Uncertain Benefit: The Public Policy of Approving Smallpox Vaccine Research

Without an accurate assessment of the prospect of bioterrorist attack, it is especially challenging to evaluate the protocols for testing smallpox vaccines in the pediatric population. Usual regulatory mechanisms cannot shepherd research protocols with benefits that can only be characterized as "uncertain" in the face of more than minimal risk.

When a protocol is placed in a government forum for analysis, the public has a unique opportunity to debate the balancing of research risks and benefits on behalf of children who are unable to assent to research themselves, as well as to express views about vaccination policy broadly. This model for review of pediatric research that may be without benefit will be especially important as challenging studies of various vaccines against a range of infectious properties, such as anthrax and severe acute respiratory syndrome (SARS), emerge. (*Am J Public Health.* 2004;94: 943–947)

Rosemary B Quigley, JD, MPH

THE PROSPECT OF bioterrorist attack has spurred a range of public policy debates about the need for vaccinating various segments of the US population against smallpox.[1] Whatever strategy is pursued—ring vaccination of those in direct contact with diagnosed smallpox patients in the event of an attack, preparatory vaccination of first responders, or voluntary population vaccination—urgency attaches to our understanding of how renewed administration of the vaccine will impact public health. In particular, is the risk involved with the administration of the smallpox vaccine outweighed by the benefit to be derived from inoculation against smallpox? A major factor in the cessation of population vaccination programs in the early 1970s was that the risk of smallpox exposure did not outweigh the side effects of the vaccine.[2] The critical issue in this respect is how real the risk of smallpox attack is in the first place. Based on intelligence that is publicly available, the potential for a smallpox incident is perhaps slightly greater than hypothetical, especially given recent revelations about unanticipated possessors of the smallpox virus.[3]

A fast-tracked protocol to evaluate the safety and effectiveness of the standard and diluted doses of the Dryvax smallpox vaccine in children aged 2 to 5 years, which was recently reviewed at the Department of Health and Human Services and the Food and Drug Administration, provided a valuable case study of this balance.[4] Given benefit that can only be characterized as "uncertain" in the face of more than minimal risk, it becomes impossible to pursue clinical research on the vaccine in children under usual regulatory mechanisms, via institution-based review. The protocol must be considered by a federal panel offering ethical analysis of the planned protocol with opportunity for public input. The ultimate decision about proceeding with this research was the domain of the secretary of the Department of Health and Human Services and the commissioner of the Food and Drug Administration. This mechanism removes the smallpox vaccine protocol from the institutional mores governing the protection of research subjects and places it in a unique forum of public policymaking.

VACCINE RISKS AND REGULATORY REVIEW

Risks

The proposed protocol involves use of the Dryvax vaccine, the same agent that was administered in population vaccination programs before 1972. Although there is a new, sterile smallpox vaccine in development, in the short-term the stockpile of Dryvax will be our only primary preventive intervention in the event of a smallpox attack. Then Dryvax will likely be administered, possibly in diluted form to maximize the number of doses while not sacrificing the successful "take" rate of the vaccine. Administration of the vaccine within 3 days of exposure is known to reduce the ultimate appearance of a smallpox case, with each case bearing an estimated 30% mortality rate.[5]

Data from the earlier smallpox vaccination of the general population suggest that Dryvax was relatively safe, with low rates of serious complications. Nevertheless, the cohort of potentially serious adverse events is daunting, including progressive vaccinia (3.2 cases/million vaccinated), generalized vaccinia (233.4/million), encephalitis (9.5/million), and eczema vaccinatum (44.2/million).[6] The risk of death from vaccination, generally resulting from 1 of the aforementioned complications, is extremely low, less than 1 death in 1 million recipients older than 1 year and 5 deaths in 1 million in recipients younger than 1 year.[7] The smallpox vaccine also poses some risk of third-party inoculation, as vaccinia can shed from the vaccination site and infect others. The possible rate of cross-infection with vaccinia is unknown, but the 1968 state surveys pegged the rate at 44.6 cases per million in a society already being systematically vaccinated. This impact may well be intensified if vaccination is resumed given the large number of naïve (previously uninoculated) individuals in the current population.

The susceptibility to having an adverse reaction after either primary or secondary exposure has presumably increased since mass vaccination was stopped because the rate of risk factors in the population has increased markedly.[8] Previous atopic dermatitis rates of

3% to 6% have increased to 6% to 22%. Also, there are more immunocompromised individuals because of the numbers of people who have HIV infection or are receiving immunosuppressive drugs for transplantation or cancer treatment, putting increasing numbers at serious risk.

