

Vaccine safety: looking forward and back

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Vaccines are among the most cost-effective health interventions. Scientifically rigorous monitoring and evaluation of vaccine safety is critical in order to develop and modify recommendations for vaccine use and in maintaining public trust necessary for the use of vaccines.

Even when governments and public health advocates are appropriate in their enthusiasm, vaccines sometimes lack advocates among caregivers or citizens. Outside of pandemics, vaccines do not engender a sense of urgency nor do they offer the satisfaction of seeing a cure. To many patients, the vaccine supporter's focus on diminished future disease probabilities may seem overly abstract.

In its own words, 'The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance'. The need for an international body that is free of commercial interests or local politics and that can bring intelligible expertise to national and local decisions is as important today as it was 20 years ago.

In December 2019, GACVS celebrated 20 years of service to the global health community. On the occasion of this anniversary, the Global Vaccine Safety Summit reviewed vaccine pharmacovigilance through two decades and reflected on the future of vaccine safety in multiple domains: novel vaccine products, methodological enhancements and adapting scientific communication efforts to evolving technologies.

Some vaccine safety issues of the 20th century involved genuine and causal, through rare, severe adverse events, such as vaccine-associated poliomyelitis. More frequently, the concerns that focused public interest were ill founded, with scientific evidence not supporting any harmful role for vaccines. Some fears came from incorrectly assuming that very low concentrations of ingredients such as aluminium adjuvants caused the

toxicity that would be expected at high doses. Other fears arose from misunderstandings of toxicology. For example, many multidose vials of vaccines contained the preservative thimerosal, an ethyl mercury compound that was confused in the public eye with methyl mercury, a known toxic agent. Still other concerns had their origin in outright fraud, such as the assertion that measles, mumps and rubella (MMR) vaccine could cause autism. Finally came the shape-shifting allegations of harm whose specifics evolved with every refutation. Vaccine-induced autoimmunity, immune overload and non-specific effects were examples of pseudomechanisms that cannot be 'disproven' because their assertions are too vague or changeable.

The 21st century vaccines brought new technologies for the prevention of diseases for which there were no prior vaccines. The new technologies raised new safety issues. There was the possibility of harm through mechanisms hitherto unseen. The initial administration of dengue vaccine, for example, appears to have put some previously uninfected persons at risk for a devastating immune reaction following a later encounter with a dengue virus. In another case, at least some preparations of pandemic influenza vaccine caused narcolepsy in teenaged recipients in Nordic countries, possibly through genetic predisposition.

The goals driving vaccine innovation have been as before—broad-based and durable immunity, ease of large-scale manufacture and transport, unthreatening administration techniques and simpler schedules. To these ends, opportunities are appearing with novel viral vectors, genetically attenuated live organisms, nucleic acid vaccines, new adjuvants, new vaccine combinations and novel delivery systems. The introduction of novel vaccines requires that we be alert to the possibility of equally novel adverse effects. Chance as ever will continue to play a sometimes deceptive role: when millions of people are vaccinated,



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'bad things' will happen in vaccinees because of a background rate of such illnesses, even in the absence of vaccination.

Mathematical methods and information technologies have evolved in response to the needs of monitoring vaccine safety while holding in check the deceptions of chance. Self-controlled case methods have proven to be exquisitely sensitive to risks that follow a consistent time course after immunisation. Large electronic health record databases or administrative health databases in developed countries are doubling as a controlled environment for assessing new vaccines and old. These ever-growing resources allow comparison of the incidence of clinical syndromes after vaccination to the incidence in non-vaccinated but otherwise similar populations. Dozens of patient factors that might modulate risk can be identified with such preassembled data. Current new and exciting mathematical territory involves anonymously yoking together diverse administrative and clinical data sources into massive studies that preserve statistical power while guaranteeing local autonomy and patient privacy.

Large population data sources can readily provide estimates of attributable risk and of long-term risk so that the benefits of vaccines can be compared against well-described and possibly population-specific estimates of vaccine risk.

As the Global Vaccine Safety Summit convened, an already emerging pandemic was not on the meeting radar. The idea that less than 1 year later vaccine solutions would already be available for public use would have sounded revolutionary. As this supplement is being published, more than 10 products against SARS-CoV-2 are already commercially available, from four continents. As anticipated during the summit, novel technologies feature prominently among those products. Given the urgency, new products are being rolled out after clinical trials of remarkable speed and size. A few, rare, acute reactions have been characterised but much remains to be learnt about the new vaccines that use nucleic acids, viral

vectors, recombinant proteins and inactivated viruses, all of which were discussed and which appear in the accompanying reports.

The past 20 years have witnessed tremendous progress in our understanding of adverse events following immunisation across every dimension discussed in the five pieces of this supplement. Vaccine safety will herald a new reality and immunisation policies will likely respond faster than ever, in great part on the basis of the post licensure information from the public and private sectors. Collecting this information is already part of the risk management plans that every product sponsor submits for regulatory approval. In an unprecedented fashion, vaccine pharmacovigilance will gain increasing attention in all corners of the world. The articles from this supplement are a demonstration of what can be the starting point for enhancing trust in vaccination programmes: thoughtful persons working assiduously to keep vaccine safety at the forefront.

Collaborators Patrick LF Zuber.

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