Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 2464–2468, March 1994
Colloquium Paper

This paper was presented at a colloquium entitled "Changes in Human Ecology and Behavior: Effects on Infectious Diseases," organized by Bernard Roizman, held September 27 and 28, 1993, at the National Academy of Sciences, Washington, DC.

Quest for life-long protection by vaccination

WALTER R. DOWDLE AND WALTER A. ORENSTEIN

Centers for Disease Control and Prevention, Atlanta, GA 30333

ABSTRACT **Life-long protection from disease through immunization can be accomplished through individual or community protection. Individual protection is the goal for vaccination against diseases that have inanimate or animal reservoirs or that pose risks for certain populations. Community protection is the goal for vaccination against diseases that are transmitted only from human to human. Community protection afforded by childhood vaccines has been highly successful against measles, rubella, mumps, and polio. However, outbreaks of measles, rubella, and mumps continue to occur, primarily because of inadequate immunization of children under age 2. Simplification of vaccination regimens, provision of incentives to care providers and parents, and increased access to care should improve vaccination rates in the United States. Better protection requires better use of available vaccines. Eradication of disease through vaccination is the ultimate goal of community protection. Elimination of the infectious agent is the most effective means of achieving life-long protection. The World Health Organization's (WHO) smallpox eradication campaign eliminated a serious disease as well as the need for a vaccine with frequent and severe adverse reactions. The discontinuation of smallpox vaccination in the United States has produced a savings of over $3 billion. Polio has been targeted by WHO for eradication by the year 2000. The eradication of polio and the elimination of the need for polio vaccination in the United States should result in a savings of $110 million per year in vaccine costs alone. Strong United States support is crucial for WHO to reach its goal. Any of the vaccine-preventable childhood virus diseases could be eradicated with sufficient national and international will. Measles and hepatitis B should be high priorities. The ultimate goal of vaccination is life-long protection of all individuals. Any disease of sufficient public health importance to warrant routine vaccination is of sufficient importance to warrant eradication wherever judged to be possible.**

Vaccines represent one of our most powerful and cost-effective prevention tools. Successful vaccination programs have led to marked reductions in disease, disability, and death (1). The successes of our current vaccination efforts raise the question of how we can eliminate the disease burdens that remain.

The ideal vaccine is one that is stable (i.e., will maintain potency under most environmental conditions), safe, administered orally in a single dose at birth, 100% effective, reasonably priced, and protective for a lifetime. Unfortunately, there is no such vaccine. Some of the vaccines currently available have one or more of these ideal characteristics, but no single vaccine has all of them. The goal of future research is to obtain vaccines as close to these ideal characteristics as possible. Such research should be targeted toward a better understanding of the host and pathogen interactions as well as the immunology of candidate vaccines.

Successful use of a vaccine requires widespread acceptance by the public, the health-care providers, and the public-health community. Such acceptance is enhanced the closer the vaccine comes to meeting the ideal set of characteristics previously mentioned. Much discussion about vaccines is devoted to assuring efficacy, but safety is equally as important. Widespread acceptance of vaccines can only be assured if the public believes vaccines will not harm them. Concerns about vaccine safety led to marked drops in pertussis vaccine coverage in Japan and the United Kingdom in the 1970s, with resultant major epidemics of whooping cough (2, 3). The quest for life-long protection needs to be accompanied by a quest for completely safe products.

Even though no vaccine today is perfectly safe or perfectly effective, with the right strategy less-than-perfect vaccines can be powerful prevention tools. Diseases can be eradicated with a strategy for vaccine use tailored to both the characteristics of the vaccine and the epidemiology of the disease.

Life-long protection from disease through vaccination can be accomplished in two ways: (*i*) individual protection—assuring a life-long immune response capable of repelling challenges individuals may receive at any time in their lives, and (*ii*) community protection—reducing or even eliminating the possibility that nonimmune individuals will be exposed to the infectious agent.

All vaccines are given to protect individuals. Individual protection is the only way to assure life-long protection against certain diseases with inanimate or animal reservoirs for infectious agents, such as tetanus and rabies (4, 5). For these diseases, vaccinated humans do not help to protect unvaccinated humans. All susceptible persons are at risk, and that risk is not modified by reducing the number of susceptibles through vaccination. Individual protection is also the only protection available when vaccines are recommended for selected populations whose behaviors place them at increased risk of disease exposure. These are vaccines needed for international travel, special life-styles, selected occupations, and other special uses. Included among these are Japanese encephalitis (6), yellow fever (7), typhoid (8), adenoviruses 4 and 7 (9), anthrax (9), cholera (10), rabies (11), and meningococcal (12) vaccines.

