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Editorial: What Can be Learned from National and International Vaccine Adverse Event Reporting Systems During the COVID-19 Pandemic?

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Abstract

Healthcare professionals have an ethical, medico-legal, and professional responsibility to report all suspected adverse events following immunization to relevant national reporting agencies as part of the process of post-marketing drug safety monitoring. In the US, the Vaccine Adverse Event Reporting System (VAERS) is co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). Data from VAERS and other national and global reporting systems show very low rates of adverse events related to currently approved SARS-CoV-2 vaccines. Populations studies have supported the findings from adverse event reporting systems. The presentation, monitoring, and reporting of adverse events related to SARS-CoV-2 vaccines may have future applications in vaccine monitoring for several other potential pandemic zoonotic infections. This editorial aims to summarize the current understanding of adverse events from current COVID-19 vaccines from global adverse event reporting systems, rather than individual case reports or anecdotal reporting in the media.

Keywords: COVID-19 • SARS-CoV-2 • Vaccines • Adverse Events • Editorial

The accelerated development of SARS-CoV-2 vaccines and regulatory approvals have resulted in millions of vaccinations being administered as part of ongoing global vaccination programs. As of October 22, 2021, the World Health Organization (WHO) has confirmed 242,348,657 cases of COVID-19, with 4,927,723 deaths [1]. By this date, a total of 6,655,399,359 SARS-CoV-2 vaccine doses were given worldwide [1].

Healthcare professionals have a professional and ethical responsibility to report all suspected adverse events following immunization (AEFI) to relevant national reporting agencies as part of the process of post-marketing drug safety monitoring [2,3]. There is a medico-legal requirement in the US to report adverse events related to vaccines [3]. The Vaccine Adverse Event Reporting System (VAERS) is co-sponsored by the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) [4]. The required reporting events include the following; errors associated with vaccine administration; serious adverse events, including death or a life-threatening event; hospitalization; significant incapacity; congenital anomaly or birth defect; a medical event may require medical or surgical intervention; cases of multisystem inflammatory syndrome (MIS); and cases of COVID-19 resulting in hospitalization or death [2,3].

The FDA has a program for monitoring the safety of authorized COVID-19 vaccines through the Center for Biologics Evaluation and Research (CBER) using passive and active safety surveillance systems [2,3]. Vaccine pharmacovigilance is organized in collaboration with CBER, the CDC, the Department of Veterans Affairs (VA), the Center for Medicare and Medicaid Services (CMS), academic and large healthcare data systems, the International Coalition of Medicines Regulatory Authorities (ICMRA), and the WHO [2,3]. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) require that all suspected side effects of COVID-19 vaccines are reported using a Coronavirus Yellow Card site [5]. In Europe, the European suspected adverse drug reactions database, EudraVigilance, records all reports of possible adverse events, or safety signals, associated with COVID-19 vaccines [6].

There have been relatively few COVID-19 vaccine-associated adverse events compared with the number of vaccinations. Currently, there are three vaccines for SARS-CoV-2 approved in the US by the Food and Drug Administration (FDA) [7]. The Janssen/Johnson & Johnson (J&J) (Ad26.COVS.2S) vaccine and the Moderna (mRNA-1273) vaccine have received emergency use authorization (EUA) [7]. In August 2021, the BNT162b2 Pfizer-BioNTech vaccine (Comirnaty) received full FDA regulatory approval [8]. Recent CDC data have highlighted the

differences in clinical outcomes between individuals in the US who have and have not been vaccinated and differences in the numbers of 'breakthrough' cases of COVID-19 between vaccines [2]. Mortality from COVID-19 in the unvaccinated during the week of August 13, 2021, was 13.23 per 100,000 population [2]. Mortality from COVID-19 in the vaccinated during the same week was <4 per 100,000 [2]. In the vaccinated population in the US, mortality from 'breakthrough' COVID-19 cases was comparatively highest in individuals vaccinated with the Janssen/J&J (Ad26.COVS.2) vaccine recipients (3.14 per 100,000), followed by the BNT162b2 Pfizer-BioNTech vaccine (Comirnaty) (1.43 per 100,000) and the Moderna (mRNA-1273) vaccine (0.73 per 100,000) [2]. Although the differences between the vaccinated groups in terms of 'breakthrough' COVID-19 cases, there is a clear message that unvaccinated individuals in the US are at greater risk from infection and death from COVID-19 [2]. Scobie and colleagues have reported similar data in a recent CDC Morbidity and Mortality Weekly Report (MMWR) [9].

