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New scientific opportunities and old obstacles in vaccine development

KENNETH S. WARREN

The Rockefeller Foundation, 1133 Avenue of the Americas, New York, NY 10036

ABSTRACT **The present status of and priorities for vaccine development are described, and the historical conditions under which vaccines have been developed are contrasted with newer technologies for such development. Current programs, the opportunities they present, and the obstacles to their implementation are summarized.**

A recent report (1) from the Institute of Medicine entitled *Vaccine Supply and Innovation* stated, "Vaccines are an elegant solution to one of the perennial problems of the human race—infectious disease. The body's own protective mechanisms are primed by specific interventions to thwart the invasion or multiplication of pathogens." Lewis Thomas has described this immunization process as one of the genuinely decisive technologies of modern medicine—it is effective, relatively inexpensive, relatively simple, and relatively easy to deliver. It is heartening, therefore, that we are now in the midst of two revolutions, the biotechnology revolution, which is providing an unprecedented opportunity to produce new and better vaccines, and the children's revolution of the United Nations Children's Fund (UNICEF), which, since the fall of 1984, has focused on immunizing all of the world's children.

Going back to the beginning, since Jenner discovered the vaccine for smallpox in 1780, approximately 20 vaccines have been developed (Fig. 1). Fewer than 10 of them, however, are in general use, and many are defective in terms of degree and duration of effectiveness and occurrence of unpleasant to lethal side effects. It has been glibly stated that approximately 20 new vaccines will be developed in the next 20 years. This, however, may be a gross understatement.

Before discussing the new vaccines being developed, the present status and priorities for vaccines will be described for both the developed and the developing world, which will be designated henceforth as North and South (2). In the North, and particularly in the United States, children are immunized against diphtheria, pertussis, tetanus, measles, polio, mumps, and German measles. A particular problem here is the occasional but severe side effects of the pertussis and polio vaccines, which are major factors in liability suits. For the elderly, influenza and pneumococcal vaccines are available, but, unfortunately, they are not being used adequately. Principal vaccines being provided to travelers are typhoid and cholera, both of which cause brief, flu-like illnesses and are relatively ineffective. A hepatitis B vaccine is now available for groups at special risk, but it is not being adequately used because of unwarranted fears of side effects.

The principal targets for vaccines in the South are children and their mothers. For children, the vaccines provided by the World Health Organization's (WHO) Expanded Programme on Immunization are bacillus Calmette–Guerin (BCG), diphtheria, pertussis, tetanus, measles, and polio (3). Of particular concern is the cumbersomeness of delivery occasioned by the necessity to keep the live virus vaccines, polio and measles, refrigerated and the questionable effectiveness of BCG for pulmonary tuberculosis. For mothers, tetanus immunization is necessary to reduce the high incidence of neonatal tetanus. Even the priorities for vaccines in the North and South are different. Major studies establishing these priorities by a formula involving cost-effectiveness analysis and decision analysis have been published by the Institute of Medicine (4, 5). The priorities for the North and South are shown in Table 1. It should be noted that these outcomes were determined not by need alone but also by the status of research in terms of the probability of vaccine development.

Since vaccines are particularly urgent in the South, the causes of childhood death are worthy of note. The major causes of mortality are diarrheas, measles, lower respiratory infections, tetanus, and malaria. UNICEF has calculated that more than 5 million children die each year from immunizable diseases, mostly measles, pertussis, and neonatal tetanus; this is not surprising since less than 20% of the children of the developing world are immunized (6). Studies done in Ghana reveal that in terms of healthy days of life lost, immunization against measles, tetanus, and pertussis would cause a 12.4% overall reduction. If significant immunization against malaria, respiratory infections, and diarrhea were added, the reduction would be more than 40% (7).

Now we come to the niggling obstacles and immense opportunities in the development and application of new and better vaccines. Opportunities are offered by the biotechnology and children's revolutions. Obstacles are raised by a Luddite* mentality toward new approaches to vaccines, conservatism and ineptitude by both industry and government, and the uniquely American problem of litigation.

