited diagnostic resources. The EU Horizon 2020 funded project DIAMONDS aims to develop a new Taxonomy of Infectious and Inflammatory Diseases based on host molecular signatures trying to diagnose MIS-C by the immunopathology pathway. The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial will soon release results from the analysis comparing treatment with IVIG and steroids. It has been observed that in many cases there are persistent neurological symptoms that need to be studied further to clarify if this is related to post-COVID-19 condition or is another complication of acute infection.

3. Risk of MIS-C according to the COVID-19 vaccination status of adolescents & Overview of MIS-C in France

Speaker: Francois Angoulvant, Professor in Paediatrics, Hospital Robert Debré, Paris, France

Prof. Angoulvant gave an overview of the epidemiology of SARS-CoV-2 infection and MIS-C in France during the different waves of pandemic. He also provided available evidence on the vaccination of adolescents against SARS-CoV-2 and the risk of developing MIS-C in the vaccinated group comparing to non-vaccinated adolescents in France. Findings showed the benefit of vaccination in all the studies from France and the United States. Prof. Angoulvant emphasised that the collection of data leading to the presenting studies was possible due to the collaboration of already established research networks across the country.

4. Overview of MIS-C in Spain and relevant research

Speaker: Alfredo Tagarro, Hospital Universitario Infanta Sofia, Madrid, Spain

Dr Tagarro presented findings from a large Spanish network, the EPICO, which includes 90 hospitals (10% of all hospitals in Spain) across the country. Among the 878 recorded paediatric hospitalisations, 163 were admitted to PICU, nine died and 186 were diagnosed with MIS-C. The MIS-C incidence was 20/100 000 of infected children and adolescents, while the estimated national incidence was eight per 100 000 population of children. He also presented the available treatment options and the recent WHO publication with recommendations on treatment of MIS-C. A retrospective study comparing IVIG, steroids and the combination of both concluded that the benefit of each drug varies depending on the studied outcome.

Discussion

It was promising that several researchers have already started collaborative projects, particularly within their countries, addressing questions on incidence and management of the syndrome. The representatives from WHO, Karen Edmond and Marta Lado, informed the audience about the MIS-C working group which continues to have regular meetings and recently published WHO treatment recommendations. WHO also invited experts among ESPID members to participate in this working group. The absence of large surveillance databases due to the lack of a European network for tracking severe cases of COVID-19 in children, including MIS-C cases and the existence of three parallel definitions (CDC, WHO, UK) are some of the problems identified from both the audience and speakers. WHO commented on the issue of the definition and informed participants that both CDC and WHO are currently reviewing their definitions. WHO will soon analyse the data from a large study in South Africa, Ethiopia, Pakistan and India that have recruited children admitted to hospital with any SARS-CoV-2 positivity as inclusion criteria and then check if they meet the criteria according to the three existing definitions.

The uncertainty of the impact of the current wave with the Omicron variant on the severity of COVID-19 in children was also discussed during the webinar. Dr Tagarro mentioned that it may be useful that ESPID publishes recommendations for the management of COVID-19 in children with support from ECDC.

Participants emphasised how important and valuable these meetings are among ESPID experts and ECDC discussing issues relating to paediatric COVID-19 and its complications. Further work is needed to explore opportunities for establishment of a European research network among experts that could support promptly strategies to tackle future threats for the paediatric population. Finally, some suggestions were discussed for a third Joint ECDC-ESPID webinar suggesting to discuss updates on COVID-19 vaccines and pharmaceuticals for children and adolescents.

Conclusions

The ongoing collaboration of ECDC with ESPID is promising and can build synergies among clinician researchers and public health in Member States to fill the gaps of knowledge in paediatric COVID-19.

Next steps

The next step arising from the webinar is for ECDC to explore the possibility of a third joint webinar with ESPID relating to vaccination against SARS-CoV-2 in children, with the participation of EMA.

Annex. Final agenda

Thursday 20 January 2022, 15.00-17.00 CET

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| 15:00-15:10 | Welcome by ECDC & ESPID chair |
| 15:10-15:25 | Presentation 1: Immunology of MIS-C and related research in children. Overview of MIS-C in Sweden.
Peter Brodin (Sweden) |
| 15:30-15:45 | Presentation 2: MIS-C: Clinical characteristics, management, outcomes, and impact of different VOC.
Elizabeth Whittaker (UK) |
| 15:50-16:05 | Presentation 3: Risk of MIS-C according to the COVID-19 vaccination status of adolescents. Overview of MIS-C in France.
Francois Angoulvant (France) |
| 16:10-16:25 | Presentation 4: Overview of MIS-C in Spain and relevant research.
Alfredo Tagarro (Spain) |
| 16:30-17:00 | Discussion <ul style="list-style-type: none">• <i>Intervention by WHO, Working Group on MIS-C</i>• <i>Discussion (All participants)</i><ul style="list-style-type: none">o <i>There are currently various definitions of the syndrome. Should we work for the development of only one standard case definition?</i>o <i>Evidence of MIS-C after vaccination of children in Europe?</i>o <i>Any change of the severity of MIS-C syndrome over time?</i>o <i>Any ongoing/planned collaborative research on MIS-C in EU?</i>• <i>Conclusions and Follow up</i> |