Lifesaving VACCINES

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About This Issue

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An Ethiopian infant receives a polio immunization in the town of Shire in Tigray Region in 2005. The male health worker administering the vaccine was a member of a mobile vaccination team, delivering immunizations door-to-door. He was one of 100,000 volunteers responding to the reemergence of polio in Ethiopia in 2004.

Vaccines save lives and prevent disease. Immunizations spare children from crippling disabilities and afflictions that rob them of thriving adolescence and productive adulthood. Routine childhood immunization programs offer youngsters the opportunity for a healthier and more robust future. When healthy children mature to become active, industrious citizens, contributing to the well-being of their families and communities, their nation becomes a better place.

All this from a potion, injected or ingested in but a moment.

This unwavering theme echoes in the articles which follow, repeated like a chorus by government officials, doctors, nurses, social workers, and volunteers. Vaccines are the most successful and cost-effective way to prevent disease known to medical science.

The hard part is making sure that vaccines are delivered and immunizations are administered to the people who need them, wherever they live, whatever their station or economic circumstance. The authors who have contributed to this publication are all devoted to that mission, and efforts they describe to achieve it have been dogged, unrelenting, and sometimes even heroic.

Secretary of Health and Human Services Mike Leavitt introduces the topic, underscoring the United States' commitment to deliver the benefits of vaccines to regions where they are lacking. U.S. Agency for International Development Assistant Administrator Kent Hill describes the actions the nation has taken to build immunization programs in developing countries and its partnership with the international community to do more. Officials from the U.N. Children's Fund and the World Health Organization describe their vaccine programs, and prominent researchers discuss their hopes for further advancement of vaccine technology to prevent more diseases and ease the suffering they cause. ■

The Editors

GLOBAL ISSUES

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http://usinfo.state.gov/pub/ejournalusa.html

Lifesaving Vaccines

4 Introduction
MIKE LEAVITT, U.S. SECRETARY OF HEALTH AND HUMAN SERVICES

5 **Sidebar** *Vaccine Milestones: Edward Jenner*

6 Reaching Every Child
KENT HILL, ASSISTANT ADMINISTRATOR, U.S. AGENCY FOR INTERNATIONAL DEVELOPMENT
The United States has a longstanding commitment to assist other nations in achieving the lifesaving benefits of vaccines and is working with the international community toward that goal.

7 **Sidebar** *The World Knows How*

8 **Sidebar** *Vaccine Milestones: Louis Pasteur*

10 The Promise of Vaccines
OSMAN DAVID MANSOOR, SENIOR ADVISOR FOR NEW VACCINES, U.N. CHILDREN'S FUND
Vaccines are the most cost-effective means of ensuring childhood survival. Immunization rates are rising steadily as health officials work to reach more children every year.

13 Success in Measles Control
A multipartner campaign to reduce measles mortality achieves a five-year goal sparing children from the most infectious of diseases.

14 One Dose at a Time
AN INTERVIEW WITH VANCE DIETZ, STEVEN STEWART, AND KAREN WILKINS, COORDINATING CENTER FOR INFECTIOUS DISEASE, U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION
Three international public health experts discuss how developing nations work to establish and maintain routine childhood immunization programs.

18 **Sidebar** *Peaceful Days, Better Lives*

19 Stopping Polio Forever: A Photo Story
CHARLENE PORTER, MANAGING EDITOR, *GLOBAL ISSUES*
The Global Polio Eradication Initiative has made tremendous progress in reducing the occurrence of polio. Massive vaccination rallies known as National Immunization Days have helped achieve the goal.

21 **Sidebar** *Vaccine Milestones: Salk, Sabin, and Polio*

25 How the World Fights the Flu
WENQING ZHANG, PROJECT LEADER FOR INFLUENZA VIROLOGICAL SURVEILLANCE AND VACCINE VIRUSES OF THE GLOBAL INFLUENZA PROGRAMME, WORLD HEALTH ORGANIZATION
The World Health Organization coordinates a global effort to monitor seasonal and avian influenza emergencies with an eye toward production of vaccines that can help prevent and ease illness affecting hundreds of millions of people worldwide each year.

27 **Sidebar** *Vaccine Milestones: Smallpox Is Dead*

29 Vaccines in the 21st Century
STANLEY A. PLOTKIN, EXECUTIVE ADVISOR TO THE CHIEF EXECUTIVE OFFICER OF SANOFI PASTEUR AND SENIOR EDITOR OF *VACCINES*
The inventor of the rubella vaccine offers a forecast of likely progress in vaccinology in the first decades of the 21st century.

31 Ending Disease, Ending Poverty
AN INTERVIEW WITH LEE HALL, CHIEF, PARASITOLOGY AND INTERNATIONAL PROGRAM, NATIONAL INSTITUTE FOR ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH; AND PETER J. HOTEZ, WALTER G. ROSS PROFESSOR AND CHAIR OF MICROBIOLOGY, IMMUNOLOGY, AND TROPICAL MEDICINE AT THE GEORGE WASHINGTON UNIVERSITY AND SABIN VACCINE INSTITUTE
Overcoming diseases that have plagued humankind for millennia and are persistent causes of poverty is within the reach of 21st century medical science, experts say.

34 **Sidebar** *A Quick Strike Against Disease*

36 What Are Neglected Tropical Diseases?
Definitions and descriptions of poverty-causing diseases.

40 Ensuring the Quality and Safety of Vaccines
A World Health Organization Fact Sheet

43 Concerns About Vaccine Safety
The National Network for Immunization Information addresses risks and safety.

46 Bibliography

47 Internet Resources

VIDEO ONLINE

- *VICTORY OVER POLIO*
  UNIVERSAL NEWSREEL
- *BANGLADESH PREPARES FOR NATIONAL IMMUNIZATION DAYS*
  UNICEF TELEVISION
- *VACCINES: SEPARATING FACTS FROM FEAR*
  THE VACCINE EDUCATION CENTER

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Introduction

HHS Photo

U.S. Secretary of Health and Human Services Mike Leavitt visits the HIV voluntary counseling and testing center in Hai Phong City, Vietnam, one stop on a multinational tour of health facilities in 2005.

Prevention is the way to wellness. That's why vaccines are so important. Not only can they prevent temporary discomfort and even permanent disability, they can eradicate disease and even prevent death.

Since Edward Jenner began inoculating against smallpox more than 200 years ago, vaccines have literally saved millions of lives. They have completely eliminated smallpox as a naturally occurring disease threat. They have made once common diseases like measles and polio uncommon—or nearly nonexistent—in the countries where they are widely used. Vaccines can even prevent some types of cancer. And U.S. scientists are continuing to develop new vaccines against many other well-established diseases and emerging threats.

The United States remains committed to developing new vaccines and spreading their benefits to those in need.

Vaccines developed by U.S. researchers against one bacterium (*Haemophilus influenzae* type b, or Hib) have virtually eliminated a leading cause of severe pneumonia, meningitis, and long-term disabilities among children in developed countries. Studies have confirmed their safety and effectiveness in developed countries. Broadening the distribution of the Hib vaccines promises to reduce the global burden of infections from that bacterium, which causes 2 to 3 million cases of serious disease and more than 380,000 deaths worldwide each year.

Since the Global Polio Eradication Initiative began in 1988, polio cases have dropped by more than 99 percent from an estimated 350,000 in 1988 to fewer than 2,000 cases in 2006. More than 5 million cases of polio paralysis and more than 250,000 polio-related deaths have been prevented due to the eradication initiative. Only four countries—Nigeria, Afghanistan, Pakistan, and India—

remain polio-endemic, and the United States remains a partner in the ongoing effort to end this crippling disease in these last remaining nations.

We're also concerned about the emergence of diseases. That's why the Department of Health and Human Services awarded more than $1 billion in contracts to develop cell-based technology for vaccines against both seasonal and pandemic influenza last year. The benefits are likely to go far beyond U.S. borders—not simply the new vaccines and the disease protection they will convey, but also the advanced techniques for creating them.

Viruses and bacteria are constantly mutating, adapting, and attacking. So it is not sufficient to build an effective vaccine to defeat one disease one time. Rather, it is critical to sustain an infrastructure that allows new vaccines to be developed and new cures to be found.

The infrastructure of adaptability is more than buildings or benches. It is freedom and accountability; competition and transparency. It is the intangible things on which innovation and invention thrive.

The United States leads the world in the discovery and development of new vaccines. I'm determined that we'll keep doing so: that we'll keep creating new vaccines and passing on their benefits to those in need.

Vaccines offer possibility and opportunity. That's why we'll keep working to expand their availability: to give people a hope, a promise, and a future. ■

Mike Leavitt
U.S. Secretary of Health and Human Services

Vaccine Milestones: Edward Jenner

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Engraved portrait of English physician Edward Jenner (1749-1823).

Different cultures around the world have made efforts to protect people from infectious diseases for hundreds of years with varying degrees of success. Records show that the Chinese practiced inoculation against smallpox as early as 1000 B.C. The process was to take a scab from a smallpox lesion, store it for a month, mix it with plant material, and then place the concoction in the nose of a patient. The majority of patients thus treated developed a milder form of the disease, and if and when they recovered, they were protected from future infection with smallpox. Similar practices were reported from India and North Africa in the 16th and 17th centuries. Some accounts credit Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople, with bringing this practice from Turkey to Great Britain in the early 18th century. The procedure was risky because those inoculated might contract smallpox, which could prove fatal.

Country folk in England had long known that milkmaids were likely to be spared the ravages of smallpox, and their resistance was somehow related to the mild pox infection they tended to acquire from the cows. Some physicians observed the same phenomena, but Edward Jenner carried out experiments to test the relationship between cowpox and smallpox in 1796. He published his results and is generally credited with being the discoverer of vaccination.

Jenner experimented by taking some pus from a lesion on the hand of a milkmaid and inoculating it into the hand of a young boy. Some weeks later, Jenner inoculated the boy with infectious material containing smallpox. Of course, such human experimentation would never be permitted today, but Jenner, and the boy, were fortunate. The experiment was a success, the boy did not become ill, and Jenner concluded that inoculation of infectious material from a mild strain of a disease could protect a person from a far more serious disease.

This then is the principle of vaccination, although the scientific basis for it would not be understood for many decades. ■

Elizabeth Fee, Ph.D., Chief, History of Medicine Division, National Library of Medicine, National Institutes of Health

Reaching Every Child

Kent Hill

© AP Images/Rodrigo Abd

A doctor checks a baby girl's respiration during a medical examination in Caquixajay, a small rural village 105 km, 65 miles west of Guatemala City, in November, 2004.

The U.S. Agency for International Development (USAID) has been involved in worldwide efforts to immunize children in developing countries for more than three decades. The agency is also a member of the GAVI Alliance, a public-private global health partnership dedicated to expanding access to vaccines in the world's poorest countries.

Kent Hill is the assistant administrator for USAID's Bureau for Global Health and a member of the board of the GAVI Alliance.

For more than half a century, medical science has recognized that widespread, routine immunization against infectious diseases can prevent the deaths of young children, sparing parents an agony that has spanned millennia. When children escape disease, they can thrive to become healthy adults, contributing to the development of more vibrant and productive societies.

Knowledge is one thing. The delivery of vaccine to children everywhere is a vastly greater challenge.

Since the 1970s, the U.S. Agency for International Development (USAID) has worked with partners across the globe to confront that challenge and help immunize children in remote and underdeveloped parts of the world.

Over the decades tens of millions of infants and children have survived the momentary discomfort and dismay of immunization to gain protection from disease.

USAID was a partner in the 1970s campaign to rid the world of smallpox. USAID provided support in the 1980s to the World Health Organization's (WHO) Expanded Immunization Programme (EPI), a campaign to expand access to immunization against childhood tuberculosis, polio, diphtheria, pertussis, tetanus, and measles. By 1990 coverage for those six diseases reached 70 percent globally, and the occurrence of those preventable but often fatal illnesses fell dramatically. Even though the news was fairly good at the global level, most of Africa and Asia remained far below the global mark of 70 percent—clearly a problem that needed attention.

We have learned that the challenge never ends and the task is never done.

In the 1990s the levels of vaccination among populations leveled off and even declined in some nations. The momentum of the EPI slowed for a variety of reasons, not the least of which was a sense that the job was done. In economically struggling nations, other priorities demanded attention. Major donors turned their attentions to other desperate problems.

By 1999 recognition of this reversal of progress led to a new initiative—the formation of the Global Alliance for Vaccines and Immunization (GAVI) [*http://www.gavialliance.org/*]. It is an alliance devoted to saving children's lives and protecting people's health through the widespread use of vaccines. A powerful alliance of governments, international organizations, vaccine manufacturers, nongovernmental organizations, and public health institutions is devoted to creating a new model for the delivery of international development aid. In pursuit of that goal, GAVI funds programs that strengthen health and immunization systems and accelerate access to new vaccines and new vaccine technologies.

Since inception, donors have committed more than $3 billion to the GAVI Fund, and more than $1 billion has already been distributed to nations implementing immunization programs. The GAVI Fund has provided multiyear grants to 73 of the world's poorest countries in order to help them build a permanent and sustainable system for delivery of immunizations to children.

The United States continues to be one of the largest donors to GAVI, having committed more than $350 million since the institution was created.

In GAVI's first five years, almost 100 million additional children received new vaccines, with 2006 efforts reaching another 38 million youngsters. WHO estimates that the premature deaths of 2.3 million children have been prevented through the efforts of the GAVI Alliance. By

The World Knows How

The world knows how to immunize its children, and the GAVI Alliance strives to provide the leadership and resources to make sure that vaccines are delivered to all the world's children, no matter how remote their homes or how poor their families.

Partners in the GAVI Alliance include national governments, from both donor nations and developing countries. Donors currently represented on the GAVI board are France, the Netherlands, Norway, the United Kingdom, and the United States. Developing nation representatives from Armenia, Cambodia, Ethiopia, and Ghana also serve on the board in 2007.

The United Nations Children's Fund, the World Health Organization, and the World Bank are also part of the alliance, along with nongovernmental organizations, such as the Bill & Melinda Gates Foundation and the International Pediatric Association.

Pharmaceutical companies from both the developed and the developing world are partners in the GAVI Alliance today, with Merck and Co., Inc., now serving on the board. The vaccine manufacturers participating in this effort produce the greatest share of the world's supply. ■

Source: http://www.gavialliance.org/index.php

reaching so many children in such a short time, GAVI is amplifying its global impact and paving the way for the introduction of future vaccines.

The GAVI Alliance now enters a new phase in which we will work toward broader goals to increase global development assistance for health, harmonize the work of the partners with strategies devised by recipient countries, and advance new, better, and more affordable technologies for the delivery of immunizations and health care.

