Vaccine Safety: Injecting a Dose of Common Sense

M ortality due to vaccine-preventable diseases is at an all-time low.1 Several diseases, including smallpox, polio, and Haemophilus influenzae type b, have been either eradicated or nearly eradicated in the United States through the almost universal use of effective vaccines. Yet during the last decade, increasing concerns (both real and imagined) regarding vaccine adverse effects and safety have arisen. In turn, this has engendered an increasing number of “antivaccine” groups, further fueling public and media concerns over a gamut of disorders—hair loss and demyelinating syndromes due to hepatitis B vaccine, autism and inflammatory bowel disease due to measles vaccine, Gulf War illness due to anthrax vaccine, mercury exposure due to the use of thimerosal as a vaccine preservative, and intussusception due to rotavirus vaccine. In addition, these protest groups have raised objections over federal mandates regarding vaccination as a condition for elementary and middle school entry. As we stand on the verge of eradicating and controlling multiple vaccine-preventable diseases, this state of affairs has raised alarm among both scientists and public health officials, as individuals and groups increasingly refuse vaccines.

While the pace of public, media, and congressional interest appears to be accelerating, concerns over vaccine safety are not new. There have always been those opposed to the use of vaccines, even in the face of overwhelming evidence of their benefit. Such was the case with the first vaccine used widely, the smallpox vaccine. Vaccine opponents thought such procedures “unnatural” and feared many ills would result from vaccination.2 Had the anti-vaccination forces prevailed, we would not have eradicated smallpox as a major cause of worldwide suffering and death. Instead, despite the fact that the vaccine is an imperfect one with the risk of occasionally fatal eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis,3 an unparalleled and breathtaking medical and scientific victory for the good of all humankind was achieved by eradicating smallpox disease.4 Similarly, because of the universal fear of polio, the introduction of an oral polio vaccine in the late 1950s was greeted with joy and thanksgiving, with the result that polio has been successfully eradicated from the Western Hemisphere, with the reasonable expectation of global eradication in the near future.5,6 Nonetheless, despite these public health triumphs, vaccines can and do occasionally cause harm. For example, the widespread use of the polio vaccine resulted in vaccine-associated paralytic polio in 1 of every 2.4 million vaccine recipients. For this reason, calls for alternate schedules and cessation of the use of this vaccine began in the mid-1980s.7 Indeed, the Advisory Committee on Immunization Practices recently recommended that, by January 2000, US children should routinely receive only inactivated polio vaccine for all childhood doses.8

Vaccines usually result in widespread and dramatic good but also occasional harm. Logically and rationally discerning cause and effect vs speculation or mere temporal associations in regard to vaccine adverse effects allows for wisdom on the part of patient and clinician in deciding whether to receive or promote a given vaccine.9 As an example of discerning cause and effect, fear of Guillain-Barré syndrome (GBS) due to influenza vaccine is still prevalent. The 1976-1977 influenza vaccine was associated with a statistically increased risk of GBS in some, but not all, groups of recipients.10 The biologic mechanism for this association has never been determined. During the 1992-1993 and 1993-1994 flu seasons, an excess risk of GBS of approximately 1 in 1 million doses delivered was found only when both seasons were combined for analysis.11 Whether these statistical associations represent cause and effect remains unclear. Nonetheless, undue fear of such adverse effects prevents some older people who are at high risk of influenza-related hospitalization or death from receiving the vaccine (or some clinicians from recommending vaccination) simply because they fear GBS. Yet, by not accepting the vaccine, such individuals accept risks that are orders of magnitude higher (such as the 20,000 excess deaths or 250,000 excess hospitalizations due to influenza observed nearly every year) than any possible risk from the vaccine. Unfortunately health care workers themselves are not immune to unfounded fears of adverse effects. Despite being at moderate risk for hepatitis B infection and its chronic sequelae, health care workers were among the last to embrace receipt of the plasma-derived vaccine, due to unfounded concerns of possible human immunodeficiency virus contamination.12,13

Finally, concern arose over the temporal association of varicella vaccination and occurrence of a rash in the first 2 weeks after its administration. Had the vaccine caused the very illness it was supposed to prevent? Polymerase chain reaction testing proved these concerns were unfounded by

Address reprint requests and correspondence to Gregory A. Poland, MD, Mayo Vaccine Research Group, Mayo Clinic Rochester, 200 First St SW, Rochester, MN 55905.
demonstrating that most rashes occurring within 2 weeks of varicella vaccination were caused by wild-type, not vaccine-type, virus.14 While the risk of an adverse event increases with the number of vaccines administered, the risk of morbid adverse effects nonetheless remains vanishingly small, and the risk of morbidity or mortality from infection and subsequent disease due to a vaccine-preventable illness remains significant.

