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# Epi Notes

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## A historical perspective on the FDA's close scrutiny of vaccine use

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By mid-March 2021, the AstraZeneca SARS-CoV-2 vaccine had been approved and was in use in more than 50 countries worldwide. Although some countries temporarily halted vaccine administration because of a possible association with an immune-mediated blood clotting disorder with thrombocytopenia, the rarity of the side effect prompted many countries to resume vaccination. German Chancellor Angela Merkel was publicly vaccinated with AstraZeneca. Yet the US would not even consider approving the AstraZeneca vaccine until US Phase 3 trials were complete.

Why does the US Food and Drug Administration (FDA) demand this extra scrutiny and oversight

of Phase 3 trials? Why delay access to a vaccine authorized for emergency use and, in some instances, approved for routine use in so many other countries, including in the UK and EU? The reason is, in part, historical.

Do you recognize the person with President John F. Kennedy below? She is Dr. Frances Kelsey, who President Kennedy awarded the Distinguished Federal Civilian Award. Why did she get the award?



In 1960, a New Drug Application (NDA) was submitted to the FDA for thalidomide, an oral medication considered safe and effective in Europe for preventing nausea in pregnancy. The company anticipated quick approval. People were already planning how they were going to spend their expected Christmas bonuses when the drug was marketed in the US. Dr. Frances Kelsey was hired by the FDA in August 1960 and assigned what was thought to be an easy first task: reviewing the thalidomide NDA.

Dr. Kelsey was not satisfied with the information as presented in the NDA and wanted more data on a medication that could affect the unborn child. Fortunately for the unborn babies in America who might have otherwise been exposed, she stood her ground amidst harsh criticism, public demand, and possibly pressure within the FDA itself. By 1961, data had accumulated indicating that thalidomide, administered during critical periods of fetal development, led to the tragic underdevelopment of limbs known as phocomelia.



Boy with phocomelia. Image courtesy of Helix Magazine, Northwestern University

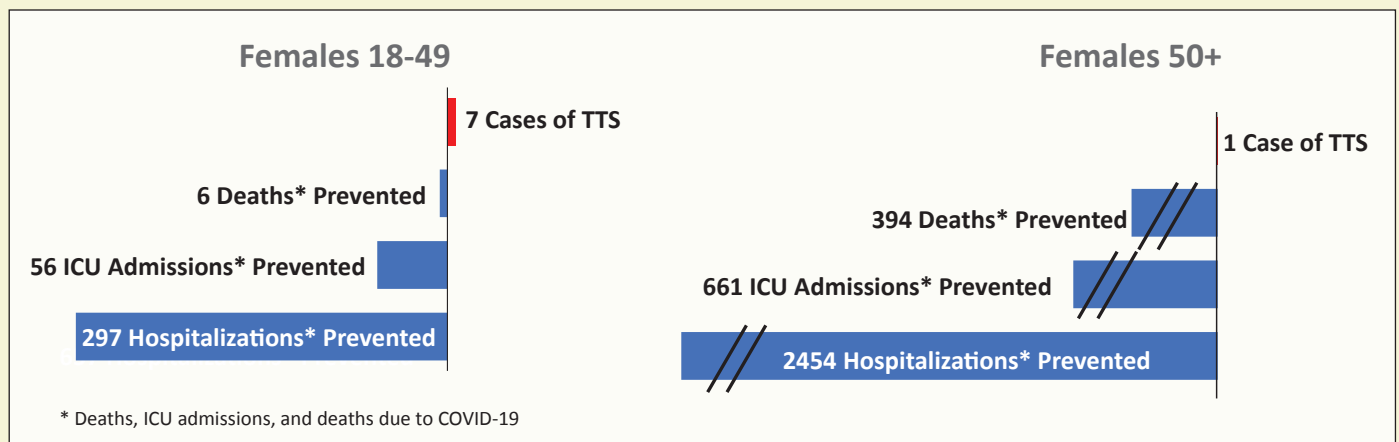
Since that time, the FDA’s scrutiny of new pharmaceuticals has become more rigorous and new systems, such as the Vaccine Adverse Event Reporting System (VAERS), have increased sensitivity for detecting rare events.

As of this writing, the European Medicines Agency is reviewing 167 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic thrombosis occurring after the administration of 34 million doses of AstraZeneca vaccine. In the US, CDC and the FDA placed the Janssen vaccine on “pause” while they investigated 6 CVST cases and looked for others. Was this an over-abundance of caution? Public health is always a balancing act: What is an acceptable individual risk to protect population health? The question becomes even harder during a pandemic.

