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Since Edward Jenner’s discovery of the smallpox vaccine 200 years ago, vaccines have been one of the most lifesaving health interventions for humankind and, conversely, one of the most underused health interventions in developing countries. The implementation of childhood vaccines in the United States and other industrialized countries led to a rapid and large decrease in morbidity and mortality from common childhood diseases. The smallpox eradication program, led by the World Health Organization (WHO) from 1967 to 1977, ended deaths from smallpox, a disease that once killed millions of children and adults each year.1

Beginning in the early 1980s, the development of routine immunization programs by WHO and UNICEF for children in developing countries led to a sustained program of administration of lifesaving vaccinations as part of primary healthcare systems. Since the launch of these routine immunization programs in most countries, more than 20 million deaths have been prevented from vaccine-preventable diseases (Fig 1). Ongoing initiatives to eradicate polio, reduce measles mortality rates, eliminate measles from discrete regions of the world, and introduce additional vaccines have been remarkably successful. However, more than 1.4 million children died from vaccine-preventable diseases in 2002, 610,000 from measles alone, suggesting that great challenges still exist to fully utilize the potential of lifesaving vaccines (WHO, unpublished data). This article reviews the status of current immunization initiatives, summarizes lessons learned, and makes recommendations for a healthier world through the use of vaccines.

Polio Eradication
The ongoing global polio eradication initiative has reduced transmission of polio from approximately 350,000 cases in 1988 to 784 cases in 2003 (Fig 2) and has reduced the number of endemic countries from 125 to just six. Only India, Pakistan, and Afghanistan in Asia, and Egypt, Nigeria, and Niger in Africa continue to have ongoing transmission of polio.2 In 2003, 10 countries reported poliovirus importations, eight from West and Central Africa. Independent commissions established by WHO have certified the interruption of polio transmission in three WHO regions (American, European, and Western Pacific) comprised of 135 countries and territories and 3 billion people.3

The partnership to eradicate polio is led by WHO, Rotary International, UNICEF, and the Centers for Disease Control and Prevention (CDC), with additional support provided by numerous countries, private foundations, and private companies. Strategies to eradicate polio include strengthening routine childhood immunization programs, surveillance for acute flaccid paralysis to detect possible cases of polio, and supplemental immunization activities to interrupt poliovirus transmission rapidly. During National Immunization Days (NIDs) to eradicate polio, all children younger than 5 years of age receive polio vaccine without regard to previous vaccination status. The successful implementation of these strategies in more than 200 countries and territories has prevented more than 250,000 deaths and nearly 5 million cases of paralysis since the initiative was launched in 1988. The inclusion of vitamin A supplementation during NIDs to children in most developing countries has reduced mortality from Vitamin A deficiency by more than 1 million children since 1988.2

Measles Mortality Reduction and Regional Elimination
The initiative led by the Pan American Health Organization (PAHO) to eliminate indigenous measles from 47 countries of the Americas appears to have been a complete success. In 2003, only 105 cases of measles were reported in these countries, including the United States (Fig 3). The majority of these cases were associated directly or indirectly with imported measles virus.4 The Eastern Mediterranean (21 member states) and European regions (52 member states) of WHO have resolved to eliminate measles by 2010. In 2003, the Western Pacific Region resolved to eliminate indigenous measles, but no target date was established.

In 2003, the World Health Assembly resolved to reduce measles mortality rates by 50 percent by 2005 compared with the number of measles-related deaths in 1999 (875,000...
The Measles Partnership, including WHO, UNICEF, CDC, American Red Cross, United Nations Foundation, and other organizations, was established in 2001 to provide political, financial, and technical leadership and support to achieve this goal. By early 2004, the Partnership appears to be on course to meet the objective and already has reduced the number of deaths to 610,000 in 2002, a 30 percent reduction in mortality compared with global measles mortality in 1999.

PAHO developed the following successful strategies to eliminate measles: (1) the implementation of initial mass vaccination campaigns for all children aged 9 months to 14 years to interrupt the transmission of measles quickly, (2) the maintenance of a high degree of population immunity by providing routine vaccination of children at 12 months of age on an ongoing basis, and (3) mass vaccination campaigns held every 3 to 4 years in which all children younger than 5 years of age born since the previous campaign are targeted regardless of previous vaccination status. The strategies designed to eliminate measles and reduce measles mortality are similar and include improving first-dose measles coverage and providing a second-dose opportunity for children through either routine immunization programs or supplemental measles campaigns. The PAHO vaccination strategies

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**Figure 1** Impact of vaccination: estimated deaths from selected diseases showing current levels of vaccination versus no vaccination, 2001. (Color version of figure is available online.)

