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COVID-19 Vaccine Safety Technical (VaST) Work Group: Enhancing vaccine safety monitoring during the pandemic

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.12.059.

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Abstract

During the COVID-19 pandemic, candidate COVID-19 vaccines were being developed for potential use in the United States on an unprecedented, accelerated schedule. It was anticipated that once available, under U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) or FDA approval, COVID-19 vaccines would be broadly used and potentially administered to millions of individuals in a short period of time. Intensive monitoring in the post-EUA/licensure period would be necessary for timely detection and assessment of potential safety concerns. To address this, the Centers for Disease Control and Prevention (CDC) convened an Advisory Committee on Immunization Practices (ACIP) work group focused solely on COVID-19 vaccine safety, consisting of independent vaccine safety experts and representatives from federal agencies – the ACIP COVID-19 Vaccine Safety Technical Work Group (VaST).

This report provides an overview of the organization and activities of VaST, summarizes data reviewed as part of the comprehensive effort to monitor vaccine safety during the COVID-19 pandemic, and highlights selected actions taken by CDC, ACIP, and FDA in response to accumulating post-authorization safety data. VaST convened regular meetings over the course of 29 months, from November 2020 through April 2023; through March 2023 FDA issued EUAs for six COVID-19 vaccines from four different manufacturers and subsequently licensed two of these COVID-19 vaccines. The independent vaccine safety experts collaborated with federal agencies to ensure timely assessment of vaccine safety data during this time. VaST worked closely

with the ACIP COVID-19 Vaccines Work Group; that work group used safety data and VaST's assessments for benefit-risk assessments and guidance for COVID-19 vaccination policy. Safety topics reviewed by VaST included those identified in safety monitoring systems and other topics of scientific or public interest.

VaST provided guidance to CDC's COVID-19 vaccine safety monitoring efforts, provided a forum for review of data from several U.S. government vaccine safety systems, and assured that a diverse group of scientists and clinicians, external to the federal government, promptly reviewed vaccine safety data. In the event of a future pandemic or other biological public health emergency, the VaST model could be used to strengthen vaccine safety monitoring, enhance public confidence, and increase transparency through incorporation of independent, non-government safety experts into the monitoring process, and through strong collaboration among federal and other partners.

Keywords

Vaccine safety; COVID-19 vaccines; Emergency Use Authorization

1. Introduction

During the COVID-19 pandemic, candidate vaccines were evaluated for potential use in the United States on an unprecedented, accelerated schedule. [1] It was anticipated that once available, under U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) or FDA approval, COVID-19 vaccines would be broadly used and potentially administered to millions of individuals in a short period of time. Intensive monitoring after authorization would be necessary for timely detection and assessment of potential safety concerns. In the United States, the FDA's Center for Biologics Evaluation and Research and the Immunization Safety Office at the Centers for Disease Control and Prevention (CDC) routinely monitor vaccine safety. CDC determined that an additional independent review and evaluation process would be important to help guide the scientific direction of safety surveillance and maintain public confidence during this national pandemic vaccination program. Building on the previous experience from the H1N1 influenza pandemic of 2009, [2] and the role of Advisory Committee on Immunization Practices (ACIP) work groups in routinely reviewing vaccine safety data during vaccination policy considerations, [3,4] CDC convened an additional ACIP work group consisting of independent vaccine safety experts and representatives from federal agencies, focused solely on COVID-19 vaccine safety. This report summarizes the structure, processes, and activities of that work group, the ACIP COVID-19 Vaccine Safety Technical Work Group (VaST), and highlights some of the actions taken by CDC, ACIP, and FDA in response to accumulating post-authorization vaccine safety data.

2. Goals and structure

VaST was established to review, evaluate, and interpret safety data following the implementation of a national COVID-19 vaccination program. The work group's goals were to advise government vaccine safety researchers on analyses, interpretation, and data presentation; to serve as the central hub for federal agencies conducting post-EUA/

licensure safety monitoring to share vaccine safety surveillance data; to liaise with the ACIP COVID-19 Vaccines Work Group on safety data presentations at the ACIP meetings and consideration of safety data in policy decisions; and to advise federal agencies on public communication of safety information. As noted, VaST's mandate included supporting the ACIP COVID-19 Vaccines Work Group, which had a broader scope than VaST, including review of available data to inform COVID-19 vaccine policy and making recommendations for use of COVID-19 vaccines in the U.S. population. [5]

Selection criteria for VaST membership were developed to ensure a comprehensive range of expertise. VaST was chaired by a member of the ACIP COVID-19 Vaccines Work Group; leadership was also provided by the Chair of the National Vaccine Advisory Committee. The workgroup was comprised of nine consultants with expertise in vaccine safety, vaccine safety surveillance, or vaccine safety methods, and included ACIP's consumer representative. The work group also included *ex officio* and liaison members from the National Institutes of Health (NIH), the FDA, the Centers for Medicare and Medicaid Services (CMS), the Indian Health Service (IHS), the Office of Infectious Disease and HIV/AIDS Policy (OIDP), the Health Resources and Services Administration (HRSA), and federal partners from the Department of Veterans Affairs (VA) and the Department of Defense (DoD) (Supplementary Table 1). As required for ACIP work groups, screening for potential conflicts of interest was conducted upon establishment of VaST, and at each VaST meeting. Annual conflict of interest statements were collected from members to ensure that financial or other conflicts were not present and/or had not changed if previously disclosed. Two CDC scientific public health professionals (LEM and MW) were responsible for organizing and managing VaST as co-leads for CDC.

3. VaST processes

Planning for VaST started in June 2020. Beginning November 16, 2020, VaST held regularly scheduled and ad hoc video conference meetings. The first meeting was to review the terms of reference for the work group, followed by meetings to review the general structure of the U.S. vaccine safety monitoring systems. Close coordination with CDC's Immunization Safety Office and FDA's Center for Biologics Evaluation and Research, as well as other U.S. vaccine safety monitoring systems, allowed for timely scheduling of data to be reviewed by VaST. The first meeting to review post-authorization safety monitoring data was December 21, 2020, approximately one week after COVID-19 vaccinations began in the United States. [5]

Starting in February 2021, specific VaST meetings were scheduled to review safety data on COVID-19 vaccines administered during pregnancy. Additional obstetrics and gynecology subject matter experts were included in those meetings (Supplementary Table 1).

VaST meetings occurred weekly or every two weeks for the first 18 months, and approximately once a month thereafter. The meetings followed ACIP work group procedures. [3] Each VaST meeting had a 60–90 min presentation and discussion session that included VaST independent vaccine safety consultant members, *ex officio* and liaison members, federal experts, invited presenters, and subject matter experts; during this time

the most recent post-authorization/approval safety data were presented. At the conclusion of these sessions, there was a 30-minute assessment session attended by the independent expert vaccine safety consultant members. During this assessment session, findings were discussed, and suggestions made regarding further data collection, analyses, communications, or other actions. CDC VaST co-leads were present at the assessment sessions to summarize and record the discussion, including specific requests of VaST members. A brief report from the assessment session was communicated to the vaccine safety monitoring systems' subject matter experts within a few days. These reports, along with meeting minutes, were also made available to all VaST members, the ACIP COVID-19 Vaccines Work Group lead and chair, and the ACIP secretariat within five days of each VaST meeting.

VaST chairs made presentations regarding VaST's interpretation of vaccine safety data at the frequent ACIP public meetings held during the COVID-19 pandemic. These followed a safety data presentation from CDC's Immunization Safety Office or other immunization safety subject matter experts and served to inform ACIP and the public about the VaST independent review and its assessments. [4] If VaST members thought a safety finding required more immediate communication, the VaST assessment was posted on the ACIP webpage. [6] After the first year of the program, VaST assessments were often incorporated into presentations by the ACIP COVID-19 Vaccines Work Group.

From November 2020 through April 2023, VaST held 73 meetings and presented 22 summary assessments or reports at ACIP public meetings. [4] In April 2023, after the evaluation of post-authorization/approval safety data for over 670 million COVID-19 vaccinations nationwide, VaST's responsibilities were transferred to the ACIP COVID-19 Vaccines Work Group, consistent with how routine vaccine safety data are reviewed by ACIP work groups.

4. Sources of data reviewed

VaST reviewed data from the CDC's vaccine safety monitoring systems, including the Vaccine Adverse Event Reporting System (VAERS) (co-managed with FDA), v-safe, CDC's COVID-19 Vaccine Pregnancy Registry, the Vaccine Safety Datalink (VSD), from FDA's Centers for Medicare Services (CMS) and Biologics Effectiveness and Safety (BEST) System, and from the IHS, VA, and DoD monitoring systems. [7,8] CDC's Clinical Immunization Safety Assessment (CISA) Project also provided information and technical expertise. The vaccine safety monitoring systems are summarized by Gee et al. [8] Several of these systems use population-based sequential testing of pre-specified outcomes to detect risk over time as immunization increases, called rapid cycle analysis (RCA) or near real time surveillance (NRS).

Pre-specified outcomes included in U.S. safety monitoring systems are summarized in Table 1. Data from vaccine safety monitoring from other countries were also critical in the early months of the program. Because Israel quickly achieved high coverage with the Pfizer-BioNTech COVID-19 Vaccine in adults ages ≥ 60 years, that was introduced in December 2020, [9] their initial vaccine safety assessments were presented to VaST. Later, when they achieved high coverage in the general population, and introduced booster doses, Israel's

safety monitoring data were followed closely for both adults and younger age groups. Several European countries introduced an mRNA and/or an adenovirus-vector COVID-19 vaccine at the beginning of January 2021, and their vaccine safety monitoring data were also followed closely. [10,11] In addition, the United States and Canada shared vaccine safety monitoring data throughout the COVID-19 vaccination program. In interpreting vaccine safety concerns and safety findings from the different systems, VaST considered consistency of findings, as well as the specific strengths and limitations of the monitoring systems and methods used. [8]

5. Timeline of COVID-19 vaccine authorizations and licensures

The timeline of FDA authorizations influenced the cadence of VaST's work (Table 2). [12–19] Through March 2023, six COVID-19 vaccines were authorized under EUA in the United States: Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), an mRNA vaccine; Moderna COVID-19 Vaccine (Original monovalent), an mRNA vaccine; Janssen COVID-19 Vaccine (Original monovalent), a replication-incompetent adenoviral vector vaccine; Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), a protein subunit vaccine; Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), an mRNA vaccine, hereafter referred to as Pfizer-BioNTech COVID-19 Vaccine, Bivalent; and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), an mRNA vaccine, hereafter referred to as Moderna COVID-19 Vaccine, Bivalent. After the initial authorizations, individual vaccine EUAs were amended to include additional uses (e.g., other age groups, use of booster doses, and additional doses for immunocompromised persons). [5] Both the Pfizer-BioNTech and Moderna COVID-19 vaccines (Original monovalent) were subsequently licensed for use in certain age groups. COVID-19 vaccines designated as "Original monovalent" contain or encode the spike protein of only the Original SARS-CoV-2 and are hereafter referred to by the names listed above.

