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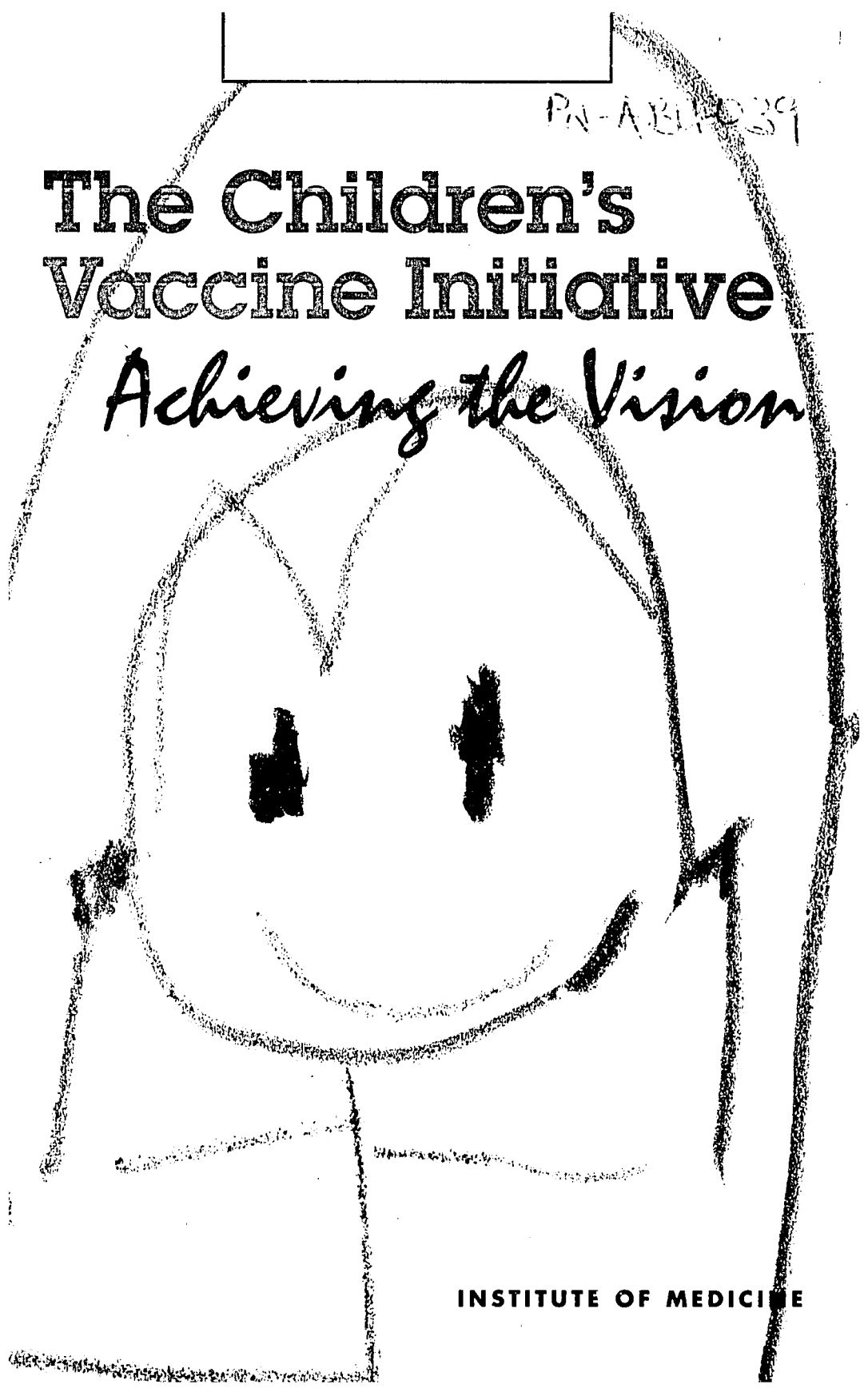
The Children's Vaccine Initiative

Achieving the Vision



INSTITUTE OF MEDICINE

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EXECUTIVE SUMMARY

The Children's Vaccine Initiative

Achieving the Vision

Violaine S. Mitchell, Nalini M. Philipose,
and Jay P. Sanford, *Editors*

Committee on the Children's Vaccine Initiative:
Planning Alternative Strategies
Toward Full U.S. Participation

Division of International Health

INSTITUTE OF MEDICINE

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

COVER: Samantha Edington (age 4 years) provided the cover drawing for this report. Thanks are also due to Stefanie Hairston (5), Mira Kelada-Antoun (4), Stephanie Howson (6), Nadia Scott (4), and Anna Stoto (6).

COMMITTEE ON THE CHILDREN'S VACCINE INITIATIVE: PLANNING ALTERNATIVE STRATEGIES TOWARD FULL U.S. PARTICPATION

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Preface

Vaccines are among the most cost-effective health interventions known. Indeed, the development and widespread use of vaccines in developed and developing countries have contributed greatly to the prevention of many devastating childhood diseases. Progress has been particularly impressive in the two decades since the establishment of the Expanded Program on Immunization under the leadership of the World Health Organization.

Unfortunately, a significant percentage of children, most in the poorest and most remote regions of the world, are not adequately immunized with existing vaccines. Underimmunization is also a problem in the United States, particularly among economically disadvantaged children living in rural and urban areas. Furthermore, no effective vaccines exist for a number of important infectious childhood illnesses. The Children's Vaccine Initiative was launched at the World Summit for Children in New York City in September 1990 to address these and other concerns related to childhood immunization.

