

Questions and Answers

Enhancing Public Confidence in Vaccines Through Independent Oversight of Post-licensure Vaccine Safety

Why is vaccine safety important?

Vaccines are administered to healthy babies, children and adults with the intent of keeping them healthy. Therefore public expectation of “first, do no harm” is extremely high.

Vaccines are one of the few human-created and directed exposures that are almost universally recommended or mandated by law. So, in addition to idiosyncratic adverse vaccine reactions that are likely to be genetic in origin, production errors could have devastating consequences on vaccine safety. For example, in the early 1960s it was discovered that the widely used early Salk and Sabin polio vaccines were contaminated with simian virus 40.

Although serious adverse events are rare, when they do occur they can detract from the public acceptance of universal vaccination, especially against diseases that are no longer prevalent in the United States. For example, even a single case of encephalitis suspected to have been caused by measles or mumps vaccines can be a significant deterrent for other parents to have their children receive this vaccine. More importantly, many serious illnesses develop with a temporal association with vaccines even though there is no causal association. Having vaccine safety experts investigate such cases and determine the likelihood of causal relationships can help preserve the public's faith in vaccines.

Vaccines have been extremely successful at controlling diseases that used to be among the leading causes of death for children. Paradoxically, because vaccines have made these diseases so rare that some public, political and media attention has shifted from the disease to the vaccine. Changes in public perception have resulted in decreases in immunization coverage and resurgence of disease in many developed countries, including concerns about the whole cell pertussis vaccine in Sweden, Japan and the UK in the 1980s, and currently MMR vaccine in the United Kingdom. In the United States, the rates of parents refusing vaccination for their children by claiming non-medical exemptions to school immunization requirements have been increasing; studies indicate that vaccine safety concerns are among the most important factors contributing to parents refusing vaccination for their children.

Why is independent oversight of the safety of licensed vaccines important?

The public must be confident that vaccines are as safe as possible, that the benefits of vaccines outweigh their risks, and that programs are in place to ensure the safety of vaccines and accurately communicate risks and benefits to the public. The credibility of the U.S. vaccine safety system has recently come into question by members of Congress, consumer groups and

the media. At issue is the fact that the organization responsible for a substantial portion of post-licensure vaccine safety activities, the National Immunization Program (NIP), Centers for Disease Control and Prevention (CDC), is also the organization which is primarily responsible for the control of infectious diseases using vaccines and purchases more than 50% of all pediatric vaccine administered in the U.S. Questions have been raised about the independence of vaccine safety activities at NIP because of these potentially conflicting responsibilities. It is important to strengthen our vaccine safety system now, before some real or perceived crisis results in loss of credibility due to competing priorities or conflicting interests.

Creating a credible and effective vaccine safety system is even more critical as we look into the future. Since few vaccine-preventable diseases are eradicable, most immunizations will continue indefinitely. As the public and providers have less and less personal experience with wild disease, obtaining accurate data on and developing methods to minimize the risks from the vaccines will be essential to maintaining public acceptance of immunizations. As in other aspects of modern life, (e.g., the recent recognition of conflicts between consulting and accounting at Enron and Arthur Anderson) credibility is enhanced by minimizing or eliminating any real or perceived conflicts of interest. The time has come for a larger societal dialogue on this important issue.

What is the difference between vaccine safety risk assessment and vaccine risk management?

Risk assessment is defined (by the National Research Council of the National Academy of Sciences) as "the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations". In the case of vaccines, vaccine safety risk assessment is the use of science to define the health risks associated with vaccination.

Risk management is "the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision. In the case of vaccines, risk management includes the majority of activities conducted by the National Immunization Program, CDC, including purchasing vaccines, supporting local and state vaccine infrastructure, and making recommendations to health care providers and the public regarding which vaccines should be given to whom. Making these vaccine recommendations requires considerations of the burden of disease, the risks (vaccine safety risk assessment) and benefits of vaccines, as well as many political, economic and logistical considerations.

