tion and reproduction. Other considerations are whether the dividing lines between high, medium, and low nutritional status in these studies were chosen in a way that revealed true functional differences, and whether the range of nutritional states represented by the study groups were wide enough; that is, were enough well-nourished women included to demonstrate within-group nutritional effects on reproductive capacity?
32. "Breastfeeding at one week of age (U.S.)" (table), Ross Laboratories *Marketing Research*, 2 February 1976.
33. B. Vahlquist, "Scandinavia case study," prepared for International Planned Parenthood Federation/International Union of Nutritional Science conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, 5–12 July 1977.
34. H. Hultin, R. Opas, S. Sarna, *Kätilölehti* **10**, 365 (1976), cited in (*33*).
35. C. Rumeau-Rouquette and M. Crost-Deniel, "France case study: breast-feeding during the neo-natal period in France," prepared for International Planned Parenthood Federation/International Union of Nutritional Science conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, 5–12 July 1977.
36. C. J. Bacon and J. M. Wylie, *Br. Med. J.* **1**, 308 (1976).
37. E. Eastman, D. Smith, D. Poole, G. Neligan, *ibid.*, p. 305.
38. A. Berg, *Nutrition Today* **12**, 18 (1977).
39. S. Almroth, "Breast feeding practices in a rural area of Jamaica" (thesis) Cornell University, 1976, as cited in M. C. Latham, "Infant feeding in national and international perspective: An examination of the decline in human lactation, and the modern crisis in infant and young child feeding practices," presented at New York Academy of Sciences Bicentennial conference on Food and Nutrition in Health and Disease, Philadelphia, 2 December 1976. The five countries studied were Philippines (Guthrie, 1964); Colombia (Meija, 1968); Nigeria (Ransome-Kuti, 1968); St. Vincent (Greiner, 1976); Jamaica (Almroth, 1976).
40. R. Buzina, "Yugoslavia case study: some problems of lactation and working women," presented at IPPF/IUNS Conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, 5–12 July 1977.
41. I. Kamel, "Egypt case study: lactation patterns in the Egyptian woman," presented at International Planned Parenthood Federation/International Union of Nutritional Science conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, 5–12 July 1977.
42. T. H. Greiner, "Breastfeeding in decline: perspectives on the causes," presented at International Planned Parenthood Federation/International Union of Nutritional Sciences conference on Lactation, Fertility and the Working Woman, Bellagio, Italy, 5–12 July 1977.
43. D. Morley, *Pediatric Priorities in the Developing World* (Butterworth, London, 1973).
44. J. B. Wyon and J. E. Gordon, in *Research in Family Planning*, C. V. Kiser, Ed. (Princeton Univ. Press, Princeton, N.J., 1962), p. 25.
45. R. L. Huenemann, "Nutrition and family planning," WHO (Nut/75.3), 1975, as cited in "Women in food production, food handling and nutrition," Report of the United Nations Protein-Calorie Advisory Group, June 1977, p. III.28.
46. R. E. Brown, "Breastfeeding as a concern for family planning programs," prepared for International Planned Parenthood Federation Workshop, Guatemala City, Guatemala, 14–16 November 1977.
47. D. B. Jelliffe, "Assessment of the nutrition status of the community," *WHO Monogr. Ser. 53*, p. 210.
48. C. E. Taylor, in *Nutrition, National Development, and Planning*, A. Berg, N. S. Scrimshaw, D. L. Call, Eds. (MIT Press, Cambridge, Mass., 1973), p. 74.
49. T. P. Schultz and J. Davanzo, "Analysis of demographic change in East Pakistan: A study of retrospective survey data," Rand Corporation, Santa Monica, Calif., 1970; cited in (*8*).
50. M. S. Teitelbaum, "Childhood mortality in relation to fertility behavior and attitudes: A literature review" (unpublished).
51. J. Knodel, *Science* **198**, 1111 (1977).
52. I. Guest, *People* **5**, 26 (1978).

Immunization Against Infectious Disease

Active immunization programs are endangered by complacency and litigation.

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The purpose of this article is to examine the current status of immunization against infectious diseases in man, including the relative importance of immunization in the control of infectious disease in the United States in this century, the efficacy and safety of vaccines, present problems with immunization programs, and prospects for the future.

Types of Immunization

There are two basic forms of immunization, passive and active. Passive immunization is the process by which whole serum or the antibody-containing fraction of serum from a human or animal known to be immune or hyperimmune to the disease in question is administered to a susceptible host. Passive immunization is of use only when exposure has just occurred or is imminent within the next few days or weeks, for the reason that the antibody proteins transferred from one individual to another are gradually broken down over a period of weeks or at the most a few months, and disappear. After their disappearance, the individual is again susceptible to the disease.

