Chapter 23
Global Immunization Challenge: Progress and Opportunities

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Learning Objectives After reading this chapter and answering the discussion questions that follow, you should be able to

- Outline important milestones in the emergence of vaccines as a means of disease control and prevention.
- Discuss factors that underpin the disparity in access to vaccines between rich and poor countries.
- Identify and appraise innovative options for financing vaccine development, and for ensuring wider access to new and underused vaccines in developing countries.
- Evaluate strategies for ensuring sustainability in vaccine development, management, and access.
- Outline priorities for future research, policy, and practice with regard to vaccine development, procurement, and access.

Introduction

Vaccines, having been developed over the last 200 years to become one of the most cost-effective and successful public health interventions, are one of the most exciting technologies in the world today. Yet every year, around 2.5 million children die from diseases that can be prevented by currently available or new vaccines. Vaccines have the potential to erase some of the most glaring global health inequities which currently shape the lives of millions. Often the most vulnerable – women, children, and adolescents in even the poorest countries, could be protected against life-threatening and debilitating disease within a generation. This chapter presents a historical perspective on the emergence of vaccines as a means of disease control and prevention over the past two centuries. Beginning with discovery of smallpox vaccine by Edward Jenner in 1796, the chapter identifies important milestones in widespread use of vaccines in global health, including

- The smallpox eradication initiative of the World Health Organization in 1970s, the Child Survival Revolution, and the Expanded Program on Immunization (EPI) of the 1980s
- The United Nations Millennium Summit of 2000 and the resulting global commitment to the Millennium Development Goals (MDGs)
- The International Conference on Financing for Development held in Mexico in 2002 and the corresponding financial commitments from high-income nations to support achievement of MDGs
- Establishment of the Global Alliance for Vaccines and Immunization in 2000 to accelerate access to new and underused vaccines in poor countries

Inequity in access to vaccines between rich and poor countries and the underpinning factors are discussed, including lack of safety and quality assurance systems in poor countries, focus of research and development on rich nations’ priorities, and the diversion of scarce resources to other emerging global health priorities. Various innovative options for financing wider access to new and underused vaccines in poor countries are explored, including the role of the International Finance Facility for Immunization (IFFIm), the Advanced Market
Commitment (AMCs), the Heavily Indebted Poor Countries (HIPCI) and Multilateral Debt Relief (MDRI) initiatives, and the Debt Buy-Down program of the World Bank. Issues of sustainability in vaccine development, procurement, and management are discussed as are priorities for future research, policy, and practice.

The first immunization – and the origin of a smallpox vaccine – is believed to have been in 1796 (Table 23.1) when British physician Edward Jenner administered fluid from a cowpox lesion obtained from a milkmaid named Sarah Nelmes.

**Table 23.1** Timeline of vaccine discoveries and global events

| Date   | Vaccine target                  | Research strategy                          |
|--------|--------------------------------|--------------------------------------------|
| 1796   | Smallpox (Jenner)              | Use of related animal virus                |
| 1881   | Anthrax                        | Chemical attenuation                       |
| 1885   | Rabies (Pasteur)               | Chemical attenuation                       |
| 1896   | Cholera                        | Inactivated whole organisms               |
| 1896   | Typhoid                        | Inactivated whole organisms               |
| 1896   | Plague                         | Inactivated whole organisms               |
| 1923   | Diphtheria (D)                 | Inactivated whole organisms               |
| 1926   | Pertussis (wP)                 | Inactivated whole organisms               |
| 1927   | Tetanus (T)                    | Use of toxoids                             |
| 1927   | Tuberculosis (BCG)             | Passage in vitro                           |
| 1935   | Yellow fever                   | Inactivated whole organisms               |
| 1936   | Influenza                      | Inactivated whole organisms               |
| 1955   | Polio (IPV)                    | Inactivated whole organisms               |
| 1957   | DTPw                           | Passage in vitro                           |
| 1958   | Polio (OPV)                    | Protein-conjugated capsular               |
| 1961   | DTP/IPV                        |                                             |
| 1963   | Measles (M)                    |                                             |
| 1965   | SMALLPOX ERADICATION UNIT AT WHO CREATED |                                             |
| 1966   | DTP/IPV                        |                                             |
| 1967   | Mumps (M)                      |                                             |
| 1969   | Rubella (R)                    |                                             |
| 1971   | MMR                            |                                             |
| 1972   | Meningococcus                  |                                             |
| 1974   | Expanded Programme on Immunization |                                             |

The first immunization – and the origin of a smallpox vaccine – is believed to have been in 1796 (Table 23.1) when British physician Edward Jenner administered fluid from a cowpox lesion obtained from a milkmaid named Sarah Nelmes.

**Table 23.1 (continued)**

| Date   | Vaccine target                  | Research strategy                          |
|--------|--------------------------------|--------------------------------------------|
| 1976   | Pneumococcus                    |                                            |
| 1979   | SMALL POX ERADICATION CERTIFIED |                                            |
| 1981   | Acellular Pertussis (aP)        |                                            |
| 1981   | Hepatitis B (HB)                |                                            |
| 1984   | Universal childhood Immunization Goal (UCI) LAUNCHED | |
| 1984   | Varicella (V)                   |                                            |
| 1986   | rDNA HB                        |                                            |
| 1988   | H. influenzae b (Hib)           | Protein-conjugated capsular               |
| 1991   | Hepatitis A (HA)                |                                            |
| 1993   | DTP/IPV/Hib                     |                                            |
| 1994   | DTPa                            |                                            |
| 1996   | DTP/IPVHB                       |                                            |
| 1996   | HBHA                            |                                            |
| 1997   | DTaP-Hib                        |                                            |
| 1997   | DTaP-IPV-Hib                    |                                            |
| 1998   | Lyme                            |                                            |
| 1998   | Rotavirus                       |                                            |
| 1999   | DTaP                            |                                            |
| 1999   | HATy                            |                                            |
| 2000   | DTaP-HB-IPV                     |                                            |
| 2000   | DTaP-HB-IPV-Hib                 |                                            |
| 2000   | Meningococcus C conjugate vaccine. |                                        |
| 2000   | Pneumococcus conjugate vaccine  |                                            |
| 2000   | GLOBAL ALLIANCE FOR VACCINES AND IMMUNIZATION (GAVI) LAUNCHED | |
| 2003   | Influenza (LAIV) Cell culture passage w/ cold adaptation | |
| 2006*  | HPV vaccine that protects against infection with four HPV genotypes was licensed; a second vaccine that protects against two HPV genotypes is likely to be licensed soon. | |

*WHO (2007a)

Sources: Andre (2003); Plotkin (2005)
to a 13-year-old boy named James Phipps. Jenner later found that the boy was “secure” to smallpox virus (Andre 2003). Louis Pasteur later coined the term vaccine in reference to the Latin word for cow: vacca.