New Technologies and Methods

Considerable success has already been achieved in improving the number of children reached with vaccines. In fact, effective and easy-to-use technologies have been important in the scale-up of developing world vaccination rates in GAVI's first few years. For example, a vaccine against hepatitis B had been available and used for more than 15 years in the developed world before GAVI came into existence. As an alliance with financial backing from its partners, GAVI moved swiftly to make hepatitis B vaccine available for use in developing countries. Acceptance and adoption of the new GAVI- supported hepatitis B vaccine was astounding—reaching more than 90 million infants in five years—and is one of the first great success stories of GAVI. In addition, GAVI was influential in encouraging vaccine manufacturers to combine hepatitis B vaccine with the established vaccine against diphtheria, typhoid, and pertussis (DTP), allowing immediate inclusion of the new product into existing delivery systems. We are now seeing the fruits of those efforts as new suppliers have entered that market, resulting in substantial price reductions for poor countries.

For years, USAID supported the development and promotion of a special type of syringe known as the auto-disable that is quick, convenient, and safe. It can be used only once, thus reducing the danger that immunization could expose patients to HIV or other diseases through syringe reuse. GAVI purchased these devices by the tens of millions to allow a wide introduction of these safe syringes into immunization programs in the world's poorest countries. GAVI provided enough syringes for each

Vaccine Milestones: Louis Pasteur

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Louis Pasteur, a chemist and the founder of microbiology, works on an experiment.

In the last quarter of the 19th century, scientists identified bacteria as the cause of many diseases, including cholera, typhoid fever, anthrax, plague, diphtheria, and tuberculosis. In France microbiologist and chemist Louis Pasteur had noticed that cultures of fowl cholera lost their virulence if they were left inactive for two weeks. When chickens were inoculated with the old cultures, they did not become ill. Furthermore, the birds remained resistant to the disease even when they were inoculated with fresh cultures. He then experimented with anthrax, a disease that was killing many cows, sheep, and goats in the countryside. Pasteur found that by keeping the anthrax bacilli for two weeks at a temperature of 42 to 43 degrees Celsius, he could greatly weaken their virulence.

In 1881 he and his colleagues inoculated 31 farm animals with the weakened anthrax cultures; a matching set of 31 animals served as controls. Several weeks later, they inoculated both sets of animals with fresh, virulent anthrax bacilli. Most of the control animals died, but of the animals given the weakened anthrax cultures, only one sheep died. Pasteur coined the term "vaccine," after the Latin *vacca*, or cow, in honor of Edward Jenner and his milkmaids.

Following this success, vaccines were developed against tuberculosis, cholera, typhoid, and other diseases. Perhaps the most dramatic development was Pasteur's vaccine against rabies, which attracted worldwide media attention. After testing the vaccine on dogs, in 1885 Pasteur inoculated a nine-year-old boy who had been badly mauled by a rabid dog. The boy's life was saved and Pasteur was hailed as a hero. ■

Elizabeth Fee, Ph.D., National Institutes of Health

country program for three years, and now all countries have taken on the cost of those syringes for routine use in their immunization programs.

GAVI has also had a positive influence on the global business of vaccine production by demonstrating to manufacturers that the developing world can be a profitable market. This activity has thus stimulated additional vaccine supply and reduced prices of some of the GAVI-funded vaccines in a timely manner compared to historical trends.

GAVI wants to be successful in accelerating the delivery of newly formulated vaccines to the developing world. In the past, broad adoption of a new vaccine in poorer nations has lagged as much as 15 to 20 years behind developed nations. In November 2006, the GAVI board approved two such proposals. The decision allows distribution of much newer vaccines, introduced in recent years in the United States and Europe, that will combat diseases that together kill an estimated 1.5 million children annually. One new vaccine targets rotavirus, which causes severe and often fatal diarrhea, and the second prevents pneumococcus, a major cause of pneumonia, meningitis, and sepsis.

The two vaccines will be introduced on a staggered scale in a limited number of countries at first to ensure the completion of additional efficacy studies.

Even as the United States is an enthusiastic member of the GAVI Alliance, USAID has independently supported a number of parallel initiatives. In addition to the development of the auto-disable syringe, USAID has funded clinical trials for vaccines to be used in developing countries and supported disease-burden assessments. To improve immunization technology, USAID has backed research to create vaccine-vial monitors, which allow vaccines to remain safely outside the cold chain for limited periods of time. This is an important advancement for teams attempting to deliver vaccines to remote villages where refrigeration does not exist or is difficult to maintain in transit.

Current and future research supported by USAID is devoted to development of a vaccine against HIV/AIDS that will be appropriate for use against developing world strains of the disease and under the prevailing conditions of those areas. We are also investing in research to develop a vaccine against malaria, a disease that is rare in the developed world but still takes 1 million lives in the developing world each year, 75 percent of whom are African children. A vaccine against malaria becomes an ever more critical need with the proliferation of malaria strains resistant to most known drug therapies.

The Potential

Even as USAID, the GAVI Alliance, and developing world nations muster new resources and ideas on expanding immunization programs to reach every child, we have learned that the rewards of our efforts could be even greater than we dreamed. A 2005 study from the Harvard School of Public Health showed that the benefits of immunization have been significantly underestimated in the past. Not only does immunization protect children from illness and death at an early age, but it also protects the child from the long-term effects of illness on growth and development. Healthier children do better in school and become more productive and higher-earning adults. In fact, the study's authors equate the value of immunization in a child's life with that of primary education.

Ensuring better health for the world's children is a gift our generation must deliver to the future. ■

The Promise of Vaccines

Osman David Mansoor

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Two health workers carry a refrigerated box containing vaccines during a two-day campaign in Gaza province in Mozambique, as both children and adults wait for immunizations in the background. To retain their potency, vaccines must be stored and transported at a constant, low temperature from the time of production to inoculation, a process known as maintaining the "cold chain."

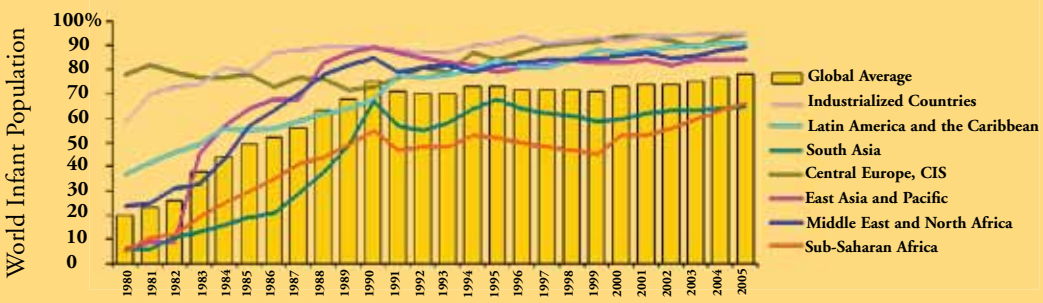
Vaccines are the most cost-effective means of ensuring childhood survival. While immunization rates in developing countries have risen steadily in recent years, health officials continue their efforts to reach more children every year.

Osman David Mansoor, MD, is a senior advisor for new vaccines in the Health Section of the United Nations Children's Fund (UNICEF). A public health physician, Mansoor came to UNICEF from the World Health Organization's Regional Office of the Pacific and the Ministry of Health in New Zealand.

Few health interventions yield greater benefits for children than immunization, a proven, cost-effective way to reduce child death and disability rates. The benefits are indisputable and the consequences of failing to sustain and enhance immunization cannot be overstated: Diseases once under control will reemerge and spread to countries where they had been eliminated. Millions of children in the developing world would become sick or disabled. Millions would die.

Vaccine-preventable diseases are estimated to cause more than 2 million deaths every year. Among those, 1.4 million are children under five. These children are dying from measles (395,000), whooping cough (290,000), and neonatal tetanus (257,000).

Figure 1
Global Immunization Against Diphtheria, Typhoid, and Pertussis



The graph portrays more than 25 years of progress in boosting the rates of childhood vaccination in increasing numbers of countries. These data focus on completion of a three-dose administration of the combination vaccine against diphtheria, typhoid, and pertussis (whooping cough).

Source: WHO/UNICEF estimates compiled August 2006

These numbers represent not merely statistics, but young lives, the human assets of a nation. When the health and futures of a nation's youngest citizens are threatened by disease, the nation cannot thrive.

These deaths are all the more tragic because these diseases can be prevented by vaccines currently recommended by the World Health Organization (WHO). An additional 1.1 million young children die every year from infections of pneumococcus, a bacteria that causes meningitis, pneumonia, or other conditions; and of rotavirus, which causes severe diarrhea.

Building on the success of the globally coordinated smallpox eradication program, achieved in 1977, WHO established the Expanded Programme on Immunization (EPI) in 1974. Over time, the effort has led to steadily increasing levels of routine immunization of children. In fact, since 1990, more than 70 percent of the world's infants have been receiving four vaccines, offering protection against six diseases: tuberculosis, polio, diphtheria, tetanus, pertussis (whooping cough), and measles.

The hundreds of thousands of children still dying from these diseases, as noted above, give urgency to the remaining work that must be completed. Adding the available vaccines for pneumococcus and rotavirus to the routine immunization regimen offers the potential to prevent many more deaths.

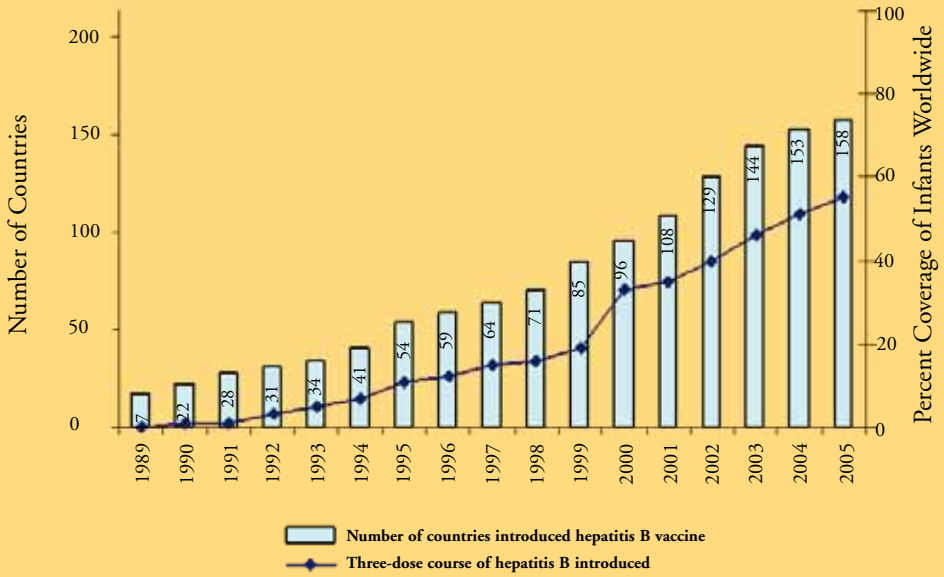
With the establishment of the Global Alliance for Vaccines and Immunization (GAVI) in 1999 and the renewed and concerted efforts of the World Health Organization (WHO), UNICEF, and other immunization partners, global immunization coverage has slowly but steadily improved in the new century. The additional investments generated by GAVI and the heightened attention given to immunization in the poorest countries are yielding results (see Figure 1).

GAVI and its alliance partners are helping to implement the 1992 WHO recommendation that all countries add hepatitis B to their EPI schedule. As a result, by 2005 more than 80 percent of countries had implemented routine hepatitis B infant immunization (see Figure 2). Protecting every child, especially those born of mothers with chronic hepatitis B infection, prevents the development of liver cancer and cirrhosis in later life.

Despite the improvements in the number of children who are routinely vaccinated, much remains to be done. In 2005, WHO and UNICEF developed the Global Immunization Vision and Strategy (GIVS), 2006-2015. The strategy sets a goal for all countries to reach at least 90 percent of infants with all recommended immunizations and at least 80 percent in every district (or equivalent). Achieving the GIVS goals will save the lives of 4 to 5 million children every year by 2015.

The poor and underserved in developing countries are consistently missing out on the life-saving protection of immunization. In 2005 more than 27 million children did not receive the three doses of diphtheria-tetanus-pertussis vaccine (DTP) needed to protect them against those diseases and 30 million were not inoculated with the required doses of measles vaccine.

Figure 2
Immunizing Infants Against Hepatitis



The graph shows progress in vaccination against hepatitis B. A 1992 resolution by the World Health Assembly for the inclusion of protection against this disease in routine programs was a benchmark in the wider availability of this vaccine. The trend took another turn upward with the organization of the Global Alliance for Vaccines and Immunization (GAVI) in 1999.

Source: WHO/UNICEF estimates compiled August 2006

To improve coverage, national and district planners need to dedicate resources and develop specific strategies to reach the currently underserved populations. Many countries already use the Reach Every District (RED) approach, which seeks greater equity and availability of routine immunization services.

In addition to protecting children from vaccine-preventable diseases, immunization programs reduce the transmission of disease in the community and protect the unvaccinated. For some diseases, such as polio, immunization can actually lead to total eradication—as happened with smallpox.

Remarkable progress has been made in expanding immunization coverage and the effort must not wane. Every child, no matter his or her socioeconomic status, deserves to be protected from disease. Immunization programs also serve as a platform to deliver other life-saving interventions such as those against malnutrition, malaria, polio, and intestinal worms. Such an integrated approach is the most effective way to protect the health of all children, including the most marginalized. It is also a cost-effective way to build up health care systems to better ensure that progress becomes sustainable and is not lost. When this happens, the overall impact of immunization on child survival becomes far greater than the sum of its parts ■

UNICEF's Ahmed Magan, Jessica Malter, and Jeff McFarland also contributed to this article

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Success in Measles Control

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Wearing the slogan "vaccinate children against measles" on his shirt, a health worker registers schoolchildren during a 2006 measles immunization campaign in Sudan. Amid continued insecurity and logistical challenges in the region, Sudan is working to vaccinate some 4.5 million children between six months and 15 years of age by the end of 2007.

It starts with a fever and a cough. Then a rash begins on the face and spreads across the body. For some children, measles infection advances to cause pneumonia or brain inflammation, which can lead to convulsions or mental retardation. Measles is among the most contagious of diseases and kills 1 to 3 percent of children in developing countries who contract it. Among children in refugee settings or the severely malnourished, the case fatality rate is much higher, killing up to one child in four with the illness.

A vaccine against this viral infection was invented decades ago and has been part of routine immunization for children in the developed world ever since. Measles vaccination progressed more slowly in the developing world, but over the past five years, governments of the region and international health agencies have made significant progress in expanding immunization programs to protect children from measles.

In 2001 the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), the American Red Cross, the United Nations Children's Fund (UNICEF), the U.N. Foundation, and other organizations launched the Measles Initiative and began an accelerated measles-control program, aiming to reduce by half the number of deaths caused by measles within five years.

The success of this effort was unveiled in January 2007 with the announcement of a 75 percent decline in deaths due to this viral disease in Africa alone and a 60 percent decline in deaths worldwide.

"One of the clearest messages from this achievement is that with the right strategies and a strong partnership of committed governments and organizations," said CDC Director Dr. Julie Gerberding, "you can rapidly reduce child deaths in developing countries."