To avoid T. S. Eliot's ending—"not with a bang but a whimper"—we will begin first with the obstacles. Fear of genetic engineering, which was reasonable as this remarkable technology was conceived, has become almost ridiculous with respect to vaccines. In the past, through trial and error and multiple passages in animals and tissue culture, infectious organisms were attenuated into nonpathogenic vaccines. There was no information on how this occurred, what were the sites that were changed, and whether the organisms might revert to virulence. Now, with genetic engineering, precise areas determining virulence can be deleted, replication of the organisms can be diminished or abolished, protective antigens can be inserted into viral and bacterial vectors, and chemical fragments of complex organisms that induce protective responses can be made available in large quantities. Nevertheless, organizations such as the Founda-

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*Luddite, a member of a band of English artisans (1811–1816) who raised riots for destruction of newly introduced machinery; a person similarly engaged in seeking to obstruct progress.

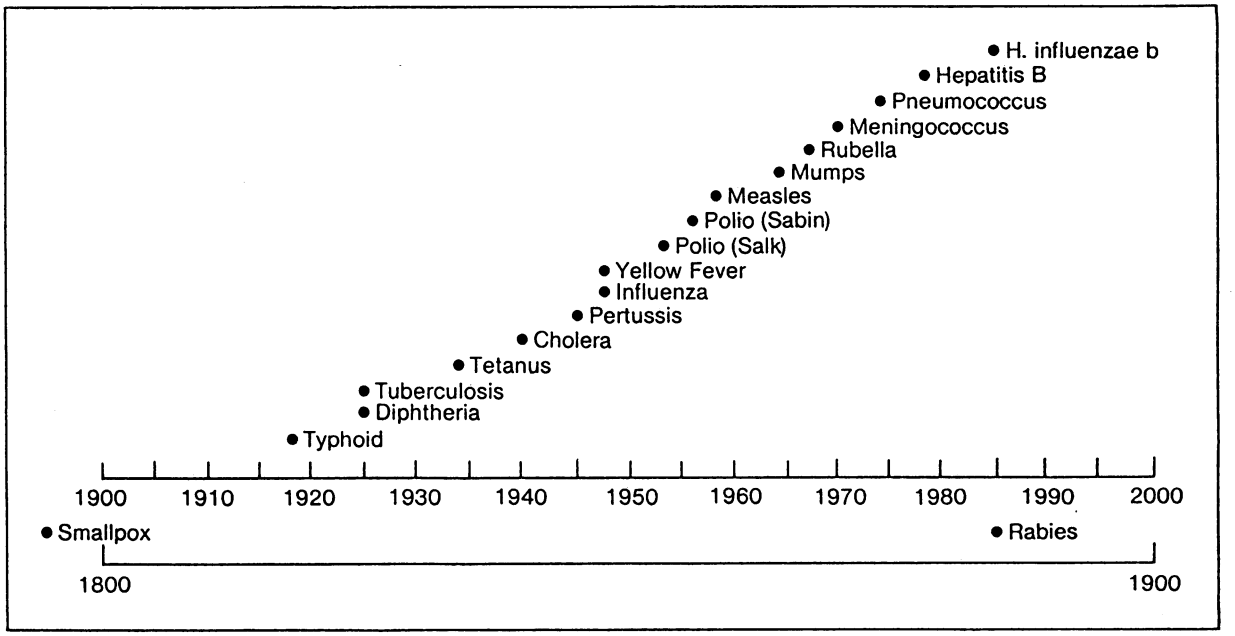

FIG. 1. Vaccines since Jenner.

tion on Economic Trends oppose the use of all gene-altered agents in the environment. A case in point is the recision of approval for a vaccine to prevent pseudorabies, a major disease of swine, cattle, and sheep. Although three nonrecombinant live pseudorabies vaccines are commercially available, this is the only one in which a gene has been precisely deleted, and that deletion prevents the virus from replicating (8–10).