Records of a similar medical approach can be found in Chinese literature dating back to the eleventh century and linked with the fight against the smallpox virus (Plotkin 2005). According to the National Library of Medicine (U.S. National Library of Medicine 2002), the practice of variolation, where small scabs of tissue containing smallpox were inhaled causing the individual to contract the disease in a mild form, reduced the mortality rate among those exposed to the disease to 1–2% as opposed to 30% when individuals contracted the disease naturally. By 1700, the practice of variolation as a response to smallpox had expanded to India, Africa, and throughout the Ottoman Empire. Variolation was first practiced in Europe by 1717 and, by 1721, in the American colonies (U.S. National Library of Medicine 2002).

The immunization field grew in the 19th and 20th centuries, with major breakthroughs in the mid- to late 20th century through discovery of vaccines that protect against such diseases as influenza, polio, and yellow fever (Table 23.1). Prior to the development of such vaccines, the loss of life from disease is illustrated in some staggering figures. For example, the influenza (or “Spanish flu”) outbreak of 1918–1919 resulted in more deaths than enemy fire in World War I (Plotkin 2005). The period of 1974–2000 can be considered a second phase in the history of immunization. The World Health Organization (WHO) launched the Expanded Program on Immunization (EPI) in 1974, expanding the smallpox eradication effort which was focused on one single vaccine into an infant program of six vaccines (against diphtheria, pertussis, tetanus, poliomyelitis, measles, and tuberculosis). At the time, less than 5% of the world’s children were immunized against these six diseases. Meanwhile, an increased degree of population mobility, for example, through commercial air travel, helped bring about the recognition that infectious disease prevention required a coordinated, global effort.

The EPI launch marked an important turning point: immunization became an international public good. In response to a 1977 World Health Assembly challenge (World Health Assembly 2003), immunization coverage rose over the next decade, with the United Nations Children’s Fund (UNICEF) declaring 80% of the world’s children under the age of 13 immunized against tuberculosis, polio, and measles by 1990 (Hardon and Blume 2005).

A number of global initiatives contributed to the progression of immunization coverage rates in the 1980s. UNICEF, with the support of other international organizations, launched the “Child Survival Revolution” in 1982 (UNICEF 1996). This initiative comprised four interventions for reducing mortality: growth monitoring, oral rehydration, breastfeeding, and immunization (GOBI). At the same time, WHO led major vertical programs to combat vaccine-preventable disease, diarrhea, and acute respiratory infections (Hardon and Blume 2005). The Universal Childhood Immunization (UCI) Goal was launched in 1984 to catalyze efforts toward universal immunization coverage. UCI aimed at accelerating EPI, capitalizing on the success in mobilizing support. As a result of these dedicated efforts, child mortality declined in many countries (Hardon and Blume 2005).

Yet, despite the overall success of accelerating immunization coverage in the period described above, significant disparities are apparent (Fig. 23.1). The expansion in coverage was largely in developed countries with large populations. One hundred and seven countries did not reach the immunization coverage of 80%, and the declaration of success did not reflect the uneven coverage within many countries – where some of the most vulnerable children in hard-to-reach areas were missed. A great success for some masked the growing divide in access between North and South.

The characteristics of the North/South divide, which remains the current global situation, developed during the 1990s. A gap in the routine immunization schedules for children in developed and developing countries emerged as new vaccines, including those for hepatitis B, Haemophilus influenzae b (Hib), varicella, pneumococcal, meningococcal, and combination formulations became a routine part of the immunization schedule for children and adolescents in high-income countries
(Hordon and Blume 2005). Research and development priorities favored those products targeting developed countries. Vaccine quality and safety, taken for granted in many countries with robust regulatory agencies, fell behind in many countries lacking an effective quality assurance program for medical products. Quality and safety issues also point to the weakness of health delivery systems in many poor countries which limited the effective rollout of routine immunization. The gap in financial commitment to maternal and child health – which underpins and drives the North/South divide in access to immunization – widened over the 1990s as scarce resources were diverted to other emerging global health priorities. Many developing countries struggled to improve or even maintain their immunization rates. The end of the decade saw an overall decline in global immunization and vaccine production, and particularly among the poorest populations in the poorest parts of the world.

The new millennium set the stage for a major shift in the global response to the growing inequities between North and South. Under the leadership of the then UN Secretary General Kofi Annan, the UN Millennium Summit, the largest-ever gathering of world leaders, was convened at the United Nations Headquarters in New York, USA, in September 2000 (United Nations Development Program 2003). At the close of the summit, world leaders unanimously adopted the “United Nations Millennium Declaration” taking on a clear obligation to act through commitment to the Millennium Development Goals (MDGs) (United Nations 2006). These goal comprised a set of time-bound and measurable goals and targets for combating poverty, hunger, disease, illiteracy, environmental degradation, and discrimination against women. Corresponding financial commitments from the developed world in the form of aid, trade, debt relief, and investment were made at the International Conference on Financing for Development in Monterrey, Mexico (IFAD 2007).