While influenza and pneumococcal vaccines are recommended for all adults ≥65 years of age and selected others with high-risk medical conditions, these vaccines do not substantially reduce population exposure to the organism (13, 14).

For each of these diseases, temporary or life-long protection can only be obtained through vaccination of each individual at risk. The ability to induce lasting protection varies

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Abbreviation: WHO, World Health Organization.

widely for available vaccines. Live attenuated viral vaccines are generally believed to induce long-term, probably life-long, protection among the great majority of individuals (9). Measles, mumps, rubella, and oral polio vaccines are in this category. Inactivated vaccines and toxoids usually induce shorter-term protection and require periodic boosters. Experience with a number of the newer inactivated vaccines, such as hepatitis B vaccine and enhanced-potency inactivated polio vaccine, is too limited to know the precise duration of immunity (15, 16). Immunologic memory, even in the absence of detectable antibody, may confer life-long protection.

Research is proceeding into new ways of developing vaccines that will lead to longer-lasting immunity. An example includes the incorporation of genes coding for key antigens of pathogens in live vectors that do not cause disease (such as vaccinia) (17). Microencapsulation of antigens in polymers, which can lead to either sustained release or pulsed release of those antigens over prolonged periods, also offers promise (18).

Most discussions of life-long protection focus on individual protection. This is an important consideration for any vaccine. However, we as a society derive far more benefit by seeking protection for all by eliminating exposure to infectious diseases.

For diseases transmitted solely from human to human, prevention of exposure can be accomplished by creating high levels of population "herd" immunity (19). Transmission of diseases such as measles is sustained when a transmitting case comes in contact with a susceptible person. After an incubation period, the susceptible person becomes contagious and the chain of transmission is maintained. The chain of transmission is broken if the transmitting case comes in contact only with immune individuals.

When there are high levels of immunity in the population, the likelihood that a transmitting case will come in contact with a susceptible person is reduced, thereby resulting in indirect protection of the few remaining susceptibles, including those too young for vaccination, those with legitimate contraindications to vaccination, and those whose vaccination fails to protect them. While there is no absolute level of population immunity short of 100% that will guarantee elimination of disease transmission, it is clear that the higher the level of immunity, the lower the probability of significant transmission (19).

For example, use of acellular pertussis vaccines in Japan among 2-year-old children led to marked reductions of pertussis among younger children who were not targets for vaccination (20). Similar effects have been seen in the United States with *Haemophilus influenzae* type b and measles (21, 22). Any effort to induce life-long immunity requires that vaccines be used and used widely among targeted groups.

It would be useful to review how well we have protected both the individual and the community with the currently available vaccines.

In the United States, there are nine vaccines routinely recommended for all children: diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, measles, mumps, rubella, hepatitis B, and polio (15, 23–28). Of these, all but tetanus toxoid can lead to community protection from widespread use, reducing disease transmission through herd immunity.

Vaccination of children with these vaccines has yielded spectacular results. Shortly after the measles vaccine was introduced in 1963, measles decreased from an annual average of >500,000 cases reported in the decade preceding licensure to <25,000 cases in 1968. Since 1968, there has been a further decrease in incidence, broken by three periods of increased incidence. Although small by comparison to the incidence before the introduction of the vaccine, they were, nevertheless, serious. During the last prolonged epidemic, >55,000 cases, 11,000 hospitalizations, and 130 deaths were recorded (CDC, unpublished data).

Rubella has shown an equally steep decline, from nearly 60,000 cases reported at the time the vaccine was licensed in 1969 to only a few hundred in recent years. As with measles, there are very few periods of increases in cases of rubella, the most recent coming during 1990 and 1991.

Mumps has shown a similar decline from 1968 to 1992.

There have been no cases of paralytic polio caused by indigenously acquired wild viruses since 1979 in the United States. There has been an annual average of approximately 8 vaccine-associated polio cases (29).