The risks of the vaccine in individuals not previously inoculated have been described in recently conducted adult trials of the Dryvax vaccine at various dilutions.[9] Across dilutions, a significant percentage of individuals in these trials experienced adverse events that were not serious but were quite debilitating for short periods of time. Almost 9% experienced fever. Headaches were common and in some cases severe. Participants reported moderate to severe muscle aches (20.6%) and chills (6.5%); 14.3% developed rashes at a site other than the vaccination site. More than one third were sufficiently ill to miss school, work, or recreational activities or to have trouble sleeping. This study raises concern about the potentially high rate of adverse events in the pediatric population.

The Bush administration had been pursuing the first phase of a national program to voluntarily vaccinate some 500 000 first responders who would be protected and able to provide care in the event of a smallpox attack, primarily civilian medical professionals.[10] Many health care workers declined vaccination, in some cases because of concern about cross-inoculating other, susceptible individuals with whom they have daily professional contact, for instance immunocompromised pediatric patients or cancer patients.[11] The voluntary program was recently halted, but not before important new risks associated with the vaccine were revealed, particularly heart inflammation in those with underlying cardiac disease.[12] Between January 24 and May 16, 2003, 37 608 civilian emergency health workers were inoculated; 108 serious adverse events were reported, including a handful of deaths, with 46 of these established as associated with the smallpox vaccine, and 539 other, nonserious adverse events were also reported.[13]

Review

Because the regulatory framework governing research in children involves vigorous requirements protecting children from unreasonable risks when there is no prospect of benefit, it is sometimes a particular challenge to conduct research in this population. Clinical research in children can be conducted under 1 of 4 guidelines in the federal rules for protection of human subjects in research: 45 Code of Federal Regulations (CFR) §46.404, §46.405, §46.406, and §46.407. Under §46.404, research may be approved if it offers no more than minimal risk. Approval under §46.405 applies when research involves greater than minimal risk but presents the prospect of direct benefit to the participant, thus justifying the risk. Under §46.406, research involving a minor increase over minimal risk and offering no prospect of direct benefit, but likely to yield generalizable knowledge about the participant's disorder or condition, is permissible. The vast majority of pediatric research is approvable by institutional review boards under 1 of these 3 regulatory categories. If a protocol does not clearly meet these criteria balancing risk and benefit, a protocol involving pediatric participants may still be approved pursuant to §46.407 if it "presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children." If it is at all approvable, the smallpox vaccine trial in a pediatric population must qualify under 1 of the previously mentioned subsections of the federal regulations.

BALANCING RISKS WITH UNCERTAIN BENEFIT

The institutional review boards reviewing the federally sponsored trial of smallpox vaccine in children differed on what interpretation of the protocol qualified it for approval under the federal rules. Institutional review boards at Kaiser Permanente and Cincinnati Children's Hospital concluded that the protocol offered the prospect of direct benefit to the pediatric participants.[14] The institutional review boards at Harbor-UCLA Medical Center did not find the research readily approvable, questioning the prospect of direct benefit and referred the protocol to the Department of Health and Human Services' Office of Human Research Protections so that an expert panel could be constituted and public input solicited.

Regarding risk, the protocol certainly involved the potential for complications more serious "than those ordinarily encountered [by children] in daily life."[15] This conclusion must be reached not for the low risk of dire outcomes resulting in disability or death, as the risks of these fates might be comparable to, say, those of walking to school along a commuter road. Rather, the potentially high risk of short-term symptoms of variable severity, with some requiring medical treatment, may make the protocol appreciably riskier than what a child would normally encounter. Although pediatric patients can generally be screened effectively for most factors indicating heightened risk after the age of 2 years, the possible range and severity of potential complications from the smallpox vaccine makes its administration more than minimally risky. The protocol also has the unique character of posing a risk to third parties. Even within this well-controlled trial, potential transmission of vaccinia, along with the increased susceptibility of the population, sets this protocol apart and contributes to an assessment of more than minimal risk. Still, these risks were once acceptably assumed in promotion of health, are well understood, and may be minimized by thorough screening.

