Good afternoon. I'm Commander Ibad Khan. I'm representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA Call COVID-19 Updates: What Clinicians Need to Know About Multisystem Inflammatory Syndrome in Children. All participants joining us today are in listen only mode.

Free continuing education is offered for this webinar. Instructions on how to earn continuing education will be provided at the end of the call. In compliance with continuing education requirements, CDC, our planners, our presenters and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planners have reviewed content to ensure there is no bias. This presentation will not include any discussion of the unlabeled use of a product or a product under investigational use. CDC did not accept commercial support for this continuing education activity.

At the conclusion of today's session, participants will be able to accomplish the following: describe sources of MIS-C surveillance data, identify resources on MIS-C symptoms and what parents and caregivers need to know before and after a diagnosis of MIS-C; list key points for healthcare providers to use when talking with families and caregivers about MIS-C; and discuss information related to COVID-19 vaccination and MIS-C.

After today's presentations, there will be a Q&A session. You may submit questions at any time during today's presentation. To ask a question using Zoom, click the Q&A button at the bottom of your screen, then type your question in the Q&A box.

Please note we receive many more questions than we can answer during our webinars. If you're a patient, please refer your questions to your healthcare provider. If you're a member of the media, please contact CDC Media Relations at 404-639-3286 or send an email to media@CDC.gov.

We have introduced self-knowledge checks throughout the presentation. We hope you enjoy these opportunities to assess your understanding of today's session. Please do not type your answers into the Q&A box, as this may disrupt the Q&A portion at the end of the session.

It is now my pleasure to welcome our presenters for today's COCA call. We are pleased to have with us Dr. Angela Campbell, Dr. Shana Godfred-Cato and Dr. Anna Yousaf who are all medical officers working on the Multisystem Inflammatory Syndrome (MIS) Unit as part of CDC's COVID-19 Response. It is my pleasure now to turn it over to Dr. Campbell. Dr. Campbell, please proceed.

Good afternoon. Thank you for the introduction. Next slide.

Great, so I'm going to start by giving an overview of what we've learned from some of our different surveillance platforms at CDC. Next slide.

Okay, so most of you probably know the intro to this, but just to make sure everyone has the same background, MIS-C is a severe syndrome characterized by an exaggerated hyper-

inflammatory response affecting multiple body systems. It was first recognized in April of 2020 in the UK, occurring in children with current or recent infection with SARS-CoV-2. By May of 2020, cases were reported in New York City and New York State. And on May 14th, CDC issued a health advisory recommending that healthcare professionals report patients meeting the MIS-C case definition to local, state, or territorial health departments in order to enhance knowledge of the risk factors, pathogenesis, clinical course and treatment of this syndrome. Next slide.

So to review, this is the MIS-C case definition. This is the definition that was established at that time and it's still in use. It was designed to be quite broad and inclusive. The criteria include an individual aged less than 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem, that's two or more, organ involvement, including cardiac renal, respiratory hematologic, GI, derm, or neuro. And there needs to be no alternative plausible diagnosis, and the person is positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen testing, or has had exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms.

The bottom part of that slide shows that we do accept subjective fever and the inflammatory marker criteria are quite broad and include any of those labs. One important caveat not on this slide is that some individuals may fulfill full or partial criteria for Kawasaki disease, but should be reported if they meet the case definition for MIS-C. And I also just wanted to comment on the age criteria, because we have been asked about this. Multisystem inflammatory syndrome has been described in adults. So I did want to mention that, although MIS-A appears to be much less common than MIS-C, and we won't be discussing the features in adults today.

I will say since becoming familiar with this case definition, I've actually learned that the American Academy of Pediatrics has published statements affirming the upper age limit for pediatrics at age 21. So it's reasonable to have this broad age spectrum for the case definition, particularly since children's hospitals generally provide care for those up to age 21. But I did just want to mention that MIS in adults does occur, although it is rare. Next slide.

So this original call for cases back in May of 2020 set the stage for our national surveillance for MIS-C. This is a passive surveillance system in which healthcare professionals voluntarily report cases of MIS-C to their state, local, and territorial health departments and then the health departments report voluntarily to CDC. Thus, we are extremely grateful for all of the clinicians who take the time to report and for our amazing partners in the health department. MIS-C is not a nationally notifiable condition, but this system does provide standardized surveillance using a case report form available on the CDC MIS-C healthcare professionals website. We have now had cases reported from 54 US jurisdictions, including all 50 states, New York City, Puerto Rico, Guam, and Washington DC. The cases reported to CDC are posted each month on the COVID data tracker MIS-C page. Next slide.

So as of January 31, 2022, we have had 6,851 cases reported with date of MIS-C onset going back to February 19, 2020. There have been 59 reported deaths. Children aged 5 to 11 are the age group most frequently affected by MIS-C, as shown in this histogram of the proportion of total reported MIS-C cases by age group. Forty-six percent of all reported MIS-C case patients

have occurred among those aged 5 to 11. And the median age is nine years and has really held steady at age eight to nine years across the pandemic. Sixty percent of case patients have been male. A disproportionate 59% of children with MIS-C are either Hispanic Latino or non-Hispanic Black. Next slide.