It is instructive to consider how we have moved from a society that celebrated the introduction of the polio vaccine to one in which vaccines are viewed with suspicion and increasingly are rejected by patients and clinicians. It is our view that a discussion of how the public views vaccine safety cannot be divorced from the culture in which we live, work, and make decisions. Many would argue that we have become a “zero risk” culture. We behave as though any risk of any harm can be reduced to zero—especially with regard to technologic risk. Our litigious society focuses on the concept that a bad outcome is a wrongful outcome and that someone must be held responsible and pay damages. Appropriately, so as to avoid accusations of malice and lawsuits for recovery of damages, government and industry work to minimize liability by minimizing risk. While this focus and the response it engenders clearly result in some level of public good, they also create a dissonant atmosphere where harm cannot be completely prevented and some risks remain irreducible or uncertain. Yet to do nothing harms the greater public good. In our society, individuals sue for spilled hot coffee and falls on rain-slick pavement. A bad medical outcome engenders plans for a malpractice suit even when no evidence exists for incompetent practice. The bad outcome itself becomes prima facie evidence of incompetence. In part, juries and judges need not ground their decisions in science but can be moved by emotion and public opinion. Further, US consumers can generally afford the manufacturers’ increases in product charges when the costs of product liability insurance and legal expenses are passed on to them. However, in the case of the controversy over whole-cell pertussis vaccine, manufacturers substantially increased the cost of pertussis vaccine in response to an ever-increasing number of lawsuits and financial liability. Due to concerns over liability, several manufacturers simply stopped producing pertussis vaccine, which resulted in a sufficient crisis that the federal government developed a vaccine injury compensation program to protect manufacturers and prevent the loss of the nation’s ability to manufacture and distribute pertussis vaccine.15-17

We propose that a “pyramid effect” is operative in the way decisions are made about vaccine safety and acceptance in our risk-intolerant society. The base of the pyramid can be imagined to resemble the benefit of a widespread public health policy such as the use of a vaccine to prevent a common disease that causes harm. It is broad in its effects. The vaccine benefits the vast majority of the public. The peak of the pyramid represents harm or risk. It is small but sharp. While it may affect very few individuals, its effects are perceived as severe and acute. The majority benefits from the vaccine but feels the benefit only indirectly or perhaps not at all. A minority may actually be harmed or perceive harm, but they perceive it sharply, acutely, and substantially. For this reason, the voices of the shareholders in the public health policy debate over vaccines are unbalanced. The majority who benefit will not champion or defend the program but are likely to be passive participants. The minority who experience or perceive harm may choose to fight against the program that they perceive as causing harm and may become passionate and vociferous opponents. In fact, they may become the only individuals who voice their opinions.

In part, the perception of risk or probability of harm in this pyramid model may arise from another problem, namely, a dilution of benefit. As the use of a safe and efficacious vaccine becomes widespread and gradually diminishes or eliminates the risk of a disease, the public’s perception of the vaccine’s value paradoxically diminishes—because the public no longer observes the disease or its aftermath. The very success of the vaccine causes its benefit to be diluted or less valued once the disease is no longer considered a high-level threat or risk. Vaccines commonly suffer from this dilution of benefit. For example, the measles-mumps-rubella vaccine has been extraordinarily successful in reducing deaths and morbidity such as sterility, encephalitis, and congenital rubella syndrome.1 However, individual parents may fail to see its current relevance for their children in that the parents do not perceive the children to be at risk and are unaware of the disease and its consequences. Naturally then such parents would fail to understand the importance of protection against these diseases. For these parents, the vaccine seems unnecessary at best and an intrusive and dangerous assault on personal liberties at worst. Further, those who claim that the measles vaccine is the agent responsible for inflammatory bowel disease or autism raise unfounded fears in others’ minds and may accuse the physician, medical industry, public health officials, and the government of incompetence and even malevolence. Unfortunately, while the overwhelming majority suffers no harm from the vaccine, they may also perceive no immediate benefit and therefore see no reason to challenge or resist the accusation. The person at the point of the pyramid, acutely harmed and intensely emotional, commands more “voice” with the media and captures the attention of the public (or Congress). The majority at the base of the pyramid, with their real but
diffuse and poorly perceived benefit, remains silent because of little or no emotional investment in the issue. The more effective a vaccine is the more powerful the dilution of benefit appears to be. Everyone gains but no one perceives that benefit.

Chen has proposed a model that attempts to define these stages of an immunization program starting with the introduction of a new vaccine, in which such programs go from the prevaccine stage to the stage of increasing vaccine coverage, loss of confidence in the vaccine (due to real or perceived adverse effects), resumption of vaccine confidence, eradication of disease, and finally cessation of vaccine use.