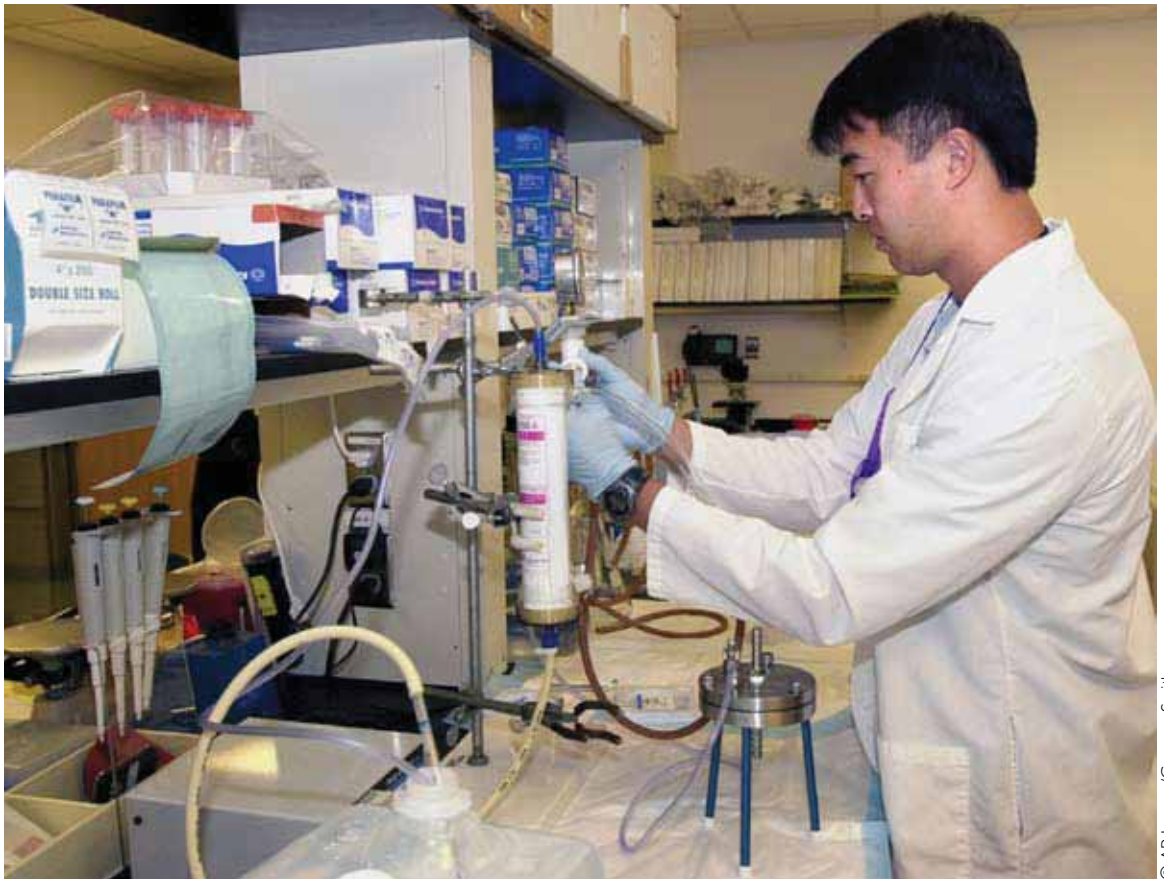
The campaign to reduce measles was based on four strategies: improving routine immunization; providing a second opportunity for measles vaccination through supplemental campaigns if necessary; improving measles care; and establishing effective surveillance. From 1999 to 2005, routine immunization coverage worldwide increased from 71 to 77 percent. This increased coverage, together with national measles vaccination campaigns in more than 40 countries, prevented an estimated 2.3 million measles deaths during that period.

The progress against the disease in Africa alone is considered unprecedented. In 1999 WHO estimated that 506,000 measles-related deaths occurred in the African region. In 2005 an estimated 126,000 deaths occurred, representing a 75 percent reduction, according to research presented in the January 20, 2007, edition of *The Lancet*.

In the more than 40 countries involved, technical and financial support for these activities was provided by national ministries of health and the Measles Initiative (see http://www.measlesinitiative.org). ■

One Dose at a Time

An Interview With Vance Dietz, Steven Stewart, and Karen Wilkins



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A biologist works in the Parasitic Diseases Laboratory at the U.S. Centers for Disease Control and Prevention in Georgia. The laboratory houses approximately 40 employees who provide state-of-the art diagnostic services to support investigation of parasitic disease outbreaks and research on these diseases.

Achieving universal, routine childhood immunization has been a goal pursued with dedication by many agencies, donors, and individuals for decades. It's a goal easily stated, but one that is achieved and sustained only with extensive logistical activities, supplies, equipment, and personnel.

Global Issues *managing editor Charlene Porter discussed the challenges of establishing routine immunization programs with specialists at the Global Immunization Division of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Dr. Vance Dietz is chief of the Global Measles Branch. Steven Stewart is a health communications specialist. Karen Wilkins is a public health advisor.*

These three CDC professionals have worked extensively in Africa, Central and South America, and South and East Asia, helping communities in developing nations strengthen their childhood immunization programs. Collectively they have spent more than 30 years working to protect children from vaccine-preventable diseases.

Question: Large-scale immunization programs are found in all developing countries with functioning governments, but what are some of the difficulties that developing countries have in sustaining universal vaccination programs?

Dietz: One of the principal issues in sustaining programs is having good political commitment. This is crucial to ensure that sufficient funding is available for immunization programs. Another important issue for sustaining programs is the presence of technically competent staff of sufficient

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A mother and son meet with a UNICEF physician at a health outreach center on a remote island in the Bay of Bengal. The 2004 Indian Ocean tsunami killed an estimated 3,500 people in the Nicobar archipelago. In the disaster aftermath, international donors have continued their work to provide basic food, shelter, and medical supplies; prevent malaria and other airborne diseases; and immunize children under five years of age.

number to run, manage, and guide these immunization programs.

Countries also need a sufficiently developed infrastructure with broad geographical coverage to actually deliver needed vaccinations and provide access to immunization services.

That being said, in almost every country, the infrastructure cannot reach all of its population either due to geographical isolation, such as in mountainous areas or river areas, or to poor urban slums. So an immunization program needs a strategy to reach those who do not have access, some sort of outreach strategy.

These are the key issues, and they become more acute during times of crisis; for example, when there's war, famine, civil unrest, or natural disaster. Inherent issues regarding the infrastructure and political commitment are the primary determinants, and in times of crisis they become more acute.

Q: Lacking some of these elements or in the face of crises, have you seen countries lose ground in their immunization programs?

Dietz: Yes. Colombia, for example, had a very good immunization program up to the late 1980s. They were innovative and the leaders in immunization in the region. Then, with the widening of the civil war that spread throughout rural areas, it wasn't safe for immunization teams to enter and vaccinate kids. That situation led to a downfall in many areas of the immunization program. So that's an example of how immunization suffers in wartime.

Then there's the case of diminishing political commitment. In the early 1990s, Venezuela mounted immunization programs through the measles elimination initiative in the Americas. They implemented many of the strategies, successfully reached very low levels of disease occurrence, and had an absence of circulation of measles. Then, from a lack of follow up and a lessened political commitment to fund the program, the immunization coverage fell and there was a huge outbreak of measles in 2002.

Stewart: When people are displaced because of natural disasters, they're at high risk from infectious diseases. We've seen that in earthquake areas in Pakistan, after the 2004 tsunami in Indonesia, and in other serious disasters. If there is quick response from the ministry of health and international donors to provide immunization services, you can prevent outbreaks.

Wilkins: I would just add one thing. When we talk about political commitment, we don't mean solely at country level. The international community also has an important role to play. Through the 1980s, right up until 1990, the World Health Organization's [WHO] Expanded Immunization Programme [EPI] had a lot of donor support, a lot of focus on immunization, and rates of coverage increased fairly rapidly. Then the donors got tired of that and went on to other things, so countries were left on their own. Or in some cases, donors brought in new and different priorities and were funding different initiatives in the countries. So the immunization coverage did backslide in a lot of countries that hadn't built up their own interest in immunization.

Things are turning around now, but the international community has a role to play in sustaining political, long-term commitment to help strengthen these programs, create the demand, and make sure the infrastructure is stable.

Dietz: I think the landscape has changed from the days when a handful of donor nations and U.N. agencies led the global immunization effort. I think the formation of the Global Alliance for Vaccines and Immunization [GAVI] has been responsible for it in a lot of ways. A variety of partners are providing funding and new initiatives are on the horizon.

Q: Let's go from this overview down to the micro view.

What are the challenges faced by a clinic in a rural area of a developing country that is just beginning to establish itself as a provider of regular immunizations?

Wilkins: Dr. Dietz mentioned earlier that the staff in this clinic must be qualified. They need to have training. They need to be supervised. They need to have the vaccine. They need to have needles and syringes. They need to keep those supplies cold, so they need to have refrigerators at least within a reasonable distance, and different countries define that differently. They also need to have created the demand among the mothers, so they have clients. The mothers, the children, the fathers have to accept immunization because in some countries some people might actually block mothers from taking children to receive vaccinations.

Buildings where clinics are housed are in some cases fairly rudimentary. They may be one room; they may be five rooms. They might just have a table underneath a tree, or they might be vaccinating in someone's house. It depends very much on where they are. But the absolute requirements are the trained personnel, needles, syringes, cold vaccines, and training.

Q: Let's pursue the demand question, the willingness of the community to accept immunization as a good thing. How difficult a hurdle is that in the countries where you have worked?

Wilkins: Most of my experience has been very positive. People not so long ago saw whole villages wiped out due to measles, and the survivors remember that. If they understand that the vaccine prevents disease, they bring their children when immunizations are offered. And they'll come from a very long distance under adverse conditions. This has been my experience in the Democratic Republic of Congo and Burkina Faso.

Generally the demand is there if the mother knows what the vaccine does, where it is available, and when it is given. People who don't finish vaccination series are asked why in surveys. It's typically because the mother either didn't know that she needed to vaccinate her child or mistakenly thought she and the child had finished the vaccination series. Very rarely did mothers say they were afraid of an adverse event occurring as a result of the immunization.

Stewart: I agree. Once the knowledge is there about the value of vaccine, parents, particularly mothers, will go to great extremes to ensure their kids get immunized, walking great distances to vaccination sites, that kind of thing. It's really quite heroic some of the measures that people take.

But there are exceptions to that. We've seen, particularly with the polio program in recent years, examples where rumors can spread. This happens most easily among illiterate populations. In places like northern India and northern Nigeria, rumors that a particular vaccine is harmful to a child's health, or that it may cause sterility or even HIV, may prevent people from participating in an immunization program.

Dietz: One personal experience of mine on this subject—I remember working in Mexico in the state of Sinaloa with seasonal migrant workers from the mountains of Oaxaca and Chiapas in the south. They were all indigenous populations. Many of them don't speak Spanish and don't acknowledge Western medicine. We would have vaccination teams going to these camps of migrant workers, and the mothers would actually pick up their kids and run from the vaccinators because they were afraid, not just of the vaccines, but of any Western medicine. I think that's becoming less of an issue as time goes on, but it is something that can happen in isolated, indigenous populations who don't have a lot of interaction with Western medicine.

Q: How do these immunization efforts with their outreach to rural areas and isolated populations serve as a stepping stone to the delivery of higher levels of medical care through these same facilities?

Dietz: In many countries immunization programs are the most developed of any public health program, offering the greatest coverage of the population. A fundamental strategy of immunization programs is to reach the hard-to-reach or the isolated, so these programs begin as outreach, but then it's really important that they take other needed services or therapies to the community. One example of outreach, when we do mass immunization campaigns, we're also providing insecticide-treated bed nets to prevent malaria infection, vitamin A tablets to prevent blindness, and deworming medication. It's important that immunization services do that.

Wilkins: Outreach works to benefit both programs. It's being built on the platform of WHO's Expanded Immunization Programme because of the greater reach achieved through those programs, as Dr. Dietz mentioned. But we're finding in some places, people have turned out for immunization campaigns enough times before that now they're making the trip to get that antimalarial bed net. Or perhaps, they wouldn't have come for a drop of vitamin A, but they would come for a vaccine, so they get both. We're finding it's working to the benefit of both programs, and we're exploring with WHO and UNICEF [United Nations Children's Fund] ways to further advance those synergies.

Q: What has been CDC's ongoing role to help developing countries improve immunization services and extend programs to more and more children?

Dietz: CDC works through WHO and UNICEF in what's referred to as a multilateral manner, meaning that we go through these U.N. agencies, and they provide the global coordination and global recommendations which help standardize policies and procedures.

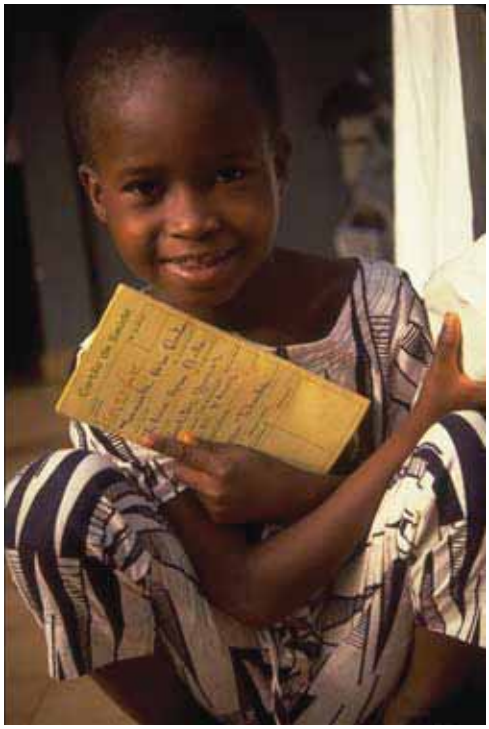
CDC provides financial support for routine immunization strengthening as well as substantial amounts for polio eradication and measles and rubella control. Much of the money for measles and polio goes directly for the actual purchase of vaccine. We also provide a considerable amount of technical assistance. We have staff that are actually seconded to WHO and UNICEF, assigned to headquarters of those agencies, and to regional and national WHO offices, which work directly with ministries of health to assess immunization programs and provide guidance on how to strengthen them. We are also very heavily involved in training surveillance staff and data managers at all levels in a health ministry, as well as staff who administer vaccines. We're also helping to and developing training materials, working with other countries at the national and district levels.

Stewart: Also, in the Global Immunization Division here in Atlanta, CDC has people who assist countries with developing annual plans of action, or even multiyear plans of action—what goals and objectives the country wants to have for the immunization program over a period of time, and what strategies will best meet those objectives.

CDC public health specialists go out to other countries to help plan large-scale vaccination campaigns and activities that will help enhance routine coverage. We'll go out and monitor large-scale campaigns, as well as look at the performance of routine services. So there are folks at CDC who spend between two and six months abroad each year to help strengthen immunization programs with individual countries.