This map shows the number of reported cases in each jurisdiction by shade of blue green color. Although I have reminded you that MIS-C was first described in the United States in the northeast, we have subsequently seen cases in the south and west predominate. Next slide.

This graph shows the seven-day moving average number of COVID-19 cases and MIS-C cases with date of onset between February 19, 2020, and January 31, 2022. You will note that these are plotted on vastly different scales with the left y-axis marking the number of daily seven-day average and MIS-C cases in units of five with a scale of zero to 30, and the right y-axis marking the number of daily seven-day average COVID-19 cases in units of 100,000 with a scale from zero to 800,000, thanks to this recent Omicron wave. So despite this difference in scale, you can see that there have been four waves of MIS-C since the beginning of the pandemic, that's the blue curve.

And that MIS-C activity peaks about a month after COVID-19 activity peaks which is the dotted line. And this is consistent with what we know from patient data. Although MIS-C often occurs with no known preceding illness, we do have reports in which people can recall a proceeding SARS-CoV-2 illness. And from those people MIS-C generally occurs two to six weeks after their SARS-CoV-2 infection. I will note that the most recent spike in COVID-19 activity on the right is associated with the Omicron variant circulation.

This grayed out area on the right side represents the most recent six weeks of MIS-C data, for which reporting of our cases is still the most incomplete. The actual number of MIS-C cases during this period and even going back into the previous wave of activity is likely larger. The previous wave reflects MIS-C associated with circulating Delta variant viruses, and we expect these numbers to continue to increase as additional case reports are incorporated. We are continuing to receive a lot of reports from this time period. Although we expect some reporting lag and have across the pandemic, it has been particularly difficult for clinicians and hospitals and health departments to keep up with MIS-C reporting in these recent exhausting weeks and months of the pandemic. Next slide.

So here's a summary of what MIS-C national surveillance provides for us. We can do a number of things with these data, including examining demographic and clinical characteristics among reported cases, examining changes in reported demographic and clinical characteristics over time, describing treatments received, and using these data toward estimation of MIS-C incidents. On the other hand, these data are not intended to provide details of the clinical course, to assess effectiveness of various interventions or treatments, to infer causality with regard to treatment and illness resolution, or to truly quantify the burden of MIS-C in the United States, at least not using these data alone. That's difficult to do because this is a passive system. Next slide.

But this MMWR was published August 14, 2020. It was actually led by Dr. Godfred-Cato who will speak next. This shows a nice example of one of the first overview papers to come from

national surveillance, in which a latent class analysis was performed to identify similarities and group the first 570 MIS-C cases reported from March through July into three distinct classes.

Patients in class one had a typical MIS-C picture in which 98% tested positive for SARS-CoV-2 by serology. All patients had cardiovascular and nearly all had gastrointestinal manifestations, often with a number of additional organ systems involved, and markedly elevated laboratory values of inflammation and markers of cardiac damage. These patients had significantly higher frequencies of shock and myocarditis relative to the other two classes, with a very high percentage, 84%, of ICU admissions. Patients in class two had more of an acute COVID-19 MIS-C combination picture. Only 16% were serology positive and 100% tested positive by RT-PCR.

These patients were more likely to have had severe respiratory involvement with pneumonia and ARDS, and 62% had ICU admission. And then patients in class three were generally younger. The median age was six years, and that's compared with nine and 10 years in class one and two respectively. This class had milder illness and relatively higher frequency of rash and mucocutaneous lesions, most similar to Kawasaki disease, with 44% admitted to the ICU. Next slide.

This slide displays multiple manuscript headers showing the contribution of MIS-C national surveillance data to our knowledge about this syndrome. We have learned which factors are linked to severe outcomes in MIS-C. Being non-Hispanic Black was shown to be a risk factor, and it's held up in multiple studies. In this paper in the bottom right corner, we describe the first 35 deaths, and we found that although Hispanic Latino and non-Hispanic Black persons, along with American Indian, Alaskan Native and Native Hawaiian Pacific Islanders, these populations comprise approximately 1/3 of the overall US population of people aged zero to 20 years. However, these groups comprise more than 2/3 of MIS-C cases, and they comprise more than 80% of these MIS-C deaths. Next slide.

Here is our most recent publication of cases in national surveillance. In this we described 4,470 cases of MIS-C reported with symptom onset from February 19, 2020 through July 31, 2021. We found that the frequency of severe cardiovascular complications, including cardiac dysfunction, myocarditis, and shock including base suppressor receipt, declined over time over those first three waves that I showed you of the MIS-C in peaks during the pandemic. We also found that clinical outcomes including length of hospitalization, receipt of mechanical ventilation, ECMO, and death improved across those first three pandemic waves of MIS-C. Next slide.

So now I'm moving on to a different system, the Overcoming COVID-19 Network. This originated as a CDC-funded Intensive Care Unit network led by Boston Children's Hospital to assess influenza vaccine effectiveness against critical illness in pediatric patients. It pivoted during the pandemic and now involves active perspective surveillance of MIS-C and severe COVID-19 in hospitalized children through a multicenter network of more than 60 hospitals in more than 30 states. We have a 60-plus page case report form, and this network has provided detailed epidemiologic and clinical data with interviews and biological specimens collected from a subset of consented cases.