As to benefit, prospects for reaping the smallpox vaccine's protective effect may have been overstated, a threat to credibility that a trial involving risk to children cannot absorb. At best, the protocol is of unknown benefit to these child participants. In the absence of more precise predictive information from the government, the risk of a smallpox attack in this country seems unlikely, though possible. The slim chance that the children in this protocol will be in close proximity to the occurrence of a smallpox case makes the prospect of direct benefit through preemptive vaccination even more remote. Given this uncertainty, the protocol cannot now be construed as having benefits that outweigh some likely harms, making it unapprovable under the usual institution-based regulatory guidelines. However, the protocol is ripe for review by the §46.407 panel to assess the research's broad-based value and the ethical conduct of the particular trial.

ETHICAL ANALYSIS OF RESEARCH IN CHILDREN

In considering the ethics of pediatric research, the federal Advisory Committee on Human Radiation

Experiments observed, "If human research never proceeded in the face of uncertainty, there would be no such experiments. How little uncertainty is acceptable in research involving children is a question that remains unresolved."[16] The committee was generally engaged with questions of uncertainty in assessment of radiation research risks; the smallpox vaccine trial raises the flip side issue of uncertain research benefits. Some ethicists considering the question of enrolling children in research have suggested that benefit to society cannot morally outweigh exposing children to more than minimal risk without prospect of direct therapeutic benefit, as children should not be used as a means to an end even with parental permission.[17,18] Furthermore, a state court has recently ruled, "We do not feel that it serves proper public policy concerns to permit children to be placed in situations of potential harm, during nontherapeutic procedures, even if parents, or other surrogates, consent."[19(p850)] Such positions become more entrenched in trials in which there is no potential for pediatric asset and parents must act as the child's consenting authority, despite having quite distinct interests from those of their child. In particular, parents may be excessively concerned about their child's security in the event of a bioterrorist attack, thus making it difficult for them to weigh true prospects of benefit. Misconceptions in calibration of risks and benefits are unfortunately common among trial participants in modern clinical research. Finally, in the case of smallpox vaccine it is tempting to suggest that it is unreasonable to object to a risk we imposed on children routinely only 30 years ago. However, there are many risks that we would not acceptably bear now that we did then, such as allowing our children to ride in cars without car seats and seatbelts. As risks and technology change, so must our assessments of what is acceptable.

This leads back to the unusual exception in the federal rules under §46.407, making possible research that offers quite small and unpredictable prospect of direct benefit but also imposes considerable risk of at least mild to moderate physical harms. This guideline allows the panel to recommend approval of the research because it "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children."[20] The smallpox vaccine protocol is the very sort of research this subsection of the rules seems designed to allow. If a bioterrorist attack occurred today, the information derived from a protocol particular to the safety and effectiveness of inoculating children with diluted vaccine might be essential, whether for incidental ring vaccination or the inception of a mass vaccination program. The protocol would also answer questions about administration methods (e.g., the number of needle pricks for the vaccine to be effective) and efficacy of site dressing in preventing shedding and third-party inoculation with vaccinia. The knowledge would also be reassuring because it is generally unreliable to extrapolate from adult studies where issues of immunogenicity are concerned. Given the urgent popular interest,[21] the smallpox vaccine is an active concern in care of children, and it is essential to have answers about the impact of the currently available vaccine in today's population as a means of preparatory public health. This reasoning recently motivated the American Academy of Pediatrics to endorse this vaccine research at this time.[22] Hesitation in describing trial enrollment as beneficial makes it seem that the 40 children to be enrolled are being placed in service to others. However, the participants are contributing to a standard of care and public health preparedness in the face of modern risks that serves the entire pediatric population, including the trial participants themselves, in the event of a smallpox attack. Otherwise, as commentators noted, "Are we really willing to potentially allow greater than 70 million children to be part of an emergency experiment because we did not do the necessary studies to prove that these smallpox vaccines are safe and effective in children?"[23(p1432)]

OTHER ETHICAL ISSUES WITH THE PROTOCOL

Approval under the last subsection of the federal rules requires an assessment by the panel that the research will be "conducted in accordance with sound ethical principles."[24] The federal rules do not provide guidance about what these principles entail, but presumably they refer to mechanisms ensuring informed consent and fairness. At least 2 aspects of the proposed pediatric smallpox vaccine trial raised questions about whether the protocol fulfilled this ethical requirement.