**Figure 2** Polio cases, 1988 to 2003
were complemented by a sensitive surveillance system, including investigation and laboratory confirmation of all cases through effective virologic surveillance, to detect suspected measles transmission.\(^7\)

**Elimination of Neonatal Tetanus**

Although neonatal tetanus was eliminated in the developed world more than half a century ago, tetanus still causes almost 180,000 neonatal deaths and 10,000 to 30,000 maternal deaths globally every year in developing countries, mostly in areas where access to clean deliveries and other health services is limited.\(^8\) In 1989, the World Health Assembly called for the elimination of neonatal tetanus, defined by WHO as less than one case of neonatal tetanus per 1000 live births in every district of every country.\(^9,10\) By 1999, only 57 countries had not yet achieved the goal, 27 of which accounted for 90 percent of all neonatal cases.\(^11\) In response, the Maternal and Neonatal Tetanus (MNT) elimination initiative was launched in January 1999, with a goal to eliminate the disease globally by 2005. A strategy document was published by UNICEF/WHO/UNFPA in 2000, in which the agreed goal of MNT elimination would be achieved by reaching all child-bearing age women at high risk for tetanus with three doses of tetanus toxoid vaccine (TT) by 2005.\(^11\) Supplemental strategies include promoting clean deliveries and improving surveillance for MNT to target interventions and sustain elimination.

Significant progress continues to be made toward elimination of MNT. By January 2004, 29 of these countries have implemented TT supplementary immunization activities, targeting 43 million women with TT and protecting approximately 34 million with at least two doses of TT. Five African countries (Eritrea, Malawi, Namibia, South Africa and Zimbabwe) have been validated provisionally by WHO as having eliminated the disease.\(^8\) An additional 9 countries (Togo, Comoros, Tanzania, Egypt, Indonesia, Iraq, Nepal, Rwanda, and Vietnam) are anticipated to be close to elimination and to be validated by the end of 2005 (UNICEF/WHO, unpublished data).

Even though TT is one of the least expensive, safest, and most effective vaccines, fewer than one in three women of child-bearing age has been immunized in some of the poorest countries. In such countries more than half of all districts are high-risk areas for the acquisition of neonatal tetanus, the infrastructure often is poor, overall immunization coverage is low, surveillance for neonatal tetanus is incomplete, and severe logistical constraints may prevent access to health services and clean deliveries. Because the bacterium *Clostridium tetani* can never be eradicated, further progress will depend on continued efforts to immunize pregnant women as an integral part of national immunization programs and to achieve high coverage with routine immunization to build primary immunity in the future to women of child-bearing age.

**Improving Routine Immunization Coverage**

Although virtually all industrialized countries have achieved coverage of more than 80 percent with childhood vaccines, coverage in the poorest countries has been significantly lower and more than 17 of the poorest countries still have coverage of less than 50 percent.\(^12\) Seven large populated countries (Bangladesh, DR Congo, Ethiopia, India, Indonesia, Nigeria, Nigeria,
and Pakistan) make the greatest contribution to the 33 million unimmunized children in the world. These countries often face multiple challenges to improving immunization coverage that need to be addressed by concerted partnership efforts and focused attention. At the UN Special Session on Children in 2002, member countries established goals to ensure full immunization with traditional vaccines (BCG, DTP, polio, and measles) of children younger than 1 year of age at 90 percent nationally, with at least 80 percent coverage achieved in every district or equivalent administrative units by 2010.

In 2003, WHO and UNICEF estimated that immunization coverage (measured by 3 doses of DTP) globally was 75 percent and that the downward trend in routine immunizations in developing countries that began in the early 1990s had been stopped. However, coverage averaged only 56 percent in countries of the African region, and 14 African countries had coverage of less than 50 percent.12

Obstacles to achieving high coverage include poor quality district planning; inadequate funding of district staff and operational costs, leading to low quality and unreliable services; and inadequate monitoring and supervision of immunization activities. In response, WHO, UNICEF, and other partners have developed a strategy of “Reaching Every District” (RED), which aims to build district capacity to address common obstacles. There are five operational components at district level:

1. Re-establishment of outreach services
2. Supportive supervision
3. Community links with service delivery
4. Monitoring and use of data for action
5. Planning and management of resources

Since 2000, the Global Alliance for Vaccines and Immunization (GAVI) has provided new funds to strengthen immunization services to 52 poor countries with low coverage (<80 percent with DTP3; GAVI web site: www.vaccinealliance.org/home/Support to Country Status). In the last 2 years, many countries, including the seven large countries, have adopted the RED strategy to improve their immunization services at the district level. Measuring the impact of GAVI funding and of implementation of the RED strategies and further refining these strategies will be important steps toward reaching the 2010 goal.