Passive immunization has been useful in the prevention of a few diseases. The administration of human immune serum globulin to a susceptible individual who has been exposed to measles or to hepatitis A is associated with clear-cut protection. Some protection is also afforded against hepatitis B and against poliomyelitis. Antitoxin made in horses and in man has some effect in preventing tetanus in a susceptible individual with a tetanus-prone wound, and it is likely that diphtheria antitoxin offers some protection against that disease. In other conditions the benefits of passive immunization are less clear.

Active immunization is the induction of an individual's own immunity by inoculation with the offending organism or some part or product thereof that has been treated in such a way as to induce clinical immunity without producing the full-blown disease. For five reasons active immunization is superior to passive immunization. First, the duration of protection, like that of the natural diseases, is frequently lifelong. With others, length of immunity is measured in years requiring infrequent booster inoculations for maintenance of protection. Second, protection is ever present and does not require recognition of exposure (in up to 50 percent of cases of tetanus in the past the inciting wound was unnoticed or too trivial to warrant attention). Third, with few exceptions serious reactions to active immunization are rare. With animal serums employed in passive immunization, serum sickness is frequent and immediate anaphylactic shock occasionally occurs; even with products of human serums anaphylaxis has been reported. Fourth, the protective efficacy of active immunization exceeds that of passive immunization, and in many instances approaches 100 percent. Fifth, active im-

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munization is less expensive than passive immunization, because vaccines are cheaper to produce than are antiserums.

There are basically five different types of preparations used for active immunization. The first of these consists of whole organisms which are killed by heat or chemically but retain the capacity to induce immunity. Examples of such killed vaccines include pertussis (whooping cough), typhoid, cholera, influenza, inactivated poliomyelitis (Salk), and killed measles vaccines. In general, killed, whole vaccines have been considered to be less efficacious than other forms of active immunization. Indeed, cholera vaccine offers only about 50 percent protection, and killed measles vaccine is no longer licensed because not only does it offer less protection than live measles vaccine but also it produces hypersensitivity to the measles virus, resulting in untoward reactions to later natural disease or immunization with live virus. An exception to the general rule that inactivated whole organism vaccines are of limited effectiveness is inactivated poliomyelitis vaccine, the widespread use of which in certain countries, such as Sweden, has resulted in eradication of the disease (*1*).

The second preparation used for active immunization includes extracted cellular fractions which have been shown to be the antigens that induce clinical immunity in man. Meningococcal vaccine consists of the polysaccharide antigen of the cell wall, and the recently licensed pneumococcal vaccine consists of the polysaccharide contained in the capsule of the organism. Although the duration of experience with these two vaccines is limited, their efficacy and safety appear to be high.

A third type of vaccine is the toxoid. In both diphtheria and tetanus the manifestations of the disease are due to the elaboration of a toxin by the organism. Toxoids are made by inactivating large amounts of toxin with formalin. Immunization with a toxoid thus produces antibodies that, rather than acting upon the organism itself, instead neutralize the toxic moiety produced during infection. Toxoids—especially that of tetanus—are highly efficacious and safe immunizing agents.

The fourth group of preparations for active immunization includes the live, attenuated viral vaccines. They are measles, mumps, rubella, live attenuated poliomyelitis (Sabin), smallpox, and yellow fever vaccines. These vaccines consist of organisms that have been passed repeatedly in the laboratory in tissue culture or chick embryos and have lost their capacity to induce the full-blown disease but retain their immunogenicity. Some, such as oral poliomyelitis, mumps, and yellow fever vaccines, produce few or no symptoms in inoculees; others may produce mild symptoms reminiscent of the natural disease. In general, live attenuated vaccines are highly efficacious in inducing lifelong immunity and with rare exceptions are unassociated with complications.

The fifth form of active immunization is the induction of infection with a benign organism that induces immunity not only to itself but also immunity that "cross-reacts" and protects against a more severe infection. Bacillus Calmette-Guérin (BCG), used to induce immunity to tuberculosis, is both cross-reactive and attenuated. It was originally derived from a strain of bovine tuberculosis which was then passed repeatedly, over many years, in laboratory culture. Indeed, the first successful attempts to immunize man by means of a cross-reactive organism occurred early in the 18th century when it was found that the deliberate infection of an individual with cowpox provided protection from smallpox. More recently, it has been shown that certain benign organisms, normal flora of man, cross-react immunologically with certain pathogenic organisms, such as pneumococci, meningococci, and *Haemophilus influenzae*, type b (*2*). Not only is it possible that these normal flora are responsible for some naturally acquired immunity in man (*3*), but also they may afford a new approach to immunization in the future.