As the protocol reads at present, the parents of the potential research participant are to be extensively screened for the child's and the family's ability to participate in the trial. However, the parents were asked to sign the informed consent allowing their child to be admitted to the trial before the investigators' review of the child's medical record and the results of blood tests for conditions including HIV status and processing of the child through the inclusion and exclusion criteria. Although an initial consent may be obtained for permission to have their child screened and the child's medical record reviewed, the informed consent for administration of the vaccine should be obtained only after these preliminary steps are complete. Potential research participants often gain understanding of the trial as they are checked against the clinical eligibility criteria, as well as by the experience of any initial tests such as blood draws. This process can enhance the all-important appreciation of the risks and burdens of the trial. If the parents have already signed the consent form for enrollment and receipt of the vaccine, it becomes much more difficult to extricate their child, despite assurances that consent may be withdrawn at any time. Although the introduction of a 2-step consent process would impose an additional task on investigators, the informed consent process would be vitally enhanced in a trial in which publicity might contribute to misapprehension about the incidence of risks and the prospect of benefit.

The protocol also made no provision for the coverage of treatment for adverse events related to receipt of the vaccine. The informed consent document stated: "If your child is injured because of this research, emergency medical care will be available. The care will not necessarily be free of charge" (original emphasis). Although such provisions for coverage are still rare and are not required under the federal regulations, both the Institute of Medicine[25] and the National Bioethics Advisory Commission[26] have recently advocated the development of a system to compensate participants for medical and rehabilitative costs resulting from research-related injuries. In the context of smallpox vaccine re-

search on otherwise healthy and nonassenting children, coverage assurances should be required because of the potential harm to the trial participants without them. There is at least the possibility that parents will be reluctant to seek medical care for moderate to severe symptoms related to vaccine administration if they face the prospect of bearing the costs associated with emergency room treatment or hospital admission. It is certainly unlikely that any private insurer would cover such research-related costs. Expense should simply not be a factor when any delay in treating an adverse event resulting from vaccination poses the risk of irreparable harm to the child. A mechanism for covering these costs, at least in the critical period, must be established, and third-party reactions to vaccinia exposure should also be covered. And given the real but remote chance of long-term injury, from an encephalitis event, for instance, the possibility of a fund for support of such individuals should at least be explored with the country's existing mechanism for vaccine injury compensation as a model.[27] Without assurances, this protocol and similar trials teeter in an ethically precarious position regarding fiduciary duties to healthy pediatric volunteers.

CONCLUSION

Given the relative rarity of §46.407 panel reviews, it seems that protocols involving more than minimal risk without a sufficient counterbalancing prospect of benefit are also unusual. More likely, institutional review boards have taken advantage of the ill-described terms imbedded in the federal rules, including variable interpretation of "risk" and "benefit."[28,29] Still, it is likely that forthcoming research—for example, trials evaluating vaccines against other infectious biological agents such as anthrax, severe acute respiratory syndrome (SARS), or the Marburg virus—will raise the need for these panel analyses. The area of genetics, especially trials assessing tests for presymptomatic risks or pharmacological targeting, may also raise issues of considerable risks in the face of uncertain benefits. An example is the expert panel constituted in August 2002 to review a protocol identifying precursors to diabetes in Japanese American youngsters.[30]

The process of public input may be influenced by panelists drawn from professional groups inclined to clinical interventions and curious about the answers to scientific conundrums. The public should maintain awareness of such reviews to take advantage of the comment period and offer a voice of skepticism when necessary. In this case, the salient question may be, is this pediatric trial one you will want to have done if a smallpox event occurs? And given such an event, is it unethical not to have done more current research with the standard or diluted vaccine in this population? The public has a unique stake in and perspective on the answer to these questions, making the trial especially appropriate for more open dialogue on research objectives. The health of children and adults alike is implicated by these vaccination policies, as exposure to a vaccinated individual is currently rare and may represent special risks for unvaccinated third parties with dermatologic or immunocompromised conditions.

Although the panel recommenders were unanimous in supporting approval of the pediatric smallpox vaccination protocol, the secretary and commissioner determined that the trial need not be conducted "in the absence of plans to use diluted Dryvax in children," presumably because the stockpile has been reinforced.[31] However, this determination left open the possibility that such study may be required as other synthetic smallpox vaccines come down the pike. Indeed, recent experience with the monkeypox outbreak in the Midwest, where smallpox vaccine was administered prophylactically to those who had come in contact with infected animals,[32] indicates that there may be numerous public health circumstances necessitating our optimal understanding of smallpox administration and dosage.

