

## EDITORIAL

## Assessing a Rare and Serious Adverse Event Following Administration of the Ad26.COV2.S Vaccine

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**In this issue of JAMA**, See and colleagues<sup>1</sup> present a case series of patients with cerebral venous sinus thrombosis (CVST) following vaccination with the Ad26.COV2.S vaccine manufactured by Janssen/Johnson & Johnson. These cases were identified through the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). The 12 patients—all women aged 18 to 59 years—developed symptoms beginning 6 to 15 days after vaccination, along with declines in platelet counts (with nadirs ranging from 9 to 127  $\times 10^3/\mu\text{L}$ ), and clinically severe clotting, including CVST (12 patients), and non-CVST thrombosis (8 patients). Of the 12 patients, 10 required intensive care, 7 also had intracerebral hemorrhage, and 3 have died. In addition to the 12 patients with CVST with thrombocytopenia described in this case series, at least 3 patients without CVST but meeting diagnostic criteria for thrombosis with thrombocytopenia syndrome (TTS) have been reported to VAERS (as of April 21, 2021), all in women aged 18 to 59 years (median age, 37 years). Of the 15 total patients, 3 have died.<sup>2</sup>

All adverse event reports raise the question of causality or coincidence. Here, the case for a causal relationship with vaccine administration includes a much higher reported rate of CVST with thrombocytopenia (approximately 5 per million women aged 18-50 years shortly after vaccination)<sup>2</sup> than the background rate (approximately 0.05-0.13 per million per month, based on estimated annual US incidence of 0.7-1.6 per million per year).<sup>3</sup> The current cases also include substantial similarities to the clinical syndrome of TTS associated with the ChAdOx1 nCov-19 vaccine manufactured by Oxford/AstraZeneca.<sup>3</sup> The Ad26.COV2.S and ChAdOx1 nCov-19 vaccines use similar technology, namely modified adenovirus vectors.

The ChAdOx1 nCov-19 vaccine-associated cases in Europe<sup>4-6</sup> share clinical and laboratory characteristics with the rare syndrome of autoimmune heparin-induced thrombocytopenia. So too do the cases reported by See and colleagues.<sup>1</sup> In all 11 patients in whom ELISA-based testing for antibodies to platelet factor 4 (PF4) in complex with polyanions were available, the result was clearly positive despite no previous exposure to heparin. These results indicate the presence of antibodies that may represent a link between the immune response to the vaccine and the clotting syndrome.

At the same time, there are many gaps in the current understanding of TTS following administration of the

adenovirus-vectored vaccines. Missing epidemiologic information includes more accurate estimates of the frequency of the syndrome and the full spectrum of thrombotic complications. The availability of an interim standardized case definition<sup>7</sup> will facilitate prospective case ascertainment through review of large linked databases and active case finding. It will also permit greater understanding of whether individuals who are otherwise at increased risk for hypercoagulation in general and for CVST in particular (for example, women taking hormonal contraceptive medications or who are pregnant) are also at increased risk for TTS. Obtaining this information will support dynamic country-specific assessments of the risks of each vaccine compared with the risk of COVID-19 disease for their populations and subpopulations.

The immune response associated with TTS also requires further characterization. For TTS following administration of the ChAdOx1 nCov-19 or Ad26.COV2.S vaccine, validated PF4-polyanion ELISAs are highly sensitive screening assays. In this case series, “second phase” functional assays for platelet-activating antibodies in patient serum samples were negative in 8 of 9 cases with available results. However, functional assay methods vary widely between laboratories, and suboptimal interlaboratory concordance has been documented.<sup>8</sup> While functional assays have generally been positive in the ChAdOx1 nCov-19-associated TTS cases, this has not been a universal finding.<sup>4,5</sup> To determine whether cases of TTS following administration of the Ad26.COV2.S and ChAdOx1 nCov-19 vaccines share a common pattern of reactivity in PF4-based ELISA and functional assays, samples from all patients identified to date should be shared and tested in a single laboratory. Additionally, information is needed on whether other adenovirus-vectored COVID-19 vaccines in global use, such as Gam-Covid-Vac (Sputnik V, Gamaleya) or Ad5-nCoV (Convidicea, CanSinoBIO), are also associated with TTS.

