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Commentary

COVID-19 vaccine safety monitoring in low and middle income countries – Time for a bold new approach

Walter Straus [a], Harvey Rubin [b],*

[a] Moderna, Inc., Cambridge, MA 02139, United States
[b] University of Pennsylvania, School of Medicine, Philadelphia PA 19104, United States

In response to the greatest pandemic in a century, vaccines targeting the SARS-CoV-2 virus were developed at unprecedented speed. As of June 24, a total of 16 different vaccines were approved for full use or authorized for limited use, including three in the US under Emergency Use Authorization (EUA). No fewer than 94 vaccine candidates were in clinical development [1].

The vaccines approved in the US under EUA each had phase III trial data with sample sizes greater than 30,000 subjects which are considered sufficient to identify common adverse events [2,3,4]. However, pharmacovigilance is the process whereby adverse events that occur at low frequency are identified and assessed.. Pharmacovigilance is an essential responsibility of national regulatory authorities that license medicinal products in their countries and of manufacturers that hold licenses for those products. A functioning pharmacovigilance system can be visualized as a chain of stepwise responsibilities, proceeding cyclically to support product safety: 1) ability to collect, manage, and analyze data; 2) review and assessment; 3) decision-making and action; 4) communication to stakeholders (health care community, consumers, manufacturers; 5) monitoring impact. [5].

In anticipation of the unique demands of introducing novel vaccines in the setting of this pandemic, major regulatory and public health bodies have strengthened and augmented their pharmacovigilance capacity. The CDC created a COVID-19 Vaccine Safety Technical (VaST) subgroup that monitors established vaccine safety surveillance systems along with novel approaches to support vaccine safety reporting in real-time (e.g. V-Safe) and a program to characterize vaccine safety in nursing home populations. In the European Union and in the United Kingdom, existing systems are being supplemented by new mechanisms to assure robust and timely safety assessment of COVID-19 vaccines deployed in the region [6].

The question remains if these programs will be sufficient to inform safety monitoring of the large number of COVID-19 vaccines that will be introduced into low and middle income countries.

Deficiencies in the infrastructure to monitor vaccine safety in many low and middle income countries is a well-recognized challenge [7]. The scarce resources available for public health are generally preferentially allocated for vaccine purchase and delivery rather than for pharmacovigilance. Recently, the WHO has proposed a threshold of at least 10 adverse events following immunization (AEFI) per 100,000 surviving infants as a basic indicator for a functional vaccine pharmacovigilance reporting system. As of 2015, while 60% of countries in the Americas met this threshold, only 27% of countries in South-East Asian and 21% of countries in African regions did, clearly indicating that AEFI reporting needs strengthening and support in these regions [8].

It may be that some investigational COVID-19 vaccines will be primarily introduced into LMICs that do not meet this indicator and where pharmacovigilance systems are rudimentary [9], raising the concern that any emergent safety concerns may not be detected, or detected late. Some COVID-19 vaccines may also be approved and introduced in the absence of late stage data, and lacking large safety databases. This systemic weakness in pharmacovigilance capacity is compounded by a pandemic that is occurring during a period of heightened global public skepticism about the usefulness and safety of vaccines. The WHO has identified vaccine hesitancy as one of 10 global public health threats (2019), threatening to reverse significant progress made in recent decades to control vaccine preventable diseases. Failure to promptly identify, assess, and address an emergent safety issue associated with any vaccine in one country has the potential to sow doubts within that country and internationally.

To date, international focus on COVID-19 control in LMICs has emphasized the development and deployment of low cost COVID-19 vaccines [10]. Through the international COVAX initiative, coordinated by WHO, CEPI, and GAVI, efforts are underway to standardize adverse event reporting, and, to provide countries with tools to conduct pharmacovigilance. Fundamentally, this strategy assumes that pharmacovigilance infrastructure and capacity will be built out during a pandemic, and places the burden on public health systems that are stretched thin. This is a necessary goal, but also an ambitious one.

The COVID-19 pandemic has taught the global public health community that we have the opportunity and the responsibility to respond proactively and vigorously. One strategy to address the urgent need for LMICs to monitor the safety of COVID-19 vaccines introduced during the pandemic might be based upon a recent innovation along with an unusual public health partner.

* Corresponding author.
  E-mail address: rubinh@upenn.edu (H. Rubin).