This Institute of Medicine report, which addresses the central question, "How can the United States participate fully in the implementation of the Children's Vaccine Initiative?," provides important background information about the status of childhood immunization in this country and abroad, the available resources and infrastructure for producing vaccines, the supply of and demand for new and improved vaccines, the multistep process of vaccine research and development, and the dynamics of developing and manufacturing new and improved vaccines.

In developing our conclusions and recommendations, the Institute of

Medicine Committee on the Children's Vaccine Initiative has drawn on the expertise of individual committee members and has sought the participation and input of many individuals connected to the research, development, procurement, and supply of vaccines both domestically and internationally. The committee recognized early on in the study process that effective and efficient vaccine distribution and delivery systems are critical to ensuring the ultimate goal of disease prevention, but because this was not included in the charge to the committee, it is discussed only briefly in this report.

It is the conclusion of the Institute of Medicine Committee on the Children's Vaccine Initiative that the current system of vaccine research and development in the United States, which leads to the development of high-quality vaccine products for the domestic market, is unlikely to produce the majority of vaccines required by the Children's Vaccine Initiative. In addition, the committee believes that although the combined resources and expertise of the public and private sectors in the United States for the development and production of vaccines are both significant and impressive, they are not integrated and are not focused effectively on meeting public health goals. These conclusions led the committee to its major recommendation: the need for a National Vaccine Authority. The committee believes that a National Vaccine Authority, through a dynamic partnership between the public and private sectors, will offer the United States an extremely powerful tool to ensure the development of novel vaccines and vaccine technologies for use in immunization programs in the United States and around the world.

Publication of this report has been preceded by considerable national discussion about the desirability of having the U.S. government take a greater role in the purchase and distribution of vaccines recommended for use in U.S. children. The Institute of Medicine Committee on the Children's Vaccine Initiative did not study, and has not taken a position on an expanded federal purchase of vaccines. I believe I speak for the committee, however, when I say that certain sections of this report have relevance to the on-going discussion.

The committee forwards its recommendations having recognized that the curtailment of the burden of disease and death in the twenty-first century throughout the world, including within the United States, is another step toward the goal of a peaceful future for ourselves and our children.

Jay P. Sanford, *Chair*
Committee on the Children's Vaccine Initiative

Acknowledgments

Being asked to serve on, or in my instance to chair, an Institute of Medicine (IOM) committee is not a role that one assumes lightly. The Institute of Medicine does not address issues which are not of significant importance and social consequence, and the challenges of serving on an IOM committee are great and demanding. At the same time, one can be assured that one's colleagues will be dedicated to the task, expert in their fields, and collegial in their approach. One can also be confident that support by the IOM leadership and staff will be exceptional.

On behalf of the Institute of Medicine Committee on the Children's Vaccine Initiative, I would like to express our sincere appreciation to the numerous individuals and organizations who gave of their valuable time to provide information and advice to the committee. The committee would like to thank all the individuals who participated in the two working group sessions in June 1992 and who are listed in Appendix I. In addition, the committee would like to thank the following individuals who provided valuable information and advice to the committee: Kenneth Bart of the National Vaccine Program; Kenneth Bernard and Linda Vogel of the Office of International Health; Frank Cano and Jane Scott of Lederle-Praxis Biologicals; Glenna Crooks of Merck and Company, Inc.; George Curlin, Carole Heilman, John LaMontagne, Pamela McGinnis, Regina Rabinovich, and Dale Spriggs of the National Institute of Allergy and Infectious Diseases; Elaine Esber, M. Carolyn Hardegree, and Amy Scott of the U.S. Food and Drug Administration; Scott Halstead and Bruce Gellin of the Rockefeller Foundation; William Haussdorf, Pamela Johnson, Caryn Miller,

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Finally, and in particular, the committee would like to express its appreciation of the Institute of Medicine staff who facilitated the work of this committee. We especially thank Violaine Mitchell, who assumed responsibility for the study midstream and was responsible for translating on-going discussions and debate into prose for further committee discussion; Nalini Philipose for her substantive and procedural contributions to the committee's work; and Dee Sutton, for her superb logistical support over the course of the study. The committee gratefully acknowledges the support and contribution of Stephanie R. Sagebiel who launched the study. Others within the IOM and National Academy of Sciences who were instrumental in seeing the project to completion were Michael Edington, Claudia Carl, and Betsy Turvene of the Reports and Information Office; Laura Baird, research librarian; Scott Jones, computer analyst; Sue Wyatt, financial associate; and Carolyn Hall, Dana Hotra, and Sharon Scott-Brown of the Division of International Health. Special thanks are due to Greg Pearson who edited and wrote sections of the report; Michael Hayes, editorial consultant; and Robert Crangle who facilitated the working group meetings

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Jay P. Sanford, *Chair*
Committee on the Children's Vaccine Initiative

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Children represent the most vulnerable segment of every society . . .
they are our present and our future.

Declaration of New York, September 1990

1

Executive Summary

Vaccines are among the most affordable and effective health interventions available today. The development, introduction, and widespread use of vaccines in industrialized and developing countries have resulted in considerable progress against some of the most devastating of human diseases. Indeed, the world's only complete victory over an infectious agent resulted from a vaccine. Smallpox, which many believe caused more death and sickness than any other infectious illness, was eradicated from the world in the late 1970s. Public health officials in the Americas are now close to declaring victory over another infectious scourge: poliomyelitis.