As part of a renewed commitment to poverty reduction and human development, the international community moved to address the growing inequalities in immunization and the unacceptable toll of infectious disease in developing countries. Marking the start of a “third phase” in the history of immunization, the Global Alliance for Vaccines and Immunization (now the GAVI Alliance) was launched in January 2000 to accelerate access to new and underused vaccines in the poorest countries. GAVI, an innovative public/private partnership, brought together the major stakeholders in immunization in order to achieve global immunization targets. These stakeholders included national governments, UNICEF, WHO, The World Bank, the Bill and Melinda Gates Foundation, the vaccine industry, public health institutions, and nongovernmental organizations (GAVI Alliance 2008a). Soon after GAVI’s launch its mandate came to include action on the child mortality target of the Millennium Development Goals – namely, a 2/3 reduction of the under-5 mortality rate by 2015 (GAVI Alliance 2008b).

In the years since GAVI’s launch, overall DTP3 coverage increased from 64% in 1999 to 73% in 2005 in GAVI-eligible countries, i.e., those with a gross national income (GNI) of less

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Fig. 23.1 Global number of unimmunized children under 5 years of age. Source: WHO/UNICEF coverage estimates 1980–2007, August 2008
than $1,000 per capita. The figures are more pronounced in the WHO African region where DTP3 coverage increased from 48% (1999) to 73% (2007) and has overtaken Southeast Asia (66% in 2007), which is now the region with most unimmunized children (WHO 2007b). Much of this increase in DTP3 coverage has been attributed, through independent evaluation, to the Immunization Services Support provided by GAVI to strengthen immunization delivery systems and infrastructure (Lu et al. 2006).

In terms of new and underused vaccine introduction, the cumulative achievement of the poorest countries to improve coverage is impressive (GAVI Alliance 2008b). Over 5 years, 88.5 million additional children were immunized against HepB3 (2000–2005). Four and a half million additional children were immunized against yellow fever in 2005, equaling a cumulative 13.1 million additional children immunized over 5 years against yellow fever. An additional 4.5 million additional children were immunized with Hib vaccine in 2005, equaling a cumulative 13.2 million additional children immunized with Hib vaccine over 5 years.

Critical to these improvements has been the ability of the GAVI Alliance to raise new and additional resources – providing funds to introduce new and underused vaccines, improve injection safety, improve immunization delivery services, and strengthen health systems. GAVI-supported countries are continuing to produce impressive results (GAVI Alliance 2008a). Despite the exciting results, we must not lose sight that the key challenges remain gaining better data on disease burden to stimulate demand and ensuring the affordability and long-term sustainability of new vaccine introduction. Until prices become more affordable, slow uptake of new vaccines in the poorest countries remains inevitable. How this challenge can be better addressed through innovative approaches is covered in the discussion on funding challenges below.

The GAVI Alliance is but one element of a growing complexity of agencies working on maternal and child health issues; while it maintains a niche focus, this requires close collaboration with partners in the broader global health community. The launch of the Global Immunization Vision and Strategy (GIVS) in 2005 (WHO/UNICEF 2005) provided a critical overarching framework that exhibits the need for coordinated mix of instruments and approaches. These approaches may be in the form of highly successful vertical campaign strategies for the global eradication of polio and control of measles, delivery of basic vaccines in conflict environments, or in the longer-term efforts to create sustainable markets for new and underused vaccines in the poorest countries. GIVS was approved by the member states of WHO and the Executive Board of UNICEF in 2005. It sets out a plan to address the global immunization challenges over the decade 2006–2015 and strives to act with equity and gender equality, in addition to personal ownership, partnership, and responsibility. Placing immunization firmly within the health system strengthening agenda, GIVS “aims to sustain existing levels of vaccine coverage, extend immunization services to those who are currently un reach ed and to age groups beyond infancy, introduce new vaccines and technologies, and link immunization with the delivery of other health interventions and the overall development of the health sector” (WHO/UNICEF 2005). The vision and goals of GIVS are a world in 2015 that highly values immunization and that has equal access to immunizations for all. This world would also support sustainable interventions in diverse social situations, changing demographics and economies, as well as being a world that will put vaccines to the best global health and security use.

Addressing the Key Challenges: Funding, Sustainability, Equity

**Funding**

Following the launch of GIVS in 2005, a WHO/UNICEF study examined the cost, financing, and impact of immunization programs in the 72 poorest countries (WHO/UNICEF 2005). Implementation of GIVS would protect more than 70 million children in the world’s poorest countries against the 14 major childhood diseases by 2015. The estimated total price tag for immunization activities for 2006–2015 in these countries is US $35 billion, one-third of which would be spent on vaccines and two-thirds of which would be spent on immunization delivery systems. The study concluded that spending on immunization will need to rise from
National budgets will ultimately fund vaccines and health services. The challenge will be to grow and sustain financing from domestic resources. How will the poorest countries reach this point? Donor funding in the interim and the growth of poor economies will determine the ability of countries to finance their health sectors. To illustrate the additional sums required, it is worth noting that the Report of the Commission for Africa (2005) recommended that donors spend around 40% of the Commission’s proposed US $75 billion package for Africa to strengthen health systems and ensure a satisfactory response to HIV and AIDS by 2010. This call for additional spending is supported by analysis which shows that many countries will be able to work within a substantially increased spending envelope for health (Foster 2005). Yet donor aid remains volatile. In health, the shortcomings of traditional aid – from poor allocation to an absence of a results-focused, coordinated effort among donors – have clearly, if not tragically, been illustrated over the last decades (Radelet and Levine 2007).

Innovative financing mechanisms provide a way to overcome some of the current limitations of aid while mitigating the political risks that many donors associate with significantly scaling up finance to developing countries, for example, through transfers such as budget support. Global Funds and Partnerships such as GAVI have shown that innovative solutions to development challenges, including raising additional finance for development, can be generated by bringing together public and private stakeholders, including the civil society. GAVI provides the leverage so that both donor and developing country governments can employ new and innovative funding strategies – such as performance-based grants and co-financing (long-term subsidy agreements) for new vaccines – which characterize GAVI as an instrument for innovative financing. While it is too early to make any conclusive statement on the long-term market-shaping impact of GAVI, an independent study states that “emerging suppliers view the GAVI market as attractive and credibility-building, with the added economic advantage of alignment with domestic or middle-income markets. This is thanks to the significant size and growth of GAVI, as well as the price levels it has provided” (Boston Consulting Group 2005).