Q: What are some of the greatest recent successes in your mind in this entire global endeavor to expand routine childhood immunization?

Dietz: One of the most recent and important achievements involves our measles mortality reduction activities. This was the result of work by the Measles Initiative, a partnership involving the United States, U.N. agencies, and other organizations. We worked in priority countries to halve the amount of measles-related deaths by 2005 compared to 1999. The data suggest that that goal has been achieved ahead of time and under budget—that globally there is actually a 60 percent reduction in mortality.



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An eight-year-old girl shows her vaccination certificate at a health center in Guinea Bissau. International assistance has helped to more than double the number of Guinean children receiving immunization coverage since 2001.

Stewart: The 20-year campaign to eradicate polio is certainly one of the most significant achievements in this area too. CDC is a spearheading partner in that initiative—along with WHO, UNICEF, and Rotary International—and we estimate that about 5 million cases of paralytic polio have been prevented because of the polio eradication initiative, and probably at least a quarter of a million polio deaths during that period as well.

Q: Those are meaningful statistics, but as professionals who have worked many years towards these goals, is there a particular place where you have seen progress that heartens you in this work?

Wilkins: I was a teacher in the Peace Corps in what's now the Democratic Republic of Congo [DRC] starting in 1978. In 1980 the doctor at the hospital recruited me in to start routine immunization with him in the health zone I was working in. We went around from village to village to village—him driving the car, his wife and the hospital nurses giving some vaccines. We were his entire team, just driving from village to village. People came from every direction to get vaccinated in response to this modest effort started by

just one individual. At that time, programs existed mainly in the cities and a few zones, like the one I was in, where one person with initiative and a vehicle would start a vaccination program on his own.

Years later in 1988, my first job with CDC was to go back to DRC and work in the immunization program. By that time, there were 306 health zones in the country and 175 of them were considered functional. So the Congolese went from coverage that was probably 11 percent to 38 percent by 1990.

Now, despite all of the war and the conflict and everything that's gone on in the D.R. Congo, almost every zone—they have 515 zones by now—503 of them are considered functional, providing routine immunization services. Their routine coverage of the childhood population is now 70 percent for measles. That's not quite up to the 90 percent level that we want every country to achieve. But they've come so far from just 20 years ago. They've gone through all these years of political unrest and managed, despite that, to bring people together in the rebel health zones and in the government health zones to continue to vaccinate children and improve their program. ■

Peaceful Days, Better Lives

Immunization saves the lives of children, a fact so widely recognized that it has influenced events over the past 20 years in ways that diplomats, dialogues, and weapons have not. Appeals to protect the children have convinced warring factions to lay down their arms and rebel forces to open their strongholds to those who deliver vaccines to children in remote areas.

These negotiated lulls in fighting are known as "Days of Tranquility," and since 1985 warriors in bitter conflicts have agreed to temporary truces to make way for massive vaccination campaigns.

It began in 1985 amidst a wrenching civil war in El Salvador. Government security forces and rebels put away their arms for three days to allow 250,000 children to be vaccinated against polio, measles, diphtheria, tetanus, and whooping cough.

Lebanon in 1987, Sudan in 1989, Sierra Leone in 1998, Burundi in 2002—in these and dozens of other places in the more than two decades since the El Salvadoran war, temporary pauses in fighting have been negotiated for the sake of protecting children from disease.

At a U.N. conference in 2004, Sierra Leonean delegate Elisabeth Levalie described how health advocates managed to get to children for vaccinations in hard-to-reach conflict areas. "We had to immunize in the rebel-held areas. So we had to devise strategies: how to get to those people, how to build the confidence that is needed." A variety of tactics and contacts were used to create peaceful corridors, she said. "We used relatives of the rebels who were in government areas to take the message to them, we used women's groups, we did advocacy."

More than 20 years after they first began, Days of Tranquility serve as an oasis of peace where immunization can be safely delivered by thousands of vaccinators—44,000, in fact, in a November 2006 immunization campaign conducted in Sudan.

UNICEF representative Ted Chaiban worked to orchestrate that campaign, calling upon violence-prone communities to ensure the safety of health workers. "Safeguarding a child's health rises above any political differences that may exist in communities," he said as the campaign to reach almost 8 million children began. "It is imperative that where fighting continues, vaccinators and monitors are guaranteed safe access, and parents are able to present their children for vaccination." ■

Stopping Polio Forever: A Photo Story

Charlene Porter

Photo Jean Marc Giboux

Children disabled by polio go to an educational and rehabilitative school in New Delhi. India is one of only four remaining nations where wild poliovirus still occurs in the environment. More than 670 cases occurred there in 2006.

In the entire history of medicine, only one disease has been eradicated through human efforts. Deadly and disfiguring smallpox was eliminated as a scourge to humankind in 1980. A vaccine made that achievement possible.

Since 1988 a second campaign has been underway to rid the world of a killer disease, and once again a vaccine is the tool that can purge a virus that has caused so much human misery. Charlene Porter is the managing editor of Global Issues.

The Global Polio Eradication Initiative (GPEI) brings together a vast network of expertise, resources, and volunteers, waging a global campaign against a lethal virus that can paralyze a child or young adult within hours, then lead to death or lifelong disability. The GPEI is considered the largest public health initiative the world has ever known.

The success of this 18-year-old campaign has been steady. Poliomyelitis appeared in 125 countries in the late 1980s; now the virus is endemic—occurs in nature—in only four countries. Twenty years ago about 350,000 people were stricken by polio each year worldwide. At press time, 1,985 polio cases were known to have occurred in 2006.

The 2006 case total reflects vast progress since the 1980s, but it also underscores the importance of diligence in disease eradication. The number of cases in 2006 is higher than the worldwide annual tolls in the early years of the decade, when fewer than 800 annual cases were detected.

© AP Images/Sayyid Azim

A three-year-old girl is held by her mother in September 2000 as she receives the inaugural polio vaccination dose by a local administrator, in the Baidoa region, Somalia.

Diligence is required from tens of thousands of health workers, volunteers, villagers, and parents, all willing to make sure that every child receives the multiple doses of vaccine required to stop the disease. That's every child, including those born tomorrow, next month, next year, and the year after that.

Ensuring the protection of every child everywhere is a goal often pursued with the precision and planning of a political or military campaign.

National Immunization Days (NIDs) are events staged in countries remaining at risk for polio. Public health professionals and thousands of volunteers mobilize mountains of supplies and resources and take them to every isolated corner in their countries to make sure that all youngsters under age five swallow the few drops of liquid that can protect them from crippling disease. In 2005, 400 million children were vaccinated in 49 countries during NID events that lasted mere days.

"It is a huge, huge, huge undertaking," said Deepak Kapur, the National PolioPlus committee chairman for Rotary International in India. Rotary is an international nonprofit service organization that first envisioned the possibility of a polio-free world. Since 1985 the organization has been a partner working with international

Photo Courtesy Kanwaljit Singh

Children flock around Dr. Kanwaljit Singh as he immunizes children in India's Bihar state during a 2006 National Immunization Days event. In one vaccination campaign, Singh went on a journey that involved "crossing two branches of the Kosi river by boat, walking across flooded plains for 15 kilometers and crossing by foot three small tributaries where water levels ranged from knee high to chest high, for a six footer [1.8 meters] like me!"

health organizations, providing the energies and commitment of its 1.2 million members around the world.

"Vaccinators are, by and large, hopeful and determined," said Dr. Kanwaljit Singh, a medical officer with the Indian National Polio Surveillance Project, who has been involved with the NIDs for more than a decade. "The mood at the immunization booths [set up in public places] is often festive and cheerful, with colorful buntings and banners, and the hustle and bustle of children playing and bringing their younger siblings for vaccination."

If children are not presented at the booths in the parks and markets, vaccination teams set out on house-to-house surveys to find every child. "It's quite an exciting experience, and quite a frustrating one at times," said Kapur. "At times, you're welcomed, and they're happy that you've traveled all the way, and very grateful that you've come in and are there to immunize their children." But Kapur has also encountered parents who don't welcome the immunization team, parents who hide their children to avoid the vaccine out of fear it will harm the youngsters.

Those unsubstantiated fears have been sown in many places, but when they occurred in Nigeria in 2003, a setback in the global eradication effort occurred.

"In certain villages, they heard the leadership say [the vaccination] will affect their children," recalled BusuYi Onabolu, deputy chair for National PolioPlus for Rotary International in Nigeria.

The virus moved swiftly into a vulnerable population that avoided immunization. In 2004 the number of polio cases doubled in Nigeria, and 12 other nations, previously declared polio-free, experienced a reappearance of the disease, which genetically linked to the strain that had been let loose in Nigeria.

Significant negotiation and discussions calmed the fears about the vaccine, Onabolu said, and in August 2004 allowed resumption of massive inoculation campaigns, which are held periodically until today. But Nigeria's battle against polio ended 2006 with more than 1,000 cases, almost 40 times the number of cases in 2000.

"We are inching forward; we believe that polio eradication will now be in sight in this country," Onabolu said. "We cannot afford to let all those years go to waste, can we?" ■

Vaccine Milestones: Salk, Sabin, and Polio

© AP Images/U.S. Postal Service

Pioneers of the polio vaccine were honored with a U.S. commemorative stamp in 2006.

Poliomyelitis has afflicted humankind since ancient times, causing muscle wasting, paralysis, and sometimes death. In the 1940s, scientists found that the poliovirus exists in three basic types and that it can be grown in tissue cultures. American researcher and physician Jonas Salk killed the poliovirus with formaldehyde and produced a vaccine. In 1954 the United States launched a nationwide testing of the vaccine with the mass inoculation of hundreds of thousands of schoolchildren. In what has become known as the Cutter incident, 200 children caught polio and 11 of them died. All the cases were traced to a single poorly made batch from one drug company. More careful production standards were developed and the vaccinations successfully resumed; as a result, the numbers of children paralyzed by polio fell dramatically.

Whereas Salk's vaccine was a killed-virus vaccine, Polish-American physician Albert Sabin developed a live-virus vaccine, using a weakened or attenuated form of the live virus. Whereas the Salk vaccine was used in the United States, 10 million children in the Soviet Union received the Sabin vaccine in 1959 in a World Health Organization test. Because it was relatively easy to produce and because it could be taken by mouth—often on a sugar cube—instead of by injection, the Sabin vaccine soon became the most popular polio vaccine around the world. Continued vigilant and coordinated use of the Salk and Sabin vaccines has now eradicated polio from most of the world's nations. ■

Elizabeth Fee, Ph.D., National Institutes of Health

"...a huge, huge, huge undertaking"

Photo Jean Marc Giboux

A polio campaign is conducted in Yemen's remote highlands. Yemen is one of 14 countries where polio cases appeared in 2006 as a result of reimportation of the virus, years after it was thought the disease was eradicated.

UNICEF/HQ05-2147/Giacomo Pirozzi

A Muslim religious leader vaccinates an infant against polio at a UNICEF-supported health center in a poor settlement on the outskirts of Kinshasa, Democratic Republic of the Congo.

© AP Images/Saurabh Das

Mothers and infants wait for polio immunizations at Takai in Nigeria's Kano state. This July 2004 event marked the state's resumption of vaccination after an 11-month ban. The ban allowed a resurgence of disease and the migration of the virus into other African nations.

Photo Jean Marc Giboux

An American volunteer from Rotary International immunizes children at a school in India's Utter Pradesh state in 2004. Rotary was one of the founding partners of the GPEI and has contributed more than $616 million to the effort, along with hundreds of millions of volunteer hours.

UNICEF/HQ05-1295/ Indrias Getachew

Two volunteers prepare for a door-to-door immunization effort, carrying insulated boxes of vaccine for use in an NID in Hamer district in southern Ethiopia in 2005. The event targeted 15 million children after an upsurge in polio cases, traceable to the suspension of polio vaccinations in northern Nigeria in 2003-2004.

© AP Images/Ou Neakiry

Cambodian health authorities enlist elephants equipped with loudspeakers to announce National Immunization Days in Phnom Penh in 1997.

© AP Images/Irwin Fedriansyah

Indonesian mothers and children queue for polio vaccination near Jakarta in 2005. A massive immunization campaign was organized when polio reappeared after a 10-year absence.

VIDEO ONLINE

• *BANGLADESH PREPARES FOR NATIONAL IMMUNIZATION DAYS*
UNICEF TELEVISION

http://usinfo.state.gov/journals/itgic/0307/ijge/ijge0307.htm

Eradication in Sight

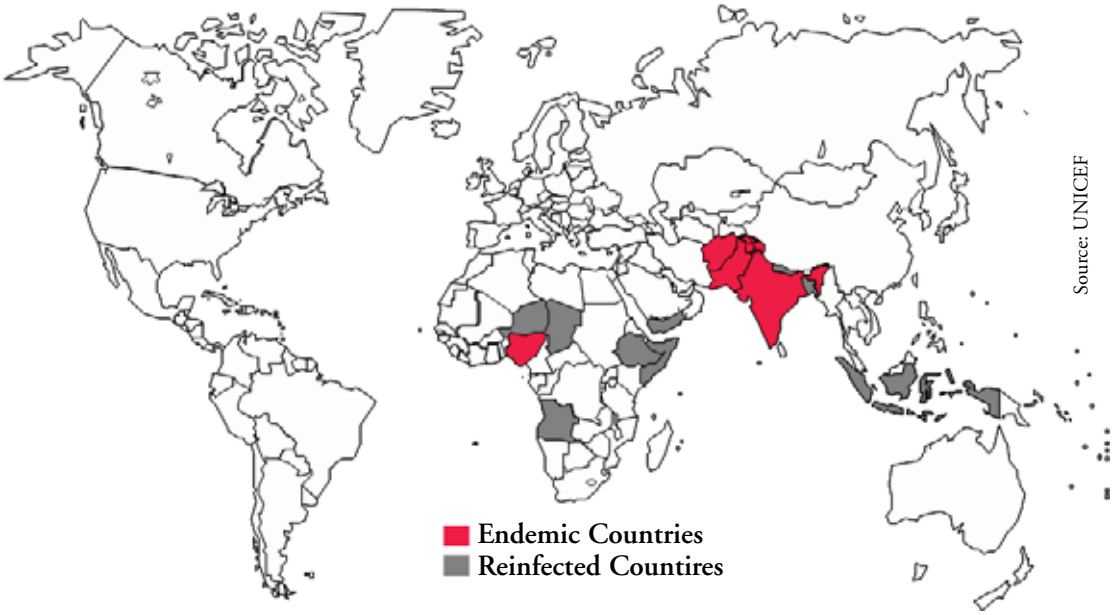
When the epic challenge to eradicate polio was first shouldered by the Global Polio Eradication Initiative in 1988, the goal was set to complete the task by 2005. That deadline has slipped past, but the campaign has not flagged. International partners and the four remaining polio-endemic nations renewed their commitment to end the transmission of polio worldwide at a February 2007 meeting in Geneva. A final attack on the poliovirus emerged from the consultation, along with a plan to raise the money to achieve that end. Hundreds of millions of dollars are required annually for the four nations with endemic virus to immunize about 250 million children each year. That diligence is required to ensure that youngsters are protected from the disease.

