State of the world's vaccines and immunization

Third edition

World Health Organization
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THE WORLD BANK

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This book is dedicated to all those individuals who work tirelessly to improve and save lives through vaccines and immunization.

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CORRIGENDA

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Please note the following:

Page 38:

Innovative regulatory pathways

Traditionally, when a national regulatory authority in a developing country considers whether to host clinical trials of a new vaccine produced in another country, or whether to adopt a new vaccine in its country's immunization programme, it would be favourably influenced if the vaccine had been approved for human use by the European Medicines Agency or the FDA. However, in 2004 and 2007, respectively, both agencies decided to no longer accept vaccines for marketing approval where they are intended for use exclusively outside their geographical jurisdictions. This decision raised a fear that the supply of new life-saving vaccines to developing countries may be hindered or delayed for lack of authoritative marketing approval.

In 2005, therefore, the European Medicines Agency introduced a mechanism, known as "Article 58", whereby it issues a "scientific opinion" based on the customary Agency process but with the addition of an evaluation of the vaccine by WHO-appointed experts from countries where the vaccine is intended to be used. This mechanism, although stopping short of formally granting a licence, involves all the steps of a regular licensing procedure. It carries enough weight to allay fears that vaccines may be introduced without having been assessed for safety and quality. Moreover, the FDA and the European Medicines Agency have agreed to work with national regulatory authorities or with networks of regulators in the regions, to provide advice on vaccine safety and efficacy as well as on clinical trial protocols. Similar collaborative agreements are being forged in other parts of the world, notably in Asia.

should read:

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Traditionally, when a national regulatory authority in a developing country considers whether to adopt a new vaccine in its country's immunization programme, it would be favourably influenced if the vaccine had been approved for human use by the European Medicines Agency (EMEA) or the FDA. However, in 2004, the EMEA decided to no longer issue marketing authorization for vaccines intended exclusively for use outside the European Union. This decision raised a fear that the supply of new life-saving vaccines to developing countries may be hindered or delayed for lack of authoritative marketing approval.

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Pages 49-50

By mid-2005, 53 countries, mostly in Africa and Asia, had begun implementing the RED strategy to varying degrees (see Fig. 6) (*32*). In 2005, an evaluation of five countries in Africa that had implemented RED found that the proportion of districts with over 80% of children fully immunized with DTP vaccine had more than doubled (*33*). More recently, a nine-country evaluation carried out by the CDC in 2007 found that the RED strategy had been adopted by 90% of all districts within these countries.

However, few of the nine countries were implementing all five components of the strategy (see Box 11). The CDC evaluation noted that further studies would be needed over a longer period to assess the effectiveness and sustainability of the strategy.

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The search for a safer, more effective cholera vaccine produced three new-generation vaccines, of which only one is available for widespread use today. This vaccine, first licensed in Argentina in 1997 and code-named WC/rBS, is made from the whole-cell *V. cholerae* linked to a genetically engineered (recombinant) fragment (B-subunit) of the cholera toxin.

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These observations have prompted countries where diphtheria is no longer endemic to extend vaccination protection beyond the primary three-dose series for infants by administering one, or sometimes two, booster doses every 10 years to adults through the diphtheria-tetanus (dT – low content of diphtheria) combination vaccine (*67*).

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Notwithstanding clear evidence of the vaccine's efficacy, by 1997 only 29 countries were using it routinely, prompting WHO to recommend its inclusion in the routine immunization programmes of *all* countries where Hib was recognized as a public health burden and where the cost of the vaccine was not prohibitive (*70*).

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At the present time, therefore, there are no compelling reasons for recommending a fourth dose of vaccine outside of the routine immunization programme.

should read:

At the present time, therefore, there are no compelling reasons for recommending a systematic booster dose.

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To date, there are no licensed vaccines against the group B meningococcus, but several vaccine manufacturers have products that are being evaluated clinically. For example, group B vaccines that have been custom-made against specific epidemic strains have been successfully used to control specific outbreaks in Brazil, Chile, Cuba, France, New Zealand, and Norway.

should read:

To date, there are few licensed vaccines against the group B meningococcus. Those vaccines that have been available during the past years were custom-made against specific epidemic strains and have been used to control outbreaks in Brazil, Chile, Cuba, France, New Zealand, and Norway.

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Death from pertussis still occurs in industrialized countries (less than 1 per 1000 cases (111)), but more rarely than in developing countries (40 per 1000 infants, and 10 per 1000 in older children (111)).

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Third edition

Acknowledgements

Writers

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Vaccines

“With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction…” [1]

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Boxes

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Acronyms

AIDS	Acquired immunodeficiency syndrome
AMC	Advance Market Commitment
BCG	Bacille Calmette-Guérin [vaccine]
CDC	Centers for Disease Control and Prevention
cMYP	Comprehensive multi-year plan for immunization
CRS	Congenital rubella syndrome
cVDPV	Circulating vaccine-derived poliovirus
DALY	Disability-adjusted life year
DTP	Diphtheria-tetanus-pertussis [vaccine]
EPI	Expanded Programme on Immunization
FDA	United States Food and Drug Administration
GIVS	Global Immunization Vision and Strategy
GMP	Good manufacturing practice
GNI	Gross national income
GPEI	Global Polio Eradication Initiative
HAV	Hepatitis A virus
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IFFIm	International Finance Facility for Immunisation
IPV	Inactivated polio vaccine
MDG	Millennium Development Goal
MDG 1	The first Millennium Development Goal
MDG 4	The fourth Millennium Development Goal
MMR	Measles-mumps-rubella [vaccine]
MNT	Maternal and neonatal tetanus
OPV	Oral polio vaccine
PAHO	Pan American Health Organization
R&D	Research and development
RED	Reaching Every District [strategy]
SAGE	WHO Strategic Advisory Group of Experts [on Immunization]
TAT	Toxin-antitoxin
UCI	Universal child immunization
UNICEF	United Nations Children's Fund
VPPAG	Vaccine Presentation and Packaging Advisory Group
VLP	Virus-like particle
WHA	World Health Assembly
WHO	World Health Organization

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Foreword

Immunization is one of the most powerful and cost-effective of all health interventions. It prevents debilitating illness and disability, and saves millions of lives every year. It is also key to achieving the Millennium Development Goals (MDGs) – commitments made by world leaders in 2000 to reduce poverty and improve human development. The contribution of immunization is especially critical to achieving the goal to reduce deaths among children under five years old (MDG 4).

Vaccines have the power not only to save, but also to transform, lives – giving children a chance to grow up healthy, go to school, and improve their life prospects. When vaccines are combined with other health interventions – such as vitamin A supplementation, provision of deworming medicine and bednets to prevent malaria – immunization becomes a major force for child survival.

Since 2000, efforts have been scaled up to meet the MDGs and the supporting goals of the Global Immunization Vision and Strategy (GIVS), developed by WHO and UNICEF. With financial support from the GAVI Alliance and other partners, more children are being immunized than ever before – over 100 million children a year in recent years. And more vaccines are increasingly being made available to protect adolescents and adults. These include vaccines that protect against life-threatening diseases such as influenza, meningitis, and cancers that occur in adulthood.

At the same time, access to vaccines and immunization is becoming more equitable. Pneumococcal and rotavirus vaccines, now available to GAVI-eligible countries, prevent the leading causes of the two main child-killers – pneumonia and diarrhoea. Their introduction provides an opportunity to scale up the use of other interventions for the prevention and treatment of pneumonia and diarrhoea to achieve better overall disease control.

Despite the progress, more must be done to target the 24 million children, mainly in developing countries, who are proving difficult to reach with vaccines. Identifying and implementing strategies to overcome the barriers to access must be a top priority, given the right of every child to protection from preventable diseases.

Innovative funding mechanisms are being put in place to help developing countries increase immunization coverage and provide new vaccines that can save even more lives. Governments too have stepped up to the mark, with increasing spending on vaccines and immunization since the year 2000. Many governments are demonstrating strong and effective leadership and national ownership of their immunization programmes – a key requisite for ensuring the long-term sustainability of immunization investments.

These are impressive achievements. But they need to be sustained and improved. New and improved vaccines are urgently needed to prevent the unacceptable toll

of sickness and deaths from diseases such as malaria, tuberculosis, and AIDS. Continued investments are essential to ensure the breakthroughs needed in the research and development (R&D) of these next-generation vaccines.

Major efforts will be needed in the coming months and years to ensure that, during the current global financial and economic crisis, hard-won gains in immunization are protected, and the development of new vaccines that could save millions of additional lives every year does not slow down.

Experience shows that economic crises can lead to government cuts in social sector spending, a decline in international development assistance, an increase in poverty, and an upsurge in deaths among children under five years old.

This must not be allowed to happen again.

The global goals have not changed. Poverty, illness, and premature deaths have not gone away. Equity and social justice are still to be achieved. These are promises to be kept.

This report is a call to action to governments and donors to sustain and increase funding for immunization in order to build upon the progress made so far in meeting the global goals. The price of failure will be counted in children's lives.

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Executive summary

Overview

Since the Millennium Summit in 2000, immunization has moved centre stage as one of the driving forces behind efforts to meet the Millennium Development Goals (MDGs) – in particular, the goal to reduce deaths among children under five years old (MDG 4).

More children than ever before are being reached with immunization: over 100 million children a year in 2005–2007. And the benefits of immunization are increasingly being extended to adolescents and adults – providing protection against life-threatening diseases such as influenza, meningitis, and cancers that occur in adulthood.

In developing countries, more vaccines are available and more lives are being saved. For the first time in documented history the number of children dying every year has fallen below 10 million – the result of improved access to clean water and sanitation, increased immunization coverage, and the integrated delivery of essential health interventions.

More vaccines have been developed and others are already in the late stages of clinical trials, making this decade the most productive in the history of vaccine development. More money is available for immunization through innovative financing mechanisms. And more creative energy, knowledge, and technical know-how is being put to use through the development of public-private partnerships – forged to help advance the immunization-related global goals.

Yet despite extraordinary progress in immunizing more children over the past decade, in 2007, 24 million children – almost 20% of the children born each year – did not get the complete routine immunizations scheduled for their first year of life. Reaching these vulnerable children – typically in poorly-served remote rural areas, deprived urban settings, fragile states, and strife-torn regions – is essential if the MDGs are to be equitably met.

In response, a major global push is under way to ensure that these difficult-to-reach children – most of them in Africa and Asia – are immunized. At the same time, new initiatives have been launched to accelerate both the development and deployment of new life-saving vaccines.

The stakes are high. WHO has estimated that if all the vaccines now available against childhood diseases were widely adopted, and if countries could raise vaccine coverage to a global average of 90%, by 2015 an additional two million deaths a year could be prevented among children under five years old. This would have a major impact on meeting the global goal to reduce child deaths by two-thirds between 1990 and 2015 (MDG 4). It would also greatly reduce the burden of illness and disability from vaccine-preventable diseases, and contribute to improving child health and welfare, as well as reducing hospitalization costs.

But even when the global goals have been met, success will be measured against an additional benchmark – whether the achievements are sustainable. Solid building blocks are being put in place – strengthening of health systems and immunization programmes, new public-private partnerships for vaccine development and immunization, new long-term global financing mechanisms, innovative and sustainable delivery strategies, and improved advocacy and communication strategies – to ensure that long-term progress is not sacrificed for short-term gains.

In addition, continued investments will be needed to accelerate the research and development of urgently needed vaccines against diseases such as malaria, tuberculosis, and acquired immunodeficiency syndrome (AIDS), which together account for over four million deaths a year and a high burden of disease, mainly in developing countries.

This edition of the *State of the world's vaccines and immunization* focuses on the major developments in vaccines and immunization since 2000. Part 1 (Chapters 1–5) examines the impact of immunization on efforts to meet the MDGs, especially the

goal to reduce deaths among children under five. It looks at the development and use of vaccines and at the safeguards that have been put in place to ensure their safety, efficacy, and quality. It sets out the progress and challenges in meeting the immunization-related global goals, and looks at the cost of scaling up immunization coverage to meet these goals, and efforts to ensure that the achievements are sustainable in the long term. Finally, it looks beyond 2015 to likely changes in the immunization landscape.

Part 2 focuses on over 20 vaccine-preventable diseases and reviews progress since 2000 in efforts to protect populations against these diseases through the use of vaccines.

Immunization and human development

Chapter 1 outlines the progress in vaccines and immunization over the past decade against the backdrop of a changing health and development landscape.

In September 2000, leaders of more than 190 countries signed the United Nations Millennium Declaration, which committed the international community to eight development goals aimed at reducing poverty and improving human development. One of these goals calls for a massive reduction in deaths among children under five years old – a two-thirds drop in the under-five mortality rate between 1990 and 2015. Most of the effort in achieving these goals is focused on developing countries, which account for over 90% of deaths among children in this age group.

In 2005, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) published the Global Immunization Vision and Strategy (GIVS) for the decade 2006–2015. With an overriding focus on the need to ensure equity in access to vaccines and immunization, the strategy sets out the steps that the immunization community needs to take in order to contribute fully to the attainment

of the MDG mortality reduction targets. Implementing the strategy calls for four main approaches: protecting more people; introducing new vaccines and technologies; integrating immunization with other components in the health system context; and immunizing in the context of global interdependence.

The global goals have added a sense of urgency to vaccine-related activities and spurred renewed efforts to complete, as far as possible, what the GIVS refers to as "the unfinished immunization agenda". The chapters which follow chart the progress made so far in completing this agenda and in meeting the global goals.

A new chapter in vaccine development

Chapter 2 highlights the surge in vaccine development over the past decade and outlines the reasons for this. It documents the unprecedented growth in the volume of traditional childhood vaccines now being produced by manufacturers in developing countries. And it reports on progress in efforts to assure the quality, safety, and effectiveness of vaccines.

The first decade of this century has been the most productive in the history of vaccine development. New life-saving vaccines have been developed for meningococcal meningitis, rotavirus diarrhoeal disease, avian influenza caused by the H5N1 virus, pneumococcal disease, and cervical cancer caused by human papillomavirus (HPV).

The vaccine industry is experiencing a new, more dynamic period. Since the year 2000, the global vaccine market has almost tripled – reaching over US$ 17 billion in global revenue by mid-2008, and making the vaccine industry one of the fastest growing sectors of industry. Most of this expansion comes from sales in industrialized countries of newer, more costly vaccines, which account for more than half of the total value of vaccine sales worldwide.

The recent surge in new vaccine development is largely due to three key factors: the use of innovative manufacturing technology, growing support from public-private product development partnerships, and new funding resources and mechanisms (see Chapter 4).

At the same time, there has been unprecedented growth in the capacity of manufacturers in developing countries to contribute to the supply of the traditional childhood vaccines. Overall, the demand for these traditional vaccines has also grown since 2000, partly to meet the massive needs of the major initiatives put in place to eradicate polio, and reduce the burden of measles and of neonatal and maternal tetanus.

Since the early 1990s, the vaccine market has changed. Growing divergence between the vaccines used in developing and industrialized countries, a drop in the number of suppliers in industrialized countries, and a reduction in excess production capacity led to a vaccine supply crisis beginning in the late-1990s. In response, UNICEF – which procures vaccines to reach more than half (55%) of the world's children – established the Vaccine Security Strategy to ensure the uninterrupted and sustainable supply of vaccines that are both affordable and of assured quality. While the strategy succeeded in reversing the fall-off in the supply of vaccines to UNICEF, vaccine supply remains heavily reliant on a limited number of vaccine manufacturers and continued vigilance is needed.

Making sure that vaccines are safe, effective, and of good quality is a pivotal element of vaccine development and deployment. It begins with the "infancy" of the vaccine, usually in the laboratory, where its components are tested for criteria such as purity and potency. It continues with clinical testing for safety and efficacy in humans, followed, after licensure, by post-marketing testing of vaccine batches for consistency of the production process, as well as surveillance to identify any potential cases of vaccine-related adverse events.

Licensure, or approval for human use, is the most crucial step in the process. The official body that grants the licence – the *national regulatory authority* – is the arbiter of whether established standards have been met to ensure that a vaccine is of assured quality.

All industrialized countries have a reliable, properly functioning vaccine regulatory system, but only about one quarter of developing countries do. The international health community has launched a series of initiatives, spearheaded by WHO, to ensure that vaccines used in national immunization programmes are "vaccines of assured quality". The initiatives include a prequalification system established by WHO to advise UN vaccine procurement agencies on the acceptability, in principle, of vaccines available for purchase, and efforts to ensure that every country has a reliable, properly functioning national regulatory authority.

Immunization: putting vaccines to good use

Chapter 3 highlights the achievements of immunization over the past decade and reports on progress and challenges in efforts to reach more people with more vaccines, to boost immunization coverage at the district level, and to target difficult-to-reach children who have not been immunized. It also sets out some of the key elements of an effective immunization programme.

Over the past decade, immunization programmes have added new and underused vaccines to the original six – diphtheria, tetanus, pertussis, measles, polio, and tuberculosis – given to young children. They include vaccines against hepatitis B, *Haemophilus influenzae* type b (Hib) disease, mumps, pneumococcal disease, rotavirus, rubella, and – in countries where needed – yellow fever and Japanese encephalitis.

Immunization averts an estimated 2.5 million child deaths a year, but despite the successes, millions of children in developing countries – almost 20% of all children born every year – do not get the complete immunizations scheduled for their first year of life.

Reaching these children will require overcoming a number of critical barriers that have slowed progress. A major barrier is the underlying weakness of the health system in many developing countries. Another is the difficulty in delivering vaccines through an infrastructure and logistical support system that is often overloaded. Yet another is a lack of understanding about the importance of vaccines – especially among the poorest populations – and a failure to actively demand access to immunization services. The threat posed by false or unsubstantiated rumours about vaccine safety is also a barrier to progress, as is the projected shortfall in funding needed to reach the global immunization-related goals (see Chapter 4).

Efforts under way to overcome the barriers to expanded immunization include the use of immunization campaigns and "outreach" operations that seek out population groups not adequately covered by routine immunization programmes. In addition, special initiatives, such as the Optimize project, have been launched to help countries manage the growing complexity of immunization logistics (delivery and storage of vaccines, for example) underpinning immunization activities.

The Reaching Every District (RED) strategy, launched in 2002, is designed to strengthen immunization delivery at the district level, by encouraging district-level immunization officials to adopt the principles of "good immunization practice", such as the identification and resolution of local problems, the organization of regular outreach vaccine delivery services, and the involvement of communities in ensuring adequate functioning of immunization services.

Another strategy aims to integrate immunization activities with other services provided by the health system. Any contact that a health worker has with a child or

mother at a health facility is also an opportunity to check immunization status and, if need be, to administer vaccines. Conversely, a mobile team offering immunization to a community can also distribute medicines, antimalarial bednets, and other health commodities or interventions.

Community participation is a key factor in raising vaccine coverage. Creating awareness of, and public demand for, the benefits of immunization is an essential component of an active immunization programme. However, it is also important to ensure that demand can be reliably met.

The availability of new vaccines against pneumococcal disease and rotavirus is expected to have a rapid and major impact in global efforts to reduce child deaths (MDG 4), prevent sickness, and, for pneumococcal disease, prevent disability. At the same time, vaccination against these diseases provides a key opportunity to actively promote the prevention and treatment of pneumonia and diarrhoea, which together account for over one third of all deaths among children under five years old.

Surveillance and monitoring are the cornerstones of immunization programmes, playing a key role in programme planning, priority setting, and mobilization of resources, as well as in monitoring trends in disease burden, and assessing the impact of disease control programmes and progress towards global goals. Since 2000, the increase in data-driven immunization initiatives (such as the RED strategy) and the need for disease data to monitor the impact of new vaccines have highlighted the need to strengthen surveillance and monitoring at all levels.

Disease surveillance systems are also expected to provide an early warning of impending or ongoing outbreaks of disease. The revised International Health Regulations, which entered into force in 2007, require WHO Member States to establish and maintain core capacities for surveillance at the local, intermediate, and national levels.

Over the past decade, progress has been made in setting up or improving surveillance systems for vaccine-preventable diseases. An example of a high-performance surveillance system is the polio surveillance network, which enables rapid detection of polio cases worldwide, and has been expanded in some countries to include measles, neonatal tetanus, yellow fever, and other vaccine-preventable diseases.

Meanwhile, as vaccine coverage has increased and the incidence of vaccine-preventable diseases has fallen – particularly in industrialized countries – there has been an increase in concern about the potential side-effects of vaccines.

Making sure vaccines are made, used, and tested in accordance with internationally accepted standards is one part of the effort to reduce the likelihood of a vaccine producing an adverse event (see Chapter 2). The other part is having an efficient post-marketing surveillance and investigation system in place that will rapidly pick up and verify any rumours or reports of adverse events allegedly related to the use of a vaccine.

Most industrialized countries have such a system, but many developing countries lack the resources or experience required. To address this, WHO has established a Global Advisory Committee on Vaccine Safety, made up of independent experts, to assess and respond to reports and rumours about vaccine safety. In addition, in 2009, WHO established a Global Network for Post-marketing Surveillance of Newly Prequalified Vaccines which have recently been introduced into national immunization programmes.

Investing in immunization

Chapter 4 looks at the costs involved in scaling up immunization since 2000, and examines the response of both new and established sources of immunization funding.

Immunization is among the most cost-effective health interventions, but what does it cost, and is the investment worth making? In the 1980s, total annual expenditure on immunization in developing countries averaged out at an estimated US$ 3.50–5.00 per live birth. By 2000, the figure had risen only slightly to about US$ 6.00 per live birth. Since 2000, GAVI Alliance (formerly known as the "Global Alliance for Vaccines and Immunisation") support for immunization enabled many low-income countries to strengthen their routine vaccine delivery systems and introduce underused vaccines, such as hepatitis B, Hib, and yellow fever. Not unexpectedly, immunization expenditure began to rise again.

By 2010, the average cost of immunizing a child is projected to rise to about US$ 18.00 per live birth. Beyond 2010, scaling up vaccine coverage with new vaccines – such as pneumococcal and rotavirus vaccines – to meet the MDGs and the GIVS goals is likely to raise the cost above US$ 30.00 per live birth.

There are several reasons for these rising costs. For a start, new and underused vaccines cost more than the traditional vaccines, although as the market and demand expands, their costs should fall. A second reason is that the increased quantities of vaccines place considerable pressure on the existing vaccine supply chain, requiring expanded storage facilities and more frequent delivery of supplies. A third is the “hidden” costs of introducing a new vaccine into a national immunization programme, such as the costs of staff training, public information, and expanded surveillance and monitoring. Fourth, is the increased cost of providing immunization services for difficult-to-reach children.

Meeting the goals of the GIVS will mean protecting children against 14 diseases – diphtheria, pertussis, tetanus, measles, polio, tuberculosis, hepatitis B, Hib, rubella, meningococcal disease, pneumococcal disease, rotavirus, and (where needed) Japanese encephalitis and yellow fever. If all countries immunize 90% of children under five years of age with these vaccines, it is estimated that immunization could prevent an additional two million deaths a year in this age group – making a major contribution to the achievement of MDG 4.

A WHO-UNICEF analysis published in 2008 estimated how much it would cost to attain the GIVS goals in 117 WHO low- and lower-middle-income Member States between 2006 and 2015. The total bill came to US$ 76 billion, including US$ 35 billion for the 72 countries that have a gross national income (GNI) per capita below US$ 1000 (as of 2006). These countries are eligible for GAVI Alliance funding and have received support for introducing underused and new vaccines as well as support to strengthen their immunization systems.

Is the investment worth making? Data on the cost-effectiveness of immunization confirm that it is. For example, the global eradication of smallpox, which cost US$ 100 million over a 10-year period up to 1977, has resulted in savings of US$ 1.3 billion a year in treatment and prevention costs ever since.

In addition to being a significant contributor to childhood deaths, vaccine-preventable diseases also constitute a major cause of illness and long-term disabilities among children both in industrialized and developing countries. The classic example of prevention of serious disability has been the prevention of paralytic polio in hundreds of thousands of children since the advent of the Global Polio Eradication Initiative (GPEI).

Of the new vaccines, the pneumococcal vaccine has been shown to be associated with a 39% reduction in hospital admissions due to pneumonia from any cause. Among children who survive an episode of pneumococcal meningitis, a large

proportion are left with long-term disabilities. Similarly, the rotavirus vaccine has been shown to reduce clinic visits and hospitalizations due to rotavirus diarrhoea by 95%.

Thus, while the impact on child deaths alone would be sufficient justification for the use of vaccines in children in developing countries, the reduction of long-term disability among children and the savings from reductions in clinic visits and hospitalization more than justify their use in children everywhere.

Immunization has other far-reaching benefits beyond the positive impact on individual and community health. A recent study by a Harvard School of Public Health team found that by keeping children healthy and in school, immunization helps extend life expectancy and the time spent on productive activity – thereby contributing to poverty reduction (MDG 1).

Who pays the bill and how? In 2007, WHO's 193 Member States were funding an average 71% of their vaccine costs (33% in low-income countries). Of these, 86% of countries reported having a separate line item for vaccines within their national budget – a measure associated with increased budget allocations to vaccines and immunization and with long-term political commitment to immunization. From the WHO-UNICEF costing analysis, it is estimated that 40% of the costs of immunization for the period 2006–2015 will be met by national governments.

Since 2000, immunization funding from multilateral, bilateral, and other funding sources has increased by 13% (not adjusted for inflation). At the same time, there has been a shift both in the way funds are channeled and in the way they are used. At the global level, some bilateral donors have increasingly used the GAVI Alliance as a channel for funding. At a country level, there has been a move away from a project-based approach to the use of broad-based funding mechanisms to support the health sector as a whole.

Health and immunization systems benefit substantially from targeted immunization efforts such as the GPEI. A substantial proportion of the investment in polio eradication has been spent on strengthening routine immunization and health systems, and on achieving the goals of the GIVS.

In recent years, several innovative public-private partnerships and new financing mechanisms have been introduced to provide predictable and sustainable external financial support to help countries meet the immunization-related global goals. The GAVI Alliance is a public-private global health partnership that provides support to countries with a GNI per capita below US$ 1000, to strengthen their health systems and immunization programmes, increase routine immunization coverage, and introduce new and underused vaccines. As of the end of 2008, the Alliance had received a total of US$ 3.8 billion in cash and pledges from public and private sector donors, and disbursed US$ 2.7 billion to eligible countries. Over the period up to 2015, the Alliance has an estimated US$ 3 billion funding gap out of the estimated US$ 8.1 billion total funding needed.

During its first phase (2000–2005), the GAVI Alliance focused on the introduction of new and underused vaccines (hepatitis B, Hib, and yellow fever). During the second phase (2006–2015) support is being expanded to new vaccines (rotavirus and pneumococcal vaccines). In addition, the GAVI Alliance Board has approved for possible future support a further package of vaccines to be offered to countries, including HPV, Japanese encephalitis, rubella, and typhoid.

To meet concerns about financial sustainability, all GAVI-supported countries were required to prepare a comprehensive multi-year plan for immunization, or cMYP. In 2007, the Alliance introduced a new co-financing system, which requires countries to pay a gradually increasing share of the cost of their new vaccines, based on a country's GNI per capita. By the end of 2008, 30 countries had begun using this system to pay for the introduction of the pentavalent vaccine (DTP-Hepatitis B-Hib), rotavirus vaccine, and pneumococcal vaccine.