6. Safety data from pre-authorization clinical trials

The safety of COVID-19 vaccines used in the United States was evaluated in placebo-controlled randomized clinical trials in tens of thousands of participants in the United States and other countries across a wide range of age groups and a diverse population. [12–14,18–20] Data from these pre-authorization COVID-19 vaccine trials informed monitoring and interpretation of post-authorization safety data and are summarized briefly here.
In most studies, COVID-19 vaccine recipients had higher rates of solicited local and systemic adverse reactions than those receiving placebo. [12,13,15,16,18,19] In trials that evaluated the original monovalent mRNA COVID-19 vaccines and Novavax COVID-19 Vaccine, Adjuvanted, solicited systemic adverse reactions were generally higher after dose 2 than dose 1; almost all participants were SARS-CoV-2 negative at baseline. [12,15,16,18,19,21,22] Serious adverse event rates reported in clinical trials were generally low overall and balanced in the vaccine and placebo groups. [12,13,15,16,18,19] Adverse event imbalances, with numerically more events in vaccine than placebo recipients, were observed for lymphadenopathy for mRNA COVID-19 vaccines and Novavax COVID-19 Vaccine, Adjuvanted, and hypersensitivity reactions for the four monovalent vaccines (in at least one age group). These events were considered plausibly related to the vaccines.

[12,13,15,16,18–21,23] A numerical imbalance was also observed for delayed injection-site reactions following Moderna COVID-19 Vaccine, which was an event also considered related to vaccine. [16,18] No anaphylaxis cases occurred in the immediate period following COVID-19 vaccination in any of the trials. [12,13,15,16,18,19] A numerical imbalance for Bell's Palsy was also observed following mRNA COVID-19 vaccines administered to adults. [15,16,18,19] In clinical trials of Novavax COVID-19 Vaccine, Adjuvanted, a numerical imbalance was observed for myocarditis and/or pericarditis, with more events in vaccine than placebo recipients. At the time of authorization, the Fact Sheet for Healthcare Providers Administering Vaccine included a Warning conveying that the clinical trials data provide evidence for increased risks of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted. [12,21] One case of Guillain-Barré syndrome (GBS) occurred following Novavax COVID-19 Vaccine, Adjuvanted and following Janssen COVID-19 Vaccine, in separate clinical trials. [12,20] In trials of the Janssen COVID-19 Vaccine, one case of transverse sinus thrombosis with thrombocytopenia occurred following vaccination. [13,20] A numerical imbalance also was observed for tinnitus following Janssen COVID-19 Vaccine. [13,20] The safety data supporting authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent included clinical trials data on the monovalent vaccine and an investigational bivalent vaccine (Original and Omicron BA.1) from the respective manufacturers. [15,16]

7. Safety topics reviewed by VaST

In addition to regular review of data from vaccine safety monitoring systems, VaST considered a variety of emerging safety concerns and topics of public interest (Table 3). The sections below provide brief summaries of these data and topics, in the order in which they were first reviewed by VaST.

7.1. Anaphylaxis following mRNA COVID-19 vaccination

Anaphylaxis following mRNA COVID-19 vaccination was discussed as a potential concern at a VaST meeting on December 21, 2020, one week after the start of the U.S. COVID-19 vaccination program. At that meeting, the first COVID-19 vaccine safety data from VAERS were presented. The early VAERS data found 21 unverified cases of anaphylaxis reported following administration of 1,893,360 first doses of Pfizer-BioNTech COVID-19 Vaccine (11.1 cases per million vaccine doses administered). [24] While anaphylaxis can rarely occur following vaccination, this rate appeared higher than that observed for other vaccines. [25] Reports of anaphylaxis following vaccination were also available from the United Kingdom, where Pfizer-BioNTech COVID-19 Vaccine had been recently introduced. [26] In the U.S. VAERS data, most (86 %) anaphylaxis cases had symptom onset within 30 minutes of vaccination; 90 % of cases occurred in women. VaST discussed the need for increasing awareness among providers and vaccine recipients about the clinical presentation of anaphylaxis, guidance for monitoring for potential signs and symptoms of anaphylaxis following COVID-19 vaccination, and the need for timely management of anaphylaxis in diverse vaccination settings. Allergy experts from CISA contributed to development of clinical guidance. CDC's updated guidance was communicated through CDC's interim clinical guidance webpages, [27] and educational activities for health care providers and

state and local partners. FDA revised the Warning on management of acute allergic reactions in the Fact Sheet for Healthcare Providers Administering Vaccine for Pfizer BioNTech COVID-19 Vaccine to include reference to CDC's guidance. [15] VaST continued to follow anaphylaxis reports once another mRNA vaccine, the Moderna COVID-19 Vaccine, was authorized. [28] CDC also included clinical guidance for this vaccine and FDA included a Warning on management of acute allergic reactions in the Fact Sheet for Healthcare Providers Administering Vaccine. [29]

VaST later reviewed updated data from active vaccine safety surveillance systems. Anaphylaxis cases were also identified in the VSD, VA and BEST. [30,31] In analyses presented to ACIP at the end of August 2021, the rate of chart-validated anaphylaxis following mRNA COVID-19 vaccination in the VSD was approximately 5 per million doses administered. [32] Clinical guidance evolved and at the time of this report stated that a 30-minute observation period should be considered for persons with a history of certain allergic reactions. [33] Of note, the mechanism of anaphylaxis following mRNA COVID-19 vaccination has been an area of ongoing evaluation in the scientific community. [34]

7.2. Mortality following COVID-19 vaccination

Because of media and public concerns regarding deaths following COVID-19 vaccination, mortality data from VAERS were presented to VaST at the third meeting on January 4, 2021. Interpretation of these data was difficult due to the passive nature of VAERS reporting, the specific reporting requirements under the EUAs, [29] and the staged implementation of the national COVID-19 vaccination program that prioritized people in long term care facilities, including older individuals with a greater mortality risk. [5,35] At that time, less than 10 % of reports included death certificates or autopsy findings because data collection was ongoing, further limiting interpretation. The most common causes of death reported were unknown or unclear, cardiovascular events, or COVID-19 infection. Based on available data, no unusual patterns of death were detected that might suggest a potential safety concern. VaST considered that data on background mortality and probability of death by age, available from death tables, were needed to interpret existing data; VaST also requested that additional mortality data from different vaccine safety monitoring systems be presented at future meetings and highlighted the need for continued studies to examine mortality.

VaST subsequently reviewed updated data on deaths at five meetings through March 2021, including a meeting focused entirely on proposed plans for evaluating deaths and data from VAERS, VSD, VA and DoD. Some of the first data available from electronic health records in VSD compared recipients of COVID-19 vaccination with those who had not received a COVID-19 vaccination but who had received one or more influenza vaccinations in 2019 through 2020. The outcome of interest was all deaths not related to COVID-19; COVID-19 deaths were excluded because vaccination is associated with a lower risk of death from COVID-19. Mortality rates and preliminary results based on a single VSD site did not show any increased risk of death following dose 1 or dose 2 of a COVID-19 vaccine. An analysis from vaccine safety monitoring among residents of 147 skilled nursing facilities assessed adverse event rates following dose 1 (n = 8,553) and dose 2 (n = 8,371) of mRNA COVID-19 vaccines compared with rates among residents who were not

vaccinated (n = 11,072). [36] There were 76 deaths in the vaccinated group versus 126 in the unvaccinated group; the lower mortality rate among the vaccinated group may be due to residual confounding. VaST also reviewed mortality data following COVID-19 vaccination from Israel, where no safety signals were identified for all-cause mortality or sudden death.

VaST continued to review data on mortality at later meetings. In a review of VAERS reports of death following mRNA COVID-19 vaccination during the first six months of the U.S. vaccination program, there were no concerning patterns. [37] A more complete VSD analysis, including approximately 11 million persons enrolled in seven VSD sites, found the adjusted relative risk (aRR) of non-COVID-19 mortality for the Pfizer-BioNTech COVID-19 Vaccine was 0.41 (95 % CI = 0.38–0.44) following dose 1 and 0.34 (95 % CI = 0.33–0.36) following dose 2. The corresponding aRRs of non-COVID-19 mortality for the Moderna COVID-19 Vaccine were 0.34 (95 % CI = 0.32–0.37) following dose 1 and 0.31 (95 % CI = 0.30–0.33) following dose 2, and following receipt of the Janssen COVID-19 Vaccine was 0.54 (95 % CI = 0.49–0.59). [38] In a novel VA study, there was no increased risk for mortality among COVID-19 vaccine recipients compared with unvaccinated individuals. Day 60 mortality risk estimates showed an 11 % reduction in all-cause mortality risk, which was driven by a reduced mortality in vaccinated persons ages 75 years and older. An updated analysis was subsequently published. [39]

7.3. Thrombosis with thrombocytopenia syndrome following Janssen COVID-19 Vaccine

Vaccine-induced immune thrombotic thrombocytopenia (VITT) was described in March 2021 in individuals who received the AstraZeneca ChAdOx1 COVID-19 Vaccine used in Europe. [10] On April 12, 2021, VaST first reviewed data on thrombosis following Janssen COVID-19 Vaccine in the United States reported to VAERS. CDC termed this condition, characterized by low platelets and venous or arterial thrombosis, more broadly as thrombosis with thrombocytopenia syndrome (TTS), because in rare instances this syndrome may occur without vaccine exposure. There had been six cases reported among recipients of the Janssen COVID-19 Vaccine (after 5.9 million doses administered); all occurred in women younger than age 50 years. Cases were clinically similar to the cases reported from Europe following the AstraZeneca COVID-19 Vaccine. [40] VaST suggested that the medical community be made aware of this finding. The next day, April 13, 2021, CDC issued a Health Alert Network (HAN) alert to ensure that the healthcare provider community was aware of the potential for this rare but serious adverse event, the appropriate management required, and the need for risk mitigation strategies. [41] That same day, April 13, 2021, CDC and FDA recommended a pause in the use of Janssen COVID-19 Vaccine while they further investigated the initial reported cases. The first ACIP meeting on this topic was held April 14, 2021. [5] After a second emergency meeting on April 23, 2021, CDC and FDA lifted the pause. Updated ACIP recommendations included a warning regarding rare clotting events in the presence of thrombocytopenia following vaccination, observed primarily among women ages 18 through 49 years. [5] FDA authorized revisions to the Fact Sheet for Healthcare Providers Administering Vaccine to include a Warning about the risk of TTS following the Janssen COVID-19 Vaccine. [42] Through ongoing safety surveillance, additional cases of TTS following receipt of Janssen COVID-19 Vaccine, including deaths, were identified in VAERS. [43] Reporting rates for TTS were 3.83 per

million doses following Janssen COVID-19 Vaccine and 0.008 per million doses following mRNA COVID-19 vaccines. Following reviews by VaST and the ACIP COVID-19 Vaccine Work Group, on December 16, 2021, ACIP held an emergency meeting to review updated data on TTS and an updated benefit-risk assessment including TTS and GBS, described further below. In January 2022, taking into consideration data on efficacy and safety, ACIP made a preferential recommendation for use of mRNA COVID-19 vaccines over the Janssen COVID-19 Vaccine. [44] VaST's rapid safety assessment contributed to this policy change, which may have prevented additional TTS cases and associated complications. On May 5, 2022, FDA limited the authorized use of the Janssen COVID-19 Vaccine to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines were not accessible or clinically appropriate, and to individuals 18 years of age and older who elected to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. For this action, FDA considered updated data on TTS and the availability of alternative authorized and approved COVID-19 vaccines which had not been shown to present a risk for TTS. [45]

