Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 39 (2021) 6017–6018

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

The next frontier in vaccine safety and VAERS: Lessons from COVID-19 and ten recommendations for action

John G. Rizk [a,*], Charles E. Barr [b,c], Youssef Rizk [d], John C. Lewin [e]

[a] Arizona State University, Edson College, Phoenix, AZ, United States
[b] Pivotal Strategic Consulting, LLC, Danville, CA, United States
[c] Diya Health, Oakland, CA, United States
[d] Department of Internal Medicine, Division of Family Medicine, Lebanese American University Medical Center – St. John's Hospital, Lebanon
[e] National Coalition on Health Care, Washington, DC, United States

Vaccination with the Johnson & Johnson vaccine, an adenoviral vector coronavirus disease 2019 (COVID-19) vaccine, started on March 2, 2021. On March 19, 2021, the Center for Disease Control and Prevention (CDC) and the Food & Drug Administration (FDA) received the first cerebral venous sinus thrombosis (CVST) with thrombocytopenia case reports to the Vaccine Adverse Event Reporting System (VAERS), and reports continued to be submitted [1,2]. In response, a health alert notification (HAN) was issued on April 13th, 2021, and the CDC and FDA recommended a pause in the Johnson & Johnson vaccine for further evaluation [3]. Owing to these reports, CVST and blood clots have caused an unfortunate public hesitancy about COVID-19 vaccination in general and has stimulated a flurry of scientific inquiry. The discussion around the issue of thrombosis with thrombocytopenia previously originated from reports of similar events following AstraZeneca's COVID-19 vaccine [1,4,5]. The European Medical Agency (EMA) and individual countries have issued several documents stating their findings about a possible link between thrombosis with thrombocytopenia and AstraZeneca's COVID-19 vaccine, and several European countries are beginning to abandon adenoviral vector vaccines in favor of mRNA vaccines [6]. More recently, cases of myocarditis following mRNA vaccines, Pfizer/BioNTech and Moderna, are being reported and investigated [7,8].

VAERS is a national vaccine safety surveillance program that helps to detect unusual or unexpected reporting patterns of adverse events for vaccines [9]. It is part of a larger vaccine safety program in the U.S. that is co-managed by the FDA and the CDC. VAERS is used to monitor the safety of vaccines once they are authorized or licensed for use, and captures spontaneous reports of health-related adverse events that occur following vaccination. If VAERS detects a new "potential signal" or pattern of adverse events following vaccination, then follow-up evaluation studies can be conducted within other vaccine safety monitoring systems. Reports are accepted from anyone, including patients, family members, healthcare professionals and vaccine manufacturers. Healthcare providers and the public are encouraged to recognize adverse events related to vaccines and to promptly report them to VAERS, as required under the emergency use authorizations (EUAs) for COVID-19 vaccines [10], and this practice also applies to drugs with EUAs [11]. Deaths related to the vaccine should also be reported. If a serious adverse event is reported, the VAERS office or CDC will request medical records. The Health Insurance Portability and Accountability Act (HIPAA) permits reporting of protected health information to public health authorities [12].

VAERS has limitations [9], since it is a passive surveillance system that relies on individuals to voluntarily report their symptoms. This renders the system subject to reporting bias, including underreporting and overreporting of very rare or very common events. In fact, most reports are of known or common side effects. Nonetheless, healthcare professionals and vaccine manufacturers are required by law to submit certain events. Additionally, reports may be incomplete or lacking in detail. VAERS is designed specifically to rapidly detect rare, serious events that may indicate a safety signal, and as a spontaneous reporting system, it is not designed to assess causality. A report to VAERS does not necessarily mean the vaccine caused the event, and the reported events are not necessarily confirmed, which may be confusing to the general public, as well as to providers and clinicians. This is compounded further by the lack of a comparison control group. Moreover, it makes it more difficult to estimate the incidence of adverse events, such as CVST with thrombocytopenia, following vaccination [13].

Despite the well-known limitations, VAERS has shown to be a model of transparency in the COVID-19 age, and is essential for ongoing monitoring of vaccine safety, especially the rapid detection of rare and severe or life-threatening events, and alerting the public and healthcare providers of concerns and guidance. The quick detection of early reports and rapid assessment of safety signals demonstrate the robustness of this system. With large numbers of individuals being rapidly vaccinated, it is incumbent on healthcare professionals on the frontlines to recognize potential vaccine adverse events including rare, serious adverse events like CVST, to VAERs. Future efforts should focus on investigating potential cases through detailed clinical and chart reviews, and also to refine analyses to better quantify risks in an attempt to develop more robust assessments to provide the necessary data to the

* Corresponding author.
E-mail address: john.rizk@lau.edu (J.G. Rizk).

https://doi.org/10.1016/j.vaccine.2021.08.006

CDC, FDA, and Immunization Committee on Immunization Practices. This will aid in analyzing individual-level data related to vaccination, and in making evidence-based recommendations.