A new, innovative source of funding is the International Finance Facility for Immunisation (IFFIm), which uses long-term legally binding commitments by donors to issue bonds on the international capital markets. The sale of these bonds provides cash that can be used by the GAVI Alliance to fund programmes. As of early 2008, the bonds had raised US$ 1.2 billion from investors worldwide.

Another innovative financing mechanism is the Advance Market Commitment (AMC) – a new approach to public health funding designed to accelerate the development and manufacture of vaccines for developing countries. Conceived in 2005 by the Center for Global Development, a pilot AMC for pneumococcal vaccine was launched in 2007 by the Governments of Canada, Italy, Norway, the Russian Federation, and the United Kingdom of Great Britain and Northern Ireland; the Bill & Melinda Gates Foundation; the GAVI Alliance; and the World Bank; with an investment of US$ 1.5 billion.

The good news is that more investment is being made in immunization and projected trends indicate growing financing in the future. Yet, without further growth, expected future funding from governments and donors will not be enough to sustain the gains already achieved towards GIVS goals and the MDGs. "The real challenge," the WHO-UNICEF 2008 analysis report concluded, "will hinge on how national governments, and the international community at large manage their roles and responsibilities in reaching and financing the goals of the GIVS until 2015."

The view from the future

Chapter 5 looks forward over the next decade and considers how the immunization landscape may have changed by 2020.

By the 2020s, the strategies put in place to reach the MDGs should have brought deaths among children under five years old to an all-time low. Polio should be eradicated, and measles eliminated in all countries. Neonatal and maternal tetanus should no longer be exerting such a heavy toll on babies and mothers, and today's underused vaccines (against Hib disease, hepatitis B, and yellow fever) may have rid the world of the lethal burden of these diseases. The use of new vaccines against pneumococcal, rotavirus, meningococcal, and HPV disease may have inspired a new, more ambitious set of international health and development goals. Vaccines may have been developed that can turn the tide against malaria, tuberculosis, and AIDS.

Over the next decade or so, an increasing number of developing countries will be using the new vaccines coming onto the market. Some of these (such as the HPV vaccine) will be given to adolescents; others (such as the influenza vaccine) will be given to adults. However, there is as yet little knowledge or experience of reaching older age groups in developing countries, except through special immunization campaigns. School-based immunization is one possible solution, especially since school attendance is increasing in many developing countries.

New vaccine delivery systems are also anticipated. Devices that use needles may have been largely replaced with new approaches such as aerosol formulations sprayed in the nose (already available for an influenza vaccine) or lungs (currently being tested for several vaccines); adhesive skin patches; drops under the tongue; and oral pills.

Another potential breakthrough is the development of an increasing number of vaccines that are heat-stable. When supplied with a vaccine vial monitor to check exposure to heat, these vaccines should be available for use outside the cold chain – greatly relieving the pressure on the cold chain and logistics.

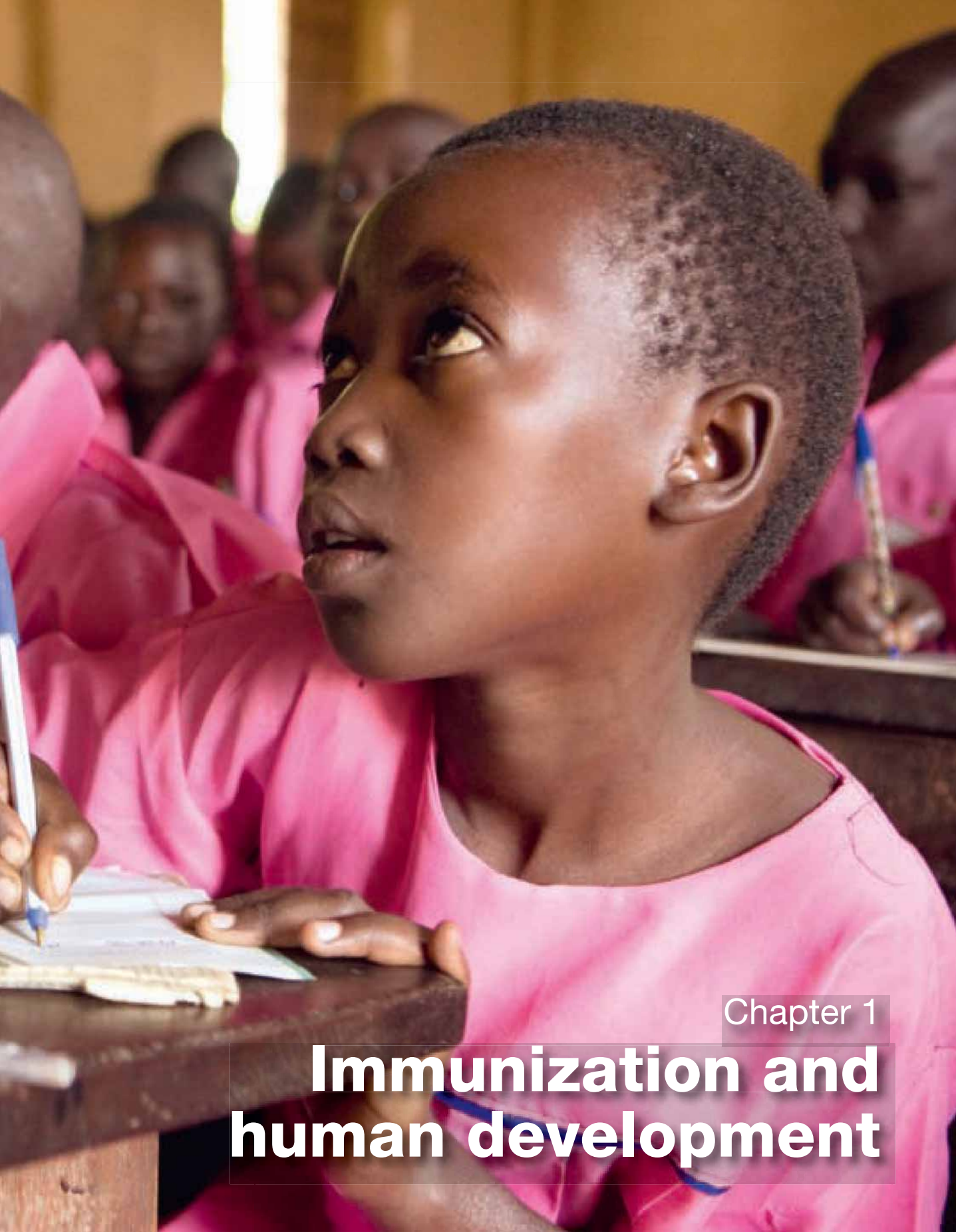
By 2020, manufacturers in developing countries may have acquired the capacity to make their own state-of-the-art vaccines tailored to meet their own specific needs. Moreover, their contribution to global vaccine supply may be on a more equal footing with the industrialized countries – a development likely to increase competition.

But the world will face fresh challenges. As of early 2009, countries throughout the world are facing economic recession and financial turmoil, which threaten to unravel hard-won gains. Climate change looms large and is likely to alter the epidemiological landscape in which vaccines and immunization operate – bringing new health challenges.

Despite this, the overall picture is one of cautious optimism, enthusiasm, energy, and dedication. Vaccines can make a major contribution to achieving the MDGs. Vaccine development is in a dynamic phase and more people are being reached with vaccines. New public-private partnerships and product development groups are becoming important drivers of vaccine development and deployment. And over the next two decades, public demand for vaccines and immunization is expected to rise. As it does so – and far into the future – there is every reason to believe that immunization will continue to be a mainstay of public health.

Part 1:

Progress and challenges in meeting global goals



Chapter 1

Immunization and human development

Key messages

- Immunization is key to achieving the Millennium Development Goals (MDGs), especially the goal to reduce deaths among children under five years old (MDG 4).
- Vaccines prevent more than 2.5 million child deaths a year.
- Available vaccines could prevent an additional two million deaths a year among children under five years old.
- The introduction of new vaccines against pneumococcal disease and rotavirus could have a rapid impact – within three to five years – on reducing the high toll of sickness, disability, and deaths among children under five years old.
- Over 100 million children are immunized every year before their first birthday.
- Around 24 million children under one year old – almost 20% of the children born every year – are not being reached with vaccines.

Since the turn of the century, several positive changes have occurred in the world of human development. People are living longer, bringing the global average life expectancy at birth to 69 years for women and 65 years for men (*2*). For the first time in documented history, the number of children under five years old dying every year has fallen below 10 million (*3*). Investment in health has taken off in earnest within the donor community – a trend reflected in the birth of several major global partnerships, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; the GAVI Alliance; and the International Health Partnership.

Too many problem areas, though, are still waiting for change. Inequalities and inequities still roam freely across the globe. About nine million children under five years old are still dying every year – most of them in developing countries. Undernutrition is an underlying factor in about one third of all deaths in children. Among all age groups, AIDS, tuberculosis, and malaria kill more than four million people a year; lower respiratory infections (mainly pneumonia) account for over four million deaths, and diarrhoeal diseases account for over two million deaths (*4*). And every year more than half a million women – almost all (99%) in developing countries – die from pregnancy-related causes (*5*). And these are only a few examples.

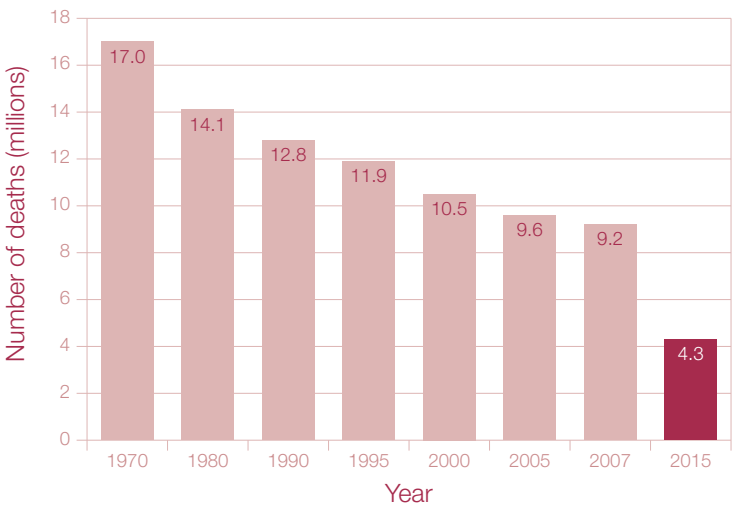
The year 2000 marked a turning point in the world's reaction to these inequities. In September of that year, leaders of more than 190 countries signed the United Nations Millennium Declaration, which committed the international community to the task of removing the "abject and dehumanizing conditions" holding more than one billion of the world's population in the grip of poverty, disease, and premature death. Alleviating the inequity of that burden is part of the task. Reducing the toll of deaths among children under five years old is another. Yet another is to seek out and remedy the preventable poverty, disease and death among neglected population groups that is hidden beneath promising regional or national indicators of progress.

One of the eight MDGs that emerged from the Millennium Declaration calls for a drastic reduction in deaths among children under five years of age, specifically, a

two-thirds drop in the under-five mortality rate between 1990 and 2015 (MDG 4). Most of the effort in achieving this goal focuses on developing countries, which account for over 90% of child deaths.

Figure 1

Trends in global mortality in children under five years old

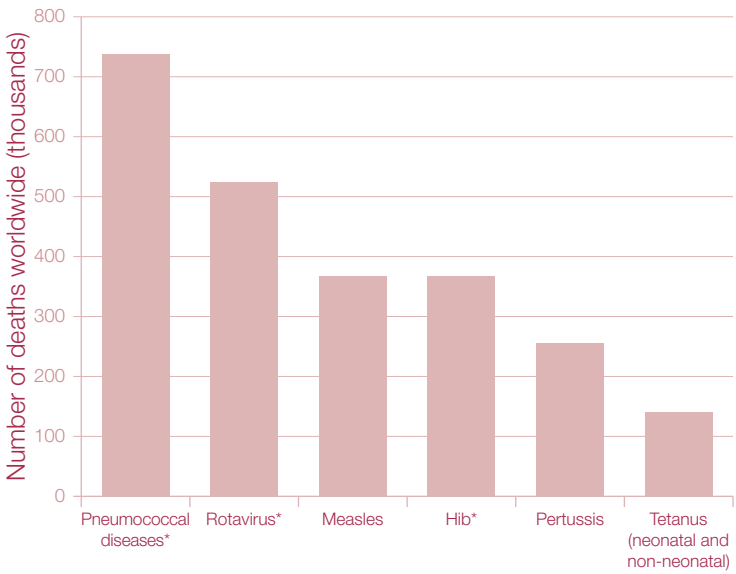


Source: UNICEF Programme Division, 2009

Immunization is key to achieving the MDGs, especially the goal to reduce deaths among children under five years old (MDG 4). Reducing these deaths means providing more children, not only with vaccines, but also with life-saving drugs, antimalarial bednets, schooling, sanitary living conditions, clean water, and other essentials that are mostly taken for granted in the better-off parts of the world. It also means addressing the global imbalance in spending on health, where developing countries – with 85% of the world's population – account for only 12% of global spending on health (*6*).

Figure 2

Leading causes of vaccine-preventable death in children under five years old, 2004



** WHO/Department of Immunization, Vaccines and Biologicals estimates based on Global Burden of Disease, 2004 estimates. Pneumococcal diseases and Hib estimates are for the year 2000.*

Source: (4)

One change, however, that could seriously imperil efforts to battle inequity, preventable disease, death, and poverty, is the collapse of global financial markets in the last months of 2008, and the economic slowdown that has since swept over the world. United Nations Secretary-General Ban Ki-moon has expressed deep concern about the impact of the crisis "particularly on the poorest of the poor and the serious setback this is likely to have on efforts to meet major goals".

Much will depend on the continued commitment of governments and the international community to sustain and build on their efforts to improve child survival and meet the MDGs. With the renewed energy and enthusiasm that now pervades the vaccine landscape, the time is ripe for accelerating the role of life-saving

vaccines and other linked health interventions in global efforts to achieve the MDGs. At the same time, efforts are needed to ensure that the benefits of immunization are increasingly extended to adolescents and adults, to protect against diseases such as influenza, meningitis, and vaccine-preventable cancers that occur in adulthood. In addition, ongoing vaccine research and development efforts must be intensified to accelerate the development of urgently needed vaccines against diseases such as malaria, tuberculosis, and AIDS, which affect millions of people every year and contribute to increasing poverty.

All countries have national immunization programmes, and in most developing countries, children under five years old are immunized with the standard WHO-recommended vaccines that protect against eight diseases – tuberculosis, diphtheria, tetanus (including neonatal tetanus through immunization of mothers), pertussis, polio, measles, hepatitis B, and Hib. These vaccines are preventing more than 2.5 million child deaths each year. This estimate is based on assumptions of no immunization and current incidence and mortality rates in children not immunized (World Health Organization, Department of Immunization, Vaccines and Biologicals, unpublished).

Today, over 100 million children under one year of age are immunized every year with the required three doses of diphtheria-tetanus-pertussis (DTP) vaccine. However, 24 million children are not being reached with vaccines: in 2007, over 10% of children under one year old in developing countries were not receiving even one dose of DTP vaccine, compared with 2% in industrialized countries.

Most of these 24 million unimmunized or incompletely immunized children live in the poorest countries, where many factors combine to thwart attempts to raise vaccine coverage rates – fragile or non-existent health service infrastructure, difficult geographical terrain, and armed conflict, to mention just three. Other unimmunized children live in countries that can afford, but have not given priority to, acquiring or maintaining the infrastructure and human resources required to deliver immunization.

And others are refugees or homeless children, beyond the reach of routine immunization. Failure to reach these different groups of children with vaccines is jeopardizing the massive efforts and funding being invested in expanding the use of currently underused vaccines (such as the Hib, hepatitis B, and yellow fever vaccines), as well as in major disease-defeating drives, such as eradicating polio, reducing child deaths from measles, and eliminating maternal and neonatal tetanus.

The good news is that strategies are being implemented to overcome these obstacles to immunization. Some strategies aim at strengthening the ability of health systems to deliver health care, including immunization; others use immunization campaigns and similar approaches to bring immunization to more people in districts where vaccine coverage is low.

Nurse Justina Munoz Gonzalez about to vaccinate four-month old Olga Damaris outside her home near the remote village of San Pablo near Murra in the Nueva Segovia state of Nicaragua.

Good news comes also from the vaccine development area. Since 2000, for example, the global vaccine supply landscape has changed. Manufacturers in developing countries are emerging as a significant presence on the vaccine market, with a perceptibly positive impact on the affordability of vaccines and the sustainability of vaccine supply. Manufacturers based in industrialized countries are

expanding their presence in developing countries and are working increasingly with international health organizations to make vaccines that are designed for use in developing countries and affordable by these countries. In addition, the development of new vaccines, and efforts to put these vaccines into use in the poorer countries, are receiving a substantial boost from more than a dozen new public-private partnerships created specifically for this purpose. And, most encouragingly, underpinning the new vaccine landscape is an influx of new financial resources and an array of new strategies and mechanisms for sustaining and managing these resources. The overall effect of these changes is to stimulate and revitalize all facets of the vaccine arena – demand, supply, and use.

Over the past decade, new vaccines have become available that protect against three organisms – the pneumococcus, rotavirus, and human papillomavirus (HPV). While HPV is a cause of premature deaths from cancers that occur in adulthood, pneumococcal disease and rotavirus diarrhoea together account for 1.3 million deaths among children under five years old – 12% of all deaths among this age group – as well as high rates of sickness and, for pneumococcal disease, disability.

In a recent analysis (*7*), WHO estimated that if all the vaccines currently available against childhood diseases are widely adopted, and if immunization programmes can raise vaccine coverage to a global average of 90%, vaccines would prevent an additional two million deaths a year among children under five by 2015 – making a major contribution to MDG 4. This projection is based on unpublished WHO estimates of the expected future cohort of children under five, and assumptions of no immunization and current incidence and mortality rates in children not immunized.

For any country, however, the decision to adopt a new vaccine cannot be taken lightly: there are issues of cost, logistics (storage space and transportation, etc.), staff training, sustainability, and other considerations. However, immunization – even with the addition of the new, more costly vaccines – remains one of the most

cost-effective health interventions. The challenge is to get vaccines into use in the countries where they are most needed, and to do so quickly.

Responding to this challenge, in 2005, WHO and UNICEF published the Global Immunization Vision and Strategy (GIVS) for the decade 2006 to 2015 (*8*).

Box 1

Global Immunization Vision and Strategy (GIVS) goals

By 2010 or earlier:

- **Increase coverage.** Countries will reach at least 90% national vaccination coverage and at least 80% vaccination coverage in every district or equivalent administrative unit.
- **Reduce measles mortality.** Globally, mortality due to measles will have been reduced by 90% compared to the 2000 level.

By 2015 or earlier:

- **Sustain coverage.** The vaccination coverage goal reached in 2010 will have been sustained.
- **Reduce morbidity and mortality.** Global childhood morbidity and mortality due to vaccine-preventable diseases will have been reduced by at least two thirds compared to 2000 levels.
- **Ensure access to vaccines of assured quality.** Every person eligible for immunization included in national programmes will have been offered vaccination with vaccines of assured quality according to established national schedules.
- **Introduce new vaccines.** Immunization with newly introduced vaccines will have been offered to the entire eligible population within five years of the introduction of these new vaccines in national programmes.
- **Ensure capacity for surveillance and monitoring.** All countries will have developed the capacity at all levels to conduct case-based surveillance of vaccine-preventable diseases, supported by laboratory confirmation where necessary, in order to measure vaccine coverage accurately and use these data appropriately.

- **Strengthen systems.** All national immunization plans will have been formulated as an integral component of sector-wide plans for human resources, financing and logistics.
- **Assure sustainability.** All national immunization plans will have been formulated, costed and implemented so as to ensure that human resources, funding and supplies are adequate.

Source: (8)

Equality and equity are central to the GIVS vision. The GIVS strategy foresees a world in which "every child, adolescent and adult has equal access to immunization", and where "solidarity among the global community guarantees equitable access for all people to the vaccines they need". Implementing the strategy calls for four main approaches: i) protecting more people; ii) introducing new vaccines and technologies; iii) integrating immunization with other components in the health systems context; and iv) immunizing in the context of a globally inter-linked, interdependent health and development system.

This report chronicles the efforts being made since 2000 to complete, as far as possible, what the GIVS calls the "unfinished immunization agenda". It is unlikely, however, that the unfinished agenda will ever be finished as new infections will undoubtedly emerge; new vaccines will continually be needed; new ways of overcoming obstacles to making use of new vaccines will have to be found; and new global crises – such as the financial crisis that has engulfed the world since the last months of 2008 – may threaten the sustainability of funding for vaccine-related activities. Nevertheless, as of early-2009, and despite the economic downturn, the vaccine community allows itself a degree of cautious optimism. If the optimism turns out to be justified, vaccines and immunization will have a good chance of realizing their potential to help make the world a safer, more equitable, place for all – not only for people alive today, but also for future generations.

Box 2

What's so special about vaccines?

Vaccines are special.

First, unlike many other health interventions, they help *healthy* people stay healthy and in doing so help to remove a major obstacle to human development.

Second, they benefit not only individuals but also communities, and even entire populations (the eradication of smallpox is a case in point).

Third, for most vaccines, their impact on communities and populations is more rapid than that of many other health interventions: between 2000 and 2007, for example, global mortality from measles was reduced by 74% (from 750 000 to 197 000 (*9*)). Today, it is estimated that new vaccines against pneumococcal disease and rotavirus could have a rapid impact – within three to five years – in reducing the high burden of sickness, disability (from pneumococcal disease), and deaths among children under five years old.

Finally, vaccines are both life- and cost-saving. Recent data show that immunization, even with more expensive vaccines, continues to be good value for money (see Chapter 4).

Not surprisingly, the United States' Centers for Disease Control and Prevention (CDC) put vaccination at the top of its list of ten great public health achievements of the 20th century. Furthermore, in 2008, a panel of distinguished economists convened by the Copenhagen Consensus Center – an international think-tank that advises governments and philanthropists how best to spend aid and development money – put expanded immunization coverage for children in fourth place on a list of 30 cost-effective ways of advancing global welfare (see Table).

Table: The ten most cost-effective solutions to major global challenges, Copenhagen Consensus 2008

	Solution	Challenge
1	Micronutrient supplements for children (vitamin A and zinc)	Malnutrition
2	The Doha development agenda	Trade
3	Micronutrient fortification (iron and salt iodization)	Malnutrition
4	Expanded immunization coverage for children	Diseases
5	Biofortification	Malnutrition
6	Deworming and other nutrition programmes at school	Malnutrition & Education
7	Lowering the price of schooling	Education
8	Increase and improve girls' schooling	Women and development
9	Community-based nutrition promotion	Malnutrition
10	Provide support for women's reproductive role	Women and development

Source: The Copenhagen Consensus 2008 (10)

Chapter 2

A new chapter in vaccine development

Key messages

- The first decade of the 21st century has been the most productive in the history of vaccine development.
- New life-saving vaccines have been developed, and others will soon be available.
- New vaccines are urgently needed to reduce illness and deaths from high-burden diseases such as malaria, tuberculosis, and AIDS.
- Most low-cost traditional vaccines are now produced by vaccine manufacturers in developing countries.
- Public-private partnerships are accelerating the availability of new vaccines.
- Systems have been put in place to ensure the safety, effectiveness, and quality of all vaccines.

A vaccine boom

Since the turn of the century, the mood in the vaccine community has been decidedly enthusiastic – and for good reason. Two diseases have been added to the list of vaccine-preventable diseases, bringing the total number to a record of over 30. In addition, the vaccine industry has put 25 new vaccine formulations on the market – several specifically designed for use in age groups (adolescents and elderly people, for example) and in populations (in developing countries, for example), that have in the past not been priority targets for vaccine developers. By the end of 2008, according to recent unpublished data, the total number of vaccine "products" (all formulations combined) had reached a record of over 120, making the first decade of this century the most productive in the history of vaccine development.

Enthusiasm also stems from the exceptionally large number of candidate vaccines in the late stages of research and development (R&D) – over 80 according to recent unpublished data. Furthermore, about 30 of these candidates aim to protect against diseases for which there are no vaccines currently available (*11*).

Explaining the new momentum

Compared with the recent past, an increase in the use of innovative vaccine technology by the R&D-based vaccine industry, and a greater sharing of technology between manufacturers in industrialized countries and emerging market producers, have played a substantial role in the current upswing in productivity of the global vaccine industry. Another stimulus to vaccine development has come from public-private product development partnerships, whose numbers have grown significantly over the past decade: there are now close to 30, of which half have appeared since the year 2000. The current surge in vaccine development is also the result of new funding resources and new funding mechanisms (see Chapter 4).

Their arrival on the scene reflects a new concern of the global health and development community over the unmet needs of developing countries for vaccines and immunization.

The unparalleled growth in vaccine development, however, has been achieved in the face of several constraints. For example, some vaccines under development against particularly complex pathogens, such as the malaria parasite and the AIDS virus, require the application of innovative research and manufacturing technologies that have only recently become available (see Box 3). The rising cost of producing a vaccine – upwards of US$ 500 million (*1*) – is also a constraining factor, due partly to increasingly stringent regulatory oversight and the resulting greater industry investment in more complex and more costly manufacturing technology. Vaccine manufacturers also face a high risk of failure: only one in four to five candidate vaccines ends up as a marketable vaccine (*12*).

Technology comes of age

Vaccine industry executives attribute much of the surge in new vaccine development to the "maturing" of breakthroughs in biotechnology that occurred in the 1980s and 1990s. A recent analysis *(13)* points to a "technological revolution [which has] removed most of the technical barriers that formerly limited vaccine developers" and to the fact that "biotechnology in the current era of vaccine development has enabled totally unprecedented advancements in the development of vaccines".

Box 3

AIDS and malaria defy science

The plasmodium parasite that causes malaria and the human immunodeficiency virus (HIV) that causes AIDS are both adept at evading human immune defences. Both are able to alter the configuration of the immunity-stimulating molecules (antigens) they carry and that would otherwise signal their presence to their host's immune system. This antigenic variability occurs not only within a single person but also between different people, different population groups, and different geographical locations. The malaria parasite also has an additional immunity-evading capability. As it passes through the different anatomical parts of its human and mosquito hosts, it turns into a different biological life-stage, presenting its host's immune system each time with a different set of antigens.

One of the most devastating properties of HIV is that it attacks its host's immune system – the very system designed to protect the human host against infections. HIV is characterized by extremely high levels of genetic variability and rapid evolution. HIV strains can easily recombine giving birth to complex recombinant or mosaic viruses – called "circulating recombinant forms" or CRFs – some of which can play an important role in regional sub-epidemics. To date, more than a dozen genetic HIV subtypes and up to 24 different recombinant forms have been reported. The impact of such enormous genetic variability on the biological properties of the virus, its transmissibility, pathogenic properties, as well as vaccine development remains unclear and complicates significantly the development of broadly effective novel prevention tools.

Reverse vaccinology

The science of genomics has provided scientists with the complete genome sequences of more than 300 bacterial species – most of them responsible for human disease (*14*). Researchers use an organism's genome to pick out the genes most likely to correspond to conserved antigens that could be used in a vaccine. Once identified, the genes can be combined and inserted into a different, rapidly multiplying organism – such as yeast – to produce candidate antigens, which are then screened for their ability to produce protective immune responses. This

approach is known as “reverse vaccinology”: it starts with a genetic blueprint of an organism and rapidly generates antigens of interest.