The Janssen/J&J (Ad26.COVS.2) is an adenoviral vector COVID-19 vaccine first given to the US population in early March 2021 [10]. However, on March 19, 2021, the FDA and CDC reported the first case of cerebral venous sinus thrombosis (CVST) and thrombocytopenia to the VAERS, followed by further reports [10]. On April 13, 2021, a health alert notification (HAN) halted the use of the Janssen/J&J (Ad26.COVS.2) vaccine, with further clinical evaluation [11]. Reports in the medical and social media contributed to vaccine hesitancy, supported by previous reports of similar events related to the Oxford/AstraZeneca (ChAdOx1 nCoV-19) vaccine [12]. Further attention in the medical and social media in Europe and reports from the European Medicines Agency (EMA) supported a possible but rare link between thrombosis and thrombocytopenia following vaccination with the Oxford/AstraZeneca (ChAdOx1 nCoV-19) vaccine [12]. Some European countries have moved from the use of adenoviral vector vaccines to predominantly mRNA vaccines [13].

Recent data from the CDC has shown that more than 408 million vaccinations for COVID-19 were administered in the US between December 14, 2020, to October 18, 2021 [14]. From these 408 million vaccinations, VAERS were notified that 8,878 individuals (0.0022%) died soon after being vaccinated [14]. Anaphylactic reactions after COVID-19 vaccination are rare. As of October 2021, the CDC reported an incidence of approximately 2-5 per million people vaccinated for COVID-19 in the US [14]. According to the CDC, vaccine-induced immune thrombotic thrombocytopenia (VITT) is also rare [14]. There have been only 47 confirmed cases of VITT, as of October 2021, following 15.2 million Janssen/J&J (Ad26.COVS.2) vaccinations [14]. The US FDA and CDC recommend that women less than 50 years of age be aware of this rare risk [14]. As of October 2021, only

two confirmed cases of VITT have been reported to VAERS, with >388 million doses of mRNA COVID-19 vaccines in the US [14]. As of October 2021, after more than 15.2 million doses of the Janssen/J&J (Ad26.COVS.2) vaccine, 233 preliminary reports of Guillain-Barré syndrome have been identified VAERS [14]. The cases of Guillain-Barré syndrome occurred two weeks after vaccination, mainly in men more than 50 years of age [14].

In 2021, there have been increasing reports of post-vaccine myocarditis and pericarditis [15]. Recent media attention has focussed on this association with mRNA SARS-CoV-2 vaccines, the BNT162b2 Pfizer-BioNTech (Comirnaty) vaccine, and the Moderna (mRNA-1273) vaccine [15]. However, Diaz and colleagues recently reported a study of the electronic patient medical records from 40 hospitals in Washington, Montana, Oregon, and Los Angeles County, California [15]. Patient records were reviewed from 2,000,287 individuals who received at least one COVID-19 vaccination, either the Moderna (mRNA-1273) vaccine, the BNT162b2 Pfizer-BioNTech vaccine (Comirnaty), or the Janssen/J&J (Ad26.COVS.2) vaccine [15]. The authors compared the number of cases of myocarditis and pericarditis between the post-vaccination period and the pre-vaccination period [16]. Twenty individuals (1.0 per 100,000) had vaccine-related myocarditis and 37 individuals (1.8 per 100,000) had vaccine-associated pericarditis [15]. Myocarditis was diagnosed at a median of 3.5 days after vaccination [15]. Four individuals developed symptoms after the first vaccination, and 16 developed symptoms after the second [15]. Nineteen patients required hospital admission, but there were no readmissions or deaths [15]. As of October 2021, VAERS received 1,638 reports of myocarditis or pericarditis in people ≤30 years who received a COVID-19 vaccine [15]. Most cases were associated with an mRNA vaccine, the BNT162b2 Pfizer-BioNTech vaccine (Comirnaty), or the Moderna (mRNA-1273) vaccine [15]. Myocarditis or pericarditis occurred mainly in male adolescents or young adults [15].

A recent publication by Klein and colleagues has reported an interim analysis from the surveillance data from the US Vaccine Safety Datalink database of 6.2 million people following 11.8 million doses of the mRNA COVID-19 vaccines, the BNT162b2 Pfizer-BioNTech vaccine (Comirnaty) or the Moderna (mRNA-1273) vaccine [16]. The study was based on content from the US Vaccine Safety Datalink database between December 2020 and June 2021 [16]. The data in this national database is updated weekly, and data is from a diverse population of vaccinated US citizens [16]. This study evaluated the increased risk for serious health outcomes at post-vaccination day 1 to day 21 [16]. The evaluated clinical outcomes included: acute myocardial infarction (AMI); Bell's palsy; cerebral venous sinus thrombosis (CVST); Guillain-Barré syndrome; myocarditis and pericarditis; stroke; pulmonary embolism (PE); and vaccine-induced immune thrombotic thrombocytopenia (VITT) [16]. Twenty-three serious health outcomes were analyzed, which

were not significantly increased at day 1 to day 21 after vaccination compared with day 22 to day 42 after vaccination [16]. The incidence of serious outcomes was not significantly increased from day 1 to day 21 after vaccination compared with day 22 to day 42 after vaccination [16]. This interim analysis showed no association between mRNA vaccines and post-vaccine myocarditis and pericarditis, CVST, or VITT [16].