Summary. Mortality and morbidity from infectious diseases in the United States have declined more than 90 percent since 1900. Factors believed to be responsible for this decline include changes in the natural history of disease, sanitation, quarantine measures, control of nonhuman vectors, antibacterial drugs, and immunization. The contributions of each of these factors differ among the various infectious diseases; except for smallpox and diphtheria control, immunization had little effect until after World War II. The success of present and future immunization programs is endangered by public and physician complacency and by complex legal and ethical problems related to informed consent and responsibility for rare, vaccine-related injury.

Control Measures in Infectious Diseases

What is the importance of immunization, past and present, in the control of infectious disease? In the United States since the turn of the century life expectancy has increased remarkably. Expected duration of life for individuals born in 1900 was 47.3 years; in 1970 it was 70.9 years (*4*). The age-adjusted death rate in 1900 was 17.2 deaths per thousand population, whereas in 1970 it was 9.5 per thousand, a reduction in mortality of 45 percent (*4*).

Table 1 indicates that most of this decline in mortality is due to diminution in deaths caused by infectious diseases. The reporting of causes of deaths in 1900 to 1904 was not strictly comparable to that of 1970; moreover, causes in the early 1900's were recorded for only about 40 percent of the U.S. population (who resided in areas with death registration), whereas records are kept for the entire population now. Nonetheless, approximately one-third of all deaths in those early years were due to infectious diseases, compared to about one of every 25 in 1970 (*4*).

Since the turn of the century the decrease in mortality has been most pronounced in younger age groups. Table 2 shows changes in death rates that have occurred in four representative age groups. The mortality rate in children 1 to 4 years of age declined 96 percent between 1900 and 1970, whereas that in the population aged between 65 and 74 years declined by only a little more than a third (*4*).

Table 3 shows that much of this change in mortality in younger age groups is due to a decrease in deaths from certain infectious diseases, including the common contagious diseases of childhood, tuberculosis, meningitis, pneumonia, and epidemic diseases such as typhoid fever, plague, and smallpox (*4*). Table 3 compares the deaths that would have been expected in children in three age groups in 1973 if the 1900 death rates from infectious disease and from all causes had prevailed in 1973. Most of the reduction in expected mortality in the age group less than 1 year of age probably relates to better obstetrical and neonatal care; less than 25 percent of the decrement can be attributed to the decline in infectious disease mortality. But in children older than 1 year of age, approximately two-thirds of the decreased mortality can be attributed to a decline in

Table 1. Crude death rates in the United States, 1900 to 1904 and 1970.

Causes	1900 to 1904		1970	
	Deaths per 100,000	Percentage of all deaths	Deaths per 100,000	Percentage of all deaths
All	1659.0	100.0	940.2	100.0
Infectious diseases	541.0	32.6	37.9	4.0
Epidemic diseases	146.8	8.8	5.4	0.6
Tuberculosis	195.5	11.8	1.8	0.2
Meningitis	33.1	2.0	0.9	0.1
Pneumonia and influenza	165.6	10.0	29.8	3.2

deaths from the above-specified infectious diseases.

To what influences can these salutary changes be attributed? How much, for example, is due to immunization? Clearly, there are multiple reasons for the decline in mortality due to infectious diseases in the United States in this century, and in many instances it is impossible to determine the relative importance of different factors. The specific factors and certain diseases upon which they may have had an effect follow.

There is little question that the natural history of some infectious diseases has changed spontaneously over the years, for reasons not entirely clear. An example of such a disease is pertussis, which exhibited a mortality rate of 12.2 per 100,000 population in the United States in 1900 (*4*). By the late 1930's, prior to widespread immunization against pertussis, the mortality rate had decreased to approximately two per 100,000. In 1975 only eight deaths due to whooping cough were recorded in the United States (*5*). Whether this reduction prior to the development of widespread immunization (and even the change subsequent to immunization) is due to variations in the organism, changes in the host, or other undetermined factors is unclear. It is possible that simple quarantine measures, intended or unintended, may have contributed to this decline prior to immunization, inasmuch as the highest fatality rates from pertussis are in young infants. Postponement of the disease until later childhood would clearly reduce mortality.

Similarly, mortality due to measles declined from 13.3 per 100,000 population in 1900 to 0.3 per 100,000 in 1955 prior to the institution of measles immunization (*4*). The reason for this is unclear; it might relate, as with pertussis, to intentional or unintentional quarantine and consequent postponement of measles to older childhood. During the years 1900 to 1910 mortality from scarlet fever and streptococcal sore throat was more than ten per 100,000 people annually; this declined to 0.5 per 100,000 by 1940, prior to any effective means of intervention with antimicrobial drugs (*4*).