The figures for the first half of 1993 show considerable improvement over the same period for 1992, with decreases in reported measles cases of >90%. With the exception of pertussis, tetanus, and rubella, all other reported cases are going in the right direction—down. The increases in tetanus and rubella are small, following record lows in 1992. We would like to think that these decreases reflect the major vaccination effort between 1989 and 1991, particularly for measles, but it is unlikely that we can take full credit. Epidemics run their course, often without the help of vaccines.

Clearly, vaccination of children has been an enormously successful public health strategy. Young parents today do not have the memories of childhood infectious diseases that parents of 40 years ago have. By all criteria, as a nation, we have accomplished even more than we dared dream when many of these vaccines were first introduced. Much of our population has never experienced these childhood infectious diseases for which vaccines are available. However, the elimination of these childhood diseases is still an elusive goal. Our job is incomplete.

Nearly all children have received the appropriate vaccines prior to entry into school or other organized settings, primarily as a result of state laws. Of children at school entry, >95% have received appropriate vaccines. Vaccination levels for children enrolled in licensed day-care or Head Start exceed 90%. These findings do not apply to children under age 2.

The most recent data from the National Center for Health Statistics in 1991 reveal that nationally, among children 19–35 months of age, coverage rates for the recommended vaccines were as follows: polio (three or more doses), 53%; DTP (three or more doses), 69%; and MMR (one dose), 82%. (DTP is diphtheria/tetanus toxoid/pertussis vaccine; MMR is measles/mumps/rubella vaccine.) Just before the measles outbreak in 1989, full vaccination coverage was <50% in some urban areas—a percentage far below that of many developing countries. Children in Cairo, Bangkok, and Bombay have better vaccination rates today than those in the inner cities of Houston or New York. Although none of the childhood vaccines have 100% efficacy, a vaccine not given has a 0% efficacy.

This low vaccination coverage rate for preschool children in the United States is not new (30). Increasing the vaccine usage in this country has been a constant challenge. At the time of the passage of the first Federal Vaccination Assistance Act in 1962, only about two-thirds of the children under 5 years of age had received each of the recommended series of vaccines.

How have we, certainly one of the most affluent countries in the world, allowed this to happen? There are no simple answers, but three points should be made. First, vaccination of the approximately 4 million children added to the United States population each year is no simple task. Full protection before 2 years of age requires that each child receive a complicated series of 14–15 doses of vaccines in four to five visits to a health care provider (15, 23–28). Second, unlike school entry, where there are laws in each state requiring

proof of appropriate vaccination, there are no laws requiring vaccination of all infants. Aside from children entering licensed day-care or Head Start, vaccination is voluntary. Third, unlike most other developed and many developing countries, the United States does not have a structured system of health care that assures parents access to providers (31). Achieving high levels of coverage is further hampered by the lack of a system of record keeping that would allow providers knowledge about the immunization status of a new patient.

In regard to the first point, combining vaccines and simplifying the dosage schedule for children <2 years of age would help considerably. Not only does the 15-dose, four- to five-visit schedule impose a major economic burden on many parents, the three to four injections per visit poses pain for the child, and anxiety for the parent and the health care provider. The complexity of the schedule leads to parental misunderstanding and confusion, with high dropout rates, missed vaccination opportunities, and higher societal costs.

The probability is high that still more vaccines will be licensed for children. The number of vaccines has become a limiting factor.

Multinational organizations have recognized the need for more efficient delivery of new and better vaccines for developing countries and in 1990 made a commitment to the production and delivery of easily administered and affordable children's vaccines. The result of that commitment is the Children's Vaccine Initiative (CVI) established by the United Nations Children's Fund (UNICEF), The United Nations Development Program (UNDP), The Rockefeller Foundation, The World Bank, and The World Health Organization (WHO). The CVI concept is largely directed toward developing countries, with special needs for an expanding number of combined, low-cost, and heat-stable vaccines.

The recent Institute of Medicine report *The Children's Vaccine Initiative 1993* describes the advantages that would accrue to the United States through support of The Children's Vaccine Initiative (32).

Children from developed, as well as developing, countries can greatly benefit from fewer and less expensive injections. It is heartening to learn that one United States manufacturer is now marketing a combined DTP and Hib (*Haemophilus influenza* b) vaccine and that several manufacturers are developing other combinations that will reduce the number of injections.

