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Global control of infectious diseases by vaccination programs

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Abstract

In both industrialized and developing countries, childhood immunization has become one of the most important and cost-effective public health interventions. National immunization programs have prevented millions of deaths since WHO initiated the 'Expanded Program on Immunization' in 1974. Smallpox was eradicated in 1979, poliomyelitis is on the verge of eradication, and two thirds of developing countries have eliminated neonatal tetanus. Global immunization coverage was at 78% in 2005. Through their impact on childhood morbidity and mortality, immunization programs are contributing to reaching the 'Millennium Development Goal 4' – a two-thirds reduction of under-five mortality by 2015. However, the failure to reach more than 20% of the world's children with existing vaccines was responsible for at least 2.5 million of an estimated 10.5 million deaths of children under 5 years, mainly in developing countries. Of these deaths, 1.4 million could have been prevented by vaccines currently recommended by WHO. Rapid progress in our understanding of the pathogenesis of infectious diseases, immunology, and biotechnology has increased the number of candidate vaccine antigens available. Pressures are growing on public health decision makers to establish evidence-based ways to decide which new vaccines should be introduced on a large scale into national immunization programs. The gap in access to new vaccines between the developing and industrialized worlds is still wide, and wealthy countries are still the first to introduce and use new vaccines. Interest from countries and partner agencies in vaccination, as one of the most cost-effective public health interventions, continues to be strong, also due to rapid progress in biotechnology and vaccine development and the emergence of global infectious disease threats, including HIV/AIDS, SARS, and influenza. The establishment of the Global Alliance for Vaccines and Immunization has focused global activities to support vaccination programs through raising considerable funds, and to assist especially poorer countries in improving and expanding their vaccination programs. Global efforts concentrate on further reducing the gap in the access to all existing vaccines between industrialized and developing countries.

Introduction

In both industrialized and developing countries, child immunization has become one of the most important and cost-effective public health interventions [1, 2]. National immunization programs have prevented millions of deaths since WHO initiated the 'Expanded Program on Immunization (EPI)' in 1974 [3]. Smallpox was eradicated in 1979 [4], poliomyelitis is on the verge of eradication [5], and two thirds of developing countries have eliminated neonatal tetanus (NT).[1] Global immunization coverage, as measured by the reported infant coverage with the third dose of diphtheria–tetanus–pertussis (DTP) vaccine (DTP3), was at 78% worldwide in 2005 [6] (Fig. 1), as compared to 20% in 1980. By the end of 2004, 153 of 192 WHO Member States had introduced hepatitis B (HepB) vaccine and 92 countries had introduced *Haemophilus influenzae* type b vaccine (Hib) into routine infant vaccination programs [7, 8], even though both vaccines are still underused in developing countries. The estimated number of deaths (from measles, pertussis and NT) prevented through childhood immunization in 2003 was more than 2 million. Infant HepB vaccination in 2003 was estimated to prevent a future 600 000 adult deaths, which would have occurred without vaccination, due to chronic liver disease and liver cancer.

However, the failure to reach >20% of the world's children with existing vaccines was responsible for at least 2.5 million of an estimated 10.5 million deaths of children <5 years in 2002 (Fig. 2), mainly in developing countries. Of these deaths, 1.4 million could have been prevented by vaccines currently recommended by WHO: >500 000 due to measles, nearly 400 000 due to Hib, nearly 300 000 due to pertussis, and 180 000 NT deaths [9, 10]. An additional 1.1 million children <5 years are estimated to have died worldwide in 2003 from rotavirus and pneumococcal disease, against which effective vaccines exist,[2] but are not yet used in developing countries [10]. Through their impact on childhood morbidity and mortality, immunization programs are already contributing considerably to reaching the 'Millennium Development Goal 4' – a two-third reduction of <5 mortality by 2015 [11]. It was estimated that improving coverage with the basic six EPI vaccines could potentially reduce <5 mortality by 13%, with another 10% mortality reduction possible following the introduction and more widespread use of Hib, pneumococcal, rotavirus and meningococcal vaccines.

In industrialized countries, mortality reduction is not the main driving force of national vaccine programs. Programs in wealthy countries recognize and mostly adhere to global vaccination goals set by WHO, and address

1 WHO Geneva: Maternal and neonatal tetanus (MNT) elimination web site at http://www.who.int/immunization_monitoring/diseases/MNTE_initiative/en/index2.html

2 See the chapter by Dr. Steele of this volume on rotavirus and section on pneumococcal vaccines later in this chapter

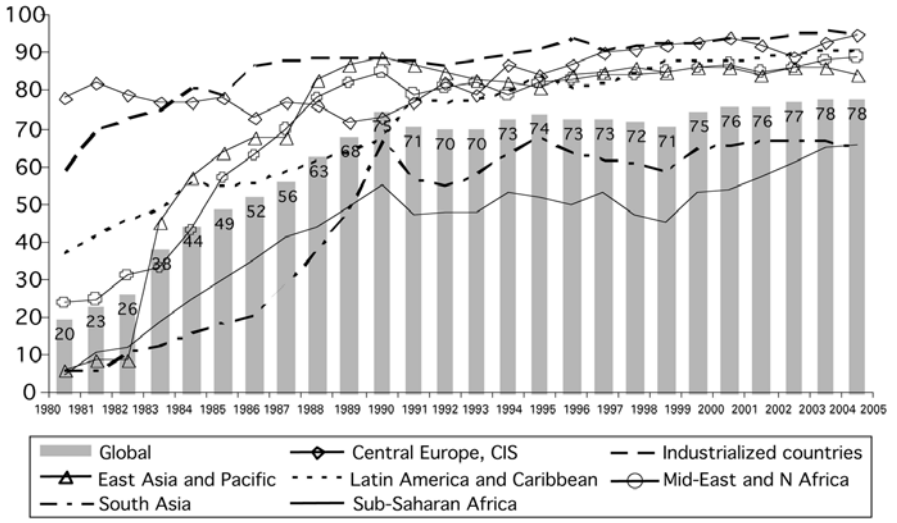


Figure 1. Annual third dose of diphtheria-tetanus-pertussis vaccine (DTP3) coverage globally and by Region, 1980–2005. Source: WHO/UNICEF estimates, 2006

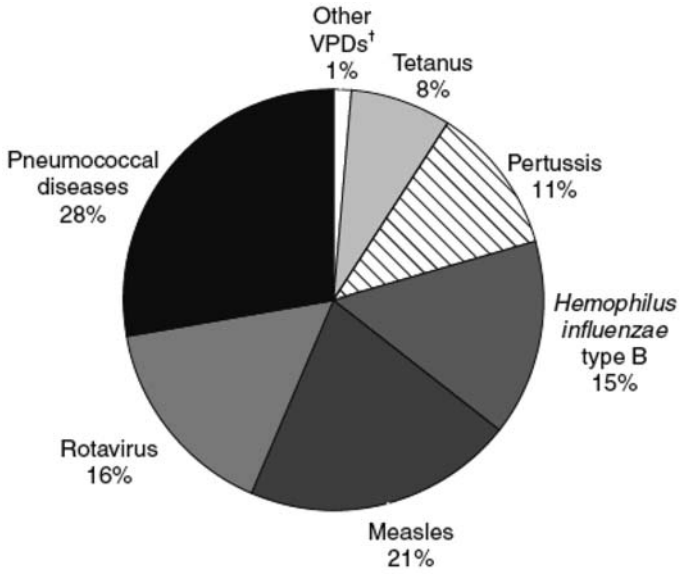


Figure 2. Percentage of deaths from vaccine-preventable diseases (VPDs) globally among children <5 years, by disease, 2002. An estimated 2.5 million deaths of children <5 years worldwide (of a total of 10.5 million deaths in this age group) are caused by diseases for which vaccines are currently available. (†) Diphtheria, hepatitis B (HepB), Japanese encephalitis, meningococcal disease, poliomyelitis, and yellow fever. In older age groups, approximately 600 000 HepB deaths are preventable by routine immunization.

potential life years saved through vaccination in cost-effectiveness analyses. Main motivators for vaccination programs in industrialized countries are morbidity reduction and improvements in quality of life, indirect societal savings and also moral causes [12]. As for vaccination programs anywhere in the world, the access to the best and most effective vaccines available is seen as a right of every child.

Rapid progress in understanding of infectious disease pathogenesis, immunology, and biotechnology has increased the number of candidate vaccine antigens available, many of which have entered clinical phases of testing for safety, immunogenicity and eventually efficacy. Pressures are growing on public health decision makers, advisers and implementers to establish transparent and evidence-based ways to decide which new vaccines can and should be introduced on a large scale into national immunization programs. While the gap in access to new vaccines between the developing and industrialized world remains wide (see below), rich countries are still the first to introduce and use new vaccines. This is illustrated by the recent licensing of the first human papilloma virus (HPV) vaccine (see later in this chapter), the second possibly cancer-preventive vaccine since HepB. HPV vaccine is now being recommended by the Advisory Committee of Immunization Practices to be included into the U.S. immunization program.

Interest in vaccination programs from countries and partner agencies continues to be strong, due to the cost effectiveness and measurable public health impact of vaccination, particularly on recent progress towards global polio eradication [5] and measles mortality reduction. Other reasons for which vaccination remains a high priority in public health are the rapid progress in biotechnology and vaccine development, and the emergence of global infectious disease threats, including HIV/AIDS, SARS, and influenza. The establishment of the Global Alliance for Vaccines and Immunization (GAVI) in 2000 [13] has focused global activities to support vaccination programs through raising considerable funds, and assisting especially poorer countries in improving and expanding their vaccination programs. WHO and UNICEF, together with other immunization partners, have recently elaborated a long-term strategic plan for 2006–2015, the Global Immunization Vision and Strategy (GIVS) [8], to guide country programs and coordinate efforts of the international immunization partnership.

This chapter describes the main currently used global immunization policies and strategies, discusses progress towards improving access of all children to vaccines worldwide, including remaining gaps between developing and industrialized countries, and provides short updates on the current status of priority and new vaccines.

Immunization policies and strategies

The 'Expanded Program on Immunization'

Established in 1974 [3], the EPI targeted to achieve 80% immunization coverage of children under the age of 12 months by the year 1990. The immunization goal was further reinforced by the Alma-Ata Declaration in 1978 [14], which identified primary health care, including immunization, as the key strategy for achieving "Health for All by the Year 2000". Interest in immunization was greatly boosted by the global eradication of smallpox in 1977 [4]. While progress towards improving overall coverage was slow in the first half of the 80s, the UN Secretary-General, in 1985, called for all countries to reach at least 80% infant coverage (Universal Child Immunization, UCI). Following renewed efforts in developing countries and by immunization partner agencies, the UCI goal was achieved in 1990.