To a considerable extent in some diseases, the decline in mortality can be attributed to man's intervention in terms of sanitary control of water supplies and refuse and proper food handling. An example of such a disease is typhoid fever. During the 5 years, 1900 to 1904, nearly 54,000 deaths from typhoid fever were recorded among the approximately 32 million residents of the death registration areas in the United States (*4*). In the year 1975, among more than 200 million people, 375 cases with three deaths were recorded (67 deaths due to all types of salmonella infections were reported for 1975) (*5*). The paucity of cases in 1975 compared to 1900 can be attributed to better sanitation and food handling. Inasmuch as typhoid fever in the past exhibited a mortality rate of 10 to 25 percent, the fact that in 1975 only three of the 375 cases succumbed to the disease is probably attributable to antimicrobial drugs.

As mentioned above, quarantine measures, intended or unintended, may have contributed in part to this decline. Mortality from tuberculosis in 1945, prior to the development of any effective antituberculous drugs, was one-fifth that of 1900 (*4*). How much of this might have been due to the identification of patients and their isolation from others, to changes in the natural history of the disease, or to other factors is unknown. The precise effect of isolation of patients with other contagious diseases at home or in hospitals specifically designed for that purpose is also unknown.

Control of nonhuman vectors has been responsible for much of the decline in mortality from some diseases, such as rabies, typhus fever, and malaria in the United States. Antimicrobial drugs effective against certain bacterial diseases have certainly contributed to the decline in mortality from infection since their development and widespread use during, and subsequent to, World War II. However, studies in Sweden have suggested that death rates from many bacterial diseases that declined subsequent to the development of antibiotic drugs were actually declining at the same rate prior to their use (*6*). Among 13 bacterial infectious diseases studied, death rates due to syphilis, non-meningococcal meningitis, and septicemia were the only ones that appeared to decline more rapidly after the introduction of these drugs. It may well be that other unknown factors, such as nutrition, changes in socioeconomic and educational status, and the like have also contributed to the decline in mortality observed in the United States since the turn of the century.

In view of the above, what has been the contribution of immunization to the decreased mortality from infectious disease in the United States? In the case of a number of diseases, immunization—though available and of some effect—has been of negligible importance. These diseases include typhoid fever, cholera, epidemic typhus fever, and plague. Far more important than immunization has been control of transmission of the infecting organisms. Thus, immunization against these diseases is reserved for those who, because of occupation or travel, cannot avoid exposure.

The disappearance of mortality from one disease (smallpox) and the rarity of deaths from two others (tetanus and poliomyelitis) can be attributed almost entirely to active immunization. Their disappearance has directly paralleled the use of immunization with no other factors seeming to exert influence. In contrast, the decline in measles mortality is a result of at least two factors. Although attack rates for measles remained the same with only year-to-year variations (200 to 400 cases per 100,000 per year—everyone had measles sooner or later) until the development of the measles vaccine, for reasons unknown mortality rates declined from approximately ten per 100,000 population during the years 1912 to 1918 to less than 0.3 per 100,000 in the 1950's before licensure of the vaccine (*5*). Since licensure, annual attack rates from measles have decreased precipitously to less than 20 per 100,000, and deaths to less than 0.01 per 100,000.

Examination of the effects of widespread measles immunization points out benefits other than reduction in mortality. For Massachusetts during the years 1965 to 1971 it was estimated that measles immunization efforts prevented more than 114,000 of 137,000 cases that would have been expected without immunization, thus averting ten deaths and 114 cases of encephalitis, of whom one-

third would have been expected to incur permanent intellectual impairment (*7*). The ultimate saving in health care costs in Massachusetts was estimated at $5.5 million. Thus, the value of immunization should not be measured only in terms of lives saved.

There is also little doubt that the rarity of diphtheria in the United States at present is due in large part to the widespread use of diphtheria toxoid, although mortality from the disease was decreasing even prior to attempts at active immunization. Between 1900 and 1920, prior to widespread effective diphtheria immunization, the mortality approximately halved. With five deaths in each of the years 1974 and 1975, the mortality rate is less than 0.02 percent of the 1920 rate (*4*).