In addition to having an MIS-C and severe COVID-19 registry, which has provided a robust amount of detailed clinical data, other investigations in this network include a study evaluating risk factors for developing MIS-C, an immunobiology study aimed at elucidating host genetic variants that may play a role. We're conducting a neurologic and neurodevelopmental outcome study. And we also are doing ongoing studies of COVID-19 vaccine effectiveness. Next slide.

So similar to the early slide showing manuscript contributions from national surveillance, these are some key manuscripts that highlight the contribution of the Overcoming COVID-19 Network to our knowledge about MIS-C.

You can see that we gained valuable information, including a clustering analysis to help distinguish from similar inflammatory conditions. The neurologic involvement associated with MIS-C and severe COVID-19 has also been described. And in addition, in the front, I highlighted this paper evaluating associations between initial treatment with IVIG plus glucocorticoids, or with IVIG alone, and the clinical outcomes. And this figure shows the results of using two analytic approaches, both finding that initial treatment of MIS-C with IVIG plus glucocorticoid was associated with a lower risk of the composite outcome of cardiovascular dysfunction on or after day two than using IVIG alone. There was also a lower risk of the components of the composite outcome, including left ventricular dysfunction, shock, adjunctive immunomodulatory therapy, and persistent or recurrent fever.

I just wanted you to have this as a reference that you can essentially see that with all of the little boxes to the left of the dotted line, that it was showing that they were associated with the lower risk of those features. Next slide.

This paper from earlier in the pandemic shows how these two surveillance platforms have worked together. We use the de-duplicated numerator of MIS-C cases from both surveillance systems -- from national surveillance and Overcoming COVID -- and then we evaluated the incidents in two ways using two denominators. One was based on population, and one on SARS-CoV-2 infections. For that denominator, we obtained this by using multipliers that had been published by our CDC colleagues accounting for under ascertainment. So using that we found an adjusted incidence of 316 MIS-C cases per million SARS-CoV-2 infections. To phrase this in terms more relatable, this is about the same as one MIS-C case in approximately 3,200 SARS-CoV-2 infections. And similar estimates have since been published from other countries. I would also just like to point out that incidence was highest among Black African American children, and also higher among Hispanic Latino and Asian Pacific Islander children compared with white children. Next slide.

So this is a little departure from MIS-C, but I did want to highlight these recent contributions of the Overcoming COVID-19 Network to studies of COVID-19 vaccine effectiveness, as we've been able to show some nice outcomes. Next slide.

Okay, so here are the highlights of the results table, excerpted from a figure from the New England Journal of Medicine paper, showing the vaccine effectiveness of COVID-19 vaccination against COVID-19 hospitalizations in 12- to 18-year-olds overall, by age group, and among

partially vaccinated children. Basically, the point estimates for vaccine effectiveness for all of these groups ranged from 94 to 97%. Next slide or next click.

It's going to add a red box. So here I wanted to point out in the added red box, that in addition to VE against overall COVID-19 hospitalizations, among those 12- to 18-year-olds hospitalized, vaccine effectiveness against ICU admission and need for life support was 98% for each. Next slide.

Okay, so here's the first of your self-knowledge checks.

The following statements regarding MIS-C during the COVID-19 pandemic are true except. A, nationally peaks of pandemic MIS-C activity follow peaks of COVID-19 activity by about one month. B, individuals aged 16 to 20 years comprise the highest proportion of MIS-C cases after SARS-CoV-2 infections. C, incidence of MIS-C is approximately 316 cases per million infections, which is about one case in 3,200 SARS-CoV-2 infections. Or D, MIS-C incidence is higher among Black African American and Hispanic Latino children compared with white children. So you're choosing the one that's not true. Next slide.

So the answer was B, because as I showed you, children aged 5 to 11 years have consistently comprised the highest proportion of MIS-C cases. So with that, I will turn the talk over to Dr. Shana Godfred-Cato to describe some of the work we have been doing with healthcare professionals and the materials that have been developed.

Thank you for that. I will be providing an overview of the MIS-C healthcare professional project including key findings and resources developed. Next slide, please.

The Multisystem Inflammatory Syndrome in Children Healthcare Professional Engagement study, which began in September of 2022, was designed to assess and address awareness, attitudes, knowledge and resource needs among healthcare professionals from various clinical settings, including inpatient, emergency, urgent and primary care. We conducted this project in four phases.

Phase one consisted of an online survey with 272 healthcare professionals conducted January 2021. And phase two consisted of in-depth interviews with 24 healthcare professionals conducted in March of 2021. Using the data collected in phases one and two, we developed and tested materials designed to address key healthcare professionals and MIS-C informational and resource needs as noted under phase three. During the final phase of the project, phase four, we engaged a variety of partners to support dissemination and monitored web traffic to and downloads of these new MIS-C materials. Next slide, please.

We partnered with Medscape to assist with recruiting healthcare professionals for the phase one online survey, the phase two in-depth interviews and the phase three material testing. We developed a screening questionnaire administered by Medscape to ensure our survey population included only healthcare professionals treating pediatric and young adult populations. Healthcare professionals who reported seeing adults only were excluded. We also sought healthcare professionals working in inpatient, emergency care, urgent care, and primary care settings to

participate in our data collection activities. And within these settings, we set quotas to ensure representation of MDs or DOs, PAs, and NPs.