Up to the early 1990s, the EPI concentrated on establishing the necessary infrastructure (vaccine cold chain, transportation, training of staff) to deliver vaccines to children, and on monitoring coverage. The program then added specific disease control goals during the 1990s: polio eradication, and accelerated control of measles and of maternal and NT (MNT) elimination.

The Children's Vaccine Initiative (CVI), which operated between 1990 and 1999, was a first and innovate attempt to create a global public-private partnership to support global vaccination and make new vaccines available to all children. However, impact of the CVI was not as strong as expected, mainly because critically important partners, such as the major vaccine manufacturers, were not yet sufficiently represented in the initiative.

Since 2000, the GAVI[3] has been very successful at re-focusing immunization activities globally. Many strategies outlined by the GIVS document support the GAVI objectives [8]: the introduction of new vaccines, the increasing integration of immunization with other health interventions, and strengthening national immunization programs within the health system context. In GIVS, new goals for the global and national EPI programs were set and supported by a wide collaboration of partners. Among others, the goals called for were:

- by 2010, achieve 90% coverage of children under 1 year of age nationally in each country, with at least 80% coverage in every district;
- by 2010, reduce measles mortality by 90% compared to the 2000 levels, and
- by 2015, reduce overall morbidity and mortality from vaccine-preventable diseases by two-thirds compared to the 2000 level.

3 GAVI partners include governments in industrialized and developing countries, UNICEF, WHO, the Bill and Melinda Gates Foundation, the World Bank (WB), NGOs, foundations, vaccine manufacturers, and technical agencies such as the US Centers for Disease Control and Prevention (CDC)

Table 1. Routine immunization schedule for infants recommended by the EPI

Vaccine	Age				
	Birth	6 weeks	10 weeks	14 weeks	9 months
BCG	X				
Oral polio	X†	X	X	X	
DTP		X	X	X	
Hepatitis B* Scheme A	X	X		X	
Hepatitis B Scheme B		X	X	X	
Haemophilus infl. type B		X	X	X	
Yellow fever					X**
Measles					X***

†In polio-endemic countries.
*Scheme A is recommended in countries where perinatal transmission of HBV is frequent (e.g., in South-East Asia). Scheme B may be used in countries where perinatal transmission is less frequent (e.g., in sub-Saharan Africa).
**In countries where yellow fever poses a risk.
***A second opportunity to receive a dose of measles vaccine should be provided for all children. This may be done either as part of the routine schedule or in a campaign.

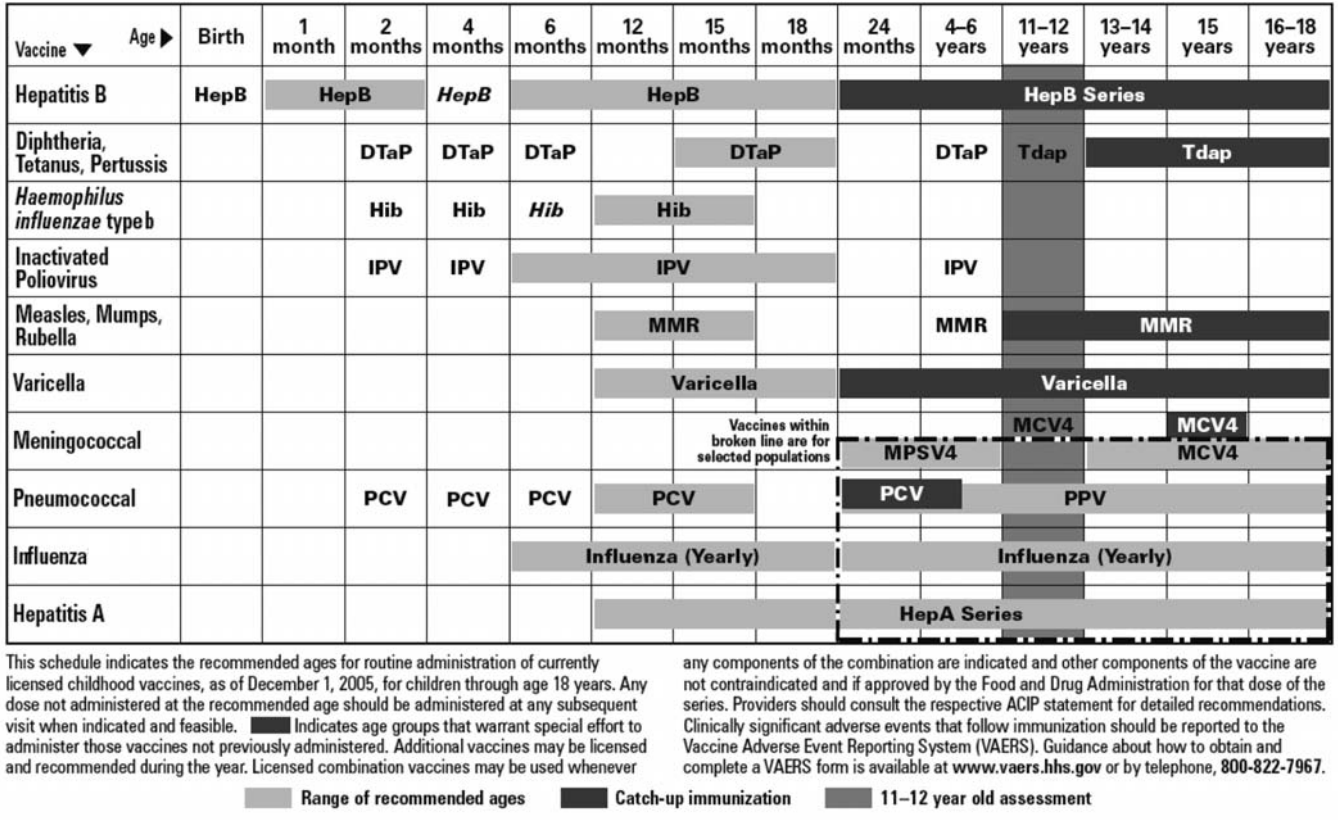
Routine infant immunization

Table 1 shows the 'basic' immunization schedule recommended by the EPI/WHO [15], which is followed in low-income and most lower middle-income[4] developing countries. Schedules in most upper middle- and high-income countries start later (e.g., 2 months), with longer intervals between doses [16, 17]. While the basic EPI schedule, with some variation, is still followed by many developing countries, vaccination schedules in middle-income and industrialized countries vary considerably, for historical, epidemiological, and economical reasons (compare the 2006 U.S. Child and Adolescent Immunization Schedule, Table 2). WHO keeps track of and publishes national immunization schedules [18]. To protect mothers and neonates against tetanus, WHO recommends implementing a five-dose tetanus toxoid (TT) schedule [19] for women of childbearing age, especially where most women in this age group have not previously received TT when they were young [20]. The different EPI contacts during the first year of life present opportunities for health education of mothers and caretakers and to deliver other basic health care interventions. For example, the measles contact at 9 months of age is used in many developing countries to administer vitamin A to children.

In developing countries, routine immunization services are delivered most commonly by midwives or nurses in a health center, offering vaccination either daily or on specific days of the week, depending on the number of children attending each day. Where health centers have large catchment

4 Based on the classification of the WB by gross national income; of 208 economies with populations of >30 000, including 184 WB member countries, 54 are 'low', 58 are 'lower middle', 40 are 'upper middle' and 56 are 'high' income.

Table 2. US recommended childhood and adolescent immunization schedule, as published by the Centers for Disease Control and Prevention at www.cdc.gov/nip/acip



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2005, for children through age 18 years. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible. ■ Indicates age groups that warrant special effort to administer those vaccines not previously administered. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective ACIP statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at **www.vaers.hhs.gov** or by telephone, **800-822-7967**.

Range of recommended ages Catch-up immunization 11–12 year old assessment

areas, regular additional 'outreach services' through staff based at the health center may be organized to reach children who live too far away from the center, and to trace children who did not come back for follow-up doses. In other areas it may be necessary to set up mobile services, which are more costly, because vaccination teams need vehicles and spend 2 or more days to reach hard-to-access population groups [21]. Any contact with a child in a facility offering EPI services, whether health center or hospital, should be used to screen the vaccination status of both the child and its mother (TT) and to offer vaccines and a basic package of non-vaccine preventative child health services. Missing opportunities to vaccinate, such as during a visit to the health facility for other reasons, still constitute a major factor contributing to low coverage.

Booster doses and 'second opportunity' for measles vaccination

Few vaccines give life-long protection after the primary series. To maintain immunity beyond childhood, booster doses are needed. To maximize returns of scarce resources, however, WHO recommends considering adding booster doses to immunization programs once they have reached routine coverage levels of 80% or higher. Boosting with BCG is not recommended, as there is no evidence of its efficacy [22].

Since many developing countries have now reached 80% coverage, they have begun to include booster doses in their schedules, based on epidemiological patterns of diseases, available resources, and health infrastructure. Events like the diphtheria epidemic in Eastern Europe in the early 1990s, or the recognition that pertussis-infected adults contribute to community spread [23] triggered renewed interest in, and importance attached to, booster doses. While high coverage with one dose of measles vaccine will reduce measles morbidity and mortality, a second vaccine dose is needed for more efficient measles reduction, or to achieve measles elimination [24]. This 'second opportunity' for measles vaccination is not intended as a true 'booster dose' but to give a second chance to seroconvert for children who did not respond to the first dose, and also to reach children who missed the first dose. Increasingly, additional measles vaccine doses in developing countries, intended to reduce measles mortality or to move towards measles elimination, are delivered through campaigns. As the EPI programs mature, WHO encourages adopting routine two-dose measles schedules, to sustain gains in measles mortality reduction [25].

Supplementary immunization activities

Immunization campaigns to supplement routine programs to increase coverage – now often referred to as supplementary immunization activities

(SIAs) – were used first during the early phase of EPI to rapidly increase coverage to reach the 1990 'universal child immunization' (UCI) goal, at that time often with poor results. More recently, SIAs are no longer used mainly to boost overall coverage, but have become the main tools for disease eradication and elimination initiatives – to achieve global polio eradication, reduce measles mortality, mainly in Africa, for measles elimination (in WHO Regions with a measles elimination goal [25]), and for TT campaigns to eliminate MNT, targeting child-bearing age women. SIAs typically target all children in a particular age group, according to disease epidemiology (5 years for polio campaigns, from 9 months to <15 years for initial measles campaigns), and regardless of previous immunization status. SIAs are used in many countries to provide other interventions, most commonly vitamin A supplementation [26], but also, for example, insecticide-treated bed nets for malaria prevention [27], or de-worming medication. With appropriate support from donors and partners, and with adequate planning, implementation and monitoring/evaluation, recent experience with SIAs to reduce measles mortality and for polio eradication has been good overall.