Dr. Kelsey resolutely demanded robust data. While a great relief to morning sickness sufferers, thalidomide was not lifesaving, and taking more time to get adequate data was prudent. In contrast, some public health experts argue that pausing Janssen vaccine administration for an extremely rare complication was the wrong move: It slowed the race to herd immunity and may increase vaccine hesitancy.

The April 23, 2021, Advisory Committee for Immunization Practices (ACIP) vote to reaffirm the recommendation for Janssen vaccine use for all persons aged 18 years and older will become a classic ethics case study evoking the principles of

**Figure 1. Estimates of the number of cases of thrombosis with thrombocytopenia syndrome (TTS) and the number of deaths, ICU admissions, and hospitalizations prevented with the administration of the Janssen vaccine among US females, per 1 million doses of vaccine given (data as of April 21, 2021).**



Source: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04-23/06-COVID-Oliver-508.pdf>

beneficence, nonmaleficence, autonomy, and justice. As of April 21, 2021, a total of 15 cases of thrombosis with thrombocytopenia syndrome (TTS) associated with Janssen vaccine were uncovered, out of 7.98 million doses administered; all were women and 13/15 were under age 50. As seen in Figure 1, the risk for TTS was estimated at 7 cases/million doses for women aged <50, and <1 case/million doses for women aged 50+. Estimates for number of deaths, ICU admissions, and hospitalizations prevented supported the ethical principles of beneficence and non-maleficence (balancing benefits against risks) and argued for approval of the vaccine even for younger women.

The biggest issue was autonomy in the form of informed consent. Of the 15 voting ACIP members, 10 voted for approval, 4 against, and 1 abstained. All who voted against agreed that Janssen should be reauthorized but expressed concern that not all young women would be adequately informed of the risk.

Justice was also a concern: “I did not object to the recommendation; I objected to the absence of any kind of guidance from us,” Dr. Sarah Long, Drexel. “This is an age group that is most at risk (of TTS) that is getting a vaccine predominantly to save other people’s lives and morbidity—not their own.”

A paragraph concerning the rare but increased risk of clotting events was added to the vaccine handout for patients and health care providers. Is that adequate? Would a more complicated recommendation be more confusing, increase vaccine suspicion, and ultimately lead to less vaccine uptake and more lives lost? If you were an ACIP voting member, what would you have recommended?

## Additional Resources

1. Advisory Committee for Immunization Practices (ACIP) April 23, 2021 Presentation slides <https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html>
2. Principles of Clinical Ethics and Their Application to Practice <https://www.karger.com/Article/Pdf/509119>



## Awareness of Multisystem Inflammatory Syndrome in Children (MIS-C) critical

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Most children with COVID-19 infection have mild symptoms and excellent outcomes; however, there is a rare complication temporally associated with SARS-CoV-2 infection that occurs weeks after a child has been infected known as multisystem inflammatory syndrome in children (MIS-C). It was first identified in April 2020 in the United Kingdom and the Centers for Disease Control and Prevention (CDC) provided a case definition in May 2020.<sup>1,2</sup>

CDC defines MIS-C as:

- An individual aged <21 years presenting with fever for more than 24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.<sup>2</sup>



Patients with MIS-C usually present with persistent fever, gastrointestinal symptoms, rash and mucocutaneous findings (Table 1).<sup>3,4</sup> Gastrointestinal symptoms (nausea, vomiting, diarrhea) appear to be very common in children with MIS-C with rates up to 92%.<sup>1,3</sup> However, symptoms of MIS-C may begin weeks after a patient is infected with SARS-CoV2 and may be vague or frequently missed. Some patients who develop MIS-C may not have had any COVID-19 symptoms at the time of their initial infection. Most children with MIS-C require hospitalization and some develop severe disease with cardiac involvement, hemodynamic instability, and shock.

Diagnosis of MIS-C requires laboratory evaluation, including tests for inflammation (CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, complete blood cell count, albumin) and tests for current or previous SARS-CoV-2 infection (RT-PCR, antigen, serologic tests). Many patients also receive cardiac testing (echocardiogram, electrocardiogram, cardiac enzymes, B-type natriuretic peptide) and evaluations of other organ systems directed by the signs/symptoms of the patient.<sup>4,5</sup>

Treatment for MIS-C includes a multidisciplinary team that focuses on the inflammatory process and supportive measures. Immunomodulatory treatments with IVIG and steroids have been the mainstays of therapy as well as thromboprophylaxis with aspirin.<sup>5</sup>



After discharge from the hospital, children typically will require follow up with subspecialty physicians.