In contrast, the more time-consuming conventional approach starts with the pathogenic organism itself, which is grown in the laboratory (a lengthy process made more complex by the fact that some pathogens cannot easily be grown in a laboratory), and from which a limited number of antigens are isolated. These are then tested for their ability to induce potentially protective immune responses.

Reverse vaccinology has not yet produced a licensed vaccine but researchers have used it to develop several candidate vaccines, some of which are currently in the late stages of clinical testing (for example, a candidate vaccine against group B meningococcus).

Conjugation technology

Conjugation technology has also spurred vaccine development. First used in the 1980s, conjugation allows scientists to link (conjugate) the sugar molecules on the outer envelopes of certain bacteria – such as the pneumococcus, the meningococcus, and the Hib bacterium – to strongly immunogenic “carrier” proteins. Older vaccines of this type relied on the sugar molecules to stimulate immunity, but usually failed to elicit protective immunity in children under two years of age. The new conjugate vaccines, however, do protect young children. In addition, unlike the older vaccines, the new conjugate vaccines stimulate the type of immune cells needed to create a long-lasting memory of the pathogen: the immunity from those cells can thus be boosted by subsequent vaccine doses or by exposure to the pathogen itself. Again, unlike the older vaccines, conjugate vaccines have even been shown to reduce the numbers of healthy carriers of the pathogen in a community, thereby producing a so-called “herd immunity” that protects even unvaccinated people from the pathogen. A case in point is the use of the

pneumococcal conjugate vaccine in the United States of America: one year after its introduction, the incidence of invasive pneumococcal disease fell by 69% among vaccinated children under two years of age – but also by 32% in adults (aged 20–39 years) and by 18% among older age groups (aged over 65 years), none of whom had ever received the vaccine (*15*).

Adjuvants

Adjuvant technology, too, has evolved. Adjuvants are substances that help a vaccine to produce a strong protective response. They can also reduce the time the body takes to mount a protective response and can make the immune response more broadly protective against several related pathogens. Progress in understanding how the human immune system recognizes the molecules carried by pathogens has led to the development of a host of adjuvants. Up to now, only five of the 20 or so types of adjuvants under development have been licensed for use in vaccines administered to humans (*16*). Several vaccine manufacturers have invested heavily in the search for safe and effective adjuvants, notably for vaccines against pandemic influenza and HPV. The malaria candidate vaccine – RTS,S/AS01 – which is due to enter advanced (Phase 3) clinical trials in Africa in 2009, has also benefited from a 15-year research programme undertaken by its manufacturer to produce an innovative adjuvant system comprising three types of adjuvant.

Cell substrates

Cells derived from humans and from animals (such as monkey kidney cells or chicken embryo cells), have been used for over 50 years as "substrates" on which the viruses used to make vaccines against viral diseases (influenza, measles, and so on) are grown. Recent advances in technology and research have led manufacturers

to explore a broad array of new cell substrates that use, for example, cells from dogs, rodents, insects, plants, and other living organisms. Some of these substrates are "immortal" – continuous cell lines that avoid the ongoing use of animals. The ultimate aim is to find technologies that will produce greater yields of vaccine virus and facilitate their harvesting from these cell substrates.

Box 4

The role of industry in vaccine research and development

The role of industry in vaccine R&D involves at least four groups of actors:

Big Pharma – with regard to vaccine production – is a group of five major pharmaceutical companies. These firms do not invest in in-house basic research (which is conducted mainly by academic institutions), and are only minor players in the applied research area. Their main role is in vaccine evaluation. They are powerful engines for the development, industrialization, registration, and marketing of vaccines, but are increasingly outsourcing some of these functions.

Biotechs concentrate on applied research, pre-clinical development, and clinical development up to Phase 2 clinical trials. They constitute the main source of innovation and account for nearly 50% of Big Pharma's financial investment in R&D. Although these companies are expected to play an increasingly important role in vaccine R&D, their ability to penetrate downstream functions such as Phase 3 clinical trials, and the industrialization and commercialization of vaccines, is often limited by structural, financial, and human constraints. As the recent case of Roche taking over Genentech in 2009 has demonstrated, the largest Biotech companies that manage to make their way to the market are usually taken over and absorbed by Big Pharma.

Producers in emerging markets and developing countries have in recent years become major suppliers of traditional children's vaccines and of a few combination vaccines. Some companies have even contributed to the development of new products. They have strengthened their industrial capability and become credible players, prompting Big Pharma to seek alliances and partnerships with them, even though their innovation potential is still limited by their regulatory environment and financial capacity. This situation is likely to evolve.

Sub-contractors are increasingly engaged in all sectors of the pharmaceutical industry, including the vaccine business. One major development is the emergence

of large sub-contractors capable of large-scale production on behalf of Biotechs and even of Big Pharma. Strategic restructuring may in the future enable some sub-contractor companies to become vaccine producers and suppliers in their own right.

Big Pharma is expected to remain a major and indispensable driver of innovation in the field of vaccines and immunization. This is because the companies in question have:

- the ability to rapidly mobilize large financial resources
- skilled technical and regulatory expertise in many domains
- a large workforce that is generally competent and well trained
- management tools which increase global competitiveness.

Although this situation is not static, fundamental change will take time. In the meantime, it is critical that non-industrial actors – while recognizing the unique role played by the vaccine industry – should be able to fully engage in dialogue and collaborate more effectively with the private sector, in particular in the context of public-private partnerships.

New licensed vaccines

Several new vaccines and new vaccine formulations have become available since the year 2000. These include:

- the first conjugate vaccine against the pneumococcus, a bacterium which, according to WHO estimates of the year 2000, causes more than 14.5 million episodes of serious pneumococcal disease and more than 800 000 deaths annually among children under five years old, as well as high rates of meningitis-related disability among children who survive (including mental retardation, seizures, and deafness);
- two new vaccines against rotavirus (replacing a previous vaccine withdrawn from the market because of adverse events) – a virus which, according to WHO 2004 estimates, accounts annually for an estimated two million hospitalized cases of severe diarrhoeal disease in children (*17*) and kills an estimated 527 000 children a year;

- the first two vaccines against HPV, a virus which causes cervical cancer. According to GLOBOCAN estimates, there were 493 000 new cases of cervical cancer and 274 000 related deaths in 2002 (*18*). The HPV genotypes 16 and 18, included in both vaccines, are responsible for 70% of cervical cancer and also cause cancers of the vulva, vagina, anus, penis, head and neck;
- the first DTP combination vaccines specifically formulated for adolescents and adults;
- the first vaccines for human use against avian influenza caused by the H5N1 virus, responsible since 2003 for the deaths and culling of tens of millions of birds, and for over 400 reported cases among people in 16 countries as of May 2009, of whom more than 60% have died (*19*). These vaccines are not envisaged at the time of writing for use in large population groups.

Vaccines in the pipeline

A large number of vaccine products are currently in the pipeline and are expected to become available by 2012. According to recent unpublished data, more than 80 candidate vaccines are in the late stages of clinical testing. About 30 of these candidate vaccines aim to protect against major diseases for which no licensed vaccines exist, such as malaria and dengue. If Phase 3 trials of the RTS,S/AS01 candidate vaccine against malaria go well, this vaccine could be licensed by 2012. If successful, it would be the first vaccine against a parasite that causes disease in humans. Several candidate vaccines are also under development against dengue, another mosquito-borne disease of major public health concern. There is no specific treatment for dengue fever – a severe influenza-like illness that can occur in more serious forms, including dengue haemorrhagic fever. Two candidate vaccines against dengue virus have been evaluated in children, and one candidate vaccine is currently being evaluated in a large-scale trial. A successful vaccine needs to confer

immunity against all four circulating dengue viruses, and evaluation of the vaccines is complex. However, researchers are hopeful that dengue vaccines will become available in the coming years.

About 50 candidate vaccines target diseases for which vaccines already exist, such as pneumococcal disease, Japanese encephalitis, hepatitis A, and cholera: however, these candidates hold the promise of being more effective, more easily administered, and more affordable than the existing vaccines.

Phase 3 malaria vaccine trial participants and their mothers (on bench) with Dr Salim Abdulla (standing left) and vaccination staff at the Bagamoyo Research and Training Centre of the Ifakara Health Institute in the United Republic of Tanzania.

Box 5

Product development partnerships

Product development partnerships are typically not-for-profit entities mandated to accelerate the development and introduction of a product, such as a vaccine. They are funded by donors to promote research and development, often through links between developing country academic programmes, biotechnology companies, and vaccine manufacturers. Product development partnerships have encouraged investment in various aspects of vaccine development, including large-scale clinical trials of vaccines against diseases prevalent in the poorest countries of the world.

Examples of product development partnerships concerned primarily with vaccine development are the:

- International AIDS Vaccine Initiative (launched in 1996)
- Global HIV Vaccine Enterprise (launched in 2004)
- Aeras Global TB Vaccine Foundation (launched in 1997)
- European Malaria Vaccine Initiative (launched in 1998)
- PATH Malaria Vaccine Initiative (launched in 1999).

Product development partnerships that lean more towards vaccine introduction than development are the:

- GAVI-funded Pneumococcal Accelerated Development and Introduction Plan (PneumoADIP)
- Rotavirus Accelerated Development and Introduction Plan (RotaADIP)
- Hib Initiative

Each of these three partnerships is ending in 2009.

The Meningitis Vaccine Project (launched in 2001) is involved in both vaccine development and introduction.

Supplying vaccines for a changing world

A rapidly expanding market

Over the first eight years of this century, the global vaccine market almost tripled, reaching over US$ 17 billion in global revenue by mid-2008, according to recent estimates (*20*). This increase represents a 16% annual growth rate, making the vaccine market one of the fastest-growing sectors of industry generally – more than twice as fast as that of the therapeutic drugs market. Most of the expansion comes from sales in industrialized countries of newer, relatively more expensive vaccines, which account for more than half of the total value of vaccine sales worldwide (*20*). These vaccines include the two second-generation rotavirus vaccines, two recombinant HPV vaccines, a varicella zoster (shingles) vaccine, and a conjugate pneumococcal vaccine (which alone totalled US$ 2 billion in sales between 2000 and 2007). The commercial success of these products, according to a recent vaccine market analysis (*21*), "is sparking renewed interest and investment in the vaccine industry, which had appeared moribund in the 1980s".

A concentrated industry

The vaccine supply scene is dominated by a small number of multinational manufacturers based in industrialized countries. As of mid-2008, five major firms producing vaccines – all Big Pharma companies – account for more than 80% of global vaccine revenue. The remaining revenue is divided among more than 40 manufacturers in developing countries.

By contrast, in terms of volume, only 14% of the vaccine required to meet global vaccine demand comes from suppliers in industrialized countries. The remaining 86% is met by suppliers based in developing countries. The striking disparity

between revenue and volume reflects the large volume of low-cost, mainly traditional vaccines produced by these developing country suppliers, primarily for use in their own or in other low- and middle-income countries – a market that represents 84% of the world's population.

The growth in the manufacturing capacity of suppliers in developing countries is also a response to increasing demand from the two United Nations public-sector procurement entities – the Pan American Health Organization (PAHO) and UNICEF (which also buys vaccines on behalf of the GAVI Alliance). The purchases of these agencies account for about 5–10% of the value of all vaccine doses produced in the world. UNICEF alone bought 3.2 billion vaccine doses in 2007 at a value of US$ 617 million (*22*) – mainly the traditional vaccines intended for use in developing countries. In 2000, 39% of vaccine doses purchased by these agencies came from suppliers in developing countries. By 2007, that proportion had soared to 60%. A good part of the increase is due to the vaccine requirements of the initiatives mounted to eradicate polio, eliminate neonatal tetanus and maternal tetanus, and reduce deaths from measles.

Planning, producing, protecting

Up to the mid-to-late 1990s, manufacturers in industrialized countries were supplying UNICEF and PAHO with large volumes of vaccines at a low price for use in developing countries. Most of these vaccines were the traditional vaccines recommended by WHO's Expanded Programme on Immunization (EPI) against the basic cluster of six childhood vaccine-preventable diseases – diphtheria, pertussis, tetanus, polio, measles, and tuberculosis. The manufacturers were able to supply these vaccines at a low price for at least three reasons. First, at that time, the richest and poorest countries were using much the same vaccines: by selling the same vaccines at higher prices to the richer countries and at lower prices to the poorer countries (i.e. via UNICEF and PAHO through a tiered, or differential, pricing arrangement), manufacturers were able to recoup their production

costs. Second, manufacturers tended to keep an excess production capacity for many of the traditional vaccines, which enabled them to supply vaccines at a low price to developing countries without having to invest in expanding production capacity. And third, up to the 1980s, there were enough vaccine suppliers to sustain competition among them, which kept vaccine prices low.

The vaccine market has since changed. The three factors conducive to low vaccine prices have evaporated. No longer do industrialized and developing countries use the same vaccines. Industrialized countries increasingly favour second-generation vaccines such as the acellular pertussis vaccine; combination vaccines such as the measles-mumps-rubella combination; and new vaccines such as the pneumococcal conjugate or HPV vaccines. No longer do manufacturers maintain excess production capacity: supply must be equivalent to demand, since the newer vaccines are more costly to make, and too costly or too perishable to keep. And in the traditional markets, with the exception of hepatitis B, there is no longer enough competition among suppliers to keep prices down: there are now far fewer suppliers from industrialized countries than before and those that remain tend increasingly to protect their products from competition through a system of patents and royalties.

Box 6

Vaccine security

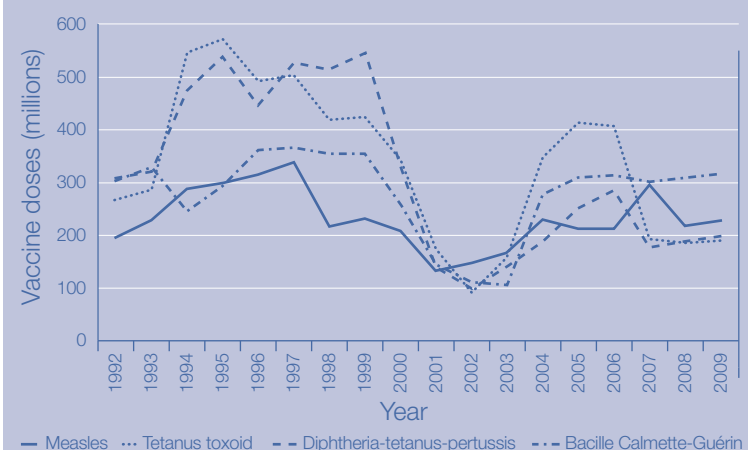
In the late 1990s, a vaccine supply crisis began, which highlighted the need for a new approach to ensure the uninterrupted and sustainable supply of vaccines of assured quality. In the run-up to this period, quantities of WHO-prequalified vaccines offered to UNICEF declined significantly, threatening immunization programmes in the 80–100 countries supported by UNICEF procurement, including over 50% of the routine vaccine requirements for the poorest countries. With growing divergence between the vaccines used in developing and industrialized countries, some manufacturers stopped production of the traditional vaccines and supplies plummeted. A critical shortage of oral polio vaccine (OPV) for immunization campaigns signaled the need for a new approach to doing business with the vaccine manufacturers.

In response, UNICEF, in consultation with vaccine manufacturers and partners, developed the Vaccine Security Strategy (*23*). The aim is to ensure the uninterrupted and sustainable supply of vaccines that are both affordable and of assured quality. The strategy includes a focus on developing a healthy vaccine market through implementing specific vaccine procurement strategies and ensuring that the key elements of accurate forecasting, timely funding, and appropriate contracts are in place. Industry reacted positively to the changes and the trend of decreasing vaccine availability was reversed.

But while the strategy succeeded in reversing the fall-off in the supply of vaccines to UNICEF, vaccine supply remains heavily reliant on a limited number of vaccine manufacturers and continued vigilance is needed.

Figure 3

Quantities of WHO-prequalified vaccines offered to UNICEF



Source: UNICEF Supply Division, 2009

Today, UNICEF is the world's largest vaccine buyer for developing countries, providing a critical pooled procurement function securing vaccines for the world's poorest children. Through its Supply Division based in Copenhagen, Denmark, UNICEF procures vaccines to reach more than half (55%) of the world's children. The Supply Division is also responsible for procuring vaccines on behalf of the GAVI Alliance. In 2007, for example, UNICEF procurement on behalf of GAVI increased by 76% to over US$ 230 million. Procurement of OPV also remains very high, with 2.3 billion doses of vaccine purchased for the Global Polio Eradication Initiative (GPEI) in 2007.

Towards vaccines of assured quality

Making and meeting standards of quality and safety

An internationally accepted system of testing vaccines for their efficacy, quality, and safety has gradually developed over the past century. In the early 1900s, the United States Food and Drug Administration (FDA) in the United States, and the Paul-Ehrlich Institute in Germany, were the first regulatory agencies created to ensure the safety of biological products, including vaccines.

Today, the system in use in all industrialized countries and in a growing number of developing countries covers three main testing phases: preclinical laboratory testing, including animal tests; clinical trials in humans; and surveillance following regulatory approval for marketing.

During the preclinical laboratory phase, a vaccine undergoes biochemical testing and evaluation in laboratory animals for, among other things, characterization of its biochemical components, potency, purity, genetic and biochemical stability, and safety in animals. The clinical (i.e. human) trial stage covers three phases. In Phase 1, the vaccine is tested in a few volunteers for safety and efficacy (immunogenicity), and for an initial indication of the appropriate dose to be used (dose-ranging). Phase 2 tests for safety, immunity-stimulating capacity (immunogenicity), dose-ranging, and efficacy in up to several hundred volunteers. Phase 3 tests for efficacy and safety in several thousand volunteers.

A vaccine that has successfully completed the preclinical and clinical trial stages is ready to be submitted to a regulatory authority for licensure – or approval for human use. A regulatory authority will, among many other things, undertake a review of how the preclinical and clinical tests were conducted and what they found. The regulators will also inspect the production site and make a detailed review of

how the vaccine was produced, starting with the raw materials and ending with the finished product, and will even check the qualifications of the manufacturer's staff.

Following licensure, post-marketing evaluation (Phase 4) involves surveillance for any adverse events. The post-marketing stage also includes testing of vaccine batches for consistency of the production process, and routine inspection of the manufacturing process to ensure continuing conformity to standards of good manufacturing practice (GMP). These inspections can take place at any stage in a vaccine's life-cycle. During the life cycle of a product, a manufacturer may wish to, or have to, introduce variations to the production process. In such cases, the variations are reported to the national regulatory authority for review and approval.

WHO's efforts to ensure the safety and quality of vaccines uses a system that first establishes international standards of vaccine efficacy, safety and quality, and then monitors the extent to which a given licensed vaccine meets those standards. Setting international standards is the role of WHO's Expert Committee on Biological Standardization. Monitoring how fully a vaccine made or used in a given country complies with these standards is the role of the country's national regulatory authority. In 1981, the Expert Committee on Biological Standardization called upon all countries to have a national regulatory authority.

All industrialized countries have a reliable, properly functioning vaccine regulatory system, but only about one quarter of developing countries do. Having an independent and functional national regulatory authority is a good start for a country wishing to ensure that the vaccines it uses meet internationally agreed standards of safety, efficacy, and quality. Vaccines that have successfully emerged from the six-function national regulatory authority oversight (see Box 7) with no "unresolved confirmed reports of quality-related problems" are regarded by WHO as "vaccines of assured quality". In 2008, about 70% of vaccines met the WHO criteria for assured quality.

Box 7

How good is a national regulatory authority?

For a country using or making vaccines, simply having a national regulatory authority is not enough. The national regulatory authority must be able to work independently (of vaccine manufacturers and of the government, for example); it must have the legal basis that defines its mandate and enforcement power; and it should perform between two and six core functions, depending on how the country acquires its vaccines.

For countries that procure their vaccines through UN agencies (UNICEF, WHO, or PAHO), core functions of the national regulatory authorities are:

(1) issuing a marketing authorization, and licensing vaccine production facilities and vaccine distribution facilities;

(2) ensuring that post-marketing surveillance is carried out, with a focus on detecting, investigating and responding to unexpected adverse events following immunization.

Two additional core functions for countries that procure their vaccines directly in the domestic or international market are:

(3) verifying consistency of the safety and quality of different batches of vaccine coming off the production line (lot release);

(4) accessing, as needed, a national control laboratory in order to test vaccine samples.

For countries that manufacture vaccines, two additional functions are required. The sixth function is also recommended for any countries that host clinical trials of vaccines:

(5) inspecting vaccine manufacturing sites and distribution channels;

(6) authorizing and monitoring clinical trials to be held in the country.

The problem, however, is that in some countries the national regulatory authority lacks the capacity – the human and material resources, the experience, the know-how, or the political backing – to assess and monitor whether a vaccine is of assured quality (i.e. compliant with GMP, safe, and effective). To address this problem, WHO launched an initiative in 1997 to strengthen the capacity of national regulatory authorities.

Strengthening national regulatory authorities

The ultimate objective of WHO's initiative to strengthen the regulatory capacity of countries is for all countries to have a reliable, properly functioning national regulatory authority. To achieve its objectives, the initiative undertakes a five-step capacity-development process tailor-made to the requirements of each individual country.

1. Defining and then regularly updating benchmarks and other tools used to assess whether a national regulatory system is capable of ensuring that the vaccines used and/or made in its country are of the required standards of quality, efficacy, and safety.
2. Using benchmark indicators and other pertinent tools to assess the national regulatory system.
3. Working with the country's regulators and other health officials in drawing up an *institutional development plan* for dealing with any shortcomings in the country's regulatory system and for building upon the existing regulatory strengths in the country.
4. Implementing the institutional development plan, which may involve technical support or staff training to perform regulatory functions.
5. Re-assessing the national regulatory authority within two years to evaluate progress.

When the initiative started in 1997, only 37 (19%) of WHO's 190 Member States, had a reliable, fully functioning national regulatory authority. By the end of 2008, the

number had risen to 58 (30%) of WHO's 193 Member States. Priority countries for the initiative are those that have vaccine manufacturers and thus contribute to the world's vaccine supply. In 1997, 20 (38%) of the 52 vaccine producing countries had a reliable, functioning national regulatory authority. By the end of 2008, the numbers had risen to 33 (69%) of 48 vaccine producing countries.

A regulators' network for developing countries

The power of networking is being applied to the quest for stronger regulatory oversight in countries where regulation is lacking or inadequate. These countries are increasingly being asked by vaccine manufacturers to host clinical trials of vaccines intended for use in developing countries. Clearly, these vaccines must be tested for their safety and efficacy in the "real-life" conditions of these developing countries. The danger is that in countries with little or no regulatory capacity, the trials may take place without due respect for international standards of good clinical practice, of ethics, and of vaccine safety, quality, and efficacy.

In 2004, therefore, WHO launched the Developing Countries Vaccine Regulators Network, aimed at strengthening the regulatory capacity of developing countries to assess clinical trial proposals and to oversee ongoing clinical trials. The network allows members to share expertise and information – particularly information about problems of vaccine safety and efficacy that may have surfaced during a clinical trial. Network participants also inspect clinical trials for their adherence to good clinical practice.

In 2006, the African Vaccine Regulatory Forum was established, and is working in much the same way as the developing countries' network – clinical trials on candidate vaccines against diseases including AIDS, malaria, and meningitis are under way in the 19 Forum countries, where regulatory oversight is weak or altogether absent.

Harmonizing and standardizing vaccine regulation

Strengthening regulatory capacity also means bringing some uniformity to the way regulatory oversight is practised in different countries and, more importantly, to the standards of safety, efficacy, and quality they apply to vaccines. At the end of 2008, 58 countries possessed a reliable national regulatory authority, but not all were applying the same regulatory standards for vaccine licensure. The problem is that vaccine manufacturers – both in developing and in industrialized countries – are increasingly seeking a global market for their products. Clearly, the diversity of regulatory standards from one country to another can seriously complicate international trade in vaccines. It can also force manufacturers to obtain separate authorizations for each intended market – a long, costly, and uncertain process that runs counter to current endeavours to accelerate the introduction of new vaccines into countries' immunization programmes. Hence the need for regulatory harmonization.

Vaccine quality testing by the Division of Biological Products at the Department of Medical Sciences, Ministry of Public Health, Thailand.

In the Americas, a Vaccines Working Group of the Pan American Network on Drug Regulatory Harmonization was set up in 2005 to work with regulatory officials from PAHO Member countries in establishing guidelines on regulatory standards for licensure of vaccines to be used in the region. In Europe, harmonization is a major objective of the European Medicines Agency, a regional regulatory authority. At present, vaccines for use in the European Union are regulated either by the European Medicines Agency itself or by a European Union Member State, in which case the licensure of the vaccine is recognized, through a mutual recognition agreement, by all other European Union states.

Another entity whose objectives include greater regulatory harmonization is the WHO International Conference of Drug Regulatory Authorities, which, since 1980, has provided regulatory authorities of WHO Member States with a forum for discussion and collaboration on the regulation of medicinal products, including vaccines.

In 1989, the WHO International Conference of Drug Regulatory Authorities laid plans for an international harmonization initiative run jointly by regulatory authorities together with pharmaceutical industry input. A year later, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was born. The Conference, held every two years, brings together the regulatory authorities and pharmaceutical industry experts of Europe, Japan, and the United States. Their aim is to harmonize technical guidelines and licensing requirements for pharmaceutical products, including vaccines. Topics chosen for harmonization relate to criteria for assessing the safety, quality, and efficacy of these products. The Conference is credited with achieving substantial progress in harmonizing technical guidelines and applications for licensing.

Generally speaking, progress towards harmonization of standards is slow but steady. An encouraging sign is that the recommendations of the WHO Expert Committee on Biological Standardization on regulatory standards for pneumococcal conjugate vaccines and vaccines against pandemic influenza – published in 2005 and 2008,

respectively – are being applied by virtually all national regulatory authorities in the world.

Innovative regulatory pathways

Traditionally, when a national regulatory authority in a developing country considers whether to host clinical trials of a new vaccine produced in another country, or whether to adopt a new vaccine in its country's immunization programme, it would be favourably influenced if the vaccine had been approved for human use by the European Medicines Agency or the FDA. However, in 2004 and 2007, respectively, both agencies decided to no longer accept vaccines for marketing approval where they are intended for use exclusively outside their geographical jurisdictions. This decision raised a fear that the supply of new life-saving vaccines to developing countries may be hindered or delayed for lack of authoritative marketing approval.

In 2005, therefore, the European Medicines Agency introduced a mechanism, known as "Article 58", whereby it issues a "scientific opinion" based on the customary Agency process but with the addition of an evaluation of the vaccine by WHO-appointed experts from countries where the vaccine is intended to be used. This mechanism, although stopping short of formally granting a licence, involves all the steps of a regular licensing procedure. It carries enough weight to allay fears that vaccines may be introduced without having been assessed for safety and quality. Moreover, the FDA and the European Medicines Agency have agreed to work with national regulatory authorities or with networks of regulators in the regions, to provide advice on vaccine safety and efficacy as well as on clinical trial protocols. Similar collaborative agreements are being forged in other parts of the world, notably in Asia.

