

Vaccines as Tools for Advancing More than Public Health: Perspectives of a Former Director of the National Vaccine Program Office

Robert F. Breiman^a

Programme on Infectious Diseases and Vaccine Sciences, International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B), Centre for Health and Population Research, Dhaka, Bangladesh

With application of new technologies and licensing of new vaccines, vaccines will soon be better by several orders of magnitude. Yet barriers impede the introduction and wide use of new vaccines. Most of the diseases for which we will have vaccines in the future have not evoked enthusiasm from public health professionals, but not consumer demand, despite ongoing high rates of disease and death. Furthermore, the public's attention turns from the now rarely occurring vaccine-preventable diseases to reports of fears and confirmed adverse events associated with the same vaccines that so effectively continue to prevent disease. New vaccines will be held to a much higher standard; thus we will need more capacity for disease studies, vaccine trials, and surveillance systems. Vaccines and immunization programs contribute to the societal fabric and are an expression of social responsibility. Vaccine research and implementation programs must have the foundation and capacity to keep pace with evolving scientific and societal realities so that their broad benefits can be fully realized.

Immunization provides immense public health benefits. It is one of the great achievements of science and public health during the 20th century [1, 2]. Vaccines are responsible for reducing a variety of formerly common and deadly infectious diseases into historical or rare curiosities. Although these accomplishments are important enough, there is another set of considerations, multifaceted, unappreciated, yet valuable, that should be recognized and examined more closely.

We are in the infancy of scientific advances that will allow us to develop new vaccines to prevent diseases never before thought preventable or only recently recognized. Yet there are indications of a growing trend in developed countries to take immunizations for granted; vaccines are poorly understood, underappreciated, and in some cases viewed as health threats

themselves [3]. Public health agencies and organizations must address this trend because societal failure to appreciate the value of vaccines is not without consequence. When we do not fully develop and exploit the opportunities that vaccines can provide, we undermine an array of present and future benefits.

BACKGROUND: WHERE VACCINES HAVE TAKEN US

In 1980, smallpox was declared eradicated as a naturally occurring disease. There is reasonable expectation that paralytic poliomyelitis will become a historical relic within the first few years of the 21st century. Global health experts believe that eradication of measles may also be possible [4]. Whooping cough, diphtheria, and tetanus, devastating throughout history and well into the 20th century, are now only rarely seen (although they would reemerge if immunizations were no longer given) [5].

The most impressive recent success story is that of invasive disease due to *Haemophilus influenzae* type b (Hib). It was the leading cause of childhood meningitis and was associated with high rates of death and sequelae. Before the introduction of vaccines, it was estimated that 445,000 cases of invasive Hib

Received 25 July 2000; revised 11 September 2000; electronically published 15 January 2001.

^a Present affiliation: National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta.

Reprints or correspondence: Dr. Robert F. Breiman, National Center for Infectious Diseases, Mail Stop D-66, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333.

Clinical Infectious Diseases 2001;32:283-8

© 2001 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2001/3202-0016\$03.00

disease occurred annually in children <5 years old worldwide, including >350,000 cases of meningitis that resulted in nearly 115,000 deaths [6]. Every pediatrician in training through the mid-1980s in the United States can recount many tragic tales of perfectly healthy children who were damaged or who quickly died as a result of Hib. Now, most pediatric residents in North America and in many other industrialized settings will not see a case of Hib during their training; 69 cases of invasive Hib disease were identified in the United States during 1998 (Centers for Disease Control and Prevention [CDC], unpublished data). This remarkable result occurred rapidly after the Hib conjugate vaccine was introduced in the late 1980s. It is of note, however, that this benefit has translated to <10% reduction in the global burden of Hib disease, because conjugate vaccines are still not used in most developing countries [6]. An additional benefit would likely be realized in developing countries when Hib vaccine is made available to them: preventing up to 20% of pneumonia cases in children [7].

Vaccines licensed during the last decade offer the possibility of prevention of chronic liver disease, cirrhosis, and hepatic cancer (recombinant hepatitis B vaccine) [8]; of pneumonia, meningitis, bacteremia, and acute otitis media (conjugate pneumococcal vaccine) [9]; and of chicken pox with its attendant discomfort, forced quarantining of children and their families, potential failure secondary bacterial infections (primarily with group A streptococcal bacteremia), and the late, painful sequela of shingles (varicella vaccine) [10, 11].