Rubella is another example of an infection, like measles, the importance of which is measured by other than mortality. Rubella itself is a mild disease, but if a woman in the first 3 months of pregnancy experiences the disease it is probable that her infant will be born with a combination of manifestations of infection known as the congenital rubella syndrome. The syndrome is often fatal in the perinatal period and survivors may exhibit permanent sequelae, including mental retardation, severe deafness, and cataracts. It is estimated that approximately 20,000 infants were born with the rubella syndrome in the United States following the 1964 to 1965 rubella epidemic (*8*). Because epidemics of rubella are expected about every 7 years, efforts were made in the United States to immunize as many children as possible prior to 1971–1972, inasmuch as they comprise the reservoir of the disease. In addition, immunization of women of child-bearing age, especially if shown to be susceptible to rubella by serologic testing, has been advocated. Though it is impossible to predict what would have happened in the absence of a rubella immunization campaign, it appears that the frequency of the congenital rubella syndrome is considerably below that expected (*8*).

Immunization against mumps is carried out primarily because the disease is a nuisance. Mortality from mumps is essentially unheard of; aseptic meningitis is a frequent and unpleasant complication without permanent sequelae. Very rarely, sterility or permanent nerve deafness occurs. Reporting of mumps is sufficiently haphazard, the disease so often misdiagnosed, and complications so rare that the effects of widespread mumps immunization are unmeasured.

Review of morbidity and mortality rates from whooping cough shows that both have declined strikingly since the 1940's, when pertussis immunization came to be used widely in the United States (*4*). However, the death rate from pertussis was already decreasing prior to widespread immunization. In 1950 the annual pertussis death rate per 100,000 infants was 24; in 1975 it was less than 0.3 (*5*). How much of this decrease is due to immunization and how much to other factors is uncertain.

Table 2. Age-specific mortality rates, 1900 and 1970, shown as deaths per 1000.

Years	Age group in years			
	1 to 4	15 to 24	45 to 54	65 to 74
1900	19.8	5.9	15.0	56.4
1970	0.8	1.3	7.3	35.8
Decline (%)	96.0	78.0	51.0	37.0

For the reason that there is general agreement that much of the recent improvement in mortality and morbidity from the common infectious diseases of childhood and from less common but dangerous diseases such as diphtheria, tetanus, and poliomyelitis is due to immunization, it is now recommended that all U.S. children receive routine immunization according to the schedule in Table 4 (*9*).

Problems with Immunization Programs

Vaccines are not perfect. Indeed, the protective efficacy of some, such as cholera and typhoid vaccines and BCG for tuberculosis, is such that control of the disease by epidemiologic and chemotherapeutic means is far more efficacious. These vaccines are only adjuncts to prevention, used under special circumstances for what added protection they afford. Even those vaccines employed for the routine immunization of children are not always 100 percent efficacious and are associated with some risk. Moreover, although these vaccines have been used for many years, data that prove efficacy for some are not adequate by 1978 standards.

Probably the safest and most effective of the immunizing agents used for routine immunization of children is tetanus toxoid. The efficacy of tetanus toxoid was well established in World War II. During the Civil War 205 cases of tetanus occurred for every 100,000 wounds (*10*). This rate was reduced to 16 per 100,000 wounds in World War I, presumably as a result of better surgical care of wounds and liberal use of tetanus antitoxin prepared in horses (*11*). By World War II all U.S. military personnel were required to accept tetanus toxoid; among more than 2.5 million injuries only 12 cases of tetanus occurred, of whom eight had not been adequately immunized (*11*). This rate of 0.44 cases of tetanus per 100,000 wounded represents a 99.8 percent reduction from the Civil War and 97 percent from World War I. In civilian populations tetanus still occurs. In 1975, 102 cases of tetanus were recorded in the United States (*12*); in all of these individuals tetanus immunization had never been given, was incomplete, or was unknown. Reactivity to tetanus toxoid is minimum. Very rare instances of anaphylaxis have been recorded, and some individuals, usually those with multiple previous injections, experience unpleasant but transient fever and malaise.

Equally efficacious is live, attenuated poliomyelitis vaccine, administered orally. During the years 1948–1952, prior to vaccine development, an average of about 38,000 cases of poliomyelitis occurred annually in the United States, of which about half resulted in paralysis (*13*). In contrast, for the 8 years, 1969–1976, when 193 million doses of vaccine were distributed, a total of 119 paralytic cases occurred, most of which were in unimmunized or inadequately immunized individuals (*5*). However, 55 of these cases were temporally associated with vaccine administration to the pa-

Table 3. Observed deaths due to infectious disease and all causes in children in 1973 compared to deaths that would be expected at 1900 rates.