However, there has also been considerable discussion and controversy about the effects of vaccination campaigns on routine immunization programs and primary health care, particularly about the impact, whether positive or negative, of the polio eradication initiative. Some observers believe that polio eradication has detracted from health service delivery and has been detrimental to an integrated approach to health systems development [28]. Several large field studies on the impact of the polio eradication initiative on health systems concluded that, while SIA planning and implementation may have been detrimental in the short term to general health services, positive long-term synergies exist between polio eradication and health systems [29] (building vaccine-preventable disease surveillance, strengthening cold chain and management and planning for routine immunization, distribution of Vitamin A), but that these synergies must be more systematically exploited [30].

The vaccine cold chain

EPI programs established a system of vaccine transport and storage at appropriate temperature – the cold chain – to assure that vaccine potency is maintained. This vaccination strategy component is particularly critical in tropical developing countries, where logistics and lack of reliable power supply and refrigeration equipment are frequent problems. The WHO recommends that the storage temperature for vaccines used in the EPI at health facilities be between 2 °C and 8 °C, a temperature range determined by the heat sensitivity of oral poliovaccine (OPV) and sensitivity to freezing of other vaccines (DTP, TT, HepB). Live vaccines (OPV, measles, BCG, yellow fever) can be stored in freezers at –20 °C. UNICEF and WHO, in collaboration with manufacturers, have set standards [31] for technologically

appropriate cold-chain equipment and helped to develop such equipment, such as ice-lined refrigerators, which can maintain appropriate storage temperature for up to 16 h during power cuts, or refrigerators run on kerosene, gas and solar power in areas without grid electricity. Vaccine temperature is monitored over time during international and domestic vaccine transport using temperature-sensitive cards. More recently, vaccine vial monitors (VVMs) [32], attached to each vial of vaccine procured through UNICEF, have greatly facilitated vaccine use in the field, particularly to extend the 'cold chain' into remote areas during polio eradication campaigns. VVMs measure and indicate 'cumulative' heat exposure by changing color once vaccine potency is threatened. It was realized more recently that inappropriate freezing of freeze-sensitive vaccines is also a problem in many countries, potentially affecting the potency of vaccines with adjuvants (HepB, combination vaccines) [33].

Immunization safety and adverse events following immunization

The goal of immunization is to protect the individual and the community from vaccine-preventable diseases. While modern vaccines are safe and effective, no vaccine is entirely without risk. Effective vaccines may produce some undesirable side effects, which are mostly mild and self limited. Many of the adverse events attributed to the administration of a vaccine are actually not caused by the vaccine, but are either due to programmatic or human error (particularly in developing countries), or are simply coincidental events, which are not causally related to vaccine administration [34]. Surveillance for adverse events following immunization (AEFIs) in many developing countries has confirmed that most adverse events temporally associated with vaccination were not causally but only incidentally associated with vaccination. In cases where the vaccine of the vaccination program is the cause of an AEFI, events resulting from inappropriate handling of vaccines ('program error') are much more common than severe events related to properties of the vaccine itself [35]. Examples for reported serious adverse events related to program error are vaccine reconstitution with the wrong diluent, administration of dangerous drugs for vaccines, contamination of multi-dose vials leading to abscesses or sepsis, or transmission of blood-borne diseases (HIV, hepatitis B or C) through contaminated needles or syringes. If allegations regarding vaccine-related AEFIs are not rapidly and effectively investigated and clarified, confidence in a vaccine or the immunization program can quickly be undermined, even if the vaccine or the vaccination program is not at fault, with possible dramatic consequences for acceptance of vaccination and disease incidence.

As successful immunization programs continue to reduce the incidence of vaccine-preventable diseases, there is increasing public concern, particularly in industrialized countries, about possible risks attributed to vaccines.

During the past decade, different vaccine antigens have been accused of contributing to increases of non-infectious diseases. Recent examples of these are false allegations linking measles-mumps-rubella vaccine to autism (United Kingdom), attributing multiple sclerosis to administration of HepB vaccine (France), and linking Hib vaccine to diabetes mellitus (Finland).

Also, when a disease has been eradicated, even extremely rare adverse events may no longer be acceptable. Following the interruption of wild poliovirus transmission in three WHO Regions, the only polio cases that still occur in OPV-using countries are vaccine associated, which has caused many countries to switch to inactivated poliovirus vaccine. In Finland, the increase in BCG-related osteitis cases, while the incidence of tuberculosis (TB) remains very low, led to switching from universal to risk-group BCG vaccination.

The programmatic importance of vaccine and immunization safety issues, including the need for monitoring and rapid investigation of AEFIs, has been increasingly highlighted by WHO. A Global Advisory Committee on Vaccine Safety was established [36], which has issued position papers on vaccine safety issues, such as the use of thiomersal as preservative in vaccines, or the safety of HepB vaccines.[5] All countries are advised to establish a system of monitoring and investigating AEFIs, and to train key health staff on AEFI surveillance, and on how to communicate effectively with the media on vaccine safety issues. High-income countries are starting to utilize new information technology and vaccine registers to monitor AEFIs in a timelier manner. Through linking of vaccine registry information to disease-specific registry information, different advanced epidemiological methods can be utilized to try to understand potential cause–effect relationships.

The safe administration of vaccines is an essential component of immunization safety, the importance of which was not fully recognized during the initial phase of the global EPI. Because of the large-scale improper use of both re-sterilizable and single-use injection equipment (inadequate sterilization, re-use of disposable needles and syringes) [37] in developing countries, WHO and UNICEF have promoted universal use of auto-disable (AD) syringe-needle units. AD syringes can only be used once because of an internal locking mechanism, and have now been widely introduced into immunization programs in developing countries [38]. UNICEF now ‚bundles' vaccine shipments with AD syringes and disposal boxes to ensure that safe injection practices are maintained.

It is estimated that <10% of all injections given worldwide are related to immunizations, and activities to promote the safety of injections in the immunization context are handled in the broader context of overall injection safety. The Safe Injection Global Network (SIGN)[6], a global partnership of interested parties, aims to prevent transmission of blood-borne

5 Position papers on immunization safety can be found at http://www.who.int/vaccine_safety/en/
6 Information on the SIGN project can be found at http://www.who.int/injection_safety/sign/en/

disease by reducing the number of unnecessary injections, and ensuring the safety of all injections, including those who apply vaccines, as well as by ensuring safe injection-waste disposal.

Another emphasis has been on proper disposal of injection equipment, such as the use of 'sharps' boxes, appropriate disposal pits, and incinerators to prevent infection of health workers through accidental needle stick injuries and reduce risk to communities [39]. There is also progress in developing needle-free injection technologies, particularly focusing on jet injectors with exchangeable nozzles.

Program monitoring and surveillance for vaccine-preventable diseases

The main aim of an immunization program is to reduce the incidence of, and in some cases to eradicate a disease. Disease-specific morbidity and mortality can best be monitored through disease surveillance systems. In poor countries, surveillance data are often not very reliable: case detection and confirmation is erratic, and laboratory equipment and reagents may not exist. Other means to help maintain and improve the quality of immunization programs are monitoring immunization coverage, measuring antibody and cellular immunity responses, and testing vaccine efficacy using different observational epidemiological methods, as well as monitoring the quality of disease surveillance (completeness and timeliness of reporting) [40].

Program monitoring and surveillance data should be available at national, sub-national and particularly at the district level. For immunization programs, main quality indicators include immunization coverage for the vaccines used, the 'drop-out rate', which measures the proportion of children who start but do not return to finish the vaccine schedule (mainly measured between the BCG and DPT3 contact), and the extent of missed opportunities for immunization. Other program components monitored include injection and immunization safety, cold-chain maintenance and social mobilization and information activities [41]. In developing countries, coverage is monitored by the 'administrative method' – a comparison of routine reports of the number of doses given to children to the estimated population in that age group, or through surveys [42]. Coverage data from different sources and at different levels has often shown considerable discrepancies. WHO and UNICEF have reviewed and compared reported 'administrative' and survey coverage data for all countries since 1980, and then developed 'best coverage estimates' for each country [10]. Best estimates are updated annually, and are often lower than results obtained by the administrative method. However, the iterative processes now used to derive coverage estimates have much improved the accuracy of available coverage data, with continuously declining discrepancies.

Many middle- and high-income countries have better demographic data available for more precise estimation of coverage: total or sample popula-

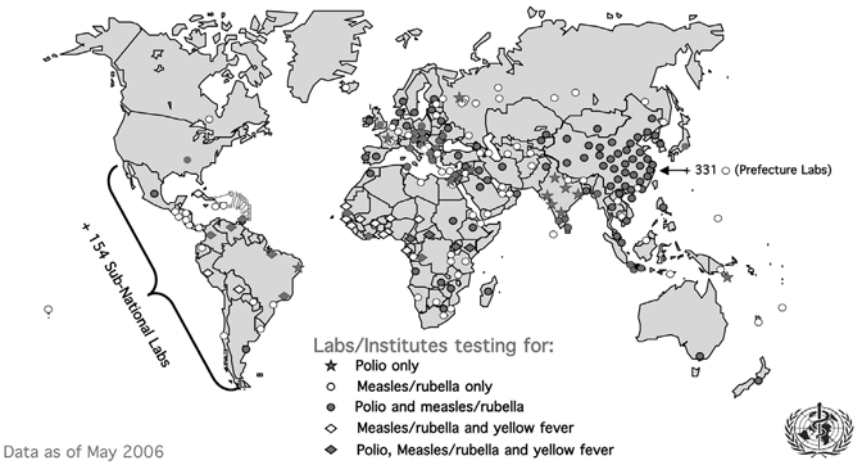


Figure 3. Global vaccine-preventable disease laboratory network. The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

tion method is used in these countries. Increasingly, individualized 'numerator data' are available, which allow evaluatation of timeliness of vaccinations in addition to coverage.