NEW VACCINES: OPPORTUNITIES FILLED WITH CHALLENGES

Our current array of vaccines is just a shadow of what realistically may become available within the next 10–15 years; their life-saving and disease-preventing potential will be orders of magnitude greater. We will likely have new vaccines to be used for classical purposes—for example, to prevent infectious diseases such as respiratory syncytial virus pneumonia [12, 13], cytomegalovirus-induced neurologic sequelae in newborns [14], herpes simplex genital infections and CNS disease [15], tuberculosis [16], malaria [17], schistosomiasis and a variety of other parasitic diseases [18, 19], hepatitis C [20], and, I hope, HIV infection and AIDS [21]. We may well have vaccines that will be used to prevent diseases that, until recently, would not have been thought to be potentially preventable by vaccination, such as autoimmune disorders, cardiovascular diseases, gastric ulcer and cancer, and a variety of other cancers [22].

In contrast to the introduction during the last century of vaccines against lethal and widely feared diseases, introduction and broad use of new vaccines will face substantial barriers. For instance, it is possible that a recently licensed highly ef-

fective conjugate pneumococcal vaccine will not be widely used in populations that would benefit the most. To take advantage of important new vaccines, several barriers must be confronted. Although cost will be the most obvious and consistent barrier, especially for immunizing highly vulnerable people in developing countries, it may not ultimately be the most important factor. Public demand and safety considerations must also be addressed.

PUBLIC DEMAND

Although enthusiasm is at a fever pitch in the public health community, there is not public clamor to prevent most of the diseases (with the exception of AIDS) for which we will have vaccines in the near future, despite often high rates of illness and suffering, complications, and death (depending on epidemiologic factors). Proactive strategies and effective techniques, when they exist, do not effectively convey the sort of information that makes public health officials so enthusiastic about developing new vaccines to health care providers, parents, policy makers, and the media. We must find a means to conduct relevant burden-of-disease studies and to communicate results effectively to a variety of audiences so the public can more clearly see and understand the face of the diseases that vaccines will be designed to prevent.

Prelicensure studies should be consistently designed so that outcome measures include those that will be relevant for decision makers and recommending bodies. That being said, there may be virtue in recommending bodies moving cautiously on initial guidelines for most new vaccines, relying heavily on existing data, limiting extrapolations to those that appear highly probable or urgently necessary, and pointing out specific research priorities. Recommendations for the use of new vaccines should be updated frequently (annually for the first few years) to highlight the dynamic process of incorporating late-breaking findings from postmarketing research. Early in the postlicensure period, when there is much yet to learn, recommendations for use, often needed quickly by clinicians, should be understood to require frequent updates to incorporate new information as it continues to be gathered. Recognizing that constant change in recommendations can create formidable difficulties for those who administer vaccines, we need to ensure that such updates are expected and manageable, and that they are appreciated as a consistent evidence-based evolution toward optimal vaccine use. Without a well-defined and well-understood process of this sort, there can be a perspective that, once recommending bodies have ruled, prospective investigations involving a new vaccine are unethical or not indicated.

Ultimately, combination vaccine packages that prevent syndromes (such as pneumonia, meningitis, acute otitis media, or diarrhea) would be more likely than etiology-based vaccines to

have a measurable impact on easily recognizable conditions. This would make them more attractive both to the public and to financial and public health managers who must set health care priorities.

SAFETY CONSIDERATIONS

Coincident with the success of immunization programs, public attention in many countries has turned away from diseases preventable by vaccine, which now occur much more rarely, toward conjectured adverse events temporally associated with vaccines. The Internet widely disseminates anecdotal experiences, hypotheses, and fears, as well as confirmed adverse events; often, when reading Internet discussions, it is difficult to discern the difference. Given the highly contagious nature of most of the associated, noneradicated pathogens, removal of community immunologic pressure (herd immunity) provided by widespread use of vaccines would result in recrudescence of disease incidence rates and epidemics [5, 23].