Expected versus observed	Age group in years		
	< 1	1 to 4	5 to 14
1973 population at risk	3,079,000	13,635,000	38,983,000
Deaths due to infectious disease			
Expected at 1900 rate	104,994	159,530	93,559
Observed in 1973	5,446	1,265	973
Deaths due to all causes			
Expected at 1900 rate	500,030	269,973	152,034
Observed in 1973	55,581	10,843	15,982

tient or a close contact. Ten occurred in recipients themselves, 34 in close contacts, and 11 in recipients or close contacts who had underlying immune deficiencies (*14*). In addition, in these vaccine-associated cases, antigenic characterization of the infecting viruses indicated that almost all were derived from vaccine strains (*15*). Thus, although the efficacy of live, attenuated poliomyelitis vaccine is very high, there is a certain low risk of disease in recipients or contacts. That risk appears to be about one per 1.6 million doses. Surprisingly, in developing countries the efficacy of oral poliomyelitis vaccine is considerably less than in the United States (*16*).

The efficacy and safety of pertussis vaccine are currently the subject of controversy. Although precise data are not available, full immunization does not guarantee permanent protection. Moreover, pertussis vaccine produces some severe or worrisome reactions, including brain damage, convulsions, and a strange screaming phenomenon in infants, the significance of which is unknown. Precise rates of these reactions are not defined because of unsatisfactory monitoring, differences among vaccines, uncertain denominators, and varying diagnostic criteria. A major handicap in developing an improved pertussis vaccine is that the protective antigen in the bacterium has not been determined, nor is it known what fraction of the organism produces the reactions. In Britain it has been questioned publicly whether the decline in pertussis mortality has any relation to the vaccine at all, which, in combination with concerns about serious reactions, has resulted in reluctance to use the vaccine on the part of both physicians and the public (*17*).

Other examples of lack of 100 percent efficacy can be given, such as the failure of measles vaccine to "take" in up to 5 percent of recipients (*18*), the occurrence of diphtheria in fully immunized individuals though the disease is milder (*19*), and the like. But the importance of these occasional failures is unknown; will the 5 percent of individuals who remain susceptible to measles in spite of immunization be protected because measles cannot establish itself in a population that is 95 percent immune? This and many other questions are unanswered.

Why are many questions unanswered and such problems unsolved in relation to vaccines?

First, it is unreasonable to expect immunization to be 100 percent efficacious (even some of the diseases themselves, such as pertussis and diphtheria, do not guarantee permanent immunity).

Table 4. Recommended schedule for the active immunization of normal infants and children. Abbreviations: DTP, diphtheria and tetanus toxoids and pertussis vaccine, combined; TOPV, trivalent oral poliomyelitis vaccine (contains all three immunologically distinct strains of attenuated poliomyelitis virus); Td, adult form of tetanus and diphtheria toxoids (the diphtheria toxoid component is reduced because of possible reactivity in individuals with several previous inoculations).

Age	Vaccines
2 months	DTP and TOPV
4 months	DTP and TOPV
6 months	DTP (TOPV—optional)
15 months	Measles, rubella, and mumps
1½ years	DTP and TOPV
4 to 7 years	DTP and TOPV
14 to 16 years (and every 10 years thereafter)	Td

Second, vaccines that have been with us for many years (such as diphtheria toxoid) were not subjected originally to well-designed, prospective controlled field trials that would meet current standards. But, in view of the presumed effect of the toxoid on the incidence of diphtheria in the United States, it is unreasonable to demand such a field trial now.

Third, many vaccines can only be tested in man because of the lack of appropriate animal models that correlate precisely with the effects of vaccines in man. Further, even in man the logistics, expense, and necessary duration of controlled field trials of disease prevention require reliance on indirect measures of protection, such as serology or skin testing. Some of these measures, such as serologic testing for immunity to pertussis, have not been shown to correlate well with clinical immunity. In some instances many years must pass before answers will be available; will a 23-year-old woman, pregnant in the year 2000, be protected against rubella by the vaccine she received in 1978?

Fourth, the climate for testing in humans is currently poor in the United States, and studies necessary to develop answers to some questions are often unacceptable to study subjects.

Fifth, the monitoring of disease, and especially vaccine reactions, is grossly inadequate in the United States, being totally dependent on the judgment and cooperation of thousands of different health providers who may not understand the need for reporting, may not care, and may fear malpractice litigation. The rarity of severe reactions is also such that isolated instances may be considered to be coincidence; it is quite possible that the Guillain-Barre syndrome has always occurred at a low rate in persons immunized against influenza, and was only recognized with the swine flu vaccine because large numbers of people received the vaccine in a limited period of time.

Finally, in view of the current low morbidity and mortality from vaccine-preventable diseases compared to years past, further vaccine development may have relatively low priority compared to research in other health problems when it comes to funding.