Largely because of the success of the Expanded Program on Immunization (EPI; established in 1974, the EPI is administered by the World Health Organization and is supported by numerous national governments, international organizations, and private foundations), some 80 percent of the world's infants are adequately immunized against six important diseases: measles, tetanus, pertussis, diphtheria, tuberculosis, and polio. This is a remarkable achievement considering that just 20 years ago a scant 5 percent were so protected. Similarly, in the United States, cases of major infectious childhood diseases have dropped dramatically as vaccines have become a standard public health tool.

Despite tremendous progress in vaccinating children against some of the common infectious diseases, significant problems remain. A full 20 percent of the world's children, many in the poorest and most remote areas of the globe, are unvaccinated. And previously successful immunization efforts are showing signs of slipping, particularly in Africa south of the Sahara. More

than 2 million deaths and 5 million cases of disability still occur annually as a result of diseases (such as measles and *Haemophilus influenzae*) that are preventable by vaccination. In addition, a number of childhood diseases for which effective vaccines are not yet available, including malaria and acute diarrheal and respiratory infections, claim millions of lives annually.

The situation in the United States is also discouraging. Although almost all school-age children are well immunized, only about half of U.S. children under the age of 2 years have received the complete set of recommended immunizations, and the problem is particularly severe in inner-city areas and among indigent populations. The resurgence of measles in 1989 and 1990 was largely due to the failure of immunization programs to reach these groups. Most developed and many developing countries have achieved higher rates of immunization among their preschoolers than has the United States.

Vaccine delivery systems and schedules in the United States and the developing world are based on and restricted by existing vaccine-related technologies. Vaccines should be given early in life, when a child is most vulnerable to vaccine-preventable diseases. Most vaccines, however, require multiple administrations and, hence, multiple and costly contacts with the health-care system. And many vaccines require constant refrigeration. The complexity of vaccination schedules in the United States and much of the developing world exacerbates two categories of problems common to many immunization programs: high dropout rates and missed opportunities for vaccination.

THE CHILDREN'S VACCINE INITIATIVE

The last decade has brought significant advances in the science of vaccinology. Genetic engineering and other new vaccine technologies offer the promise of revolutionizing the ways that vaccines are made and simplifying the ways in which they are administered to children. It was the recognition of the role that science might play in developing new vaccines and improving currently available vaccines, and a perception that the translation of scientific advances into new vaccines needed by developing countries was lagging, that led to the Children's Vaccine Initiative (CVI).

The CVI is both a concept and an organization. The concept of the CVI was launched at the World Summit for Children in New York City in September 1990. The purpose of the CVI is to harness new technologies to advance the immunization of children. At the summit, it was proposed that the ideal CVI vaccine should be given as a single dose (preferably orally), effective when administered near birth, heat stable, contain multiple

antigens, effective against diseases not currently targeted, and affordable.

Making vaccines heat stable would eliminate the need for constant refrigeration, a critical limiting factor in the success and coverage of EPI programs in many countries. Combining more than one antigen into a single dose (as is now done with diphtheria and tetanus toxoids and pertussis vaccine [DTP], for instance) could dramatically reduce the number of vaccines and the costs required to immunize a child fully. Some characteristics of a CVI vaccine will be of public health value to the United States. Indeed, U.S. vaccine manufacturers are investing in research to develop new combination vaccines and simpler methods for administering vaccines. In addition, a new range of vaccines needs to be developed against diseases for which vaccines are not yet available.

The organization of the global CVI has evolved since the World Summit for Children. At the outset, the founders of the CVI (the Rockefeller Foundation, United Nations Development Program, United Nations Children's Fund, the World Bank, and the World Health Organization) recognized that no single agency or organization has the resources and capabilities to achieve the goals of the CVI. They recognized further that the CVI needed to involve many different entities to achieve the vision of the CVI. This recognition led to the formation of the CVI consultative group which is composed of representatives of national immunization programs, multilateral, governmental, and nongovernmental organizations, and commercial and public-sector vaccine manufacturers. The consultative group meets annually and provides an international forum for discussion of new CVI initiatives and for marshaling broad-based support for the CVI. The activities of the CVI itself are carried out through task forces and product development groups. The task forces examine strategic, logistic, and policy issues relevant to the industrial development and introduction of CVI vaccine products, including such areas as quality control, epidemiologic capability in developing countries, and global vaccine supply. The product development groups promote, facilitate, and manage projects leading to the development of vaccines and related products. The three current product development groups are focusing their efforts on a single-dose tetanus toxoid vaccine, a heat-stable oral polio vaccine, and an effective measles vaccine for administration earlier in life (see Chapter 2). The global CVI is headquartered at the World Health Organization in Geneva, Switzerland.

THE INSTITUTE OF MEDICINE REPORT

The Institute of Medicine (IOM) was asked by the two agencies responsible for formulating the U.S. response to the CVI–the U.S. Agency

for International Development and the U.S. Public Health Service–to advise them on how to maximize U.S. private- and public-sector participation in the CVI.