Even without such combinations, the United States has demonstrated that it can vaccinate the vast majority of its children when immunization is linked to something more valuable—i.e., requirement for entry to school (33). In those settings, barriers to immunization are overcome. The need for school laws to assure immunization of schoolchildren has led some to feel that we will reach our goals for 2-year-old children only if there are also laws requiring the vaccination of preschool children. It is not clear how such laws would be written or how they might be enforced if passed. In any event, there seems to be no visible legislative support for such laws at present.

As to the final point, the absence of a single health infrastructure to assure vaccination of those <2 years of age means that the full responsibility for vaccination rests with the parents, who are frequently poorly informed about the needs for early vaccination. In contrast to the United Kingdom, where providers are held accountable for immunizing their patients, most providers in the United States do not receive rewards or suffer consequences depending upon the immunization status of their patients (34).

Congress and the current administration are determined to close the vaccination gap. The President's budget for 1994 contains funds for increased purchasing of vaccines, building state and local infrastructure for vaccine delivery, and conducting public education and outreach. The goal for 1996 is 90% vaccine coverage for most of the recommended vaccinees and zero incidence of most of the vaccine-preventable childhood diseases.

Thus, in our quest for life-long protection by vaccination, our first responsibility is to a better use of the vaccines that we already have.

The ultimate goal of community protection is disease eradication. The most effective means of providing life-long protection through vaccination is elimination of the infectious agent. Several factors related to disease and vaccines make the eradication of an infectious disease possible. Diseases that should be the easiest to eradicate with effective vaccines are characterized by person-to-person transmission, humans as the only natural host, absence of an inanimate reservoir, limited duration of shedding of the organism when infected, no long-term carrier state, and a distinctive, clinically apparent syndrome to facilitate case detection and response. Appropriate vaccines should be characterized by high efficacy at preventing not only disease but also infection and transmission. Such vaccines should be easy to use and stable and should provide long-term duration of protection with a limited number of doses. Finally, and critically, there must be commitment to eradication at both the international and national levels. Some of the viral diseases for which vaccines are available have many of the biological characteristics desirable for eradication, although the commitment of the international community remains a challenge.

Smallpox vaccine represents an ideal example of life-long protection. The story of the eradication of smallpox is well known (35). The World Health Organization (WHO) Smallpox Eradication Program ran from 1966 to 1980. The last case of smallpox occurred in 1977 in Somalia.

When the WHO eradication program began in 1967, smallpox was endemic in 33 countries, with an estimated 10–15 million cases and 2 million deaths. Perhaps less well known was the high human toll associated with routine vaccination against smallpox. In the United States in 1968 alone, 9 people died from complications of primary vaccination; >8000 had complications requiring medical attention, and >200 were hospitalized, 4 being permanently disabled (36). Untold numbers of other vaccinees had adverse reactions not requiring medical attention.

The smallpox vaccine was not ideal. Adverse reactions were common, and the duration of protection was limited. Eradication was achieved despite these shortcomings through a strategy tailored specifically to the epidemiology of smallpox—targeted vaccination in the immediate vicinity of cases otherwise known as "ring vaccination" or "search and containment" (35). Eradication eliminated not only a serious infectious disease but also eliminated the need to use a vaccine that had accompanying adverse reactions.

The total U.S. contribution to the smallpox eradication campaign was $32 million, an investment that has been returned every 2.5 months since 1971 (37). The discontinuation of smallpox vaccination in the United States resulted in a direct savings since 1983 of >3 billion dollars (J. D. Sencer and N. W. Axnick, cited in ref. 35, p. 1365). These savings continue to accrue day after day and year after year, thus making these funds available for other pressing public health needs.

Today the debate focuses on the final destruction of smallpox virus stocks held by the Centers for Disease Control and Prevention (CDC) in Atlanta and the Institute of Viral Preparations in Moscow.

Ten years after the last smallpox case, the World Health Assembly called for eradication of another virus disease, polio (39, 40). The target dates were for the American region by 1990, the western Pacific and European regions by 1995, and worldwide by 2000.

Through the efforts of WHO's Expanded Programme on Immunization, donor agencies, multinational organizations, and individual countries, an estimated 84% of the infants born in 1990 were immunized against polio. The decreases in the number of cases of polio reported to WHO, although considered a fraction of the total cases, have been encouraging.