7.4. COVID-19 vaccination during pregnancy and reproductive health outcomes

Pre-authorization COVID-19 vaccine clinical trials did not enroll pregnant persons; therefore, post-authorization vaccine safety data in this group provided important information for the vaccination program. During two years of regular meetings, VaST reviewed data regarding the safety of COVID-19 vaccination during pregnancy and possible associations of COVID-19 vaccination with other reproductive health outcomes (Table 4). [46–54] At some of the first VaST meetings, v-safe data related to reactogenicity in pregnant persons were reviewed. Soon after, CDC's COVID-19 Vaccine Pregnancy Registry was established in December 2020. [48] The first VaST meeting devoted entirely to vaccination in pregnancy was on February 1, 2021, when VaST reviewed plans for monitoring maternal immunization in various safety surveillance systems and by the manufacturers. At that time, there were 62 reports to VAERS among pregnant people. Approximately 21,000 pregnant people were enrolled in v-safe and 550 were enrolled in CDC's COVID-19 Vaccine Pregnancy Registry. Later that month, VaST reviewed further data from VAERS, v-safe and the registry. Among pregnancy-related adverse events reported to VAERS, the most frequently reported was spontaneous abortion, but the reporting rate among vaccinated pregnant persons was substantially lower than background rates. Data from v-safe found that adverse health impacts and reactogenicity were similar among pregnant and non-pregnant vaccine recipients. The CDC COVID-19 Vaccine Pregnancy Registry found that rates of pregnancy and infant outcomes were consistent with background rates. Data on safety of vaccination in pregnancy were included in a public ACIP presentation on March 1, 2021. [55]

VaST reviewed data from the U.S. monitoring systems regarding COVID-19 vaccine safety (primarily following mRNA COVID-19 vaccines) in pregnancy monthly for the next five months and then every three to four months. In the VSD, COVID-19 vaccination in pregnancy was not associated with either preterm birth or small for gestational age at birth. [49] Results consistently showed no increased risk among vaccinated compared with unvaccinated people when stratified by mRNA COVID-19 vaccine dose, or by second or

third trimester vaccination; however, the number of first-trimester exposures was small and risk for first-trimester vaccination could not be calculated. In August 2022, VaST received data updates from multiple safety systems evaluating vaccination in pregnancy, including the CDC COVID-19 Vaccine Pregnancy Registry regarding maternal outcomes (22,951 enrollees) and infant outcomes among live births (N = 20,764); data from VSD on spontaneous abortion and stillbirth surveillance; data from v-safe on injection site and systemic reactions and adverse health impacts, including following booster doses; and VAERS. [50,51,53] VaST also reviewed information on vaginal bleeding, including post-menopausal bleeding following COVID-19 vaccination, from VAERS and v-safe. [54] Data from VSD showed that post-menopausal bleeding following COVID-19 vaccination was uncommon (0.2 %).

VaST's overall assessment was that data from both existing and newly created systems for monitoring the safety of COVID-19 vaccination in pregnancy and reproductive health during the pandemic were robust. Data regarding safety of COVID-19 vaccination during pregnancy showed no safety concerns. Furthermore, there was no concerning impact of vaccination on other aspects of reproductive health. VaST encouraged continued monitoring of COVID-19 vaccination in pregnancy. A session on COVID-19 vaccination during pregnancy was included at the ACIP public meeting on October 19, 2022. [56] Since VaST's last review of these data, additional analyses and publications have continued to show no safety concerns with use of COVID-19 vaccines in pregnancy. [57,58]

7.5. Myocarditis and pericarditis following mRNA COVID-19 vaccination

Myocarditis and pericarditis following mRNA COVID-19 vaccination were first discussed by VaST in April 2021, when the work group reviewed data from the U.S. including from DoD [59] and VAERS, [60] and from Israel's national immunization program. [61] Cases occurred most frequently in adolescent and young adult males within 7 days following receipt of dose 2 of an mRNA COVID-19 vaccine. The DoD monitoring was one of the first systems to note that rates of myocarditis in young adult males following mRNA COVID-19 vaccination were higher than expected. On May 17, 2021, VaST reviewed updated data from multiple U.S. vaccine safety monitoring systems including from VAERS and VSD. Although there were no statistical signals, demographic and clinical characteristics of cases being reported were similar across these safety systems. VaST issued a report stating that information about this potential adverse event should be provided to clinicians to enhance early recognition and appropriate management of myocarditis symptoms following vaccination. [6]

VaST continued to focus on myocarditis and pericarditis following mRNA COVID-19 vaccination and reviewed the epidemiology, clinical course, and background rates of myocarditis before the COVID-19 pandemic. Background rates of myocarditis are highest in adolescent and young adult males, the same age group as the reported cases following mRNA COVID-19 vaccination. [62] VaST encouraged close monitoring and longer-term follow-up studies to assess the clinical course of myocarditis following mRNA COVID-19 vaccination. With more data available, VAERS analyses showed that in the 30-day window following dose 2 of an mRNA COVID-19 vaccination there was a higher number of

observed than expected myocarditis and pericarditis cases in 16 through 24-year-old males. Data from the VSD RCA at that time did not show that rates of myocarditis and pericarditis in a 1–21 day risk window interval following COVID-19 vaccination differed from those in a comparison interval, but this analysis was not stratified by age. On May 24, 2021, VaST issued a second report on myocarditis and pericarditis, [6] and CDC updated clinical considerations regarding myocarditis and pericarditis with input from individual CISA cardiologist experts. [63] FDA authorized revisions to the EUA Fact Sheet for Healthcare Providers Administering Vaccine for both the Pfizer-BioNTech and Moderna COVID-19 vaccines to include a Warning about myocarditis and pericarditis following vaccination, and revisions to the Fact Sheets for Recipients and Caregivers to include information about risks of myocarditis and pericarditis. Data on myocarditis and pericarditis following COVID-19 vaccination were presented to ACIP on June 23, 2021. [64,65]

Myocarditis and pericarditis, although rare, were the major adverse events of concern following mRNA COVID-19 vaccination; estimated rates were included in benefit-risk assessments for mRNA COVID-19 vaccine recommendations discussed by the ACIP in June 2021 and at subsequent meetings. [64,66] ACIP determined that vaccination benefits outweighed risks (expected myocarditis cases following vaccination) in all populations for which vaccination had been recommended, including adolescent and young adult males. [64] However, the balance of benefits and risks varied by age and sex because cases of myocarditis were primarily identified among adolescent and young adult males, and the risks of poor outcomes related to COVID-19 increase with age. CDC provided clinical guidance regarding evaluation of myocarditis following mRNA COVID-19 vaccines, as well as considerations for administering a second dose in persons who developed myocarditis following a first dose. [33,63,64] CDC and FDA continued to periodically update education and communication materials about myocarditis and pericarditis following receipt of mRNA COVID-19 vaccines. [15,16,29,33,63]

From June 2021 through March 2023, VaST continued to review data on myocarditis and pericarditis as they became available from passive and active vaccine safety monitoring systems, and as mRNA COVID-19 vaccines were authorized for use in younger age groups and for booster doses, and as approved for use as a two-dose series in certain age groups (Table 2). These data were from the United States, [30,67–71] Israel, [72,73] and Canada. [74] Although not statistically significant in all systems, higher risks were consistently observed in adolescent and young adult subgroup analyses, particularly among males. Once analyses were formally stratified by age, statistically significant signals were identified in the RCA and NRS activities conducted by the CDC's VSD and the FDA's BEST. [30,68] The incidence continued to vary markedly by age and sex, with a disproportionate number of cases in male persons, notably among adolescents and young adults following dose 2 and first booster doses. Available data from safety monitoring systems showed no elevated risk for myocarditis or pericarditis in children younger than age 5 years. [69,75]

Other data on myocarditis and pericarditis reviewed by VaST included analyses from the United States and Canada regarding possible risk differences between the two mRNA COVID-19 vaccines. [74,76–78] In studies where direct comparisons could be made, some data suggested that the risk of myocarditis and pericarditis might be higher following

vaccination with Moderna COVID-19 Vaccine relative to Pfizer-BioNTech COVID-19 Vaccine; however, findings were not consistent across all U.S. monitoring systems. Variation in methodology in these studies could have contributed to differences in findings. Furthermore, small numbers of cases led to uncertainty in risk estimates.

To begin to assess longer-term potential effects, three-month follow-up data on myocarditis cases from VSD were presented to VaST in August 2021. [32] In addition, data from a follow-up study of myocarditis cases reported to VAERS, including information obtained at least 90 days after symptom onset, were presented in November 2021. These data supported previous observations showing that most cases had recovered symptomatically by the time of hospital discharge or shortly thereafter. Follow-up through January 2022 for 519 eligible patients ages 12 through 29 years has been published, [79] and showed that most (81 %) individuals in the cohort were considered recovered by their healthcare providers, and quality of life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age. About half of patients had a symptom that could potentially be associated with myocarditis in the two weeks prior to the survey, and nearly half of patients with follow-up cardiac MRIs had residual late gadolinium enhancement. The clinical importance of these MRI findings remains unclear. [80] CDC is conducting additional follow-up of cases at least one year after myocarditis onset in patients not considered fully recovered. Similar follow-up data were available from the DoD. VaST encouraged further follow-up and noted that additional data will be available through studies conducted by vaccine manufacturers (required by FDA), [81,82] and by academic centers worldwide.