The next few slides will show a snapshot of some of our phase one online survey findings. Next slide, please.

One aspect we assessed was healthcare professionals' confidence in conducting a variety of activities related to knowledge of practice guidelines, diagnosis and reporting of patients with MIS-C or suspected cases of MIS-A. As shown on the slide, we asked healthcare professionals to indicate their level of confidence as not at all confident, somewhat confident, or very confident. As you can see on this bar chart, we found that nearly 2/3 of inpatient healthcare professionals were very confident in assessing clinical and practice guidelines compared to just over 1/3 of emergency care, urgent care, and primary care healthcare professionals.

The percent of healthcare professionals reporting not at all confident ranged from 7% of emergency care professionals to 13% of primary care professionals, as shown in the gray boxes at the bottom of each bar. Next slide, please.

As shown here, in the second bar chart, just over half of all inpatient healthcare professionals responded that they were very confident with MIS-C diagnosis compared to 31% of emergency care, 18% of urgent care, and 21% of primary care healthcare professionals. Again, as shown by the gray portions of each bar, the percentage of healthcare professionals who reported not at all confident with MIS-C diagnosis ranged from 8% for inpatient healthcare professionals to 13% of urgent care and primary care professionals. Next slide, please.

The third bar chart shows healthcare professional confidence in providing information required for MIS-C reporting. As you can see by the darker blue sections of the bars, healthcare professionals who report very confident with providing required information for MIS-C case reporting range from 42% for inpatient providers to 23% for primary care providers. As shown by the gray section of the bars a range of 15 to 20% of healthcare professionals across settings were not at all confident with MIS-C reporting. Next slide, please.

As part of the online survey, we also assessed healthcare professionals' level of confidence in communicating with parents and caregivers about the diagnosis, treatment and follow up of MIS-C. We saw significant differences in the level of confidence healthcare professionals have in talking with caregivers about MIS-C diagnosis or treatment across clinical settings as shown by these bar graphs. As you can see by the dark purple sections, over 50% of inpatient healthcare professionals reported they were very confident with talking to parents about MIS-C diagnosis and treatment, compared to 35% or less across healthcare professionals from emergency care, urgent care, and primary care settings. Next slide, please.

These next two bar graphs show that a smaller percentage of healthcare professionals across clinical settings were very confident when speaking with caregivers about MIS-C follow up or answering MIS-C questions. As shown in the third bar graph from the right, 1/3 of all healthcare professionals or less reported they were very confident in talking to caregivers about MIS-C follow up, again with the greatest percentage observed among inpatient healthcare professionals.

Strikingly, we saw a range of 31 to 41% of all healthcare professionals who were not at all confident in speaking to parents about MIS-C follow up. The bar graph on the right shows healthcare professional confidence in answering parent or caregiver MIS-C questions. Nearly 42% of inpatient healthcare professionals noted they were very confident in answering questions compared to 20% of emergency care, 15% of urgent care, and 19% of primary care healthcare professionals. Nearly 20% of emergency care and 22% of urgent care healthcare professionals reported not at all confident. Across all four questions, inpatient healthcare professionals consistently had greater level of confidence in communicating with caregivers about MIS-C. Next slide, please.

We also asked healthcare professionals completing the online survey about the most needed MIS-C resources. Factsheets, decision guide and algorithms, and materials to give to parents were the resource needs most cited. As shown by the first horizontal bar chart at the top of the slide, a greater percentage of emergency care, urgent care, and primary care healthcare professionals noted needing factsheets compared to inpatient healthcare professionals. Nearly 2/3 of all healthcare professionals reported that they needed decision guides or algorithms. And between 41 to 58% reported a need for materials to give to families. Other resource needs cited by healthcare professionals included medical association or professional society guidance documents and prompts in the electronic medical record. As shown by the second bar chart on this slide, when we looked at resource needs by healthcare professional type, we found that a greater percentage of nurse practitioners and physician assistants reported a need for factsheets. The nurse practitioners recorded a greater need for decision guides and materials to give to families. Next slide, please.

From the in-depth interviews conducted in March of 2021, we heard firsthand about the key questions that remained about MIS-C. For many healthcare professionals, the lack of direct experience with seeing a patient with MIS-C was one of the biggest challenges, as illustrated by the quote shown here. The lack of experience made healthcare professionals feel less confident in being able to recognize MIS-C in their patients. Next slide, please.

The flow diagram shows the process we used to develop the healthcare professionals MIS-C materials and the key outputs from each step. As shown in step one, we synthesize survey and interview data to develop a list of priority healthcare professional resource needs related to MIS-C. We used this list to develop material concepts, which resulted in the recommendation to develop four MIS-C informational materials for healthcare professionals. Once the materials were developed and designed, we conducted testing with a sample of 282 healthcare professionals to ensure the materials met their needs. Similar to the phase one survey and the phase two interviews, they included MDs and DOs, PAs, and NPs that work in inpatient, emergency care, urgent care and primary care settings. Feedback collected from the original material testing survey provided insights about aspects of the materials to revise to ensure information was clear, concise and useful for healthcare professionals, parents and caregivers.

In the end, the four materials were finalized based on healthcare professionals' feedback and posted to the CDC website. The important thing to note about our process is the continued engagement with healthcare professionals in the field. Next slide, please.

