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Commentary

Beyond the jab: A need for global coordination of pharmacovigilance for COVID-19 vaccine deployment

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As of March 2021, over 40 COVID-19 vaccine candidates were either in phase 3 clinical trials or had received conditional approval for emergency use [1]. The Pfizer/BioNTech, Moderna, Oxford/AstraZeneca and Johnson and Johnson vaccines have been approved for emergency use by multiple regulatory authorities. The Gamaleya Sputnik-V, Sinopharm, Sinovac and CanSino vaccines have been approved for emergency use in many countries though not yet by stringent regulatory authorities. By April 2021, over 950 million vaccine doses had been administered worldwide but distribution has been very unequal; 40 doses/100 individuals in North America vs 1.1 doses/100 individuals in Africa [2,3].

The roll out of vaccines requires robust pharmacovigilance systems and global coordination of post-licensure surveillance [4] including real-time information sharing, open source data repository and a strong communication component. The WHO Global Vaccine Safety Initiative aims to standardize reporting of adverse events following immunization (AEFI) and adverse events of special interest (AESI) [5]. The WHO manual for COVID-19 vaccine safety surveillance outlines the minimum requirements at global, regional and national levels for passive surveillance with the ability to detect and investigate AEFIs, safety signals or clustering events as well as determine causality for defined AESI [6] Countries with well-established pharmacovigilance systems are encouraged to establish active surveillance to investigate AESIs through cohort monitoring, sentinel surveillance or e-Health platforms.

It is plausible to envision that many well-established regulatory authorities and pharmacovigilance platforms may be overwhelmed by the sheer number of AEFIs reported over the next year as rollout continues. The 2009 H1N1 swine flu influenza pandemic and vaccination roll out taught us that few countries' pandemic preparedness

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plans adequately addressed vaccine safety monitoring [7]. Pharmacovigilance platforms were unable to confirm or exclude associations between AEFIs and the H1N1 vaccine and this contributed to eroding vaccine confidence. Thus, global coordination with scientists, medical and public health professionals, and pharmaceutical/manufacturing companies, along with increased capacity to analyze and report real-time events are of paramount importance to ensure robust pharmacovigilance of COVID-19 vaccines [8].

By definition, very rare AEFIs (< 1/10.000) are usually not detected prior to licensure but rather once vaccines are widely used within a countries' immunization programs. In the setting of global COVID-19 vaccine introduction, extremely rare AEFIs such as thrombocytopaenia, disseminated intravascular coagulation, or cerebral venous sinus thrombosis were identified and reported in some countries through their robust pharmacovigilance systems, confirming that these systems work as expected. Based on these systems, regulatory bodies and advisory committees evaluate the data and risk-benefit to make determinations of any changes in use. This can lead to temporary pauses in vaccination for further evaluation, and/or to a recommendation to add potential rare adverse events to the product information.

Given the extensive global media coverage, accurate and widespread communication is critical to convey complex messages relating to signal evaluation, causation and risk-benefit at a time when news is increasingly consumed through the filters of social media and internet search algorithms. Thus, robust and transparent pharmacovigilance programs must be coupled with sophisticated communication strategies and international efforts to combat vaccine misinformation which can erode trust, create social discord and promote one vaccine over others for financial or political interests [9].

In addition to the standard vaccine safety surveillance issues, COVID-19 vaccines pose additional challenges to post-licensure surveillance, complicating the risk-benefit assessment of safety signals. These include multiple authorized or approved vaccine types, potential interchangeability of vaccine types, dose interval flexibility and, high comorbidities in the target population. Additional concerns may emerge as the Covid19 vaccines are rolled out in low- and middle-income countries (LMIC) where a high prevalence of malnutrition and infectious diseases may impact the type of AEFIs and immune responses observed in the context of less robust pharmacovigilance programs. The Brighton Collaboration (https://brightoncollaboration.us) global research safety vaccine network) has harmonized global safety assessment tools and definitions for COVID-19 vaccines which are regularly updated.

Challenges still lie ahead to ensure alignment, transparency and interconnectivity across different systems and rapid feedback from national to global level. This should involve broad stakeholders at global as well as regional level. For example, the African Vaccine Regulatory Forum [10] pools regional resources, and such efforts may increase resilience in areas of the world with less robust pharmacovigilance systems.

The longer SARS-CoV-2 transmission is sustained, the higher the probability that new variants emerge; potentially less sensitive to existing vaccine protection. The global community thus finds itself fully engaged in a race to reduce deaths and relieve pressure on health systems but also to prevent community transmission and emergence of new variants. It is still unclear how countries around the world will collect, analyze and share real-world safety and effectiveness data for subsequent decision-making. It should be stressed to stakeholders, including governments, ministries of health and international funders that investment in halting the COVID-19 pandemic does not stop at mass immunization. The timely generation and dissemination of post-vaccination safety data will inform data-driven policies, promote vaccine confidence, and accelerate establishment of herd immunity necessary to end the COVID-19 pandemic.

Declaration of Competing Interest

MEB and PH are developers of a COVID-19 vaccine construct, which was licensed by Baylor College of Medicine to Biological E Ltd., a commercial vaccine manufacturer for scale up, production, testing and licensure. MG participates in one of eight SARS-CoV-2 vaccine development projects supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) since March 2020. SG is cofounder of Vaccitech and has a patent on ChAdOx1 nCoV-19 licensed to AstraZeneca. MH is Founder and Managing Director of SaudiVax. JPF and GK are members of the WHO SAGE Working Group on COVID-19 vaccines. GK is independent director of Hilleman Laboratories Private Limited and Vice Chair of the Board, Coalition of Epidemic Preparedness Innovations (CEPI). DK reports grants from Bill and Melinda Gates Foundation (BMGF) and grants from CEPI. JK reports personal fees from SK biosciences. HL reports grants and honoraria from GlaxoSmithKline for training talks and from Merck as a member of the Merck Vaccine Confidence Advisory Board, outside the submitted work. TS reports grants from National Institute of Allergy and Infectious Disease and Fast Grants and research contracts from GlaxoSmithKline, and ViiV Healthcare. SS reports grants from Ansun BioPharma, Astellas Pharma, Cidara Therapeutics, F2G, Merck, T2 Biosystems, Shire Pharmaceuticals, Shionogi, and Gilead Sciences, outside the submitted work; and personal fees from Amplyx Pharmaceuticals, Acidophil, Janssen Pharmaceuticals, Reviral, Intermountain Healthcare, Karyopharm Therapeutics, Immunome, and Celltrion, outside the submitted work. All other authors declare no conflict of interests. The authors views and opinions in the Commentary do not necessarily represent the views, decisions, or policies of the institutions, universities, or health systems with which they are affiliated.

Author contributions

DN wrote the first draft of the manuscript. PH, MEB, and BL managed the process of review. All authors contributed equally and provided critical feedback, reference sources, and critical revisions for intellectual content and verified the information presented here.

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