7.6. Guillain-Barré syndrome following Janssen COVID-19 Vaccine

On June 14, 2021, VaST reviewed data on GBS following Janssen COVID-19 Vaccine. In VAERS, there were 80 reports of GBS following Janssen COVID-19 Vaccine; the reporting rate for GBS was higher following Janssen COVID-19 Vaccine than the mRNA COVID-19 vaccines. In the VSD, chart-confirmed GBS incidence following Janssen COVID-19 Vaccine also was much higher than following mRNA COVID-19 vaccines; however, in the overall VSD population, there were no statistical signals for GBS in the 21 days following Janssen COVID-19 vaccination. Following these reports, VaST determined that more data were needed to make any conclusions. VSD obtained additional medical records and applied the GBS Brighton Collaboration case definition. VaST continued to review data on GBS from multiple safety monitoring systems. On June 28, 2021, VaST issued a report about GBS, stating that the number of preliminary cases of GBS reported to VAERS following Janssen COVID-19 Vaccine was greater than the number of expected GBS cases. [6] Although rare, GBS emerged as a second important adverse event of concern following Janssen COVID-19 Vaccine. On July 12, 2021, FDA authorized revisions to the EUA Fact Sheet for Healthcare Providers Administering Vaccine to include a Warning about GBS and to the Fact Sheet for Recipients and Caregivers to include information about GBS following receipt of Janssen COVID-19 Vaccine. [83]

As more data accumulated in the U.S. vaccine safety monitoring systems, the VSD helped to further define the risk of GBS. [84] There was no increased risk of GBS following mRNA

COVID-19 vaccination; however, the unadjusted incidence rate of GBS per 100,000 person-years during the 1–21 days following Janssen COVID-19 Vaccine was 32.4 (95 % CI, 14.8–61.5), significantly higher than the background rate; [85] the adjusted rate ratio (RR) during 1–21 days versus 22–42 days was 6.0 (95 % CI, 0.8–147.8). In a direct comparison of GBS risk among Janssen COVID-19 Vaccine versus mRNA COVID-19 vaccine recipients, the adjusted RR was 20.6 (95 % CI, 6.9–64.7). As noted above, in January 2022 ACIP made a preferential recommendation for use of mRNA COVID-19 vaccines, taking into consideration data on efficacy and safety, including risks for TTS and GBS. [44]

7.7. Simultaneous COVID-19 vaccination with other vaccines

VaST first reviewed data on simultaneous administration of COVID-19 vaccines with other vaccines in October 2021, and again in April and June 2022. VSD found only small numbers of simultaneous administration of COVID-19 vaccines with several different routine vaccines. Data from v-safe showed that respondents who simultaneously received influenza vaccine and booster doses of Pfizer-BioNTech or Moderna COVID-19 vaccines were slightly more likely to report any local and systemic reactions in the week following simultaneous vaccination than respondents who received only a booster dose of an mRNA COVID-19 vaccine. [86] Monitoring of simultaneous COVID-19 vaccination with influenza and other vaccines is ongoing in observational studies and in three prospective clinical studies being conducted by CISA. [87–89]

7.8. COVID-19 vaccination in children

VaST reviewed data on vaccine safety in successively younger age groups as they became available. FDA authorized use of Pfizer-BioNTech COVID-19 Vaccine as a primary series (see definition of primary series in footnote of Table 2) in 5 through 11-year-olds in October 2021 and as a primary series in 6 months through 4-year-olds in June 2022. [5] FDA authorized use of Moderna COVID-19 Vaccine as a primary series in children and adolescents 6 months through 17 years of age in June 2022. Pfizer-BioNTech COVID-19 Vaccine post-authorization safety data for ages 5 through 11 years were first reviewed by VaST in November 2021, and then at multiple meetings in 2022. As of February 2022, >16 million vaccine doses had been administered to children ages 5 through 11 years in the United States. VAERS received 7,578 adverse event reports; 97 % were classified as nonserious. Among the 194 serious reports, 15 myocarditis cases were verified; 8 occurred in boys following dose 2 (reporting rate 2.2 per million doses). Among 48,795 children ages 5 through 11 years enrolled in v-safe, most reported reactions were mild-to-moderate in severity and were most frequently reported the day following vaccination and following dose 2. [70] In the VSD, there was no safety signal in children for any pre-specified surveillance outcome following administration of 726,820 doses. VaST's conclusion was that most reported adverse events were mild and there were no concerns raised in active surveillance. VAERS reporting rates of myocarditis and pericarditis following COVID-19 vaccination in children ages 5 through 11 years were substantially lower than those observed among older individuals, including adolescents ages 12 through 15 years. [70] In June and July 2022, VaST reviewed further safety data in children, including the first data on Moderna COVID-19 Vaccine. There were few safety data on the Moderna COVID-19 vaccine in children ages 5 through 11 years due to limited use at that time. However, reports to VAERS

and v-safe did not raise any new concerns; reports were consistent with data reported in other age groups. VaST noted that no cases of myocarditis or pericarditis had been reported.

Safety data following mRNA COVID-19 vaccines among children younger than age 5 or 6 years were first reviewed by VaST in June 2022. By the end of August 2022, over 1 million doses had been administered to children ages 6 months through 5 or 6 years and over 23,000 children in this age group were enrolled in v-safe following mRNA COVID-19 vaccination. [69] The most frequent systemic reactions reported to v-safe among children ages 6 months through 2 years were irritability or crying. [71] Among children ages ≥ 3 years, injection site pain was the most frequently reported reaction. VAERS received a total of 1,017 reports of adverse events following vaccination among children ages 6 months through 5 years; 98 % were classified as nonserious and there were no reports of myocarditis. [71] In VSD, through mid-August 2022, there was no statistical signal for any pre-specified surveillance outcome for either mRNA COVID-19 vaccine in this age group. [69] Data through March 2023 were published. [90]

At a July 2022 VaST meeting, as well as at previous meetings, VaST conveyed concern about administration errors in children reported to VAERS, including errors related to failure to add the appropriate amount of diluent for certain presentations of Pfizer-BioNTech COVID-19 Vaccine for some age groups. [71,91] VaST members advised that the information on administration errors be communicated to providers. Subsequently, CDC's clinical guidance, which already contained information on how to prevent administration errors, was expanded. [33] CDC initiated multiple educational efforts to reduce vaccine administration errors.

7.9. Bivalent COVID-19 vaccines

Bivalent mRNA COVID-19 vaccines were authorized by FDA on August 31, 2022, for use as a single booster dose in certain age groups (Table 2); VaST first reviewed relevant data from safety monitoring systems on October 24, 2022. The first VAERS and v-safe data on booster doses of bivalent mRNA COVID-19 vaccines were published on November 3, 2022. [92] Through October 23, 2022, nearly 14.4 million persons ages ≥ 12 years had received a booster dose with Pfizer-BioNTech COVID-19 Vaccine, Bivalent and 8.2 million persons ages ≥ 18 years had received a booster dose with Moderna COVID-19 Vaccine, Bivalent. There were 5,542 VAERS reports among persons ages ≥ 12 years; 96 % were non-serious. Vaccination errors were the most common reports (35 %); most of these reports did not include an adverse event. Among 251 VAERS reports classified as serious, five were reports of myocarditis and four were pericarditis. In v-safe, reporting frequencies of reactions and health impacts following bivalent vaccine booster doses were similar to those following dose 1 or dose 2 of an mRNA monovalent COVID-19 Vaccine. In the VSD RCA, 461,595 persons had received a bivalent COVID-19 vaccine dose at the time of the October 2022 VaST review; there was no statistical signal for any pre-specified surveillance outcome. VaST later reviewed data from other vaccine safety systems. In the VA RCA, there were no safety signals for any pre-specified outcomes following 466,369 booster doses of Moderna COVID-19 Vaccine, Bivalent or 469,364 booster doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Similarly, the FDA CMS NRS did not detect any safety signal

in analyses of three different age groups, including more than 7 million vaccine recipients ages ≥ 65 years.

During the subsequent weeks, the VSD RCA detected a statistical signal for ischemic stroke among persons ages ≥ 65 years following a booster dose with Pfizer-BioNTech COVID-19 Vaccine, Bivalent; VaST first reviewed the VSD data on January 9, 2023. Ischemic stroke (which included transient ischemic attack for VSD surveillance) was one of the pre-specified outcomes in the VSD RCA. This analysis, as in many VSD RCA analyses during the COVID-19 pandemic, used a concurrent comparator method: risk of prespecified outcomes during 1–21 days (risk interval) following vaccination compared with risk in vaccinated individuals who were 22–42 days following a dose of bivalent COVID-19 vaccine. The statistical safety signal for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent was first detected in the VSD RCA in November 2022 when the adjusted RR was 1.92. Over time the adjusted RR attenuated, and after January 2023 only intermittently met statistical significance. There was no statistical safety signal for ischemic stroke following a booster dose with Moderna COVID-19 Vaccine, Bivalent. A supplemental analysis comparing Pfizer-BioNTech COVID-19 Vaccine, Bivalent boosted to un-boosted concurrent comparators who were eligible for a booster dose of bivalent COVID-19 vaccine found an adjusted RR of 1.07 (95 % CI: 0.89–1.28). VSD investigators noted that many patients with ischemic stroke had received both Pfizer-BioNTech COVID-19 Vaccine, Bivalent and high-dose or adjuvanted influenza vaccine at the same visit. In addition, the peak uptake of COVID-19 and influenza vaccines in this age group occurred around the same time in VSD. Additional analysis in persons ages ≥ 65 years evaluating simultaneous administration of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent with high-dose or adjuvanted influenza vaccine showed an adjusted RR of 1.65 (95 % CI 1.02–2.72) for ischemic stroke, while a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent without concomitant influenza vaccine showed an adjusted RR of 1.19 (95 % CI 0.87–1.62). [93] VaST's conclusions were that possible unmeasured confounding could be contributing to the findings, but that further investigation of the safety of concomitant administration of the bivalent COVID-19 mRNA vaccines and high-dose or adjuvanted influenza vaccine was needed.