We have ample reason to be confident about the safety and quality of vaccines that are currently used routinely as part of the childhood immunization schedule [24]. Vaccines are among the safest of pharmaceuticals. However, in the current environment, vaccines will be held to a higher standard of safety than what was accepted during the last century. Considering that more immunizations that will be given in the future, many of them simultaneously, we will need to be more vigilant than ever in ensuring that high levels of safety and effectiveness are documented. Safety needs to be considered not just for individual vaccine antigens or vaccines to prevent a single disease. The effect of giving multiple vaccines to prevent a large number of diseases must be continuously evaluated to ensure that we can document and understand any level of harm that is introduced and that overall benefit is measurable and substantial. Although a goal of absolute zero risk is not possible to achieve for any intervention, by continuing to strive for it, we will remain confident about the vaccines we use and communicate that confidence credibly.

Premarketing investigations, especially phase III studies, will need to have greater capacity to evaluate clinically important short- and longer-term adverse events of moderate incidence (for example, an RR of 1.5 for association with an event that has a background rate of 4%–5%). We currently tend to refer to phase III studies as “efficacy studies”; we should refer to them as “safety and efficacy studies” and ensure that they are designed to detect specific serious safety outcomes of moderate incidence. Large and diverse postmarketing systems, which would include enhancements to the Vaccine Adverse Events Reporting System and the current Vaccine Safety Datalink maintained by the Centers for Disease Control and Prevention [25], for detecting and defining serious adverse events of low

incidence, events with delayed onset, or both, will be needed to provide reassurance against the onslaught of allegations, and when risks are confirmed, to redesign vaccine policy to minimize the risks. Although we can be somewhat reassured because our existing postmarketing surveillance systems detected the association between rhesus rotavirus vaccine and intussusception, new resources must be identified to activate enhanced efforts in this arena to provide greater capacity for early detection of unanticipated serious risks.

After all this good work is done, the greatest challenge that will remain is to effectively communicate the findings. It is not always easy to do so [26]. Improved techniques for meaningful communication of disease surveillance, effectiveness, and safety information appropriate for a variety of audiences must be developed, evaluated, and constantly updated. Communication will need to be bidirectional so that, in addition to providing essential information, we who work in public health can understand the perceptions and concerns of parents, providers, and the public at large (and a variety of subpopulations) and can find ways to address them.

THE BIGGER PICTURE: THINKING ABOUT VACCINES IN A SOCIETAL CONTEXT

For most scientists and health care providers, it is clear how vaccines directly impact health and how vaccinology as a discipline contributes indirectly to other scientific advances that impact our well-being. What might not be recognized when we focus only on the obvious accomplishments is how vaccines and immunization programs contribute to our societal fabric. They have provided a rationale for enhanced health care approaches and systems. They confer tools with which the best impulses of humanity can be realized through philanthropy and humanitarianism, and they provide an essential ingredient to addressing barriers to global economic development. It is these attributes that should be understood and nurtured so that it will be possible to derive the greatest good from them.

SOCIAL RESPONSIBILITY

During the 20th century, use of vaccines became an index of social responsibility. With the exception of tetanus vaccine, which prevents disease transmitted from the environment, available vaccines prevent diseases that are transmitted from person to person. Pathogens such as measles virus, poliovirus, mumps virus, varicella virus, rubella virus, *Corynebacterium diphtheriae*, *Bordetella pertussis*, and Hib are highly contagious. Vaccines against these pathogens reduce the burden of disease primarily by preventing infection and illness among those who have been vaccinated. However, these vaccines also work by reducing transmission to people who are not immune, either be-

cause they have not been immunized (or previously infected with the pathogen) or because they have not had an adequate or sustained response to immunization.

For each vaccine, there is a small but measurable proportion of immunized people whose bodies will not mount protective immune responses. In most cases, this is not because of recognized chronic or immunosuppressing conditions. For instance, even with the efficacy of measles vaccine of 95%, outbreaks will occur in groups of healthy children when <90% of the children have been vaccinated [27]. Although highly efficacious among healthy children, Hib vaccine can have an efficacy as low as 86% in the setting of poor and underimmunized communities [28]. There are social implications in the fact that immunizations are tools not only to directly protect immunized individuals, but also to protect an entire group of people, some of whom may not be afforded protection directly. For settings such as school or day care, where contagious infectious diseases could rapidly spread, there is a strong public health and legal basis for mandating that all children receive safe and effective vaccines against such diseases [29, 30]. This is perhaps the most visible and rewarding modern day evidence of our social contract—the responsibility that our individual actions be beneficial to all, or at least not harmful.