As a catalyst for further innovation in finance, GAVI has had a critical role in developing two further mechanisms for financing vaccine introduction and development: the International Finance Facility for Immunization (IFFIm) and Advance Market Commitments (AMCs). The IFFIm, launched in 2006, is a pilot of the larger International Finance Facility (IFF) that was originally proposed by the Government of the United Kingdom in 2005 to double global aid for development and to accelerate the availability of funds through the GAVI Alliance in 70 of the poorest countries around the world. The mechanism takes long term (20 years), legally binding commitments from donors (IFFIm 2008) and borrows against them for 10 years in the capital markets, producing upfront finance and thus stabilizing a portion of aid flow to developing countries. Because of the innovative “frontloading” funding program, an anticipated IFFIm investment of US $4 billion is expected to prevent 5 million child deaths between 2006 and 2015 and more than 5 million future adult deaths from hepatitis B-related liver disease. Advance Market Commitments (AMCs) provide legally binding promises, usually offered by governments or other financial entities, to guarantee a viable market if a vaccine is successfully developed. This ensures revenues will be generated from the newly developed vaccine that will match those of other comparable medicines. AMCs speed the development of new vaccines by enabling biotech and pharmaceutical companies to successfully invest in vaccine development (IAVI 2005).

Beyond the clear benefit of providing long-term, predictable finance to countries, allowing them to make longer-term budgeting and planning decisions, the predictable funding for immunization through IFFIm has the potential to leverage significant market benefits by allowing bulk purchasing of vaccines. The predictability and legally binding nature of the financial commitment provides strengthened negotiating power and the ability to negotiate longer-term arrangements with suppliers, generating lower prices and therefore more vaccines for the same envelope of funds.
A second market-shaping innovative mechanism – an “advance market commitment” (AMC) pilot for a pneumococcal vaccine – was launched in February 2006. An AMC is a financial commitment to subsidize the future purchase, up to a pre-agreed price, of a currently unavailable vaccine – if an appropriate vaccine is developed and providing the demand exists when the vaccine is finally produced. By guaranteeing that the funds will be available to purchase vaccines once they are developed and produced, the AMC mimics a secure vaccine market and takes away the risk that countries will not be able to afford a high-priority vaccine, addressing current market failure: vaccines that would prevent millions of deaths facing long delays before they are developed, tested, and produced for use in the poorest developing countries.

By establishing a valuable market, AMCs provide incentives for private investment in the development of vaccines against neglected diseases. Such a “pull mechanism” is not an alternative, but is highly complementary to other public and philanthropic interventions in the health sector and, more generally, in development aid. AMCs will be most effective when combined with push interventions because of the network effects of the increased number of scientific researchers working on the target diseases as well as the enhanced probability that scientific research swiftly translates into the production of effective and safe vaccines. Push interventions include public and philanthropic funding of research through academia, public–private partnerships, and other bodies. The private resources mobilized by successful AMCs would act in synergy with initiatives to expand immunization (e.g., GAVI and IFFIm) and strengthen health systems.

The success to date of raising funds through innovative financing instruments will continue to catalyze more thinking on both innovative means for raising and delivering development aid and how to better align these new instruments with more traditional aid streams. Debt relief is an emerging area in innovative financing for health which could usefully be applied to accelerate sustainable vaccine introduction. The two major broad initiatives for debt relief are the Heavily Indebted Poor Countries Initiative (HIPC) and Multilateral Debt Relief Initiative (MDRI) programs.

The HIPC Initiative was launched by the International Monetary Fund (IMF) and the World Bank in 1996 and aims to reduce debt for heavily indebted poor countries that face unsustainable debt burdens, that are pursuing reform programs, and that have developed a poverty reduction strategy paper. The HIPC estimates providing debt assistance in the amount of US $68 billion dollars in debt relief, funded by bilateral creditors and multilateral lenders, to a total of 32 countries (Table 23.2). An additional nine countries are eligible for the HIPC initiative and may wish to use the debt relief services in the future (International Monetary Fund 2007a). HIPC debt relief represents only a relatively small share of government spending (about 5% for Burkina Faso between 2001 and 2004). However, where social expenditures also represent but a small part of the government budget, HIPC debt relief can have a considerable impact on social sectors. Several HIPCs are using HIPC funds to scale up immunization financing. For example, in Benin, in 2004, 22% of the EPI program was funded by HIPC resources (International Monetary Fund 2008).

| Table 23.2 Four generic categories of vaccines in relation to disease burden and reliability of markets |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Category of vaccine            | Developing countries | Industrialized countries | Examples       |
|                                | Disease burden    | Current markets  | Disease burden | Current markets |
| Global market vaccines         | Large             | Small            | Large          | Large           |
| Industrialized market vaccines | Small             | Small            | Large or moderate | Moderate         |
| Impeded vaccines               | Large             | Small            | Large          | Large           |
| Developing market vaccines     | Large             | Small            | Small          | Small           | Hib conjugate; HepB; Rotavirus; Lyme disease; RSV; Malaria; tuberculosis; typhoid; Shigella |

Source: WHO (2000)
Taking the HIPC a step further, the Multilateral Debt Relief Initiative (MDRI) was launched by the group of eight industrialized countries (G8) in 2005 and will provide 100% cancellation of debt owed by HIPCs to the International Development Association (IDA), to the African Development Fund (AfDF), and to the IMF (International Monetary Fund, 2007b). This program enacts up-front, irrevocable debt cancellation for eligible countries (Table 23.2). The main objective of the MDRI is to enable HIPCs to mobilize funding for poverty reduction programs in order to reach the Millennium Development Goals. The intent is that additional resources made available through debt relief should be allocated to poverty alleviation programs. But as there is no formal obligation to allocate resources relieved by the MDRI to any specific sector, competition between departments for the use of these extra resources is likely. Potential impact of the MDRI on health system strengthening and on financing immunization programs could be significant. As annual amounts of debt service relief will be significant in many HIPCs, especially around 2020–2030, a small percentage of these resources could have a reasonable impact on the health sector and in particular on immunization financing.