The IOM, with financial support from the U.S. Agency for International Development, six U.S. Public Health Service entities (the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration, Health Resources Services Administration, National Institute of Allergy and Infectious Diseases, National Vaccine Program Office, and the Office of International Health), the Pharmaceutical Manufacturers Association, the United Nations Development Program, and the World Health Organization, Children's Vaccine Initiative embarked in February 1992 on an 18-month study to:

- identify and explore major economic, legal, regulatory, policy, and other factors that influence, both negatively and positively, the development, production, introduction, and supply of vaccines; and
- recommend ways to enhance cooperation and participation among all relevant U.S. sectors in the realization of the CVI.

To conduct its work, the IOM convened an 18-member committee with a wide range of relevant expertise. The full committee met five times between February 1992 and February 1993. In addition, two multidisciplinary working groups comprising members of the IOM committee and other experts from concerned organizations met in June 1992. The committee members drew heavily on the proceedings of the working groups and their own experiences in identifying the major factors influencing U.S. participation in the CVI, reaching consensus on the relative importance of those factors, and recommending an approach to maximizing that participation.

COMMITTEE FINDINGS

Resources and Infrastructure

On the international front, national governments oversee immunization efforts in their respective countries. The Pan American Health Organization (PAHO), United Nations Development Program (UNDP), United Nations Children's Fund (UNICEF), World Health Organization (WHO), and the World Bank all contribute in various ways to efforts to develop vaccines and immunize the world's children. Furthermore, many nongovernmental organizations, such as the Rotary Foundation and Save the Children Fund, play a critical role in promoting protection from disease through immuniza-

tion around the world. Although international commitment to universal childhood immunization is strong, the financial support for immunization activities provided by such agencies as WHO, UNICEF, and the Rotary Foundation has not kept pace with rising costs and increased demand for immunizations. In some cases, financial support for immunization activities has actually declined.

An extensive array of public agencies and private firms is involved in vaccine-related activities in the United States. Each year, the federal government spends hundreds of millions of dollars conducting research on new and improved vaccines, ensuring the safety of existing vaccines, purchasing and distributing vaccines to the states, and conducting educational and other outreach activities to encourage vaccine use.

The majority of basic research in the United States that leads to the development of new or improved vaccines is funded or conducted by the federal government, although a significant amount of basic research is conducted and funded by the private sector. Product-oriented research and development is conducted largely by established vaccine manufacturers and newly emerging biotechnology firms (development-stage firms). Over the last 10 years, development-stage firms have emerged as a new force in the area of applied vaccine research and early-stage product development. However, neither development-stage firms nor the federal agencies involved in vaccine research currently have the capability of manufacturing vaccines on a large scale. This is also true for Massachusetts and Michigan, the only two states that currently produce vaccines. The capacity to scale up and manufacture vaccines on a large scale rests almost entirely with a handful of commercial vaccine manufacturers.

Despite the substantial number and capabilities of U.S. government agencies, private firms, and other organizations involved in vaccine-related activities, and despite specific legislation mandating a national vaccine plan, there has been no overall strategy guiding research, production, procurement, and distribution of vaccines in the United States. As noted in a recent IOM report, ". . . the overall process of vaccine development, manufacturing, and use in the United States is fragmented. There is no direct connection between research and development on the one hand and use of vaccines on the other. The various decision makers do not work together; in fact, they respond to different pressures" (Institute of Medicine, 1992, p. 157). Similarly, and with specific regard to the CVI, the absence of a domestic strategy has, in the committee's judgment, impeded full U.S. participation in the CVI. U.S. government agencies interact with the global CVI virtually independently of each other.

Vaccine Demand and Supply

Demand

The potential size of the worldwide pediatric market is determined by two factors: the annual worldwide birth cohort (approximately 143 million live births per year) and the number of vaccines a child receives through adolescence.

Procurement of pediatric vaccines for the developing world tends to be highly concentrated, characterized by purchases of large numbers of doses by national governments or international agencies such as UNICEF or PAHO. UNICEF is the largest single buyer of vaccines for use in the developing world. In 1992, the fund purchased 850 million doses of childhood vaccines at a total cost of $65 million. The prices of vaccines procured by UNICEF are very low (it costs less than $1.00 to purchase vaccines to immunize a child against the six diseases mentioned above) and, until recently, have risen little more than the rate of inflation each year. Most companies that supply vaccines to UNICEF do so to utilize their excess capacity and charge prices that cover the marginal costs of production (costs of producing additional doses of vaccine in a fully capitalized and operational facility). Some major European suppliers of vaccine to UNICEF have indicated that the very low prices quoted to UNICEF are unlikely to be sustained into the future. Notably, no U.S. vaccine manufacturer has participated in the bidding or procurement process for UNICEF vaccines since 1982, the year in which a U.S. vaccine manufacturer was severely criticized in the U.S. Congress for selling vaccine at a lower price to developing countries than to the U.S. government for domestic needs. This continues to be a sensitive issue in the United States.

Compared with other pharmaceuticals, the demand for childhood vaccines in the United States is predictable, but limited. There are two major classes of buyers of childhood vaccines in the United States: the public sector (including the federal and state governments) and the network of private-sector physicians, health maintenance organizations, hospitals, pharmacies, and clinics across the country. Currently, a little more than half of all vaccines purchased are bought through 1-year contracts with federal or state funds at federally negotiated prices. In 1993 and as this report goes to press, President Clinton is proposing changes in the way that the federal government purchases and distributes pediatric vaccines.

