COVID-19 VACCINES AND SERIOUS ADVERSE EVENTS FOLLOWING IMMUNIZATION: ACTION NEEDED!

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Vaccines are held to a very high safety standard because of their important role in the control of serious infectious diseases. Canada has a robust vaccine safety system with rigorous testing required in the preclinical and clinical trials followed by careful pre-approval scrutiny of the clinical trials data to determine if the vaccine should be approved and if so for whom, how and when. These pre-approval trials must be large enough to determine efficacy, and to identify common adverse events. If the vaccine is not efficacious, or if there are common serious adverse events attributable to it, then it does not receive approval.

However, these pre-approval trails—usually well less than 100,000 participants—are not large enough to find very rare (<<0.01%) serious adverse events attributable to the vaccine. These very rare events can only be detected post-approval, once millions of people have been immunized. Finding the very rare serious 'adverse events following immunization' (AEFI), and then systematically and carefully determining if there is or is not a causal relationship to the vaccine and/or the program delivery system is an important element in Canada's vaccine safety system. This data is important to our understanding not only of the vaccine, but of the vaccine in different populations and under different real-world conditions, and of the target disease as well. And this data is used to refine vaccine recommendations and further assure ongoing safety of the vaccine and the vaccine program.

Canada's post-approval safety surveillance system is largely structured and undertaken at the provincial level. Unfortunately, there are many ways that data is collected and recorded, and not collected. For children there is a paediatric hospital-based national active surveillance network for detection of vaccine failure, serious AEFIs, and selected infectious diseases that are, or will be, vaccine preventable. Data collection is standardized, the nurses who collect it are well trained, and the assessment of the data is rigorous. In contrast, detection of serious AEFI in adults and in children not admitted to these hospitals is primarily a passive system, which means that healthcare providers are expected to recognize a serious AEFI and then report it. Although every province and territory has legislation (or subordinate regulations) that addresses the identification and reporting of serious AEFIs, there is an absence of a single, agreed-upon definition applicable across the country.

For example, seven jurisdictions (Newfoundland & Labrador, Nova Scotia, Prince Edward Island, New Brunswick, Saskatchewan, Northwest Territories, Yukon) fail to legislatively define an AEFI. Some of these jurisdictions may offer a definition in their provincial Immunization Manual (e.g., Nova Scotia). Two jurisdictions, Québec and Nunavut, provide very broad definitions (i.e., mandating the reporting of all, even minor potential side effects). The remaining jurisdictions (Ontario, Manitoba, Alberta, British Columbia) define reportable AEFIs, but they use differing definitions, and those definitions tend to be stringent and fail to distinguish between non-serious and serious AEFIs. Non-serious AEFIs (e.g., mild injection-site pain, redness, itching, minor headache or low-grade fever, etc.) should not require reporting by busy healthcare professionals. Such common events are already known from the pre-approval clinical trials, and reporting could overburden the system, pulling resources from more consequential activities. Those administering vaccinations should anticipate such mild reactions and prepare patients for their possibility. In contrast, as noted, to ensure the new vaccines are indeed safe,

healthcare workers need to report serious AEFIs (e.g., events that are life-threatening or lead to death, hospitalization, significant disability, or congenital anomaly).

A consequence of this diversity (or paucity) of definitions is that there is no common or shared standard toward which healthcare providers and regulators tasked with clinical surveillance are working. Their responsibility to report AEFIs—a responsibility which falls to different people in different jurisdictions—will result in different phenomena being reported in different jurisdictions; something considered reportable in one province may not qualify in another. This makes it very challenging, to efficiently collect and assess the safety data, or to meaningfully compare jurisdictions, or get a useful snapshot of national conditions. The result is that decisions both about vaccines and about the 'system' are made more complex and difficult.

Given the roll-out of the first COVID-19 vaccines in Canada, this is an area where the law requires immediate reform and harmonization. A useful model is offered by the Council for International Organizations of Medical Sciences and the World Health Organization Working Groups on Vaccine Safety, which define an 'AEFI' as: "Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the [usage] of the vaccine [and] may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease." Importantly, a 'serious AEFI', which is what we would want our front-line healthcare professionals to report, is defined as: "An AEFI which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect".

To accurately and effectively identify and address AEFIs, our vaccine safety system must have (1) a common understanding of what constitutes an AEFI and a serious AEFI, and (2) an active and systematic way to:

a. identify that a medical event has followed temporally from a vaccination;
b. determine the nature and parameters of the medical event;
c. document serious medical events and their sequelae, and the timeframe relative to vaccination;
d. report the event and evidence to a central authority;
e. place the file before an independent body of experts to determine in a consistent and scientifically reliable manner whether:
    i. the vaccine (i.e., an ingredient or element of its manufacture);
    ii. the vaccine program (i.e., the delivery, storage, or administering system);
    iii. an immunization stress response (i.e., an independent physiological response); or
    iv. an unrelated condition that is coincidental (i.e., not related to immunization),
    v. has caused the medical event;
f. report confirmed serious AEFIs attributable to the vaccine or the program to all public health actors across Canada, including to those administering programs, those administering vaccines, those who will see patients with medical indications;
g. report these AEFIs to appropriate bodies globally.

Until Canada has, at base, a common definition of AEFI and serious AEFI, different definitions (and standards) will be applied from jurisdiction to jurisdiction, and Canada's vaccine safety system will not operate optimally. Similarly, Canada needs an active national system for handling serious AEFIs. Legislative movement on this issue will not only facilitate the management and defeat of COVID-19, it will enhance Canada's immunization safety program generally.