The GAVI Alliance partners are currently exploring options for using debt relief – in the form of an International Development Association (IDA) buy-down – to specifically support countries' vaccine programs. In addition, a number of bilateral debt relief programs may also offer an opportunity for targeted debt relief. IDA buy-downs are currently being explored as new innovative financing mechanisms for vaccines. IDA is member of the World Bank Group. It provides long-term loans (also called concessional loans or credits) and grants to the poorest of the developing countries, particularly those that are severely constrained by conflict, epidemics, and debt. A buy-down refers to a third party paying off all or part of a specific IDA credit on behalf of the government upon successful achievement of pre-determined performance indicators. The World Bank began an IDA buy-down pilot in 2003, when it provided the governments of Nigeria and Pakistan with roughly $48 million in IDA credits for the purchase of vaccine to help achieve the global polio eradication objective. The Bill and Melinda Gates Foundation, Rotary International, and the United Nations Foundation agreed to pay off the IDA credits upon successful achievement of the performance indicators, in this case receipt and distribution of vaccine and specified polio immunization coverage levels.

Innovative financing, while not a magic bullet, will nonetheless offer a range of new possibilities for countries to help reach the significant increases in finance required to meet the MDGs. Ultimately, the real test will be whether the donor community is successful in working together to ensure traditional aid is aligned to a mixed instrument approach. This has been done before. Bangladesh, one of the poorest countries in the world, has achieved the most radical improvements in reproductive health the world has ever seen. This has impacted significantly on women’s and child mortality and morbidity, their social status and economic growth – despite poverty, poor governance, political upheaval, and an apparent lack of any potential for economic growth in the early years. The key was that for 20 years from the mid-1970s, through a mixture of aid instruments, donors and multilateral agencies provided substantial, predictable but coordinated financial and technical support for salaries, a radical expansion in the workforce (notably paramedics), associated infrastructure, and “expensive” reproductive commodities which the government delivered through state and civil society structures.

**Sustainability**

It has become clear that new technologies such as vaccines or antiretrovirals (ARVs) for HIV have the potential to deliver a generational leap in achieving the MDGs. The health gains made in Europe over 150 years could be achieved in Africa over a 10–20-year period (WHO/UNICEF 2005). Of the more than 10 million annual child deaths, an estimated 25% could be avoided through immunization with existing and newly developed vaccines such as pneumococcal and rotavirus vaccines. Procurement of essential health commodities is an area where this can be carried forward without risk to macroeconomic stability. Yet without basic health systems – essential for the sustainable availability of medical products – the poor will never access these benefits.
Despite evidence of the cost-effectiveness of vaccines in particular and the economic and social benefits of health in general, the track record of national and donor budget allocations to date is not good. GAVI-eligible countries have very modest health budgets, with government health spending across Africa, for instance, averaging $13–$21 per capita and with many countries below $10. Responding to the needs of poor countries by investing in the critical foundation for the delivery of basic health services requires a long-term view. While vertical approaches have been effective at raising the profile and funding levels for vaccines, countries must now be supported to move systematically to introducing the full range of vaccines in immunization programs as part of integrated maternal and child health services. With expensive new vaccines coming to market (for example, three doses each of pentavalent (DTP-HepB-Hib), rotavirus, and pneumococcal conjugate vaccines could amount to more than US $35 per child) it is clearly no longer appropriate to focus on financial sustainability of a single product in isolation from broader system sustainability.

Moving toward a truly sustainable planning framework will not be a simple endeavor, yet it represents an exciting opportunity for the GAVI Alliance partners. One challenge will be to gather the information on demand and future prices required by countries to inform longer-term planning and decision making. UNICEF’s commitment and global procurement ability over the years has brought great benefits in terms of quality, security, and better prices for such long established vaccines as BCG, DPT, measles, and polio. But it has become clear that this procurement model is most effective in mature markets with overcapacity and competition, and notably capacity in countries located in emerging markets (e.g., India, Brazil, Indonesia, and Cuba).

New or combination vaccines such as DTP-HepB-Hib challenge the established means of procurement, where cost limits the ability of donors to deliver affordable products to the poorest parts of the world. It is only through competition that the prices of new vaccines will become affordable to the poorest countries. Clearly the key to success will be the ability to mobilize additional donor funds, but to use those funds in such a way that the vaccine market is shaped to promote competition and to bring prices within reach of the poorest countries.

Beginning in 2007, GAVI support shifted toward national co-financing (as opposed to GAVI providing vaccines free). This is based on the intent by the GAVI alliance partners to ensure that GAVI financial support is seen by all stakeholders as time limited and to ensure that countries move to a fuller ownership of their immunization program, including the introduction of new vaccines. Co-financing therefore aims at supporting and stimulating evidence-based priority-setting within the immunization program and within the health sector more generally. Financial commitments, however small, also generally require a higher level of government engagement. Through this approach, which will be evaluated in 2010, GAVI Alliance partners are working to help countries to be on a trajectory of eventual independence from GAVI support, acknowledging, however, that, for most of the GAVI-eligible countries this is likely to require a very long time.