Box 8

Prequalification – flagging vaccines fit for public purchase

In 1987, a prequalification system was established by WHO to advise United Nations vaccine procuring agencies on the acceptability, in principle, of vaccines available for purchase by these agencies.

In order to be included in the list of WHO prequalified vaccines (*24*), a vaccine must, inter alia, be licensed and be under continuous regulatory oversight by an independent, fully functioning national regulatory authority in the country where the vaccine is manufactured.

The United Nations procuring agencies invite tenders only for vaccines on WHO's list of prequalified vaccines. In addition, many countries that do not use these procuring agencies but buy vaccines directly from manufacturers also use the WHO list to select vaccines for purchase.

The prequalification process, in addition to assessing individual vaccines, also determines how well the national regulatory authority of the country where the vaccine is made is fulfilling its regulatory role in enforcing manufacturers' compliance with WHO recommended standards.

Prequalification status normally lasts for two years, after which the vaccine is reassessed to determine if it – and the manufacturer – still meet the standards required to retain prequalification status.

The prequalification system is widely credited with contributing to the growing number and proportion of quality vaccines being supplied by manufacturers in developing countries, such as Brazil, Cuba, India, Indonesia, and Senegal. In the early 1990s, for example, manufacturers in industrialized countries were supplying all the vaccines purchased through United Nations agencies. By 2008, more than half were coming from manufacturers in developing countries.

Not surprisingly, applications for prequalification evaluation have escalated in recent years. They are coming not only from manufacturers in developing countries, but also from those in industrialized countries. As of mid-2008, all five major multinational companies of the Big Pharma marketed products that had passed a prequalification assessment.

Chapter 3

Immunization: putting vaccines to good use

Key messages

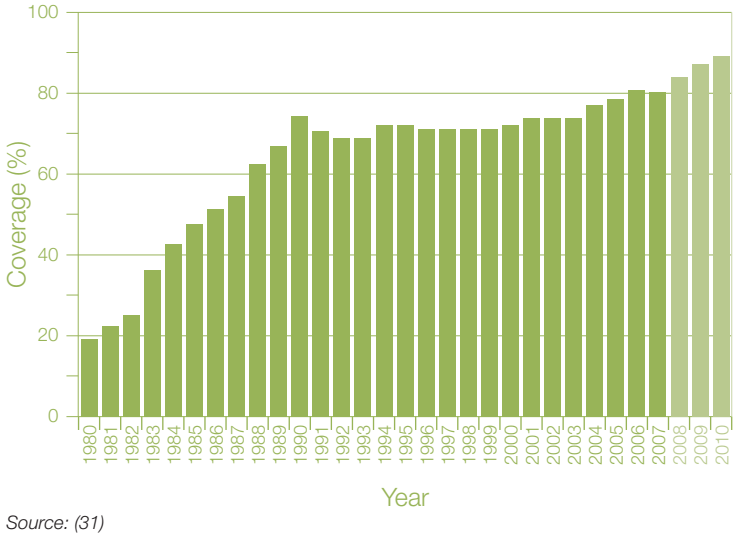
- From 2000 to 2007, intensified vaccination campaigns resulted in a 74% reduction in measles deaths globally.
- Polio has been eradicated in three of WHO's six regions and is today endemic in only four countries – down from 125 countries in 1988.
- Integrating immunization with the delivery of other health interventions can boost immunization coverage and accelerate the achievement of MDG 4.
- Targeted immunization strategies for difficult-to-reach populations increase equity in access to vaccines.
- Weak health systems are a major constraint on the effectiveness of immunization programmes.
- Strong and effective leadership, and national ownership of immunization programmes, are key components of a successful national immunization programme.
- There is a need to foster increased public demand for vaccines.
- Disease surveillance and monitoring programmes need to be strengthened at all levels.
- False or unsubstantiated rumours about vaccine safety can undermine immunization programmes and cost lives.

Year after year, immunization programmes the world over have been administering vaccines to young children to protect them against a cluster of common childhood diseases – diphtheria, tetanus (including tetanus in mothers and newborns), pertussis, measles, polio, and tuberculosis. Increasingly, with the development of new and improved vaccines (see Chapter 2) more diseases are being added to this traditional childhood cluster of vaccine-preventable diseases. They include hepatitis A, hepatitis B, Hib disease, mumps, pneumococcal and meningococcal disease, rubella, and more recently, rotavirus diarrhoea, and cancers due to HPV. In addition, immunization programmes are increasingly reaching out to other population groups – older children and adolescents (for meningococcal disease and HPV disease), elderly people (for pneumonia, shingles, and influenza), and people exposed to locally prevalent diseases (for yellow fever and Japanese encephalitis).

The main focus, though, of national immunization programmes and of the EPI, which WHO created in 1974 to establish and coordinate the work of these

Figure 4

Global three-dose DTP coverage for 1980–2007 and goals for 2008–2010



Source: (31)

programmes, is still on infants. As of 2007, about 80% of children under one year old were receiving the full three-dose schedule of the DTP vaccine, which serves as a measure of how well immunization programmes are functioning (see Fig. 4). The life-saving impact of national immunization programmes is impressive (see Box 9).

Box 9

The impact of immunization

The selected data below testify to the impact of immunization in achieving its main objective: to reduce the number of children dying, falling ill, or being disabled as a result of diseases that can be prevented by vaccines.

- Every year immunization averts an estimated 2.5 million deaths among children under five years old.
- Between 2000 and 2007, the number of children dying from measles dropped by 74% worldwide, from an estimated 750 000 to an estimated 197 000 children (*9*). In addition, immunization prevents sickness as well as lifelong disability, including measles-related deafness, blindness, and mental disability.
- In 1988, polio was endemic in 125 countries and paralyzing an estimated 350 000 children every year (close to 1000 cases a day) (*25*). By the end of 2007, polio had been eradicated in three of WHO's six regions – the Region of the Americas, the European Region, and the Western Pacific Region. In mid 2009, indigenous poliovirus remained endemic in only four countries: Afghanistan, India, Nigeria and Pakistan. The numbers of new cases reported for these four countries in 2009 as at end June were: Afghanistan: 10; India: 89; Nigeria: 321; and Pakistan: 20 (*26*).
- Following implementation of the rubella elimination strategy in the Americas, the number of reported cases of rubella declined by 98% between 1998 and 2006 (*27*).
- By 2000, 135 countries had eliminated neonatal tetanus (*25*) and by 2004, annual deaths from neonatal tetanus had fallen to an estimated 128 000, down from 790 000 deaths in 1988 (*28, 4*).

The unfinished immunization agenda

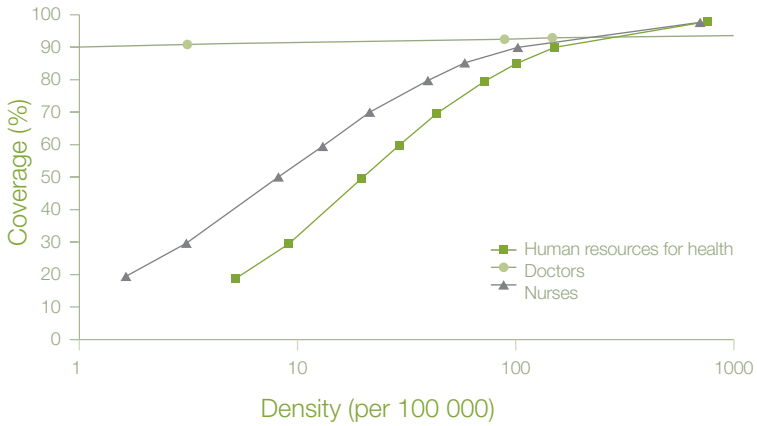
Remarkable progress has been made in reducing disease incidence and deaths from vaccine-preventable diseases. But a lot remains to be done in order to achieve the targets of the GIVS set by WHO and UNICEF (see Chapter 1). Those targets call, among other things, for all countries to be immunizing by 2010 at least 90% of their total child population under five years old, and at least 80% of children under five in every district throughout the country.

Achieving these targets will not be easy. One critical barrier is the underlying weakness of the health systems in many developing countries. The ability of health systems to deliver services such as immunization is often constrained by a lack of political and financial commitment, poor management skills, and weak monitoring and information systems. This is compounded by a severe shortage of health workers, due to high rates of sickness and deaths, and the loss of health workers to higher-paid jobs overseas. Many health workers that remain are often poorly distributed across the country, inadequately trained and unsupervised, badly paid, unmotivated, and often have skills that are ill-matched to the work they have been assigned to do.

Recent reports by WHO (*29,30*) have warned that countries experiencing the greatest difficulties in meeting the MDGs – mainly in sub-Saharan Africa – face absolute shortfalls in their workforce. Of the 57 countries worst affected by extreme shortages of health workers, 36 are in Africa, where AIDS and worker migration have depleted the health workforce. Countries in Africa account for 24% of the global disease burden but have only 3% of the world's health workers. Figure 5 illustrates how immunization coverage is affected by the density of health workers.

Figure 5

Immunization coverage and density of health workers



Source: (29)

In a poorly functioning health system it is difficult to ensure equity in access to immunization, and as a result, there may be a high degree of variability in immunization coverage. There are unreached populations and immunization failures in every country but 73% of the children currently unreached with three doses of DTP immunization live in just 10 countries – all in Asia and Africa (*31*).

Many of the unimmunized children live in isolated rural areas without easy access to health facilities. Some live in fragile states where public services are weak or non-existent and where access to health facilities may be severely restricted due to ongoing conflict. Others live in poor, densely populated urban areas and informal settlements, or among displaced populations that are on the move and especially difficult to reach. Some – like the children of "illegal" immigrants in urban areas, or the many children whose births go unregistered – may not even officially "exist". In India, recent studies have also highlighted a number of social factors that may inhibit mothers from seeking immunization, including gender, religion, and social status (caste). Additional operational research is needed in other regions to confirm these findings.

In addition to a weak health system, another barrier to achieving the GIVS targets, also rooted in the overall health system, is the difficulty of delivering vaccines – especially the newer vaccines – through an infrastructure and logistical support system that in many developing countries is characterized by poor vaccine stock management, poor vaccine handling and storage, and high wastage. Against this backdrop, the introduction of new vaccines, some with non-standard characteristics – i.e. single dose in pre-filled glass syringes as opposed to multi-dose vials – require new vaccine management strategies and increased storage capacity, putting a huge strain on an already weak supply chain.

A third barrier – especially among the poorest populations – is a lack of information and understanding about the importance of vaccines and immunization. In some communities, the value of an intervention that "helps healthy people to stay healthy" may suffer in comparison with medicines that can visibly heal the sick. And where parents lack a basic understanding of how vaccines work, children may be vaccinated once but fail to return for the required follow-up doses. To counter these and other misconceptions, well-targeted information and social mobilization campaigns are needed to transform a community's "passive acceptance" of immunization into a well-informed demand for vaccines that can protect their children against life-threatening diseases.

A fourth barrier relates to the fear of immunization, fanned by reports of adverse events that are rumoured or suspected of being related to vaccines. With ever-increasing access to Internet-based information, an unsubstantiated rumour about vaccines can rapidly circle the globe and undermine immunization services, sparking outbreaks of disease and untold deaths. Since fear of vaccines and immunization often stems from a lack of information, people need to know how safe a vaccine is and how it can reduce disease and deaths.

A fifth barrier, addressed in Chapter 4, is the need to secure additional financing to meet a projected shortfall in funding needed to achieve the global immunization

goals. This comes amid growing concern that the current global financial and economic crisis may have an adverse effect on the funds available for development assistance, including for immunization.

The following sections outline the steps being taken to overcome the barriers to achieving global immunization goals.

Box 10

Strengthening health systems – the six building blocks

In an effort to promote a common understanding of what a health system is, WHO has defined six "building blocks" that make up a health system (*30*). The aim is to clarify the essential functions of a health system and set out what a health system should have the capacity to do.

- Good **health services** are those which deliver effective, safe, quality personal and non-personal health interventions to those who need them, when and where needed, with minimum waste of resources.
- A **well-performing health workforce** is one that works in ways that are responsive, fair and efficient to achieve the best health outcomes possible, given available resources and circumstances (i.e. there are sufficient staff, fairly distributed; they are competent, responsive and productive).
- A well-functioning **health information** system is one that ensures the production, analysis, dissemination and use of reliable and timely information on health determinants, health system performance and health status.
- A well-functioning health system ensures equitable access to essential **medical products, vaccines and technologies** of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use.
- A good **health financing** system raises adequate funds for health, in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment associated with having to pay for them. It provides incentives for providers and users to be efficient.
- **Leadership and governance** involves ensuring strategic policy frameworks exist and are combined with effective oversight, coalition-building, regulation, attention to system-design and accountability.

Extending the benefits of immunization equitably within countries

In 2002, 135 of WHO's Member States were reaching a national average of more than 80% of children under one year old with the full three doses of the DTP vaccine. A closer look, though, found that in some of these countries, there were districts where fewer than 50% of the children were receiving the full three doses of this vaccine.

In 2002, therefore, WHO, UNICEF, and other partners devised the Reaching Every District (RED) strategy, which takes the district as its primary focus and aims to improve equity in access to immunization by targeting difficult-to-reach populations. The strategy provides support – including training – to ensure that district-level immunization managers apply the principles of "good immunization practice". These principles call for district health officials to identify local immunization-related problems and oversee remedial action, while ensuring that vaccines are delivered regularly in all districts. "Outreach" staff take vaccines to hard-to-reach villages and make sure that all the children are vaccinated. The RED strategy also calls for timely collection of data on vaccine coverage and other vaccine-related activities (logistics, supply, and surveillance), proper supervision of immunization health workers, and involvement of communities in the planning and delivery of immunization services. The expertise, knowledge, and human resources of the GPEI were used to plan and implement the RED approach in many countries, working in close collaboration with national immunization programmes and key partners, notably the GAVI Alliance.

By mid-2005, 53 countries, mostly in Africa and Asia, had begun implementing the RED strategy to varying degrees (see Fig. 6) (*32*). In 2005, an evaluation of five countries in Africa that had implemented RED found that the proportion of districts with over 80% of children fully immunized with DTP vaccine had more than doubled (*33*). More recently, a nine-country evaluation carried out by the CDC in 2007 found that the RED strategy had been adopted by 90% of all districts within these countries.

However, few of the nine countries were implementing all five components of the strategy (see Box 11). The CDC evaluation noted that further studies would be needed over a longer period to assess the effectiveness and sustainability of the strategy.

Box 11

Reaching Every District (RED)

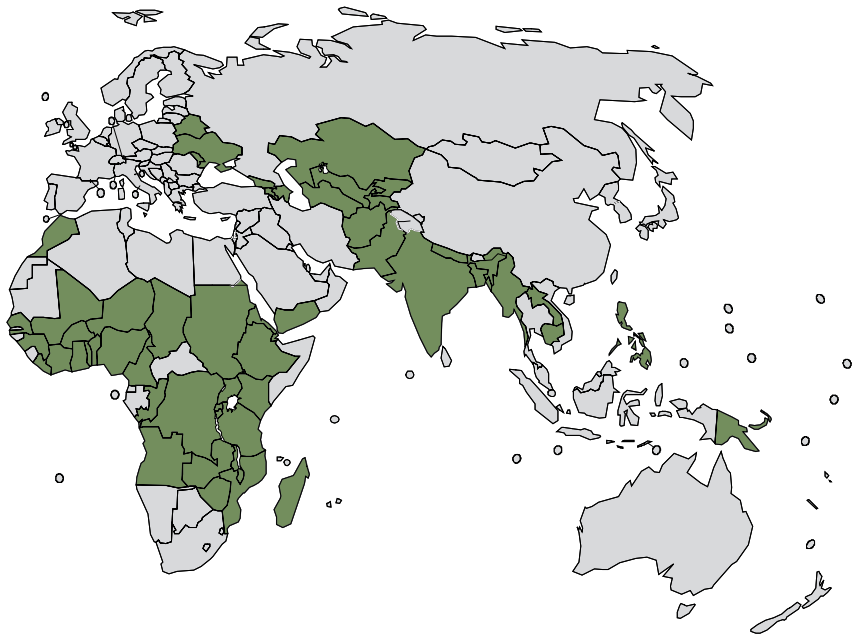
The Reaching Every District (RED) strategy aims to improve equity in access to immunization by targeting difficult-to-reach populations. It involves:

- re-establishment of regular outreach services;
- supportive supervision and on-site training;
- community links with service delivery;
- monitoring and use of data for action;
- better planning and management of human and financial resources.

Special measures are needed to ensure that difficult-to-reach populations are reached with vaccines and other health interventions. These include efforts to:

- map (geographically, socially, and culturally) the entire population – through micro-planning at the district or local level – in order to identify and reach the target populations at least four times a year;
- reduce the number of immunization drop-outs (incomplete vaccination) through improved management, defaulter tracing, and social mobilization and communication during immunization contacts, and by avoiding missed opportunities to vaccinate;
- strengthen the managerial skills of national and district immunization providers and managers, and develop and update supervisory mechanisms and tools;
- provide timely funding, logistics support, and supplies for programme implementation in every district.

Figure 6
Countries implementing the RED strategy in 2005



Source: (32)

Reaching more children through campaign strategies

Immunization is mostly delivered by health workers as a pre-defined series of vaccines, administered in a given schedule to children of a given age. In many countries, tetanus toxoid vaccine is also provided to pregnant women, in order to prevent maternal and neonatal tetanus. It is mostly during contacts in health centres that such vaccines are given, or in the case of pregnant women, during antenatal care visits. In remote areas, where access to health centres is very limited, immunization may be partly, or entirely, provided through outreach services. In some very isolated villages, access may only be possible during certain periods of the year, and mobile teams are needed to deliver vaccines and other essential health interventions.

In countries with well-functioning health systems and where the populations have good access to the system, routine immunization contacts may be sufficient to control vaccine-preventable diseases. However, so-called “supplementary immunization activities” may be needed to improve protection at population levels – for example, to achieve some of the global elimination or eradication goals, or to stem outbreaks. In these scenarios, a mass-mobilization campaign-style approach is adopted, during which all individuals receive a certain vaccine, often regardless of prior immunization. Efforts to eradicate polio, eliminate measles, and eliminate maternal and neonatal tetanus all rely on this approach – in addition to routine immunization – either nationwide or targeted at selected high-risk areas only. For example, measles “catch-up” campaigns are used to reach children who may have missed out on measles immunization during their first year of life and children who may not have developed a protective immune response when immunized the first time round. Campaigns have also been used to control outbreaks of measles, yellow fever, diphtheria, and epidemic meningococcal meningitis.

A health worker marks a child's finger to show that measles vaccine has been administered — during measles vaccination campaign in Côte d'Ivoire in November 2008.

A campaign has the potential to rapidly reach more children, especially those missed by routine immunization. And they tend to cover more equitably all socioeconomic sections of the target population. Uptake of measles vaccine in a campaign in Kenya showed equal uptake of over 90% in all wealth quintiles, compared to routine immunization that reached less – only 60% – of the poorest wealth quintile (*34*).

Box 12

Mass-mobilization to extend the reach of immunization

Through mass-mobilization, the campaign-style approach to immunization often manages to reach more people than can be reached through the regular immunization contacts. The "immunization weeks" in many American and European countries, and the "child health days" in numerous African countries, have been using mass-mobilization techniques to ensure universal coverage as much as possible.

The child health days were originally introduced by UNICEF to deliver vitamin A supplementation, but now offer an integrated package of preventive services that can include, depending on local needs, vitamin A, immunization, deworming tablets, growth monitoring, and insecticide-treated bednets. They are usually conducted twice a year and target a large proportion of the population. During 2008, over 52 countries conducted child health days, compared with 28 countries in 2005. Over the same period, the number of countries conducting child health days in east and southern Africa almost doubled from 10 to 18, and tripled in west and central Africa from 5 to 16.

Immunization weeks in the Americas have proved particularly effective in reaching difficult-to-reach people, such as those living in isolated border communities where immunization coverage is limited. Debates, workshops, training sessions, exhibitions, and media events are among the activities on the agendas of these weekly campaigns. In Europe, immunization weeks have mainly had a social mobilization function. Immunization weeks are now organized in 30 countries in Europe – up from 9 in 2003; immunization weeks in the Americas are now organized in 45 countries – up from 19 in 2003.

All this requires a strong support system, from micro-planning logistics to well-trained health workers, supported by adapted communications and monitoring mechanisms. These are very much the same components that are the basis of any health care system or any other public health programme.

Greater awareness fuels demand

Renewed efforts are needed to ensure that the public, policy-makers, and health workers understand the vital importance of immunization for both children and adults. This is critical in maintaining support for national immunization programmes and in providing information about the introduction of new vaccines and technologies to a national immunization schedule.

Parents in particular need to understand why they should seek immunization. In some cases mothers may understand why their children need to be immunized, but they may lack awareness of the need for follow-up doses to complete the schedule. Others may refuse immunization for social or cultural reasons.

There is a need for grass-roots mobilization for immunization at community level, especially in areas where there is high illiteracy and poor access to the media. Countries need to ensure that innovative methods are used to reach these communities – for example, through engaging a network of community leaders such as religious leaders, women's associations, and village volunteers. The active involvement of community members to assist health workers – by informing the community about an upcoming immunization session, helping to track children who are due for their next dose of vaccine, and helping to identify newborns or pregnant women, for example – is one way of building up trust, and ensuring that the community is motivated to demand immunization and is fully engaged as a partner, not just a recipient of vaccines.

Creating demand in communities, though, is only one side of the coin. The health system – particularly the health workers who vaccinate community members – must also be able to reliably meet that demand. Weak immunization performance and a failure to deliver services due to transport problems, staff shortages, inadequate supplies, or a break in the cold chain, can lead to a loss of confidence and fall-off in demand for immunization.

Despite longstanding efforts by the international community, particularly UNICEF, to create awareness of and demand for vaccination among community members, many communities still do not actively seek immunization. Low demand persists because of poor understanding about the benefits of vaccines, misconceptions about vaccine safety, perceived inconvenience or difficulty in accessing services, and low prioritization of immunization – especially among people who are barely surviving.

The basic message so far has been relatively simple: *Diseases are a threat. Take the vaccine and prevent the disease*. But for some of the newer vaccines the situation is more complex. Rotavirus and pneumococcal vaccines, for example, will only prevent a proportion of all cases of diarrhoea and pneumonia respectively, because not all causes of diarrhoea and pneumonia are vaccine-preventable. But even though the message is not so simple, immunization against these diseases creates an opportunity to actively promote the prevention and treatment of diarrhoea and pneumonia, which together account for over 36% of deaths among children under five. This includes early and exclusive breastfeeding, access to community case management, zinc supplementation, reduction of malnutrition, hand-washing with soap, and control of environmental risk factors such as water and sanitation (for diarrhoea) and indoor air pollution (for pneumonia).

Box 13

Reaching out to communities

In an effort to increase demand for immunization among community members, UNICEF has identified some fundamental communication approaches to help health workers and local public health officials provide information about vaccines.

- Improve the quality of vaccine delivery services before trying to convince community members of the need to use them.
- Adapt immunization services to the local culture so that community members can come to trust them.
- Engage local leaders as spokespersons for immunization, especially traditional and religious leaders, who usually have high credibility and a large following among community members.
- Identify strategies for reaching women: they are the primary caretakers of young children but usually have less access to mass media and often face obstacles to accessing health services.
- Emphasize that the disease constitutes a threat but a threat that can be reduced by vaccination, as well as by key behaviours such as breastfeeding.
- Explain how to access local immunization services.
- Engage marginalized or underserved communities, which often suffer greater disease burdens than other segments of society.
- Evaluate the impact of the communications strategy on vaccine coverage rates and on efforts to improve knowledge of, and trust in immunization services.

Surveillance and monitoring: essential health system functions

In addition to its key role in programme planning and monitoring, priority setting, and mobilization and allocation of resources, an effective disease surveillance system provides the critical intelligence that is needed to guide an immunization programme. It provides the information needed to monitor trends in disease burden

and the impact of disease control programmes, as well as the data needed to guide public health policy and to monitor progress towards global goals.

The GIVS goal to vaccinate 90% of children at the national level and 80% in each district by 2010 (see Chapter 1), and related approaches, such as the RED strategy, that rely heavily on the use of data to drive strategic interventions, have highlighted the need to strengthen routine surveillance and monitoring at all levels.

Over the past decade, progress has been made in setting up or improving regional, national, and global systems for the surveillance of vaccine-preventable diseases. An example of an outstanding, high-performance surveillance system is the global polio surveillance network, which enables rapid detection of polio cases throughout the world, especially in developing countries. In many developing countries where disease surveillance systems are weak, polio surveillance systems have been expanded to include reporting on other vaccine-preventable diseases such as measles, neonatal tetanus, and yellow fever.

In addition to the need to improve case-based surveillance and outbreak response for diseases such as measles and polio, surveillance systems need to be strengthened for other vaccine-preventable diseases. The availability of new vaccines to combat diseases such as Hib, meningococcal disease, pneumococcal disease, and rotavirus diarrhoea provides the potential to significantly reduce childhood illness and deaths. Effective surveillance systems are indispensable in guiding the decision-making process for the introduction of new vaccines, monitoring the impact of these new vaccines on disease patterns, and conducting post-marketing surveillance to ensure the safety of all newly introduced vaccines.

Disease surveillance and monitoring systems are also expected to give an early warning of impending or ongoing disease outbreaks – providing a first line of defence against the threat of emerging or pandemic diseases, including influenza.

The revised International Health Regulations, which entered into force in mid-2007, require Member States to establish and maintain core capacities for surveillance at the local, intermediate, and national levels. The regulations stipulate that countries should be able to detect, provide notification of, and take initial steps to control outbreaks of diseases of global health importance. This intelligence provides a platform for high-level advocacy for surveillance support within countries, and a new opportunity to build on synergies between different existing surveillance systems.

In 2007, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) endorsed a new Global Framework for Immunization Monitoring and Surveillance. This framework calls for: alleviating health system barriers to surveillance; building capacity for surveillance at national, regional, district, and health facility levels as well as in sentinel sites, where appropriate; assuring quality data; and linking surveillance of vaccine-preventable diseases and immunization monitoring with other national surveillance systems.

Efforts to strengthen immunization surveillance, monitoring, and evaluation can also help alleviate "system-wide" barriers, through providing better data to improve health system management. For example, immunization surveillance data on coverage and drop-out rates can be used as an indicator of the equity of health system performance – a measure of its ability to continue to provide health services to difficult-to-reach populations (*35*).

Box 14

What it takes to run a successful national immunization programme

- Political motivation.
- Strong and effective leadership and national ownership of immunization programmes.
- Country-driven policies, planning, monitoring, and reporting.
- An effective National Immunization Technical Advisory Committee to help facilitate evidence-based decision-making at country level.
- Sound decision-making on which vaccines to schedule, based on local, regional, and global data.
- Use of routine surveillance data (immunization coverage, vaccine use and wastage, and incidence of diseases) for programme management.
- The capacity for efficient financial planning, including multi-year planning and a budget line for immunization in the national health budget, as well as knowledge of available international funding mechanisms.
- A well-functioning national regulatory authority.
- A motivated, well trained, and well supervised staff.
- A surveillance system for detecting, investigating, and responding to adverse events following immunization.
- Cold-chain facilities and logistics.
- A well-functioning health system that facilitates the delivery of immunization to all communities.