The battle against this crippling disease may be hardest fought in these four final countries, and it may require several more years. Still, the eradication of polio in 189 nations—and the health of the children who live there—is no small achievement for this 19-year campaign.

World Polio in 1988

Source: UNICEF

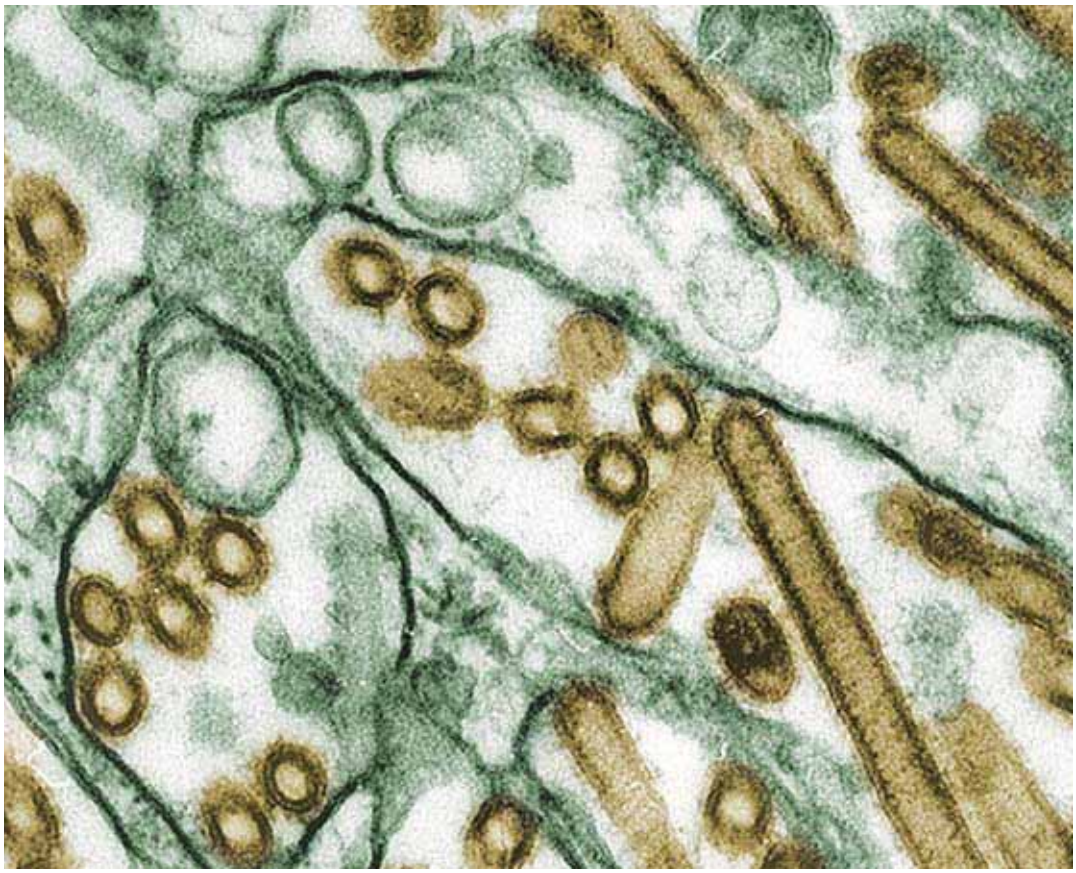
Active Polio March 2007



Source: UNICEF

How the World Fights the Flu

Wenqing Zhang



CDC/Courtesy of Cynthia Goldsmith, Jacqueline Katz, and Sherif R. Zaki

This colorized, microscopic view depicts the avian influenza H5N1 virus in gold, grown in another cell medium shown in green. Increasing numbers of human infections from H5N1 occurring since 2004 caused health officials to become concerned that this virus, or one like it, has the potential to spark a global influenza pandemic with widespread human, social, and economic costs.

The World Health Organization coordinates a global effort to monitor seasonal and avian influenza emergencies for the production of vaccines that can help prevent and ease illness affecting hundreds of millions of people worldwide each year.

Wenqing Zhang, MD, is project leader for the Influenza Virological Surveillance and Vaccine Viruses of the Global Influenza Programme of the World Health Organization, based in Geneva, Switzerland.

Every year more than 250 million doses of influenza vaccine are produced that help to protect the world's population against influenza infections. For more than 50 years, the process by which an effective vaccine is developed and manufactured has relied on the international cooperation of a wide range of public health partners brought together under the coordination of the World Health Organization (WHO) in the Global Influenza Surveillance Network.

Influenza is caused by a virus that is passed easily from person to person, most often through droplets and aerosols created by people when they cough or sneeze. Usually the virus infects mainly the upper respiratory tract, the nose, throat, and bronchi, but in severe cases, the virus can spread to the lungs. Most people recover within one or two weeks without the need for medical treatment; however, for the very young, the elderly, and those suffering from

WHO Photo/Garrett Smythe

Virus samples are prepared at one of the National Influenza Centres participating in the global network of laboratories monitoring annual changes in influenza viruses.

certain medical conditions, influenza can pose a serious risk to health and can result in other complications such as pneumonia and even death.

Influenza causes outbreaks and infections throughout the world. In regular "seasonal" epidemics, up to 15 percent of the population can be affected, resulting in up to 500,000 deaths every year. In the tropics, influenza outbreaks occur year-round. The principal and most effective measure for preventing influenza is annual vaccination. Influenza vaccines have been in use for more than 60 years, and they have been proved safe and effective in preventing both mild and severe outcomes of influenza. Each year, it is thought, influenza vaccines can reduce the risk of serious illness or death in the elderly and reduce illness by up to 90 percent in healthy adults, resulting in substantial health and economic benefits.

The antigenic properties of a virus are the characteristics that will induce the response of the body's immune system to infection by the virus. By their very nature, influenza viruses are constantly undergoing antigenic changes. This means that the composition of influenza vaccines must be reviewed and adjusted each year to ensure that they match the antigenic properties of the viruses in circulation.

A Global Network

Worldwide monitoring of influenza viruses through surveillance is the mechanism by which the evolution of circulating viruses can be monitored. In 1952 a WHO expert committee recommended the establishment of an extensive international network of laboratories to conduct the necessary surveillance and provide WHO with the information it required to advise its member states on the most effective influenza control measures. The WHO Global Influenza Surveillance Network, or GISN, has been in operation ever since, functioning in all regions of the world under the coordination and administration of WHO headquarters.

GISN now includes more than 110 National Influenza Centres (NICs) located in 87 different countries and areas around the world, as well as four highly specialized WHO Collaborating Centres for Reference and Research on Influenza. These four Collaborating Centres are located in Atlanta, Georgia, United States; in London, United Kingdom; in Melbourne, Australia; and in Tokyo, Japan. Another Collaborating Centre in Memphis, Tennessee, United States, is focused primarily on studying the ecology of influenza in animals.

The NICs are the backbone of GISN. They are laboratories that have been designated by their country's top health officials as the national focal point for influenza surveillance with the necessary capacity and expertise to perform their role. An NIC is responsible for collecting or receiving specimens and viruses obtained from patients who are ill. Every year more than 175,000 clinical specimens are collected from patients worldwide. Some of these specimens yield viruses through a process known as viral isolation. The NIC undertakes a preliminary analysis and then forwards some virus isolates thought to be representative of viruses circulating in the population to one of the four specialized Collaborating Centres for further characterization.

An NIC is the key point of contact between WHO and a given country's health authorities on any matter regarding the surveillance of influenza. The NIC informs

WHO and other members of GISN about viruses in circulation, unusual viruses that may have been detected, and important or unusual outbreaks. It produces weekly reports on influenza activity in the country during the influenza season, which are published in the WHO *Weekly Epidemiological Record [www.who.int/wer]*, and provides information on the influenza epidemiological situation to FluNet *[www.who.int/flunet]*, a Web-based tool for the support and coordination of national and global influenza surveillance and reporting.

Many NICs also provide training and technical support to other network members in the region on the collection of specimens and the preliminary characterization of influenza viruses.

Ensuring Effective Vaccines

The four specialized WHO Collaborating Centres receive influenza virus isolates from NICs around the world and conduct advanced analysis of the antigenic and genetic profile of the viruses. This information helps to assess the significance of the antigenic changes among recent circulating viruses and determines whether current viruses differ substantially from existing vaccine viruses. The centres also help to monitor the evolution of the viruses and their ongoing susceptibility to influenza antiviral drugs. They also conduct serological studies in collaboration with other key national reference laboratories, such as the Center for Biologics and Evaluation and Research of the Food and Drug Administration in the United States, the National Institute for Biological Standards and Control in the United Kingdom, and the Therapeutic Goods Administration of Australia. In these serological studies, the antibodies that develop in response to current influenza vaccines are tested to ascertain whether viruses contained in the vaccines still match circulating viruses. That information is critical to knowing whether the existing composition will need to be updated in order to have an effective vaccine for the next season.

Twice a year, WHO convenes a consultation between the Collaborating Centres and the key reference laboratories involved in influenza vaccine selection and development to review the results of recent analysis. WHO is then able to recommend which influenza viruses should be used in the development of influenza vaccines

Vaccine Milestones: Smallpox Is Dead

U.S. National Archives Photos

This case of smallpox was "made mild" by a vaccination, according to the caption on this undated photo from the U.S. Army Medical Museum.

The most dramatic vaccine success story in the more than 200-year history of vaccines is the eradication of smallpox in 1980. Smallpox was targeted for eradication for several reasons: It was transmitted from human to human and had no animal reservoir; an effective heat-resistant freeze-dried vaccine existed that could protect in a single dose; and practical diagnostic tools were available for the ready identification of smallpox infection.

The World Health Organization adopted the goal of eradicating smallpox in 1959, but progress was fairly slow until the Intensified Global Eradication program was launched in 1967. The strategy was to launch mass vaccination campaigns in each country, ensure the potency and stability of the vaccine, and cover at least 80 percent of the population. Those campaigns were followed by rigorous disease surveillance to detect outbreaks and target them with focused containment measures. Whenever an "index" case of smallpox was reported, all close contacts of the index case were vaccinated, and then all close contacts of those people would also be vaccinated. This method effectively isolated the index case and broke the chain of transmission.

The last case of smallpox was identified in Somalia in 1977. The search for smallpox cases lasted for another two years, and in 1980, the World Health Organization declared that "smallpox is dead!" ■

Elizabeth Fee, Ph.D., National Institutes of Health

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The U.S. health care sector goes to great lengths to encourage immunization against seasonal flu. Volunteers assisted the Oklahoma City-County Health Department in a mass flu immunization exercise as the 2006 flu season began. Cars lined up at an immunization drive-through, allowing the inoculation of more than 1,700 people in a few hours.

for the next season for each the northern and southern hemispheres.

The Collaborating Centres provide extensive training for laboratory staff from National Influenza Centres and other laboratories. Every year the centres update the standard antigens and sera used by the NICs in the network to diagnose seasonal influenza and provide advice as needed on the most appropriate and up-to-date laboratory methods for the diagnosis of influenza. The centres can provide assistance to countries on responding to an outbreak of influenza, particularly if it should have pandemic potential. They also provide WHO with recommendations and guidance on how to improve the global system of influenza surveillance.

A New Challenge

Recently the emergence of a new, highly pathogenic strain of the influenza virus, H5N1, has raised alarms that an influenza pandemic may be imminent, with the potential to cause high levels of illness and death and widespread social and economic disruption. This has presented the surveillance network with significant technical and operational challenges that fall beyond its established role in detecting and protecting against seasonal influenza.

H5N1 differs substantially from seasonal influenza viruses. It is a newly emerging animal virus that is highly pathogenic in poultry and has crossed the species barrier to infect humans. Handling the virus requires higher levels of laboratory containment, and few NICs have the necessary experience required to diagnose H5N1 infection or to respond to H5N1 outbreaks. As a result, much of the heavy workload of the NICs has been falling on the Collaborating Centres. In 2004 WHO established an ad hoc network, known as the WHO H5 Reference Laboratories, to help with diagnosing human H5N1 infections. This move will allow the Collaborating Centres to continue to conduct more advanced analysis of H5N1 viruses to assess the risk of pandemic and to develop the necessary diagnostic reagents (substances used to detect or measure H5N1), test protocols, and candidate H5N1 vaccine viruses.

In its more than 50-year history, the Global Influenza Surveillance Network has played a central role in global efforts to address influenza in all of its forms and has proven itself to be an exemplary model of international cooperation. The partners in this system have established technical standards and norms for influenza surveillance and diagnosis and have enabled millions of doses of vaccines to be produced and administered. While GISN continues to protect the world's population from epidemics of seasonal human influenza, it is now also helping countries around the world respond to the H5N1 threat and prepare for the next influenza pandemic. ■

The opinions expressed in this article do not necessarily reflect the views or policies of the U.S. government.

Vaccines in the 21st Century

Stanley A. Plotkin

Stanley A. Plotkin, MD, is the executive advisor to the chief executive officer of sanofi pasteur, the largest company in the world devoted solely to human vaccines. He is an emeritus professor of pediatrics at the University of Pennsylvania and the developer of the rubella vaccine currently in use, as well as codeveloper of the newly licensed rotavirus vaccine. Plotkin is senior editor of Vaccines*, the standard textbook in the field.*

It has been often remarked that predicting the future is fraught with error, and that it is much easier to predict the past. Nevertheless, I believe certain tendencies in the field of vaccine development are likely to flourish in the near- and long-term future, and so I venture to make the following 10 predictions:

• The development of combined vaccines containing multiple valences will increase. Valence is the number of different antigens in a vaccine—a trivalent vaccine has three antigens, for example. An antigen is a chemical substance, usually a protein that stimulates the immune system to produce an antibody specific to the antigen. As the schedule for early childhood vaccination becomes more crowded with new vaccines, and as we deal with disease syndromes having multiple causes, it will be necessary to combine vaccines so that fewer injections are given. These combinations of vaccines will not be simple to develop, as the immunologic rules of interference among vaccines are not well described.

• Although many vaccines are administered to infants under the age of one year, protection is slow to develop because of the immaturity of the immune system. In fact, immunity may fade later in childhood if no booster doses are given. The specific factors that contribute to the immaturity are just becoming known, and I anticipate that immunologic adjuvants—substances that enhance responses to vaccination—will come into use in infancy.

• Sexually transmitted diseases, respiratory diseases transmitted by crowding, infections that cause cancer later in life, and infections transmitted from mothers to their fetuses all require vaccination before adolescence begins. Thus, the age of 11 to 12 years will become a time for administration of many newly emerging vaccines to provide protection during early adult life.