It is important, however, to realize that both government and industry foster the activities of the Luddites by simple failure to follow rules and procedures. In the pseudorabies case, the U.S. Department of Agriculture, without notifying a key scientific committee, approved the first field test for the use of a living gene-altered agent. The Foundation on Economic Trends immediately jumped into the breach and received considerable publicity. Within 2 weeks, after the vaccine went to the proper committee, it was approved (8–10). Industry has also afforded the Luddites ample opportunities. Advanced Genetic Sciences provided an example, when to prevent frost damage to strawberries, a bacterial gene for a protein that causes the formation of ice crystals was deleted. The company failed to inform local residents prior to field testing and, in fact, had previously injected trees with the bacteria in noncontainment facilities, thus offering opportunities for obstruction (11–13).

Both government and industry have shown conservatism in the sense of tolerating vaccines that would be completely unacceptable today. The perfect example is the highly defective pertussis vaccine, which may cause screaming fits and mental retardation and has remained unaltered for decades. Another example is a genetic engineering firm that was asked whether their hepatitis B vaccine contained the highly effective pre-S moiety; their reply was no and what they had was good enough anyway.

Table 1. Priorities for new vaccine development

North	South
Hepatitis B	*Streptococcus pneumoniae*
Respiratory syncytial virus	*Plasmodium* spp.
Hemophilus influenzae b	Rotavirus
Influenza A and B	*Salmonella typhi*
Herpesvirus varicellae	*Shigella* spp.

The litigation problem is all too well known; suffice to say that it has resulted in the decline of companies producing vaccines in the United States to a bare minimum!

In a recent editorial in *Nature (London)* entitled "New Technology of Medicine" (14) John Maddox pointed out that in spite of the great promise of biotechnology there has been "some disappointment in the air" concerning the output of "artificially engineered versions of naturally occurring materials" and with "the genetic manipulation of plants." He displayed optimism, however, about "vaccines, the classical tools of preventive medicine" noting the vaccinia vector and the progress of vaccine development for malaria and schistosomiasis. As a matter of fact at a workshop on vaccine innovation and supply convened by the Institute of Medicine in April 1986 in response to a request by Congress it was noted that the U. S. Army has 42 vaccines under development, the National Institutes of Health (NIH), 28, and the Rockefeller Foundation, with its relatively meager resources, 6. Great concern was expressed about funds for development of the vaccines and for a dearth of staff at the Food and Drug Administration to facilitate their passage through regulatory channels.

This work on vaccines has occurred in spite of a quite remarkable lack of available funds. As early as 1981–1982 the National Institute of Allergy and Infectious Diseases planned a program of accelerated development of new vaccines but it never received additional funding from Congress. NIH and the Agency for International Development (AID) funding for vaccines has remained constant over the 8 years. Only the Department of Defense has increased expenditures (15). But scientists, enchanted with the possibilities, have been "bootlegging" vaccine research onto other grants. Recently, WHO began a new programme in vaccine development out of their own funds. These were quickly supplemented with major grants from the Pew Memorial Trusts and the Rockefeller Foundation. In addition, the latter foundation has developed an integrated program called vaccinology (a word coined by Jonas Salk) that runs from basic through developmental to applied vaccine research. It also includes transfer of technologies for vaccine production to the developing world and application as described below.

The remarkable thing about the application of biotechnology to vaccines is the multiplicity of approaches now available and that their number is constantly increasing. First,

through the use of monoclonal antibodies and genetic probes the correct antigens are identified. Then, through genetic engineering in bacteria, yeasts, or mammalian cells large amounts of antigen/vaccine are produced. But so much more can be done: genes for virulence, or replication, or production of ligands and toxins can be deleted. Genes for protective antigens can be inserted into living viral (vaccinia) or bacterial (*Salmonella typhi*) vectors. Fragments of proteins as small as 12 amino acids, which can be produced by chemical synthesis, are being developed as vaccines.