Optimizing the delivery of vaccines

As new vaccines come on the scene (see Chapter 2) and as more vaccine doses are needed to immunize more people in more age groups, the logistics and infrastructure needed to transport vaccines safely and efficiently from the manufacturer to the

end user – without jeopardizing their potency – have in many countries become increasingly complex. In some regions, cold storage facilities are inadequate to cope with the massive increase in the volume of vaccine being shipped, which is now greatly inflated by the high-volume packaging of the new vaccines. This logistical challenge, coupled with the rising cost of vaccines, means that managers must be able to maintain lower levels of vaccine stocks, accurately forecast vaccine demand, reduce wastage, and prevent break-downs in cold-chain equipment, which can interrupt the supply of vaccines and entail major financial losses.

In some cases, the increased volume of packaging used for a new vaccine exceeds the cold storage space available at the country level. In addition, there are major implications for the cost and logistics of international transport. For example, the first shipment of pneumococcal conjugate vaccine (679 500 doses) to Rwanda in March 2009, required over 40 cubic metres of storage space in the national cold storage. But the shipping volume was even higher at 370 cubic metres. As a result, a plane had to be chartered to deliver the vaccine to Rwanda.

In addition, the packaging and presentation of these new vaccine products – often single-dose presentation, pre-filled glass syringes, and bulky packaging – have implications not only for storage but for service delivery strategies, waste disposal, and the need for training and supportive supervision.

In 2007, WHO and a non-profit organization, PATH, with the support of the Bill & Melinda Gates Foundation, launched Optimize – a global effort to help countries manage the growing complexity of immunization logistics. Optimize aims to make use of technological and scientific advances to help guide the development of new products and ensure maximum efficiency and safety in the field.

For 30 years, countries have relied on the same system to store and transport vaccines safely from manufacturers to recipients – the cold chain – which keeps vaccines at controlled temperatures throughout. As long as vaccines could be

acquired at low cost and in large quantities, this system worked, despite high wastage rates (more than 50% for some vaccines) and high maintenance costs.

Today, as new, more costly vaccines arrive on the market, the landscape is changing. In addition, technology innovations that protect these vaccines and reduce waste – such as single-dose vials and prefilled syringes – require significantly more space on trucks and in refrigerators, putting even more pressure on the system. However, there is relief in other areas: some of the vaccines that currently pass through the system are now heat-stable, and the addition of the vaccine vial monitor – a small sticker that indicates exposure to heat – may mean that these vaccines can move out of the cold chain altogether.

Tetanus toxoid vaccines, with vaccine vial monitors attached, being packed at a vaccine manufacturing facility in Bandung, Indonesia.

Optimize is working directly with manufacturers and countries to identify problems and test solutions that could have a global application. One possible solution could be to use the passively cooled carts used to deliver fruit and vegetables to European supermarkets, to transport vaccines within developing countries. These carts use no electricity as they are charged with well-insulated plates that have been pre-refrigerated or frozen and that maintain consistently cool temperatures for long periods of time. They are also are capable of carrying a significantly higher volume than traditional vaccine cold boxes, and could help reduce costs.

Elsewhere, in response to the high energy costs and unreliable power supply in developing countries, Optimize is examining the use of battery-free solar refrigerators as a possible means of improving the reliability and efficiency of refrigeration systems at health centres and clinics.

Another initiative is the establishment of an inter-agency advisory group to recommend vaccine presentations and packaging for use by developing countries. The Vaccine Presentation and Packaging Advisory Group (VPPAG) provides a forum for representatives of UN agencies, experts involved in public sector delivery of vaccines, and industry representatives – both the International Federation of Pharmaceutical Manufacturers Association (IFPMA) and the Developing Country Vaccine Manufacturer's Network (DCVMN) – to discuss vaccine presentation and packaging issues in order to support the development of products tailored for use in developing country settings.

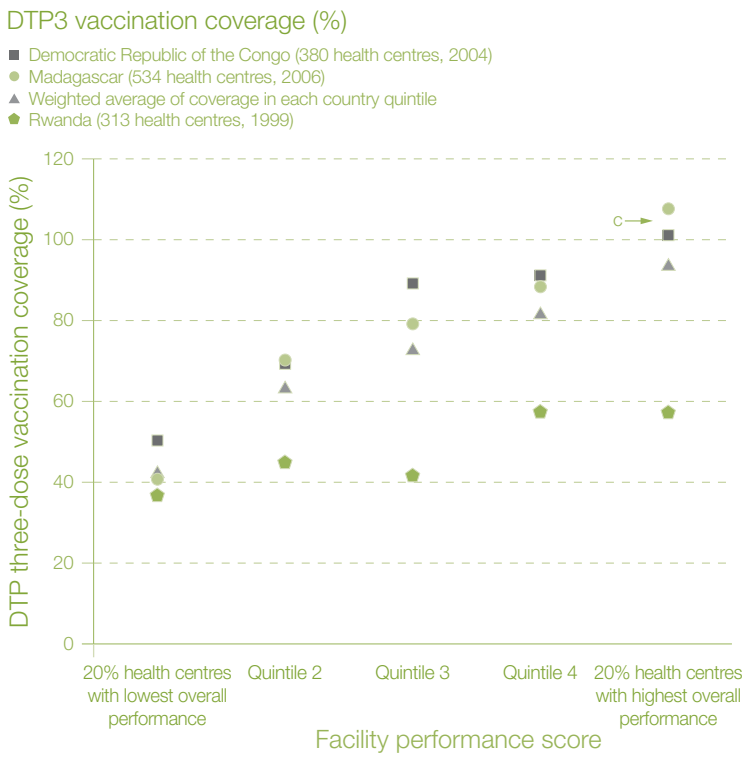
VPPAG was established in 2007 by the GAVI Alliance to respond to industry requests in relation to the packaging and presentation of the pneumococcal conjugate vaccine and rotavirus vaccine. In 2008, WHO took over the role of convening VPPAG, and the work of the group was broadened to look at presentation and packaging formats for the HPV vaccine, as well as to develop a more generic presentation and packaging guideline to address the range of potential new vaccines in the development pipeline.

Linking interventions for greater impact

The primary health care approach, as an efficient, fair, and cost-effective way to organize the development of health systems, is back on centre stage. Immunization, as one of many components of a country's health system, is well-placed to benefit from this increased visibility. This is because in many countries, immunization has always been an integral part of the health system and has benefited from the health system's synergistic potential. There is clear evidence, for example, that where health centres offer a range of services, vaccine coverage rates tend to be higher.

Figure 7

More comprehensive health centres have better vaccination coverage[a,b]



[a] Total 1227 health centres, covering a population of 16 million people.
[b] Vaccination coverage was not included in the assessment of overall health-centre performance across a range of services.
[c] Includes vaccination of children not belonging to target population.

Source: (36)

For years, immunization programme managers have urged health workers to use any and every contact with a child in a health centre to check the child's (and mother's) immunization status and to vaccinate if needed. Conversely, immunization can benefit the delivery of other health interventions. For people with limited access to health centres, an immunization outreach or mobile team may offer the only contact they have with the health system: providing more health commodities (such

as medicines, bednets, and nutritional supplements) or health services (such as checking children's growth and giving antenatal advice) to these people, who are often among the least served by the health services, can have a positive health impact. Immunization campaigns, too, bring together large numbers of children and their parents into a limited place over a limited time, and can offer interventions to many people that they have previously missed out on.

Child collecting an insecticide treated net to protect against malaria during measles vaccination campaign in Côte d'Ivoire in November 2008.

In addition to the direct health benefits, there are other advantages in combining targeted health interventions. The provision of a range of preventive and curative services may result in increased trust in the health system by the community, as more of their demands are met. Meanwhile, well-planned linkages between interventions may involve the pooling of human and financial resources, joint training, improved management, and a reduction in costs through shared transport and distribution mechanisms. However, experience has shown that platforms offering multiple interventions can have a negative impact on coverage unless the interventions are well-targeted; good logistics systems are in place to ensure accurate forecasting, supply, and delivery; human resources are adequate; and there is good monitoring and evaluation.

Examples of linked interventions include the following.

- Since 2001, routine and supplementary polio and measles immunization activities have been used to deliver insecticide-treated bednets (which, when used properly, substantially reduce malaria).

- In 2008, integrated supplementary immunization activities against measles resulted in the distribution of over 35 million doses of vitamin A, 30 million doses of deworming medicine, and more than 5.6 million insecticide-treated bednets (*37*). Distributing these interventions as part of measles immunization campaigns can serve to rapidly increase demand for measles immunization, while targeting hard-to-reach people with additional interventions capable of reducing mortality in children under five years old.

- The GPEI calculated that by the end of 2006, using its OPV immunization activities to deliver vitamin A tablets had helped to avert 1.25 million deaths worldwide (*38*).

- The Accelerated Child Survival and Development programme – set up in 2002 and managed with support from UNICEF and the Canadian International Development Agency (CIDA) – was established to help increase the delivery of a package of key health interventions in districts of 11 African countries with high under-five mortality rates. A 2008 evaluation found that rapid impact on mortality rates could be achieved through the package of interventions – especially through the distribution of vitamin A and bednets.

Combating fear with knowledge and evidence

As vaccine coverage has increased and the incidence of vaccine-preventable diseases has fallen – particularly in industrialized countries – immunization has become a victim of its own success. As the diseases prevented by immunization have become less frequent and less visible, concern about the potential side-effects of vaccines has increased.

In both developing and industrialized countries, loss of public confidence in a vaccine due to real or spurious links to adverse events can curtail or even halt immunization activities, with potentially disastrous consequences. For example, a scientifically flawed, but widely publicized 1999 British study (*39*) linking the measles-mumps-rubella (MMR) combination vaccine to autism, has fuelled continuing anxieties among parents about the safety of the vaccine and has caused a decline in vaccine coverage in many countries: ten years later, measles is making a comeback in several industrialized countries, including Austria, Israel, Italy, Switzerland, and the United Kingdom. The CDC reported record numbers of measles cases in the United States for the first seven months of 2008 – many in children whose parents had refused vaccination. Another well-known case in point concerns Nigeria, where in 2002–2003 rumours that the OPV was being used to lower the fertility of young girls brought polio immunization to a halt for 12 months in several states: the result was a nationwide polio epidemic that ultimately spread to 20 previously polio-free countries in Africa, Asia, and the Middle East.

Dealing with such rumours and with adverse events following immunization requires an efficient post-marketing surveillance and investigation system that can assess whether these events are truly caused by vaccines. Part of that system should provide for communication of the findings to health workers, health officials, parents, and the general public. Communication has to be truthful without fanning fears that could compromise future vaccination activities and diminish their benefits. Most industrialized countries have such a post-marketing surveillance and

investigation system. Developing countries are, on the whole, making progress in detecting and dealing with reports of adverse events. There are still many countries, though, that do not have the experience or resources needed to investigate rumours or reports of adverse events following immunization and to restore public confidence.

In 1999, WHO set up a Global Advisory Committee on Vaccine Safety, made up of independent experts, to respond promptly, efficiently, and with scientific rigour, to rumours and reports related to vaccine safety. Recent topics dealt with by the Committee include:

- alleged links between the hepatitis B vaccine and multiple sclerosis (*"no evidence found of such a link"*, the Committee observed);

- alleged links between thiomersal, a vaccine preservative (known as thimerosal in some countries), and autism in children (*"no evidence of toxicity in children or adults exposed to thiomersal in vaccines"*);

- a higher than normal risk of Bacille Calmette-Guérin (BCG)-related disease in HIV-positive children vaccinated with BCG (*"evidence suggests a higher risk and that BCG vaccine should not be used in HIV-positive children"*);

- the risk of administration of multiple vaccines overloading a child's immune system (*"no evidence to support any risk of immune overload"*);

- the safety of newly licensed rotavirus vaccines (*"pre-licensing safety profiles reassuring but careful post-marketing surveillance required at country level"*).

Box 15

Vaccine Safety Net for quality web sites

"Is this new rotavirus vaccine likely to produce side-effects in my baby?"

"Can a pregnant woman be vaccinated against tetanus without risking health problems for herself and her unborn baby?"

"How safe is the new vaccine against the human papillomavirus?"

To find answers to such questions, members of the general public, health officials, and health practitioners may well turn to the Internet. The web sites they find are as likely to present inaccurate, unbalanced, misleading, or unjustifiably alarming information as they are reliable information. In 2003, to tip the balance in favour of reliable information, WHO, prompted by its Global Advisory Committee on Vaccine Safety and other members of the health and development community, began a "Vaccine Safety Net" service, which lists web sites that contain vaccine safety information and that a WHO team has approved as being sound and credible. To meet the required standards, web sites must, among other requirements, disclose their ownership and their sponsors, as well as their sources of information and their data protection policy.

As of March 2009, the Vaccine Safety Net listed 29 web sites (*40*).

Remarkable progress, huge challenges

The immunization achievements are immense but so too are the challenges that lie ahead in meeting the immunization-related MDGs and those of the GIVS (in particular, the GIVS goal to reach 90% immunization coverage nationally and at least 80% in each district by 2010 – see Chapter 1). Reaching the 24 million children a year who remain unvaccinated will not be easy. Success will depend on better use of surveillance and monitoring data at the local level to identify and target these difficult-to-reach children. It will also require the use of operational research to help identify innovative approaches and solutions that are tailored to local needs.

Efforts to reach the global goals have focused on overcoming some of the main barriers to increasing immunization coverage. These barriers include the constraints in some countries of weak health systems, the difficulty of delivering vaccines, the failure of many governments to mobilize populations and establish a well-informed demand for vaccines, the global threat posed by false or unsubstantiated rumours about the safety of vaccines, and the projected shortfalls in funding. New global alliances have been forged to help address these and other challenges – attracting new financing for immunization and bringing together people from the public and private sector and civil society with the collective knowledge, experience, technical know-how, and problem-solving ingenuity needed to get the job done.

But even when the global goals have been met, success will be measured against an additional benchmark – ensuring that the achievements are sustainable. The solid building blocks that are being put in place – health system and immunization programme strengthening, new long-term global financing mechanisms for immunization (see Chapter 4), dynamic global health alliances and public-private partnerships, and more responsive information and communication strategies – should help to ensure that long-term progress has not been sacrificed for short-term gains.

Box 16

Strengthening post-marketing surveillance of newly licensed vaccines

In recent years, concern has been growing over the possibility that the investigation of an adverse event following the routine use of a newly licensed vaccine may not be undertaken as rapidly or reliably in the sometimes difficult conditions of developing countries as it is in industrialized countries. This concern prompted WHO to set up in 2009 a Global Network for Post-marketing Surveillance of Newly Prequalified Vaccines. This Network brings together selected developing countries to share information about adverse events following immunization, through a harmonized approach. Member countries will submit data on adverse events to a common database housed at the Uppsala Monitoring Centre – a WHO Collaborating Centre – in Sweden. They will share among themselves information about adverse events following immunization, and will forge strong links between their national immunization programmes, regulatory authorities, and national pharmacovigilance centres. The Network will share safety data among member countries and, on a wider scale, data will be shared with other countries, vaccine manufacturers, and United Nations vaccine supply agencies.

In 2006, PAHO set up a surveillance network comprising five member countries – Argentina, Brazil, Mexico, Panama and the Bolivarian Republic of Venezuela – that operates on much the same lines as the global network.

Chapter 4

Investing in immunization

Key messages

- Immunization remains one of the most cost-effective health interventions, even with newer, more expensive vaccines.
- By keeping children healthy, immunization helps extend life expectancy and the time spent on productive activity, thereby contributing to poverty reduction (MDG 1).
- Since the year 2000, government spending on vaccines and immunization has been increasing.
- Since 2000, the level of development assistance for immunization has increased by about 13%.
- Since 2005, bilateral donors are making use of broad-based funding mechanisms and partnerships to support the health sector as a whole.
- New sources of funding and innovative funding mechanisms are providing long-term, predictable funding for immunization.
- There remain funding shortfalls to be addressed if global goals are to be reached.

First came the vaccines: by the early 1970s, vaccines against about 20 diseases had become available, and in most countries were being used for high-risk population groups (travellers, the military, and so on), or for occasional mass campaigns, but not routinely in a systematic organized manner. Then, starting in the mid-1970s, came the EPI – set up to establish and coordinate, on a global scale, the systematic use of vaccines by national immunization programmes and thereby to protect as many children as possible in the world against six infectious diseases (diphtheria, tetanus, pertussis, measles, polio, and tuberculosis). In the mid-1980s, came the evidence that these immunization programmes could, in a matter of a few years, protect millions of children from disease and death (*41*). By the early 1990s, the drive for universal child immunization (UCI) launched by UNICEF, WHO, and other partners, had helped raise immunization coverage to a global average of about 80%.

Throughout this sequence, though, and to this day, questions have arisen about the economics of immunization. Immunization is clearly effective, but what does it cost? Is it cost-effective? And who pays for it?

These questions are being asked with growing insistence as new vaccines are becoming available; as new funding sources and resources are materializing; and as new goals, such as the MDGs and the GIVS goals (see Chapter 1, page 2), are calling for large reductions in child and maternal mortality, and thereby stepping up the pressure to maximize the life-saving potential of immunization.

What does immunization cost?

In the 1980s, total annual expenditure on immunization for low-income countries averaged US$ 3.50–5.00 per live birth. By 2000, the figure had risen only slightly to about US$ 6.00 per live birth. Support for immunization from the GAVI Alliance, which began in that year, allowed many of the poorest countries of the world to

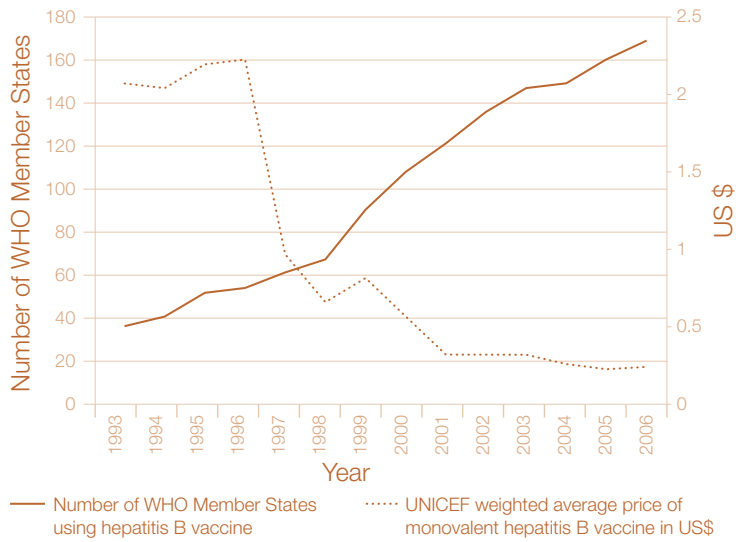
strengthen their routine vaccine delivery systems and to introduce underused vaccines, such as those against yellow fever, hepatitis B, and Hib into their immunization programmes. Not unexpectedly, immunization expenditure began to rise again.

By 2010, the cost per live birth for immunization with the traditional vaccines plus the hepatitis B and Hib vaccines is likely to reach US$ 18.00 per live birth. Beyond 2010, scaling up vaccine coverage with newer vaccines to the levels needed to meet the MDGs and the GIVS goals is likely to exceed US$ 30.00 per live birth.

There are several reasons for the rising costs of immunization. First, the price of new and underused vaccines is higher than the older vaccines – the prices of these new and underused vaccines are in the dollars per dose compared with a few cents per dose for the traditional ones. Vaccines (and injection equipment) have now replaced human resources and operational costs as the most expensive component of immunization. In the 1980s, human resources and operational costs accounted for the bulk of immunization costs, compared with only about 15% for the costs of vaccines. Today, efforts to accelerate the adoption by developing countries of the most recently developed vaccines (the pneumococcal conjugate vaccine, the rotavirus vaccine, and the HPV vaccine, for example) could bring the share of the vaccine component to 60% of the total costs. However, the vaccine costs should fall as these newer vaccines become more widely used, as vaccine production methods become more efficient, as the market and demand for these vaccines expands, and as multiple suppliers (including manufacturers from developing countries) enter the market. The price of the hepatitis B vaccine, for example, has fallen steeply over the past decade or so (see Fig. 8).

Figure 8

Relation between the number of WHO Member States using hepatitis B vaccine and the UNICEF weighted average price for the monovalent vaccine



Source: WHO: based on programme data received from WHO Member States and UNICEF weighted average price for monovalent hepatitis B vaccine

Second, because vaccines are temperature sensitive, the expansion of immunization schedules with underused and new vaccines (particularly the pneumococcal conjugate vaccine, rotavirus vaccine, and HPV vaccine), will increase the quantities of vaccines that need to be stored in the cold chain. The increased quantities of vaccines need to be managed, stored, and transported, and will place considerable pressure on existing national vaccine supply chains. As such, the immunization system will require additional investments to cope.

Third, introducing underused and new vaccines come with additional costs of training staff to safely administer and dispose of the waste, costs of updating and printing new vaccination cards, and costs associated with expanding surveillance and monitoring activities to cover the added disease or diseases, and informing communities about the benefits of the vaccines.

Fourth, reaching the 20% hard-to-reach children who are not receiving the full three-dose schedule of the DTP vaccine is increasingly difficult and costly, as many of them are hard to reach for reasons of geography, civil strife, or lack of sufficient health service resources (see Chapter 3). In addition, to reach more children with vaccines, many countries need to rely on outreach services and supplementary immunization activities, such as mass vaccination campaigns and child health days. These strategies require increasing investments in immunization.

To put a price tag to these rising costs for immunization, a WHO and UNICEF analysis, published in 2008 (*7*), calculated how much it would cost to attain the GIVS goals in 117 WHO low- and lower-middle-income Member States between 2006 and 2015. The total bill came to US$ 76 billion. For the 72 poorest countries, the bill came to US$ 35 billion – enabling them to protect more than 70 million children. These countries however, are eligible for GAVI Alliance funding and have received support for introducing underused and new vaccines, as well as support to strengthen their immunization systems.

The remaining 45 countries are those whose GNI per capita classify them as lower-middle-income countries according to the World Bank classification (*42*). Thirty-five of these countries are unable to benefit from GAVI Alliance funding and face increasing difficulties in financing the introduction of underused and new vaccines. The total population in these lower-middle-income countries is nearly two billion, including about 30 million children. In some of these countries, many people live on less than US$ 2 per day and require support from national authorities and the international community to meet their basic needs, including immunization. There are a number of strategies that could help to assist the lower-middle-income countries to access new and underused vaccines, including technical assistance in disease surveillance, evaluation, prioritization, and decision-making; enhanced participation of the private health sector in provision of immunization services; identification of new financing opportunities; and inter-country collaboration to address the challenge of vaccine procurement, manufacturing, and vaccine quality assurance.

Is the investment worth making?

The investments in immunization continue to increase, and efforts to meet internationally accepted goals will add substantially to the cost of immunization. For WHO and UNICEF, the GIVS goals are necessary stepping stones to achieving MDG 4. Meeting the GIVS goals (see Chapter 1, page 2), would mean protecting children against 14 diseases – diphtheria, pertussis, tetanus, measles, polio, tuberculosis, hepatitis B, Hib, rubella, meningococcal disease, pneumococcal disease, rotavirus diarrhoea, and (in certain areas) Japanese encephalitis and yellow fever.

Yet, is the investment worth making? If all countries manage to reach 90% of children under five years old with these vaccines, then by 2015 immunization could prevent an additional two million deaths a year in this age group, making a major contribution to meeting MDG 4. This would represent a major reduction (60–70%) since 2000 in the number of under-five deaths from vaccine-preventable diseases.

In addition, recent data show that immunization, even with more expensive vaccines, continues to be good value for money and a proven cost-effective health intervention (*43, 44, 45, 46, 47, 48, 49*). An extreme example is its ability to remove a disease altogether from the world's public health landscape, as in the case of smallpox, or from vast areas of the world, as in the case of polio. Eradicating smallpox cost US$ 100 million over a 10-year period up to 1977. That investment, according to one estimate (*50*), has since been saving the world about US$ 1.3 billion a year in treatment and prevention costs.

In addition to being a significant contributor to child deaths, vaccine-preventable diseases also constitute a major cause of illness and disabilities among children both in industrialized and developing countries. The classic example of vaccines preventing serious disability has been the prevention of paralytic polio in hundreds of thousands of children since the advent of the GPEI. In addition, prior to the widespread use of the measles vaccine, measles was the leading cause of

blindness in children in developing countries, accounting for an estimated 15 000–60 000 cases of blindness every year (*51*). Other complications of measles that result in severe neurological disabilities are the post-infectious encephalitis and the subacute sclerosing panencephalitis (SSPE). Congenital rubella also, which is associated with deafness, blindness, and severe mental retardation, can be prevented through immunization.

Among the newer vaccines, the pneumococcal vaccine has been shown to reduce severe acute otitis media – one of the commonest childhood illnesses that requires medical attention in industrialized countries. More recently, use of the pneumococcal vaccine was shown to be associated with a 39% reduction in hospital admissions due to pneumonia from any cause (*52*). A large proportion of children who survive an episode of pneumococcal meningitis are left with long-term disabilities: a recent study in Bangladesh showed that close to half the children had either a neurological deficit, such as hearing or visual loss, or a developmental deficit (*53*).

Similarly, rotavirus diarrhoea is a common cause of clinic visits or hospitalization among children in both industrialized and developing countries. In a large clinical trial conducted in 11 countries in North America and Europe, use of the rotavirus vaccine was shown to reduce clinic visits and hospitalizations due to rotavirus diarrhoea by 95% (*54*). In Africa, for every 100 vaccinees, rotavirus vaccine prevented three cases of severe rotavirus diarrhoea that required hospitalization (*55*).

Thus, while the impact on child deaths alone would be sufficient justification for the use of vaccines in developing countries, the reduction of long-term disability among children and the cost savings from reduction in clinic visits and hospitalization more than justify their use in children everywhere.

The cost-effectiveness equation for immunization, however, should take into account more than its positive impact on individual and community health. By keeping children healthy, immunization lengthens life expectancy and the time

spent on productive activity, and thereby contributes to a reduction in poverty (the first Millennium Development Goal, MDG 1). As a Harvard School of Public Health team recently found in a study on the economics of immunization in countries receiving GAVI Alliance support, "Healthy children perform better at school, and healthy adults are both more productive at work and better able to tend to the health and education of their children. Healthy families are also more likely to save for the future; since they tend to have fewer children, resources spent on them go further, thereby improving their life prospects" (*56*).

Who pays the bill and how?

The WHO and UNICEF analysis to calculate how much it would cost to attain the GIVS goals (*7*), not only estimated the total price tag, but also matched this against estimated future funding, and calculated the estimated shortfalls between 2006 and 2015. For the 72 poorest countries, an estimated funding flow of US$ 25 billion to support immunization is expected to become available from government, multilateral, and other sources (including the GAVI Alliance). Against a total immunization bill of US$ 35 billion in these countries, this leaves an unfunded mandate and funding gap of US$ 10 billion. Hence, about a US$ 1 billion shortfall needs to be financed every year if the GIVS goals and MDG 4 are to be achieved.

In order to get a clearer understanding of who pays the immunization bill, it is useful to look at each funding source separately.