As a society we select vaccines for which the population benefits outweigh the risks of adverse events and for which there is a substantial burden of disease morbidity and mortality in the population. We must keep in the forefront of any discussion of vaccine safety the understanding of this benefit-risk balance. Vaccines can and do cause harm and may even theoretically carry unknown risks. Vaccines are immunobiologics, and all immunobiologics have been associated with adverse effects, from the frequent occurrence of brief and mild local inflammation following tetanus toxoid injection to the rare occurrence of paralytic polio following administration of the oral polio vaccine. The whole-cell pertussis vaccine may rarely result in hypotonic, hyporesponsive episodes. The hepatitis B vaccine can cause a febrile reaction in a small percentage of newborn infants, which could lead to an unnecessary medical evaluation if not presumptive antibiotic treatment. The rotavirus vaccine appears to increase the risk of intussusception in the weeks that follow the first dose of vaccine in infants. These adverse effects complicate decision making about vaccines at the individual and societal levels, in part because it is impossible to know all the possible risks of a given vaccine until it is used widely in the population.

A current example is that of the rhesus reassortant rotavirus vaccine and the association with intussusception. In modern vaccine development, prelicensure studies identify only frequent adverse events, regardless of whether the adverse events are mild, moderate, or severe. In the case of the prelicensure studies of the rotavirus vaccine, approximately 10,000 children received the vaccine. While 5 children did suffer from intussusception, so did 1 child among the 5000 controls; the rates of intussusception were not statistically different between the 2 groups. This is not surprising, as prelicensure studies are unlikely to identify statistically significant rare adverse events that occur at rates in the range of greater than 1 of 1000 to 10,000. We depend on a system of postlicensure follow-up studies by the manufacturer, large linked databases, and continued monitoring through a governmental passive reporting system (the Vaccine Adverse Events Reporting System) to identify unexpected adverse effects of vaccines. This system in fact allowed public health officials to quickly detect the increase in intussusception cases following rotavirus vaccination and to declare a moratorium on use of the vaccine, followed shortly by the manufacturer’s withdrawal of the vaccine from the market. Antivaccine groups see this episode as evidence that vaccines are unsafe, while scientists and public health officials see this as proof that the detection system for adverse events works. What is unclear to the antivaccine groups is that one can never prove or disprove absolute safety of a vaccine or completely eliminate all uncertainty or risk of an adverse event. We are only able to lower the probability of an adverse event into an interval of extraordinary frequency. This is the nature of scientific proof in clinical trials and of the difficulty in demonstrating cause and effect. In turn, these risk probability concepts and results are extremely difficult to articulate clearly to a risk-averse public.

Despite such irreducible uncertainties, the modern use of vaccines has clearly benefited more than harmed. Over the last century, the human life span has increased 20 to 25 years. It is postulated that this profound change in life span has resulted from 2 major changes: clean water and sanitation and the control of infectious diseases. To the latter, we must give credit to the development and widespread population use of vaccines. As an example, diseases such as measles, mumps, rubella, diphtheria, tetanus, smallpox, and polio have been either reduced from their baseline levels by 98% to 99% in the United States or completely eradicated as in the case with smallpox and polio. Such results are unprecedented in human history and are an outcome of the nearly universal population use of multiple safe and effective vaccines.

Maintaining the current success of disease control by vaccines and extending that success to other potentially vaccine-preventable diseases (such as group B streptococcus, herpes simplex, human papillomavirus, cytomegalovirus, and others) is threatened. This may be due in part to an eroding trust on the public’s part regarding the safety and efficacy of vaccines, an erosion of trust in “experts” and the government, and the (generally) poor attempts on the part of the health community to communicate the risks and benefits of vaccines to the public. Moreover, any discussion of risk suffers from the “hidden” nature of many communicable diseases and their complications. Lay people and even clinicians may not feel the urgency for varicella immunization, for example. Many recall chickenpox as a mild childhood annoyance and have little experience with varicella as a disease with considerable attendant morbidity and mortality. Thus, most do not perceive varicella as a real threat, despite the fact that it is a highly contagious human virus causing 100 deaths per year.
in the United States and resulting in hospitalization of approximately 1 of every 164 persons with varicella.25,26 Contrast this with the incredible demand and uptake of the polio vaccine in the late 1950s and early 1960s, because everyone at that time understood the risks of disease and of not being protected by vaccine. They regularly witnessed the devastation caused by polio on their community, friends, and family. Thus, the perception of both disease and vaccine risk within a culture may heavily influence choices regarding immunization. In addition, others have commented on the growing role of the current antivaccine movement in the United States and Europe and have documented the consequences of such groups’ actions in creating fear of receiving vaccines such as pertussis, the resultant lower immunization coverage rates, and the inevitable reemergence in morbidity and mortality due to those diseases.27