In South Carolina, as of April 14, 2021, there have been 102 cases of MIS-C reported in children between 0 and 18 years. Their distribution is displayed by region in Figure 1 and by characteristics in Table 2. Of the 102 cases, 61.8% required intensive care unit admission and there have been 2 reported deaths. Hematologic (98%), cardiac (94.1%), and gastrointestinal (92.25%) involvement were the most common systems affected in the children in SC. Despite only representing approximately 30% of SC's children and adolescents, African Americans represented 52.9% of MIS-C cases. This disproportionate burden has also been seen in other studies across the US.<sup>1</sup>

MIS-C is a new condition that is reportable to the regional health department. As the COVID-19 pandemic evolves through the utilization of vaccines in adults and new variants, awareness of MIS-C is critical as it is a serious and sometimes fatal complication of SARS-CoV-2 infection in children.

## References

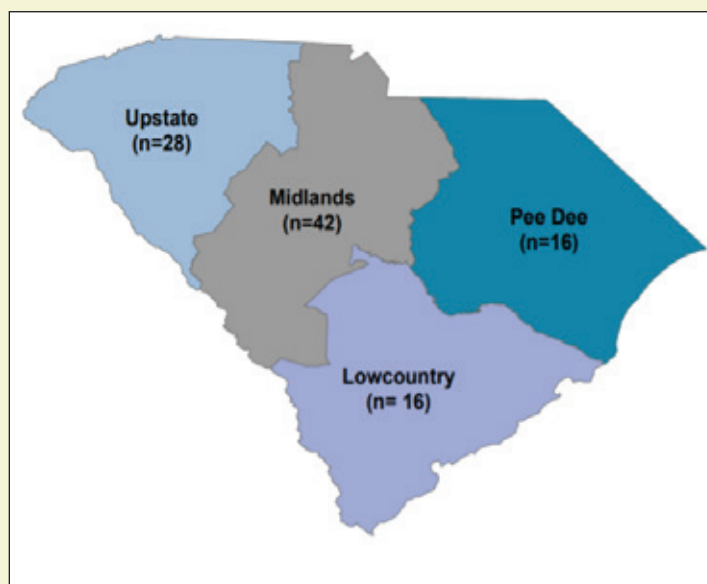
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**Table 1: Signs and Symptoms of MIS-C**

• <b>Fever</b>	• <b>Myalgias/arthralgias</b>	• <b>Cardiac symptoms</b> (tachycardia, chest pain)
• <b>Mucosal changes</b> (conjunctivitis, oral lesions)	• <b>Hand/foot swelling</b>	• <b>Neurologic symptoms</b> (headache, altered mental status)
• <b>Respiratory symptoms</b> (cough, congestion, shortness of breath, tachypnea)	• <b>Gastrointestinal symptoms</b> (nausea, vomiting, diarrhea, abdominal pain)	• <b>Rash</b>

**Table 2: Characteristics of MIS-C Cases in South Carolina, as of April 14, 2021**

PATIENT CHARACTERISTIC	TOTAL NUMBER (%)
Male/Female	51 (51%)/51 (51%)
Black or African American	54 (52.9%)
White	35 (34.3%)
Other Race	13 (12.8%)
Systems Involvement	
Hematology	100 (98%)
Cardiac	96 (94.1%)
Gastrointestinal	94 (92.25%)
Dermatology	63 (61.8%)
Neurology	51 (49.5%)
Respiratory	46 (45.1%)
Renal	22 (21.6%)