So this is your second self-knowledge check. Healthcare professionals from which practice setting were the most comfortable and treating a patient with MIS-C and communicating with caregivers? A, primary care settings. B, emergency care settings. C, urgent care settings, and D, inpatient settings. Next slide, please.

So the providers that work in inpatient settings have the most confidence. So MIS-C healthcare professional engagement projects surveyed providers in four practice settings and found that inpatient providers were the most comfortable and caring for and communicating with caregivers about MIS-C. Depending on the scenario, inpatient providers were 70 to 90% somewhat confident or very confident. Next slide, please.

Now I will walk you through the four MIS-C materials developed through our healthcare professional engagement study. Next slide, please.

The first handout highlights information to help healthcare professionals, particularly those working in outpatient settings, communicate the key symptoms of MIS-C and how to recognize it to parents and caregivers.

As you can see, the resource was kept clear and concise so it could be shared with and easily understood by families. We found healthcare professionals appreciated the clarity and ease of understanding and said they would share the resource with their patients' families. One important aspect of this factsheet was clearly showing the fever icon at the top of the symptoms chart. For a diagnosis of MIS-C, a fever plus one or more of the additional symptoms are needed to meet criteria. The intention was to show that a combination of symptoms was needed in order to try and decrease confusion on when patients should be referred for an evaluation for possible MIS-C. Next slide, please.

This resource was developed based on our survey and interview findings particularly our findings that less than 1/3 of healthcare professionals working in an outpatient setting were very confident in diagnosing MIS-C or talking with families about MIS-C diagnosis. Next slide, please.

This resource can be found on CDC's MIS-C webpage and can be shared electronically or downloaded and printed. A QR code was also included so parents could scan and have it on their phone after a clinical visit. Next slide, please.

Next, I will walk you through two of the resources developed for parents and outpatient healthcare professionals highlighting what parents need to know. This first resource highlights key information parents and caregivers need to know about MIS-C. This material was designed to address the lack of confidence noted among outpatient healthcare professionals around having conversations with families about MIS-C diagnosis and treatment and addressing patients' questions related to MIS-C. The second resource on the right highlights key information parents need to know after MIS-C diagnosis, including what to expect when a child is receiving treatment in the hospital and after discharge from the hospital.

Again, this resource was developed based on the needs of outpatient healthcare professionals, specifically the lack of confidence in speaking with families about what might happen if they're sent to the hospital and MIS-C follow up care. Next slide, please.

Both of these factsheets were intended to educate parents and caregivers about two points in time when they would most likely have the highest level of uncertainty or stress: when concerned about a possible MIS-C diagnosis and after discharge from the hospital with a diagnosis of MIS-C. The materials were still intended for use with a healthcare professional to support the conversation at these points in time, so parents and caregivers felt educated and understood. Next slide, please.

These resources can also be found on CDC's MIS-C webpage and a QR code is also included. Next slide, please.

Each of these three materials were translated and made available in Spanish on the CDC MIS-C webpage. Next slide, please.

So the fourth material we developed was designed to be a resource that could help healthcare professionals talk with parents about MIS-C and address key questions about the condition. This material went through a more in-depth round of revision following the online material testing survey, because we received extensive feedback about the specific questions healthcare providers had received, and those they would like help trying to address with families. Next slide, please.

Shown here, the resource includes information to help address caregivers' key questions about MIS-C, including risk factors, incidents, symptoms, treatment during hospitalization and follow ups and long-term effects. Next slide, please.

Unlike the previous three materials, this material exists on its own webpage. This is because we intended for this material to be used directly by healthcare professionals prior to or during conversations with parents and caregivers, but not necessarily shared with parents and caregivers. Also, this material was designed as a webpage rather than a PDF, so it can be easily updated as new information becomes available. The webpage location is noted in the bottom gray box. Next slide, please.

To ensure healthcare professionals were made aware of these new resources, we specifically used communication channels mentioned by healthcare professionals during our phase one and phase two research.

In addition, as mentioned, these materials were never intended to be direct to consumer materials, or something a parent and caregiver would find on their own and used to diagnose their child. They were always intended for healthcare professionals to use on their own or with parents or caregivers. Therefore, we used a two-pronged approach to dissemination. CDC's healthcare professionals channels included social media channels and networks like COCA and direct outreach to healthcare professional associations. They specifically targeted associations who are most likely to have members who treat pediatric and young adult populations.

As a result, since September 2021, there have been over 1. 5 million pageviews of the MIS-C material pages and over 50,000 downloads of the MIS-C PDF resources. We thank those organizations for the support of this important material. Now, I will hand it over to Dr. Yousaf.

Good afternoon, everyone. Thank you, Shana. So, I would like to cover three different topics that all relate to COVID-19 vaccination and MIS-C. Next slide, please.

So first, I will discuss the CDC's interim clinical considerations for use of COVID-19 vaccines in people who have had MIS-C and have not yet been vaccinated. Then I will cover reporting of MIS-C in people who have received COVID-19 vaccine before onset of MIS-C. And then I will finish by discussing a study of COVID-19 vaccine effectiveness in preventing MIS-C. Next slide, please.

So the CDC has provided interim clinical considerations for the use of COVID-19 vaccines in people with a history of MIS-C who have not yet been vaccinated. These clinical considerations can be found at the link at the bottom of this slide under the section titled COVID-19 Vaccination and SARS-CoV-2 Infection.