Surveillance for vaccine-preventable diseases is an essential program component to measure the impact of vaccines used in routine immunization programs. Surveillance should provide 'data for decision-making' through the ongoing systematic collection, analysis and interpretation of surveillance data, which enables program managers to take decisions on planning, implementation and evaluation of immunization programs. High-quality surveillance remains particularly critical for polio eradication [43] and regional measles elimination [44] efforts, to detect remaining chains of virus circulation and reliably monitor progress towards interruption of transmission. Reliable surveillance data are also critical to establish baseline 'disease burden'[7] [45] in countries considering introducing a new vaccine into their immunization program.

Laboratory confirmation is important for some vaccine-preventable diseases, particularly those with eradication or elimination goals. A global poliovirus lab network (Fig. 3) consisting of 145 laboratories all around the world [46] provides critical information to the polio eradication effort,

7 WHO's immunization programme maintains a web site on vaccine-preventable disease burden estimation at http://www.who.int/immunization_monitoring/burden/estimates_burden/en/index.html

including primary virus isolation from stool specimens, intratypic differentiation to distinguish wild- from vaccine-type polioviruses, and genetic sequencing of isolated viruses to track transmission paths of virus strains around the world.

A global measles laboratory network has been established, which has utilized much of the polio laboratory infrastructure; often housed at the same institutions as polio labs, measles labs use similar systems for specimen transport, data management, communication and reporting of results. The measles network's primary roles are confirmation of suspected measles cases using IgM testing and genetic characterization of measles viruses. Measles laboratories also perform serological diagnosis of yellow fever in countries in Africa and Latin America where yellow fever is prevalent. Regional rotavirus laboratory networks are also emerging in some regions [47]. Together with the planned expansion of the African 'Paediatric Bacterial Meningitis Laboratory Surveillance Network', a global vaccine-preventable disease laboratory (both virological and bacteriological) network is evolving [48], which will be a crucial component of the future of vaccination described in GIVS.

Current status, remaining problems, and progress achieved

The global immunization program has been supported by a degree of commitment and cooperation by the health sector and many other partners, within and outside of government, and from both the public and private sector, which has not been seen before for other health programs. However, the wider benefits of immunization are not reaching all children. Children in lesser developed countries still have less access to immunization services than those in wealthier countries, often because political commitment to, and funding available for, health is low, and health service delivery systems are weak and badly managed. Typically, the range of vaccines accessible to poorer children is smaller, and they are at greater risk from unsafe immunization practices. While some low-income countries have made substantial progress in increasing coverage, coverage remains low in others.

While global aggregate coverage was relatively stagnant at 70–75% throughout the 1990s (Fig. 1), coverage increased during the 2000s and reached 78% (DTP3 coverage) in 2005 (UNICEF/WHO best estimate[8]), with relatively greatest increases in Africa.

Such aggregate global coverage masks wide variations both between and within sub-regions [49] (Fig. 1). In 2004, DTP3 coverage was over 90% in industrialized countries, countries of Central Europe, the former Soviet Union (Commonwealth of Independent States, CIS) and Latin America and the Caribbean, while coverage was 88% in countries of the Middle East and

8 Available at http://www.who.int/immunization_monitoring/en/globalsummary/wucoveragecountrylist.cfm

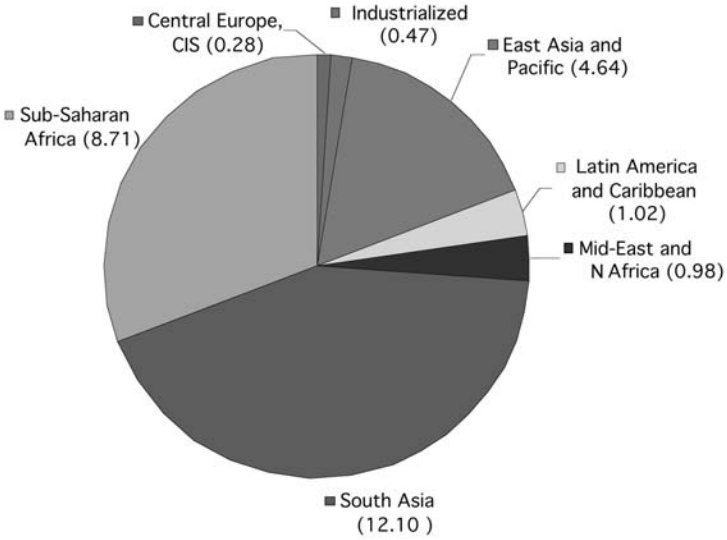


Figure 4. Estimated 28 million infants were not fully immunized (DTP3), 2005, representing a 78% global immunization coverage.

North Africa, 86% in East Asia and the Pacific, 67% in South Asia and 65% in sub-Saharan Africa. At these coverage levels globally, 28.2 million of the estimated 125 million newborns in 2005 were not fully immunized, including 12.1 million in South Asia (8 million in India alone), 8.7 million in sub-Saharan Africa, and 4.6 million in East Asia and the Pacific (Fig. 4).

Also, regional averages conceal variations in coverage between countries. Some developing countries – notably Bangladesh, and Latin American countries, increased coverage substantially, while coverage rates actually fell in other low-income countries, particularly in parts of sub-Saharan Africa. In 2005, coverage in Somalia was 35%, and in Nigeria 25%, down from coverage rates which were twice as high one decade earlier.

In Europe, the economic and social changes following the break-up of the Soviet Union triggered a considerable decline in investment in immunization services and in immunization rates in countries in east and central Europe and countries of the former Soviet Union (CIS), which led to the re-emergence of diseases such as diphtheria. A major diphtheria epidemic occurred in the early 1990s in Eastern Europe, in which more than 30 000 people died [50]. There continues to be great disparity between vaccines available in the high-income countries of Europe and those with economies in transition.

In many developing countries, children are not reached by immunization because they either live in remote areas beyond the reach of health services, or because they are not accessible in conflict zones [51]. Children may also be excluded because their parents fail to register their birth, or do not make use of existing immunization services. Great inequalities exist between the

poorest and wealthiest population groups [52] within some countries: the wealthiest 20% of children in India, Nigeria and Cote d'Ivoire, for example, are four times more likely to be immunized than the poorest children in the same country. Immunization 'drop-out', i.e., failure to complete the full immunization schedule, is also highest among the poorest population groups.

To identify and target children who remain unvaccinated, countries have increasingly introduced and strengthened district-level monitoring and surveillance activities, which reflects crucial differences in coverage and disease incidence, often concealed by province- or national-level averages, and allows taking corrective action. Many of the children who are not reached by vaccination either live in remote, hard-to-access areas, or belong to hard-to-reach groups, like nomads and seasonal migrants. Reaching and vaccinating these children involves the use of outreach and mobile teams, and is much more costly than immunizing children in an urban area. Low coverage in many densely populated urban or peri-urban slums and low-income areas, due to lack of health services, presents another challenge.

The "Reach Every District" (RED) strategy[9], launched jointly by WHO and UNICEF in 2003, is a new approach aimed at assisting developing countries to strengthen immunization services at district level. Fifty-three countries have implemented the RED strategy, which encourages supportive supervision, strengthening of district immunization management, regular outreach services, community links with service delivery, improved data management, and improved planning based upon data, also using lessons learned through polio eradication.

GIVS [8] recommends that, to reach everybody targeted for immunization, national programs should use a combination of approaches, including both routine services and SIAs (immunization campaigns), attempting to reach every child at least four times per year. National commitment to immunization services should be strengthened by assuring that human resources and financial planning for immunization is included in national budget allocations, in the wider health sector context.

GIVS proposes that comprehensive multi-year national immunization plans (cMYPs), including detailed budgets and yearly workplans, should become a main tool to develop and maintain sustainable, well-performing immunization services. CMYPs for immunization provide countries with a method for identifying critical areas and resource needs, and with opportunities to track progress. At least 40 countries are now developing these cMYPs [49], which include cost estimates for all immunization activities and outline future initiatives to improve vaccine coverage and extend vaccination to unreached populations. GIVS stresses the importance of the district level in planning, implementing, and evaluating immunization services, and

9 RED strategy WHO website at http://www.who.int/immunization_delivery/systems_policy/red/en/index.html

endorses the continued use of the RED approach (see above) to accomplish this objective.

GIVS also highlights the importance of communication and social mobilization activities to inform communities and ensure there is community demand for immunization and confidence in its benefits and safety. Communities and non-governmental organizations (NGOs) and other interest groups should be directly engaged in immunization activities.

Immunization service delivery

In many developing countries, a main contributing factor to ill-functioning immunization services is the fact that overall health services, often due to years of neglect and under-investment, are poorly managed and unable to meet the basic health needs of the population. In these settings, the immunization infrastructure – buildings, vehicles and vaccine cold-chain equipment – is in a poor, often non-functional state. Storage in badly maintained cold-chain equipment may compromise vaccine potency, and non-functional sterilizing equipment may leave injection equipment contaminated.

Weak managerial skills, poor staff pay and motivation, failure to plan and budget effectively, and the lack of effective disease surveillance and reporting systems undermines the effectiveness of disease control and immunization systems, which are left unable to provide services to those in greatest needs. There is an alarming mismatch in some countries between the health needs of the population and the size of the health workforce, the mix of skills available, and the geographical location of health workers, with a severe shortfall of health personnel in rural areas in most developing countries (e.g., 85% of the population in Cambodia live in rural areas, but only 13% of health workers are based there) [53].

In some countries (Somalia, Afghanistan, South Sudan), conflict has destroyed or severely compromised the health infrastructure. Public health systems in sub-Saharan Africa are overwhelmed by the increasing burden of HIV/AIDS, exacerbated by HIV-related illnesses, absenteeism and deaths among health workers.

Since overall 'system-wide barriers' such as human resource capacity, logistics and overall financial resources seriously affect immunization services, these barriers will need to be addressed in joint action with all other parts of the health sector. However, efforts to strengthen immunization services can also help to reduce overall barriers to the equitable delivery of health services, for example by capitalizing on the well-established access of immunization services to children and women. Linkage of immunization contacts with routine health checks, or with the delivery of other essential health interventions, such as vitamin A, de-worming treatments and insecticide-treated bed nets to prevent malaria, has considerable impact on child health and reducing child mortality.