National governments

Since the launch of the EPI in 1974, the financing of vaccines and immunization in developing countries has largely been made possible through support from the global international health community – primarily from multilateral and bilateral

sources and from international development banks. In the 1970s and 1980s, huge investments were made to reach the 1990 goal of universal child immunization (UCI), including important investments in equipment and infrastructure.

However, after 1990, donor funding to sustain routine immunization services began to dwindle, with most of the funding for vaccines and immunization focused toward disease control and eradication initiatives. At the same time, many governments of developing countries became complacent about the need to use their own domestic resources to pay for their basic vaccines and immunization. As a result, immunization performance suffered and vaccination coverage stagnated throughout the 1990s.

Notable exceptions to this were the countries in the Americas, which already had access to a regional funding mechanism for vaccines. In 1979, PAHO established a revolving fund to help all countries in the region become more self-sufficient in the purchase of vaccines for routine immunization. The pooled fund is able to secure low vaccine prices through large volume contracts with manufacturers. The mechanism enables participating countries to buy vaccines, using local currencies, with payment not due until up to 60 days after delivery. As a result, the majority of countries in the Americas are today almost entirely self-sufficient in the financing of vaccines and immunization – with over 90% of immunization costs paid for out of national government resources.

Another part of the success of the PAHO model for financing immunization was the requirement that countries create a specific budget line item in the national budget for the purchasing of vaccines. The presence of this separate budget line within a country's national health budget contributed significantly to increasing government financing of vaccines and routine immunization in the Americas, the reason being that budget line items give visibility to immunization as a permanent presence within the national planning and budgeting process. Budget line items also facilitate resource tracking and allow for greater accountability of expenditures. And, most

importantly, they signal a long-term political commitment that could protect budget allocations for immunization during economic downturns.

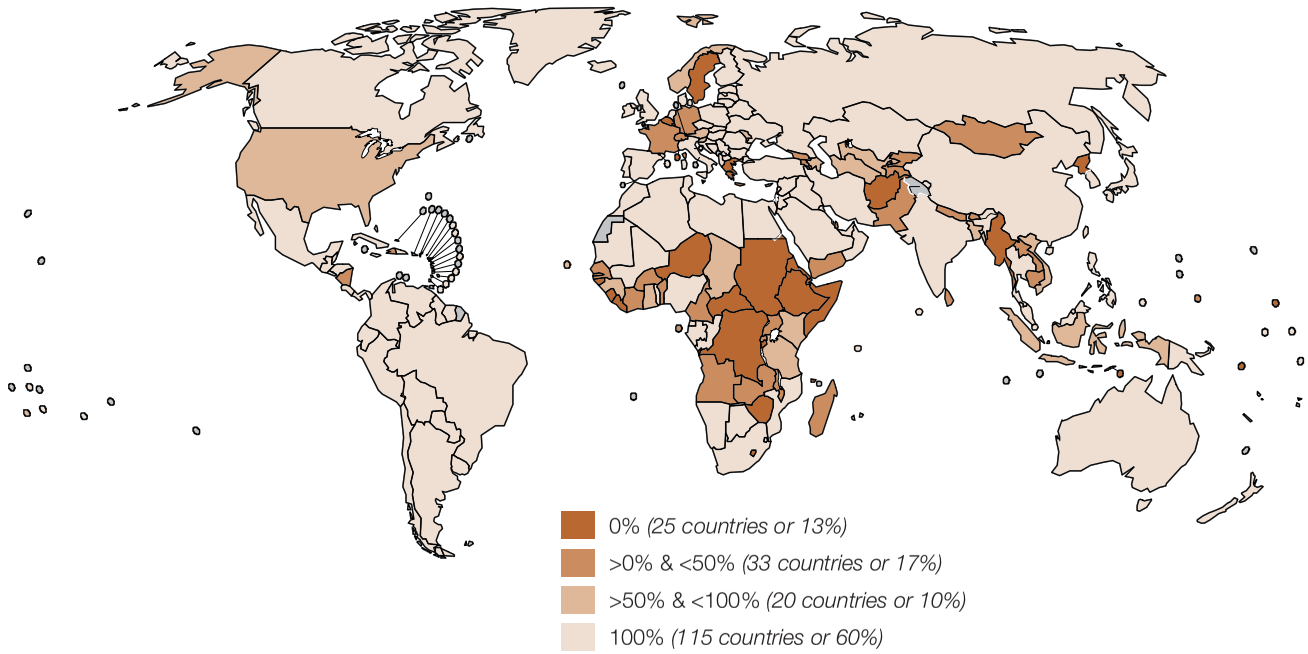
A WHO analysis of immunization financing indicators from 185 countries collected through a joint WHO and UNICEF monitoring system, confirmed that breaking out vaccine purchases as a line item in the national health budget is indeed associated with increased governmental budget allocations to vaccines and routine immunization (*57*).

In 2007, WHO's 193 Member States were funding an average 71% of their vaccine costs (33% in low- and lower-middle-income countries). Of these, 86% of countries reported having a line item for vaccines within their national health budgets (75% of the 117 low- and lower-middle-income countries).

From the 2008 WHO-UNICEF costing analysis *(7)*, it is estimated that 40% of the costs of immunization for the period 2006–2015 will be met by national governments. Other studies have shown that since the year 2000, governments' spending on vaccines and immunization has been increasing at a steady rate.

Figure 9

Government funding of vaccines for routine immunization, 2007



Source: (57,71)

Multilateral, bilateral, and other donors

If the 2015 Millennium Development Goals are to have any chance of being achieved, international development assistance, according to a widely quoted estimate (*58*), needs to double from the current US$ 50 billion per year. Moreover, it should be spent primarily on the poorest countries. As mentioned above, immunization alone will require an additional US$ 1 billion a year over the decade 2006–2015, in order to help meet the MDGs. Many donor governments have pledged to raise their development assistance to 0.7% of their gross domestic product, but few have fulfilled that pledge.

Since the start of GAVI support in 2000, funding for immunization from multilateral, bilateral, and other funding sources increased by 13% (not adjusted for inflation), from an average of US$ 2.6 per infant to US$ 3.0 per infant. Overall financing from multilateral, bilateral, and other external donor sources is projected to average US$ 2.7 per infant between 2005 and 2010, remaining more or less at its baseline level.

Starting in 2005, however, the donor funding environment began to change. At a global level, bilateral donors began to increasingly use the GAVI Alliance as a channel for funding. At a country level, they started moving away from providing direct support to individual projects or interventions, and were making increasing use of broad-based funding mechanisms, or partnerships, to support the health sector as a whole.

The Global Polio Eradication Initiative

In addition to the broader immunization financing mechanisms, a number of public-private partnerships have been established to deliver targeted immunization goals. Such targeted efforts offer substantial benefits for broader immunization objectives –

a contribution which often goes unrecognized. A striking example of this is the wide-ranging impact of the worldwide investment in the Global Polio Eradication Initiative (GPEI), a public-private partnership launched in 1988 and spearheaded by WHO, Rotary International, the CDC, and UNICEF.

Since 1988, more than US$ 6 billion in international resources has been invested in the GPEI, in addition to an estimated equal amount in the form of in-kind contributions at the national level. A substantial proportion of this amount has been allocated to the strengthening of routine immunization and health systems, and towards meeting the GIVS goals (see Chapter 1). About 50% of the annual GPEI budget is spent on polio supplementary immunization activities such as the purchase of polio vaccine and transport of vaccinators. However, the remaining 50% is used for training of health staff, district-level micro-planning, refurbishment of vaccine cold-chain systems, and for scaling up the technical capacity of networks for surveillance and monitoring of vaccine-preventable diseases.

The GPEI is increasingly funded through innovative financing mechanisms. In addition to ongoing support through traditional donor engagement, such mechanisms include innovative funding partnerships between Rotary International and the Bill & Melinda Gates Foundation; a one-time contribution in 2007 from the International Finance Facility for Immunisation (IFFIm); and a budget allocation from the G8 Group of countries, which includes not only development aid but also domestic resources.

Another funding mechanism is the Investment Partnership for Polio, launched in 2003 by the World Bank, Bill & Melinda Gates Foundation, Rotary International, and the UN Foundation. This involves the use of long-term “soft loans” issued by the International Development Association (IDA) – the concessionary lending arm of the World Bank – to enable countries to buy oral polio vaccine. When the recipient country’s polio eradication programme has been completed, the Investment Partnership for Polio will then “buy down” the loans – effectively turning them into grants – through the use of a trust fund established by the

Bill & Melinda Gates Foundation, Rotary International, and the UN Foundation. As of early 2009, two countries – Nigeria and Pakistan – are making use of this funding mechanism.

The GAVI Alliance

The GAVI Alliance is a public-private global health partnership that includes governments in industrialized and developing countries, international organizations (UNICEF, WHO, and the World Bank), foundations (notably, the Bill & Melinda Gates Foundation), non-governmental organizations, vaccine manufacturers from industrialized and developing countries, civil society, and public health and research institutions. All the partners have signed the Alliance's declared mission "to save children's lives and protect people's health by increasing access to immunization in poor countries".

The GAVI Alliance offers all eligible countries support, primarily for vaccines and immunization, but also to strengthen health systems and the work of civil society organizations, and to ensure the safety of immunization. To be eligible for GAVI Alliance support, countries must have a GNI per capita of less than US$ 1000. They must also have a costed comprehensive multi-year plan for immunization (cMYP). Up to 2005, 75 countries were eligible for GAVI Alliance support. In 2003, the number of countries dropped to 72, due to changes in GNI per capita.

As of the end of 2008, the GAVI Alliance had received a cumulative total of US$ 3.8 billion in cash and pledges from public and private sector donors (including US$ 1.2 billion from the sale of IFFIm bonds), and had disbursed US$ 2.7 billion to eligible countries. Over the period up to 2015, the Alliance has an estimated funding gap of US$ 3 billion out of the estimated US$ 8.1 billion total funding needed.

During its first phase, from 2000 to 2005, the GAVI Alliance focused on vaccines against hepatitis B and Hib – especially those used in combination with the DTP vaccine. The Alliance also focused on yellow fever vaccine in areas at risk for this disease. The GAVI-supported vaccines, which are recommended by WHO because they are safe, cost-effective, and known to have significant public health benefits, had previously remained largely unavailable to poor countries. During the Alliance's second phase, which runs from 2006 to 2015, the focus of financial support has expanded to include rotavirus and pneumococcal vaccines.

By the end of 2008, thanks to GAVI Alliance support, it is estimated that over 192 million children had been immunized against hepatitis B; nearly 42 million against Hib disease; and 35.6 million against yellow fever. GAVI Alliance support for these underused vaccines and for vaccination against diphtheria, tetanus, and pertussis had, according to GAVI Alliance and WHO estimates, averted 3.4 million premature deaths.

Under the GAVI Alliance's "immunization services support" programme, launched in 2000, countries receive funds over a two-year period – the so-called "investment phase". In the third year, they receive a bonus of US$ 20 per additional child vaccinated compared with the previous year. An evaluation exercise conducted by the Alliance in 2007 estimated that about 2.4 million children had been immunized with the full three doses of DTP vaccine – children who would not have immunized without the Alliance's immunization support programme.

To meet concerns about financial sustainability, all GAVI-supported countries were required to prepare a financial sustainability plan (now replaced by a cMYP). An analysis of 50 of the financial sustainability plans reveals an upward trend since 2000 in both national and external sources of funding for routine immunization.

In 2007, as part of its second phase, the GAVI Alliance introduced a co-financing system, whereby countries eligible for support are required to pay a gradually

increasing share of the cost of the vaccines provided through the Alliance, based on their GNI per capita. The aim is not only to assist countries on the path to greater financial sustainability, but also to encourage them to base their decisions about vaccine introduction on solid evidence about the burden of disease targeted by a vaccine, and the affordability and likely cost-effectiveness of using the vaccine. By the end of 2008, 30 countries were using the co-financing system to pay for the introduction of the pentavalent (DTP-Hepatitis B-Hib) vaccine, rotavirus vaccine, and pneumococcal vaccine.

New financing mechanisms

The International Finance Facility for Immunisation

The International Finance Facility for Immunisation (IFFIm) is a multilateral development institution created to accelerate the availability of predictable, long-term funds for health and immunization programmes through the GAVI Alliance in 70 of the poorest countries in the world.

Launched in 2006 as a pilot project of the International Finance Facility (IFF), and promoted by the United Kingdom Government, IFFIm was created as a development financing tool to help the international community achieve the MDGs. Donors contribute to the IFFIm by making long-term legally binding commitments or grants to support immunization activities in poor countries. As of the end of 2008, seven countries – France, Italy, Norway, South Africa, Spain, Sweden, and the United Kingdom – had made commitments totalling US$ 5.3 billion over a 20-year period. The World Bank acts as financial adviser and treasury manager to the project.

The IFFIm uses these commitments to issue bonds on the international capital markets. The sale of these bonds provides cash that the IFFIm gives to the GAVI Alliance and that can be used immediately to fund the Alliance's programmes. The

IFFIm's first bond offering, in November 2006, raised US$ 1 billion from institutional investors worldwide. A second offering, in March 2008, raised US$ 223 million from private investors in Japan.

Advance Market Commitment

Conceived in 2005 by the Center for Global Development, and carried forward by five bilateral donor governments, the Bill & Melinda Gates Foundation, the GAVI Alliance, and the World Bank, the Advance Market Commitment (AMC) is a new approach to public health funding. Its aim is to stimulate the development and manufacture of vaccines specially suited to developing countries.

Through an AMC, donors commit money to guarantee the price of vaccines once they have been developed, thus creating the potential for a viable future market. However, donor funds are not provided until after the proposed vaccines have met stringent, pre-agreed technical criteria, and developing countries request them. These commitments provide vaccine makers with the incentive to invest the considerable sums required to conduct research and build manufacturing capacity. Companies that participate in an AMC make legally binding commitments to supply the vaccines at lower and sustainable prices after the donor funds made available for the initial fixed price are spent. As a result, governments of developing countries are able to plan and budget for their immunization programmes – with the assurance that vaccines will be available in sufficient quantity, at a price they can afford, for the long term.

The Governments of Canada, Italy, Norway, the Russian Federation, and the United Kingdom, together with the Bill & Melinda Gates Foundation, have committed US$ 1.5 billion to a pilot AMC targeting pneumococcal disease. It is estimated that pneumococcal vaccines – if made widely available in developing countries – could save over seven million lives by 2030.

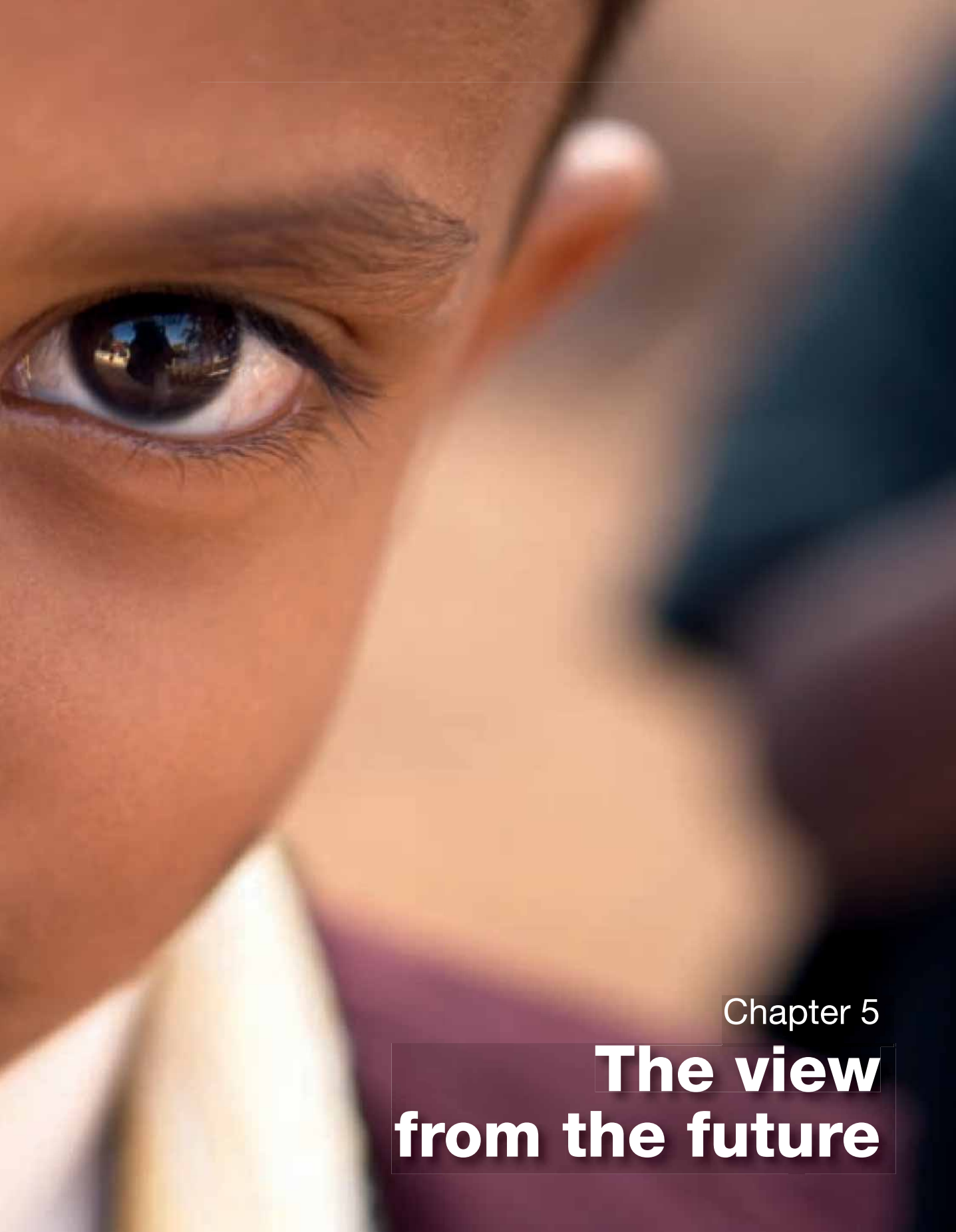
A concluding conundrum

If children's lives are worth saving – and who would doubt that they are; if vaccines save lives – and the evidence is clear that they do; and if the world has the means of making, buying, and using vaccines, as it surely does: then why are children still dying from diseases that vaccines can prevent?

The answer to this conundrum lies perhaps in the difficulty of choosing between conflicting priorities. The choices are made primarily by governments. Between 2006 and 2015, some 40% of all funding for routine immunization is estimated to come from national government funds. As the current economic downturn unfolds, it will be important for governments to sustain and, when possible, increase these investments in immunization.

For a government faced with competing priorities, choosing is not easy. Vaccines will not prevent all diseases or all child deaths. But vaccines can prevent much of the needless suffering caused by infectious diseases – enough to help create a space where families can busy themselves with things other than sheer survival.

The good news is that more investment is being made in immunization, and the future projections indicate increasing financing. Today, as never before, governments have an unprecedented number of partners willing to help pay for vaccines and immunization. Yet, expected future funding from governments and donors will not be enough to sustain the gains already achieved towards GIVS goals and the MDGs. "The real challenge," the WHO-UNICEF analysis report *(7)* concluded, "will hinge on how national governments, and the international community at large manage their roles and responsibilities in reaching and financing the goals of the GIVS until 2015."



Chapter 5

The view from the future

Key messages

By the 2020s:

- child deaths from infectious diseases are expected to be at an all-time low;
- polio should be eradicated, and measles eliminated in all countries;
- today's new vaccines against pneumococcal disease, rotavirus, meningococcal disease, and HPV are expected to have inspired new health and development goals;
- hopes remain high that new vaccines will be available to combat malaria, tuberculosis, AIDS, and other diseases.

This report paints a picture of where the many and diverse activities relating to vaccines and immunization stand today. Some of these activities are well on the way to achieving their objectives. Others are stalling, for one reason or another. But the overall picture is one of cautious optimism, enthusiasm, energy, and dedication.

Clearly, vaccines and immunization can make a major contribution to achieving the MDGs and thereby reduce the gross inequities that create an ever wider gap between the haves and have-nots (Chapter 1). The vaccine world, too, has set a number of goals: its GIVS identifies the targets to be reached if immunization is to lend its full potential to achieving the MDGs.

Vaccine development presents a dynamic picture (Chapter 2) – safer and more effective vaccines coming off an exceptionally rich pipeline; more efficient ways of making vaccines; more vaccine producers in developing countries; innovative regulatory mechanisms; more efficient ways of ensuring maximum vaccine safety and efficacy; and more partnerships harnessing the combined strengths of the public and private sectors to spur development of even better vaccines.

Administration of measles vaccine through the aerosol route could facilitate measles immunization efforts, especially mass campaigns.

To meet the goals of the GIVS, more people need to benefit from the life-saving, disease-preventing power of vaccines. A groundswell of activities and projects – some new and some newly revitalized – are working to achieve this goal (Chapter 3). More people are being reached with vaccines, including groups – such as adolescents, elderly people, women outside child-bearing age – and members of hard-to-reach communities – who have been neglected to some degree by traditional immunization policies, where the main focus has been on infants and young children.

New strategies have also been put in place to accelerate the integration of immunization programmes within the health systems of countries, and to expand the use of these programmes to deliver other health interventions. When linked with other health interventions – to prevent and treat childhood pneumonia, diarrhoea, and malaria, for example – immunization becomes a driving force for child survival and for meeting MDG 4.

A new, ambitious plan to create a global network for the surveillance and monitoring of vaccine-preventable diseases is also taking shape. And less recent, but no less exciting, are the achievements of major thrusts to remove the burden of three diseases: polio is close to being eradicated, deaths from measles have plunged to record lows, and maternal and neonatal tetanus is well on the way to being eliminated (see Box 17).

Funding to pay for all these activities is clearly on a more solid footing than it was a decade ago (Chapter 4). Innovative mechanisms for mobilizing and channeling donor funds have created new incentives among almost all players on the vaccine and immunization stage, from the vaccine industry to the health ministry. Donors – both multilateral and bilateral – have increased their generosity and are currently financing about a fifth of immunization costs worldwide. Governments – even of some of the poorest countries – are spending more on vaccines and immunization. To some extent, the entire field of vaccines and immunization is buoyed by an

Box 17

The future of immunization

How will immunization change over coming decades?

Today, in most developing countries, routine immunization schedules have gone beyond the six traditional childhood vaccines – diphtheria, tetanus, pertussis, measles, polio, and tuberculosis. Vaccines against hepatitis B, Hib, rubella, pneumococcal disease, and rotavirus – and, in areas where they are needed, vaccines against yellow fever and Japanese encephalitis – are being used in a growing number of countries.

Over the next decade or so, increasing numbers of developing countries should be using the new vaccines coming onto the market. Some of these vaccines (such as the HPV vaccine) will be given to adolescents; others (such as the influenza vaccine) to adults. Moreover, booster doses of some of the traditional vaccines, such as those against tetanus, diphtheria, and pertussis, will be given to older children, adolescents, and adults, and will need to be integrated into the immunization schedules of developing countries (as they are today in industrialized countries). In many countries, second doses of the measles vaccine will be offered through routine immunization programmes to children beyond their first birthday.

The problem is that, with the exception of special immunization campaigns, there is little knowledge or experience about how to reach older age groups in developing countries. School-based immunization is a possibility, especially as school attendance is growing in many developing countries.

Over the next decade, delivering vaccines into the human body may, to a large extent, have done away with devices that use needles. Some needle-free approaches are already appearing, and others are still in the experimental phase. They include vaccines in aerosol formulations that are sprayed into the nose (already available for an influenza vaccine), or lungs (currently being tested in humans with a measles vaccine, and in monkeys with an HIV or HPV vaccine); adhesive skin patches; drops under the tongue; and oral pills.

Another potential breakthrough is the development of an increasing number of vaccines that are heat-stable. When supplied with a vaccine vial monitor to check exposure to heat, these vaccines should be available for use outside the cold chain – greatly relieving the pressure on the cold chain and logistics.

unprecedented influx of new wealth. However rough the path into the future may be in some places, today's vaccines and immunization scene clearly bears the mark of progress.

The world, as it enters the final years of this decade, is facing a massive financial and economic crisis, which raises the question: How long can the dynamo that drives progress in the vaccine arena continue to function? A look at the forces driving the dynamo may hold some clues.

More funds from more sources are clearly a driving force for all areas of work on vaccines and immunization. The effects of these funds have rarely been so visible. Since 2000, health aid has doubled, according to one report (*59*). As of early 2009, with the financial world in turmoil, cash is scarce. Views differ about the potential impact of the economic downturn on future donor health funding. Optimists remain hopeful that the MDGs will exert a strong enough "pull" on the donor community to provide predictable, sustainable funding; that the current momentum within the vaccine community and the current soaring trends in the life-saving achievements of vaccines will motivate the donor community to keep immunization high on their priority lists; and that it will encourage donors to sustain and even increase financial support well beyond the 2015 deadline for achieving the MDGs.

Increasingly, partnerships are becoming important drivers of vaccine development and deployment. The GAVI Alliance – a public-private global health partnership – is a prime example of this trend. Its partners span almost the entire spectrum of vaccine and immunization activities: private foundations and governments of industrialized countries; industry, in both developing and industrialized countries; civil society organizations; and international health and development organizations (WHO, UNICEF, the World Bank, and others). Perhaps the most crucial partners are the developing countries, whose governments are responsible for choosing and using the vaccines that are available. Current efforts, that should bear fruit in the future, are being made to assist these governments in making decisions about vaccines and

immunization – decisions that should be made on the strength of sound evidence. In the long term, government ownership of national immunization programmes, including country-driven policies, strategies, monitoring, and reporting, should ensure the sustainability of today's investments in immunization.

Another force likely to drive future vaccine development and expand immunization coverage is public demand for vaccines and immunization services. Over the next two decades that demand should rise. For one thing, more vaccines are likely to become available against more diseases, thereby boosting the popularity of immunization. For another, more people are likely to have access to more education and to have a greater awareness of the benefits of immunization. Their claim to a share of these benefits is likely to become bolder. Public demand in developing countries is likely in the future to be as strong as it is today in industrialized countries. But growing awareness of the benefits of vaccines is also likely to increase concerns over their safety. Vaccine producers and regulators will no doubt feel increasing pressure to ensure that vaccines are safe, and vaccine advocates will feel the need to offset rumours and doubts with even more timely, accurate information than they provide today.

Certainly, the vaccine supply landscape is likely to have changed by 2020. Judging from current trends, developing countries may well have acquired the capacity to make their own state-of-the-art vaccines that meet their own specific needs. And their contribution to global vaccine supply may well be on a much more equal footing with industrialized countries than it is today – a development likely to increase competition.

As for vaccine development, one driving factor is the progress being made in devising, adapting, and using advances in vaccine science and technology. Will those advances continue? And will they justify the setting of new goals for combating vaccine-preventable diseases and deaths? Looking into the 2020s, the MDGs should have brought child deaths from infectious diseases to an all-time low. Polio

should be a thing of the past, and measles eliminated in all countries. Neonatal and maternal tetanus should no longer be exerting such a heavy toll on babies and their mothers. Today's underused vaccines – against Hib disease, hepatitis B, and yellow fever – may well have rid the world of the lethal burden of these diseases. Surely today's new vaccines – against pneumococcal, rotavirus, meningococcal, and HPV disease – will have inspired tomorrow's new goals for going beyond the life-saving achievements of the current international health and development goals. And surely, vaccine science and industrial inventiveness will have produced high-performance vaccines capable of turning the tide against malaria, tuberculosis, AIDS and other diseases that seem, today, unconquerable.