We recommend several measures to be considered in an effort to improve vaccine-related adverse event reporting and assessment, and to make informed decisions:

1. *Improve Surveillance Systems:* Increase utilization of active vaccine safety surveillance systems (e.g. electronic health databases, hospitals/clinics charts). This approach should be done in parallel with passive surveillance, and can help draw causal inferences and improve estimates of the number and incidence rates of vaccine-related adverse events.
2. *Support Surveillance in Lower-Income Countries:* Support implementation of passive and active surveillance systems in low- and middle-income countries. This will help identify predisposing factors in specific populations and particular ethnic subgroups.
3. *Facilitate Non-Electronic Data Collection:* Extend adverse event data collection to locations where data documentation is difficult to acquire (e.g. facilities without electronic health records, patients without medical reimbursement plans). The use of optical character recognition (OCR), natural language processing technology (NLP), and artificial intelligence (AI) can help extract pertinent information from faxed and paper documentation sources.
4. *Improve Vaccine-Specific Data Collection:* Continue to improve characterizing, filtering and prioritizing adverse events based on vaccine type (e.g. mRNA, adenoviral vector), population (e.g. sex, age, pregnancy status, history of illness, immunodeficiency), and type of adverse event (e.g. blood clots, Guillain-Barré syndrome, bell's palsy, myocarditis). A harmonized list of prioritized adverse events will foster comparability across different surveillance systems and allow for timely evaluation of potential safety signals [14].
5. *Improve Data Interoperability:* Link vaccine registries to healthcare databases. This will enrich data availability and accuracy in longitudinal cohorts to improve signal detection, evaluation of risk factors, and estimating incidence of adverse events.
6. *Enhance Patient/Clinician Follow-up:* Improve healthcare provider follow-up with patients who experience vaccine-related adverse events. This will provide opportunity for optimal care and early intervention, longitudinal follow-up data in VAERS, and opportunity to participate in appropriate registries and research studies.
7. *Improve Regulatory and Public Health Collaboration:* Promote collaborations between national regulatory authorities and immunization programs in an effort to standardize assessments of vaccine-related adverse events, enhance consistency of interpretations, clarity of communications, and accelerate data dissemination.
8. *Improve Inter-regional Data Sharing:* Establish formal inter-regional collaborations to promote sharing of vaccine data and global assessment of vaccine safety. This, for example, will help assess whether other adenoviral vector vaccine, such as Gam-Covid-Vac (Sputnik V, Gamaleya) or Ad5-nCoV (Convidecia, CanSinoBIO), are also associated with vaccine-induced immune thrombotic thrombocytopenia.
9. *Enhance Data Accuracy:* Ensure completeness and accuracy of essential information (vaccine type, date of vaccination, patient history, etc.) collected from adverse event reporting systems.
10. *Improve Data Transparency and Provenance:* Maintain transparency in reporting adverse events, including sources of data and analytical methods, assumptions and limitations. This is central to public confidence, and will enable timely and accurate policy decisions to be made. Any additional warnings should be added to the vaccine label and other educational materials.

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.

References

[1] Rizk JG, Gupta A, Sardar P. Clinical characteristics and pharmacological management of COVID-19 vaccine-induced immune thrombotic thrombocytopenia with cerebral venous sinus thrombosis [published online ahead of print, 2021 Aug 10]. JAMA Cardiol 2021. https://doi.org/10.1001/jamacardio.2021.3444.

[2] See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination. JAMA 2021;325(24):2448. https://doi.org/10.1001/jama.2021.7517.

[3] 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;70:651–6. https://doi.org/10.15585/mmwr.mm7017e4.

[4] 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(22):2092–101. https://doi.org/10.1056/NEJMoa2104840.

[5] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384(22):2124–30. https://doi.org/10.1056/NEJMoa2104882.

[6] Ledford H. COVID vaccines and blood clots: five key questions. Nature 2021;592(7855):495–6. https://doi.org/10.1038/d41586-021-00998-w.

[7] Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine 2021;39(29):3790–3. https://doi.org/10.1016/j.vaccine.2021.05.087.

[8] Karron RA, Key NS, Sharfstein JM. Assessing a rare and serious adverse event following administration of the Ad26.COV2.S vaccine. JAMA 2021;325(24):2445–7. https://doi.org/10.1001/jama.2021.7637.

[9] Vaccine Adverse Event Reporting System (VAERS). Retrieved from: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html [accessed June 21, 2021].

[10] Rizk JG, Forthal DN, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, et al. Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic. Drug Discov Today 2021;26(2):593–603. https://doi.org/10.1016/j.drudis.2020.11.025.

[11] Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs 2020;80(13):1267–92. https://doi.org/10.1007/s40265-020-01367-z.

[12] VAERS. Information for healthcare providers. Retrieved from: https://vaers.hhs.gov/resources/infoproviders.html [accessed June 21, 2021].

[13] Vaccine-induced Thrombotic Thrombocytopenia (VITT) and COVID-19 Vaccines: What Cardiovascular Clinicians Need to Know. Retrieved from: https://www.acc.org/latest-in-cardiology/articles/2021/04/01/01/42/vaccine-induced-thrombotic-thrombocytopenia-vitt-and-covid-19-vaccines [accessed: April 21, 2021].

[14] Lee GM, Romero JR, Bell BP. Postapproval Vaccine Safety Surveillance for COVID-19 Vaccines in the US. JAMA 2020;324(19):1937–8. https://doi.org/10.1001/jama.2020.19692.