Immunization services can also assist through establishing 'best practices', which offer opportunities to strengthen overall health services. For example, polio eradication has in most developing countries led the way in strengthening national disease surveillance systems, including the establishment of a global virological laboratory network (see Fig. 3), and in strengthening cold-chain systems. Polio eradication activities have also shown that it is possible to reach each and every child in a country, including those in hard-to-reach or conflict-affected areas [51] or which are hard to access for other reasons. In many countries, the district-level micro-planning approach ('bottom-up') [54] used to prepare for polio campaigns has been very helpful to better define and map populations for routine immunization; microplanning lessons learned during polio eradication now form a core component of the RED strategy.

Improving access to under-used and new vaccines

Even though the market for vaccines in developing countries is potentially huge, with <130 million children born each year, vaccines for developing countries currently account for only 18% of the global US$ 6 billion vaccine market. While a number of new vaccines have become available over the last two decades, most poorer countries have not been able to pay for them in the public health services. This has widened the divide in access to new vaccines between wealthy and poorer countries. Even in wealthy countries it is no longer self-evident that a new vaccine gets introduced universally: the inclusion of pneumococcal conjugate vaccine has more than doubled the vaccine budget in those countries where introduced. Cost-effectiveness calculations have gained an important role in the decision-making about the introduction of new vaccines in many countries.

In addition to lack of funding, the inadequate disease surveillance and reporting systems in developing countries made it difficult to establish the disease burden and potential benefits and cost effectiveness of new vaccines. Lack of demand for a newly introduced vaccine can have a long-term impact on both supply and price. A vicious circle ensues, which keeps the vaccine out of reach of developing countries: manufacturers will limit the scale of production if demand in developing countries is low or uncertain, and the low production volume ensures that prices remain high.

Unequal access to Hib vaccine is an example. While the widespread use of Hib vaccines since the early 1990s has almost eliminated Hib-related disease in developed countries, many developing countries have had neither the capacity to establish the burden of Hib disease, nor the resources to afford the vaccine. As a result, an estimated 4.5 million unvaccinated children died in developing countries from Hib-related diseases, mainly pneumonia and meningitis, in the same period.

Vaccine-manufacturing research agendas still neglect needs of children in developing countries. There are three main underlying problems: the low demand for new vaccines in developing countries, the neglect by manufacturers of vaccines for mainly developing country markets, which are considered ‚low profit', and differences in the prevalence of causative organisms between developed and developing countries (e.g., different spectrum of pneumococcal serotypes between industrialized countries and the developing world, see above).

New vaccines go through a lengthy and very costly research and development phase, with investments of more than US$ 500 million or more per vaccine, and periods of 12–15 years until licensing. Initially high prices are set for new vaccines, so that development costs are recouped and a profit can be made. The manufacturer's exclusive rights to the vaccine are patent-protected for an initial 20-year period. Only then can other manufacturers start to produce the vaccine without paying royalties, which will lead to price reductions.

Through the support of the GAVI and the GAVI Fund, major progress was achieved in making under-used and new vaccines available in developing countries. Within Phase 1 of GAVI support for new vaccines, countries were eligible to apply for vaccines and funding to introduce HepB vaccine, Hib vaccine and yellow fever vaccine as required. Breakthroughs in the development of new vaccines are occurring, which revolutionize the way vaccines are conceptualized, produced, and administered. It will be critical that the needs of both developed and developing countries are taken into account when setting vaccine research and development agendas. Combination vaccines that include DTP with other antigens (e.g., HepB and Hib) simplify vaccine delivery and will be increasingly available during the next decade. Wider use of combination vaccines in developing countries will depend on making them 'affordable' for developing country immunization programs.

Decisions on the introduction of under-used or new vaccines into national immunization programs must be based on evidence showing the target disease burden, the safety of the vaccine on individual and population level, and on economic analyses defining the extent to which a new vaccine is ‚affordable' and cost effective, and to assure that its use is sustainable in the long run, within the country's budgeting and planning context. Countries should be empowered to evaluate their own needs and priorities, particularly to enable them to determine which of a number of several new vaccines will be easiest to integrate into the immunization program and represents the best opportunity for the investment of limited resources.

GAVI has established innovative mechanisms to support the development and introduction of new vaccines, such as the 'accelerated development and introduction plans' (ADIPs) for two new priority vaccines – rotavirus and pneumococcal conjugate vaccine. ADIPs include efforts to assist countries to establish credible forecasts of vaccine demand (based

mainly on disease burden and vaccine efficacy) early in the vaccine cycle, i.e., before manufacturers begin the lengthy development and scale-up process. Early demand forecasts will also allow countries to secure sustainable financing from national and external sources. It is hoped that the 'ADIP' strategy could advance the introduction of rotavirus and pneumococcal vaccines by 6 or more years in developing countries. Similarly, the introduction and wider use of Hib vaccine is supported by an international partnership of interested parties through the 'Hib Initiative' (see below).

Funding of immunization programs

National governments in all countries have primary responsibility to assure the sustainable financing of their national immunization program. However, as routine immunization coverage has not improved or fallen in many low-income countries, and newer vaccines remain out of reach for those children in greatest need, consensus has grown that equal access to vaccines should be considered as a 'global public good', and that financing of immunization, particularly for the poorest countries, should be a joint global responsibility.

While self-sufficiency remains the ultimate goal, the GAVI works with countries towards increasing the financial sustainability of immunization programs, as measured by a country's ability to mobilize both domestic and external funding on a reliable basis, and to use funds efficiently to achieve immunization targets. This is accomplished by strengthening national capacity for financial planning within the immunization program and the Ministry of Health, by committing increased national budget allocations for vaccines, and by using the existing Interagency Coordinating Committees (ICCs) for immunization to ensure adequate and appropriate donor support to the government.

The GAVI channels resources to a country's immunization programs through the GAVI Fund (formerly The Vaccine Fund). While the GAVI Board sets the policies for selecting which countries and programs may access GAVI Fund resources, the GAVI Fund manages existing funds and raises new financial resources, and channels them to developing countries' health systems. The support provided by the GAVI to date – in the form of multi-year grants to countries to support immunization services, new and under-used vaccines and injection safety – has been critical in many developing countries. Grants are made based on a strict application process in which country proposals are reviewed by a panel of independent experts drawn from a wide geographic and technical base.

As of April 2006, a total of almost US$ 3.3 billion has been raised in traditional funding from government and private sources, including US$ 1.7 billion actually received. Of this amount, US$ 1.5 billion has been committed to directly support countries, with US$ 603 million disbursed.

In addition, France, Italy, Spain, the United Kingdom, Sweden, Norway, Brazil, South Africa and other countries have recently committed nearly US$ 4 billion to immunization over the next decade, using an innovative new mechanism called the 'International Finance Facility for Immunization (IFFIm)'. By borrowing against commitments made by the donors, the IFFIm will raise funds, which will be disbursed through the GAVI Fund.

Within Phase 1 of GAVI support, 75 low-income countries (with a per capita gross national income of less than US$ 1000 per year) have received support. The resources that have been received have been used to help to (a) strengthen healthcare delivery systems, (b) boost coverage with established vaccines (against diphtheria, tetanus, pertussis, TB, measles and polio), (c) introduce under-used vaccines where needed (hepB, Hib and yellow fever); (d) ensure immunization safety, and (e) accelerate the development of, and affordable access to, priority new vaccines for developing countries (e.g., against rotavirus, pneumococcal disease and meningitis types A and C). Approximately two thirds of the resources received by GAVI-eligible countries are used to purchase vaccines and supplies, while one third supports capacity strengthening and infrastructure.

In Phase 2 of GAVI support starting in 2006, 72 countries are eligible to receive help, and further areas of country support are initiated. Countries will be able to apply for funding support to reduce health system barriers to improved primary health care and vaccination programs, thereby addressing fundamental barriers to improved vaccination coverage and program efficiency. In addition to HepB, Hib and yellow fever vaccines, it is anticipated that the GAVI will provide support to the introduction of further new vaccines, after having considered their investment potential through an investment case process. Both conjugate pneumococcal and rotavirus vaccines are expected to gain support from GAVI, followed in future by other, newer vaccines as they become available for general use.

In addition to the support directly to countries, the GAVI provides funding for specific research projects or areas of agency support through its workplan. Thus, areas such as vaccine management, healthcare waste management and coverage reporting quality improvement are supported by GAVI.

It will be critical for the international immunization partners to continue to secure and sustain financing for immunization, including through long-term commitments by existing public and private funding entities and new long-term financial mechanisms, to support research, development, production and use of new vaccines.

Brief updates on priority current, under-used and new vaccines

While several existing vaccines, such as those against Hib, yellow fever, influenza, pneumococcus, Japanese encephalitis and rubella, are readily

Table 3. Current and future vaccines and supportive technologies.

Current vaccines	New or improved vaccines anticipated by 2015
• BCG [a]	• Dengue [d]
• Cholera (inactivated and live) [b]	• DTaP (with two P antigens) [d]
• DTP and DTP-based combinations [a]	• Enterotoxigenic *Escherichia coli* (ETEC) [d]
• *Haemophilus influenzae* type b [a]	• Group A streptococcus [d]
• Hepatitis A [a]	• Human papilloma virus [c]
• Hepatitis B [a]	• Influenza for pandemic response
• Influenza [a]	• Japanese encephalitis (improved) [c]
• Japanese encephalitis (inactivated and live) [b]	• Malaria [d]
• Measles [a]	• Measles (aerosol) [c]
• Meningococcus (polysaccharide and conjugate) [a]	• Meningococcus A (multi-serotype conjugate) [c]
• Mumps [a]	• New combinations of existing vaccines [d]
• Pneumococcus (polysaccharide and conjugate) [a]	• Pneumococcus (improved conjugate or protein-based) [c]
• Polio (OPV and IPV) [a]	• Polio (inactivated vaccines based on Sabin strains) [c]
• Pseudomonas [b]	• Polio (monovalent OPV type 1) [d]
• Rabies [b]	• Respiratory syncytial virus [d]
• Rift Valley fever [b]	• Rotavirus [c]
• Rubella [a]	• Severe acute respiratory syndrome (SARS) [d]
• Tetanus toxoid [a]	• Shigella [d]
• Tick-borne encephalitis [b]	• Typhoid (conjugate) [d]
• Typhoid [b]	• West Nile fever [d]
• Varicella [a]	
• Yellow fever [a]	
Available but underused immunization supportive technologies	**New immunization supportive technologies anticipated by 2015**
• Pre-filled injection devices	• Jet injectors
• Vaccine vial monitors on all vaccines	• Thermostable vaccines
	• Vaccine aerosols
	• Vaccine nasal sprays
	• Vaccine patches
[a] *Available for immediate use in routine immunization.*	[c] *In a late stage of development.*
[b] *Available for specific regions or circumstances.*	[d] *Licensing expected in 2010–2015.*

from [8].

available but under-used, new vaccines against rotavirus, certain pneumococcal serotypes targeted with conjugate vaccines, meningococcus and HPV have recently been licensed and are gradually being introduced in high-income countries. At the same time, research on vaccines against major infectious diseases such as malaria, HIV/AIDS, TB and pandemic influenza is underway, as well as against some 'orphan' infectious disease, including leishmaniasis and hookworm infestation (see Tab. 3). The following short summaries provide updates on the most important current, under-used and new priority vaccines.[10]

10 Please note that rotavirus disease and rotavirus vaccines are described in the chapter by Dr. Steele of this volume.

Poliomyelitis: progress towards eradication

Following significant progress towards interrupting wild poliovirus transmission in the Americas, all Member States of WHO passed a resolution in 1988 to eradicate polio globally by the year 2000 [55]. The global eradication initiative is based on implementing the following main strategies: (a) to maintain the highest possible routine infant immunization coverage against polio, (b) to conduct large-scale SIAs[11] with OPV over a few days, using house-to-house vaccine delivery, and targeting children aged < 5 years, regardless of previous immunization status, and (c) to detect circulating wild poliovirus through maintaining high-quality surveillance for all cases of acute onset flaccid paralysis in children < 15 years in all countries, with stool specimen collection and laboratory testing for wild poliovirus [56].