Given the lack of data on the safety of COVID-19 vaccines in people with a history of MIS-C or MIS-A, a conversation between the patient, the guardians and the clinical team or a specialist is strongly encouraged to assist with decisions about the use of COVID-19 vaccines. Several experts consider the benefits of COVID-19 vaccination that is reduced risk of severe disease, including potential recurrence of MIS-C after SARS-CoV-2 reinfection, to outweigh a theoretical risk of an MIS-C-like illness or the risk of myocarditis following COVID-19 vaccination for people who meet certain criteria. Next slide, please.

These several experts suggest administering COVID-19 vaccine to persons with a history of MIS-C when all of the following criteria are met. One, clinical recovery has been achieved, including return to normal cardiac function.

Two, it has been 90 days or more since their diagnosis of MIS-C. Three, they are in an area of high or substantial community transmission of SARS-CoV-2 or otherwise have an increased risk for SARS-CoV-2 exposure and transmission. And four, onset of MIS-C occurred before any COVID-19 vaccination. There are also additional factors when considering individual benefits and risks. And these may include increased personal risk of severe COVID-19 such as age or underlying conditions, and also timing of immunomodulatory therapies. ACIP's general best practice guidelines for immunization can be consulted for more information about that. Next slide, please.

Now I'm going to discuss reporting of MIS-C in people who have received COVID-19 vaccine before onset of MIS-C. As part of the US COVID-19 Vaccine Safety Monitoring Plan, MIS after COVID-19 vaccination was prespecified as an adverse event of special interest because of the known association between SARS-CoV-2 infection and MIS. Vaccination providers are required to report MIS that occurs after COVID-19 vaccination to the Vaccine Adverse Event Reporting System, or VAERS, under the COVID-19 vaccine emergency use authorizations. VAERS is coadministered by the CDC and the FDA.

On the bottom right, I am showing an excerpt from VAERS listing what post-vaccination conditions are required to be reported under COVID-19 vaccine EUA. As you can see, MIS included in that list. Adverse events after COVID-19 vaccination including MIS can be reported to VAERS at the link seen at the bottom of this slide, vaers.hhs.gov. Reports can be made by healthcare professionals, public health providers, or members of the public. Next slide, please.

As part of its ongoing response to monitoring MIS-C, CDC conducted an investigation into MIS-C occurring after vaccination in persons aged 12 to 20 years from December 2020 through August 2021. This investigation looked at reports of potential MIS-C made to the CDC's MIS-C national surveillance system, to VAERS, and through clinician or health department outreach to the CDC, including reports through the Clinical Immunization Safety Assessment project, or CISA project, which provides clinical consultations on vaccine safety questions.

This investigation identified 21 people with an illness meeting the CDC MIS-C case definition after COVID-19 vaccination out of 21 million people aged 12 to 20 years who had received one or more doses of COVID-19 vaccine during the same time period. Thus, the investigation concluded that MIS-C after COVID-19 vaccination is rare, with an overall reporting rate of one case per million vaccinated people. Potential contribution of COVID-19 vaccination, if any, to the development of these MIS-C illnesses is unknown and could not be explored using surveillance data. And most of the people with MIS-C after COVID-19 vaccination in this investigation, 15 out of 21 cases or 71%, also had laboratory evidence of past or recent SARS-CoV-2 infection.

When evaluating people with potential MIS-C after COVID-19 vaccination, anti-nucleocapsid antibody testing may be helpful to identify those who have had SARS-CoV-2 infection. This is because anti-nucleocapsid antibodies are indicative of past or recent SARS-CoV-2 infection, whereas anti-spike protein antibodies can be induced either by SARS-CoV-2 infection or by COVID-19 vaccination. Anti-nucleocapsid antibody testing would ideally be from a sample obtained before administration of intravenous immunoglobulin. Providers should report potential cases of MIS-C after vaccination to VAERS at the VAERS website. Next slide, please.

Now, I would like to focus on an evaluation of the effectiveness of Pfizer-BioNTech COVID-19 vaccine in preventing MIS-C among persons aged 12 to 18 years. This evaluation used to test negative case control design by comparing the odds of antecedent full vaccination between MIS-C case patients and hospitalized controls without evidence of SARS-CoV-2 infection during July 1 - December 9, 2021. Full vaccination was defined as a receipt of two doses of Pfizer-BioNTech COVID-19 vaccine with receipt of the second dose 28 days or more before hospital admission. The 28-day time period was selected because a person is considered fully vaccinated against COVID-19 14 days or more after receipt of the second dose. And MIS-C generally occurs approximately two to six weeks after SARS-CoV-2 infection, with most cases occurring by the fourth week. Cases where persons with an illness meeting the CDC MIS-C case definition, there were two hospitalized control groups.

The first control group was comprised of patients with one or more symptoms consistent with COVID-19, but with a negative result from a SARS-CoV-2 RT-PCR or antigen test. These were the test negative controls. The second control group was comprised of patients without

symptoms compatible with COVID-19, who might or might not have received SARS-CoV-2 testing. These were the syndrome negative controls. Eligible controls were matched to case patients by site, age group which were 12 to 15 years and 16 to 18 years, and case patient hospitalization date within plus or minus approximately three weeks. The evaluation included 102 MIS-C case patients and 101 hospitalized controls from 24 pediatric hospitals in the Overcoming COVID-19 Network. Next slide, please.