In closing, it should be emphasized that any results indicating the relative safety of a vaccine dose in a pediatric research population should not necessarily be readily applied to consideration of broader population vaccination schemes. In this smallpox vaccine protocol, the chance of a serious adverse event's occurring was thankfully limited because of what would no doubt have been vigorous screening of potential trial participants and their contacts for pertinent risk factors. It would be virtually impossible to replicate this intensive and controlled circumstance in a nonresearch setting, especially in an emergency. Nevertheless, we can derive security from certain research information about the appropriate response in the event that a smallpox incident necessitates vaccination of pediatric patients. A scientifically verified vaccination protocol will promote clear heads in a crisis and minimize the potential of any cascading tragedy affecting children. ■

About the Author

The author is with the Baylor College of Medicine, Houston, Tex.

Requests for reprints should be sent to Rosemary B. Quigley, One Baylor Plaza, IREL 401, Houston, TX 77030 (e-mail: rquigley@bcm.tmc.edu).

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Enhancing Public Confidence in Vaccines Through Independent Oversight of Postlicensure Vaccine Safety

Daniel A. Salmon, PhD, MPH, Lawrence H. Moulton, PhD, and Neal A. Halsey, MD

The National Immunization Program of the Centers for Disease Control and Prevention is responsible for controlling infectious diseases through vaccination, but the program also plays a key role in postlicensure vaccine safety assessment. The time has come to separate postlicensure vaccine safety assessment from vaccine risk management as recommended by the National Research Council of the National Academy of Sciences.

The National Transportation Safety Board offers a useful model for developing an independent National Vaccine Safety Board that would have the authority to leverage resources and expertise of various government agencies, academia, and industry to oversee postlicensure vaccine safety investigations. Such a board would have been useful in recent vaccine safety concerns, and its independence from government programs would ensure optimal vaccine safety and enhance public confidence in vaccines. (*Am J Public Health.* 2004;94:947–950)

VACCINES SAVE THOUSANDS

of lives every year, but may cause side effects (e.g., mild fever, localized reactions) and rare serious adverse events (e.g., anaphylaxis, vaccine-associated paralytic polio). Vaccines are held to a higher safety standard than other biologics because vaccines are given to healthy persons and are required for school attendance.[1] Most of the safety questions that arise almost every year about licensed vaccines—such as hypotheses about vaccines causing diabetes, multiple sclerosis, and other chronic diseases—prove to have little or no scientific basis. But new adverse events are discovered from postlicensure investigations such as intussusception following rhesus rotavirus vaccine[2] and Guillain–Barré syndrome associated with the 1976 swine influenza vaccine.[3,4] Other concerns may indicate the need for changes in products or policy even when definitive data on causal associations may be absent, for example, removal of thimerosal from vaccines administered to infants and children because of theoretical risks.[5,6] The debate about the reintroduction of smallpox vaccine has heightened public awareness of safety issues because this vaccine causes more serious adverse events than other routinely administered vaccinations.[7,8] The public must know that vaccine safety concerns are taken seriously and investigated by independent professionals whose primary responsibility is safety, not financial gain, public image, or program goals.

RISK ASSESSMENT VS RISK MANAGEMENT

Risk assessment is defined as "the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations" and risk management as "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."[9(p3)] The National Research Council of the National Academy of Sciences recommends that federal agencies "maintain a clear conceptual distinction between assessment of risks and consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessment should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies."[9(p151)] A companion report from the National Resource Council highlights the importance of including interested and affected parties so that risk characterization addresses relevant issues.[10]

The importance of separating risk assessment from risk management was shown in Europe after the loss of public confidence in the safety of the food

supply because of bovine spongiform encephalopathy.[11] 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.[12] The European Union is establishing a food safety group implementing this policy.

Another example of the importance of separating risk assessment from risk management is the recently publicized $1.4 billion settlement of a conflict of interest case reached with a group of Wall Street firms. This investment scandal highlights the hazards of not having independent checks and balances in place between those who advise on the risks/merits of goods and those who may be perceived to benefit from that advice. Although these potential conflicts existed on Wall Street for a long time, it took a major stock market devaluation to bring them into question. Many firms have separated their equity research (risk assessment) and investment banking (risk management) operations in order to rebuild public trust.