While the initial goal of global eradication by the year 2000 was not met, progress has been extraordinary nevertheless. Supported by an international polio eradication partnership spearheaded by Rotary International, WHO, UNICEF and the U.S. CDC, and involving millions of health workers and volunteers, the number of polio-endemic countries[12] was reduced from >125 in 1988 to only 4 during 2005: Nigeria, India, Pakistan and Afghanistan. Three WHO Regions have already been certified free of indigenous wild poliovirus: the Americas (Western Hemisphere), Western Pacific and European Region, which together encompass 134 countries and territories, with more than 3 billion total population.

The transmission of type 2 wild poliovirus, which was last found in 1999, has been interrupted globally [57]. Type 3 wild poliovirus transmission is now restricted to small foci in northern Nigeria and northern India, and a joint virus reservoir between southern Afghanistan and central Pakistan. Monovalent OPVs (types 1 and 3), which result in significantly higher type-specific seroconversion rates compared to trivalent vaccine, were re-licensed in 2005. Monovalent OPV1 has been extensively used in both endemic countries and those affected by outbreaks, and was critical in stopping indigenous transmission in Egypt. Use of monovalent OPV3 has begun in high-risk areas of northern India, and monovalent OPV3 will be used in the other remaining type 3 wild virus foci.

Since 2003, virus exported from the remaining endemic areas, mainly from Nigeria, re-infected 25 previously polio-free African and Asian countries and resulted in several major outbreaks. However, transmission and outbreaks following importation dating back to 2003–2004 have stopped, and outbreaks beginning in 2005 are resolving. New importations and outbreaks in 2006 – Bangladesh, Democratic Republic of Congo, Namibia – were detected

11 SIAs are conducted either at the national, 'National Immunization Days (NIDs)', or subnational level, 'sub-NIDs'.

12 Countries where circulation of indigenous wild poliovirus has never been interrupted

early and are likely to be contained rapidly, because response activities were initiated more timely than for the 2003–2005 series of outbreaks.

It has now been recognized that SABIN-strain polioviruses have the potential to both revert to neurovirulence and start to circulate, particularly in areas with low population immunity [58]. Since 1999, six polio outbreaks caused by circulating vaccine-derived polioviruses have been recorded, which were all rapidly controlled with SIAs using OPV.

The highest priority for the global polio initiative in 2006 is to urgently interrupt virus transmission in the remaining endemic countries, where intensified eradication activities continue, including large-scale SIAs with monovalent OPV1 or trivalent OPV, depending on the epidemiological situation, every 6–8 weeks throughout the year. With continued high frequency of SIAs in the polio-affected countries, active or 'silent' refusals have become an issue negatively impacting on the quality of campaigns in some population groups. To ensure community acceptance and compliance, social mobilization and communication activities have become critical to the success of SIAs, and will be a key priority in 2006. Community awareness of the risks of wild poliovirus transmission needs to improve, including the public's understanding of the need for repeated campaigns and of the benefits of multiple doses of OPV for children. Continuing and worsening conflict situations in parts of Afghanistan and Somalia have become a serious impediment to interrupting transmission in these areas, since very limited or no access to the affected areas makes it very difficult or even impossible to vaccinate children. While progress in Asia, particularly in Pakistan and India, continues, Nigeria, particularly in ten states in northern Nigeria where SIAs continue to miss >40% of target children, remains the single greatest threat to global polio eradication through possible renewed international spread of wild polioviruses.

Measles: progress towards mortality reduction and elimination

Despite the availability of measles vaccination for over 40 years, an estimated >30 million cases of measles, with >500 000 deaths from measles, occurred among children aged <5 years in 2002. In many communities in measles-endemic areas, the protective effects of the vaccine are well-known and the vaccine is in high demand. However, throughout the 1990s, reported global routine immunization coverage with measles vaccine was only about 70%. In developing countries with the goal of measles mortality reduction, measles vaccine should be given at 9 months of age. In these settings, the measles dose is given more than 6 months after the last EPI contact, and drop-out rates may be high.

Based on criteria for the feasibility of global disease eradication, after polio, measles was the next disease singled out for regional elimination and possible eradication within the next 10–15 years [59, 60]. Four WHO

Regions have established regional measles elimination goals: the Americas (by 2000), European Region (by 2010), Eastern Mediterranean Region (by 2010), and Western Pacific Region (by 2012) [61]. The regional measles elimination initiatives are part of a global initiative to achieve measles elimination in the four Regions as planned, and to reduce measles mortality by 50% by 2005, compared with the 1999 level. This latter target has been achieved [61a] as a result of efforts in high-measles-burden countries, with the support of the 'Measles Partnership'. Global measles control is based on four main strategies [62]:

– achieving high routine immunization coverage with measles vaccine given at 9 months of age
– providing a 'second opportunity' for measles vaccination either through the routine immunization program or measles SIAs targeting the age group in which most susceptibles have accumulated, both to increase the chance that children not vaccinated before now get a dose of measles vaccine, and to allow children who did not sero-convert to the first dose to gain immunity
– establishing an effective system to monitor coverage and conduct measles surveillance with integration of epidemiological and laboratory information
– improving clinical management of every measles case, e.g., administering Vitamin A.

Following the initial large catch-up campaign, follow-up measles SIAs are conducted at regular intervals (e.g., every 3–5 years), targeting children born since the initial catch-up campaign. On the basis of well-planned and intense implementation of these strategies in all countries, the last measles case from endemic transmission in the Americas, which was also the first WHO Region to interrupt transmission of indigenous wild poliovirus, occurred in November 2002 [63].

Maternal and neonatal tetanus: progress towards elimination

Since WHO in 1989 called for global elimination of MNT,[13] the estimated number of deaths from NT, a disease almost exclusively linked to poverty, was reduced from an estimated 800 000 worldwide in the 1980s to 180 000 in 2002. Despite this impressive progress, the goal of eliminating MNT by 2005 has not yet been achieved. While MNT has been essentially eliminated in the Americas and northern Africa [64] as of end-2005, 49 countries remained that were considered as not having eliminated MNT, including large countries like China, India and Nigeria [65]. Main reasons for missing the global elimination goal are continued relatively low TT coverage of

13 <1 NT case per 1000 live births at district level.

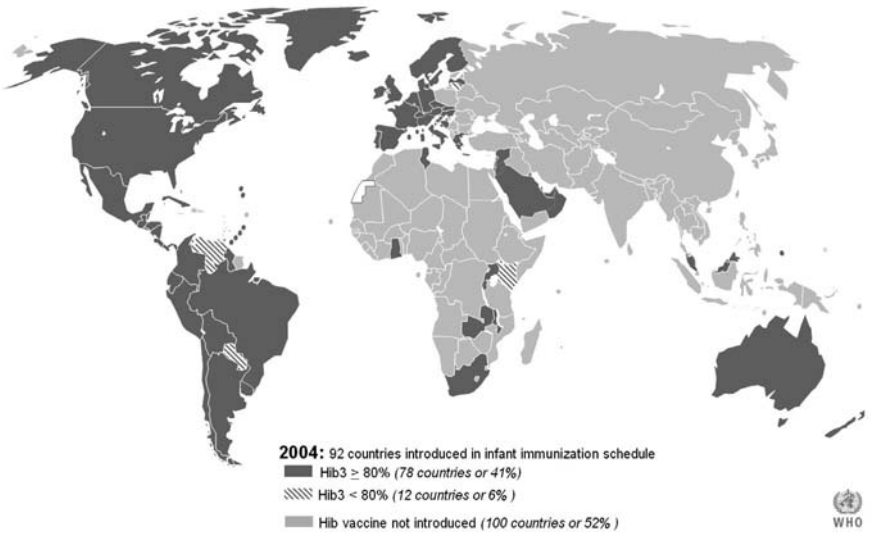


Figure 5. Countries using Hib vaccine in routine immunization program, by Hib vaccine coverage, 2004. Source: WHO/UNICEF estimates, 2005

pregnant and child-bearing age women: opportunities to vaccinate pregnant women visiting antenatal clinics or other health centers offering immunization are frequently missed. Also, in many developing countries, mothers continue to deliver under unhygienic circumstances.

To overcome the rather slow progress towards MNT elimination, a "high-risk approach" has been introduced, which targets all women of child-bearing age in high-risk areas using campaign-style immunization (SIAs) with three doses of TT (or Td) with an interval of at least 4 weeks between doses 1 and 2, and of at least 6 months between doses 2 and 3. Promotion of clean deliveries is also part of this approach. Between 1999 and 2005, approximately 64 million women worldwide received at least two doses of TT through this strategy.

Haemophilus influenzae *type B vaccine*

Wherever thorough studies have been performed, Hib has been shown to be an important cause of childhood meningitis and a major cause of bacterial pneumonia in children. Although little population-based incidence data are available from most of Asia and the newly independent States of the former Soviet Union, Hib is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths globally, each year. The most

important manifestations of Hib disease, pneumonia and meningitis, are seen mainly in children < 5 years of age, particularly infants.