Over the next decade, the ability of developing countries to achieve sustainable introduction of new technologies will be largely dependent on how donor funds are provided, particularly whether there is a shift toward long-term, predictable aid and if innovative financing instruments are appropriately aligned and taken to scale. The other key determinant will be sustained political support for health and for vaccines by developing country governments. Guyana is an example of a country that has been highly successful in achieving high immunization coverage and is the first GAVI-supported country to fully finance the purchase of pentavalent vaccine from its national budget (United Nations 2007). Guyana’s continuing success is in part due to a very strong political commitment at the highest levels to finance the national immunization program, including efforts to protect it from economic shocks and shifts in donor priorities. More broadly, there has been a remarkable growth in the health budget from US $6.5 per capita in 1991 to US $61 in 2006 (excluding overseas development assistance). This accounts for 10% of national expenditure, while the government’s goal is to reach 15% (Ministry of Health, Guyana 2002; Editorial, PharmacoEconomics and Outcomes News, 2007).
The Ministry of Health China/GAVI Hepatitis B Vaccination Project is another example of where political commitment and clear financial partnership have brought remarkable results through a 5-year US $76 million project, co-funded equally by the Government of China and the GAVI Alliance. Hepatitis B virus (HBV) is endemic in China where over one-third of the world’s HBV carriers reside. In 1999–2000, it was estimated that HBV was responsible for 280,000 deaths annually, over one-third of the global death toll estimated to be between 600,000 and 700,000. Since 2002, China has immunized 19.1 million children in the country’s poorest and most remote western and central provinces against hepatitis B, reducing their risk of developing a deadly and common liver cancer. In the western provinces, the campaign, with technical guidance from WHO and UNICEF, has reached almost 80% of newborns with a birth dose of vaccine in 2005, up from 47% in 2002 (World Health Organization 2006, China – GAVI Project Annual Reports).

From an equity point of view, GAVI’s condition of support to the Ministry of Health, China, was that vaccines be made available at no cost (removing the previous charge). This policy was subsequently adopted across China for all vaccines.

**Equity**

While the spread of HIV and AIDS has led to recent discourse on health as a global security issue, most arguments – and certainly those related to maternal and child health – have at their root the principle of equity and the belief that health is a basic human right. Equity in health has been defined (for measurement and operationalization) as “the absence of systematic disparities in health (or in the major social determinants of health) between groups with different levels of underlying social advantage/disadvantage – that is wealth, power or prestige” (Brave-man and Gruskin 2003). The 2004 World Development Report, *Making Services Work for Poor People*, noted that “the concern for equity is either a social choice or based on the notion that health is a human right” (World Bank 2004). As an ethical or social justice issue, equity in health is therefore a critical element for consideration and measurement, particularly when looking at the trade-offs and choices made around financial sustainability issues discussed in the previous section.

Many of the disparities in health result from social determinants such as poverty, access to services, education, gender, and ethnicity. Harnessing the potential of new medical technologies, such as vaccines, to reach underserved groups will take concerted effort and in some cases, explicitly defined political choices. New vaccines against human papilloma virus (HPV) provide the opportunity for such a political choice: to ensure that all women, rather than just those in wealthy countries, are provided with a vaccine that will prevent most cervical cancer cases. HPV vaccines, as the first vaccines to focus primarily on women’s health, provide the global health community an unprecedented opportunity to tackle a key neglected women’s health issue – one which especially impacts on the poorest women.

Cervical cancer is not difficult to prevent; yet, it affects an estimated 490,000 women each year and leads to more than 270,000 deaths (Ferlay et al. 2006). It is largely a disease of poor women who have limited access to health services; about 85% of women dying from cervical cancer live in developing countries (Fig. 23.2) (Ferlay et al. 2006). The lack of effective cervical cancer prevention interventions – part of a regular medical checkup for women in wealthy countries – is a major factor in the high rates of cervical cancer among poor women. If current trends in women’s health continue, there are projected to be over 1,000,000 new cases of HPV annually by the year 2050 (Boyle 2004).

Many challenges must be addressed before HPV vaccine can reach the millions of girls and young women who would benefit from it, especially those living in the developing world where the need is greatest. With the right combination of scientific, educational, and financing efforts, HPV vaccine could become available globally within a few years. Accelerating access to HPV vaccine could make cervical cancer – the second most common cancer among women worldwide – a rarity in just a few decades.
Another social determinant of health is where one lives. Within large developing countries, such as India, Nigeria, or China, there are significant inequities in the population’s health. Disparities in access to, and utilization of, services within these countries are often a result of factors such as geography, social barriers, conflict, and weak governance. Of the 28 million children that missed out of immunization in 2005 more than 75% live in 10 countries (Fig. 23.1). India and Nigeria stand out as countries with the largest number of unimmunized children in the world.

Reaching MDG 4 will thus require a significant increase in investment in immunization – both domestic and external – in countries with large numbers of unimmunized children who account for more than half of all vaccine-preventable deaths among children less than 5 years of age. With some states or regions in some of these countries being equal or larger in population to many countries, a fresh state- or region-based approach will likely be required, with a focus on the poorest. For example, child and maternal mortality rates in the poorest eastern provinces of China equal or exceed those found in much of Africa (World Bank 2005). Despite economic growth, equity is worsening. National political commitment in such countries will be key. A program approach, tailored to country-specific challenges, will be required. Additional long-term finance (domestic and global) will be critical to support that political commitment. New technology, including new and better vaccines, will be vital.

**Vaccine Research Priorities**

**Which Vaccines for the Future?**

Research and development for vaccines and other essential health commodities point to another disparity between North and South and constitute a market failure. Priorities in the global allocation of resources for vaccine research and development do not match the global burden of death and disease. Few resources are allocated to tackling diseases that disproportionately affect people in developing countries; new vaccines are therefore expensive and out of the reach of the poor. This discrepancy between need and reality is illustrated in Table 23.2, illustrating that normal market mechanisms do not work for the poor.

Among the vaccines currently under development, the three most needed today in terms of their potential public health impact are for AIDS, TB, and malaria. Jointly, these diseases account for over 5 million deaths per year or around 50%
of all infectious disease deaths. The total investment in vaccines against these diseases is far lower than their importance as dictated by disease burden and it will probably take at least 5–10 years before a vaccine against any of these diseases is available. In the past two decades, advances in biotechnology have resulted in the licensure of new vaccines such as Hib, acellular pertussis, HepB, and attenuated varicella. Most of the basic scientific breakthroughs have been generated in research institutions in the public sector whereas the cost for clinical development is borne by the pharmaceutical industry. This requires heavy investments that need to be recouped from profits. The markets needed to recoup these investments are in industrialized countries that can afford to buy.