• The elderly suffer a natural aging of the immune system, both with respect to antibody production and cellular responses to infection or vaccination. Here again, we are beginning to understand the defects that come with age, and correction of these defects should improve the efficacy of vaccines in an increasingly aged population.

• Two new strategies have become widespread for experimental vaccine development: injecting humans with DNA segments from pathogenic microorganisms that produce protective proteins after injection, and inserting genes from pathogens into harmless microorganisms that serve as carriers, or vectors, for production of immune responses. Although each strategy separately may generate useful vaccines, the combination of the two in a so-called "prime-boost sequence" provides synergy. Thus, there will be vaccinations consisting of

© AP Images/Charles Dharapak

The Iomai Corporation is developing needle-free vaccines and immune system stimulants targeting influenza and pandemic flu. The director of plant operations looks over an automated vaccine patch manufacturing machine at company headquarters in Gaithersburg, Maryland, near Washington, D.C.

prime-boost regimens, particularly in those cases where antibodies are insufficient to give complete protection.

• Intramuscular or subcutaneous injections have served us well as the means to introduce vaccines into humans. However, there are limitations to the feasibility of numerous injections and theoretical reasons for preferring other routes of immunization. Thus, intranasal, aerosol, and oral routes of administration are being intensively explored for certain vaccines. Moreover, transcutaneous immunization using patches, microneedles, and other ingenious technologies to pass vaccines through the skin is promising.

• Malaria, tuberculosis, and HIV are major targets of vaccine development. Short-term protection against malaria has already been achieved, and I foresee the extension of protection by combining several malaria antigens in one vaccine, although I suspect that regular boosters will be necessary to maintain protection.

• Prospects for a vaccine that protects against adult tuberculosis are good. This will be based on the current BCG vaccine. The Bacillus Calmette-Guérin vaccine, developed at the Institut Pasteur in Lille, France, in the early 20th century, is effective in children but does not prevent the infection in adults. Insertion of genes that code for additional protective proteins should improve BCG.

• HIV has proven to be a difficult target for vaccination, but a vaccine that reduces the seriousness of infection and prolongs life, even while not preventing the disease completely, is likely to be the product of current clinical trials. The development of a vaccine that prevents infection entirely is less likely in the near future.

• Influenza remains a banal but deadly infection. Although the vaccines we have are very beneficial, better protection will be derived from the inclusion of more influenza proteins, adjuvants, and the combined use of live and killed vaccines. ■

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Ending Disease, Ending Poverty

An Interview With Lee Hall and Peter J. Hotez

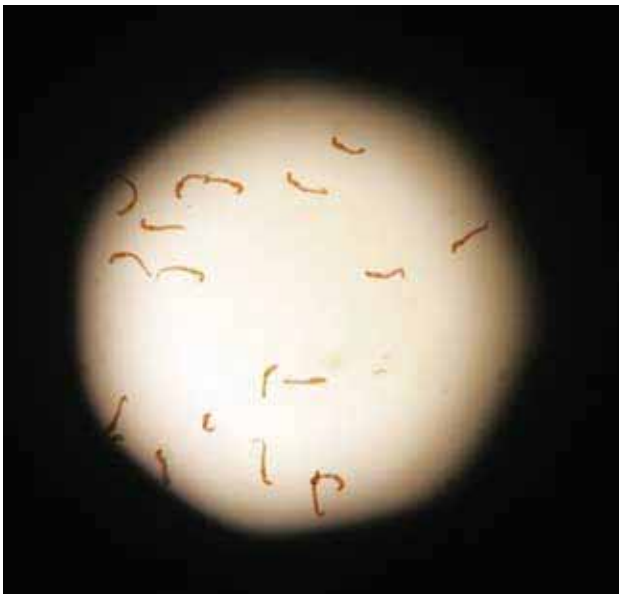
It is a widely accepted fact that vaccines are among the safest and most cost-effective ways available to prevent disease and improve the overall level of health in a population. That fact balances on two uncertain variables: Has science found a vaccine effective against a given disease? If so, can that vaccine be delivered to an entire vulnerable population?

Global poverty might be significantly reduced if the answers to those two questions were "yes" when it comes to a certain class of ancient diseases. Neglected tropical diseases (NTDs) disproportionately affect people of the poorest nations, while they are almost unheard of in the industrialized world. But there is a growing recognition that an invigorated effort to prevent these diseases and their resulting disability and dysfunction could have an enormous impact on improving the quality of life and alleviating poverty in many nations.

Two experts in this field discussed these developments with Global Issues *managing editor Charlene Porter. Lee Hall, MD, chief of the Parasitology and International Programs Branch at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and Peter J. Hotez, MD, PhD, Walter G. Ross Professor and Chair of Microbiology, Immunology, and Tropical Medicine at the George Washington University and Sabin Vaccine Institute, have been watching developments in this area of medicine and health policy.*

Question: Dr. Hotez, you've referred to these diseases as the "biblical diseases." What does that name suggest about the long history of these ailments and how severely they have plagued the human race?

Hotez: The "biblical diseases" refer to a set of tropical diseases that are sometimes known as the neglected tropical diseases. It's a group of primarily 13 infections that are chronic and disabling in their nature, and they occur almost exclusively among the world's poorest people.



© AP Images/Ric Feld

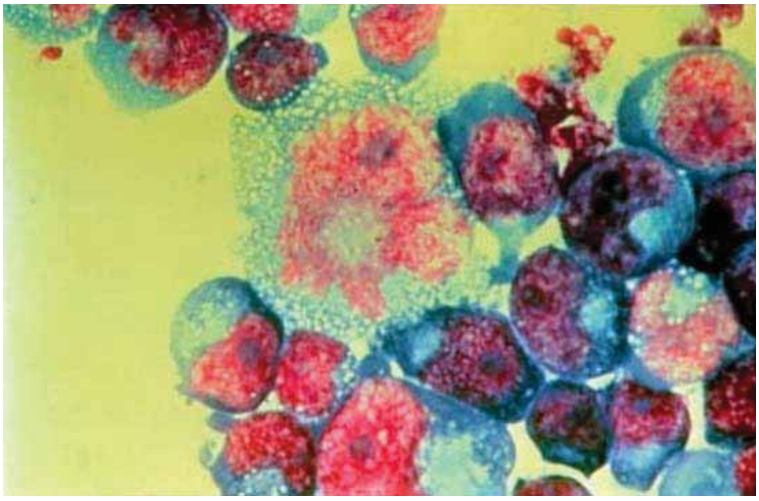
Schistosoma mansoni worms cause schistosomiasis. The parasitic, microscopic worm found in contaminated water penetrates human skin, causing illness that plagues more than 200 million across the globe.

Of the 2.7 billion people who live on less than $2 a day, approximately half have one or more of these diseases. Their common features are that they are disabling and have huge impacts on the growth and development of children, on pregnancy and pregnancy outcome, and on worker productivity and capacity. Because of those features and their chronic, disabling nature, they're able to keep the poorest populations mired in poverty. The diseases themselves promote poverty.

These are a group of afflictions that have occurred in humans since ancient times. You can find vivid descriptions of these neglected tropical diseases in ancient texts—in the Bible, the Talmud, the Bhagavad-Gita, the writings of Hippocrates, Egyptian papyrus. They're sometimes referred to as biblical diseases because of their very ancient character.

So when you look at the neglected tropical diseases in aggregate, they're as important as AIDS, they're as important as malaria, and they're as important as tuberculosis. Now we have a great opportunity to do something about them in a very substantive way.

Q: Dr. Hall, why is it that there has not been a great



Courtesy Dr. Tom Folks, NIAID

T-cells are a key component of the immune system, and their function is impaired when infected with HIV virus, as shown here.

deal of attention paid to the development of vaccines for these conditions in the past? And how do you see the situation changing?

Hall: There's been a lot of interest in intervention in these diseases for a long time, but it has waxed and waned. Back in the early part of the 20th century when there were Western military forces deployed in these world regions, there was actually a fair amount of interest. Then as those military forces were pulled back, interest began to wane.

Over the past couple of decades, there has been a complete change in technology, in biotechnology, and how we approach these diseases now. These diseases typically are caused by organisms that are much more complex than many of the viral and bacterial diseases we usually think about. With newer technologies, we're in a position to address the science that underlies many of these diseases and start to develop new interventions.

Another key factor that has changed is our recognition of the interconnectedness of the globe. The areas where these diseases have predominated, as Peter said, were impoverished. They did not have the ability to translate this unmet medical need into some sort of global demand that could be recognized by the pharmaceutical industry and capitalized upon in order to produce new interventions.

That is now changing, and we realize these diseases are a product of poverty and contribute to poverty. As new technologies make new tools available, we can actually break this cycle of disease by bringing these interventions to where they are most needed.

Hotez: One of the great challenges that we face now is that our technology has, in some sense, raced ahead of our ability to distribute products to the people who need them. How do you establish a company that's going to make a product for people who can't afford to pay for the product when they live on less than $2 a day? You can never expect a for-profit organization that's responsible to its shareholders to take the leadership in making these vaccines.

One of the ways that we've been working to overcome that challenge is to work with the National Institutes of Health, work with the Bill and Melinda Gates Foundation, to set up new nonprofit organizations that are actually going to make vaccines. We're looking at a new paradigm where vaccines will not only be made by large pharmaceutical companies, but we'll create a new entity—sometimes known as PDPs or Product Development Partnerships—that's going to take the lead in making vaccines for things like onchocerciasis or schistosomiasis.

That's going to help revolutionize all the wonderful technology that the National Institutes of Health has funded over the past two decades. That's now going to be leveraged into manufacturing this new generation of products.

Q: The AIDS epidemic also brought greater recognition in the donor community about the importance of a population's overall health in overcoming poverty and maintaining national security. Isn't there heightened recognition that other tropical diseases also merit attention on those grounds?

Hotez: Absolutely. There's this very fascinating, but still not completely well-defined relationship between health and security. If you look at the nations of the world that have been engaged in conflict over the last 20 years, the vast majority of them suffer from neglected tropical diseases.

Think of where the hot spots have been over the last two decades. They've been places like Somalia, Sierra Leone, and Liberia. The common feature is that they all suffer from high rates of malaria, neglected tropical diseases, and HIV/AIDS. That may be more than just coincidence. There may be an opportunity now to use health and prevention as a means of reducing conflict and reducing tensions in these most devastated nations.

Q: Dr. Hall, let's explore further the advances in

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A Nicaraguan boy stands near his mother, who was diagnosed as having leishmaniasis cutaneous, also known as mountain leprosy, during a 2005 outbreak northeast of Managua.

biotechnology that are helping you address these diseases. Where is the progress being made?

Hall: Let's start with malaria, for example. We know that the three components necessary to maintain the parasite's life cycle are the parasite, the mosquito vector, and the human host. We now have completely sequenced genomes for all three of them. That allows us to study in a much more rigorous way the whole life cycle at a genomic and a molecular level. We're now beginning to achieve that same level of scientific knowledge with a number of these other diseases.

For example, we now have fully sequenced the genomes of the parasites that cause leishmaniasis, Chagas' disease, and African trypanosomiasis. They are all very closely related, and yet they have certain distinct features. We can do some comparative studies with these now and understand better how the parasites actually function and what determines their ability to cause disease. There are research groups that are sequencing the genome for the vectors that transmit some of these parasites like the species of fly that transmits human African trypanosomiasis, and we'll soon have that information as well.

We have already sequenced the human genome and understand a variety of biochemical pathways in the human host. By comparing genomes and biochemical pathways between the parasite and the human host now, we hope to be able to identify pathways and targets that are unique to the parasite and not shared by the human host. Those unique features then allow us to identify leads for new drugs, diagnostics, and vaccines. I chose three protozoan parasites as examples, but we're rapidly approaching the same situation for diseases caused by parasitic worms, such as filariasis [also known as elephantiasis] and for schistosomiasis.

Q: Dr. Hotez, you mentioned the various partnerships that are taking shape to help achieve those ends. Explain how an increasingly sophisticated pharmaceutical industry in the developing world is also contributing.

Hotez: One of the things that is happening along with the Product Development Partnerships is that the partnerships will actually include what we call public sector vaccine manufacturers in developing countries. I'll give you an example. I head an organization called the Human Hookworm Vaccine Initiative, which is part of our Global

Network for Neglected Tropical Disease Control *[http://www.GNNTDC.org]*, and the Human Hookworm Vaccine Initiative is based at the Sabin Vaccine Institute. It's a Product Development Partnership with the goal of making a new recombinant antigen vaccine for human hookworm infection, a disease of 576 million people in the developing world.

In Washington, D.C., we've been able to make pilot-scale amounts of vaccine for early-phase clinical testing, which is underway in Brazil. The problem is the amount we can make in our laboratories through the PDP here in Washington is limited, and certainly not enough to vaccinate all of Brazil or all of the Americas.

So we've now partnered with an organization known as Instituto Butantan, which makes 86 percent of the vaccines for Brazil, including their own recombinant hepatitis B vaccine. So now our scientists are working with this public sector vaccine manufacturer in Brazil in a collaborative manner. They're coming up here; we're going down there and transferring our technology so that they can do the scale of production for all of the Americas. We look forward to the opportunity of working with public sector vaccine manufacturers in this group of low-income and middle-income countries that also have endemic tropical diseases and have great pockets of poverty, and yet have somehow managed to overcome their poverty and achieve a certain level of innovation that they can actually make their own vaccines. We call these types of countries IDCs, Innovative Developing Countries, low- and middle-income countries that have gone that next step to take on biotechnology and do it in a very sophisticated way.

They include countries such as Brazil, China, Indonesia, India, Thailand, and Malaysia, and we think that these countries and their public sector vaccine manufacturers could lead the way in making a whole new generation of products for the developing world.

Q: That trend has been driven to a degree by the AIDS epidemic in these countries. Dr. Hall, what are the recent findings about the biologic interrelation of these diseases with AIDS?

Hall: There are lots of studies going on to try to define that relationship and see how these diseases might affect each other, whether HIV makes them worse, whether these diseases actually contribute to making HIV worse. We've not defined that relationship as closely as we would like, but our knowledge base in this area is rapidly expanding.

Hotez: Two very exciting papers were published in 2006 in *AIDS*, one of the leading HIV/AIDS journals. One of them looked at women living in Zimbabwe with schistosomiasis, a worm infection, and showed that a large percentage of those women—up to 75 percent—have lesions resulting from the presence of these parasitic

A Quick Strike Against Disease

The Global Network for Neglected Tropical Disease Control is an alliance of the major public-private partnerships devoted to the control of the most prevalent neglected tropical diseases (NTDs) worldwide. The Global Network is advancing a plan to control these diseases through the integrated administration of the "rapid-impact package," so named because the drugs can be quickly deployed with rapid reductions in morbidity and disability, improvement in well-being, and, in some cases, interruption of transmission. The package is comprised of a combination of up to four drugs, all of which have been in use, tested, deployed and utilized by millions for more than a decade. Combining these drugs in an integrated health care package is a new approach that deemphasizes specific tropical diseases and, instead, focuses on neglected populations with multiple tropical infections. Worldwide, there are a total of 56 countries with five or more endemic NTDs. Most of these are in sub-Saharan Africa where the rapid-impact package will be deployed extensively.