But, of course, new goals will likely face new challenges. The world is currently facing the challenges of economic recession and financial turmoil. Climate change is already a major challenge and is likely, over coming decades, to alter the epidemiological landscape in which vaccines and immunization operate.

"The business of predicting," as Nobel laureate Niels Bohr is often quoted as saying, "is very difficult, especially when it's about the future". Which is another way of saying: the future holds more questions than answers. About one thing, though, there is no question. Immunization works. It has worked in the past. It is working in the present. And short of a radical change in human biology, there is every reason to believe that immunization will continue far into the future to be a mainstay of human health.

Part 2:

Diseases and their vaccines

Cholera – exploring the use of available vaccines

Often referred to as one of humankind's "most devastating diseases", cholera was for centuries a permanent feature of life in the slums and poverty-stricken villages of India, where outbreaks have occurred since the early 1800s. Ships sailing from the Bay of Bengal during an 1817 epidemic are believed to have brought the disease to Europe in bilge water contaminated with the causative organism, *Vibrio cholerae*. From there, the disease spread eastwards throughout Europe and Asia, and westwards to the Americas. Since 1817, there have been seven major cholera pandemics in areas of South America, Africa, Europe, and Asia (*60*). The seventh pandemic, which is still ongoing, began in 1961 in Indonesia, then spread through Asia and Africa, and finally reached Latin America early in 1991 (*60*).

V. cholerae is transmitted by contaminated water and food and, like typhoid fever, is associated with poverty, poor hygiene, and inadequate sanitation. The disease typically begins with an acute attack of diarrhoea and copious vomiting, rapidly followed by dehydration, and, in the absence of treatment, renal failure and death (*1*). About 80% of cholera episodes are of mild-to-moderate severity. Cholera usually responds to prompt administration of oral rehydration salts to replace lost fluids. In the past, before the advent of fluid replacement therapy, up to 50% of infected people died from the disease. Today, the risk of death is less than 3%, on a global average (*61*).

The number of cholera cases reported to WHO annually has remained relatively constant since 1995, varying from 100 000 to 300 000 cases per year, with Africa accounting for more than 94% of the total. In 2006, a total of 236 896 cases were notified to WHO from 52 countries: 31 out of 46 African countries experienced an outbreak of cholera and reported a total number of 202 407 cases with 5259 deaths (*62*). Globally, the actual number of cholera cases is known to be much higher; the discrepancy is the result of underreporting due to fear of unjustified travel and trade-related sanctions, limitations of surveillance systems, such as inconsistency in the case definition and a lack of a standard vocabulary (*61*), and this perhaps represents 10-20% of all cases (*63*). The problem may be less acute following the change, in 2005, in the International Health Regulations (IHR) that replaces compulsory public notification of cholera with a more discreet outbreak response arrangement between affected countries and WHO. Today, no country requires proof of cholera vaccination as a condition for entry.

The causative agent of cholera was first discovered in 1854 by the Italian scientist Filippo Pasini, and "re-discovered", seemingly independently, in 1884 by the German microbiologist Robert Koch. In that year, the first cholera vaccine was made and began to be used in Spain. It consisted of the killed whole cholera bacterium and was administered by injection. Over subsequent years, several injectable whole-cell cholera

vaccines made their appearance and were used in millions of people in several countries, including India and Russia. Reported efficacy of these early vaccines varied widely.

The year 1959 saw licensure of the first cholera vaccine to benefit from modern manufacturing technology, and the first to be submitted to reliable scientific scrutiny. However, several well-designed studies in Asia found that the vaccine possessed only limited efficacy and caused a significant number of side-effects.

The search for a safer, more effective cholera vaccine produced three new-generation vaccines, of which only one is available for widespread use today. This vaccine, first licensed in Argentina in 1997 and code-named WC/rBS, is made from the whole-cell *V. cholerae* linked to a genetically engineered (recombinant) fragment (B-subunit) of the cholera toxin. Field trials in Bangladesh, Mozambique, and Peru found the vaccine to be effective and safe. It does have shortcomings, though. First, it requires two doses given one week apart and taken with liquid (a buffer solution to neutralize stomach acid) – two factors that complicate its use, particularly in epidemics. Second, its protective capability takes about three weeks to develop after administration of the first dose. Protection is highest during the first six months after vaccination but lasts for up to three years (*64*). Third, it is effective only against the 01 *V. cholerae* strain (serogroup): until recently, this strain was the most frequent cause of epidemics but in 1992 a second serogroup, 0139, was identified as the cause of epidemics in Bangladesh and India, and has since been implicated in a growing number of outbreaks in Asia.

From a public health standpoint, the WC/rBS vaccine, despite its shortcomings, is the only new-generation cholera vaccine recommended for use by travellers to cholera-endemic areas, and the only one to have been used in mass vaccination campaigns. Over the period 2003–2006, it was successfully deployed in mass campaigns carried out in Indonesia, Mozambique, and the Sudan. Since 2006, WHO has recommended that in complex emergencies, the use of cholera vaccine should be considered by governments in the context of other public health priorities (*61, 65*).

As of mid-2008, WHO's cholera control policy (*61*) calls, in the first instance, for the improvement of basic sanitary conditions and hygiene. Guided by its Global Task Force on Cholera Control, WHO is weighing how best vaccines might be used to supplement these basic measures, particularly in areas, such as urban slums, or in conditions, such as epidemics, where these measures are particularly difficult to apply.

Meanwhile, the vaccine R&D pipeline holds the promise of several new vaccines which, if they fulfil their promise, would confer long-lasting immunity against all predominant strains of *V. cholerae* after oral administration of a single dose, would be affordable by developing countries, and would not require or overload current cold-chain facilities.

Diphtheria – controlled by vaccines but waiting to resurface

Diphtheria is a disease of the upper respiratory tract caused by the bacterium *Corynebacterium diphtheriae*. Most cases run a mild course with only sore throat and fever, and often no symptoms at all. The organism, however, secretes a toxin that can cause inflammation of the pharynx, larynx, and trachea, and when the toxin travels in the blood or lymph system, it can attack just about any organ in the body, including the heart (resulting in myocarditis) and nervous system (resulting in polyneuritis) (*1*). In more than 10% of cases, the disease is fatal (*66*). The latest WHO estimates for 2004 put the number of deaths worldwide at 5000, of which 4000 are in children under five (*4*). *Corynebacterium diphtheriae* also causes a cutaneous infection that is a further source of transmission, and may confer some protection against the respiratory disease.

The hallmark of diphtheria is a greyish-white membrane (a pseudomembrane) that forms on throat tissue. When this membrane spreads downwards into the larynx, it can cause death by suffocation. French physician Pierre Bretonneau, who in 1825 performed the first successful tracheotomy to save the life of a patient threatened by suffocation from the leathery membrane, gave the name “diphtheria” to the disease (from the Greek word for “leather”) (*1*). However, the earliest detailed descriptions of the disease date from ancient Syrian, Egyptian, and Greek writings (*1*). Two millennia later, in 1883, *Corynebacterium diphtheriae* was identified in a German laboratory as the causative agent.

Diphtheria is highly contagious. The organism spreads through direct physical contact or air-borne droplets. Throughout history, devastating epidemics have made diphtheria one of the most feared childhood diseases (*67*). Known as “the strangler” in Spain and “the gullet disease” in Italy, diphtheria swept across Europe in the 17th century. Towards the end of the following century, a major epidemic occurred in Europe and spread to the United States, killing about 50% of infected people. By the beginning of the 20th century, the disease was causing about 150 000 cases and 13 000 deaths annually in the United States, mostly in infants and young children. Diphtheria epidemics continued to ravage Europe over subsequent decades: in 1943, about one million cases and 50 000 deaths occurred, and a similar number of cases and deaths were believed to be occurring every year in developing countries at the time (*67*).

Meanwhile, in 1907, experiments had begun on using a toxin–antitoxin (TAT) solution to induce protective immunity. The rationale was that the toxin would stimulate immunity and the antitoxin (antibodies) would counteract the toxicity of the toxin and prevent it from causing disease in the recipient (*1*). Starting in 1910, several cities in Europe and the United States set up immunization programmes to administer the TAT complex. Thanks to this prophylaxis, the average death rate among infected people declined from about 50% to under 15%.

In the early 1920s, researchers discovered that they could attenuate the diphtheria toxin by exposing it to certain chemicals or to heat, without depriving it of its immune-stimulating (immunogenic) properties. The resulting product was a safer vaccine, less likely to cause allergic reactions than the TAT complex. To this day the toxoid has remained, with only minor modifications, the standard diphtheria vaccine and one of the safest and effective in the immunological arsenal.

In 1974, national routine immunization programmes working with WHO's newly created EPI, began using the diphtheria toxoid as one of the components of the DTP combination vaccine. By 1980, 20% of the infant population was receiving the full three-dose series of DTP (*41*). By the end of 2007, 81% of all infants worldwide were protected with three doses of DTP (*41*). Over the same period, reported cases worldwide fell by more than 95%, from 97 774 to 4273 (*41*) (reported case numbers rarely reflect true numbers but the trend certainly shows a convincing inverse relationship to vaccination coverage).

Diphtheria is no longer endemic, and high vaccine coverage rates in most countries have mostly eliminated the risk of epidemics. However, in countries with low (<50%) routine immunization coverage the risk of epidemics is still high. In the 1990s, a particularly alarming epidemic broke out in countries of the former Union of Soviet Socialist Republics following a drop in vaccination coverage. If nothing else, this outbreak served as an object lesson in the risk countries face when they lower their vaccination guard.

Since 1990, diphtheria outbreaks have also occurred in Africa, the Middle East, Asia, and South America (*41*). Paradoxically, some of the affected countries had relatively high reported vaccination coverage rates (*67*). The paradox is still the subject of debate. Another observation fuelling debate is the high percentage of adult cases in these epidemics, even where infant vaccination coverage was high and adults were receiving booster vaccine doses.

These observations have prompted countries where diphtheria is no longer endemic to extend vaccination protection beyond the primary three-dose series for infants by administering one, or sometimes two, booster doses every 10 years to adults through the diphtheria-tetanus (dT – low content of diphtheria) combination vaccine (*67*). Some countries with high infant vaccination coverage rates are giving booster doses of diphtheria toxoid to older children to compensate for the loss of natural immunity that they would have acquired from exposure to the bacterium had it still been circulating. Re-vaccination of health-care workers and using the dT combination vaccine (rather than the tetanus toxoid alone), for prophylaxis against tetanus following injury are additional safeguards some countries are adopting to lower the risk of a diphtheria outbreak (*67*).

Haemophilus influenzae type b (Hib) – increased attention for this little known but lethal disease

Since the mid-20th century, *Haemophilus influenzae* type b, or Hib, has been known by epidemiologists to cause meningitis, pneumonia, and other serious infections in infants and young children. WHO estimates of the year 2000 attribute to this bacterium an annual toll among the under-fives of nearly 8.1 million cases of invasive disease and pneumonia of which 363 000[1] are fatal (*68*). Hib also causes potentially severe inflammatory infections of the face, mouth, blood, epiglottis, joints, heart, bones, peritoneum, and trachea.

Yet, beyond the epidemiologists and public health analysts of the vaccine community, the burden of Hib disease is still not widely appreciated. One reason is the difficulty in detecting this bacterium as a common cause of pneumonia and meningitis cases, especially in developing countries. The problem is complicated by the fact that in many parts of the world, clinicians have treated these diseases with antibiotics, thereby masking the role of Hib.

Since the early 1980s, researchers used conjugation technology to develop several vaccine products that were highly immunogenic and conferred protection on all age groups. Wide use of this Hib "conjugate" vaccine enabled several countries – both industrialized and developing – to virtually wipe out Hib disease. Moreover, large-scale studies in Africa and Latin America, and more recently also in Asia, found a substantial reduction in the burden of pneumonia and meningitis in countries that had used the vaccine widely. One African trial, in particular, showed a drop in pneumonia incidence of just over 20% in Gambian children (*69*).

Notwithstanding clear evidence of the vaccine's efficacy, by 1997 only 29 countries were using it routinely, prompting WHO to recommend its inclusion in the routine immunization programmes of *all* countries where Hib was recognized as a public health burden and where the cost of the vaccine was not prohibitive (*70*). Over the next few years, however, both these conditions were to prove deterrents to Hib introduction for many countries.

Following the WHO global recommendation, and with growing demand for the vaccine together with increasing supply, the cost of the three doses of the single-antigen Hib vaccine had fallen to approximately US$ 10, and is now beginning to see even more

[1] reflects only deaths in HIV-negative children; an additional 8000 deaths are estimated to occur in HIV-infected children.

significant declines. In 2000, the GAVI Alliance began offering financial support for procurement of the vaccine to its then-75 eligible countries (i.e. those with a per capita gross national income of less than US$ 1000). The year 2005 also saw the birth of the Hib Initiative, a consortium of four public health entities (WHO, Johns Hopkins Bloomberg School of Public Health, the London School of Hygiene and Tropical Medicine, and the CDC), that was set up, with GAVI Alliance support, to speed up the adoption of Hib vaccine (*70*).

By late 2008, 135 countries had adopted the vaccine in their routine immunization programmes (Fig. 10) and a further 25 countries are expected to do so before the end of 2009, bringing the total to 160 countries, or 83% of all 193 WHO Member States (*71*).

Figure 10
Countries introducing Hib vaccine 1997 to 2008

Source: (71)

Hib vaccines are administered at the same time as DTP, often in combination vaccines that also include the DTP and hepatitis B antigens. In industrialized countries, the infant vaccination schedule with Hib conjugate vaccines is usually followed by one further dose during the second year of life. In most other countries, the Hib vaccine is only used for younger infants. Recent data from Latin America and Africa suggest that Hib disease can be eliminated with a three-dose regimen. At the present time, therefore, there are no compelling reasons for recommending a fourth dose of vaccine outside of the routine immunization programme. However, it is not yet known whether the protection conferred by the primary three doses will last a lifetime or if susceptibility to Hib infection could appear later in life. To help dispel such doubts, countries using Hib vaccines need to sustain surveillance for bacterial meningitis. Prompt detection of a resurgence of Hib disease could enable an appropriate vaccination response to be made.

Hepatitis A – paradox and potential

Hepatitis A is an acute illness caused by a virus (HAV) transmitted through the faecal-oral route. It is characterized by jaundice, dark urine, fever, anorexia, and abdominal discomfort, with the symptoms related to age. Infection with HAV does not become chronic. Most people recover after a few weeks. Severe complications are rare, but the risk of death increases with age, and case fatality may range from zero in children under 5 years old to 1.5% in people aged over 60.

The paradox of hepatitis A is that the very countries in which the disease is most prevalent are those where it has least visibility; in countries where its incidence is lower, outbreaks of the disease are very evident. In developing countries, HAV infects more than 80% of the population before adolescence, and 70% of children under six years of age may have no symptoms. In contrast, in industrialized countries with better sanitation, young children may not be infected, but during outbreaks, older children and adults who do not have immunity, may be ill with jaundice for up to two months, with the result that the disease is the most commonly reported of vaccine-preventable diseases in these countries. But this paradox also defines the potential: when countries improve their socioeconomic conditions, hepatitis A becomes more visible and controlling the disease through vaccination becomes a possibility.

Inactivated hepatitis A vaccines were licensed in the United States in 1996, where their use led to a dramatic decline in cases. Similar drops in incidence have been seen in other countries or areas of countries, such as Israel, Italy, and Spain.

Currently, WHO recommends that the results of appropriate epidemiological and cost-benefit studies should be weighed carefully before deciding on national policies on

immunization against hepatitis A (*72*). In highly endemic countries, HAV infects virtually all young children, without causing symptoms but effectively protecting the population against symptomatic hepatitis A disease in later life. In such countries, large-scale hepatitis A vaccination is not required. In countries of intermediate endemicity where a relatively large proportion of the adult population is susceptible to HAV, and where hepatitis A represents a significant public health burden, large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation. In regions of low endemicity, vaccination against hepatitis A is indicated for individuals with increased risk of contracting the infection.

Evidence from use of the vaccine in the United States and other countries, suggests that universal hepatitis A vaccine introduction can reduce the disease to very low nationwide incidence rates, raising the possibility of ultimately eliminating the disease.

Hepatitis B – the first vaccine against cancer

Of the many viruses known to cause hepatitis, the hepatitis B virus (HBV) inflicts the heaviest public health burden. The infection spreads by exposure to blood or other body fluids of an infected person, as in sexual contact, through a skin wound, or through use of an infected needle or syringe, and, in the case of infants, from an infected mother during childbirth. People infected with HBV are between 50 and 100 times more infectious (to others) than those infected with HIV. Further, the HBV virus is capable of remaining viable for over one week on contaminated environmental surfaces.

In most cases, the infection runs an acute course lasting from one to three months. Symptoms include jaundice, malaise, loss of appetite, nausea and vomiting, fever, muscle pain, and fatigue. They may be mild or, as in most infants and children, totally absent.

The most feared effect of HBV is chronic or lifelong infection – feared because it can lead to death from cirrhosis or cancer of the liver (*1*). More than 350 million people in the world today have chronic hepatitis B infection, according to a WHO estimate (*73*). About 90% of infants infected during the first year of life develop chronic infection, compared with 30% of children infected between one and four years, and less than 5% of people infected as adults (*1*). In 2002, an estimated 600 000 deaths occurred from chronic HBV infection.

In 1982, the first hepatitis B vaccine – the first vaccine against a human cancer – became available. Over the next decade, studies showed that the vaccine could protect about 95% of recipients from HBV infection. In 1992, WHO called on all countries to use the vaccine in their routine immunization programmes. Where transmission of the infection

during childbirth is common, as it is in several developing countries of WHO's South-East Asia Region, the first vaccine dose should be given to babies within 24 hours of birth. WHO also urges countries to vaccinate adults at risk of infection, such as health-care workers exposed to blood or other body fluids, dialysis patients, prison inmates, injecting drug users, household and sexual contacts of chronically infected people, and those with multiple sexual partners.

Adoption of the vaccine in routine immunization programmes was slow to take off. By 1997 – the WHO deadline for universal adoption of the vaccine in infant immunization programmes – only 62 countries had adopted the vaccine and only 14% of children were receiving the full three doses (*41*). Limited recognition of the burden of HBV infection and lack of funds to deploy the vaccine were among the main obstacles to wider introduction of the vaccine. Over subsequent years, WHO-sponsored research on the disease burden in developing countries did much to raise awareness of the infection and its consequences. The advent of the GAVI Alliance in 2000 helped to erode the financial obstacles to introducing the vaccine, at least for the poorer countries of the world. By the end of 2007, 171 of WHO's 193 Member States were using the vaccine in their infant immunization schedule.

The impact of vaccination on acute HBV infection is difficult to evaluate, since it requires intense surveillance for acute disease and laboratory confirmation. On the contrary, the impact on chronic HBV infection is easier to assess, thanks to blood (serological) tests for hepatitis B infection markers. Several countries achieving high vaccine coverage rates have seen a substantial reduction in the prevalence of chronic infection. Communities in China, for example, that began reaching high vaccine coverage rates in the late 1990s, showed a 90% drop by 2006 in the prevalence of chronic HBV infection in children under five years old (*74*).

Box 18

Hepatitis B control in China: reducing disparities

Every year, 280 000 people in China die from liver cancer or cirrhosis, accounting for almost one third of all HBV-related deaths worldwide. Even within this alarming statistic there are marked disparities between rich and poor provinces. Overall, approximately 60% of the population has a history of HBV infection. Almost 10%, or 120 million people, are chronically infected with HBV and risk early death from liver disease.

In response, China has made major investments in improving delivery of the hepatitis B vaccine. Hepatitis B vaccination for infants was introduced in 1992, with the recommendation that the first dose be given within 24 hours of birth. The cost of immunization, however, was a barrier to disadvantaged high-risk populations. In 2002, therefore, the Health Ministry made the vaccine universally available through the national immunization programme. This was followed, in 2005, by a Ministry decision to abolish all fees for recommended infant vaccinations. It is estimated that this initiative – a five-year, US$ 76 million project co-funded equally by the Government of China and the GAVI Alliance – has averted over 200 000 premature deaths due to chronic HBV infection.

By 2010, China aims to reduce chronic HBV infection rates to less than 1% in children under five years of age. To achieve this goal, women are encouraged to give birth in hospitals, and every hospital must keep enough vaccine available for administration of the birth dose. A high-profile nongovernmental organization, China Hepatitis Prevention and Control, is raising public awareness of the need to have all infants fully immunized with hepatitis B vaccine from birth and to avoid discriminating against people already infected with HBV.

The outcome of these measures has been dramatic: a surge in national birth dose coverage from 29% in 1997 to 82% in 2005, and a drop in the chronic infection rate over the same period to less than 2% of children under five. Some western provinces only attained around 70% of birth dose coverage by 2006, which may be due to the higher proportion of home births in those areas. The disparity is declining, but more work is needed for China to reach its national goals (*74*).

Growing confidence in hepatitis B vaccination has prompted WHO's Western Pacific Region – where all countries use the vaccine – to set a HBV control goal, namely, the reduction by 2012 of the average regional prevalence rate of chronic HBV infection to less than 2% in children under five years old. In 2008, the WHO Strategic Advisory Group of Experts (SAGE) strongly recommended that "all regions and associated countries develop goals for hepatitis B control appropriate to their epidemiologic situations."

The numbers of countries adopting the hepatitis B vaccine and the numbers of regions setting disease reduction goals show encouraging trends. But there are still challenges confronting HBV control efforts. Although close to 90% of the 193 WHO Member States were using the vaccine by the end of 2007, only 65% of children were receiving it. In countries whose national immunization schedule includes a hepatitis B vaccine dose at birth, there could be areas where most childbirths take place at home: in such areas, reaching babies with the "birth dose" of vaccine is problematic. Efforts are under way to make mothers and immunization providers in such areas more aware of the importance of protecting newborn infants with this initial vaccine dose. Moreover, in many countries, health workers and other high-risk groups are not being vaccinated in sufficient numbers. WHO is working with these countries to close this gap. A third problem is the continuing risk of HBV transmission from unsafe injection practices and blood transfusion procedures: efforts are under way to reduce this risk.

Human papillomavirus – a second cancer vaccine

It is estimated that, in 2002, there were 493 000 cases of cervical cancer and over 274 000 related deaths (*18*). More than 80% of these cases and deaths occurred in developing countries. Worldwide, and in developing countries, cervical cancer is the second most common cancer in women, after breast cancer (*75*). The highest incidence rates are in sub-Saharan Africa and Latin America, and also in parts of Asia (India alone accounts for nearly a quarter of cases occurring annually in the world) (*76*). In all cases, the causative agent is human papillomavirus (HPV).

Widespread use of screening (Papanicolau) tests by industrialized countries in the 1960s and 1970s brought incidence down by more than six-fold, to less than eight cases per 100 000 (*77, 76*) in industrialized countries. In most developing countries, however, the relatively high cost of screening was prohibitive (*78*).

Up to about 20 years ago, HPV infection was generally considered a cause of relatively harmless, if unsightly, warts on the skin and genital area, in both women and men. In the mid-1980s, DNA analysis by German researchers revealed the presence of genes

from the virus in cervical cancer cells taken from thousands of women. The virus was clearly a "necessary cause" of cervical cancer, i.e. its presence is necessary for cervical cancer to develop (it is not, however, a "sufficient cause": its presence will not always produce cancer). This evidence put to rest beliefs that over the centuries had invoked such things as toads, witchcraft and male secretions (smegma) as causes of cervical cancer. One cause, postulated by Italian physician Rigoni-Stern in 1842, was close to the truth: observing that nuns never died of cervical cancer, he assumed that sexual activity was to blame.

Today, HPV is known to be transmitted through sexual contact – not only penetrative sexual intercourse, but also sexual skin-to-skin contact. Contributing to the risk of HPV infection are factors such as early age of sexual activity, cigarette smoking, prolonged use of oral contraceptives, and co-infection with HIV, chlamydia, or herpes simplex virus (*77*). Most cases of HPV infection produce no symptoms. In more than 90% of cases, the infection disappears spontaneously (*1*). In the remaining cases it persists, and in 10–12% of these cases, it progresses over the next 20 to 30 years to cancer (*1*).

Cervical cancer is not the only cancer attributable to HPV, although it is the most common, accounting for about 90% of all HPV-related cancers. HPV also causes most cases (about 90%) of anal cancer, many cases (40%) of vulvar and penile cancers, and a small proportion (12%) of head and neck cancers (*1*).

There are probably more than 200 genetically distinct types (genotypes) of HPV virus (*76*). About 106 are known to cause disease in humans, and of these, 13 genotypes account for more than 95% of oncogenic HPV infections and have been labelled "high-risk" HPV types (*76*). Within a few years of starting sexual activity, more than 50% of sexually active women become infected with these high-risk types (*76*).The peak incidence of HPV infection is in the 16–25 year age group (*77, 78*), although the peak incidence of the HPV-related cancer is between 45 and 64 years (*77*).

The relative frequency of high-risk HPV genotypes (with types 16 and 18 causing about 70% of infections (*78*)) is fairly constant over all regions of the world (*77*). "Low-risk" HPV genotypes – those rarely associated with anogenital cancer – include types 6 and 11, which cause 90% of anogenital warts and cause a relatively rare but potentially life-threatening disease of the larynx – recurrent respiratory papillomatosis (RRP) – that occurs mostly in children under five years old.

Work on developing a vaccine against HPV began in the 1980s. Initial experiments using live attenuated or killed whole virus in animals gave promising results, but research quickly came up against two stumbling blocks. First, getting the virus to grow in the quantities needed to produce a vaccine proved difficult. Second, the whole virus contains

genes (oncogenes) that cause cancer and could present a risk to vaccine recipients. The solution to both problems lay in the structure of the HPV virus itself. Covering the virus is an outer shell (capsid) consisting of about 360 proteins. When the shell is taken apart and the proteins are put into an appropriate chemical solution, they automatically arrange themselves to form a new empty shell that is an exact copy of the original. This artificial shell, commonly known as a "virus-like particle" (VLP), contains no genes or other potentially risky or infectious viral material, but produces as strong a protective immune response in animals as the original whole virus. It can also be readily produced in large quantities.

In 2006, an HPV vaccine – the second against a human cancer (the hepatitis B vaccine was the first) – became available, followed a year later by another HPV vaccine. Both vaccines are based on VLP technology. One, a two-antigen (bivalent) vaccine, has VLPs carrying two HPV genotypes – 16 and 18 – which cause about 70% of cervical cancer in most parts of the world (*77*). The other vaccine, a four-antigen (quadrivalent) vaccine, has VLPs carrying the same HPV 16 and 18 genotypes but also 6 and 11, which cause about 90% of genital warts in women and men (*78*). In large-scale clinical trials in industrialized and developing country settings, both vaccines protected more than 90% of recipients against HPV infection. By the end of 2008, the bivalent vaccine was licensed in 90 countries and the quadrivalent in 109 countries.