VaST also considered data regarding bivalent COVID-19 vaccines from other safety systems. A VA RCA did not find a statistical signal for ischemic stroke following a booster dose of Pfizer-BioNTech Vaccine, Bivalent or Moderna COVID-19 Vaccine, Bivalent. Analysis in the FDA CMS NRS found no increased risk for ischemic stroke following a booster dose of these vaccines among persons ≥ 65 years. However, these analyses did not specifically evaluate simultaneous administration of a booster dose of bivalent mRNA COVID-19 and influenza vaccines. VaST noted that VAERS monitoring found no evidence of a safety concern for ischemic stroke following a booster dose of either bivalent mRNA COVID-19 vaccine. Furthermore, no safety concerns were detected for ischemic stroke following monovalent Pfizer-BioNTech or Moderna COVID-19 vaccines administered as a primary series or booster dose in U.S. or in global monitoring. CDC and FDA are conducting additional epidemiologic analyses regarding simultaneous vaccination with bivalent mRNA COVID-19 vaccines and influenza vaccines. [93]

7.10. Novavax COVID-19 Vaccine, Adjuvanted

VaST reviewed data on Novavax COVID-19 Vaccine, Adjuvanted in September 2022, about 6 weeks after an EUA was issued. However, at that time, only 24,125 doses had been administered. There were 62 reports (57 non serious) to VAERS, with no reported cases of myocarditis, and 179 v-safe registrants. There were not enough vaccine recipients in VSD to conduct a safety RCA. After VaST's safety review was transferred to the ACIP COVID-19 Vaccines Work Group, further safety data on this vaccine were published. [94]

7.11. Tinnitus and hearing loss following COVID-19 vaccination

In response to public interest in tinnitus following COVID-19 vaccination and the more frequent reports of tinnitus among vaccine recipients compared to those receiving placebo as noted in the Janssen COVID-19 Vaccine trial, on November 14, 2022, VaST reviewed data on tinnitus and hearing loss from VAERS and VSD. Most reports (86 %) of tinnitus in VAERS were non-serious. For Pfizer-BioNTech COVID-19 Vaccine, there were 21.6 reports per million doses administered and for Moderna COVID-19 Vaccine 22.7 reports per million doses administered. For hearing loss, there were 0.6 reports per million doses of Pfizer-BioNTech COVID-19 Vaccine and 0.5 cases per million doses of Moderna COVID-19 Vaccine administered. The analysis from VSD included tree-based data mining, temporal scans, and incidence comparisons for tinnitus cases. [95] There were no clusters of hearing-related outcomes for any of the tree-scan analyses. The tinnitus incidence per 10,000 person-years, based on 140 days of follow-up, was 78 following Pfizer-BioNTech COVID-19 Vaccine, 107 following Moderna COVID-19 Vaccine and 85 following Janssen COVID-19 Vaccine. The background incidence for tinnitus is 116 per 10,000 person-years, higher than rates reported following vaccination. [96] Further analyses are planned in VAERS, and VSD. VaST acknowledged the challenges of tinnitus investigation due to its high prevalence in the population and potential for delayed presentation for care. [96]

8. Summary of sequential monitoring of pre-specified outcomes

In addition to the safety concerns and specific topics summarized above as well as routine vaccine safety data, VaST regularly reviewed findings regarding the pre-specified sequentially monitored outcomes in vaccine safety monitoring systems including those from CDC's VSD, the VA, and FDA's CMS and BEST (Table 1). The analyses in these systems differed in the comparison groups used and in specific analyses conducted. Most included evaluations for individual vaccines, for mRNA COVID-19 vaccines combined, for primary series and booster doses, by sex, and by age group. In these systems, identified signals require further evaluation to determine if they are real or due to confounding or other artifacts. Among the many prespecified outcomes, the analyses identified very few statistical signals.

In the final VSD RCAs of the primary vaccine series among persons ages ≥ 12 years, there were statistical signals prompting further evaluation for myocarditis and pericarditis, acute myocardial infarction (AMI) and venous thromboembolism (VTE). [97] The myocarditis and pericarditis signal was found in analyses of events following dose 2 of Pfizer-BioNTech COVID-19 Vaccine, those following both doses of Pfizer-BioNTech COVID-19 Vaccine

combined, and those following dose 1 and dose 2 of both mRNA COVID-19 vaccines combined. The AMI signal was following dose 2 of Pfizer-BioNTech COVID-19 Vaccine and following dose 2 of Pfizer-BioNTech and Moderna COVID-19 vaccines combined. The VTE signal was following dose 2 of Pfizer-BioNTech COVID-19 Vaccine, following both dose 1 and dose 2 of Pfizer-BioNTech COVID-19 Vaccine combined, and following both dose 1 and dose 2 of Pfizer-BioNTech and Moderna COVID-19 vaccines combined. These signals appeared in the latter stages of the Original monovalent mRNA COVID-19 vaccination program and were not observed following booster vaccination with the Original monovalent mRNA COVID-19 vaccines or following vaccination with either of the bivalent mRNA COVID-19 vaccines. Most of the cases for these outcomes were in older adults. Similar findings in the FDA NRS for AMI and pulmonary embolism (PE) (a known complication of VTE) were further assessed by FDA using self-controlled methods (see below). In the VSD RCAs, there was also a signal for Bell's Palsy following Janssen COVID-19 Vaccine and booster doses of Pfizer-BioNTech COVID-19 Vaccine in persons ages ≥ 12 years. This signal was also evaluated by FDA (see below).

In the VA RCAs, the only statistical signal was for anaphylaxis following dose 1 of Pfizer-BioNTech and dose 2 of Moderna COVID-19 Vaccines. There was no statistical signal in the RCA following booster doses of the bivalent mRNA COVID-19 vaccines at the time of this report.

In the FDA CMS NRS for primary series mRNA COVID-19 vaccination, statistical signals were initially detected among persons ages ≥ 65 years for PE, AMI, disseminated intravascular coagulation (DIC) and immune thrombocytopenia (ITP). NRS detects statistical signals but cannot be used to establish causality because of limited control of confounding and bias. Accordingly, follow-up using more robust self-controlled methods were used. After further evaluation, only PE still met the statistical threshold for a signal. [98] A signal detection study of booster doses with monovalent COVID-19 vaccines among persons ages ≥ 65 years based on the ratio of observed post-vaccination rates compared to historical rates (expected rates) detected signals for Pfizer-BioNTech COVID-19 Vaccine and Bell's Palsy, as well as for Moderna COVID-19 Vaccine and myocarditis and pericarditis. To evaluate these signals following primary series and booster doses of monovalent COVID-19 vaccines among persons ages ≥ 65 years, FDA conducted self-controlled case series studies and found no consistent risk of PE. [99] Further, there was no increased risk for AMI, ITP, DIC, Bell's Palsy, or myocarditis and pericarditis following monovalent mRNA COVID-19 vaccines (primary series and booster doses). [99] In the FDA BEST NRS among individuals ages 12 through 64 years, 15 adverse events did not meet the threshold for a statistical signal. The only statistical signals were the previously detected ones for myocarditis and pericarditis, and for anaphylaxis. [30] In the FDA BEST NRS covering the period from EUA date to mid-2022 among individuals ages 5 through 17 years, only myocarditis or pericarditis met the statistical threshold for a signal following Pfizer-BioNTech COVID-19 Vaccine primary series vaccination for ages 12 through 17 years. [100] In the NRS for bivalent mRNA COVID-19 vaccines, no statistical signals were detected at the time VaST reviewed data.

9. Discussion

This report provides an overview of the organization and activities of VaST and describes data reviewed as part of a comprehensive effort to monitor vaccine safety during the COVID-19 pandemic. Some of the actions taken by CDC, ACIP, and FDA in response to accumulating post-EUA/licensure vaccine safety data are also included. The independent vaccine safety experts on VaST provided critical assessments of the vaccine safety data. VaST worked closely with the ACIP COVID-19 Vaccines Work Group that used safety data from safety monitoring systems and VaST's assessments for consideration in benefit-risk assessments and guidance for COVID-19 vaccination policy. [5]

Early in the COVID-19 vaccination program, several safety concerns emerged, which were evaluated concurrently, including anaphylaxis, TTS, myocarditis and pericarditis, and GBS. In addition, VaST addressed topics for which there was no evidence of safety problems, but for which public concerns had been voiced, including mortality following vaccination, adverse events following vaccination during pregnancy, and other reproductive health outcomes. VaST assisted the robust efforts of the agencies and organizations conducting safety monitoring to identify additional needed analyses, communicate efforts and actions, and to provide a regularly scheduled process for independent review of the large amount of data being generated. In the second year of the vaccination program VaST continued to evaluate safety concerns and assessed safety of simultaneous vaccination (e.g., influenza and COVID-19 vaccination), COVID-19 vaccination in children, bivalent COVID-19 vaccines booster doses, and tinnitus. These evaluations provided guidance to federal safety monitoring efforts, provided a forum for U.S. government vaccine safety systems to share and compare information, and assured that a group of independent experts was promptly and continuously reviewing vaccine safety data.

Several safety outcomes need continued monitoring. These include myocarditis and pericarditis, particularly as more data accumulate in younger age groups and more follow-up data become available for cases that occur following COVID-19 vaccination. Further data on vaccination in pregnancy are expected and these should continue to be reviewed and shared with the public and policy makers. It is important to recognize that early detection of initial statistical signals from sequential surveillance activities, like those conducted using RCA and NRS methods, do not themselves establish a causal association between an outcome of interest and vaccination. These results represent preliminary findings only, and more robust confirmatory epidemiologic analyses are needed, often including more comprehensive assessments for confounding and possible selection bias. Such studies were or are being conducted to further evaluate some of the initial statistical findings in the RCA and NRS.

In April 2023, VaST transitioned review of COVID-19 vaccine safety data from ongoing vaccine safety monitoring to the ACIP COVID-19 Vaccines Work Group. A few weeks later, on May 11, 2023, the U.S. federal COVID-19 public health emergency declaration ended. [101] As updated COVID-19 vaccines are authorized and recommended, there will be ongoing review of vaccine safety. [102] In the event of a future pandemic or other biological public health emergency, the VaST model could be used to help strengthen public

health monitoring, confidence and transparency through incorporation of independent, non-government vaccine safety experts into a dedicated vaccine safety monitoring process that includes strong collaboration among federal and other partners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data statement

This article is summary of data from surveillance projects and studies conducted by a variety of organizations. Most of these data have been published or presented publicly. We will not be sharing any data not available publicly.

Abbreviations:

ACIP	Advisory Committee on Immunization Practices
AMI	acute myocardial infarction
BEST	Biologics Effectiveness and Safety System
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
EUA	Emergency Use Authorization
DoD	Department of Defense
GBS	Guillain-Barré syndrome
HAN	Health Alert Network
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NIH	National Institutes of Health
NRS	near real time surveillance
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PE	pulmonary embolism

RCA	rapid cycle analysis
TTS	thrombosis with thrombocytopenia syndrome
VA	Department of Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
VTE	venous thromboembolism

References

[1]. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. Nature 2021;589:16–8. [PubMed: 33340018]

[2]. Salmon DA, Akhtar A, Mergler MJ, et al. Immunization-safety monitoring systems for the 2009 H1N1 monovalent influenza vaccination program. Pediatrics 2011;127(Suppl 1):S78–86. [PubMed: 21502251]

[3]. CDC. Advisory Committee on Immunization Practices: Work Groups. Available at: https://www.cdc.gov/vaccines/acip/committee/downloads/Work-Group-Guidance-508.pdf. Accessed September 28, 2023.

[4]. CDC. Advisory Committee on Immunization Practices (ACIP). Available at: https://www.cdc.gov/vaccines/acip/index.html. Accessed September 28, 2023.