This evaluation published in MMWR in early January, found that vaccine effectiveness of two doses of Pfizer-BioNTech vaccine against MIS-C was 91%, with a 95% confidence interval of 78% to 97%. Ninety-seven out of 102 or 95% of hospitalized children with MIS-C were unvaccinated. Of the five children hospitalized with MIS-C who were fully vaccinated, none required respiratory or cardiovascular life support, such as invasive mechanical ventilation, vasoactive infusions or ECMO, compared with 39% of unvaccinated MIS-C patients who did. Next slide, please.

In summary, this evaluation found that two doses of Pfizer-BioNTech COVID-19 vaccine reduced the likelihood of MIS-C by 91%. Of the people hospitalized with MIS-C during the study, 95% were unvaccinated, and none of the vaccinated people hospitalized with MIS-C required life support. This analysis provides support that vaccination of children and adolescents is highly protective against MIS-C and underscores the importance of vaccination of all eligible children. Next slide, please.

Now it's time for a self-knowledge check. Which of the following are criteria to be considered when making decisions about starting COVID-19 vaccination in an unvaccinated child who has a history of MIS-C? The answer is all except one of these. A, clinical recovery has been achieved including return to normal cardiac function. B, it has been 90 days or more since diagnosis of MIS-C. C, when they are in an area of high or substantial community transmission of SARS-CoV-2 or otherwise have an increased risk for SARS-CoV-2 exposure and transmission. Or D, duration of hospitalization. All right. Next slide, please.

So the correct answer is D, duration of hospitalization. Answers A, B and C are all criteria that should be considered when making decisions about starting COVID-19 vaccination in an unvaccinated child who has a history of MIS-C.

Regardless of duration of hospitalization, times should be allowed for full recovery from MIS-C and for discussion to occur between the family and healthcare provider as to when the right time for vaccination would be. Next slide, please.

So to summarize the overall contents of this COCA Call, the CDC's response to monitoring MIS-C includes both passive and active complementary surveillance systems. These are the national health department reported surveillance, Overcoming COVID-19 Network and integrated surveillance for MIS-C after vaccination. The CDC has other focused epidemiologic investigations that are ongoing, including evaluations of incidents, risk factors, and outcomes of MIS-C.

MIS-C resources are available to support healthcare professionals, and these include handouts on MIS-C symptoms and what caregivers need to know, key points for healthcare professionals to use when talking with families and caregivers about MIS-C, and clinical considerations regarding COVID-19 vaccination. Next slide, please.

Lastly, here is a list of resources. And these will also be provided on the COCA website. Thank you.

And now we have time for questions.

Presenters, thank you so much for providing our audience with such timely information. We will now go into our Q&A session. Please remember to ask a question using Zoom, click the Q&A button at the bottom of your screen and type your question. Our first question asks, how should clinicians report cases of MIS-C to CDC's national surveillance systems? And when it comes to case definitions, do you have any plans for these case definitions? Do you expect them to change?

Yeah, thanks. This is Dr. Campbell. I'll take that one. I think, you know, we've really gotten all of our states and many of the territories on board now with reporting. And so clinicians would go through their local, state, or territorial health department, and then those in turn report cases to us. I think each state and each jurisdiction sort of varies in the approach to that. Each hospital actually I think varies in the approach to that. But you would go through your health department. And I saw there were a couple of other questions about some of the future contents of the case definition, and so I'm glad that a few people have wondered about that.

We are actually actively in the process of revising the case definitions, and in the process of that, working to make a more efficient case report form. So in working on this, our discussions have been informed by the data that we've collected on cases reported to the national surveillance system, as well as that robust data set of Overcoming COVID-19. And then another data set at CDC that was from a study designed to look at features of MIS-C compared with COVID-19, Kawasaki disease, and toxic shock syndrome. Because these can sometimes be difficult to distinguish from MIS-C. So we interrogated all of these data sets so that we could refine the case definition a bit and remove some of the features, particularly even some of the organ systems that don't seem to contribute to the inclusion as a case.

And then we are also trying to define the criteria, not trying to -- we're planning to define the criteria for inflammation and the SARS-CoV-2 laboratory testing more clearly and more precisely than the broader definition. We are actually already working with CSTE, the Council of State and Territorial Epidemiologists. And the plan is that we will be working with them over the next several months. And there would be voting at the June CSTE annual conference on the new case definition. So it won't come tomorrow, it won't come in time for the cases that are likely to follow the Omicron COVID wave but we are working on that.

Thank you.

Thank you very much. This is a question we're seeing in a few different forms and essentially boils down to, when should patients be referred to a higher level of care so they can be evaluated for MIS-C?

Thank you for that. This is Shana. I'll take that question. But first, I want to acknowledge those who commented partnering with the American Academy of Family Physicians and they're a very strong partner of ours. And you're absolutely right, they're one of our great collaborators in this effort.