Several different Hib conjugate vaccines are available, which are all highly effective. Their use has virtually eliminated invasive Hib disease from much of the industrialized world, and from The Gambia [66, 67]. In vaccine efficacy trials and case-control studies in Africa and Latin America, Hib vaccine reduced the incidence of overall pneumonia [68]; in Indonesia, the vaccine protected against invasive Hib disease but not against pneumonia [69].

In 1998, WHO recommended that Hib vaccine should be included in routine infant immunization, as appropriate to national capacities and priorities. More recently, the WHO Immunization Strategic Advisory Group of Experts (SAGE) recommended global implementation of Hib vaccination unless robust evidence exists of low disease burden or overwhelming impediments to implementation [70]. Hib conjugate vaccines have now been introduced in 92 countries worldwide (Fig. 5); however, most of these countries are high- or middle-income countries of Western Europe, the Americas, and the Middle East. In Asia and Africa, lack of disease burden data, lower disease burden (Asia) and relatively high vaccine cost ($ 2.50 per dose) has so far impeded the introduction of Hib vaccine into routine immunization programs.

With a grant from the GAVI, the Hib Initiative[14], a global consortium of academic and public health experts, works on evidence-based decision making regarding the use of the Hib vaccine at the country level. The Hib Initiative provides a focus on national-level decisions about vaccination through strategic coordination among partners and donors, support for studies to measure disease burden, and advocacy for Hib vaccine introduction. GAVI funds Hib vaccine introduction in several African countries in Africa, and will expand this support to additional eligible countries.

Where the disease burden is unclear, the Hib Initiative is collaborating with governments and researchers to further define the scope of the disease. One example of such a project is a collaborative research among the Indian government and local researchers in three sites to define the burden of Hib disease in India. It is expected that this project will help support decisions on Hib vaccination programs throughout South Asia.

To support local surveillance capacity for bacterial vaccine-preventable diseases, WHO has established a network of laboratories to assist in diagnosing and confirming bacterial meningitis in children. In many areas, these regional bacteriological laboratory networks for meningitis are now expanding their capacity to perform blood cultures in anticipation of the surveillance needs associated with newer vaccines such as pneumococcal vaccines.

14 http://www.hibaction.org/about.html

Hepatitis B vaccine

Even though safe and efficacious vaccines have been available for more than 20 years, HepB infection remains a significant public health problem globally, and is second only to tobacco as a recognized cause of a major cancer in humans. The majority of infections and chronic HBV surface antigen (HBsAg) carriers are caused by vertical (mother-to-child) and horizontal (child-to-child) transmission. While rarely causing acute hepatitis in young children, 90% of those infected perinatally and 30% infected in early childhood will become long-term HBsAg carriers, at high risk for chronic liver disease and liver cancer. An estimated 600 000 deaths every year are attributed to chronic HBV infection and its serious consequences, including liver cirrhosis and hepatocellular cancer [71].

HepB vaccine is considered to be very cost effective in endemic countries [71]. The vaccine was found to be highly effective in reducing carrier rates from >8% to <2% in immunized groups of children in a number of countries, including The Gambia, Hong Kong (SAR), Singapore, Taiwan (China), and Alaska [72]. The incidence of hepatocellular carcinoma in children of 10–14 years of age in Taiwan fell significantly 10 years after a universal infant HepB vaccine program was initiated [73].

The World Health Assembly recommended in 1992 that all countries should integrate HepB vaccine into their routine infant immunization programs by 1997. High coverage with the primary vaccine series among infants has the greatest overall impact on the prevalence of chronic HBV infection in children and should be the highest HBV-related priority. Lack of awareness of the link between early infection and delayed serious morbidity and mortality in adults [74] has been one of the reasons for the delayed introduction of the vaccine into infant immunization programs around the world.

Different schedules are used for HepB immunization in national programs, depending on the local epidemiological situation and programmatic considerations (see Tab. 1). In countries where a high proportion of HBV infections are acquired perinatally, the first dose of HepB vaccine should be given as soon as possible (<24 h) after birth. In countries where a lower proportion of HBV infections are acquired perinatally, the relative contribution of perinatal HBV infection to the overall disease burden, and the feasibility and cost effectiveness of providing vaccination at birth, should be carefully considered before a decision is made on the optimal vaccination schedule.

Catch-up strategies targeted at older age groups or groups with risk factors for acquiring HBV infection should be considered as a supplement to routine infant vaccination in countries of intermediate or low HepB endemicity. In such settings, a substantial proportion of the disease burden may be attributable to infections acquired by older children, adolescents and adults. In all countries, large-scale routine vaccination of infants rapidly reduces the transmission of HBV.

As of 2005, 158 of 192 WHO Member States have introduced HepB vaccination in their routine infant immunization schedules. This is a sevenfold increase compared to the number of countries using this vaccine in 1990, resulting from continued global advocacy for universal infant HepB vaccination, for which disease burden data is now well established [75], and a sharp drop in the price of the vaccine, now about $0.27 per dose of single antigen vaccine, and the assistance for the purchase and delivery of HepB vaccine from the GAVI. The target of the GAVI is for all its focus countries with adequate immunization systems to introduce this vaccine into routine immunization programs by 2007. The availability of this first ‚vaccine against cancer' to the majority of the world's children will have a significant impact on long-term morbidity and mortality from chronic liver disease and hepatic cancer.

Yellow fever vaccine

Yellow fever is endemic in tropical regions of Africa and South America where 44 countries (33 in Africa and 11 in South America) are considered to be at risk. In francophone Africa, intensive preventive mass vaccination campaigns nearly eliminated yellow fever during the 1950s, but subsequently vaccine coverage waned and epidemics occurred in the 1980s. Currently, 500 million people are considered at risk for the disease in Africa. Although WHO Member States are required to report yellow fever cases under the International Health Regulations, reported data underestimate the true incidence of the disease. Studies indicate that yellow fever morbidity and mortality are underestimated by a factor of 10–500; every year, an estimated number of 200 000 cases and 30 000 deaths are estimated to occur.

Since the late 1980s, there has been a reemergence of yellow fever epidemics [76]; more than 80% of all yellow fever cases reported to the WHO were from Africa. Of the 33 "at-risk" countries in Africa, 16 reported at least one outbreak from 1980 to 1999. During the period 2000–2004 alone, 16 countries reported one or more outbreaks, with a total of 1927 cases and 425 deaths reported.

Yellow fever control strategies include preventive vaccination (routine and supplementary mass campaigns), case-based surveillance with laboratory confirmation and rapid vaccination response in the event of an outbreak. The most cost-effective approach is to incorporate yellow fever vaccine in the routine national immunization program. This will prevent more yellow fever cases and deaths than emergency vaccination responding to outbreaks. The World Bank's 1993 Development Report [77] strongly endorsed adding yellow fever vaccine to national immunization programs of at-risk countries. A study in Nigeria [78] estimated that the cost of routinely providing yellow fever vaccine through the national program would be about US$0.65 per

fully immunized child. The cost of emergency vaccination would be much higher, about US$7.84 per person.

All countries at risk in the Americas, and 22 of the 33 African countries have included the vaccine in their routine immunization program. However, coverage is generally poor in Africa, lagging behind measles vaccine coverage, even though both vaccines are supposed to be given at the same visit. Routine coverage improved in many countries once GAVI began in 2000 to support routine yellow fever vaccination in GAVI-eligible countries at risk for yellow fever. In 2002, the GAVI Board accepted to fund a 6 million-dose vaccine stockpile for outbreak response and preventive campaigns (SIAs) to reduce the number of susceptibles in wide age groups; these SIAs began in some countries in 2004. Yellow fever case-based surveillance was set up in 15 of 33 African countries at risk, and a laboratory network consisting of 22 laboratories was established. Most of these laboratories currently test samples and report to WHO.

Although much progress has been achieved in yellow fever control in Africa, a large proportion of the population remains susceptible in countries at-risk, creating the potential for future outbreaks, which could be particularly explosive if they occur in urban areas. Advocacy and further resource mobilization are urgently needed to accelerate the progress made thus far in achieving yellow fever control.

Pneumococcal vaccines

Streptococcus pneumonia or pneumococcus (Pnc), is considered as one of the major bacterial pathogens causing a multitude of childhood infections [79]. The spread of HIV infection has increased the incidence of Pnc disease, especially in many resource-poor countries where anti-HIV treatment is not readily available. Children infected with HIV/AIDS are 20–40 times more likely to contract Pnc disease than those without HIV/AIDS [80]. According to WHO more than 1.6 million people die every year from Pnc infections – primarily pneumonia and meningitis – including more than 800 000 children <5 years old; 40% of all acute lower respiratory tract infection, and 35% of all meningitis in children is caused by Pnc. For each invasive, potentially deadly Pnc infection, there are from 10- to over 100-fold milder clinical infections caused by Pnc.

Pnc disease can be prevented by (a) direct protective effect of the vaccine on vaccinated individuals (both Pnc polysaccharide vaccine, PPV, and Pnc conjugate vaccine, PCV) and/or (b) indirect protective effect *via* reduced transmission of the pathogen to susceptible, nonvaccinated individuals (PCV only, since the mucosal protection provided by PPV is insignificant).

The 23-valent PPV is recommended and used mostly in high-risk group children >2 years of age since the vaccine is poorly immunogenic in younger

children [81]. To date, four different types of PCVs have been developed for large-scale clinical trials. They consist of different selection of Pnc serotypes ranging from 7 to 11, and different carrier proteins. All are immunogenic and safe on individual level. So far only the 7-valent PCV with mutant diphtheria toxoid as carrier protein has been licensed (in 76 countries by early 2007), but formally introduced into immunization programs in only 15 countries. The public health impact of the vaccine has been unexpectedly high: in the U.S., where the 7-valent conjugate vaccine has been used in the national program for children since 2000, over two thirds of the impact of the vaccine is obtained *via* the indirect herd effect, and is seen as a significant reduction in invasive Pnc disease in adults [82, 83]. Recent cost-effectiveness estimations have shown that life years across ages can now be gained at much lower cost [84], compared to earlier estimates [85].

The public health benefit arising from both the direct and indirect effects is further enforced by the reduction of the incidence of vaccine-preventable Pnc strains resistant to antimicrobials [86]. A Phase III trial of a 9-valent Pnc conjugate vaccine in the Gambia unexpectedly showed that overall, all-cause mortality in study children was decreased by 16% [87], indicating that Pnc vaccines may eventually become powerful tools with impact on overall global childhood morbidity and mortality.