Supply

Vaccines are manufactured in both developed and developing countries

around the world by a range of producers, from vaccine divisions of large pharmaceutical companies to national institutes. Pasteur Mérieux Sérums et Vaccins (France) and SmithKline Beecham (United Kingdom) are the two largest suppliers of vaccines internationally and to UNICEF. There are also a number of national institutes in Europe and many developing countries that supply vaccines to meet their national needs. With a few exceptions, most national institutes have meager resources to conduct research on new and improved vaccines and have limited production capacities compared with those of commercial vaccine manufacturers. At this time, approximately 60 percent of the DTP used in developing countries is produced in the country in which it is used, and 80 percent of the children in the world are born in a country that produces at least one vaccine used in EPI. A number of countries are seeking to expand their capacity to manufacture additional vaccines to meet their domestic needs. There are, however, mounting concerns about the quality of vaccines produced in those countries that do not have a functional and independent regulatory authority.

Vaccine development and manufacture in the United States is an almost entirely commercial enterprise. Twenty years ago a dozen entities were making vaccines for U.S. children. Today, for a variety of reasons, nearly all childhood vaccines used in the United States are manufactured by four private companies. The supply of two vaccines is dependent on sole-source suppliers. The only two remaining public-sector vaccine manufacturers in the United States are the Michigan Department of Public Health and the Massachusetts Biologic Laboratories. Both entities manufacture vaccines to meet state needs, and both have active research and development programs with links to the private sector.

Innovation

The research and development of new and improved vaccines by commercial manufacturers exclusively for developing country markets is limited at best. The low prices quoted to UNICEF/PAHO cover the marginal costs of vaccine production, but they do not appear to provide sufficient market incentives for international vaccine companies to invest in research and development for exclusively developing-world vaccines.

Furthermore, despite a number of successful programs such as the WHO/UNDP Program for Vaccine Development or the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases, there is no significant international or multinational fund dedicated to the early stages of vaccine development and pilot testing of developing world vaccines.

New and improved vaccines that are developed and manufactured for

industrialized-country markets do "trickle down" eventually (sometimes after many years) to some developing countries. By and large, however, the costs of new vaccines are beyond the means of most developing countries and such international buyers as UNICEF and PAHO. As a consequence, no new vaccines have been added to the UNICEF procurement system since its inception, despite recommendations by the World Health Organization that hepatitis B vaccine be included in national immunization programs.

The current vaccine development process in the United States, from basic research through to the production, distribution, and marketing of vaccine products, while poorly integrated, does lead to the development and production of new vaccines for the domestic market, primarily because vaccine manufacturers perceive there to be adequate returns on their investment. The current vaccine development system in the United States rarely leads to the development of vaccines intended for developing-country use, simply because such vaccines are perceived to be without sufficient returns on investment. In some cases, however, vaccines developed by or for the U.S. Department of Defense have been introduced into some developing countries on an *ad hoc* basis by commercial manufacturers.

Investing in New and Improved Vaccines

Private-sector manufacturers in the United States pursue the development of vaccines that both are technically feasible and have a market in industrialized countries. In some instances, a company may invest in the development of a technology with applications to the vaccine needs of both the United States and the developing world. For example, microencapsulation technology is under active investigation in the United States and abroad as a means of achieving a single-dose vaccine. In other instances, a company may be willing to undertake the development of a vaccine that is needed primarily in the developing world, if there are predictable markets of sufficient size and profitability. Such markets include members of the U.S. armed forces, U.S. travelers to developing nations, and wealthy segments of indigenous populations. In most instances, however, the development of new vaccines or improvements in existing vaccines targeted to populations in the developing world cannot be justified by commercial manufacturers. It is unrealistic to expect commercial vaccine manufacturers to bear the sole responsibility for the high-risk development and manufacture of vaccine products, such as those envisioned by the CVI, if the revenues received by manufacturers remain low.

Generally, a commercial manufacturer begins the process of vaccine development when scientific research has yielded promising results and when

"proof of principle" (proof of principle is the point in research and development when the feasibility of a particular product or process is determined) has been established. The decision takes into account two critical factors: the technical feasibility and complexity of developing the vaccine and market considerations. Market considerations include the likelihood of a return on investment and the anticipated rate of return on investment, the availability of patent protection (and freedom from third-party claims of patent rights), and the potential costs of liability exposure.

Even if the technological feasibility of developing a vaccine product is established, commercial manufacturers may be unwilling to pursue development. The anticipated costs associated with research and development may be too high, patent issues may be too complex, the licensing process may present unacceptable obstacles, and the risks of liability may appear too great. The net effect of all of these concerns is increased risk. When the possibility of financial reward is perceived to be low, as is true under the present procurement system for most EPI vaccines, risk aversion will run high.

Stages of Vaccine Development

The process of vaccine development, manufacture, and use is often described as if it occurs in an ordered and linear fashion. In reality, taking a vaccine from the laboratory bench to the point at which a child is vaccinated is a difficult, complex, and iterative process. (The multiple stages of vaccine development are outlined in Chapter 6.)

The committee identified a number of impediments that hinder the ability of the U.S. public and private sectors to pursue the development and production of new and improved vaccines, including vaccines of potential use to the CVI.