The CDC and FDA VAERS make clear that reports of adverse events to VAERS following COVID-19 vaccination, including deaths, do not prove that the vaccine was the cause [2,3]. Global vaccination programs aim to vaccinate entire populations as rapidly as possible. Global populations include the elderly and patients with acute and chronic comorbidities, with expected ongoing health problems and all-cause mortality. However, several lessons continue to be learned as surveillance programs evolve for COVID-19 vaccine-related adverse events [17]. It is clear from the effects of misinformation on vaccine programs that evidence-based recommendations will increasingly rely on surveillance data to make informed decisions [17]. It is now more important than ever to ensure that clinical recommendations are evidence-based. The clinical evidence will come from coordinating active global surveillance data from electronic health records, rather than individual case reports or anecdotal reporting [17]. Surveillance systems in developing countries require urgent support, as there are still gaps in the surveillance data between ethnic groups [17]. There is also a need to identify associations between increased

vaccine-associated adverse events and different patient groups, including the immunosuppressed [17]. Collaboration is required between national regulatory authorities and national immunization programs to standardize adverse event evaluation and disseminate clinical information obtained from national and international vaccine adverse event reporting systems during the COVID-19 pandemic [2,3].

Lessons learned from the presentation, monitoring, and reporting of adverse events related to SARS-CoV-2 vaccines to prevent COVID-19 may be applicable in the future to monitor vaccines for several other potential pandemic zoonotic infections [17,18]. There may be relevant lessons for implementing vaccination programs for infections due to rabies, Ebola, Zika, HIV-1, and future mRNA vaccines for possible pandemic avian influenza [7,18].

Conclusions

At this time, vaccine compliance and public confidence in vaccine programs during the COVID-19 pandemic and beyond can only be maintained by accurate information available to national and international vaccine adverse event reporting systems. Therefore, all healthcare professionals should be aware of their ethical and medico-legal responsibility for timely, clear, and accurate vaccine adverse event reporting to national and international systems, such as the VAERS.

References:

1. World Health Organization (WHO) Coronavirus (COVID-19) Dashboard. Continually updated. Available from: <https://covid19.who.int>
2. Centers for Disease Control and Prevention (CDC). COVID-19. Vaccine Adverse Event Reporting System (VAERS). Continually updated. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vaers.html>
3. Centers for Disease Control and Prevention (CDC). Report an adverse event. Vaccine Adverse Event Reporting System (VAERS). Continually updated. Available from: <https://vaers.hhs.gov/reportevent.html>
4. Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (CIOMS). Definition and application of terms for vaccine pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS); 2012. Available from: https://vaccine-safety-training.org/tl_files/vs/pdf/report-of-cioms-who-working-group.pdf
5. National Health Service England (NHSE). COVID-19 vaccination programme Standard operating procedure Management of COVID-19 vaccination clinical incidents and enquiries. 2021. Available from: <https://www.england.nhs.uk/coronavirus/publication/standard-operating-procedure-management-of-covid-19-vaccination-clinical-incidents-and-enquiries/>
6. European Medicine Agency (EMA) EudraVigilance pharmacovigilance database and reporting system. Continually updated. Available from: <https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance>
7. Parums DV. Editorial: mRNA vaccines and future epidemic, pandemic, and endemic zoonotic virus infections. *Med Sci Monit.* 2021;27:e932915
8. Parums DV. Editorial: First full regulatory approval of a COVID-19 vaccine, the BNT162b2 Pfizer-BioNTech vaccine, and the real-world implications for public health policy. *Med Sci Monit.* 2021;27:e934625
9. Scobie HM, Johnson AG, Suthar AB, et al. Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status – 13 U.S. Jurisdictions, April 4-July 17, 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:1284-90. Available from: <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7037e1-H.pdf>
10. See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination. *JAMA.* 2021;325(24):2448
11. MacNeil JR, Su JR, Broder KR, et al. Updated recommendations from the advisory committee on immunization practices for use of the Janssen (Johnson & Johnson) COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients – United States, April 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:651-56
12. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med.* 2021;384(22):2124-30
13. Ledford H. COVID vaccines and blood clots: Five key questions. *Nature.* 2021;592(7855):495-96
14. Centers for Disease Control and Prevention (CDC). COVID-19. Reported Adverse Events. October 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>
15. Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA.* 2021;326(12):1210-12

16. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events After COVID-19 mRNA vaccination. *JAMA*. 2021;326(14):1390-99
17. Rizk JG, Barr CE, Rizk Y, Lewin JC. The next frontier in vaccine safety and VAERS: Lessons from COVID-19 and ten recommendations for action. *Vaccine*. 2021;39(41):6017-18
18. Parums DV. Editorial: A decline in influenza during the COVID-19 pandemic and the emergence of potential epidemic and pandemic influenza viruses. *Med Sci Monit*. 2021;27:e934949