**Figure 1: Cases of MIS-C by region in South Carolina, as of April 14, 2021**

## 2021 School and Childcare Exclusion List

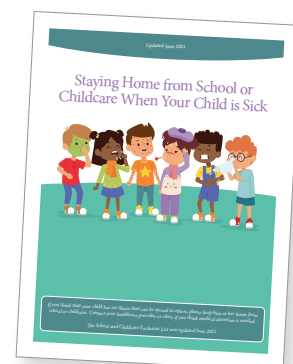
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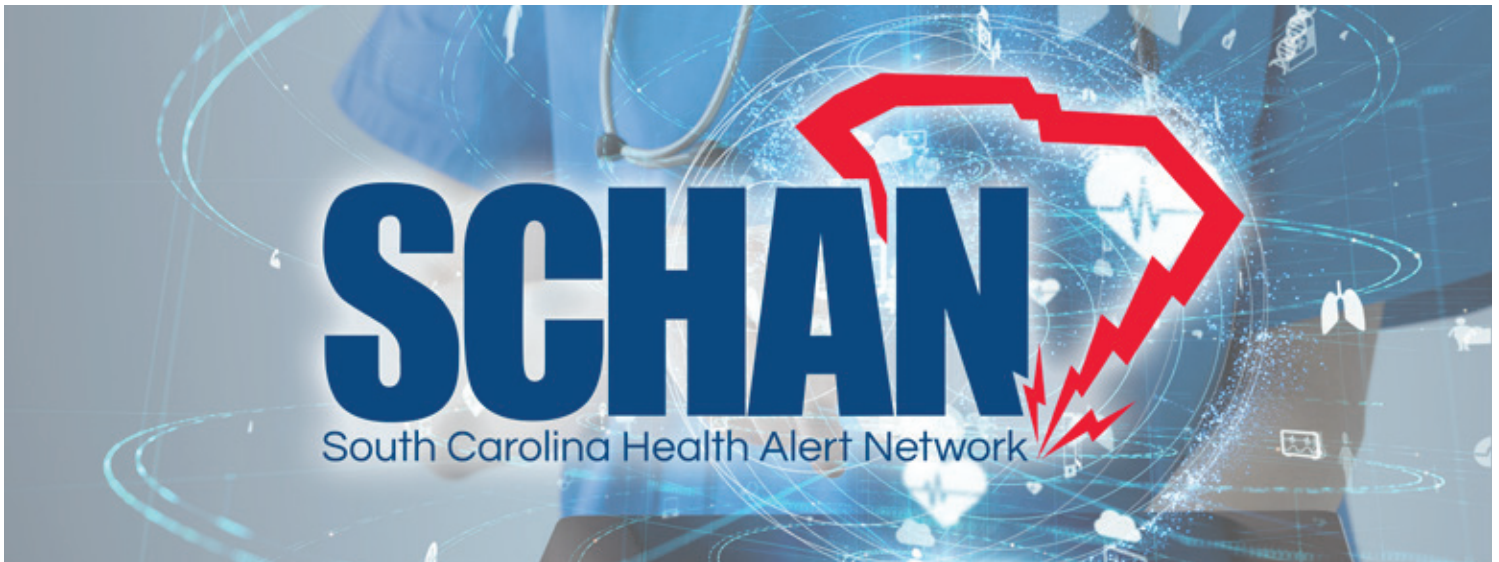
The School and Childcare Exclusion List has routinely been updated annually and made available January 31 of each year. South Carolina Regulation 61-20 requires that DHEC publish an Official School and Childcare Exclusion List of Contagious or Communicable Diseases to include specific conditions for the duration of school or childcare exclusion.

These conditions and criteria apply to both students and staff. In 2019, the decision was made to update the School and Childcare Exclusion List for the start of each new school year.

The current **2020 School and Childcare Exclusion List** can be found on the **DHEC website**. A brochure for parents is also available on the website in **English** and **Spanish**.



Please contact the DHEC Division of Acute Disease Epidemiology (803-898-0861) with any questions about the School and Childcare Exclusion List.



## South Carolina Health Alert Network helps keep health care providers in the know

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The South Carolina Health Alert Network (SCHAN) is a web-based emergency notification system used by DHEC to distribute health alerts and advisories from the Centers for Disease Control and Prevention (CDC) and DHEC. DHEC uses the SCHAN to notify health care providers of guidance, clusters, outbreaks, and other events of public health significance. The notifications are sent by email to organization-defined points of contact who then forward the message to appropriate recipients within their organization.

If you are a public health professional interested in receiving health alerts from the South Carolina Health Alert Network via email, you may sign up

by completing a [South Carolina Health Alert Network Registration Form](#). Once your registration is approved, your contact information will be added to the ReadyOp system, which is used to distribute health alerts.

Have you previously registered for SCHAN, but are no longer receiving health alerts? Your contact information may not be current, which could delay rapid alerts and notifications. If you would like to update your contact information, you may also complete a [South Carolina Health Alert Network Registration Form](#).

If you missed any of the previously distributed health alerts, you may visit the SCHAN webpage on the DHEC website at [scdhec.gov/HAN](http://scdhec.gov/HAN).

Please email the DHEC Health Alert Network Coordinator at [SCHAN@dhec.sc.gov](mailto:SCHAN@dhec.sc.gov) with any questions about the South Carolina Health Alert Network.



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