Pilot Production

In the committee's judgment, a serious bottleneck to vaccine development is the relative scarcity of facilities that are used to manufacture pilot lots of vaccine according to FDA standards of current "Good Manufacturing Practices," an extensive body of regulations for manufacturing pharmaceuticals and biologics. Many of the vaccines currently under development, including those envisioned by the CVI, involve novel and experimental technologies and are directed against diseases for which there are no suitable animal models for evaluating vaccine efficacy. This new generation of

vaccines will need to be evaluated early on and over time in carefully conducted human trials. Any vaccine used in safety and immunogenicity tests must be produced in a pilot production facility that meets "Good Laboratory Practices," and preferably current Good Manufacturing Practices. Although a number of private firms have the capability of producing pilot lots of vaccine on a small scale, few are able to produce pilot lots of vaccine that meet current Good Manufacturing Practices, and even fewer are able to scale up to large scale manufacture. Indeed, with the exception of a handful of publicly owned pilot production facilities operating in the United States, the capability of producing pilot lots of vaccine according to current Good Manufacturing Practices rests almost entirely with commercial vaccine manufacturers. For the most part, however, commercial pilot production facilities are oversubscribed and precedence is given to products with the highest commercial potential.

Clinical Trials

Clinical trials, especially phase III studies, are expensive (up to $20 million) and administratively and scientifically complex, and they must be carried out in locations with adequate health-care infrastructures. Although the vaccine evaluation units sponsored by the National Institute of Allergy and Infectious Diseases are a widely recognized and appreciated resource, many CVI vaccines will need to be tested in immunologically naive infants overseas, and this will pose additional challenges.

Scale-up and Large-Scale Manufacture

Manufacturers confront one of the most difficult, complex, time-consuming, and resource-intensive aspects of vaccine development when the decision is made to take a vaccine produced in small amounts in a pilot facility and scale up production to commercial levels. Licensing new and improved vaccine products also is complex and time-consuming, both for the manufacturer and for the U.S. Food and Drug Administration.

Technology Transfer

The international transfer of vaccine-related technology for CVI vaccines to developing countries raises several other potential problems. Many of the vaccines contemplated for use under the CVI will require production techniques and manufacturing facilities that are proprietary and, in some

cases, more advanced than those that now exist outside of the United States and other developed nations.

A STRATEGY TO ENHANCE U.S. PARTICIPATION

Achieving the challenging vision of the CVI requires international commitment to the development and production of a new generation of vaccines. It is not only the health of those in the developing world that is at stake; the growing problem of immunization in the United States, especially among economically disadvantaged children, is a major concern.

Over the course of this study it has become increasingly clear to the committee that the current system of vaccine research, development, and manufacture in the United States that leads to the development of high-quality vaccines for the domestic market is not likely to produce the vast majority of vaccines needed for the CVI. This is primarily because most CVI vaccines targeted to developing countries lack the market potential of vaccines intended for the domestic market and do not provide adequate returns on investment in research and development.

At the same time, the committee recognizes that the scientific base for the development of new and improved vaccines in the United States is extensive and impressive and that new approaches and techniques to vaccine construction currently in research and development will revolutionize the ways that vaccines are made and delivered to children. The committee believes further, however, that U.S. public- and private-sector resources devoted to vaccine-related activities could be focused more effectively on meeting global public health needs.

The committee spent a great deal of time considering ways to maximize U.S. public- and private-sector participation in the global CVI and ensure that CVI vaccines are developed, manufactured, and made available to national EPI programs. The committee evaluated and rejected two major strategies for achieving full U.S. participation in the CVI (see Appendix D for a full discussion of strategies and options considered). The first strategy would have provided additional resources to federal agencies for CVI-related vaccine research and development. In addition, changes would have been made in the ways that the United States participates in the purchase and delivery of vaccines internationally. The second would have given the federal government the primary role in *all* phases of vaccine development, including large-scale vaccine manufacture and distribution. Both strategies were rejected because neither capitalized on the unique strengths and expertise of the newly emerging biotechnology firms and vaccine manufacturers in the United States, and neither strategy was thought likely to result in

the timely development, production, and introduction of affordable CVI vaccines to developing countries.

The committee concurs with the findings of the recent Institute of Medicine report, *Emerging Infections* (Institute of Medicine, 1992), that the current process of vaccine innovation in the United States is fragmented and that an integrated process is required to ensure that needed vaccines that lack well-paying markets are developed and manufactured. The committee notes, however, that when stable, predictable, and long-term returns can be expected, commercial vaccine manufacturers have demonstrated their ability to manage and oversee the entire spectrum of activities required to take a vaccine from the point of proof of principle through to the point of production and distribution.

In the committee's view, the success of U.S. participation in the CVI will depend ultimately on effective cooperation and collaboration among government, universities, and most critically, the private sector, including both biotechnology firms and established vaccine manufacturers.

In the committee's judgment, the optimal way to maximize U.S. public- and private-sector participation in the global CVI and ensure that CVI vaccines are developed and manufactured for developing countries is to empower an entity to organize and manage an integrated process of CVI vaccine development and manufacture that not only builds and capitalizes on the strengths of the existing system but also has the capability and mandate to manage the vaccine development process from beginning to end. At this time, no federal entity, with the possible exception of the U.S. Department of Defense, has the capability of undertaking the breadth and range of activities required to ensure the integrated development, production, and procurement of CVI vaccines. In the committee's view, the development of new and improved vaccines for use in the industrialized countries and the developing world is unlikely to occur unless there is an entity that has the mandate to manage and oversee the process from start to finish.

Because the private sector alone cannot sustain the costs and risks associated with the development of many CVI vaccines,

the committee recommends that an entity, tentatively called the National Vaccine Authority (NVA), be organized to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of important public health need.