Although immunization mandates provide a shining example of social responsibility, they are often misunderstood. This social contract should not be taken lightly or used beyond its intent. In the 21st century, as each new vaccine becomes available, we must closely examine the science to determine whether and in what specific settings and circumstances there is a public health basis to mandate its use. It is the responsibility of the immunization and public health communities, particularly at the state and local levels, and, from a larger perspective, society, to examine and define mandates in the current context of an increasing number of vaccines that will prevent diseases with differing impact and epidemiology. Defining and communicating effectively the public health basis for immunization mandates is needed to protect their crucial public health benefit.

RATIONAL HEALTH PROGRAMS

Vaccines are central to our modern-day focus on prevention of disease in children, which we now recognize as the key to healthy, productive, and long lives. Primary and booster vaccine schedules create 4 opportunities (at ages 0, 2, 4, and 6 months) during infancy for the provider and the parent to focus on prevention. Since the 1950s, these encounters have evolved into well-baby checks, so that there is emphasis not only on administration of vaccines, but also on prevention of accidental injury and harmful exposures and on early detection of diseases. The industry of prevention for young children that has been catalyzed by immunizations has not reached its full potential

for adolescents and adults, for whom the primary focus for provider-patient interaction is still therapeutic intervention.

What novel approaches can we find to better use the opportunity provided by administration of vaccines to bring prevention more into the balance for health care for older children and adults? Surely a more concerted effort, applying greater resources to adult immunization programs, would result in more successful prevention of a number of diseases among adults. Given the scenario of greater focus on adult and adolescent immunization, vaccine administration should also provide a valuable venue for physicians and health care providers to foster more dialogue with adolescents, providing them with better tools to avoid tobacco, alcohol, and drug dependency; to prevent unwanted pregnancy, AIDS, and other sexually transmitted diseases; and to intervene when there are signs of homicidal or suicidal behavior. In one sense, immunizations can provide a bridge to another era, when clinicians took the time to address concerns beyond the acute afflictions that led to the office encounter, although to accomplish this, the tension between the need for efficiency and the desire for more holistic care must achieve a different balance than exists in today's cost-driven health care environment.

Vaccines are also on the forefront in finding solutions to complex barriers that block taking full advantage of information technology for health purposes. During the 21st century, computerized medical records may vastly improve patient care by making it possible for physicians to have instant access to comprehensive data on their patients, which will enable them to diagnose and treat illnesses more accurately and more quickly. Medical databases will also revolutionize medical and public health research, making it possible to more fully understand clinical disease manifestations, risk factors, and incidence. By creating local and state electronic immunization registries and linking them nationally, physicians will have quick access to immunization status of a child, which has become a significant issue in an increasingly mobile society and with the current environment of frequent changes of medical provider and health plans. Registries will help providers stay on top of an increasingly intricate immunization schedule and will provide reminder systems to systematically minimize missed opportunities for immunization. There are a variety of other benefits as well, including consolidating the immunization record, minimizing

overimmunization (i.e., administering more vaccines than indicated), allowing for a comprehensive evaluation of immunization coverage and identification of areas where public health efforts should be bolstered, and ultimately providing a basis for national surveillance for adverse events temporally linked with immunization.

Before we can take advantage of information technology for these purposes, solutions must be implemented for critical is-

sues, such as ensuring privacy and confidentiality of data; ensuring that access can be limited to those who have a medical need to use the data; ensuring active provider participation; addressing technical and operational concerns related to software compatibility and hardware; and providing adequate resources to maintain the registries. The National Vaccine Advisory Committee has, through a series of hearings and deliberations, developed a set of recommendations for a national plan of action to address these barriers [31]. There is basis to predict that fully reliable and secure local and state immunization registries will have immense value, increasing people's comfort with this resource and, ultimately, speeding the development of other computerized systems for enhancing health care. In states where registries have been in operation for some time, they have been used successfully to identify children for reimunization when they received subpotent lots of vaccine and to monitor the implementation of new vaccine recommendations [32].

VACCINES AND HUMANITARIANISM

It is in the nature of humankind to do good, even in the presence of poverty, war, or natural disasters. Although this is obviously the view of an eternal optimist, there is evidence for this claim in global immunization efforts. During disease eradication efforts, bilateral agreements have been crafted in many regional conflicts and civil wars so that health officials could enter arenas of conflict and immunize susceptible people. This has occurred even under the most horrific circumstances, where man's inhumanity to man has been on display. Could it be that recognizing a common enemy—a highly contagious and lethal pathogen—can serve as a unifying force and a first step toward resolving deadly conflicts?