But to answer that question, parents and healthcare professionals should monitor children with a known or suspected history of SARS-CoV-2 infection or exposure for symptoms of MIS-C. MIS-C typically presents about two to six weeks after infection of SARS-CoV-2. And symptoms include fever and multiorgan dysfunction. Common symptoms include abdominal pain, vomiting, diarrhea, rash, non-purulent conjunctivitis and dizziness. Many of these symptoms can overlap with acute COVID-19 or other viral illnesses.

But patients with MIS-C generally present quite sick and require hospitalization, at a minimum for supportive care. Depending on the level of suspicion for multiorgan dysfunction associated with MIS-C, there are several lab tests that can be useful for further evaluation, including but not necessarily limited to CRP, ESR, CBC, CMP, BMP, and troponin. Certainly any patient with any of the warning signs and symptoms such as trouble breathing, pain or pressure in the chest that doesn't go away, confusion or unusual behavior, severe abdominal pain, irritability, or inability to stay awake, and then discoloration of the skin pale gray or blue. And then these patients should be referred immediately to the emergency room. Thank you.

Thank you very much. Our next question is regarding the safety data about children who got MIS-C after receiving the COVID-19 vaccine. Now that the younger children ages 5 to 11 are able to be vaccinated, are you also receiving reports of children who develop MIS-C shortly after they get this vaccine?

Yeah, this is Anna, I'll take this question. So we have been monitoring potential cases of MIS-C after vaccination in children 5 to 11 years old. And as of February 4, we've identified 10 children who received COVID-19 vaccine and then developed an illness that met CDC MIS-C case definition. And we are investigating an additional 20 potential cases. But of the 10 children that we identified that have an illness meeting that MIS-C case definition, seven also had lab evidence of past or recent infection.

Thank you very much. Our next question also seems to focus on vaccination a little bit. The question asks, do you know if it's possible to develop MIS-C after having been vaccinated for COVID-19? So from like, say, a breakthrough case of COVID?

Yeah, Anna. I'll comment on that from the surveillance perspective. I don't think I mentioned, we added vaccination questions to our case report form last May. Those fields weren't widely completed initially. But they have been more now.

And so we are keeping an eye on how many cases reported to national surveillance are in children who've been vaccinated and sort of the timing around that. And I know that there have been at least 20 or so so far, last I looked, that these kids had been vaccinated like two to six months before their MIS-C onset. So you know, would really seem like a long enough window that they got a subsequent SARS-CoV-2 infection, basically a breakthrough infection and they did present with MIS-C. I've seen a few questions -- I'm trying to kind of have my answer address some of the others. We don't currently collect -- we don't have a field right now that's collecting information on booster doses.

But we are planning to add that. And so I can't really comment on fully vaxxed and boosted children having been reported who developed MIS-C. There was another question I thought. Oh, we also haven't really looked -- well, we have looked but haven't really seen any obvious differences in the clinical characteristics of the kids who were reported after having been fully vaccinated and getting MIS-C after what seems like a breakthrough infection. So I think that that addresses the comments I saw about breakthrough.

It does seem that it can happen. I don't think we're able to really comment on rates or how often, but we have seen some kids. I think the other thing I want to add is I've seen some questions about whether children can get MIS-C twice. So the answer is yes, but it seems to be very infrequent. I think, you know, we've got 6,000-some children reported to us so far.

And I think we're only aware of two or three, really that seem to have had true MIS-C illness twice after two separate infections. Thanks. I think that's all. I think that addresses your question and more for now.

No, thank you very much. That's very helpful information. And we have time for just one more question. So speaking about what you refer to as the number of cases you've seen and the time that you've seen them over, can you please sort of address generally what you know about the long-term effects of MIS-C and what we know about that so far?

This is Shana. I can take that one. There are a couple of studies that are currently going on to look at kind of mid-term and long-term effects of patients who have been diagnosed with MIS-C. One of those studies is also comparing the effects in patients who were hospitalized with COVID-19. I can't comment on long COVID versus MIS-C effects, or even those in association with the patients who are hospitalized with COVID, because we don't have that cohort in the study.

But there will be some data coming out hopefully in the next couple of months looking at those differences in how those children recover over time. I can say overall, the reports we're hearing are that children tend to do very well after MIS-C. But we want to look at this a little more, you know, collect this a little more of a study fashion than our anecdotal reports that we've been getting. So thank you for that question.

And actually, Shana -- sorry, this is Angie, Dr. Campbell. I just wanted to mention, we're also asking some of these questions in the Overcoming COVID Network. And similarly have data that we're almost done working through looking at longer-term, well, two- to three-month

outcomes in children who've had MIS-C and acute COVID hospitalizations, as well as the more detailed neurologic case control that I mentioned. We're actually doing pretty extensive neuro psychiatric testing on children who've had MIS-C and either sibling or community controls to describe longer term neuro psychiatric, neurodevelopmental effects.

Thank you.

One more point that I wanted to make quickly is I think somebody asked about the treatment of steroids alone versus steroids with IVIG or IVIG alone. And some of these studies are going to look at the treatment, kind of the mid- to long-term effects of these patients based on the treatments they received. So hopefully, we'll have a little bit of information to share about that.

Thank you so much. I really appreciate that. I want to thank everyone for joining us today with a special thanks to our presenters. All continuing education for COCA Calls are issued online through the CDC Training and Continuing Education Online System at https://TCEOLS.CDC.gov.

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Have a great day.