Why wouldn't CDC's credibility with the public extend to vaccine safety investigations?

Generally, CDC is highly credible in the eyes of the public. This reputation is based on years of assessing health risks and providing recommendations on how to reduce or eliminate such risks. CDC's credibility is not only derived from scientific excellence but also from the fact that CDC does not have a vested interest in the economic consequences of its risk assessment activities.

The National Immunization Program (NIP) (and NIP-equivalents worldwide) plays an increasing role in vaccine procurement and ensuring high vaccine coverage in order to prevent disease. In this sense, the NIP is somewhat of an anomaly at the CDC as NIP must consider the viability of the vaccine industry in order to optimize research and development of new vaccines and an adequate supply of currently licensed vaccines. Furthermore, with the addition of the Vaccines for Children (VFC) program in the 1990s NIP benefits directly from the overhead derived in ~ \$1 billion in vaccine purchases annually. Unlike other arenas of CDC investigations, NIP has arguably a real or perceived vested interest in how many vaccines are sold. This in turn may impact the perceived creditability of NIP's vaccine safety studies.

Why is there a need to make a change in the organizational structure for post-licensure vaccine safety assessment? Is the system broken?

The Institute for Vaccine Safety does **NOT** believe that the scientific components of our current system for post-licensure vaccine safety assessment are broken. Parents, politicians, health care providers and the media should be assured that the science underlying the U.S. system for ensuring the optimal safety of vaccines is among the best in the world. In fact, many countries have modeled their vaccine safety systems after the U.S. system. CDC deserves credit for these achievements. Vaccine safety investigations often require complex epidemiological studies. CDC successfully identifies rare risks associated with vaccines by using advanced statistical and epidemiological methods and the development of infrastructure, such as the Vaccine Safety Datalink project, that allows studies to be conducted in a timely manner.

However, several non-scientific aspects of the current U.S. vaccine safety system can be improved. The credibility and effectiveness of study findings would be enhanced by providing independence (and separation) of risk assessment activities from vaccine risk managers, both of which currently take place at NIP. The public must know that vaccine safety concerns are taken seriously and investigated by independent professionals whose primary responsibility is safety, not public image or program goals. Furthermore, adequate funding for vaccine safety research must not rely on a zero sum competition with other NIP funding priorities.

What are the advantages and disadvantages of organizational separation of vaccine safety risk assessment from vaccine risk management?

Organizational separation of risk assessment from risk management is one option for ensuring the independence of vaccine safety investigations. The National Research Council of the National Academy of Sciences states that "the advisability of organizational separation hinges on comparison of its benefits and costs in particular agencies and programs". It is beyond the scope of this review to conduct the in-depth analysis of costs and benefits of organizational separation of vaccine safety activities from vaccine promotional activities.

Some advantages of separating post-licensure vaccine safety assessment from the NIP include:

- Institutional clarity of mission and focus (eliminating confounding objectives);
- Speed, efficiency and timeliness of responses to emerging vaccine safety issues;
- Improving credibility and public confidence in vaccines and the U.S. immunization program.

Some potential disadvantages of separating post-licensure vaccine safety assessment from the NIP include:

- Limiting communication between risk assessors and risk managers;
- Duplication of efforts leading to inefficient use of resources;
- Public misperception that investigating a vaccine safety issue automatically means that the claim is valid.

Also, the ready access to large numbers of personnel trained in epidemiologic investigations is necessary to carry out investigations such as Guillan-Barre syndrome after the swine influenza vaccine and intussusception after rhesus rotavirus vaccine. Thus, a temporary solution to the current problem may be to separate vaccine safety activities from oversight by NIP personnel within CDC.

A more detailed analysis of the benefits and costs of organizational separation of risk assessment from risk management is warranted. An overall cost/benefit analysis will be greatly dependent on the specific administrative and organizational arrangements of an independent vaccine safety group and the success of implementation. Several strategies successfully used by other risk assessment groups may be useful in optimizing benefits and reducing costs.