**Introduction of Newer Vaccines**

The introduction of newer vaccines, including hepatitis B (HepB), Haemophilus influenzae type B (Hib), pneumococcal conjugate, varicella, and others already has made a substantial impact on morbidity and mortality rates from these diseases in industrialized countries.12 However, in 2002, more than 3 million deaths resulted worldwide from HepB, Hib, yellow fever, rotavirus, pneumococcus, and meningococcus. Although effective vaccines against HepB, Hib, and yellow fever are available, access to these vaccines by children in developing countries has been limited by insufficient supply, relatively high vaccine costs, scarce financial resources, and weak immunization systems. Since its inception in 2000, GAVI has brought together major stakeholders on immunization from both the public and the private sectors in a partnership to facilitate the introduction and sustainable access by all children, in particular those from the poorest countries, to important new and underutilized vaccines.* Through GAVI, developing countries are beginning to share in these benefits. Estimates of the number of lives saved through vaccination vary widely, but millions of deaths will be prevented through the use of currently available vaccines licensed since 1982.

HepB vaccine, available since 1982, is becoming available to most children in the world. By 2002, 141 Member States had introduced universal HepB vaccine, and WHO estimated that global coverage with HepB-containing vaccines reached 44 percent in 2002, a sharp increase from the less than 10 percent coverage reported in the early 1990s.12 Hib conjugate vaccines, available in industrialized countries since the early 1990s, largely are vaccines of high- and middle-income countries and only recently has the use of this vaccine started to penetrate the poorest countries through the efforts of GAVI. Yellow fever vaccine now is given universally in 29 of 44 endemic countries.

Rubella vaccine, available since 1969 in the United States, has been introduced in 124 countries.13 Rubella vaccine is not recommended in countries with less than 80 percent coverage for fear that limited use of rubella vaccine will protect only a small cohort of children while simultaneously shifting the average age of disease to young adults, potentially increasing the incidence of congenital rubella syndrome. Pneumococcal vaccine has much larger potential to impact health, but its use is limited by its high cost even in developed countries.

Equally impressive is the documentation of the lives that potentially could have been saved by vaccination but were not. Approximately 3 million children and adults die each year from diseases that currently are or soon will be preventable by vaccine. The promise of vaccines has been filled only partially as a result of the failure to introduce new vaccines in the poorer countries and continued low immunization coverage in many of these countries. GAVI creates an opportunity for countries to introduce new vaccines with assistance from a specially created Vaccine Fund for a period of 5 years. However, some challenges have emerged:

- There is a limited global supply of preferred products, especially combination vaccines such as DTP-HepB and DTP-HepB-Hib
- Many of the weakest countries fail to reach the 50 percent coverage required by GAVI for consideration of funding to introduce new vaccines
- Countries may have to change their immunization

*The stakeholders include WHO, UNICEF, World Bank, national governments, international development banks, bilateral agencies, NGOs, the Bill and Melinda Gates Foundation, the Children’s Vaccine Program at the Program for Appropriate Technology for Health (PATH), foundations, public health programs, and representatives of the vaccine industry from both developing and developed countries.
schedules more than once in response to the various vaccine formulations available.

- The high cost, especially of Hib-containing vaccines, in proportion to the budgets of many developing countries, threatens sustainability after the end of GAVI support.

Although many new vaccines will become available during the next few years, an essential concern is that countries make fully informed decisions about their use. The decisions should depend on many factors, including disease burden information, cost benefit, sustainable financing, and the ability to provide equitable access to their populations.