This packaging approach has been successful with early childhood vaccines. By packaging a combination of vaccines and inoculating infants against different diseases at the same time, the costs are diminished and the benefits are enhanced.

Identification of the first countries to be included in the Global Network's rapid-impact treatment scheme is currently underway.

The Global Network is based in Washington, D.C. ■

worms. As a consequence, they have a threefold increased risk of acquiring HIV.

So what if you could be giving drugs for parasitic worm infections at the same time you're giving antiretroviral drugs for HIV/AIDS? The great thing about these parasitic worm drugs is they're cheap, less than 20 cents a dose, and could be given to large populations fairly easily. That's why we set up this Global Network for Neglected Tropical Disease Control: to find a way to administer these antiparasitic drugs to large populations. We think treating these worm infections throughout sub-Saharan Africa will clearly have a huge benefit in terms of health impact because of the diseases that the worms cause, but a secondary impact could also result from actually reducing the transmission of HIV/AIDS.

By adding an additional 20, 30, 40, or 50 cents to the hundreds of dollars spent each year per person on antiretrovirals in large AIDS treatment programs such as the President's Emergency Program for AIDS Relief, you could possibly double your impact. But the studies are still at an early stage.

Q: Dr. Hall, Dr. Hotez has mentioned the drugs that can be very cheap and available to treat many of these conditions; but why is it that vaccines still seem preferable even when drugs would be available?

Hall: There are a number of reasons. First of all, for some diseases, it's going to be very hard to develop vaccines even with a great deal of technology. Parasites themselves are fantastic immunologists and have actually developed ways to escape the immune response, and they've been doing this longer than we have thought about it, so it's a real challenge.

In other situations, where we can develop vaccines, we want to develop them because we would like to prevent disease, rather than treat it. The pathology of these diseases is really cumulative as it occurs over time, whether it's schistosomiasis or filariasis or some of these other diseases. There's a gradual build up of disease, and treatments of an advanced disease aren't going to necessarily reverse that pathology.

We'd like to catch people early on and prevent disease, so they don't develop these diseases.

Hotez: I agree, and at the Global Network, what we think is going to be the important way to move forward on tropical diseases is not looking at the choice of either drugs or vaccines, but in fact, the two need to be linked in a tightly coordinated, controlled program.

Q: To conclude then, is there a single development in this field that you think is the most promising for short-term delivery?

Hall: One has to look at research as a long-term endeavor. The pace of research is accelerating as a result of success with genome sequencing and a variety of post-genomics activities. That's really where we're going to see a lot of progress in the near future.

In addition to that, a number of candidate vaccines have already entered clinical development. Peter has mentioned the Hookworm Vaccine Initiative. There are also vaccines that are in development now for schistosomiasis and for leishmaniasis as well. Those are very exciting.

We're at a fantastic point in the research where activities are moving forward in this area, and they're beginning to accelerate because of the technology.

Hotez: We have a great opportunity now to control morbidity [the incidence of disease] from the seven most prevalent neglected tropical diseases—ascariasis, hookworm, trichiuriasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma—through a program of integrated control that employs donated and generic drugs. Better controlling those seven diseases could make a huge impact on these co-infections that occur among the very poorest populations of sub-Saharan Africa, Southeast Asia, and the Americas. We're going to see dramatic gains in health, education, and economic development and, possibly, even biosecurity as a consequence of widespread use of these drugs.

One of our projects at the Global Network on NTD Control is the distribution of a rapid-impact package of drugs. With this package of drugs, which are proven, safe, inexpensive treatments for these conditions, we could eventually either reduce the morbidity or control the seven most prevalent neglected tropical diseases. In addition, for two of the NTDs—lymphatic filariasis and trachoma—we could even interrupt their transmission and eliminate them as public health problems.

So while we're doing widespread administration of the rapid-impact package, we want to step up our research and development efforts to focus in on the development of new vaccines for the other diseases that we want to eliminate —hookworm, schistosomiasis, leishmaniasis, and Buruli ulcer—and some of these other very important neglected tropical diseases. ■

The opinions expressed in this interview do not necessarily reflect the views or policies of the U.S. government.

What Are Neglected Tropical Diseases?

© AP Images/Zoe Selsky

This Colombian soldier shows sores on his arm and face from the disease leishmaniasis. He caught the disease while on patrol in the jungles of southern Colombia and received treatment at a base near Bogota.

Definitions and descriptions of poverty-causing diseases are compiled from U.S. and international agencies.

These diseases almost exclusively affect impoverished people living in rural areas or poor urban slums of low-income countries. They are caused by parasitic worms, bacteria, and protozoa. They can be fatal, but they primarily cause chronic lifelong disabilities, leading to disfigurement, impaired child development, poor pregnancy outcomes, and impaired worker productivity.

Victims of neglected tropical diseases also encounter serious stigma in their communities, adding social consequences to their health problems. As a result, neglected tropical diseases affect the health of poor populations, and they mire infected individuals in poverty. On national and regional scales, their effects are so dire that these diseases are considered conditions that promote and perpetuate poverty.

HIV/AIDS, tuberculosis, and malaria are also considered by some to be "neglected." Large-scale funding is now being invested in these "big three diseases," however, while no broad initiatives are underway for the 13 major parasitic and bacterial infections comprising the neglected tropical diseases. Vaccine programs are in early research and development for all the neglected tropical diseases cited here.

Helminth/Intestinal Worm Infections

Hookworm is an intestinal parasitic worm of humans that usually causes intestinal blood loss leading to iron-deficiency anemia and malnutrition. As a result, heavy infection with hookworm can create serious health and educational problems for preschool and school-aged children, and for women of reproductive age, including pregnant women, and for persons with low iron reserves. An estimated 600 million people are infected. Recent economic estimates indicate that chronic hookworm infection in childhood reduces future wage-earning capacity by 40 percent.

Onchocerciasis is an infection caused by a parasitic worm, which is spread by the bite of an infected blackfly. It is also called river blindness because the transmission is most intense in remote African rural villages, located near streams. Persons with heavy infections will usually have dermatitis, eye lesions, and/or subcutaneous nodules. The global prevalence is approximately 18 million, of whom about 270,000 are blind and another 500,000 have visual impairment.

Schistosomiasis, also known as bilharzia, is a disease caused by parasitic worms found in water contaminated with human waste. Schistosoma parasites can penetrate the skin of persons who are wading, swimming, bathing, or washing in contaminated water. The first symptoms are rashes or skin irritations, followed later by fever, chills, cough, and muscle aches. People who are repeatedly infected for many years may experience damage to the liver, intestines, and bladder and kidneys. In Africa, schistosomiasis is a leading cause of chronic renal failure. Approximately 200 million people are infected worldwide, resulting in 280,000 deaths annually.

Protozoan Infections

Amebiasis is a disease caused by a one-celled parasite that thrives in unsanitary conditions. The symptoms often are quite mild and can include loose stools, stomach pain, and stomach cramping. Amebic dysentery is a severe form of amebiasis associated with stomach pain, bloody stools, and fever. Some patients go on to develop an amebic liver abscess. Amebiasis is among the world's most prevalent parasitic illnesses, affecting an estimated 500 million people.

Chagas' disease is an infection caused by a parasite carried by blood-sucking triatomine bugs, which live in cracks and holes of substandard housing from the southern United States to southern Argentina. Worldwide, it is estimated that 16 to 18 million people are infected with Chagas' disease. Of those infected, 50,000 will die each year. For about one-third of the persons who get Chagas' disease, chronic symptoms and heart failure develop 10 to 20 years after infection. For those who develop chronic symptoms, the average life expectancy decreases by an average of nine years.

© AP Images/Edgard Garrido

In Tegucigalpa, Honduras, a city employee fumigates a house during a campaign to kill mosquitoes carrying dengue fever.

Leishmaniasis is a parasitic disease spread by the bite of infected sand flies. The disease may come in a cutaneous form, causing skin sores, or in a visceral form affecting the internal organs of the body. Skin sores caused

© AP Images/Wong May

This banner displayed in Singapore is part of a multimillion dollar government effort to promote preventive measures against the breeding of mosquitoes that spread dengue fever.

by leishmaniasis may take months or years to heal if untreated. Organ damage resulting from the visceral form of the disease can lead to death. This parasite is now endemic in 88 countries on five continents—Africa, Asia, Europe, North America, and South America—with an estimated 12 million people affected worldwide .

Bacterial Infections

Buruli ulcer is a disease caused by infection with *Mycobacterium ulcerans*, which is transmitted to humans through an unknown mechanism. Infection causes formation of large ulcers usually on the legs or arms, leading to extensive destruction of skin and soft tissue. Patients who are not treated early often suffer long-term disfigurement and functional disability, such as restriction of joint movement. Buruli ulcer has been reported in more than 30 countries mainly with tropical and subtropical climates, but limited knowledge of the disease and its occurrence in poor rural communities make global estimates of case numbers difficult.

Chlamydia is the world's most common sexually transmitted disease (STD) and can cause long-term damage to a woman's reproductive organs. Though symptoms of chlamydia are usually mild or absent, serious complications that cause irreversible damage, including infertility, can occur unnoticed before a woman ever recognizes a problem. Chlamydia also can cause discharge from an infected man and pain and itching in urination. Complications among men are rare. Another important form of human chlamydia infection is known as trachoma, which is nonsexually transmitted and results in visual impairment or even blindness. It is the most common infectious cause of blindness in the world. Currently, 8 million people are visually impaired as a result of trachoma, and 84 million suffer from active infection.

Leprosy is a bacterial disease with an incubation period of about five years. Symptoms can take as long as 20 years to appear. It is transmitted through close contact with untreated cases via droplets from the nose and mouth. Leprosy mainly affects the skin and nerves. If untreated,

progressive and permanent damage to the skin, nerves, limbs, and eyes may result. Leprosy is a curable disease, and treatment provided in the early stages averts disability. The global occurrence has dropped dramatically from more than 5 million annual cases in 1985 to fewer than 300,000 in 2004.

Leptospirosis is a bacterial disease that affects both humans and animals. The early stages of the disease may include high fever, severe headache, muscle pain, chills, redness in the eyes, abdominal pain, jaundice, hemorrhages in skin and mucous membranes, vomiting, diarrhea, and a rash. Human infection occurs through direct contact with the urine of infected animals or by contact with a urine-contaminated environment, such as surface water, soil, and plants. Because the symptoms are similar to other diseases, leptospirosis is often not recognized, and a precise number of cases worldwide is not known.

Treponematoses encompass a group of diseases caused by one of several different strains of the spirochete bacterium. The group includes yaws, a disease of the skin, bones, and joints passed from one person to another through bacteria carried by eye gnats or entrance of the bacteria through a cut. Bejel, or endemic syphilis, is a chronic skin and tissue disease caused by a related strain of bacteria, producing lesions on the limbs and trunk and inflammation of the leg bones. Pinta is another condition in this family of diseases, and it also produces skin lesions. The several strains are distinct to different world regions, and they usually can be treated with antibiotics. Together the diseases affect about 25 million people.

Viral Infections

Dengue is a mosquito-borne infection found in tropical and subtropical regions around the world. Dengue fever is a severe, flu-like illness that affects infants, young children, and adults, but seldom causes death. Dengue hemorrhagic fever (DHF) is a potentially lethal complication, characterized by high fever, hemorrhagic phenomena—often with enlargement of the liver—and in severe cases, circulatory failure. WHO currently estimates there may be 50 million cases of dengue infection worldwide every year.

Japanese encephalitis is a disease caused by a virus transmitted to humans through a mosquito bite. Mosquitoes pick up the virus from feeding on domestic pigs and wild birds. Mild infections occur without apparent symptoms other than fever with headache. More severe infection is marked by quick onset, headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, occasional convulsions, and spastic paralysis. Japanese encephalitis is the leading cause of viral encephalitis in Asia with 30,000 to 50,000 cases reported annually. ■

Sources: International Leptospirosis Society; International Trachoma Initiative; U.S. Centers for Disease Control and Prevention; University of California, Berkeley; World Health Organization; the Global Network for Neglected Tropical Disease Control.

Ensuring the Quality and Safety of Vaccines

World Health Organization Fact Sheet
(Excerpted)

Photo courtesy sanofi pasteur

At their production facility in France, sanofi pasteur technicians culture the viruses that will be used in an inactivated—or killed—polio vaccine.

Vaccines must be held to a very high standard of safety. Stringent measures are taken to ensure quality and safety in the research and development, manufacturing, licensing, transport, storage, and use of vaccines, and in the disposal of needles and other equipment after vaccinations are carried out.

Research and Development

Like other pharmaceutical products, vaccines are first carefully evaluated for effectiveness and potential harmful effects in vitro [in an artificial environment] and in animals. If good safety results are achieved, phased trials with humans begin.

Phase I clinical trials examine safety and immune responses to candidate vaccines. Such trials generally have 20 or fewer participants, usually healthy adults. These trials are meant to identify any obvious or commonly occurring adverse reactions. Phase II trials, which may have from 50 to several hundred participants, help researchers to determine the optimum vaccine composition for achieving protection while ensuring safety.

Phase III trials are designed to see if a vaccine actually prevents a disease as intended, and to provide further safety information. They serve as the final gatekeepers prior to vaccines' introduction for wider use in the general population. Phase III trials involve thousands to tens of thousands of people of the intended age. In general, Phase

III trials include a control group receiving a placebo. Subsequent adverse events (or medical incidents that may or may not be the result of vaccination) and the rates of occurrence of target diseases are compared between the groups of vaccinated and unvaccinated persons. Should significant safety issues arise during a human trial at any phase, mechanisms are in place to stop the study and stop administration of the vaccine. If there are significant safety concerns, the vaccine does not go forward for licensing.

Safety Monitoring of Licensed Vaccines

Once vaccines are licensed for general use and are administered to large populations, monitoring continues to identify less common adverse events, events that may occur after a long time, or events that may occur in specific subgroups of the target population.

Typically, monitoring of licensed vaccines is done through spontaneous reporting systems, whereby adverse events that follow immunization are reported to health authorities. Sometimes post-licensing monitoring is conducted in more formal Phase IV trials.

Detection of an adverse event following immunization does not necessarily mean the event was caused by the vaccine. Determination of a cause-and-effect relationship requires further investigation.

Manufacturing

Numerous regulations ensure the safety and quality of vaccines. They include the precise identification (characterization) of starting materials, compliance with the principles of good manufacturing practices, the use of detailed control procedures, and the independent release of vaccines on a lot-by-lot basis by national regulatory authorities. Responsibility for quality and safety rests with the national regulatory authority (NRA) in the country of manufacture and, where exported, with the NRAs of the receiving countries.