The WHO estimate of the number of cases of paralytic polio has been reduced from >400,000 annually in 1980 to 127,000 annually today. China, for example, reported a 58% decrease in cases between 1989 and 1991. Polio-free zones are beginning to emerge in North Africa, southern and eastern Africa, the Middle East, Europe, and the Pacific Rim. In the Western Hemisphere, the last case of paralytic polio caused by a wild virus was identified in 1991 (41, 42).

There are still enormous challenges ahead. India, Pakistan, and Bangladesh account for two-thirds of the cases reported to WHO. The Indian subcontinent will remain a reservoir of polio, reinfecting other countries, unless major progress is made over the next few years. There are also the ever-present wars and civil disruptions that interfere with the expanded immunization programs.

Much more help is needed from the developed world if the eradication effort is to succeed. Specific polio eradication efforts, including vaccine production and distribution, disease surveillance, and laboratory networks cost money. However, full investment in the effort to eradicate polio could pay enormous dividends. In the United States, eradication would mean discontinuing the use of the vaccine, resulting in savings of approximately $110 million per year in vaccine costs alone—independent of administration costs. Eliminating the use of oral vaccine would also eliminate the annual average of eight or so vaccine-associated cases of poliomyelitis that occur in the United States each year (29).

In fact, with time, there is no good reason why any of the current childhood viral diseases for which vaccines are available could not be eradicated. Measles, while potentially most difficult to eradicate as a result of its high communicability, deserves highest priority because of its substantial health consequences (43, 44). Before vaccination, WHO estimated measles caused 2.5 million deaths annually, most of which were in the developing world.

Measles decreases with high levels of vaccination. An example includes the apparent termination of measles transmission recently in much of the United States, where only 167 cases were reported during the first 26 weeks of 1993—the lowest total ever reported (45). Innovative strategies may be needed, but there is promise. For example, mass campaigns vaccinating all children between 9 months and 14 years of age (regardless of prior vaccination history) in the English-speaking Caribbean and multiple Latin American countries have led to virtual elimination in many areas (46).

Hepatitis B must also be considered a potentially eradicable disease, despite the high carrier rates in many developing countries. In the United States, there are an estimated 1 to 1.25 million chronic hepatitis B carriers (15). Eradication will require a lifetime, or maybe two, but it, too, is doable.

Experience today with hepatitis B virus vaccine has been encouraging. Universal immunization of an Alaskan (47) population with a virus carrier rate in some groups of >30% reduced the number of clinical hepatitis B cases to zero in <5 years.

Results of childhood hepatitis B virus vaccination programs in several countries where hepatitis B virus infection is highly epidemic are very encouraging. In Taiwan (48), perinatal and routine infant hepatitis B vaccination have resulted in a decline of chronic hepatitis B infection identified among children from 10% to 2.2% after 5 years. In Gambia (49), the overall prevalence of hepatitis B infection among children declined from 53% to 9%, and the prevalence of chronic hepatitis B declined from 12% to 0.5% within 6 years after the introduction of routine infant hepatitis B vaccination. In American Samoa (38), prevalence of hepatitis B infection among children declined from 23% to 11.5%, and prevalence of chronic hepatitis B declined from 7% to 1.5% within 4 years after the implementation of perinatal, routine infant, and catch-up hepatitis B vaccination programs.

In conclusion, the ultimate goal for vaccination is not simply long-term protection of the individual but also long-term protection of all individuals. The epidemiology of many infectious diseases allows for societal protection when high levels of immunity in the population are achieved, even if that immunity level is not 100%. But those high levels of immunity must be sustained with high dollar costs to society. Any reduction in effort or funding can lead to return of disease. Instead, our objective should be eradication of the infectious agent whenever feasible. The quest is not simply for better vaccines. The quest that will lead us to our goal will be through a better understanding of the epidemiology of vaccine-preventable diseases and an elucidation of the strategies for vaccine use. Any disease of sufficient public health importance to warrant routine vaccination is also of sufficient importance to warrant reasonable attempts at eradication.