What other factors have contributed to the current antivaccine ethos? In part, the federal government’s response to concerns over vaccine safety and its role in vaccine delivery at the population level may inadvertently stimulate negative responses from the populace. Mandatory federal programs with punitive consequences for failure to comply, as opposed to “promotive” immunization programs, are felt to be an important reason underlying vaccine nonacceptance.28 For example, mandating an increasing number of vaccines that the public has been ill educated to accept or understand breeds concern, suspicion, and, in some cases, resentment. Evidence for this is the number of antivaccine groups that frequently cite this very issue. Additionally, federal attempts to institute childhood immunization registries in each county and each state may further fuel concerns about the role of government in individual health affairs and raise additional privacy concerns. In turn, these factors feed into the cultural milieu in the United States of questioning authority, particularly the right of the government, to “coerce individuals to have themselves or their children vaccinated.”28

In addition, the widespread electronic information network and ease of communication now allow all voices to be heard in the public debate, without regard to the authenticity or agenda of the information presented. Thus, we see the propagation of Web sites with misguided and, in some cases, simply wrong information presented as established scientific fact. Inappropriate actions by opinion leaders also contribute to suspicion regarding vaccines. Recent examples include the widely reported congressional hearings on vaccine safety and actions taken by the French government to suspend temporarily the adolescent hepatitis B immunization program in that country (they have since restored the program).

How then do public health and individual practitioners proceed in such an environment? To protect the public health, vaccinologists, scientists, and public health officials must participate in the current debate over vaccine safety, risks, and benefits and carefully examine the consequences of individual and collective societal decisions about vaccines. They must do this with solid scientific data and with skills in transmitting such information despite irreducible uncertainties. Policymakers and public health officials must develop an explicit framework or “decision map” on which to make rational and explicit decisions about the deployment of vaccines. Doing so facilitates public debate and understanding and provides a basis by which we can defend decisions that occasionally result in unexpected, unacceptable risks and the retreat from a previous recommendation. Public health officials must recognize that such a process may result in the viewpoint that not all vaccines should necessarily be received by everyone, without regard to individual or group risk, simply because such a vaccine exists.

We propose that practical first steps include ensuring that physicians, nurses, and other health care workers are better informed and educated regarding vaccines and risk-benefit issues regarding vaccines. This education process needs to start during professional education and extend throughout continuing education. Ample evidence suggests that frontline providers have inadequate knowledge about vaccines and vaccine administration programs.29,30 In addition, in partnership with federal, state, and public health programs, we must once again create a culture whereby immunization against infectious diseases is seen as the right thing to do and is reestablished as the prevailing cultural norm. Streefland et al28 comment that “the imminent expansion of vaccination schedules with more vaccines and vaccine combinations will only enhance parents’ doubts and trigger discussion. It will stress parents’ perception that, in vaccination practice, ‘experts’ are making fundamental decisions about their children’s health, without consultation or providing the option to exempt.” For this reason, our own view is that the role of the government is to inform, educate, recommend, and even provide incentives for immunization—but not to mandate without exclusion acceptance among the civilian population. Informed refusal must remain an acceptable choice in a free democracy, and the culture of informed consent, with both religious and philosophical exemption, must be maintained. The difficult balancing act will be in determining the right of the state to control an infectious disease and the right of the individual to choose. This might be partly resolved by considering (with informed refusal) universal immunization against those diseases that pose unacceptable risks to others in the community.

In addition, increasing the funds available for vaccine research, including funding for the development of safer and more effective vaccines,31 and establishing large, long-
term postmarketing safety studies are important steps. A major priority should be to set aside research funds dedicated to finding and understanding genetic (and other) factors predictive of severe vaccine adverse events. Finally, government and the health care industry would be wise to fund social research aimed at understanding immunization acceptance behaviors of the public in general and specific ethnic groups with low vaccine uptake in particular.

As a society, it is in our interest to protect ourselves against the morbidity and mortality of diseases we can prevent with vaccines. It is also to our benefit to minimize any harm that may arise from such vaccines. But we must recognize that to maximize widespread benefits, we must be prepared to incur some lesser risks, and in the final analysis, government and public health officials must be prepared to engage in the hard work of forming partnerships with vaccine experts and the public in order to make decisions that are seen as benefiting both the individual and society. Coupled with informed debate, we must use science, technology, and common sense to our maximum advantage, while maintaining rights of freedom of choice, in order to choose wisely among the growing number of vaccines and deploy the optimal set of vaccines for each individual and for society as a whole.

Gregory A. Poland, MD
Mayo Vaccine Research Group, Clinical Pharmacology Unit, and Division of General Internal Medicine
Robert M. Jacobson, MD
Department of Pediatric and Adolescent Medicine and Mayo Vaccine Research Group, Clinical Pharmacology Unit
Mayo Clinic Rochester
Rochester, Minn

REFERENCES