The NVA would be an organization within the U.S. government capable of reducing the risks and costs to industry associated with the development of CVI vaccines. The NVA would encourage private-sector firms, both

biotechnology firms and commercial vaccine manufacturers, and academic and public-sector entities to develop products required for the CVI and would have an in-house capability to conduct applied research and development and manufacture pilot lots of vaccine.

The NVA would take full advantage of new and existing mechanisms for encouraging private-sector involvement in CVI-related research and development. Ideally, these might include guaranteed purchases of vaccine,[1] investment-tax credits for firms undertaking CVI-related activities, access to an NVA pilot production facility, financial and technical assistance with clinical trials, and provisions for limiting liability. In its agreements with private-sector partners, the NVA would retain the right to transfer the technology that it owns to developing countries, as appropriate. All such agreements would include strategies to ensure that whatever products result are affordable to markets in the developing world. The committee is well aware that the price of a vaccine cannot be determined at the outset of its development. However, the NVA could absorb many of the costs and risks associated with vaccine development.

It is likely that many vaccines would be developed exclusively by outside firms and entities with funding from the NVA. Other vaccines may require parallel tracks of development with collaboration between the private sector and the NVA. A few may require substantially more NVA involvement. The NVA would seek to transfer the responsibility for vaccine development to the private sector at every stage of the product development cycle, however. The NVA would support six broad areas of vaccine product development:

- vaccines used primarily in developing countries (e.g., shigella, cholera, salmonella, malaria, and dengue);
- improvements in existing vaccines which while not leading to a high market return would make them easier to distribute and administer or that would allow them to achieve immunity earlier in high-risk populations (e.g., heat-stable polio, single-dose controlled-release tetanus toxoid and other childhood vaccines, and a more immunogenic measles vaccine);
- development of simple, low-cost vaccine manufacturing technologies that could be easily transferred to vaccine manufacturers in developing countries;
- exploitation of vaccine technologies that are nonproprietary and therefore of little interest to commercial manufacturers who desire market exclusivity;
- adaptation and introduction of currently available vaccines (e.g., pneumococcal conjugates) and new vaccines, including combination vaccines, to developing countries; and

- vaccines for which there are small or limited markets or that are otherwise unprofitable.

The NVA would work with and make maximal use of existing resources at the U.S. Agency for International Development, the Centers for Disease Control and Prevention, the U.S. Department of Defense, the U.S. Food and Drug Administration, and the National Institutes of Health through interagency agreements for the conduct of basic research and clinical trials. Personnel from other government agencies and the private sector could be assigned to work at the NVA. Vaccines that are developed by the NVA and its partners would be licensed to commercial or public-sector manufacturers in the United States or to public-sector manufacturers in the developing world. The NVA would be an international resource and would work closely with the global CVI and multilateral organizations and institutions to ensure that vaccines developed by the NVA meet international needs.

The NVA would be a federal, or federally supported, entity. To be successful, it would have to have some characteristics not common to governmental organizations. The NVA would need to be able to purchase needed supplies and equipment quickly, renovate facilities, and build new research laboratories and pilot production facilities. It would need to have in-house regulatory expertise and staff experienced in negotiating issues related to intellectual property rights. In addition, some provisions must be made to limit the exposure of NVA's private-sector partners to claims of vaccine-related injury.

To be successful, the NVA must maintain a balance between its public health mission and its entrepreneurial activities. Having a board of directors drawn from the public health community, global CVI, multilateral organizations, U.S. government agencies, developing countries, academia, and the private sector (commercial manufacturers and biotechnology firms) would ensure that the NVA adheres to its mission.

The committee estimates that the up-front capital expense of establishing the NVA could range from $30 million to $75 million. The actual cost would depend on whether existing public-sector vaccine research and manufacturing capabilities are expanded or a new, freestanding unit is constructed and staffed. Each year, the NVA would require between $25 million and $45 million for grants, contracts, cooperative agreements, and other mechanisms to support its goals. Assuming annual operating costs and administrative services of $150,000–200,000 per person and a complement of 150–200 full-time staff, the annual operating budget would total $30 million. A total budget of $55 million to $75 million (extramural contracts and intramural operations) would be required. The NVA could also subsidize the vaccine prices paid by UNICEF and other agencies, and it could provide higher returns to private developers and manufacturers,

where appropriate. Additional funds would need to be provided for this purpose.

The committee discussed where a new operational entity charged with the development of CVI products might be located (see Chapter 7 and Appendix D). A number of existing agencies might serve as home to the NVA, including the U.S. Agency for International Development, the Centers for Disease Control and Prevention, the Department of Defense, the U.S. Food and Drug Administration, the National Institutes of Health, and the National Vaccine Program Office. It is also possible, however, that the organization should be placed in a new, independent office.

Rather than recommend a specific site for the new entity, the committee developed a set of points to consider that it feels define the most important characteristics of any potential home for the NVA. These include the correlation of the existing agency's current mission to the mission of the NVA, the existing agency's intellectual and corporate culture and history, its track record in developing vaccines, and any potential conflicts of interest that may result from taking on the duties of the NVA. Although some agencies might meet more of the criteria than others, this fact alone does not necessarily identify the most appropriate location for the NVA. It is the committee's firm belief, however, that the NVA must be an operational entity with the capability, resources, and mandate to manage the entire spectrum of the vaccine development process from proof of principle to the procurement of required vaccines. At this time, no federal agency has the multidisciplinary capability required to manage the integrated development, production, and procurement of needed vaccines.