Why use the National Transportation Safety Board (NTSB) as a model? What are the strengths and weaknesses of using the NTSB as a model for vaccine safety?

The Institute for Vaccine Safety has proposed that the National Transportation Safety Board (NTSB) may be a model for considerations of independent vaccine safety risk assessment. There are many similarities in key stakeholders in both the aviation and vaccine domains:

- Manufacturers: airplanes - Airbus/Boeing; vaccines - Aventis, Merck, GlaxoSmithKline
- Regulators: airline - Federal Aviation Administration (FAA); vaccines - Food and Drug Administration (FDA)
- Promoters: airline - NASA; vaccines - NIP
- Risk assessor: airline - NTSB; vaccines - Vaccine Safety Group at NIP.

In both aviation and vaccine safety, the public must be confident in safety in order to expose themselves to the risks, however small, associated with participation. Often, investigation of risks involves difficult and, at times, incomplete science. The outcomes of vaccine and aviation safety investigations often include substantial legal and monetary implications. Society benefits from airline travel and from vaccine programs, but adverse outcomes disproportionately affect a small number of persons.

We recognize that there are also some fundamental differences between airline safety and vaccine safety. Most notably, NTSB is administratively distinct from the government agency (FAA) that promotes the airline industry while the risk assessors of vaccines are located within the government agency (NIP) that also promotes vaccines. NTSB has the power to convene an investigation team using the “parties” model with the appropriate stakeholders. For vaccine safety investigations, independent review is provided by the Institute of Medicine (IOM) Immunization Safety Review Committee. However, this committee excludes anyone with past experience in immunization or immunization safety. Also, the committee only investigates issues upon request and with funding from CDC. The NTSB has standing “emergency” resources for its investigations, whereas for vaccines, the resources must be raised through regular government funding processes.

Another difference is the focus of the investigation. Whether a crash has occurred is not in dispute with aviation safety; the focus of the investigation is finding the cause of the accident. However, in vaccine safety investigations, the focus is determining whether the adverse event was caused by a vaccine (i.e., is this a true vaccine side effect or just a coincidental event falsely attributed to the vaccine). In time, advances in our scientific understanding will allow vaccine safety investigations to focus on the pathophysiological mechanisms.

Because the NTSB has evolved to meet the specific needs of aviation safety, one cannot expect the NTSB model to be perfect for vaccine safety. Nonetheless, given the similarities in the types of stakeholders in both domains and the great success of the NTSB in ensuring public confidence in aviation safety, the NTSB serves as a useful model in thinking about and planning for vaccine safety activities. The aviation model also has been seen as a model for reducing medical errors and improving patient safety. Other models that could also be considered include food and chemical safety; the U.S. Chemical Safety Board has been modeled after the NTSB, and Europe is currently considering an independent group to ensure food safety. Vaccine safety should build on the lessons learned in other areas of product safety.

Why should CDC and FDA maintain experts in vaccine safety?

NASA, FAA and airlines manufacturers maintain expertise in aviation safety. Likewise, CDC and FDA should maintain experts in vaccine safety as knowledge in these areas is critical to the successful accomplishment of agency goals. The larger issue is whether these agencies should lead post-licensure vaccine safety investigations or if it would be better for an independent group to take the lead in such investigations with the agencies joining as “parties”. CDC has large numbers of trained personnel located throughout the United States who can participate in intensive investigations if the need arises. This expertise must be maintained and used to respond to potential vaccine safety situations. However, there should be independent oversight of the overall investigations.

Would the creation of an independent group to oversee vaccine safety assessment produce duplication of governmental efforts?

An independent group to oversee vaccine safety assessment could create some duplication of governmental efforts. Since the public has supported advancements in aviation safety, it would be useful to determine whether the public and their representatives would also be willing to pay an additional price for an independent vaccine safety assessment group. Furthermore, some duplication of expertise is not always a wasteful strategy as safety systems often use an “onion skin” theory of safety – i.e., safety procedures are layered on top of each other so that, if one procedure were somehow removed or found ineffective, there would be a duplicate safety measure directly below.