1. Orenstein, W. A. (1993) *Future Directions*, 26th National Immunization Conference Proceedings, June 1–5, 1992, St. Louis (Centers for Disease Control and Prevention, Atlanta), pp. 13–22.
2. Cherry, J. D. (1984) *Curr. Probl. Pediatr.* **14**, 1–78.
3. Kimura, M., Kuno-Sakai, H. (1990) *Lancet* **336**, 30–32.
4. Smith, L. D. (1978) *Health Lab. Sci.* **15**, 74–80.
5. Anderson, L. J., Nicholson, R. G., Tauxe, R. V. & Winkler, W. G. (1984) *Ann. Intern. Med.* **100**, 728–735.
6. Centers for Disease Control and Prevention (1993) *Morbid. Mortal. Wkly. Rep.* **42** (RR-1), 1–15.
7. Centers for Disease Control and Prevention (1990) *Morbid. Mortal. Wkly. Rep.* **39** (RR-6), 1–6.
8. Centers for Disease Control and Prevention (1990) *Morbid. Mortal. Wkly. Rep.* **39** (RR-10), 1–5.
9. Hinman, A. R., Orenstein, W. A., Bart, K. J. & Preblud, S. R. (1990) in *Principles and Practice of Infectious Diseases Immunization*, eds. Mandell, G. L., Douglas, R. G., Jr., & Bennett, J. E. (Churchill Livingstone, New York), 3rd Ed., pp. 2320–2334.
10. Centers for Disease Control and Prevention (1988) *Morbid. Mortal. Wkly. Rep.* **37**, 617–624.
11. Centers for Disease Control and Prevention (1991) *Morbid. Mortal. Wkly. Rep.* **40** (RR-3), 1–19.
12. Centers for Disease Control and Prevention (1985) *Morbid. Mortal. Wkly. Rep.* **34**, 255–259.
13. Centers for Disease Control and Prevention (1993) *Morbid. Mortal. Wkly. Rep.* **42** (RR-6), 1–14.
14. Centers for Disease Control and Prevention (1989) *Morbid. Mortal. Wkly. Rep.* **38**, 64–68, 73–76.
15. Centers for Disease Control and Prevention (1991) *Morbid. Mortal. Wkly. Rep.* **40** (RR-13), 1–25.
16. Centers for Disease Control and Prevention (1987) *Morbid. Mortal. Wkly. Rep.* **36**, 795–798.
17. Anonymous (1985) *Bull. WHO* **63**, 471–477.
18. Eldridge, J. H., Hammond, C. J., Meulbroek, J. A., Staas, J. K., Gilley, R. M. & Tice, T. R. (1990) *J. Controlled Release* **11**, 205–214.
19. Anderson, R. M. & May, R. M. (1982) *Science* **215**, 1053–1060.
20. Noble, G. R., Bernier, R. H., Esber, E. C., Hardegree, M. C., Hinman, A. R., Klein, D. & Saah, A. J. (1987) *J. Am. Med. Assoc.* **257**, 1351–1356.
21. Adams, W. G., Deaver, K. A., Cochi, S. L., Plikaytis, B. D., Zell, E. R., Broome, C. V. & Wenger, J. D. (1993) *J. Am. Med. Assoc.* **269**, 221–226.
22. Schlenker, T. L., Bain, C., Baughman, A. L. & Hadler, S. C. (1992) *J. Am. Med. Assoc.* **267**, 823–826.
23. Centers for Disease Control and Prevention (1991) *Morbid. Mortal. Wkly. Rep.* **40** (RR-10), 1–28.
24. Centers for Disease Control and Prevention (1991) *Morbid. Mortal. Wkly. Rep.* **40** (RR-1), 1–7.