The evolving disease burden in developing countries will bring new diseases into prominence while sometimes allowing old ones to resurface. This will influence priorities for vaccine research (Table 23.3). The Severe Acute Respiratory Syndrome (SARS) epidemic, the outbreak of avian influenza, and the emergence of bioterrorism threats such as Anthrax have led to new research avenues for vaccines against these infections. The threat of a reassorted influenza pandemic virus strain has highlighted the need for more resources and attention to the development and distribution of effective flu vaccines.

### Table 23.3: New vaccines required

| Non-questionable vaccines | Close to or already licensed vaccines (but not totally suited to the developing country burden of disease) | Neglected vaccines | Others | New threats |
|---------------------------|-------------------------------------------------------------------------------------------------|-------------------|--------|-------------|
| HIV, TB, Malaria          | Meningococcus, Streptococcus pneumonia, Rotavirus, Human papilloma virus | Shigella, Dengue, Japanese encephalitis, Leishmaniasis, Schistosomiasis, Cholera | Respiratory Syncytial virus, Herpes simplex, Enterotoxigenic Escherichia coli | SARS, Anthrax, Smallpox, pandemic influenza |

Source: WHO/UNICEF (2005)

**New Vaccine Administration Routes**

Alternative administration routes for vaccines would greatly contribute to improving immunization program safety and potentially reduce the quantity of contaminated waste which needs to be safely disposed. This could help avoid needle transmission of blood-borne pathogens and ease vaccine delivery strategies where non-professionals can administer vaccines. New administration routes such as oral, nasal, and transcutaneous are currently being explored. One option currently being explored through collaboration by WHO, PATH, and the Serum Institute of India is focusing on the development of a measles aerosol vaccine that could make a big difference in eliminating this disease by facilitating administration, during mass campaigns (Burger et al. 2008). The measles aerosol vaccine is useful in situations where the availability of trained medical personnel, who can safely administer injections, is limited. Immunogenically in studies, the aerosol vaccine was proven effective >80% of the time among infants <9 months of age and 86–100% among infants >9 months and school-aged children (Henao 2000). This vaccine continues to be tested in clinical trials in order to find the most appropriate and effective aerosol delivery method.

Another interesting option is the concept of using plant-derived or edible vaccines that involve encoding protective antigens from pathogens into transgenic plants (Mor et al. 1998). The plants are processed so that they can deliver a uniform dose of vaccines. Human clinical trials have been conducted with bananas and raw potatoes, which showed encouraging antibody responses (Sala et al. 2003). Plant-derived vaccines are formed when a gene is integrated with a plant nucleus or chloroplast genome. This transforms higher plants (e.g., tobacco, potato, tomato, and banana) into bioreactors for the production of subunit vaccines for oral or parental administration (Sala et al. 2003). The potential advantage of this technology could include thermostability, low investment needs, multivalency, and oral administration.
**New Immunization Technologies**

New technologies that strengthen vaccine delivery are under development. Priority is given to such technologies that will (a) expand access, (b) improve safety, and (c) cut the cost of immunization programs. They include the following five technologies:

(i) **“Sharps” processing:** The increased use of auto-disable (AD) syringes (syringes which lock themselves after a single injection) has greatly improved the safety of immunization programs by avoiding the reuse of contaminated syringes and reducing risks of transmission of blood-borne pathogens such as hepatitis B, hepatitis C, and HIV (Lloyd 2000). This success is, however, highlighting another problem which the health sector is facing, that of the handling of contaminated medical waste. In the case of immunization, this is mainly related to the disposal of used syringes and needles (these syringes represent between 5 and 10% of all injections given in the health sector but nevertheless the push to introduce AD syringes is increasing the pressure on immunization programs to tackle this challenge). Sharps are rarely disposed of at the point of use. Since sharps are transported to the point of destruction, the risk of infection from accidental exposure to sharps must be minimized. Four different technologies are being explored for this purpose: corrosive disinfectants, thermosterlizing, needle destruction, and plastic melting (Lloyd 2000). However, none of these options is currently sufficiently developed to be put into use in the field.

(ii) **Monodose pre-filled devices:** Vaccine wastage constitutes a considerable cost to immunization programs. Monodose presentations eliminate wastage and the risk of contamination. When the monodose is pre-filled into an injection device, it increases quality and safety at the point of use. UniJect® is one such device that has been tested with HepB and tetanus toxoid (TT) (Lloyd 2000). Village health workers can administer it. Currently, major obstacles reside in the cost of the device and the need for additional cold storage space when multidose presentation is exchanged for monodose, but ultimately, the objective would be to provide an increasing number of immunizations with monodose preparations that would not require increased cold chain capacity.

(iii) **Needle-free injections:** Needle-free injectors deliver vaccine at high velocity into the skin without penetration of a needle, thereby reducing the risk of transmission of blood-borne pathogens (WHO 2007c). Technologies are being developed for both mono- and multidose presentations. Multidose injectors available have not been found safe and new models are under development. There are several monodose models available; however, they are not feasible for large-scale programs because of regulatory obstacles and high cost (WHO 2000).

(iv) **Thermostable vaccine:** Vaccine distribution and storage without a cold chain would considerably simplify the delivery system, reduce cost, and allow for integrated supply mechanisms. Removal of vaccines from the cold chain should be the highest priority for technology research. Sugar glass drying is one such technology that has shown great promise (Lloyd 2000). It can be used to produce multivalent vaccines that are completely heat stable, except under extreme climatic conditions. The high cost of regulation/licensing and the uncertainty about market prospects in industrialized countries have so far impeded the development and use of this technology.