To support rapid assessment of COVID-19 safety in the US, the CDC has developed and implemented V-Safe, a smartphone-based app into which patients voluntarily provide basic information (demographic information, vaccine received) which then automatically sends a daily text (for one week, then less frequently, out to 12 months) to inquire whether they have experienced specific local and systemic adverse events following vaccination. Clinically important events are reported to the CDC. Data are collected by a 3rd party organization with expertise in data management, which aggregates and summarizes the data. This information is then passed through to VAERS, compliant with data privacy requirements. VAERS follows up as appropriate with vaccines for additional information. The CDC analyzes and shares findings with the public health community in a timely manner. Within less than two months following approval (under EUA), V-safe had already recorded at least one health check-in for 2.1 million or the 21.8 million recipients of one of the two vaccines that were available.

We recognize that the V-Safe system was developed by Oracle for CDC where data are collected, managed, analyzed and housed by Oracle. Given current constraints on CDC, large private sector data processing and analytics companies are necessary partners for the efficient operation of V-Safe. We suggest that storage is not prohibitively expensive and even 100 TB or 1petbyte (PB) is manageable and could be a component of a public private partnership. The data analysis costs also relatively minimal because it can be handled by the same machine(s) hosting the storage. What's App or one on the many mobile money platforms (like M−pesa https://www.safaricom.co.ke/personal/m-pesa) are widely used in LMICs with minimal problems. These platforms are more than adequate to carry out both storage and analytics, highlighting the need for the fundamental realization that public private partnerships are the optimal solution to this important problem (see below for the calculation [11]).

We strongly recommend that a program incorporating elements of V-safe be considered by the global health community and national regulatory authorities for development and deployment into LMICs as an adjunct to existing pharmacovigilance infrastructure. Doing so might involve the active participation of cell phone providers in these countries, a proposal that might at first glance seem far-fetched; however, there is precedent. Public Private Partnerships (PPPs) between cell phone carriers and other energy providers such as solar power companies and public health have already been forged to strengthen vaccine delivery capacity in some LMICs. Energize the Chain (EtC), a non-profit organization, forges the formation of public–private partnerships between Ministries of Health, and the private sector to provide reliable access to electric power for vaccine refrigerator operation. Cell phones are nearly ubiquitous in LMICs and the cell tower companies maintain power using the electric grid supplemented by local generators to assure reliable 24x7 connectivity, even in regions considered "off-grid." [12]. The nearly ubiquitous and unique connectivity provided by the mobile phone and cell tower sectors, their capability to support data analytics, and their demonstrated desire to contribute to the health and well-being of the communities they serve in LMICs, provide a natural partner in the effort to implement robust, linguistically and culturally sensitive pharmacovigilance

algorithms. The construction of adverse event reporting by patients, could be modeled after V-Safe, and adapted to local needs and regulations.

This proposal has numerous advantages. It offers the ability to rapidly detect emergent safety issues as vaccines are distributed and administered to large numbers of patients. Compared with the current standard in many countries, it may accrue a much larger number of safety reports, and in a manner that is largely resource sparing for chronically under-equipped pharmacovigilance departments. The technology is easily scalable. Data collected could readily be aggregated and provided to national regulatory authorities to monitor vaccine safety and inform implementation programs, and also with the public (e.g. through additional phone texts). By facilitating the collection of adverse event reports, a V-Safe like approach has the potential to enhance standardized reporting, bypassing inherent limitations in manual data entry, and providing data that can more efficiently be reviewed and assessed. It may also (through the prospective evaluation of reporting frequency over time), contribute to more effective monitoring of regulatory actions made to support product safety. A well-functioning PV system ultimately requires all of its components to function well. Maintaining public trust in COVID-19 vaccines is essential to control of the pandemic.

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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[10] https://www.who.int/initiatives/act-accelerator/covax.
[11] As an example, a single text message that is sent or received on WhatsApp uses about 5 kilobytes of data. A 1-minute audio call will use about 0.1MB of data on average. A 1-minute video call will use about 5MB on average. If 1 billion people get the vaccine -even if 20 percent want to report an adverse event –200 million users. Say the data in the report is 100 kilobytes——that is a total of 20,000,000,000 kilobytes or 20,000 gigabytes. 20GB cost about 10 dollars a month in many mobile networks. For entire operation 10,000 dollars a month or 120,000 USD a year.
[12] https://www.towerxchange.com/the-first-covid-19-vaccines-are-coming-how-can-you-help-overcome-the-cold-storage-challenge/.