However, duplication of effort can be reduced or eliminated by incorporating strategies already used by other safety programs. For example, the NTSB uses the “party system” which is a process whereby key select players who have significant expertise representing different concerns get together to facilitate the investigation. The NTSB leads the investigation but is able to leverage its own resources and utilize information (often proprietary) and expertise of affected

parties. For example, the NTSB may require an engine to be dismantled but, rather than building and maintaining the facilities to do so, they use the party system where a manufacturer completes the engine dismantling and an NTSB investigator oversees the process to ensure that it is done properly. Likewise, an independent vaccine safety group could reduce duplication of efforts by utilizing expertise from other organizations. For example, CDC could provide epidemiological expertise and personnel for vaccine safety investigations.

Are there examples from other public health, medical and governmental programs where safety assessment has been separated from programs that promote industry?

There are many examples of government programs that have separated safety assessment from programs that promote industry. The NTSB is one such example, as is the Chemical Safety Board (modeled after the NTSB). The Chemical Safety Board investigates chemical incidents and hazards, determines root causes, and issues safety recommendations.

The importance of separating risk assessment from risk management was illustrated in Europe after the loss of public confidence in food safety because of bovine spongiform encephalopathy. A white paper issued by the European Department of Agriculture, Fisheries and Food in 2000 recognized the need to reestablish public confidence in food safety and recommended a separation of risk assessment from risk management. The European Union is establishing a food safety group to implement this policy.

Unfortunately, separation of risk assessment from risk management often occurs after a tragic mistake when retrospective review points out conflicts of interest. It is our hope that proper independence of vaccine safety can be done proactively, before a specific incident causes a loss of public confidence.

How would an independent National Vaccine Safety Board ensure that the vaccine safety assessments utilize the best science?

A National Vaccine Safety Board would be comprised of experts in immunology, vaccines, epidemiology, biostatistics, internal medicine, pediatrics, infectious diseases, toxicology, risk assessment, risk communication, and policy. Additionally, a party system could be used to bring in experts from government agencies, academia and industry. Resources would be required to adequately fund a National Vaccine Safety Board which would need to be flexible to address emerging issues.

Are there examples of how the "Party" system has been used in vaccine safety investigations?

Yes, CDC currently has a Yellow Fever Vaccine Workgroup that was formed in 2001 after discovery of previously unidentified serious reactions to yellow fever vaccine. The Workgroup has all the same stakeholders as a "Party" system in aviation: NIP's Immunization Safety Branch as the safety experts, CDC's Division of Global Migration and Quarantine (DQ) as the risk manager for travelers, FDA as the regulator, yellow fever vaccine manufacturers, academic and clinical researchers in both vaccine safety and travel medicine, the World Health Organization, and representatives in Brazil, where they have seen similar yellow fever vaccine complications. The Workgroup has worked well together and advanced our scientific understanding of yellow fever vaccine reactions.

Another example is The Brighton Collaboration, created to globally standardize accepted case definitions for adverse events following immunizations (www.brightoncollaboration.org). Stake holders from government agencies (CDC, FDA), industry and academia have worked together to produce much needed case definitions so that vaccine safety researchers worldwide have a common vocabulary.

Would the creation of an independent group to assess vaccine safety post-licensure, such as a National Vaccine Safety Board, resolve the problem of vocal opposition to vaccines?

There will always be some people who will never be convinced that vaccines are safe. However, many persons who are labeled as "anti-vaccine" are expressing concerns that they or their family members had after experiencing an adverse event following immunization. Most such persons deny that they are "anti-vaccine" but note that they are advocating for a safer vaccine (as well as compensation for their added medical expenses). Given the imperfect state of current vaccine safety science, undoubtedly some controversial vaccine safety issues will remain even with the establishment of a National Vaccine Safety Board. Nevertheless, for the vast majority of the public, a National Vaccine Safety Board that was properly constituted with adequate independence, objectivity, and transparency would improve the trust in immunization programs as has occurred with the implementation of the NTSB.