**Vaccine Management**

Vaccines are delicate products that are easily destroyed if handled incorrectly. Vaccine management spans a spectrum of aspects involving the use and disposal of vaccines, from the manufacturers to the end-users, for which plans must be in place and regularly updated to ensure an effective and efficient service delivery including (i) inventory and forecasting; (ii) stock control; (iii) in-country distribution; (iv) storing and handling; (v) equipment replacement; (vi) procedures for the use of vaccine; (vii) monitoring of vaccine storage; (viii) transport management; and (ix) operational management. All of these areas would benefit significantly from
research efforts to find alternative and innovative approaches. For instance, the heavy reliance on the cold chain remains a major economic and logistical burden on programs. The possibility of taking greater advantage of the real thermostability of vaccines and the increasing use of the Vaccine Vial Monitor by taking vaccines “out of the cold chain” is a field which has only begun but could potentially revolutionize immunization delivery (Table 23.4). Vaccine Vial Monitors are heat-sensitive circular labels, no wider than a centimeter, that change color as vaccines are exposed to heat. They are time–temperature indicators used to (i) ensure that the vaccines have not been damaged by excessive exposure to heat, (ii) identify weaknesses in the cold chain, and (iii) take vaccines beyond the cold chain to reach out to children who have no access to fixed health facilities. Health workers can use the Vaccine Vial Monitor color to tell if the vaccine has been overexposed to heat and whether or not it is safe for immunization. This indicator cuts down on the uncertainty of vaccine safety due to potential temperature changes during transport along the cold chain. Therefore, the vaccine vial monitor reduces waste.

Conclusion

Immunization remains one of the most cost-effective of all public health interventions. Maternal and child health-related MDGs will be difficult to meet without significantly scaling up the coverage of existing vaccines and successfully introducing new pipeline products – ensuring that research and development priorities are aligned with the diseases for which preventative technologies are needed most. Financing this effort, however, poses a considerable challenge. A serious commitment to closing the North/South divide and meeting MDGs will require a joint approach that involves increased investment by developing country governments and better, more stable aid flows from donors. Increased investment, particularly in the social sector, will be critical to finance costs such as system building that require large amounts of sustained finance. In-kind investments in commodities can be scaled up rapidly without major concerns around absorptive capacity or macroeconomic stability. Long-term, predictable aid flows are also needed to reduce volatility and provide increased certainty over future budget flows to enable better planning in countries.

As a global community, we must start approaching our work from a perspective that evaluates who is taking on the burden of risk – it clearly should not be the poorest countries. Risk analysis is a common tool in the private sector – companies only take decisions based on the probable level of risk it implies for them. Yet the donor community consistently places the poorest countries in a position where it is very difficult for them to make choices of how or whether to radically scale up access to basic services. The donor community, including the GAVI Alliance and the international financial institutions, needs to develop strategies to reduce financial and political risks. This means adjusting processes and requirements to support the long-term integrated plans of developing countries. The financial risks of development strategies must be more equitably shared between donors and national governments. Development will be led by developing countries when they are enabled to plan ahead;

| Table 23.4 | New vaccines required |
|------------|-----------------------|
| Commodity  | Trends/developments   | Implication for logistics systems |
| Vaccines   | GAVI is expanding access to new vaccines and financing vaccine development | Newer vaccines often require more storage space and additional training for staff |
|           | New vaccine delivery technology may reduce reliance on cold chain | Reduced dependence on cold chain may make it more feasible to integrate vaccine logistics with other commodities |
|           | Increased focus on safe injection, new injection equipment, and better disposal of sharps | New technology may also reduce vaccine waste |
|           | Shift from donations to purchases | More staff, training, and systems are needed to manage procurement |
when donors act on their recognition of the importance of predictable and long-term aid flows to meet the MDGs. Development will only happen when poor and vulnerable people are ensured equitable access to basic services. Accelerating the sustainable introduction of new and underused vaccines is part of realizing this ambition.

**Key Terms**

| Acellular pertussis          | Haemophilus influenza vaccine (Hib)               | Rotavirus vaccine          |
|------------------------------|--------------------------------------------------|---------------------------|
| Advance market commitment (AMC) | Hepatitis B vaccine (HBV)                        | Severe Acute Respiratory Syndrome (SARS) |
| Attenuated varicella         | Human papilloma virus (HPV) vaccine              | Smallpox                  |
| Auto-disable (AD) syringes    | Immunization coverage                           | Tetanus toxoid (TT)       |
| BCG                          | Immunization delivery systems                    | Vaccine distribution      |
| Breastfeeding                | Immunization programs                            | Vaccine management        |
| Cervical cancer              | Immunization rates                               | Vaccine market            |
| Child Survival Revolution    | Influenza                                        | Vaccine production        |
| Cold chain                   | International Finance Facility for Immunization (IFFIm) | Vaccine quality          |
| Cold chain capacity          | Measles aerosol vaccine                          | Vaccine safety            |
| Diphtheria, pertussis, tetanus vaccine (DPT) | Oral rehydration therapy (ORT)                  | Vaccine vial monitor      |
| Expanded Program on Immunization (EPI) | Pneumococcal conjugate vaccines | Vaccines                  |
| Global Alliance for Vaccines and Immunization (GAVI) | Polio                                             | Variolation               |
| Global immunization targets  | Population mobility                              | Vertical programs         |
| Growth monitoring            |                                                  |                           |

**Questions for Discussion**

1. What factors account for the disparity in immunization coverage between developed and less developed countries?
2. What is the GAVI Alliance? How does its mission compare with those of Global Immunization Vision Strategy (GIVS)?
3. What major barriers confront the GAVI Alliance and GIVS in their efforts to ensure equity in access to new and underused vaccines in developed and less developed countries?
4. In a narrative of about 1,000 words, describe the meaning and mission of the following initiatives:
   a. International Finance Facility for Immunization (IFFIm).
   b. Advance Market Commitments (AMCs).
5. How successful are IFFMs and AMCs in accomplishing their mission?
6. Outline and discuss potentially viable strategies for ensuring sustainability in procurement, access, and uptake of vaccines in less developed countries. What are the major barriers?
7. What should be the priorities for future vaccine research and development globally? Provide justification for your position.

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