The World Health Organization (WHO) helps strengthen the regulatory capacities of NRAs through periodic assessments against a published set of indicators. WHO also provides technical support to NRAs where appropriate.

Vaccine Transportation and Storage

Vaccines must constantly be kept at optimal temperature, typically at between 2 degrees and 8 degrees Celsius, from the place of manufacture to the point of use. This is a logistical challenge, especially in developing countries. The network set up to ensure that the required temperature is maintained is called the "cold chain." Refrigerators, ice packs, and cold boxes are employed on airplanes, helicopters, and trucks, and in various storage locations; in areas not reached by road, chilled vaccine carriers are transported by hand to reach the point of use.

If electricity is not available, gas, kerosene, or even solar-powered refrigerators or freezers may be used. Most refrigerators and related equipment can be selected to meet WHO-UNICEF Performance Quality and Safety standards. Staff at international, national, and local levels are trained to manage cold chain networks. They include technicians, shippers, customs officers, pilots, drivers, government officials, health workers, and community leaders. Among other things, they monitor the temperature of the vaccines and discard those that have exceeded the established limits.

Vaccine vial monitors (VVMs)—temperature-sensitive labels—can be attached to vaccine vials and indicate through a change in color whether an individual vial has been exposed to heat that is likely to have damaged the vaccine. These labels have been successfully used to monitor vaccines taken beyond well-established cold chain settings, such as clinics, to field sites used for mass immunization campaigns. In these latter settings, which may be remote and without any access to refrigeration, the vaccines need to be kept in containers with cold packs. The VVM vial labels enable health care providers to determine at a glance if a vial has been kept within the needed temperature range or not.

Safe Injections

Many vaccines are delivered by injection. WHO promotes safe injection practices as a priority. Vaccine-related injections are safe for the recipient when a health worker uses a sterile syringe, a sterile needle, and a sterile technique for each injection. They are safe for health workers when needle-stick injuries are avoided. They are safe for the community when used needles, injection equipment, and vaccine waste are disposed of in such a

way as to avoid injuries from potentially contaminated needles and to minimize pollution.

For immunization, WHO recommends the exclusive use of syringes with auto-disable features that prevent reuse; these are now available, inexpensive, and widely employed. In addition, WHO recommends the immediate disposal of used needles and syringes into puncture-resistant safety boxes, a practice fast becoming the standard around the world. Equipment and safety procedures continue to be improved.

The General Risks of Vaccines

No vaccine is perfect—that is, no vaccine provides full protection against its target disease for every person who receives it, and no vaccine is completely risk-free for every person who receives it. Experience has shown that most adverse events are not actually caused by vaccines; the majority are coincidental (occur at the same time but are not related), while others are related to preventable errors in the storage, handling, or administration of vaccines.

While vaccines can cause reactions, these tend to be minor, such as a sore arm, redness or minor swelling at the injection site, or low-grade fever. Extremely rarely, there are more serious consequences. For example, anaphylaxis (immediate, severe allergic reaction leading to shock) has been noted at a rate of one per 1 million persons receiving measles vaccine, and vaccine-associated paralytic polio occurs in approximately one in 2.5 million Oral Polio Vaccine (OPV) doses administered. The risk of these more serious reactions must always be weighed against the major benefits of protecting large numbers of people against serious and even life-threatening diseases.

Periodically, concerns about vaccine safety are raised that later prove to be unfounded. For example, there is no valid evidence of a causal link between measles vaccine and autism, a topic that has been extensively reviewed by the Global Advisory Committee on Vaccine Safety and several other expert bodies. Similarly, no valid evidence has been found to support an alleged link between whole-cell pertussis vaccine and brain damage, or hepatitis B vaccine and leukemia or multiple sclerosis. ■

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Concerns About Vaccine Safety

In developed countries where routine childhood immunization has been in place for decades, some diseases have virtually disappeared, and the memories of their fatal or disabling consequences have been forgotten. Most parents in the developed world have never seen a child paralyzed by polio or brain-damaged by measles. As a result, fear of these diseases does not haunt parents as it once did.

At the same time, widely broadcast news stories about pharmaceutical recalls and drug tampering episodes have heightened public concerns about product safety and the reliability of recommendations from the medical establishment. That climate has contributed to resistance among some parents to the regimen of immunizations recommended by government agencies and medical professionals. The Internet has provided a forum in which these fears are further heightened by the rapid transmission of information, which is sometimes misleading or inaccurate.

Many governmental, international, and professional organizations are responding to the concerns about vaccines. The National Network for Immunization Information, for example, offers parents this advice about vaccines.

The homepage of www.immunizationinfo.org. The National Network for Immunization Information (NNii) is affiliated with a broad range of respected medical societies and provides the public with current, scientifically valid information related to immunization.

Vaccine Safety and Risk Perception

No vaccine is 100 percent effective; no vaccine is 100 percent safe. As with any drug, there are risks and side effects with vaccines, although serious side effects are mostly rare. However, there is a much higher standard of safety expected of preventive vaccines than for drugs because:

- Vaccines are generally given to many people, most of whom are healthy. People tolerate far less risk from *Haemophilus influenzae* type b vaccines than the antibiotics used to treat the diseases it causes, for example.
- Many vaccines are given to children at the ages when developmental and other problems are being recognized for the first time. Because a developmental problem was spotted at about the same time as immunizations were received does not mean that one caused the other.
- Some vaccines are mandated by law in order to protect the health and welfare of the public. Some people think that this violates their civil rights.

Research shows that people respond better to some types of risks than others.

Natural risks (such as infectious diseases) are better tolerated than man-made risks (such as vaccine side effects). Also, risks that affect adults are better tolerated than risks affecting children. Risks that are perceived with unclear benefits may be less tolerated than risks where the benefits are understood.

Take, for example, measles and the MMR (measles-mumps-rubella) vaccine. Since these diseases are no longer epidemic in developed countries, some parents incorrectly assume that the risk of contracting the disease is lower than the risk of their child experiencing an adverse reaction to MMR. They conclude that there may be little benefit from immunizing their child, hence there may seem to be no reason to take the risk of an adverse event. However, there was a mumps outbreak in the United States in 2006, probably introduced from the epidemic in Great Britain. These infections are just a plane ride away.

Perception of risk depends on people's experiences and knowledge. A person who experienced an adverse event

after vaccination—or thinks that they know someone who did—will perceive vaccines as riskier than a person who has not. Conversely, one who has survived a vaccine-preventable disease—or a physician who has treated that disease—will likely be an advocate for vaccines.

Although concerns about vaccine safety are valid and necessary we must carefully examine each claim about the risks of immunizations:

- Is the claim relying on scientific data (for example, large, controlled studies published in respected scientific journals) or on anecdotes (personal stories of sick persons)?
- Are the claims based on facts or are they personal opinions?

Missing Information

When up-to-date, complete, and scientifically valid information about vaccines is available, parents can make informed decisions. Without this information many may develop a false sense of security and regard immunizations as unimportant.

Unfortunately, when a community has low immunization rates, many children, including some who have been immunized, are placed at risk of harm if a highly communicable disease like measles is introduced into the community. With global travel an everyday occurrence, measles may be introduced from another country at any time, posing a threat to communities with low immunization rates. For instance, in March 2004, the U.S. Centers for Disease Control and Prevention (CDC) published information about a student flying from India to Cedar Rapids, Iowa, while incubating measles, as well as cases of measles among children who had recently been adopted from China (see CDC's report at *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm53d319a1.htm*).

Like parents, scientists and scientific review groups need data to evaluate vaccine safety concerns. Vaccine safety research often requires very large and often expensive studies that have not been conducted. So when a vaccine safety concern is suggested, the necessary data to support or reject the hypothesis may not yet have been collected—in fact sometimes this may take several years of research. This often leaves scientific review groups like the Institute of Medicine (IOM) Vaccine Safety Committee with insufficient data to be able to fully evaluate vaccine safety concerns.

Another example of missing information arose from a case concerning the hypothesis that the use of thimerosal, a mercury-containing preservative, in vaccines caused autism. This idea was first suggested in 1999, and the ensuing controversy demonstrates the dilemma of insufficient data. In 2001, when the Institute of Medicine's Immunization Safety Review Committee first examined the issue, it stated that the available evidence was inadequate to decide. In other words, the information was missing. By 2004, however, much more scientific data was available, and the IOM committee was able to conclude that the data favored rejection of a link between vaccines and autism.

> Some vaccine safety concerns persist despite the evidence against them.

Misinformation

Some vaccine safety concerns persist despite the evidence against them. Even when the concern is resolved for most in the scientific community, suspicions about safety may remain an issue for others with vested interests, such as lawyers, journalists, or well-intentioned but misinformed parents.

In spite of the substantial evidence now available that allows rejection of the hypothesis that vaccines cause autism, there are some who continue to state that there is a causal association. These claims, once based on missing information, now fall into the category of misinformation.

Unfortunately, the misinformed person with a fixed opinion about vaccines has many sophisticated tools to disseminate misinformation, creating confusion about vaccine safety. Misinformation comes in many packages and may be widely publicized by the media and others causing lowered immunization levels and heightened disease risk.

Misinformation about vaccines is frequently encountered on the Internet. Some Web sites, for instance, oppose the immunization of infants and children. They express a variety of claims that are largely unsupported by peer-reviewed scientific literature.

Misinformation Web sites tend to ignore or distort scientific studies, instead relying on emotionally filled anecdotes about bad things that happened to children or coincided in time with vaccine administration.

Unfortunately for communities, antivaccination movements have also had a negative effect on public health through the years. One study published in *The Lancet* in 1998 showed that movements against the whooping cough vaccine caused whooping cough epidemics in several countries. ■

Adapted by Global Issues *with permission, from an article by Martin G. Myers and Diego Pineda (2007) "Vaccine Misinformation" © National Network for Immunization Information. The original is available at* http://www.immunizationinfo.org/immunization_issues_detail.cfv?id=52.

NNii is affiliated with the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, the American Nurses Association, the American Academy of Family Physicians, the National Association of Pediatric Nurse Practitioners, the American College of Obstetricians and Gynecologists, and the American Medical Association.

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Video Online

• *Vaccines: Separating Facts from Fear*

The Vaccine Education Center of the Children's Hospital of Philadelphia (CHOP) has produced an online video, *Vaccines: Separating Facts from Fear*. In this excerpt (used with permission), CHOP's Dr. Paul Offit, chief of the Division of Infectious Diseases and director of the Vaccine Education Center, talks to parents about their concerns as other physicians and parents recount their experiences.

http://usinfo.state.gov/journals/itgic/0307/ijge/ijge0307.htm

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Internet Resources

Online resources about vaccines, research, and routine immunization programs

U.S. GOVERNMENT RESOURCES

Centers for Disease Control and Prevention (CDC)
National Immunization Project
http://www.cdc.gov/nip/default.htm

Department of Health and Human Services
National Vaccine Program Office
http://www.hhs.gov/nvpo/

Food and Drug Administration
Center for Biologics Evaluation and Research
http://www.fda.gov/cber/vaccines.htm

National Institutes of Health
Vaccine Research Center
http://www.vrc.nih.gov/VRC/

U.S. Agency for International Development
Immunization Basics
http://www.immunizationbasics.jsi.com/

INTERNATIONAL ORGANIZATIONS

Global Alliance for Vaccines and Immunizations
http://www.gavialliance.org/

Pan American Health Organization
Immunization
http://www.paho.org/english/ad/fch/im/Vaccines.htm

World Health Organization
Expanded Programme on Immunization
http://www.wpro.who.int/sites/epi/overview.htm

World Health Organization
Immunizations, Vaccines and Biologicals
http://www.who.int/immunization/en/index.html

CHILDHOOD VACCINATIONS

Childhood Immunization Support Program
http://www.cispimmunize.org/
The Childhood Immunization Support Program, supported by the American Academy of Pediatrics, offers information on immunization for parents.

PATH
http://www.path.org/vaccineresources
PATH is an international, nonprofit organization working toward sustainable, culturally relevant solutions to enable communities worldwide to break longstanding cycles of poor health.

Vaccine Education Center
http://www.chop.edu/consumer/jsp/microsite/microsite.jsp?id=75918
The Children's Hospital of Philadelphia, Pennsylvania, sponsors this site devoted to dispelling misconceptions and misinformation surrounding childhood vaccines.

DISEASE VACCINE INITIATIVES

Aeras Global Tuberculosis Vaccine Foundation
http://www.aeras.org/
Aeras works to develop new vaccines against tuberculosis and ensure availability to all who need them. A nonprofit organization, Aeras receives support from the Bill & Melinda Gates Foundation, the U.S. Centers for Disease Control and Prevention, and the Government of Denmark.

AIDS Vaccine Advocacy Coalition
http://www.avac.org
Founded in 1995, the nonprofit AIDS Vaccine Advocacy Coalition (AVAC) seeks to promote accelerated research and global delivery of AIDS vaccines.

Center for HIV-AIDS Vaccine Immunology
http://chavi.org/
The Center for HIV-AIDS Vaccine Immunology (CHAVI) is a consortium of universities and academic medical centers established by the National Institute of Allergy and Infectious Diseases to solve problems in HIV vaccine development and design.

Global Polio Eradication Initiative
http://www.polioeradication.org/

International AIDS Vaccine Initiative
http://www.iavi.org
The International AIDS Vaccine Initiative (IAVI) is a nonprofit organization operating in 23 countries and working to speed the search for a vaccine to prevent HIV infection and AIDS.

Malaria Vaccine Initiative
http://malariavaccine.org
The mission of the Malaria Vaccine Initiative (MVI) is to accelerate the development of promising malaria vaccine and to ensure its availability and accessibility in the developing world.

Smithsonian Institution
Whatever Happened to Polio?
http://americanhistory.si.edu/polio/index.htm

Tuberculosis Vaccine Fact Sheet
http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250120.htm

RESOURCES FOR HEALTH PROFESSIONALS

Allied Vaccine Group
http://www.vaccine.org/
This site is a portal dedicated to presenting scientific information about vaccines.

Immunization Action Coalition
http://www.immunize.org/
http://www.immunize.org/catg.d/noneng.htm
The Immunization Action Coalition works to increase immunization rates and prevent disease by creating and distributing educational materials for health professionals and the public.

National Foundation for Infectious Diseases
http://www.nfid.org/index.html
The National Foundation for Infectious Diseases is a nonprofit group working to educate the public and healthcare professionals about the causes, treatment, and prevention of infectious diseases.

National Network for Immunization Information
http://www.immunizationinfo.org/
The National Network for Immunization Information (NNii) works to provide scientifically valid information related to immunization. NNii is an affiliation of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, and other related associations.

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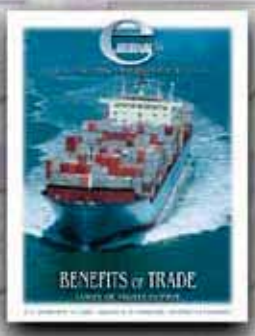

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