With respect to the status of improvement of present vaccines the genome for *Mycobacterium tuberculosis* has been cloned. An acellular vaccine is being field tested for pertussis. The major toxin gene has been deleted from cholera and living oral typhoid vaccines have been developed that penetrate into the gut mucosa and then slowly die because of inability to metabolize galactose or a requirement for aromatic amino acids. The complete three-dimensional structure of the polio virus has been determined, a protective antigen derived from polio viral protein 3 has been inserted into polio viral protein 1, and the site of virulence for polio has been located, a single amino acid.

Enormous progress is being made on the greatest killers of children, the diarrheas, respiratory infections, and malaria. Not only are vaccines being tested for rotavirus (attenuated animal viruses), enterotoxigenic *Escherichia coli* (a synthetic vaccine combining both the heat-stable and the labile toxins), cholera, and typhoid but protective genes for *Shigella* have been added to the suicidal *Salmonella typhi* vectors. It is possible that protective antigens for all of the major diarrheal diseases can be added to the typhoid bacillus. For the respiratory infections, the protective carbohydrate antigens of *Streptococcus pneumoniae* (pneumococcus) are being fused to protein carriers to render them effective in children below 2 years of age. Respiratory syncytial virus has been cloned and all but one of its proteins has been sequenced. For *falciparum* malaria, two sporozoite (infective stages injected by mosquitoes) vaccines are in clinical trials, one genetically engineered and the other synthetic and consisting of 12 amino acids. Blood-stage vaccines are in advanced stages of development in both Sweden and Australia, with one group focussing on synthetic vaccines and the other, on genetic engineering and vaccinia vectors. With respect to the complex helminth organisms, many laboratories have produced protective monoclonal antibodies against schistosomiasis. Using them several groups have extracted protective antigens and at least two have cloned these antigens. For filariasis, a protective antigen has been isolated and cloned and, for hookworm, a putatively protective antigen has been cloned. Work is proceeding on hepatitis A, parainfluenza, dengue, influenza, herpes, rabies, *Mycobacterium leprae*, leishmaniasis, amebiasis, and many others. There is a plethora of vaccines for hepatitis B including those isolated from infected human sera and those genetically engineered. One of the latter is the first genetically engineered vaccine approved for human use. Since hepatitis B virus is a major cause of hepatocellular carcinoma it constitutes the first anticancer vaccine. Finally, antifertility vaccines have been studied for some time with pioneering work being done in India. An anti-β human chorionic gonadotrophin vaccine is now being tested in Australia.

All of this work would be useless if the vaccines were not being used. In 1977 the Centers for Disease Control observed that only about 70% of American children were immunized with our standard vaccines. After a major campaign, which involved the strengthening of school entry requirements, the level is now 98%. The use of vaccines by groups at special risk such as the immunologically depressed or those exposed to blood or its products continues to be poor (16).

In December 1982 UNICEF announced a "Children's Revolution" emphasizing four cost-effective means to rapidly decrease childhood morbidity and mortality in the developing world (6). Jonas Salk and Robert McNamara then suggested a major emphasis on immunization; this led to a meeting in Bellagio, Italy, in 1984 entitled "Protecting the World's Children: Vaccines and Immunization within Primary Health Care" (3). A task force for child survival was organized by the five sponsoring agencies, UNICEF, WHO, the United Nations Development Program, the World Bank, and the Rockefeller Foundation, to coordinate a global effort. In the fall of 1985 a second meeting was held in Cartagena, Colombia, to report on progress. Colombia has achieved 80% coverage, and major campaigns were underway in El Salvador, Burkina Faso, Senegal, Nigeria, and Turkey. India has begun to immunize all of its children as a memorial to Indira Gandhi and China has pledged to increase its coverage from 50% to virtually all of its children (17).

And so the feedback loop has been established. The children of the world are being immunized, and if the power of biotechnology to produce new and better vaccines is fostered, the well-being of children throughout the world, both North and South, will be remarkably improved.

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