The lack of visibility of vaccine-preventable diseases in the United States has also resulted in a certain amount of complacency in both health professionals and the public. In 1975 only 116 deaths were reported from diseases against which children are routinely immunized (Table 4) (*5*). This has resulted in less than the optimum number of children being immunized (*20*). For example, in 1975 only 64.8 percent of 1- to 4-year-old children had received three or more doses of poliomyelitis vaccine, compared to 73.9 percent in 1965. The low was 1973 with 60.4 percent. Only 75.2 percent of 1- to 4-year-olds had received three or more doses of diphtheria and tetanus toxoids and pertussis vaccine, and 65.5 percent measles vaccine. This latter deficit resulted in localized outbreaks of measles with more than 41,000 cases in 1976; how small the proportions of the population immune to poliomyelitis and diphtheria must be before substantial outbreaks occur is unknown. Curiously, it was estimated that 12.6 percent of children less than 5 years of age in the United States received smallpox vaccination in 1975 (*20*), although the Public Health Service recommended against its routine use in 1971 (*21*).

Because of public and professional complacency related to routine immunization, the U.S. Public Health Service in 1973, in cooperation with the American Academy of Pediatrics, state and local health agencies, and other groups, initiated an annual effort designating October as "Immunization Action Month." Though some improvement in proportions of children immunized may have occurred, too many remain without protection (*20*). Accordingly, in 1977 the Department of Health, Education, and Welfare under Secretary Joseph A. Califano and Assistant Secretary for Health Julius B. Richmond established enhanced public programs directed at achieving adequate immunization of 90 percent of all children by October 1979. The programs include increased public education, funding for local and national coordinating efforts, mandated monitoring of immunization status in publicly supported

child health programs, cooperative efforts with other public and private agencies, and enforcement of school entry immunization requirements. That these efforts may be effective is the fact that during the first 6 months of 1977 doses of measles vaccine administered in public clinics exceeded those for the first 6 months of 1976 by 69 percent (*22*).

Major problems with the potential of compromising immunization programs seriously are those of informed consent and litigation surrounding vaccine-related injuries. Largely as a consequence of these closely related problems, the production of measles, rubella, mumps, and oral poliomyelitis vaccines is limited to one manufacturer in the United States. Six other producers of one or more of these vaccines have ceased providing them in recent years. Because of litigation and judgments awarded the victims of injury from vaccines, advocacy has developed for a system of public recompense for those individuals inadvertently injured by programs of accepted public health merit. The need for individual informed consent concerns many physicians; is it possible to fully and fairly inform patients and parents of the benefits and risks associated with a given vaccine, and do they have the background and perspective to make appropriate decisions? Should we combine a system of public recompense for vaccine injury with a system of public informed consent for mandatory immunization, rather than individual consent? If the public is to assume responsibility for those few permanently injured by a vaccine, should the public also accept responsibility for the individual who refused immunization and ended up permanently in an institution as a consequence of measles encephalitis? These are not easy questions to answer.

Because of the problems cited above, including the need for further research and development in vaccines, unsatisfactory rates of immunization, and concerns about supply, liability, and informed consent, the Assistant Secretary for Health established work groups charged with examining these problems and proposing answers. These work groups suggested many solutions, including alternatives, too numerous to review here (*23*). But among the most important of the recommendations was that of a National Immunization Commission, with representation from both biomedical and nonbiomedical areas, and reporting to the Administration and Congress. The broad charge to the commission would include all aspects of furthering appropriate immunization activities in the United States, from research to implementation. A major advantage of such a commission would be that of developing understanding of, and support for, immunization programs outside the biomedical community.

Prospects for the Future

The apparent success of viral vaccines developed in the past 20 years has stimulated pursuit of further immunizing agents including bacterial vaccines in which progress has been slower (*24*). The meningococcal and pneumococcal vaccines, recently licensed, appear appropriate for certain high-risk groups (*24*). The sequelae of meningitis caused by *Haemophilus influenzae*, type b, in young children warrant efforts to develop a protective vaccine (*24*). These three polysaccharide vaccines are further justified by the appearance of resistance of the offending organisms to the formerly effective chemotherapeutic drugs (*24, 25*). A major problem, however, is the poor response elicited in infants (*24*). Exploration of vaccines against Gram-negative organisms responsible for sepsis in debilitated patients and young infants and against group B streptococci has been initiated (*24*). Though not yet licensed, a vaccine against *Mycoplasma pneumoniae*, the causative agent of primary atypical pneumonia, has been shown to be effective in military populations in whom the disease is of importance (*24*). Preliminary background work directed at vaccines against gonorrhea and syphilis is under way (*24, 26*). Although work has progressed in relation to vaccines for the common respiratory diseases of man, the multiplicity of causative viruses makes such vaccines unlikely in the near future (*27*). Though of little importance in the United States, a vaccine effective against malaria would be of maximum benefit elsewhere in the world where the vector control measures, so successful in this country, have failed (*28*).