A National Vaccine Safety Board would not eliminate vaccine safety controversies or antivaccine activities. Proactive improvements in our vaccine safety system will not convince those who are absolutely and unequivocally opposed to vaccination. A National Vaccine Safety Board would, however, fulfill the majority of the public's expectation of an organization that conducts independent, objective, transparent and credible vaccine safety investigations. This in turn would reduce the potency of anti-vaccine arguments and improve the public's confidence in vaccines.

What is the difference between the Institute of Medicine (IOM) Immunization Safety Review (ISR) Committee and the proposed National Vaccine Safety Board?

There are several major differences between the IOM ISR Committee and the proposed National Vaccine Safety Board. The first is how perceived conflicts of interest are dealt with. The IOM ISR Committee excludes anyone with prior experience in immunization or immunization safety from serving on the committee. Experts are also excluded if they have received immunization funding from government sources or industry or if they have served on government advisory committees. This exclusion of expertise is problematic. The National Vaccine Safety Board would create independence administratively, representing the best of both separation and integration with its "Party" model. The IOM ISR Committee also can only review studies conducted by others, as they do not have the resources or charge to conduct their own studies. In contrast, the National Vaccine Safety Board would "get its hands dirty" by conducting actual vaccine safety investigations.

How would an NVSB be funded?

There are many possible funding sources for a National Vaccine Safety Board. One potential source is the surcharge already levied on vaccines through Public Health Law 99-660 that created the Vaccine Injury Compensation Program. Each vaccine antigen is currently taxed \$0.75, so a combined MMR vaccine is charged a \$2.25 surcharge. These funds go directly into the Vaccine Injury Compensation Program. To date, these funds have been used exclusively for vaccine injury compensation. Currently, the trust fund has a nearly \$2 billion surplus. This represents roughly \$100 million per year in surcharges greater than compensation claims paid (the program has been in existence for less than 20 years). This surplus of \$100 million per year could be redirected to vaccine safety activities, such as funding a National Vaccine Safety Board, while maintaining the \$2 billion surplus in the program to ensure long-term financial integrity. This would be a budget neutral funding proposal and is clearly within the intent of the legislation that created the Vaccine Injury Compensation Program.

Would the creation of an NVSB tell the public that vaccines are not safe? Would any adverse medical health outcome investigated by the NVSB be assumed by the public to be caused by a vaccine?

Creation of a National Vaccine Safety Board would send a clear message to the media, health care providers and the public that the federal government takes vaccine safety very seriously. Efforts would be required to accurately and effectively convey the proactive nature of the National Vaccine

Safety Board to the public. Experience with other programs, such as the NTSB, has not suggested that public perception assumes a lack of safety based upon existence of an independent group to investigate safety issues. A National Vaccine Safety Board would have been useful for promptly addressing several recent vaccine safety issues including concerns about associations between *Haemophilus influenzae* type b vaccines and diabetes; measles-mumps-rubella vaccine and autism; and hepatitis B vaccine and multiple sclerosis. If an independent panel such as a National Vaccine Safety Board had been available to point out the relatively low value of anecdotal reports and ecological data, these issues might not have created as much controversy as has taken place.

How would a National Vaccine Safety Board benefit CDC, FDA, the Vaccine Injury Compensation Program, vaccine companies, the public?

An NVSB would benefit governmental vaccine programs at the CDC, FDA and the Vaccine Injury Compensation Program by improving the abilities of these agencies to focus on primary missions rather than being distracted with reoccurring vaccine safety issues. These agencies, along with vaccine companies and the public, would benefit from a National Vaccine Safety Board as it would improve public confidence in the safety of vaccines.