Wood et al.[13] have advocated the establishment of an independent, comprehensive, and systematic program of postmarketing drug surveillance. They argue that the Food and Drug Administration (FDA) lacks the resources for adequate postlicensure surveillance and FDA staff members are potentially biased as "their recommendation for approval involves substantial personal identification with that approval, and it is unlikely that those who recommend a drug for approval could later conduct a dispassionate evaluation of possible harm due to that drug."[13(p1853)] To address this unmet need, Wood et al. propose a board, modeled after the National Transportation Safety Board (NTSB), with sufficient funds to mount its own ongoing studies or hold open public hearings resulting in recommendations to the FDA.

ASSESSMENT VS MANAGEMENT IN IMMUNIZATION PROGRAMS

Postlicensure surveillance for serious adverse events will always be needed because the full safety profile of a vaccine can only be determined after the vaccine has been administered to large numbers, often millions, of persons. The need for independence in postlicensure safety monitoring is stronger for vaccines than for drugs because of the large and increasing role that the federal government plays in purchasing vaccines and promoting immunization activities. The primary responsibility of the National Immunization Program is to control infectious diseases through vaccination (risk management). However, the National Immunization Program also plays an important role in postlicensure vaccine safety studies (risk assessment).

The need for separation of risk assessment from risk management in immunization programs was first pointed out after the swine flu immunization program in 1976, when a major effort was launched to vaccinate the US population against an anticipated influenza pandemic that never occurred.[14] Investigations conducted by the Centers for Disease Control and Prevention (CDC) revealed that the vaccine caused Guillain-Barré syndrome, and the program was widely considered a failure because the risk of a pandemic was not reassessed after the initial decision to vaccinate was made.[14,15] The CDC has provided effective epidemiological investigations of many other important vaccine safety issues, including the "Cutter incident" (in which some of the original Salk polio vaccine manufactured by Cutter Laboratories in 1955 was not fully inactivated, resulting in 260 cases of polio)[4] and intussusception associated with rhesus rotavirus vaccine.[16] CDC coadministers the passive Vaccine Adverse Event Reporting System with the FDA and maintains an active surveillance system that has been very valuable in assessing vaccine safety concerns.[17–19] Recently, the CDC funded the Clinical Immunization Safety Assessment network that will provide additional investigations into postlicensure adverse events.[20] However, the success of these activities does not guarantee that the handling of future crises will be viewed positively by the public.

The FDA has statutory responsibility for vaccine safety including licensure of vaccines and oversight of manufacturing, but ensuring public confidence in vaccines is not a primary FDA responsibility. As pointed out by Wood et al.,[13] the FDA may suffer from a lack of independence and lack the resources to fully explore safety issues. Other government agencies (National Institutes of Health, Health Services Resource Administration, Department of Veterans Affairs, Department of Defense) and nongovernmental groups (pharmaceutical companies, disease advocacy organizations) have important roles in vaccine safety, but each of these groups also has primary missions or other goals that may interfere or at times conflict with its vaccine safety activities.

CURRENT VACCINE SAFETY SYSTEM

One attempt to create an independent organization to help coordinate the federal agencies involved in the national vaccine effort is the National Vaccine Program Office (NVPO).[21] The NVPO is charged with achieving the highest level of prevention of human disease through immunization and the highest possible level of prevention of adverse reactions to vaccines. The NVPO director reports to the assistant secretary for health, Department of Health and Human Services. Separation of vaccine risk assessment and risk management will not be achieved by the NVPO. In 1995, Congress removed all funding for NVPO and subsequently NVPO activities from this location have been limited because of a small staff and a very limited budget. Also, the assistant secretary for health no longer has the organizational authority intended in the legislation that created the NVPO. This position has been removed from direct authority over agencies; consequently, the NVPO no longer has any real authority over the CDC or the FDA.

The CDC, FDA, and NVPO have external advisory committees to provide independent advice to these agencies. These committees include individuals who are independent of the government agencies, but the committees are limited in the scope of questions addressed. They have no authority over the agency activities, research, funding, or final decisions. Additionally, some committee members depend on these agencies and

vaccine manufacturers for research funding.

The Institute of Medicine Immunization Safety Review Committee has provided some degree of independent vaccine risk assessment by conducting reviews of specific vaccine safety issues, including possible associations between measles-mumps-rubella vaccine and autism,[22] hepatitis B vaccine and multiple sclerosis,[23] thimerosal and learning disabilities,[24] and multiple immunizations and immune dysfunction.[25] However, the reviews were conducted months or years after the concerns were raised. The committee reviewed only available scientific data, as the committee does not have the authority or resources to conduct its own scientific studies or in-depth investigations.