[5]. Oliver SE, Wallace M, Twentyman E, et al. . Development of COVID-19 vaccine policy—United States, 2020–2023. Vaccine. 2023 Dec 29. [In press].

[6]. COVID-19 Vaccine Safety Technical (VaST) Work Group Reports. Available at: https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html. Accessed September 28, 2023.

[7]. CDC. COVID-19 Vaccine Reporting Systems Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-systems.html. Accessed September 28, 2023.

[8]. Gee J, Shimabukuro TT, Su JR, et al. Overview of U.S. COVID-19 Vaccine Safety Surveillance Systems. Vaccine; [Manuscript submitted for publication].

[9]. Muhsen K, Cohen D. COVID-19 vaccination in Israel. Clin Microbiol Infect 2021;27:1570–4. [PubMed: 34384875]

[10]. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021;384:2092–101. [PubMed: 33835769]

[11]. Tsang RS, Joy M, Byford R, et al. Adverse events following first and second dose COVID-19 vaccination in England, October 2020 to September 2021: a national vaccine surveillance platform self-controlled case series study. Euro Surveill October 2020;2023:28.

[12]. FDA. Novavax COVID-19 Vaccine, Adjuvanted. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/novavax-covid-19-vaccine-adjuvanted. Accessed September 28, 2023.

[13]. FDA. Janssen COVID-19 Vaccine. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine. Accessed September 28, 2023.

[14]. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine - United States, February 2021. MMWR Morb Mortal Wkly Rep 2021;70:329–32. [PubMed: 33661860]

[15]. FDA. Pfizer-BioNTech COVID-19 Vaccine; Archived Fact sheets for Healthcare Providers, Recipients and Caregivers, including translations. Available at: https://www.fda.gov/media/167193/download?attachment. Accessed September 28, 2023.

[16]. FDA. Moderna COVID-19 Vaccine; Archived Fact sheets for Healthcare Providers, Recipients and Caregivers, including translations. Available at: https://www.fda.gov/media/167192/download?attachment. Accessed September 28, 2023.

[17]. FDA. Approval Letter - SPIKEVAX. Available at: https://www.fda.gov/media/155815/download?attachment. Accessed September 28, 2023.

[18]. FDA. SPIKEVAX. Available at: https://www.fda.gov/vaccines-blood-biologics/spikevax. Accessed September 28, 2023.

[19]. FDA. COMIRNATY. Available at: https://www.fda.gov/vaccines-blood-biologics/comirnaty. Accessed September 28, 2023.

[20]. FDA. Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021. FDA briefing document. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. Available at: https://www.fda.gov/media/146217/download. Accessed September 28, 2023.

[21]. FDA. Vaccines and Related Biological Products Advisory Committee Meeting June 7, 2022. FDA Briefing Document Novavax COVID-19 Vaccine Available at: https://www.fda.gov/media/158912/download. Accessed September 28, 2023.

[22]. FDA. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. Available at: https://www.fda.gov/media/144245/download. Accessed September 28, 2023.

[23]. FDA. Vaccines and Related Biological Products Advisory Committee Meeting October 26, 2021. FDA Briefing Document EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 5 through 11 years of age. Available at: https://www.fda.gov/media/153447/download. Accessed September 28, 2023.

[24]. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep 2021; 70:46–51. [PubMed: 33444297]

[25]. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol 2016;137:868–78. [PubMed: 26452420]

[26]. Medicines and Healthcare Products Regulatory Agency (MHRA). MHRA statement on guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination. Available at: https://www.anaphylaxis.org.uk/mhra-statement-on-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination/. Accessed September 28, 2023.

[27]. CDC. Interim Considerations: Preparing for the Potential Management of Anaphylaxis after COVID-19 Vaccination. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html. Accessed September 18, 2023.

[28]. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. MMWR Morb Mortal Wkly Rep 2021;70:125–9. [PubMed: 33507892]

[29]. FDA. Emergency Use Authorization. Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. Accessed September 28, 2023.

[30]. Lloyd PC, Hu M, Wong HL, et al. Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years. Vaccine 2022;40:6481–8. [PubMed: 36195472]

[31]. Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA 2021;326:1390–9. [PubMed: 34477808]

[32]. Klein NP. Rapid cycle analysis to monitor the safety of COVID-19 vaccines in near real-time within the vaccine safety datalink: myocardtiis and anaphylaxis. Advisory Committee on Immunization Practices (ACIP), August 30, 2021. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/04-COVID-Klein-508.pdf. Accessed September 28, 2023.

[33]. CDC. Use of COVID-19 Vaccines in the United States - Interim Clinical Considerations Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed September 28, 2023.

[34]. Zhou Z-H, Cortese MM, Fang J-L, et al. Evaluation of association of anti-PEG antibodies with anaphylaxis after mRNA COVID-19 vaccination. medRxiv 2023: 2023.04.11.23288372.

[35]. Dooling K, McClung N, Chamberland M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Allocating Initial Supplies of COVID-19 Vaccine - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1857–9. [PubMed: 33301429]

[36]. Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine 2021;39:3844–51. [PubMed: 34092431]

[37]. Rosenblum HG, Gee J, Liu R, et al. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe. Lancet Infect Dis 2022;22:802–12. [PubMed: 35271805]

[38]. Xu S, Huang R, Sy LS, et al. COVID-19 Vaccination and Non-COVID-19 Mortality Risk - Seven Integrated Health Care Organizations, United States, December 14, 2020-July 31, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1520–4. [PubMed: 34710075]

[39]. McConeghy KW, Dahabreh IJ, Jiang R, et al. Early Mortality After the First Dose of Coronavirus Disease 2019 Vaccination: A Target Trial Emulation. Clin Infect Dis (manuscript accepted for publication).

[40]. Shay DK, Gee J, Su JR, et al. Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine - United States, March-April 2021. MMWR Morb Mortal Wkly Rep 2021;70:680–4. [PubMed: 33956784]

[41]. CDC. Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine. Available at: https://emergency.cdc.gov/han/2021/han00442.asp. Accessed September 28, 2023.

[42]. FDA. Janssen COVID-19 Vaccine EUA Fact Sheet for Healthcare Providers Available at: /www.fda.gov/media/146304/download. Accessed September 28, 2023.

[43]. See I, Lale A, Marquez P, et al. Case Series of Thrombosis With Thrombocytopenia Syndrome After COVID-19 Vaccination-United States, December 2020 to August 2021. Ann Intern Med 2022;175:513–22. [PubMed: 35038274]

[44]. Oliver SE, Wallace M, See I, et al. Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices - United States, December 2021. MMWR Morb Mortal Wkly Rep 2022;71:90–5. [PubMed: 35051137]

[45]. FDA. Coronavirus (COVID-19) Update: FDA Limits Use of Janssen COVID-19 Vaccine to Certain Individuals. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-janssen-covid-19-vaccine-certain-individuals. Accessed September 28, 2023.

[46]. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. N Engl J Med 2021;385:1533–5. [PubMed: 34496196]

[47]. Moro PL, Olson CK, Clark E, et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 - October 2021. Vaccine 2022;40:3389–94. [PubMed: 35489985]

[48]. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med 2021;384:2273–82. [PubMed: 33882218]

[49]. Lipkind HS, Vazquez-Benitez G, DeSilva M, et al. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth - Eight Integrated Health Care Organizations, United States, December 15, 2020-July 22, 2021. MMWR Morb Mortal Wkly Rep 2022;71:26–30. [PubMed: 34990445]

[50]. Moro PL, Olson CK, Zhang B, Marquez P, Strid P. Safety of Booster Doses of Coronavirus Disease 2019 (COVID-19) Vaccine in Pregnancy in the Vaccine Adverse Event Reporting System. Obstet Gynecol 2022;140:421–7. [PubMed: 35926203]

[51]. DeSilva MB, Haapala J, Vazquez-Benitez G, et al. Medically Attended Acute Adverse Events in Pregnant People After Coronavirus Disease 2019 (COVID-19) Booster Vaccination. Obstet Gynecol 2023;142:125–9. [PubMed: 37167612]

[52]. DeSilva M, Haapala J, Vazquez-Benitez G, et al. Evaluation of Acute Adverse Events after Covid-19 Vaccination during Pregnancy. N Engl J Med 2022;387:187–9. [PubMed: 35731916]

[53]. Kharbanda EO, Haapala J, DeSilva M, et al. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. JAMA 2021;326:1629–31. [PubMed: 34495304]

[54]. Wong KK, Heilig CM, Hause A, et al. Menstrual irregularities and vaginal bleeding after COVID-19 vaccination reported to v-safe active surveillance, USA in December, 2020-January, 2022: an observational cohort study. Lancet Digit Health 2022;4:e667–75. [PubMed: 35961858]

[55]. Shimabukuro TT. COVID-19 vaccine safety update. Advisory Committee on Immunization Practices (ACIP), March 1, 2021. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf. Accessed September 28, 2023.

[56]. CDC. Advisory Committee on Immunization Practcies (ACIP) presentation slides: October 19–20, 2022. Available at: https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html. Accessed September 28, 2023.

[57]. Kharbanda EO, Haapala J, Lipkind HS, et al. COVID-19 Booster Vaccination in Early Pregnancy and Surveillance for Spontaneous Abortion. JAMA Netw Open 2023;6:e2314350. [PubMed: 37204791]

[58]. Ciapponi A, Berrueta M, Parker EPK, et al. Safety of COVID-19 vaccines during pregnancy: A systematic review and meta-analysis. Vaccine 2023;41:3688–700. [PubMed: 37012114]

[59]. Montgomery J, Ryan M, Engler R, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol 2021;6:1202–6. [PubMed: 34185045]

[60]. Oster ME, Shay DK, Su JR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA 2022;327:331–40. [PubMed: 35076665]

[61]. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med 2021;385:2140–9. [PubMed: 34614328]

[62]. Kyto V, Sipilä J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. Heart 2013;99:1681–4. [PubMed: 24064227]

[63]. CDC. Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html. Accessed September 28, 2023.

[64]. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–82. [PubMed: 34237049]

[65]. ACIP Presentation Slides: June 23–25, 2021 Meeting. Available at: https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html. Accessed September 28, 2023.

[66]. Shimabukuro T. COVID-19 Vaccine Safety Updates. Advisory Committee on Immunization Practices (ACIP), October 20, 2021. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/06-COVID-Shimabukuro-508.pdf. Accessed September 28, 2023.