It is also important to determine the full clinical spectrum of TTS, including whether subclinical cases with thrombocytopenia and occult thrombosis are occurring. Such information will be essential for defining risk groups and guiding the development of diagnostic algorithms. One challenge is that headache was the initial presenting symptom in 11 of 12 patients in the case series reported by See et al, yet headache is a frequent symptom and a common benign event after vaccination. A better understanding of TTS pathogenesis will also inform the approach to treatment, including appropriate anticoagulant use.

As these important questions are being addressed, policy makers must make decisions under conditions of uncertainty. Faced with similar safety signals, nations have taken different policy approaches. As of this writing, Norway and Denmark have suspended using the ChAdOx1 nCov-19 vaccine. Iceland and Germany have limited the use of the ChAdOx1 nCov-19 vaccine to people older than 60 years. The UK states that “it is preferable for adults aged <30 years without underlying health conditions that put them at higher risk of severe COVID-19 disease, to be offered an alternative COVID-19 vaccine, if available.”<sup>9</sup> Canada is offering the ChAdOx1 nCov-19 vaccine to all adults, with additional warnings on the vaccine label. Similarly, after an initial pause, and on the recommendation of the Advisory Committee on Immunization Practices, the US has permitted the use of the Ad26.COV2.S vaccine in all adults with information on the risk of TTS added to educational materials.

An essential concept in evaluating the safety of medical products is making the appropriate comparison to assess the potential risks and benefits. When compared to no vaccine, the benefits of vaccination with the Ad26.COV2.S vaccine far exceed the risks for all groups at this time. This is the key issue for much of the world, where the adenovirus-vectored vaccines are often the most (and in many cases the only) readily available option and will save many lives.

However, in the US and other places where mRNA vaccines are widely accessible, the point of comparison shifts. No cases of TTS have been confirmed following administration of more than 180 million doses of the mRNA vaccines in the US.<sup>2</sup> Certainly, even among people in risk categories for TTS, the Ad26.COV2.S vaccine will still be needed for individuals with allergies to components of the mRNA vaccine and for those who live in remote locations where the cold chain for transport and storage of mRNA vaccines cannot be maintained. Aside from these and other limited scenarios, US public health agencies and clinicians should consider recommending mRNA vaccines as safer options for those who may be at substantially higher risk for TTS after Ad26.COV2.S vaccination, currently women younger than 50 years.

Would such advice lead to more illnesses and deaths? At the Advisory Committee on Immunization Practices meeting, a presentation from CDC estimated that more than 1000 people could die in the US if the Ad26.COV2.S vaccine were restricted to those older than 50 years.<sup>3</sup> The CDC model, however, did not consider whether these deaths could be prevented through increased use of mRNA vaccines.

Another consideration is the value of the single-dose regimen for the Ad26.COV2.S vaccine, particularly for difficult-to-reach populations, such as individuals experiencing homelessness, compared with the 2-dose regimen for mRNA vaccines. The short-term data on the effectiveness of the first dose of the mRNA vaccines in the general population in a nonresearch setting are relevant and reassuring,<sup>10</sup> and public health departments and community organizations can develop mechanisms to help people receive a second dose. Difficult-to-reach populations are also less likely to be able to access the health care system in the event that they experience signs and symptoms that may be indicative of TTS.

The national COVID-19 vaccination effort will continue apace even as it adapts to emerging evidence about TTS. Strong endorsements of the value of vaccination can be paired with communication strategies to support decision-making in diverse communities, followed by vaccine access that respects the choices made.

There are also important implications for global vaccination efforts. Even as nations appropriately affirm the clear value of the adenovirus-vectored vaccines for their populations at this time, the international community should work together to better understand TTS and its management. Simultaneously, work must accelerate to broaden the diversity of vaccines available for global use.<sup>11</sup> Beyond the short-term need for vaccine donations, particular attention should be paid to the utility and availability of mRNA vaccines by enhancing thermostability, increasing production capacity, and facilitating technology transfer.

In the US and around the world, public health systems successfully identified a rare but serious clinical syndrome that may occur following administration of adenovirus-vectored COVID-19 vaccines, and many nations quickly responded. Now the hard work begins.

#### ARTICLE INFORMATION

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