25. Centers for Disease Control and Prevention (1989) *Morbid. Mortal. Wkly. Rep.* **38** (S-9), 1–13.
26. Centers for Disease Control and Prevention (1989) *Morbid. Mortal. Wkly. Rep.* **38**, 388–392, 397–400.
27. Centers for Disease Control and Prevention (1982) *Morbid. Mortal. Wkly. Rep.* **31**, 22–26, 31–34.
28. Centers for Disease Control and Prevention (1990) *Morbid. Mortal. Wkly. Rep.* **39** (RR-15), 1–18.
29. Strebel, P. M., Sutter, R. W., Cochi, S. L., Biellik, R. J., Brink, E. W., Kew, O. M., Pallansch, M. A., Orenstein, W. A. & Hinman, A. R. (1992) *Clin. Infect. Dis.* **14**, 568–579.
30. Stehr-Green, P. A., Zell, E. R. & Eddins, D. L. (1993) *J. Am. Med. Assoc.* **270**, 1932.
31. The National Vaccine Advisory Committee (1991) *J. Am. Med. Assoc.* **266**, 1547–1552.
32. Mitchell, V. S., Philipose, N. M. & Sanford, J. P. (1993) *The Children's Vaccine Initiative* (Inst. of Medicine, Natl. Acad. Press, Washington, DC), pp. 1–221.
33. Orenstein, W. A., Hinman, A. R. & Williams, W. W. (1992) in *The Impact of Legislation on Immunisation in the United States*, Proceedings of the Second National Immunisation Conference, Canberra, 27–29 May 1991, Canberra, Australia (Public Health Assoc. of Australia, Canberra), pp. 58–62.
34. Salisbury, D. (1992) in *The Immunization Program in England*, 25th National Immunization Conference Proceedings, June 10–13, 1991, Washington, DC (Centers for Disease Control and Prevention, Atlanta), pp. 49–52.
35. Fenner, F., Henderson, D. A., Arita, I., Jazek, Z. & Ladnyi, I. D. (1988) *Smallpox and Its Eradication* (World Health Org., Geneva).
36. Sencer, J. D. & Axnick, N. W. (1973) in *International Symposium on Vaccination Against Communicable Diseases, Monaco, March 14–17, 1973*, Immunobiological Standardization Symposia Series, ed. Perkins, F. T. (Karger, Basel), Vol. 22, pp. 37–46.
37. Ogden, H. G. (1987) in *CDC and the Smallpox Crusade*, DHHS Publ. No. (CDC) 87-8400 (Centers for Disease Control, Atlanta), pp. 1–141.
38. Mahoney, F. J., Woodruff, B. A., Erben, J. J., Coleman, P. J., Reid, E. C., Schatz, G. C. & Kane, M. A. (1993) *J. Infect. Dis.* **167**, 203–207.
39. Wright, P. F., Kim-Farley, R. J., DeQuadros, C. A., Robertson, S. E., Scott, R. McN., Ward, N. A. & Henderson, R. H. (1991) *N. Engl. J. Med.* **325**, 1774–1779.
40. Hinman, A. R., Foege, W. H., DeQuadros, C. A., Patriarca, P. A., Orenstein, W. A. & Brink, E. W. (1987) *Bull. WHO* **65**, 835–840.
41. DeQuadros, C. A., Andrus, J. K., Olive, J. M. & deMacedo, C. G. (1992) *Annu. Rev. Public Health* **13**, 239–252.
42. DeQuadros, C. A., Andrus, J. K., Olive, J. M., Da Silveira, C. M., Eikhof, R. M., Carrasco, P., Fitzsimmons, J. W. & Pinheiro, F. P. (1991) *Pediatr. Infect. Dis.* **10**, 222–229.
43. Hopkins, D. R., Hinman, A. R., Koplan, J. P. & Lane, M. J. (1982) *Lancet* **i**, 1396–1398.
44. Hinman, A. R. (1982) *Rev. Infect. Dis.* **4**, 933–936.
45. Centers for Disease Control and Prevention (1993) *Morbid. Mortal. Wkly. Rep.* **42**, 813–816.
46. Pan American Health Organization (1990) *Bull. Pan Am. Health Org.* **24**, 240–246.
47. Wainwright, R. B., McMahon, B. J., Bulkow, L. R., Parkinson, A. J., Harpster, A. P. & Hadler, S. C. (1991) in *Proceedings of the 1990 International Symposium on Viral Hepatitis and Liver Disease: Contemporary Issues and Future Prospects*, eds. Hollinger, F. B., Lemon, S. M. & Margolis, H. (Williams & Wilkins, Baltimore), pp. 762–765.
48. Tsen, Y. J., Chang, M. H., Hsu, H. Y., Lee, C. Y., Sung, J. L. & Chen, D. S. (1991) *J. Med. Virol.* **34**, 96–99.
49. Whittle, H. C., Inskip, H., Hall, A. J., Mendy, M., Downes, R. & Hoare, S. (1991) *Lancet* **337**, 747–750.