Editorial

Vaccidents and adversomics

Perhaps the greatest factor in vaccine “hesitancy” and vaccine refusals relates to fear of vaccine side effects. Such fear extends across the continuum from legitimate questions about possible side effects to fears unanswerable or not resolvable due to either lack of data or innumeracy, and finally to illogical fears sparked by internet sites and anti-vaccine groups. Inherent in such fears, and in public health authorities’ and physician’s responsibility to answer questions and provide information, are the notions of risk and probability. Some vaccine side effects are predictable—i.e. “you will experience mild soreness that spontaneously resolves within 24h at the injection site”. Other side effect risks are currently unknowable and not currently predictable—i.e. the risk of encephalitis after smallpox vaccine.

This latter concept of unpredictable, accidental side effects after receipt of a vaccine – a concept I have labeled “vaccidents” – is worthy of thoughtful reflection, and, I believe, of a new field of study termed “adversomics” [1]. Adversomics refers to the general study of vaccine adverse side effects at the molecular/genetics/proteomics level. In particular it should focus on understanding the pathophysiology, mechanism(s), prediction, and prevention of vaccine-induced side effects. Vaccident refers to the side effect itself, and by its melding with the word accident or accidental, signals that the side effect is both unintentional and inherently a probability determination or relative risk that currently can only be approximated at the population, but not individual level. This concept may prove to be helpful, at least among the vaccine hesitant, as it appeals to the readily accepted notion of probability determination and inherent risk that currently can only be approximated at the population, but not individual level. This concept may prove to be helpful, at least among the vaccine hesitant, as it appeals to the readily accepted notion of probability determination or relative risk that currently can only be approximated at the population, but not individual level. This concept may prove to be helpful, at least among the vaccine hesitant, as it appeals to the readily accepted notion of probability determination or relative risk that currently can only be approximated at the population, but not individual level.

In an analogous manner, most vaccine side effects, though uncommon or rare, still occur with greater frequency than say, airline crashes. Despite the rarity of airline crashes, a sophisticated infrastructure (under the direction of the FAA), specific tools, and predetermined processes support in-depth investigations into such events, with the result that airline safety has continually improved and the risk of an airline crash substantially diminished over time. In turn, this has increased the level of trust and use among the flying public.

Conceptually, a model such as the FAA needs to be fully designed and implemented, and just as robust around vaccine safety. As the tools necessary to understand the cause and prediction of serious vaccidents are likely to be molecular and have genetic predictors, adversomics seems a suitable name for this field of inquiry, and harkens to scientific content areas that support studies of these phenomenon—including the burgeoning fields of immunogenetics and immunogenomics [2].

The FAA safety model has current parallels in vaccine safety. The Centers for Disease Control and Prevention (CDC) has primary responsibility for monitoring the safety of US-licensed vaccines and contributes to developing the evidence base to inform safe vaccination practices. Importantly, CDC has put considerable resources and expertise into the establishment of an Immunization Safety Office (ISO) (http://www.cdc.gov/vaccinesafety/index.html). Assets supporting ISO’s mission include the Vaccine Adverse Events Reporting System (VAERS), the Vaccine Safety Datalink Project (VSD), and the Clinical Immunization Safety Assessment Network (CISA). Additionally, the Vaccine Analytic Unit partnership with the Department of Defense and other partnerships, such as with the Brighton Collaboration involving scientists from over 70 countries who have developed standardized case definitions for vaccine adverse events, measurably contribute to vaccine safety science.

Finally, in the US, vaccine safety is also a part of the mission of other agencies, including the Food and Drug Administration’s Center for Biologics Evaluation and Research (CBER), the Military Vaccine Agency (MILVAX) within the Department of Defense, and of individual vaccine manufacturers who have reporting requirements in regards to notifications about vaccine safety events. But that may be part of the problem, and not the solution. If everyone has part of the responsibility, then no one wholly “owns” it. It may be time to give greater responsibility and oversight to an “FAA-like” entity such as the ISO once vaccines are licensed through the FDA.