Of late, immunizations have become a focal point for substantial contributions from philanthropic organizations, financial institutions, and wealthy nations. The Bill and Melinda Gates Foundation has recognized the importance of better use of relatively new vaccines in the poorest countries to prevent serious diseases, such as Hib meningitis, pneumonia, and acute and chronic liver disease due to hepatitis B, and pledged \$750 million over 5 years to a fund that will be used to purchase these vaccines. Use of philanthropic funds to efficiently gain the greatest good is not always easy. The Gates Foundation has recognized that immunization programs are a highly visible method for which substantial good should be easily demonstrable. Such enormous generosity can be "chemotactic." Governments, including those of the United States, Canada, the European Union, and Japan, are now considering how they can contribute to the same effort and can more aggressively support research on developing vaccines against some of the world's deadliest scourges, such as HIV infection, malaria, and tuberculosis. In his final State of the Union Address in 2000

[33], President Bill Clinton said "America must help more nations to break the bonds of disease. Last year in Africa, 10 times as many people died from AIDS as were killed in wars—10 times. The budget I give you invests \$150 million more in the fight against this and other infectious killers. And today, I propose a tax credit to speed the development of vaccines for diseases like malaria, TB and AIDS. I ask the private sector and our partners around the world to join us in embracing this cause. We can save millions of lives together, and we ought to do it." Major lending institutions, such as the World Bank and the Asian Development Bank, have also become more visible, considering grants and low-interest loans to assist poorer nations with vaccine purchase, and, in some cases, supporting laboratory and epidemiologic research relevant to development of vaccines of specific import for poorer, less developed countries.

THE GLOBAL ECONOMY

Pure humanitarianism is not the only cause of recent efforts in the area of global vaccinations. It is hard for a low-income country to raise its level of productivity if the potential of its youth is diminished by the complications of disease and by premature death. Although Jeffrey Sachs, an economist at Harvard University, notes that illness and mortality from a variety of infectious diseases are not only a result of poverty but are themselves a cause of impoverishment, he has pointed out that multinational companies are unlikely to make investments in countries where substantial health risks exist. By having an available safe and effective modality to prevent *Plasmodium falciparum* malaria, he argues that companies will be much more willing to invest in production facilities in developing countries, particularly in sub-Saharan Africa. In our global economy, such investments may be necessary for many countries to lower their currently high poverty rates. The resulting interconnectedness means that wealthier nations can no longer remain uninterested. Science and technology must be mobilized to address the problems "which help to keep poor countries poor" [34].

The 21st century will undoubtedly provide opportunities and raise public health challenges not yet imagined. It is reasonable to expect that immunizations and vaccinology will be at the forefront in addressing many of these challenges. There is much work yet to be done to ensure that vaccine research and development, as well as vaccine implementation programs, have the foundation and capacity to keep pace with evolving scientific and societal realities. We will need to give much more sustained attention to proactive communication, education, outreach, and information exchange so that the wide array of health and societal benefits of immunization efforts are understood, appreciated, and sought. We should not shrink from

the challenges that must be addressed, because in the end, challenges faced squarely will yield new opportunities for greater positive impact. As has been said before, “The only difference between stumbling blocks and stepping stones is the way you use them.”