The limiting factor turning countries away from introducing PCV into national childhood programs both in rich and resource-poor countries has been the inhibitive cost of the vaccine. This, coupled with the underestimation of both overall Pnc disease burden and lack of understanding of the potential of the herd impact, has meant that so far (by early 2007) only 16 countries have included Pnc vaccine into routine immunization programs. GAVI currently supports efforts towards the early introduction of Pnc conjugate vaccine in three developing countries: Bangladesh, the Gambia and Kenya [88].

Meningococcal vaccines

Neisseria meningitidis, or meningococcus, causes serious bacteremic disease globally. In the so-called meningitis belt of sub-Saharan Africa, large epidemics occur every 5–10 years. Asymptomatic carriage of meningococcus is very common during times when outbreaks occur, while symptomatic disease caused by meningococcus mostly manifests as rapidly advancing meningitis and sepsis with high case fatality rate and approximately 20% of surviving cases developing neurological sequelae. Serotypes and groups (A, B, C, W, Y) causing meningococcal disease vary by geographic location and time. While responsible for most meningococcal disease in sub-Saharan Africa, group A meningococcus has been almost non-existent in Europe and the U.S. for over 50 years. In Europe overall, approximately two thirds of the reported cases have been caused by serogroup B, about one third by serogroup C,

with a small number of cases caused by serogroups Y, W-135, or A [89]. In several European countries (United Kingdom, Ireland, Spain, Netherlands, Germany) where serogroup C has reached relatively high levels, a new monovalent meningococcal C conjugate vaccine was introduced on a nation-wide scale, targeting young children and teenagers (catch-up vaccination), which rapidly changed the epidemiology of the disease during this decade.

Since the licensure of the new 4-valent meningococcal conjugate vaccine in the U.S. in 2005, this vaccine is now recommended for prevention of meningococcal infection in pre-teens, adolescents and high-risk adults. This recommendation is largely based on newer epidemiological data showing a considerable risk of meningococcal disease in late adolescence, most of which is preventable with vaccine [90, 91]. In other high-income countries, the older meningococcal polysaccharide vaccine, composed of capsular polysaccharide, is still recommended to children from 2 to 10 years of age, and to travelers to endemic or epidemic areas.

In developing countries struggling with outbreaks and the changing serogroup profile of meningococcus, the polysaccharide vaccine has remained the cheapest alternative, although it does not protect the very young. It is bought in significant amounts annually. An important Meningitis Vaccine Project was launched in 2001 under the auspices of GAVI, WHO, the Gates Foundation and Program for Applied Technology in Health (PATH) to develop a bivalent A and C group conjugate vaccine for the endemic countries with direct African country involvement in the development work. A two-pronged vaccine introduction strategy is envisioned: (1) one-dose mass vaccination campaigns with a group A containing meningococcal conjugate vaccine for 1–30 year olds, and (2) routine infant immunization with one, two or three doses of meningococcal conjugate vaccines integrated with routine EPI schedules. The project includes clinical evaluation (sites, protocols) of meningococcal conjugate vaccines ("MenAfriVac") as well as licensing strategies, which need to be adapted to both routine and mass vaccination strategies. The Phase I study was carried out in India, i.e., the country of production, and the Phase II studies will start in latter part of year 2006 in Mali and the Gambia. Following licensure, two or more countries will be chosen for initial introduction of conjugate vaccine. Discussions held with the WHO AFRO, African health ministries and other African representatives have highlighted the need to select countries based on specific criteria, for example, burden of meningococcal disease, epidemiological and laboratory capacity, capacity for vaccine delivery, and status of other vaccination efforts (i.e., polio eradication, measles elimination).

Human papillomavirus vaccine

Cervical cancer is the leading cause of cancer mortality among women in developing countries. Approximately 500 000 new cervical cancer cases are

estimated to occur annually, leading to about 250 000 deaths each year [92]. Over 99% of cervical cancer cases are linked to genital infection with HPV, which is the most common viral infection of the reproductive tract worldwide [93] and infects an estimated 660 million people annually. The most prevalent oncogenic HPV strains associated with cervical cancer is HPV type 16, but types 18, 45, 33 and 31 have also been identified. HPV types 16 and 18 account for 65–70% of cervical cancers globally, although the proportion varies in different regions. The burden of disease attributable to HPV infection is, however, not limited to cervical cancer, but includes an even greater proportion of pre-malignant cervical lesions, as well as anal, penile and other reproductive system cancers. Additionally, low-risk HPV types, such as 6 and 11 are responsible for 90% of genital warts or condylomas.

While HPV infection resolves spontaneously in the majority of people, it can develop into chronic infection which, in some women and if not treated, may progress to cervical cancer. The peak incidence of HPV infection occurs in adolescents and young women, while cervical cancer typically follows 20–30 years later. The disease represents a major health inequity, as 80% of cervical cancer deaths occur in developing countries [94], where pelvic examination and treatment of pre-cancerous lesions is often not available. Industrialized countries have greatly reduced deaths from cervical cancer through screening programs that allow early detection and treatment. Secondary prevention programs for cervical cancer exist in developing countries, but are mostly under-funded and sub-optimally managed; they have not resulted in the profound reductions in cervical cancer morbidity and mortality observed in the industrialized countries of Europe and North America.

The definitive identification of certain types of HPVs as the etiological agents in cervical carcinogenesis led to the rapid development of HPV vaccines [95], and their subsequent testing in human populations with excellent results. To date, sub-unit bivalent (types 16 and 18) and quadrivalent (types 6, 11, 16, and 18) HPV vaccines have been developed and found to be highly immunogenic. They elicit significant humoral and robust cell-mediated immune responses at levels higher than those observed in naturally acquired infections. These vaccines are also highly efficacious in preventing persistent type-specific infections as well as associated cervical cytological abnormalities and pre-cancerous lesions.

Because HPV is spread by sexual contact, and the high-risk years for infection are roughly from ages 18 to 25, the best subjects for vaccination are thought to be pre-adolescents or adolescents. The first HPV vaccine licensed in the USA in mid-2006 was a quadrivalent vaccine,[15] which has already been recommended for routine use for girls and women aged 11–26 years of age by the U.S. Advisory Committee on Immunization Practices (ACIP).

15 Gardasil® by Merck

The introduction of HPV vaccine constitutes an effective new strategy to reduce morbidity and mortality from cervical cancer, but will not replace screening and early treatment. Also, while there has been considerable recent progress in vaccine development, the natural history of HPV and cervical cancer and geographic variations in the type-specific prevalence of HPV present unique challenges related to the introduction and acceptance of HPV vaccines. It will not be easy to communicate the public health benefit of preventing a very common, albeit usually harmless, sexually transmitted infection that has only a remote possibility many years in the future of progressing to cervical cancer. The impact of a vaccine, particularly if administered to young adolescents, will not be measurable for decades to come – the amount of time it would take for girls to reach an age when they might otherwise have developed cancer. Socio-cultural issues regarding the vaccination of pre-adolescent and adolescent with HPV vaccine will need to be addressed with great sensitivity. Studies are under way to prepare for HPV vaccine use in developing countries, particularly to find out which socio-cultural factors will determine vaccine acceptance and reaching sufficient coverage. Guidelines on HPV vaccine use need to be developed through an integrated approach with adolescent health, reproductive health and cancer control programs at national and international levels.

Other new vaccines under development

There are several other new vaccine antigens in different preclinical and clinical phases of development, which, if successful and eventually implemented in national programs, will have a major impact on public health globally. These include vaccines against malaria, HIV, and TB, as well as against dengue fever, schistosoma, different enteric pathogens, *Streptococcus* A and others. The three most urgently needed vaccines today are vaccines to prevent HIV/AIDS, TB and malaria. Together, these three diseases account for over 5 million deaths worldwide each year, about half of all deaths from infectious diseases. There is no effective vaccine against HIV/AIDS or malaria. The existing widely used TB vaccine (BCG) offers only limited protection against childhood forms of the disease.

Safe and cost-effective vaccines against each of these diseases would prevent millions of deaths every year and help countries in their social and economic recovery. They would also help lower the increasing threat of antimicrobial resistance to existing treatments in the worst-affected countries. However, current levels of investment in vaccine research and development do not reflect the magnitude of the threat that these diseases pose to this and future generations. Although HIV/AIDS and TB also occur in the developed countries (albeit at a much lower level) and a malaria vaccine would be useful for the expanding travelers' market, most of the vaccine sales would be in the developing world. The uncertain demand for new

vaccines in developing countries has deterred vaccine manufacturers from long-term investment in the development of vaccines against HIV/AIDS, malaria and TB, which remain three of the most scientifically challenging vaccines ever investigated.

Several formidable scientific obstacles have so far have prevented these much-needed vaccines reaching licensure and large-scale production. The pathogen may be so variable that it has the potential to escape vaccine-induced protection within a short period of time (malaria, HIV). For other diseases, such as dengue virus, the pathogenic mechanism of the disease or the protective antigenic epitope may not be known to the level of detail needed.

The status of development of new vaccines against TB can illustrate the hurdles of new vaccine development in general. The existing BCG vaccine is the most frequently used vaccine worldwide, is low in cost, and protects infants against severe forms of disease, such as TB meningitis and miliary TB. However, the efficacy of BCG against pulmonary forms of disease is variable [96]. Genomic sequencing of *Mycobacterium tuberculosis* has opened the way towards a more rational approach to screening for antigens with protective capacity against TB. Promising approaches to TB vaccine development include protein subunit vaccines, DNA vaccines expressing protective *M. tuberculosis* genes, rationally attenuated live *M. tuberculosis* vaccines and modifications to BCG to boost its immunogenic properties. New live mycobacterial vaccines will benefit from the experience with BCG and BCG production; candidate vaccines are likely to have both good priming and initial protection. Like BCG, they also are expected to provide an adjuvant effect for other vaccines given at the same time. The main issues with new live mycobacterial vaccines relate to quality control and mutant stability. These new vaccines will have to be as safe as BCG, but at the same time significantly more efficacious, which will make it difficult to assess them clinically.

The new subunit vaccine candidates, on the other hand, have better stability, are likely to be good for boosting rather than priming, and could be combined with other vaccines. Main concerns for sub-unit vaccines are that repeated use of the same vectors (such as MVA-antigen 85A) may decrease their efficacy, and adjuvants may be needed to obtain the protective effect, which will most likely increase cost. There is also some concern about risk of enhancement of pathology. The most effective future TB vaccination strategy may be to combine different vaccine candidates, using a prime-boost approach, as described in a recent comprehensive review [97] of 'state of the art' and future perspectives of TB vaccine development.

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