No doubt, as further vaccines appear, a point may be reached at which the costs of some vaccines in terms of logistics, dollars, and untoward effects outweigh the health benefits to be expected. But this point has not been reached yet; the pneumococcal and meningococcal vaccines appear to be valuable preventive measures, and others mentioned above should be pursued as potential solutions to currently unsolved problems of infection. Further judgments should be made by the proposed Commission on Immunization, with technical consultation from already functioning groups such as the Surgeon General's Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Public Health Association, the National Institute of Allergy and Infectious Diseases, and the Bureau of Biologics and its vaccine advisory panels.

References and Notes

1. P. Halonen, data presented at Workshop on Poliomyelitis Vaccines, American Academy of Pediatrics, Evanston, Ill. (1975).
2. J. B. Robbins *et al.*, *J. Allergy Clin. Immunol.* **56**, 141 (1975).
3. R. Gold, I. Goldschneider, M. L. Lepow, T. F. Draper, M. Randolph, *J. Infect. Dis.* **137**, 112 (1978).
4. These data were derived and recalculated from Bureau of the Census, *Historical Statistics of the United States, Colonial Times to 1970*, part 1 (Department of Commerce, Government Printing Office, Washington, D.C., 1975); Bureau of the Census, *Special Reports, Mortality Statistics, 1900 to 1904* (Departments of Commerce and Labor, Government Printing Office, Washington, D.C., 1906); National Center for Health Statistics, *Vital Statistics of the United States, 1973*, vol. 2, *Mortality*, part A (Department of Health, Education, and Welfare, Public Health Service, Rockville, Md., 1977).
5. Center for Disease Control, *Reported Morbidity and Mortality, Annual Summary, 1976* (Department of Health, Education, and Welfare, Public Health Service, Atlanta, Ga., 1977).
6. E. Hemminki and A. Paakkulainen, *Am. J. Public Health* **66**, 1180 (1976).
7. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **21**, 178 (1972).
8. S. Krugman and S. L. Katz, *N. Engl. J. Med.* **290**, 1375 (1974).
9. *Report of the Committee on Infectious Diseases* (American Academy of Pediatrics, Evanston, Ill., 1977).
10. W. H. Holmes, *Bacillary and Rickettsial Infections* (Macmillan, New York, 1940).
11. G. Edsall, *J. Am. Med. Assoc.* **171**, 417 (1959).
12. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **26**, 401 (1977).
13. T. Francis *et al.*, *Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine* (School of Public Health, University of Michigan, Ann Arbor, 1957), p. 29.
14. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **26**, 329 (1977).
15. Institute of Medicine, *Evaluation of Poliomyelitis Vaccines* (National Academy of Sciences, Washington, D.C., 1977).
16. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **26**, 247 (1977).
17. *Whooping Cough Vaccination. Review of the Evidence on Whooping Cough Vaccination by the Joint Committee on Vaccination and Immunization* (Department of Health and Social Security, Her Majesty's Stationery Office, London, 1977); Parliamentary Commissioner for Administration, *Whooping Cough Vaccination* (Her Majesty's Stationery Office, London, 1977).
18. A. S. Yeager, J. H. Davis, L. A. Ross, B. Harvey, *J. Am. Med. Assoc.* **237**, 347 (1977).
19. Center for Disease Control, *Diphtheria Surveillance, Report No. 11, 1969-1970 Summary* (Department of Health, Education, and Welfare, Public Health Service, Atlanta, Ga., 1971).
20. Center for Disease Control, *United States Immunization Survey: 1975* (Public Health Service, Atlanta, Ga., 1976).
21. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **20**, 339 (1971).
22. Data presented by A. Hinman to Committee on Infectious Diseases, American Academy of Pediatrics (1977).
23. *Reports and Recommendations of the National Immunization Work Groups* (submitted to the Office of the Assistant Secretary for Health, JRB Associates, McLean, Va., 1977).
24. Symposium on Current Status and Prospects for Improved and New Bacterial Vaccines, J. B. Robbins and J. C. Hill, Eds., in *J. Infect. Dis.* **136**, S1 (1977).
25. Center for Disease Control, *Morbidity and Mortality Weekly Report* (Public Health Service) **27**, 1 (1978).
26. J. B. Baseman, *J. Infect. Dis.* **136**, 308 (1977).
27. A. S. Evans, *Communicable and Infectious Diseases*, F. H. Top and P. F. Wehrle, Eds. (Mosby, St. Louis, ed. 7, 1972), p. 511.