Of all the vaccines currently being developed, the three most urgently needed today are vaccines to prevent HIV/AIDS, tuberculosis (TB), and malaria. No effective vaccines against HIV/AIDS or malaria have been developed. Although the existing TB vaccine (BCG) offers limited protection against childhood forms of the disease, protection against the most common adult form is limited. A successful vaccine against HIV is thought to be scientifically feasible. Some candidate vaccines are at different levels of clinical testing, but efficacy against naturally occurring HIV remains to be demonstrated. For malaria, although significant progress has been attained in vaccine development, an effective vaccine is considered to be at least 10 years away. Research into new TB vaccines to replace BCG has produced some potential candidates, but it is not likely that anything will be available for about 8 to 10 years.

**Surveillance for Vaccine-Preventable Diseases**

Because the purpose of immunization is to reduce the incidence of vaccine-preventable diseases, effective surveillance is vital to monitor declines in incidence, to focus vaccination efforts, and to detect outbreaks. The most notable recent achievement in surveillance worldwide has been the establishment of surveillance systems for acute flaccid paralysis (AFP) in almost every country in the world in support of the eradication of polio. Even countries in emergency situations such as Afghanistan and Angola have well-functioning AFP surveillance systems that effectively direct polio immunization activities to interrupt circulation of wild poliovirus. The AFP surveillance system includes a laboratory network that not only confirms suspected polio cases rapidly but also provides genetic information on each virus to determine its origin, vital in the late stages when only a few cases remain. The achievements of AFP surveillance have led to new efforts to improve surveillance for a variety of other diseases including measles, yellow fever, and neonatal tetanus using the same AFP system for detection, reporting, investigation, and laboratory confirmation of cases. In addition, substantial progress has been made in developing countries to establish effective laboratory-based surveillance to define bacterial causes for meningitis and to determine disease burden to justify vaccination programs.

During the last 10 years, WHO has made important advances in coordinating global surveillance for vaccine-preventable diseases. These advances include a more complete and timely collection of data from member countries, development of electronic data collection systems, advances in use of improved mapping to describe the epidemiology of diseases, and improved mechanisms for providing feedback to member countries and the public.

Surveillance for polio eradication has provided resources and developed skills and expertise, but for many developing countries the challenge will be to sustain their surveillance systems, particularly the human and laboratory resources required for effective surveillance, after polio finally has been eradicated.

**Lessons Learned From Successful Immunization Initiatives**

The last 20 years have been filled with numerous global and regional immunization initiatives involving at least six vaccine-preventable diseases. Much can be learned from the successes and failures of these initiatives, including the following lessons:

- The burden or potential burden of disease must be sufficiently great that governments, donors, and communities are supportive. Documentation of the burden of disease is a prerequisite for weighing global immunization priorities and determining where to apply limited global resources. Clearly, the number of truly global immunization initiatives that governments and donor organizations will support is limited.
- Effective vaccines must be available to achieve the objectives. Although the morbidity and mortality from TB exceed those from all other vaccine-preventable diseases, the protection effected by BCG vaccine is not enough to achieve substantial disease reduction targets for TB.
- Country leadership and community buy-in are essential to achieve specific vaccination objectives. Despite the importance of global and regional objectives and international partners, ultimate success within a country usually is determined by the level of governmental support and community acceptance of a vaccination initiative.
- Effective partnerships are critical to galvanize political support and mobilize resources. Further, effective partnerships are needed to use resources efficiently. The global polio eradication initiative has benefited enormously from the effectiveness of Rotary International in political advocacy, fund-raising, volunteers, and “doing whatever it takes to get the job done.”
- Surveillance systems are necessary to measure results. In the absence of effective surveillance systems, health
workers tend to measure process and activities only, potentially leading to enormous waste and the failure of an initiative. Surveillance systems usually require a laboratory component. The standardization and coordination of laboratory surveillance across countries and regions of the world is one of the most important challenges of immunization initiatives.

- The development and implementation of global and regional immunization initiatives inevitably leads to efforts to add secondary health objectives. This development occurs because of the multitude of extremely serious health problems facing the world’s poorest countries and the inadequacy of resources to address these concerns. Secondary health objectives must be complementary and synergistic. The addition of Vitamin A to polio vaccination campaigns (both Vitamin A and polio vaccine are administered orally in developing countries) represents an excellent example of a secondary strategy that helped to improve children’s health significantly without compromising the primary objective of eradication of polio.

- Funds to support implementation of vaccine initiatives are imperative. In middle-income countries, the addition of limited funding can help to galvanize the governmental machinery (health workers, media, treasury officials, etc.) in support of immunization initiatives. In the poorest countries, international donors may need to pay for most of the costs of immunization initiatives, particularly in countries affected by war or civil conflicts.