[67]. Lou J, Hur SC, Huang N, Pandey L, Thakkar B, Donahue M, et al. Incidence rates and clinical characteristics of patients with confirmed myocarditis or pericarditis following COVID-19 mRNA vaccination: experience of the Veterans Health Administration through October 9, 2022. Open Forum. Infect Dis 2023;10(7):ofad268. [PubMed: 37469619]

[68]. Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B, Klein NP. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med 2022;175:1169–771. [PubMed: 36191323]

[69]. Shimabukuro T COVID-19 vaccine safety update: Primary series in young children and booster doses in older children and adults. Advisory Committee on Immunization Practices (ACIP), September 1, 2022. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/05-COVID-Shimabukuro-508.pdf. Accessed September 28, 2023.

[70]. Hause AM, Shay DK, Klein NP, et al. Safety of COVID-19 Vaccination in United States Children Ages 5 to 11 Years. Pediatrics 2022;150(2):e2022057313. [PubMed: 35581698]

[71]. Hause AM, Marquez P, Zhang B, et al. COVID-19 mRNA Vaccine Safety Among Children Aged 6 Months-5 Years - United States, June 18, 2022-August 21, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1115–20. [PubMed: 36048728]

[72]. Mevorach D, Anis E, Cedar N, et al. Myocarditis After BNT162b2 COVID-19 Third Booster Vaccine in Israel. Circulation 2022;146:802–4. [PubMed: 36067275]

[73]. Witberg G, Magen O, Hoss S, et al. Myocarditis after BNT162b2 Vaccination in Israeli Adolescents. N Engl J Med 2022;387:1816–7. [PubMed: 36260842]

[74]. Abraham N, Spruin S, Rossi T, et al. Myocarditis and/or pericarditis risk after mRNA COVID-19 vaccination: A Canadian head to head comparison of BNT162b2 and mRNA-1273 vaccines. Vaccine 2022;40:4663–71. [PubMed: 35750537]

[75]. Goddard K, Donahue JG, Lewis N, et al. Safety of COVID-19 mRNA vaccination among young children in the vaccine safety datalink. Pediatrics 2023;152.

[76]. Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet 2022;399:2191–9. [PubMed: 35691322]

[77]. Goddard K, Lewis N, Fireman B, et al. Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination. Vaccine 2022;40:5153–9. [PubMed: 35902278]

[78]. CDC. COVID-19 vaccination and myocarditis and pericarditis. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#myocarditis-pericarditis. Accessed September 28, 2023.

[79]. Kracalik I, Oster ME, Broder KR, et al. Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study. Lancet Child Adolesc Health 2022;6:788–98. [PubMed: 36152650]

[80]. Hadley SM, Prakash A, Baker AL, et al. Follow-up cardiac magnetic resonance in children with vaccine-associated myocarditis. Eur J Pediatr 2022;181:2879–83. [PubMed: 35482094]

[81]. FDA. Pfizer-BioNTech Regulatory Information (Emergency Use Authorization). Available at: https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/pfizer-biontech-covid-19-vaccines#additional. September 28, 2023.

[82]. FDA. Moderna COVID-19 Vaccine Regulatory Information (Emergency Use Authorization). Available at: https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/moderna-covid-19-vaccines#additional. Accessed September 28, 2023.

[83]. FDA. Coronavirus (COVID-19) Update: July 13, 2021. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-july-13-2021#:~:text=The%20warning%20in%20th. Accessed September 28, 2023.

[84]. Hanson KE, Goddard K, Lewis N, et al. Incidence of Guillain-Barré Syndrome After COVID-19 Vaccination in the Vaccine Safety Datalink. JAMA Netw Open 2022;5:e228879. [PubMed: 35471572]

[85]. Gubernot D, Jazwa A, Niu M, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine 2021;39:3666–77. [PubMed: 34088506]

[86]. Hause AM, Zhang B, Yue X, et al. Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination in the US. JAMA Netw Open 2022;5:e2222241. [PubMed: 35838667]

[87]. Simultaneous mRNA COVID-19 and IIV4 Vaccination Study Available at: https://www.clinicaltrials.gov/ct2/show/NCT05028361?lupd_s=08%2F01%2F2021. Accessed September 28, 2023.

[88]. Safety of Pediatric COVID-19 Vaccination. Available at: https://clinicaltrials.gov/study/NCT05157191?cond=Observational%20pediatric%20COVID-19%20vaccine&rank=1. Accessed September 28, 2023.

[89]. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children. Available at: https://clinicaltrials.gov/study/NCT06038617?cond=simulaneous%20COVID&rank=1. Accessed September 28, 2023.

[90]. Goddard K, Donahue JG, Lewis N, et al. Safety of COVID-19 mRNA vaccination among young children in the vaccine safety datalink. Pediatrics 2023;152(1):e2023061894. [PubMed: 37278199]

[91]. Hause AM, Baggs J, Marquez P, et al. Safety Monitoring of Pfizer-BioNTech COVID-19 Vaccine Booster Doses Among Children Aged 5–11 Years - United States, May 17-July 31, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1047–51. [PubMed: 35980875]

[92]. Hause AM, Marquez P, Zhang B, et al. Safety monitoring of bivalent COVID-19 mRNA vaccine booster doses among persons aged ≥12 Years - United States, August 31-October 23, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1401–6. [PubMed: 36327162]

[93]. Shimabukuro T, Klein NP. COVID-19 mRNA bivalent booster vaccine safety. Vaccines and Related Biological Products Advisory Committee meeting, February 24, 2023. Available at: https://www.fda.gov/media/164811/download. Accessed September 28, 2023.

[94]. Romanson B, Moro P, Su JR, et al. Safety Monitoring of Novavax COVID-19 Vaccine Among Persons Aged ≥12 Years — United States, July 13, 2022–March 13, 2023. MMWR Morb Mortal Wkly Rep 2023;72:850–1. [PubMed: 37535499]

[95]. Yih WK, Daley MF, Duffy J, et al. A broad assessment of covid-19 vaccine safety using tree-based data-mining in the vaccine safety datalink. Vaccine 2023;41:826–35. [PubMed: 36535825]

[96]. Jarach CM, Lugo A, Scala M, et al. Global Prevalence and Incidence of Tinnitus: A Systematic Review and Meta-analysis. JAMA Neurol 2022;79:888–900. [PubMed: 35939312]

[97]. Klein NP. COVID-19 vaccine safety surveillance. Advisory Committee on Immunization Practices (ACIP), September 12, 2023. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/07-COVID-Klein-508.pdf. Accessed September 28, 2023.

[98]. Wong HL, Tworkoski E, Ke Zhou C, et al. Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older. Vaccine 2023;41:532–9. [PubMed: 36496287]

[99]. Shoaibi A, Lloyd PC, Wong HL, et al. Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the U.S. Vaccine 2023;41:4666–78. [PubMed: 37344261]

[100]. Hu M, Wong HL, Feng Y, et al. Safety of the BNT162b2 COVID-19 Vaccine in Children Aged 5 to 17 Years. JAMA Pediatr 2023;177:710–7. [PubMed: 37213095]

[101]. CDC. End of the Federal COVID-19 Public Health Emergency (PHE) Declaration. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-health/end-of-phe.html. Accessed September 2, 2023.

[102]. ACIP Presentation Slides: September 12, 2023 Meeting. Available at: https://www.cdc.gov/vaccines/acip/meetings/slides-2023-09-12.html. Accessed September 28, 2023.

Table 1

Pre-specified health outcomes in U.S. vaccine safety monitoring systems during the COVID-19 pandemic.

Outcome	VAERS	VSD	VA	DoD	CMS	BEST
Acute disseminated encephalomyelitis	x[a,b]	x	x	x		
Acute myocardial infarction (AMI)	x	x	x	x	x	x
Anaphylaxis	x	x[c]	x	x	x	x
Appendicitis	x	x	x	x	x	x
Acute respiratory distress syndrome		x[c]		x		
Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)	x[a]		x[c]	x		
Ataxia	x[a,b]					
Autoimmune disease	x[a]					
Bell's palsy	x	x	x	x	x	x
Chronic inflammatory demyelinating polyneuropathy	x[a,b]					
COVID-19	X[a]					
Death	x			x		
Disseminated intravascular coagulation	x	x	x	x	x	x
Encephalomyelitis/Encephalitis				x	x	x
Encephalitis	x	x	x			
Encephalomyelitis	x[a,b]	x	x			
Encephalopathy	x[a,b]	x	x	x		
Guillain-Barré syndrome	x	x	x	x	x	x
Immune thrombocytopenic purpura		x	x	x	x	x
Kawasaki disease	x	x				
Meningitis	x[a,b]		x	x		
Meningoencephalitis	x[a,b]	x	x	x		
Multiple sclerosis	x[a,b]					
Multisystem Inflammatory Syndrome in Adults (MIS-A)	x	x[c]	x[c]	x	x[e]	x[e]
Multisystem Inflammatory Syndrome in Children (MIS-C)	x	x[c]				x[e]

Outcome	VAERS	VSD	VA	DoD	CMS	BEST
Myelitis	x[a,b]	x	x	x		
Myocarditis / pericarditis	x	x	x	x	x	x
Narcolepsy / cataplexy	x	x[c]	x	x	x[d]	x[d]
Non-anaphylactic allergic reactions	x[a]					
Optic neuritis	x[a,b]					
Seizures / convulsions	x	x	x			
Stroke	x		x			
Non-hemorrhagic stroke (NHS)		x	x		x	x
Hemorrhagic stroke (HS)		x	x		x	x
Thrombocytopenia	x	x				
Thrombosis with thrombocytopenia syndrome and/or cerebral venous sinus thrombosis	x	x		x	x	x
Thrombosis at uncommon site (including intracranial, intraabdominal, portal, renal, or other veins) with thrombocytopenia				x	x	x
Thrombosis at common site (AMI, DVT, HS, NHS, or PE) with thrombocytopenia					x	x
Transverse myelitis (TM)	x	x	x	x	x	x
Vaccination during pregnancy/adverse pregnancy outcomes	x			x		
Venous thromboembolism (VTE)	x	x	x	x	x	x
Pulmonary embolism (PE)		x	x	x	x	x
Deep vein thrombosis (DVT)			x	x	x	x

Note: “x” indicates an outcome that was prespecified for monitoring in the system; pre-specified outcomes in each system varied depending on age group and vaccine. The Indian Health Service is not included in this table, because there were no pre-specified outcomes in the monitoring systems.

Abbreviations: VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; VA, Department of Veterans Affairs Warehouse; DoD, Department of Defense; DoD uses the Defense Medical Surveillance System and the Defense Health Agency Immunization Healthcare Division; CMS, Centers for Medicare & Medicaid Services; BEST, Biologics Effectiveness and Safety System.

[a]Health outcomes are monitored, but adverse event reports are not abstracted.

[b]Diagnoses are grouped and monitored as “Other clinically serious neurologic AEs” in VAERS.

[c]Health outcomes are counted, and no sequential analysis is conducted.

[d]Only includes narcolepsy.