References

- Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900–1999. *MMWR Morb Mortal Wkly Rep* **1999**; 48:241–3.
- Centers for Disease Control and Prevention. Achievements in Public Health, 1900–1999: impact of vaccines universally recommended for children—United States, 1990–1998. *MMWR Morb Mortal Wkly Rep* **1999**; 48:243–8.
- Ward BJ. Vaccine adverse events in the new millennium: is there reason for concern? *Bull World Health Organ* **2000**; 78:205–15.
- Omer MI. Measles: a disease that has to be eradicated. *Ann Trop Paediatr* **1999**; 19:125–34.
- Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* **1998**; 351: 356–61.
- Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clin Microbiol Rev* **2000**; 13:302–17.
- Mulholland K, Levine O, Nohynek H, Greenwood BM. Evaluation of vaccines for the prevention of pneumonia in children in developing countries. *Epidemiol Rev* **1999**; 21:43–55.
- Schafer DE, Sorrell MF. Hepatocellular carcinoma. *Lancet* **1999**; 353: 1253–7.
- Black S, Shinefield H, Ray P, et al. Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 37,000 infants and children: impact on pneumonia, otitis media and an update on invasive disease—results extended follow-up of the efficacy trial cohort [abstract O-19]. In: Abstracts of the Second International Symposium on Pneumococci and Pneumococcal Diseases (Sun City, South Africa). Johannesburg: South African Institute of Medical Research, **2000**.
- Peterson CL, Mascola L, Chao SM, et al. Children hospitalized for varicella: a prevaccine review. *J Pediatr* **1996**; 129:529–36.
- Gershon AA, LaRussa P, Steinberg S, Mervish N, Lo SH, Meier P. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. *J Infect Dis* **1996**; 173:450–3.
- Breiman RF, Butler JC, McInnes PM. Vaccines to prevent respiratory infection: opportunities on the near and far horizon. *Curr Opin Infect Dis* **1999**; 12:145–52.
- Gonzalez IM, Karon RA, Eichelberger M, et al. Evaluation of the live attenuated cpts 248/404 RSV vaccine in combination with a subunit RSV vaccine (PPF-2) in healthy young and older adults. *Vaccine* **2000**; 18:1763–72.
- Plotkin SA. Cytomegalovirus vaccine. *Am Heart J* **1999**; 138:S484–7.
- Stanberry LR, Cunningham AL, Mindel A, et al. Prospects for control of herpes simplex virus disease through immunization. *Clin Infect Dis* **2000**; 30:549–66.
- Breiman RF, Ginsberg A. Summary of proceedings of international symposium on tuberculosis vaccine development and evaluation. *Clin Infect Dis* **2000**; 30(Suppl 3):S199–200.
- Ballou WR, Kester KE, Stoute JA, Heppner DG. Malaria vaccines: triumphs or tribulations? *Parassitologia* **1999**; 41:403–8.
- McManus DP. The search for a vaccine against schistosomiasis—a difficult path but an achievable goal. *Immunol Rev* **1999**; 171:149–61.
- Abath FG, Montenegro SM, Gomes YM. Vaccines against human parasitic diseases: an overview. *Acta Trop* **1998**; 71:237–54.
- Abregnani S, Houghton M, Hsu HH. Perspectives for a vaccine against hepatitis C virus. *J Hepatol* **1999**; 31(Suppl 1):259–63.
- Rousseau MC, Moreau J, Delmont J. Vaccination and HIV: a review of the literature. *Vaccine* **1999**; 18:825–31.
- Gellin B, ed. The Jordan report: accelerated development of vaccines. Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases. Bethesda, MD: National Institutes of Health, **1998**.
- Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. *JAMA* **1999**; 282:47–53.
- Stratton KR, Howe CJ, Johnston RB Jr, eds. Adverse events associated with childhood vaccines: evidence bearing on causality. Vaccine Safety Committee, Institute of Medicine. Washington, DC: National Academy of Sciences, **1993**.
- Chen RT, DeStefano F, Davis RL, et al. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. *Bull World Health Organ* **2000**; 78:186–94.
- Breiman RF, Zanca JA. Of floors and ceilings: defining, assuring, and communicating vaccine safety. *Am J Public Health* **1997**; 87:1919–20.
- Mossong J, Muller CP. Estimation of the basic reproduction number of measles during an outbreak in a partially vaccinated population. *Epidemiol Infect* **2000**; 124:273–8.
- Jafari HS, Adams WG, Robinson KA, Plikaytis BD, Wenger JD. Efficacy of *Haemophilus influenzae* type b conjugate vaccines and persistence of disease in disadvantaged populations. *Am J Public Health* **1999**; 89: 364–8.
- Jacobson v. Commonwealth of Massachusetts*, 197 US 11 (1905).
- Zucht v. King*, 260 US 174 (1922).
- National Vaccine Advisory Committee. Development of community- and state-based immunization registries: report of the National Vaccine Advisory Committee (NVAC). Available at: http://www.cdc.gov/nip/registry/i_recs.htm. Accessed 12 January **1999**.
- Centers for Disease Control and Prevention. Progress in development of immunization registries—United States, 1999. *MMWR Morb Mortal Wkly Rep* **2000**; 49:274–8.
- Clinton WJ. State of the union address [transcript]. January 27, **2000**. Available at: <http://www.whitehouse.gov/WH/SOTU00/sotu-text.html>.
- Balms for the poor. *The Economist*. 14 August **1999**.