* * *

Vaccines are among the most cost-effective public health interventions available. Efforts to strengthen U.S and global vaccination efforts should be based on the research and development of new and improved vaccines. This committee forwards the recommendation for a National Vaccine Authority having recognized and struggled with the burden and discomfort that the proposal of creating a new entity brings.

An entity such as the NVA would fulfill a critical public health need and has the potential to protect children around the world while building on and strengthening public- and private-sector partnerships in the United States. The creation of an NVA will, for the first time, ensure the feasibility of a coherent program of development and production of CVI vaccines within the context and mandate of the 1986 legislation (P.L. 99-660) authorizing the National Vaccine Program and requesting the National Vaccine Plan.

The committee believes that the NVA, through a partnership between the public and private sectors, will offer the United States a new tool for ensuring the development of novel vaccines and vaccine technologies for use in immunization programs around the world and in the domestic public health arena.

The creation of an NVA-administered development and procurement program for CVI vaccines could greatly reduce the barriers to entry into vaccine production that many new biotechnology firms now face. By providing a market "springboard," this program could support the growth of U.S. biotechnology firms, potentially contributing to expansion in the sources of supply for other types of vaccine products, contributing to the growth of a U.S. biotechnology industry, and aiding in the bolstering of U.S. competitiveness in this important sector. In addition, U.S. participation in the CVI would constitute an extremely powerful, yet inexpensive contribution to developing countries. In the committee's view, the United States can and should play a decisive role in achieving the vision of the Children's Vaccine Initiative.

NOTE

1. This proposed mechanism resembles the defense procurement process. During the 1950s and 1960s, DOD procurement played a critical role in launching a number of small, start-up firms in the semiconductor and computer electronics industries. By providing large purchase orders to producers of semiconductors that met its specifications, the DOD enabled fledgling producers to expand their revenues. These producers would have found it more difficult to enter commercial markets for their devices, because these markets are associated with much higher marketing and distribution costs. Analyses of the semiconductor and other high-technology industries have argued that the effects of DOD procurement were more important than the effects of DOD research and development contracts on the entry and growth of new firms.

REFERENCE

Institute of Medicine. 1992. Emerging Infections. Washington, D.C.: National Academy Press.

A Rationale for U.S. Participation in the CVI

Childhood immunization has led to remarkable declines in the incidence of sickness and death caused by vaccine-preventable diseases. This, in turn, has resulted in tremendous savings in costly and often long-term treatments.

Perhaps the greatest potential of immunization is the eradication of disease and the elimination of the need to vaccinate. The well-planned use of an effective vaccine made this goal a reality in the case of smallpox. By no longer having to vaccinate against this scourge, the United States alone is estimated to save $120 million per year. Hundreds of millions more are saved indirectly because of reductions in morbidity and mortality.

Polio is targeted as the next disease to be eradicated from the globe. Following an intensive vaccination campaign, there has not been a case of polio in the Americas since August 1991. Since the virus can be imported and spread from other parts of the world endemic for the disease, the United States and all countries in the Americas must be vigilant and continue to vaccinate against poliomyelitis. Vaccine-preventable diseases continue to occur in many nations of the world, often with a devastating impact on unimmunized segments of the population. There have been recent outbreaks of diphtheria in the Ukraine, measles in Somalia, and polio in Israel, to name but a few.

The United States has a long history of supporting immunization programs in other countries. Beyond the humanitarian underpinning of these efforts lies enlightened self-interest–it is in the United States' best interests to contribute to a world in which other nations are free from disease, disability, and their frequent correlate, poverty.

Vaccine-preventable diseases are an economic drain on developing countries. Developing countries that are able to sustain a healthy and productive work force–through effective disease prevention activities, including immunization–are more likely to become vibrant and full partners in the international community. As such, they not only are able to support a domestic economy but also provide a market for the goods and services of other countries. Currently, according to the U.S. Department of Commerce, almost a third of all U.S. exports go to the developing world, and this amount is likely to increase in the years to come.

Critics argue that vaccinating more of the world's children will lead inevitably to more people, more poverty, and a greater drain on finite natural resources. It is true that over 80 percent of births occur in so-

Continues

called developing countries. Yet it has been demonstrated in many different settings that enhancing child survival leads to a decline, not an increase, in the birth rate. Families that can be assured that a child will survive are more likely to have fewer children.

Although most of the attention of the global Children's Vaccine Initiative (CVI) is focused on the needs of children in the developing world, most of the vaccines and technologies that will be developed are of importance to children in the United States. Vaccines that are effective in a single dose–either through enhanced immunogenicity or the use of technologies such as sustained release–will be of great value in the United States. The reemergence of a number of dangerous infectious diseases poses new challenges. New and more effective vaccines against pneumonias, measles, meningitis, and tuberculosis are needed in both the United States and developing countries.

By supporting global efforts at health promotion, an initiative like the CVI clearly has indirect economic benefits for the United States. There are direct benefits too. A significant number of scientists working on new and improved vaccines are based in the United States–in universities, in government laboratories, in biotechnology firms, and in vaccine manufacturing companies. Many of the world's most innovative vaccine manufacturers are U.S.-based. Thus, supporting the CVI will, to a large extent, support the U.S. scientific and biotechnology enterprise and can advance the development of vaccines for the public health needs in the United States. And investing in and supporting vaccine development and immunization programs will have guaranteed and lasting dividends to us all.