[e]Only included in the descriptive analysis not the rapid cycle analysis, as MIS requires a COVID-19 diagnosis and therefore historical rates cannot be estimated.

Table 2

COVID-19 vaccines with authorizations and licensures in the United States, December 2020 through March 2023.

Vaccine	Vaccine platform	Emergency Use Authorization (EUA) by FDA	Licensure by FDA
Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)[a]	mRNA vaccine	December 11, 2020: authorized for use in persons ages ≥ 16 years as a two-dose series. Subsequently authorized for use in persons 6 months through 15 years as a primary series,[b] and for first and second booster doses in certain age groups. [15]	August 23, 2021: FDA approved use in persons ages ≥ 16 years as a two-dose series. Comirnaty is the proprietary name for the licensed vaccine. [19] July 8, 2022: FDA approved use in adolescents 12 through 15 years.
Moderna COVID-19 Vaccine (Original monovalent)[a]	mRNA vaccine	December 18, 2020: authorized for use in persons ages ≥ 18 years as a two-dose series. Subsequently authorized for use in persons 6 months through 17 years as a primary series,[b] and for first and second booster doses in certain age groups. [16]	January 31, 2022: FDA approved use as a two-dose series in persons ages ≥ 18 years. Spikevax is the proprietary name for the licensed vaccine. [17]
Janssen COVID-19 Vaccine (Original monovalent)[a]	Replication-incompetent adenoviral vector vaccine	February 21, 2021: authorized for use in persons ages ≥ 18 years as primary vaccination. Subsequently authorized for use as first booster dose in persons ages ≥ 18 years.[c] [14]	
Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)[a]	Protein subunit vaccine with Matrix-M adjuvant	July 13, 2022: authorized for use in persons ages ≥ 18 years as a primary series.[b] [12] Subsequently authorized for use in persons 12 through 17 years as a primary series[b] and as a first booster dose in certain persons ages > 18 years.	
Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)	mRNA vaccine	August 31, 2022: authorized for use in persons ages ≥ 12 years as a single booster dose.[d] [15] Subsequently authorized for use in persons 6 months through 11 years as a single booster dose.	
Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)	mRNA vaccine	August 31, 2022: authorized for use in persons ages ≥ 18 years as a single booster dose.[d] [16] Subsequently authorized for use in persons 6 months through 17 years as a single booster dose.	

[a] Original monovalent refers to COVID-19 vaccines that contain or encode the spike protein of only the Original SARS-CoV-2.

[b] With the December 11, 2020, authorization of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the December 18, 2020, authorization of the Moderna COVID-19 Vaccine (Original monovalent), the vaccination regimen for each vaccine was a two-dose series. Subsequently, with authorization of a booster dose of each of these vaccines, the two-dose series was described as a primary series. In this paper, use of "primary series" for Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine (Original monovalent) includes doses 1 and 2 of the vaccines, irrespective of timing of administration during authorized use. A primary series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (no longer authorized for use in the United States) was two doses for individuals 5 years of age and older and three doses for individuals 6 months through 4 years of age. On December 8, 2022, FDA revised the third dose in the 3-dose primary series authorized for individuals 6 months through 4 years so that the third dose was provided with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (no longer authorized for use in the United States). A primary series of Moderna COVID-19 Vaccine (Original monovalent) (no longer authorized for use in the United States) was two doses. A primary series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (no longer authorized for use in the United States) was two doses. Primary vaccination with Janssen COVID-19 Vaccine (no longer authorized for use in the United States) consisted of a single dose.

[c] May 5, 2022, FDA limited the authorized use of the Janssen COVID-19 Vaccine to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines were not accessible or clinically appropriate, and to individuals 18 years of age and older who elected to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. FDA revoked the EUA on June 1, 2023.

[d] The initial authorization covered use as a single booster dose after either: 1) completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine.

Table 3

Main topics reviewed by the COVID-19 Vaccine Safety Technical Work Group, December 2020 through April 2023.

Safety topic	COVID-19 vaccine	Date first reviewed	VaST interpretation[a]
Anaphylaxis	Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)	December 2020	Data reviewed supported this outcome as a safety concern; vaccination guidance modified accordingly.
	Moderna COVID-19 Vaccine (Original monovalent)		
Mortality	All available COVID-19 vaccines	January 2021	Data reviewed did not identify safety concerns.
Safety of vaccination in pregnancy and reproductive health outcomes	All available COVID-19 vaccines	February 2021	Data reviewed did not identify any safety concerns for maternal, pregnancy, or infant outcomes.
Thrombosis with thrombocytopenia syndrome	Janssen COVID-19 Vaccine (Original monovalent)	April 2021	Data reviewed indicated this outcome as a safety concern; vaccination guidance modified accordingly.
Myocarditis and pericarditis	Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)	April 2021	Overall data reviewed indicated this outcome as a safety concern; vaccination guidance modified accordingly.
	Moderna COVID-19 Vaccine (Original monovalent)		
Guillain-Barr é syndrome	Janssen COVID-19 Vaccine (Original monovalent)	June 2021	Data reviewed indicated this outcome as a safety concern; vaccination guidance modified accordingly.
Simultaneous vaccination of COVID-19 vaccines with other vaccines	Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)	October 2021	Data reviewed did not identify safety concerns.[b]
	Moderna COVID-19 Vaccine (Original monovalent)		
Pediatric age group, 5 or 6 through 11 years	Pfizer-BioNTech COVID-19 vaccine (Original monovalent)	November 2021	Data reviewed did not identify safety concerns.
	Moderna COVID-19 Vaccine (Original monovalent)	July 2022	
Pediatric age group, 6 months through 5 or 6 years	Pfizer-BioNTech COVID-19 vaccine (Original monovalent)	June 2022	Data reviewed did not identify safety concerns.
	Moderna COVID-19 Vaccine (Original monovalent)		
Bivalent vaccine booster doses	Pfizer-BioNTech COVID-19 Vaccine, Bivalent	October 2022	Data reviewed from one vaccine safety system suggested a potential safety concern for ischemic stroke following Pfizer-BioNTech COVID-19
	Moderna COVID-19 Vaccine, Bivalent		Vaccine, Bivalent in persons ages ≥ 65 years; evaluations are ongoing. No other safety concerns identified.[c]
Tinnitus and hearing loss	Pfizer-BioNTech COVID-19 Vaccine (Original monovalent)	November 2022	Data reviewed did not identify safety concerns.
	Moderna COVID-19 Vaccine (Original monovalent)		
	Janssen COVID-19 Vaccine (Original monovalent)		

Abbreviations: VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; CMS, Centers for Medicare & Medicaid Services; BEST, Biologics Effectiveness and Safety System.

[a]Indicates VaST interpretation of evidence through end of VaST meetings in April 2023; see text for more information.

[b] Data available primarily for influenza vaccination.

[c] VSD rapid cycle analysis detected a statistical signal for Pfizer-BioNTech COVID-19 Vaccine (November 2022; first reviewed by VaST January 2023). No other VSD rapid cycle analysis pre-specified surveillance outcomes signaled in any age groups for either of the bivalent mRNA COVID-19 vaccines. On May 31, 2023, FDA and CDC released a statement saying the agencies determined that the current evidence does not support a safety concern for ischemic stroke following bivalent COVID-19 booster doses: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cdc-and-fda-identify-preliminary-covid-19-vaccine-safety-signal-persons-aged-65-years-and-older.

Table 4

Pregnancy and reproductive health outcomes following COVID-19 vaccination reviewed by the COVID-19 Vaccine Safety Technical Work Group.

Outcome	Safety System and Findings
Maternal outcomes	v-safe: Any injection site reaction, any systemic reaction, and any health impact[a] had similar or lower frequency than observed in analogous vaccine dose in the non-pregnant adult population [48] VAERS: Empirical Bayesian data mining did not detect any disproportionality alerts for pregnancy-specific[b] or non-pregnancy-specific adverse events in persons who received primary series vaccination during pregnancy. Crude reporting rate was below published background rate. [47,50] COVID-19 Vaccine Pregnancy Registry: Reported outcomes of interest were within published background rates. [56] VSD: COVID-19 vaccines were not associated with an increased risk of the clinically serious acute adverse events, evaluated in retrospective, observational, matched-cohort study. [51,52]
Pregnancy outcomes	
Spontaneous abortion	VAERS: Empirical Bayesian data mining did not detect any disproportionality alerts for primary series. [47] Crude reporting rate following primary series and booster doses below published background rate. [47,50] COVID-19 Vaccine Pregnancy Registry: Cumulative risks of spontaneous abortion among women who received vaccination during pregnancy were within the published background rates. [46] VSD: COVID-19 booster vaccination in pregnancy was not associated with spontaneous abortion. [53,57]
Stillbirth	VAERS: Empirical Bayesian data mining did not detect any disproportionality alerts for primary series. Crude reporting rate following primary series and booster doses below published background rate. [47,50] COVID-19 Vaccine Pregnancy Registry: Stillbirth rate among the pregnancy registry participants was not higher than published background rate. [48,56] VSD: No concerning patterns observed in surveillance of stillbirths following a booster dose of COVID-19 vaccine in pregnancy.
Preterm delivery or small for gestational age	VAERS: Empirical Bayesian data mining did not detect any disproportionality alerts for primary series. [46] Crude reporting rate for preterm delivery following primary series and booster doses below published background rate. [47,50] VSD: COVID-19 vaccination during pregnancy was not associated with preterm birth or small-for-gestational-age at birth overall, stratified by trimester of vaccination, or number of vaccine doses received during pregnancy, compared with unvaccinated pregnant persons. [49]
Infant outcomes [c]	VAERS: Empirical Bayesian data mining did not detect any disproportionality alerts for primary series. [46] Crude reporting rates for infant outcomes following primary series and booster doses below published background rates. [47,50] COVID-19 Vaccine Pregnancy Registry: Incidence rates of outcomes of interest were within published background rates. [48,56]
Menstrual irregularities or vaginal bleeding	VAERS: Among cases reported, few vaginal bleeding cases were serious. v-safe: ~1% of female v-safe participants reported menstrual irregularities. [54] VSD: Post-menopausal bleeding following COVID-19 vaccination was uncommon.

Abbreviations: VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink.

COVID-19 Vaccine Pregnancy Registry refers to the registry managed at CDC.

“Maternal” is used here to include women and other people who are pregnant or postpartum.

VaST also reviewed a CISA study in progress: Observational Maternal COVID-19 Vaccination Study - Full Text View - ClinicalTrials.gov.

[a] Health impacts include: unable to do normal daily, unable to work, required medical visit.

[b] Empirical Bayesian data mining found disproportional reporting for “prolonged labor” following Janssen vaccine, but confounding factors present.

[c] Infant outcomes include neonatal death, birth defects, infant in intensive care unit (diverse abnormalities).