Such an infrastructure is important as I believe that the 21st century will lead to identifying genetic characteristics associated with definable risks for specific serious vaccine adverse events. In fact, this idea is among the important vaccine safety goals of the draft National Vaccine Plan that is being developed by the National Vaccine Program Office (NVPO) (http://www.hhs.gov/nvpo/vacc_plan/). Evidence for the recognition of the importance of immunogenetics in vaccine safety is the work that the ISO is doing in finalizing a scientific agenda that includes goals related to understanding the potential genetic basis of vaccine adverse events (http://www.cdc.gov/vaccinesafety/Activities/agenda.html).

In 2008 for example, with support from NVPO, ISO hosted a conference on “Understanding the Genetic Basis of Vaccine Safety”. ISO has also sponsored a variety of studies to assess genetic factors associated with vaccine adverse events, including studies of genetic risk factors for Guillain–Barre Syndrome after vaccination, rheumatoid arthritis in persons receiving hepatitis B vaccine, wheezing and immune response after influenza vaccination in
children, yellow fever vaccine associated viscerotropic syndrome and neurologic disease, and vaccine-associated hypersensitivity reactions. Such work is vitally important as part of the science base giving enhanced confidence in population- and individual-level vaccine recommendations.

Given the large scope of this area of inquiry, it would be helpful for NVPO to include in its agenda the coordination of basic and clinical research with other federal partners (e.g. NIH and FDA) in addition to ISO, as well as to expand collaboration with clinical, laboratory, genetic, and statistical experts to conduct research studies investigating the role of host genetics in vaccine adverse events on a more multinational, global basis. The field of adversomics, like most areas of science, would benefit from a multinational, cross-disciplinary approach where vaccinologists, safety experts, immunologists, bioinformaticists, statisticians, and clinical trial experts have a forum within which to easily collaborate. The need for statistical power in genotype-phenotype and genome-wide association studies demands so. The formation of such a forum can only occur with an understanding of the value to the world’s health in doing so, funding, leadership, and the availability of cutting edge, high throughput technology. The end result will be to not only make vaccines safer at the population and individual levels, but also to generate new insights into immune, hypersensitivity, and adverse responses to vaccines, and finally, to inform new vaccine development. The ingredients necessary to implement this vision, and the technology needed, though still relatively nascent; are available. The ISO, in partnership with the NIH and perhaps FDA could “jump start” such work by developing funding mechanisms and programs directed at adversomics, and begin to engage other countries who have set up ISO-like counterparts.

Consideration also has to be given to the substantial resource requirements needed to gather enough cases of a given serious adverse event in order to have sufficient power to understand immune profile and genetic differences between subjects who experience a vaccident, and those who do not. Individual investigators do not have the leverage nor the resources to do such studies, and over-arching agencies such as NIH, CDC, or NVPO must take the lead in such endeavors. Doing so allows the development of genotype-phenotype databases critical to making rapid progress in the field, and to moving quickly to the point where such events may be predictable and/or inform newer, and even safer vaccine development. Ideally such research will receive funding priority at the NIH, but importantly, must also become a priority in other countries biomedical research agendas. In part this relates to the relative rarity of serious vaccidents, thus requiring huge numbers of individuals to receive a given vaccine in order to identify the “one in a million” who develop a serious or life-threatening complication; and because the genetics of specific populations and ethnicities may mean that genetic prediction of vaccidents will lead to different genetic risk profiles in different races/ethnic populations.

In the near future it is highly likely that whole genome sequencing will become faster and cheaper, such that it is readily available and routinely performed. Genetic prediction is already used to make informed therapeutic decisions regarding cancer treatments, as well as drug treatment for depression, hypertension, and other diseases. As genotype-phenotype and genome-wide association study databases are built to the point of containing large enough numbers to be statistically meaningful, it is clear that important insights will be revealed, likely leading to the concept of personalized vaccinology. Personalized vaccinology will allow us to precisely define the need for a given vaccine, the likelihood of developing a protective immune response, the number of doses needed, the likelihood of a vaccident, and perhaps even what type of vaccine formulation would be necessary for a given individual. This frame shift, from population-level vaccine recommendations to individualized or personalized recommendations, will mark the beginning of a new and exciting second “golden era” of vaccinology [3].

References

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