The benefits of global and regional immunization initiatives have been discussed by several authors and include the following:

- Increased enthusiasm and support for immunizations by political leaders; vaccinating children is good politics. Funding for health programs, especially immunizations, has increased in a number of low- and middle-income countries. Public enthusiasm has increased as a result of the media events and other celebrations of immunization.13

- The infrastructure for immunization systems and other public health programs has been strengthened by the push to achieve global and regional immunization initiatives. Surveillance systems, computer infrastructure, communications systems, laboratory infrastructure, cold chain storage for vaccines, transportation, training, and management capacity all have benefited from the polio eradication and measles initiatives.14

- Improved efficiency has resulted from the collaboration of governments, UN agencies, NGOs, and the private sector. Rotary International and the Bill and Melinda Gates Foundation both have produced innovation that has benefited immunization programs.

- As was learned from the smallpox eradication program, the immunization initiatives of this generation are training the public health leaders of the next generation.

Accelerating the Benefits of Immunization in the Future

The widespread use of vaccines has produced enormous health benefits for millions of children and adults. However, the unused potential of vaccines, especially newer and more expensive vaccines, is disturbing. The profound disparity between vaccine coverage among the world’s richest and poorest children is a grave worry.

The receipt of life-saving vaccines by the world’s richest and poorest children is a measure of social equity. Perhaps the most critical challenge in bridging the “social equity gap” is ensuring that all governments and all communities treat children’s vaccines as an essential element of human rights. The World Bank, through its Poverty Reduction Initiative and other efforts recently has taken a step in this direction. The United Nations, through UNICEF and WHO, is equally supportive in voicing concerns. The collective will of all donor governments, the private sector, and international organizations and foundations must become the voice of action that insists that governments make life-saving vaccines available to all children.

Permanent solutions must be found for the chronic underfunding of vaccination programs, particularly in low-income countries. The development status of a country should be measured in part by its provision of vaccines for children. A permanent global endowment should be established to support the provision of vaccines for children in the most impoverished countries in the world, especially those where war and dysfunctional governments inhibit the availability of vaccines to most children. Private foundations, in cooperation with development agencies and donor governments, could amass the funds needed to ensure that a perpetual reserve fund provides the most disenfranchised children with vaccines.

Strategic alliances should be developed and strengthened to promote collaboration of the most practical and important health interventions with vaccination programs. Such alliances should include expansion beyond the distribution of vitamin A as part of vaccination campaigns potentially to include insecticide-treated bed nets for malaria, other vitamin and mineral supplements, and even drugs to prevent mother-to-infant HIV transmission.

Adult vaccinations are largely a feature of immunization programs in industrialized countries and for the wealthy in middle- and low-income countries. Yet the potential to save human lives through adult vaccinations is at least equal to the potential of children’s vaccines. The world must focus first on providing vaccines to children. But the underused potential of vaccines to save lives will never be met fully until adult vaccination programs become a feature of health programs in all countries.

The availability of funding often drives health programs. Few events have spurred funding for health-related issues as has the threat of bioterrorism. Nonmilitary spending on bioterrorism preparedness by the U.S. government has exceeded $12 billion since 2001.15 Less pronounced increases have
occurred in other industrialized countries. Additionally, the severe acute respiratory syndrome (SARS) epidemic, coupled with the threat of a global flu pandemic, has increased governmental and public perceptions about the need for surveillance and response systems. Global immunization officials need to make a stronger case that funding for global surveillance and response systems for vaccine-preventable diseases should be among the highest priorities. Few people would argue against a rationale that fever and rash surveillance for measles would help to better prepare for potential smallpox attacks. Stronger children and adult vaccination systems globally would improve our ability to respond against attacks with vaccine-preventable agents.

Summary

Tremendous achievements were made from the 1950s through the end of 2003 to develop vaccines, to implement vaccination programs, and to begin to realize the health benefits that accrue from effective immunization programs. The eradication of smallpox and achievements toward the global eradication of polio, elimination of measles in the Americas, and reductions in mortality from complications of measles document the enormous potential of vaccines. However, the gap that exists between industrialized and developing countries in economics, sanitation, education, and other indicators of the quality of life is augmented further by the substantial differences in the availability and use of vaccines. One of the greatest challenges in global public health during the 21st century is to eliminate the immunization gap between the children of the comparatively wealthy and the poor.

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