This committee is insufficient to meet the timely needs of vaccine safety risk assessment and communication to the public at times of uncertainty. The CDC and the National Institutes of Health determine the issues addressed and could theoretically overlook important issues. Although the committee has broad expertise important for studying vaccine safety, it excludes both experts with potential financial, professional, or personal conflicts of interests with vaccine manufacturers and individuals who have served on vaccine advisory committees for the FDA, CDC, or the American Academy of Pediatrics.[26] These exclusions foster impartiality, but the consequent reduction of vaccine expertise is a potential problem.

THE NATIONAL TRANSPORTATION SAFETY BOARD MODEL

Lessons learned from other government experiences suggest the need for an independent system that can conduct timely assessments of vaccine risk.[27] The CDC and state and local health departments' expertise and capacity to mobilize resources in conducting large-scale epidemiological investigations will be needed, but the oversight should be independent of the CDC and the FDA. As there are many similarities between vaccine safety and transportation safety, the NTSB is a useful model for considering the separation of risk assessment and risk management for vaccine safety. The NTSB was established in 1967, charged by Congress to investigate every civil aviation accident in the United States and significant accidents in the other modes of transportation and to issue safety recommendations aimed at preventing future accidents.[28] The NTSB is responsible for maintaining the government's database on civil aviation accidents and also conducts studies of significant transportation issues. The NTSB was initially established as an independent group, although it relied on the Department of Transportation for funding and administrative support. In 1975, the inherent conflict with the Department of Transportation was recognized and the NTSB was established as an independent agency. The NTSB makes recommendations to appropriate parties, including the Federal Aviation Administration. It does not have regulatory authority, but more than 80% of its recommendations are implemented.[29]

To achieve the objective of ensuring optimal safety, the NTSB is given legal authority beyond what is typically given to governmental agencies, including the ability to write subpoenas to obtain data that are needed for effective investigations. The NTSB is thus empowered to bring regulatory and industry entities together through a "party system" to examine safety issues and reduce risk where feasible. The party system is a process whereby key select players with 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. The public perceives the NTSB as highly credible and values air transportation safety. According to a recent RAND report:

> The agency enjoys the reputation of being the most important independent safety investigative authority in the world; the caliber of its investigations has become the international standard. . . . The NTSB's unique role in transportation safety is contingent on the ability of the board members and the professional staff to conduct independent investigations of accidents and major incidents, and in so doing, to assure public confidence in the safety of our national transportation system.[28(pv,1–2)]

NATIONAL VACCINE SAFETY BOARD

There is a need for similar independent reviews and credible public communication to ensure public confidence in vaccine safety through a National Vaccine Safety Board (NVSB). The NVSB mission to monitor postlicensure vaccine safety could be achieved by (1) funding and conducting vaccine safety investigations; (2) bringing together experts from government, industry, and academia to review all available scientific information and determine causal associations between vaccines and adverse events; (3) making recommendations to government and industry to improve vaccine safety; and (4) disseminating safety findings to the public. Achieving these goals would require persons with a broad range of expertise, including immunology, vaccines, epidemiology, biostatistics, internal medicine, pediatrics, infectious diseases, toxicology, risk assessment, risk communication, and policy.

An NVSB 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 an NVSB had been available to point out the relatively low value of anecdotal reports and ecological data, these issues might not have created so much public concern.

An NVSB would require the authority to use a party system and independent funding to conduct and oversee safety investigations. Although an NVSB would not eliminate vaccine safety controversies or antivaccine activities, the NVSB would fulfill the expectation that the public will be informed promptly and objectively when vaccine safety issues arise and as new information becomes available. The development of an NVSB could create a vibrant system for ensuring the safest vaccine system possible and maintaining public confidence in the safety of vaccines. Our system for ensuring optimal vaccine safety and public confidence in vaccines should be strengthened now, before some real or perceived crisis results in loss of credibility due to competing priorities or conflicting interests. ■

About the Authors

The authors are with the Institute for Vaccine Safety, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Md.

Requests for reprints should be sent to Daniel A. Salmon, 615 N Wolfe St, Suite 5034, Baltimore, MD 21205 (e-mail: dsalmon@jhsph.edu).

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Contributors

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