In late 2008, the SAGE established global recommendations for HPV vaccination (*79*). These recognize the importance of HPV disease burden worldwide and recommend that HPV vaccination should be included in national immunization programmes where: prevention of cervical cancer and/or other HPV-related diseases are a public health priority; introduction of the vaccine is feasible; financing can be secured and is sustainable; and the cost-effectiveness of vaccination strategies in the country or region have been considered. The primary target population should be girls prior to initiation of sexual activity, with specific age ranges based on local data on age of sexual debut (most commonly 9 or 10 to 13 years). It is also recommended that in countries where it is feasible and affordable, older adolescent girls should be considered as a secondary target population, provided this is cost-effective and does not distract from the success of vaccinating the primary target. Vaccination of men to prevent cervical cancer in women is not recommended as this is unlikely to be cost-effective for cervical cancer prevention if high coverage is achieved in the target population. The SAGE also recommends that where possible, vaccine introduction should be in concert with a national cancer prevention programme that includes education, screening, and diagnosis and treatment of precancerous lesions. In April 2009, WHO issued a position paper based on these recommendations (*80*).

Influenza – keeping scientists guessing

Influenza, commonly called "flu", is a respiratory illness caused by a virus (*1*). The name is Italian for "influence", the word used by 16th century Italians to denote several illnesses believed to be caused by "the heavens" or "the stars". Symptoms of influenza last about a week on average, and include fever, sore throat, headache, aches and pains, chills, loss of appetite, and fatigue. About 30–50% of infected people have few or no symptoms (*1*). Children and elderly people are particularly vulnerable to infection and to the risk of developing severe complications, which may require hospital care. In the United States, up to 40 000 influenza-related deaths have been reported in severe influenza seasons (*1*). Worldwide, influenza infections are responsible for between 250 000 and 500 000 deaths a year on average (*81*).

The influenza virus spreads via tiny droplets released into the air when an infected person coughs or sneezes. The virus has a preference for the cold, dry air typical of the winter season in temperate climes. Every year, about 5–10% of adults and 20–30% of children come down with seasonal influenza (*82*). In tropical countries the illness occurs with less or no seasonality.

Influenza also occurs in an often devastating, pandemic form. Pandemics have been documented throughout the ages with the most recent pandemics occurring in 1918, 1957 and 1968. In 1918, the most devastating pandemic on record infected about half the world's population and killed an estimated 20–50 million people (*82*). Since pandemics tend to occur every 40 years or so, public health experts have been monitoring the H5N1 strain during the past few years, fearing that a new pandemic might be imminent.

The two types of influenza virus that cause illness in humans were identified in the 1930s and 1940s. Both types (A and B) are extremely efficient at evading the human immune system. By constantly altering their surface molecules and thereby mutating into new strains from one season to the next, they ensure that the immunity a population develops against the infection in one season will not protect the population in the following season. In other words, the influenza virus enjoys a constantly renewed pool of susceptible people from one season to the next.

This so-called antigenic drift mechanism also gives vaccine researchers, using WHO's 85-country Global Influenza Virus Surveillance Network, the task of predicting, several months before the onset of the influenza season every year, which proteins (or antigens) from the virus, should be included in an influenza vaccine so as to protect against the probable new virus strain.

The first commercial influenza vaccine – a relatively crude product consisting of an inactivated (or killed) whole influenza virus – became available in 1945. Whole-virus influenza vaccines are still used in some countries, but since the 1970s most countries use vaccines that are purer and produce fewer, albeit minor, side-effects.

A live attenuated influenza vaccine has been available since 1967. This is administered by nasal spray and is therefore easier to use in children, whereas the inactivated vaccine is administered mainly by intramuscular or subcutaneous injection. The live attenuated vaccine has also been found to stimulate a broader immune response against new viral strains resulting from antigenic drift, than the inactivated vaccine (*1*).

Currently available influenza vaccines protect about 70–90% of recipients provided their antigen composition closely matches that of the viruses circulating at the time (*82, 83*). There is evidence that these vaccines are effective enough to reduce the number of hospitalizations in a population by 25–39% and to reduce the number of deaths by 39–75% (*82*). About 75 countries, mostly industrialized, offer influenza vaccination to high-risk population groups, such as elderly people.

In 2003, the World Health Assembly called on Member States that use influenza vaccines to provide vaccination to at least 50% of their elderly population by 2006, and 75% by 2010. Firm data regarding progress in meeting the goal is difficult to obtain, especially from countries where almost all of the influenza seasonal vaccinations are offered by private health-care providers.

Box 19

Pandemic influenza – the H5N1 threat

Between 2003 and April 2009, fears of an influenza pandemic, or worldwide epidemic, focused on influenza viruses belonging to the subtype H5N1, which continue to circulate in birds but have also infected mammals, including people. Since 2003, H5N1 influenza viruses have spread through Africa, Asia, Europe, and the Middle East, causing the deaths or culling of tens of millions of birds in more than 27 countries. As of May 2009, 429 people in 16 countries had been infected with the H5N1 avian influenza virus according to reports of laboratory confirmed cases received by WHO (*19*). What is particularly worrying about this virus is its capacity for rapid geographical spread, its long-lasting persistence in birds, and its high pathogenicity (more than 60% of infected people have died from the infection).

Two H5N1 influenza vaccines have been developed. One was awarded a United States licence in 2007 and was provided for a United States stockpile. Another was licensed by the European Medicines Agency in 2008. Several countries, including Finland, Mexico, Switzerland, and the United Kingdom, have begun stockpiling H5N1 vaccine in preparedness for a pandemic and several multinational manufacturers have pledged to contribute millions of doses of vaccine to a potential WHO stockpile.

In February 2009, new global capacity figures for the production of influenza vaccine were published (*84*). These indicate that seasonal influenza vaccine capacity is expected to increase considerably from 2009 to 2014. Likewise, production capacity for producing H5N1 vaccine has increased, due to overall capacity expansion, antigen-sparing techniques, and yield improvements. Despite this improvement, supply does not yet meet global needs.

Meanwhile, seasonal vaccine production capacity is rising faster than annual demand – which is currently less than 500 million doses per annum – and current stockpile demand. If demand does not exist to utilize this excess capacity, however, manufacturers are likely to rationalize some of it, creating further shortages at the time of a pandemic.

In view of this, some countries consider that it is a matter of health security for them to acquire the technology to produce influenza vaccine domestically. This prompted WHO to initiate in 2007 an influenza vaccine production technology transfer project. As of the end of 2008, six vaccine manufacturers in developing countries had undertaken development activities for influenza vaccines, and more projects are expected to begin in 2009.

Box 20

Pandemic influenza – the H1N1 threat

In April 2009, pandemic influenza concerns expanded from H5N1 to a novel strain of influenza A (H1N1) virus. First circulating in North America, the virus has rapidly spread across the world. By the end of May 2009, 13 398 laboratory-confirmed cases had been reported in 48 countries (*85*).

Although disease caused by the H1N1 virus has generally been mild, severe illnesses resulting in hospitalization and a total of 95 deaths have occurred in Canada, Costa Rica, Mexico and the United States. Although too early to determine the impact of the emergence of the virus, large community-wide outbreaks and school outbreaks have been reported (*86*).

As soon as the first human cases of the H1N1 virus became known, WHO initiated communication with the pharmaceutical and vaccine industry and discussions with experts from other relevant fields began. In respect of vaccines, consultations focused on review of the epidemiology of infections and associated disease burden, potential vaccine options, the status of seasonal vaccine production and potential production capacity for an H1N1 vaccine, and the timing of a potential recommendation to initiate commercial scale production of an H1N1 vaccine. The WHO Collaborating Centers and Essential Regulatory Laboratories began work to develop candidate vaccine viruses.

At the time of writing, regular communication with all those involved in vaccine production and regulation is ongoing in order to ensure appropriate and timely decisions relating to protection against the H1N1 virus through vaccination are made. The considerable work undertaken by WHO and partners in recent years to put in place expedited processes for regulation and licensing in the event of a large-scale epidemic or pandemic is already proving to have been a wise investment.

Japanese encephalitis – a regional scourge, waning but still present

Japanese encephalitis is a viral disease transmitted by mosquitoes of the *Culex* species, which pick up the virus from animals – mainly wild water birds and pigs. As such, it is a disease of rural areas. Virus circulation has been demonstrated in many Asian regions within the tropical and temperate climate zones. At least 50 000 cases and 10 000 deaths are estimated to occur every year, mostly among children under ten years old (*87, 4*). In temperate areas of Asia, the disease occurs in regular epidemics, whereas in southern, tropical areas, such as parts of India, Nepal, Thailand, and Viet Nam, it is present in an endemic, or more permanent form (*88*). Over the past years, surveillance has intensified in many countries, but there is still a need to both better define the burden of disease and to extend surveillance in order to define populations at risk.

Only about 1 in 250–500 of infected people develop clinical disease (*87*), which is fatal in 10–30% of cases (*89*). Symptoms can be relatively mild, with fever, cough, nausea, vomiting, and diarrhoea; or severe with inflammation of brain membranes or a polio-like flaccid paralysis (*90*). Permanent sequelae, such as cognitive and language impairment and motor deficits, account for much of the burden of the disease.

The first Japanese encephalitis vaccines were produced in the late 1930s in the Union of Soviet Socialist Republics and Japan. They consisted of chemically inactivated virus taken from the brains of infected mice. After World War II, research institutes in Japan produced several refined versions of this mouse-brain vaccine, which were subsequently manufactured and used in many Asian countries. Since its introduction in the mid-1950s into Japan's immunization programme, reported cases of Japanese encephalitis in Japan have plummeted.

In the 1960s, an inactivated vaccine was developed in China based on virus grown, not from mouse brain, but from cultured cells. This vaccine was used in China from the 1970s to the 1990s and was subsequently replaced by a new, live vaccine using the so-called SA14-14-2 strain, which is being used widely in routine programmes and mass campaigns to immunize children from 1 to 15 years of age in several countries, including China and India (*91*). In 2005, China incorporated the live vaccine into its routine immunization programmes. The vaccine has turned into the most widely used product against the disease, and benefits from a competitive price. It is not currently WHO-prequalified, but plans have been established for a submission.

A number of new Japanese encephalitis vaccines are in development and some are approaching licensure. One – a live, attenuated vaccine – consists of a genetically engineered combination of the yellow fever vaccine with a fragment of the Japanese

encephalitis virus strain SA14-14-2. If it fulfils its promise, this so-called "chimeric" vaccine may produce long-term protection with a single dose, and allow concurrent administration with the measles vaccine. Another – an inactivated vaccine, based again on the SA14-14-2 strain, and produced in cell culture – is about to reach licensure, promising a simplified immunization schedule as compared with the mouse-brain vaccine. It is anticipated that several Japanese encephalitis vaccines should be on the market soon for use in endemic countries, and WHO-prequalification of one or several products is expected (*92*).

Immunization, together with higher standards of living and urbanization, has brought the incidence of Japanese encephalitis down to a handful of cases per year in the more developed Asian countries, such as Japan and the Republic of Korea (*1*). Experts warn, however, that the virus is still circulating in the pig populations of many of these countries, indicating that the risk of human infection and disease is still very much present, should immunization programmes be discontinued (*1*).

WHO recommends that immunization against Japanese encephalitis be integrated into national immunization programmes in all areas where the disease is a public health problem. In countries where the disease is endemic and where Japanese encephalitis vaccination is not yet incorporated into the national immunization programme, the immunization strategy with the greatest potential impact on public health, according to WHO, consists of a one-time mass campaign, followed by incorporation of the vaccine into the routine immunization programme (*87*).

Measles – record progress but risk of resurgence is high

Measles is an extremely contagious viral disease, which – before the widespread use of the measles vaccine – affected almost every child. High-risk groups for complications from measles include infants, and people suffering from chronic diseases and impaired immunity, or from severe malnutrition, including vitamin A deficiency (*93*).

Routine measles vaccination – giving one dose of vaccine to infants – began in developing countries in the mid-1970s. Many industrialized and several developing countries have since added a second dose given to children between one and seven years of age (depending on the country). By 2000, 72% of the world's children were receiving at least one dose of measles vaccine (versus 16% in 1980); annual reported cases had dropped by 80% (from 4.2 million in 1980 to 853 000); and annual estimated deaths had dropped by 70% (from 2.5 million in 1980 to 750 000) (*1*). By 2002, WHO's entire Americas Region had eliminated measles (i.e. had no indigenous cases, as distinct from imported cases, for more than 12 months) (*94*).

Despite these results, in 2000, measles was still the leading cause of vaccine-preventable deaths in children, and the fifth leading cause of death from any cause in children under five years old (*95*). Responding to this situation, in 2001, the American Red Cross, UNICEF, the United Nations Foundation, the CDC, and WHO launched the Measles Initiative aimed at reducing the death rate from measles in Africa, where nearly 60% of measles deaths were occurring (*96*). In 2007, major financial support for the Initiative was provided on a one-time basis by the IFFIm through the GAVI Alliance.

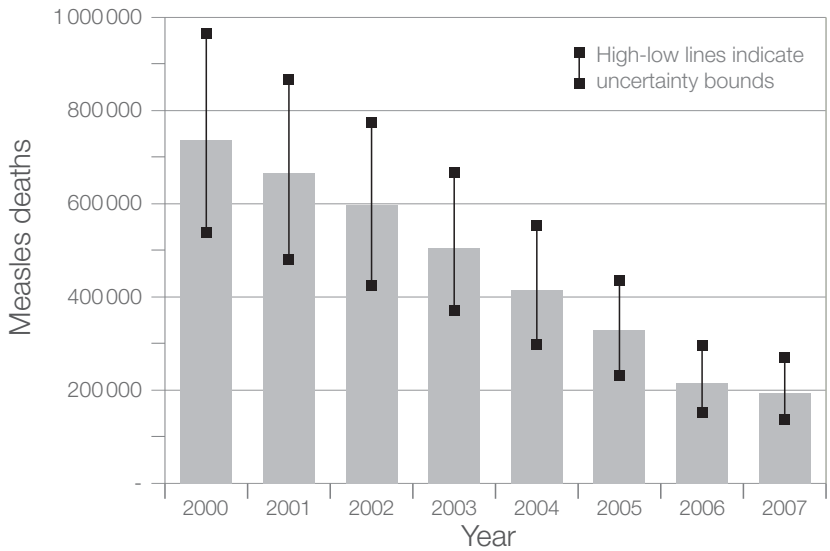
In 2004, the Initiative extended its mandate to other regions (notably Asia) where measles was a significant burden and marked 47 high-burden countries for priority action. The Initiative aimed to boost routine immunization coverage to more than 90% of children under one year of age in every district of these countries and to maintain coverage at over 90%. Supplementary mass immunization campaigns were to be conducted periodically, targeting all children between nine months and 14 years of age, with "follow-up" campaigns every two to four years targeting children between nine months and five years of age. Increased emphasis was to be placed on laboratory-backed surveillance of new measles cases and monitoring of vaccination coverage.

The Initiative's efforts gained impetus when in 2003, the World Health Assembly called on WHO Member States to halve measles deaths by the end of 2005, compared with 1999 estimates. In 2005, the World Health Assembly endorsed the even more ambitious GIVS goal, namely, a 90% reduction, by 2010, of measles mortality, compared with 2000 estimates (see Chapter 1). By the end of 2006, the Measles Initiative had surpassed the goal to halve measles deaths by 2005: end-of-year estimates for 2005 showed a 60% drop in global measles deaths since 1999 (i.e. from 873 000 to 345 000 deaths) (*96*).

For many measles observers, the 2010 GIVS goal calling for a 90% reduction in measles mortality compared with 2000 estimates can be achieved. Estimates for 2007 show a record-breaking 82% global vaccination coverage rate, up from 72% in 2000, with most of the increase coming from Africa's surge in coverage to 74%, up from 56% (*97*). Most significantly, estimated annual measles deaths had dropped by 74% from 2000–2007, to 197 000 globally. The Eastern Mediterranean and African Regions, with a 90% and 89% fall in deaths respectively, accounted for most of the global decline, thereby reaching the 2010 mortality reduction goal three years ahead of schedule.

Figure 11

Estimated measles deaths 2000–2007



Source: (97)

The road ahead, however, holds a number of hurdles to achieving measles mortality-reduction goals:

- As of 2007, there were still 197 000 measles deaths occurring annually – 69% of them in the WHO South-East Asia Region (*97*). The main reason is because mass vaccination campaigns have not yet begun in India. In addition, while routine measles vaccination coverage has risen from 61% in 2000 to 73% in 2007, it is the lowest among all six WHO regions (*97*).

- An estimated 23 million children under one year of age were, in 2007, still not receiving their first dose of measles vaccine through routine immunization: about 15 million (65%) of these children are living in eight populous countries: India (8.5 million), Nigeria (2 million), China (1 million), Ethiopia (1 million), Indonesia (0.9 million), Pakistan (0.8 million), Democratic Republic of the Congo (0.6 million), and Bangladesh (0.5 million).

- Sustaining the decline in measles deaths will call for all districts in all 47 high burden countries to be vaccinating at least 90% of children before their first birthday, and to be conducting follow-up supplementary immunization activities every two to four years.

- Looking to the future, as yet there is no global consensus on global elimination or eradication of measles. Four of the six WHO regions have elimination goals – the Americas (for 2010), Europe (2010), the Eastern Mediterranean (2010), and the Western Pacific (2012). Meanwhile, reducing global measles mortality remains the overriding concern.

Meningococcal disease – still a deadly menace across Africa

The meningococcus (*Neisseria meningitidis*), is a major cause of meningitis and is permanently present (endemic) in every country in the world (*98*). It is also present, as a colonizing bacterium, in the nose and throat tissues of about 10–25% of the world's population – the healthy carriers (*1*). For reasons that are not clear, in a small number of these healthy carriers, the organism becomes invasive and, in most cases, the resulting disease is meningitis. In 5% to 15% of cases, the clinical disease is pneumonia or, more alarmingly, a severe blood infection (fulminant septicaemia) or joint infection (septic arthritis) (*1*). Early symptoms of meningococcal disease include high fever, headache, stiff neck, nausea and vomiting.

Before antibiotics became available, 70–80% of those infected died, usually within a day or two. Treatment with antibiotics has reduced the death rate among infected people to less than 15% (*98*), but about 20% of survivors have important sequelae, of which the most severe include loss of a limb, epilepsy, mental retardation, and deafness. WHO estimates that about 500 000 cases of meningococcal disease occur every year worldwide (*98*) causing 50 000 deaths.

Other causes of meningitis are viruses and other bacteria, notably Hib and the pneumococcus (*Streptococcus pneumoniae*). The meningococcus, however, is the only bacterial cause of meningitis that causes epidemics. With the advent in the 1940s of antibiotics, together with the availability of hospital-based intensive care units, large-scale epidemics began to peter out in industrialized countries, although the disease remained endemic, causing isolated cases, clusters of cases and, in some instances, epidemics. On average, since the year 2000, more than 7000 cases have been reported in western Europe and about 3000 in the United States (*1*).

In Africa, major epidemics have been occurring over the past 100 years (*1, 98*) – most of them in the so-called "African meningitis belt" that spans sub-Saharan Africa from Senegal in the west to Ethiopia in the east (*99*). In 1996 to 1997, the largest epidemic in history swept across the belt, causing over 250 000 cases, an estimated 25 000 deaths, and disability in 50 000 people. Large epidemics tend to recur in the meningitis belt every 7–12 years, against a backdrop of smaller annual epidemics (*100*). Although the

annual epidemics are smaller, they are still large enough to disrupt the health services and damage the already fragile economies of the 25 countries in the belt, not to speak of the social lives of its nearly 400 million inhabitants (*100*).

Work on a vaccine against the meningococcus began in the 1890s (*1*). The early meningococcal vaccines, developed between 1900 and the 1940s, were effective enough to elicit an immune response but not pure enough to avoid untoward reactions in vaccine recipients.

Efforts to develop a vaccine need to take into account the distribution of different strains of meningococci. Researchers have identified 13 different meningococcal groups, based on the organism's outer sugar capsule. Five groups – A, B, C, Y, and W-135 – are associated with most cases of severe disease and epidemics. Broadly speaking, groups A, B, and C, account for most cases and epidemics in the world. Group A is predominant in Africa and Asia and is the main cause of epidemic meningitis in sub-Saharan Africa; group B occurs in many regions; group C occurs mainly in North America, Europe, and Australia; and group Y is gaining importance in the United States. Group W-135 has only recently emerged as a cause of epidemics in Africa and the Middle East. A vaccine against one group does not confer cross protection to another group.

By the mid-1970s the first modern "polysaccharide" vaccines were introduced, and were based on the carbohydrate capsule (polysaccharides) surrounding the organism. Between the late 1970s and the mid-1980s, several polysaccharide vaccines became available, targeting one (A, C, Y, or W-135), two (A and C), or four (A, C, Y, and W-135) meningococcal groups. However, as with the polysaccharide vaccines developed against Hib and the pneumococcus, they gave little or no protection to children under two years of age. Other age groups were protected but for only three to five years, and the vaccines conferred no "herd" or community immunity, whereby even the unvaccinated are protected. Despite their shortcomings, polysaccharide meningococcal vaccines were used, with mixed results, either for routine preventive vaccination (in China and Egypt), or for selected high-risk groups during epidemics.

Since 1999, four new-generation conjugate vaccines (see Chapter 2) have appeared, targeting one (group C) or four groups (A, C, Y, W-135). At least five more candidate conjugate vaccines are in the late stages of development.

To date, there are no licensed vaccines against the group B meningococcus, but several vaccine manufacturers have products that are being evaluated clinically. For example, group B vaccines that have been custom-made against specific epidemic strains have been successfully used to control specific outbreaks in Brazil, Chile, Cuba, France, New Zealand, and Norway.

In industrialized countries, particularly in Canada and Australia, and countries in Europe, the incidence of meningococcal meningitis was falling prior to the introduction of conjugate vaccines, and their introduction has accelerated the decrease in disease rates. This is not the case in developing countries, where high endemic disease rates still occur, with the additional problem of periodic major epidemics. This situation is very likely to improve – at least for the African meningitis belt, where a new, inexpensive group A conjugate vaccine is in the late stages of development and is expected to be ready for use in 2010 (see Box 21).

Box 21

A new meningococcal vaccine to control meningitis in Africa

It was the year 2001. All the ingredients were in place: the conviction that it had to be done and could be done; the knowledge needed to prepare a meningococcal vaccine; and the international partnership to develop a vaccine. By 2010, a vaccine against group A meningococcus is expected to be available for use in a huge swathe of Africa, home to nearly half a billion people. Meningococcus A is believed to cause some 85% of meningococcal meningitis cases in Africa.

In 2001, WHO and PATH – with funding from the Bill & Melinda Gates Foundation – created the Meningitis Vaccine Project, with the single goal of developing a new, affordable group A conjugate vaccine (*101*). A Dutch firm agreed to manufacture vaccine-grade group A polysaccharide, and an Indian vaccine manufacturer provided the carrier protein (tetanus toxoid) that would be linked (conjugated) to the polysaccharide to create a new vaccine that would induce a strong, durable immune response. Scientists from the FDA helped to overcome the administrative and legal hurdles, and transferred a new conjugation technology to the Indian manufacturer, who, with Project support, undertook the development, scale-up and production of the vaccine.

This new group A conjugate vaccine will cost no more than US$ 0.50 a dose and has been shown to be safe and highly immunogenic in clinical trials in the Gambia, India, Mali, and Senegal (*102, 103, 104, 105*). Project officials hope it will be licensed and ready for use before the end of 2009. Health officials in the 25 countries that make up the African meningitis belt and that stand to benefit most from the new vaccine are optimistic: at a September 2008 meeting in Cameroon, ministers from all 25 countries pledged to start making plans to introduce the vaccine as soon as it becomes available (*106*).

If all goes well, by 2015, nearly 300 million people will have been vaccinated in the 25 belt countries and, assuming vigorous herd immunity, more than 400 million people will be protected against death and disability from the meningococcus.

Mumps – not always mild, not yet conquered

Two of the features of mumps – swelling around the ears (parotitis, or inflammation of the salivary glands) and painful swelling of one or both testes (orchitis, or testicular inflammation) – were described in the fifth century BC by Hippocrates, the founder of medicine. A second milestone was the detailed account of the course of the disease, including its occasional involvement of the central nervous system, made in the late 18th century by Scottish physician Robert Hamilton. And the third was the discovery in the 1930s by United States pathologists that a virus was the causative agent. Two decades later, the first mumps vaccine was undergoing tests in humans (*1*).

Historically, mumps has been generally regarded as a relatively benign, self-limiting illness affecting mainly children aged five to nine years. Most cases involve little more than a week or two of influenza-like symptoms with earache and soreness around the jaws. About 20–40% of infections produce no symptoms at all. Nevertheless, the need for vaccination is based on solid arguments. For one thing, in pre-vaccine days, the disease was disabling enough to be a significant cause of absenteeism of young children from school, of adolescents from higher educational institutions, and of soldiers from army duty (*1*). For another, complications of the disease can be severe, and on rare occasions, fatal: among the most feared complications of mumps are meningitis, encephalitis, and pancreatitis. Deafness in one or both ears is among the most disabling. Yet another argument is the sheer prevalence of the infection, which can spread throughout an entire community and pose an ever-present risk of severe complications. This alone would justify protection of the community by vaccination (*107*).

More than 13 mumps vaccines – all live, attenuated vaccines – exist today and can protect about 80% of recipients (*1*). Each of these vaccines is based on a different strain of the mumps virus. They are available as single (monovalent) vaccines, or as a component of the bivalent measles-mumps or trivalent measles-mumps-rubella (MMR) vaccine. Since the 1960s, mumps vaccination has been used primarily in industrialized countries but increasingly also in countries in economic transition (*108*). Some countries (13 at the end of 2007) administer only one dose, given at 12–24 months of age. Most (101 at the end of 2007) give a second dose in later childhood, most often in the form of the MMR vaccine. With the two-dose MMR schedule, mumps vaccination is highly cost-effective, according to economic analyses published in 2004, particularly in countries where direct and indirect costs are substantial. Direct costs include medical treatment (mainly for hospitalization and treatment of meningitis and encephalitis), and indirect "societal" costs related to reduced work productivity of patients and carers, and also disrupted school attendance (*107*).

WHO recommends routine mumps vaccination as a two-dose schedule for countries that have efficient child vaccination programmes, countries that can sustain high vaccine coverage rates, and those that regard mumps as a public health priority (*108*). The first condition is based on the fact that in areas where routine mumps vaccination reaches less than 80% of infants, there are still enough susceptible children to sustain transmission of the infection and to infect non-immune (susceptible) adolescents and young adults – a population group more likely than young children to develop severe complications. Knowing whether mumps can be regarded as a public health priority is a problem for many developing countries. Mumps, despite WHO urging, is not yet a notifiable disease in most countries. Most cases run a generally mild course and thereby escape official notice. The result is that reported case numbers are believed to reflect less than 10% of the true incidence of the disease. Active surveillance efforts could to some extent solve the problem, but many countries lack the motivation and resources to implement these for a disease traditionally considered of marginal public health importance compared with more visible scourges, such as malaria, pneumonia, and measles.

As of the end of 2007, 114 countries were administering mumps vaccine, compared with 104 countries at the end of 2002. In virtually all countries where routine mumps vaccination has been adopted, the incidence of mumps has plunged to negligible levels (*1*). The effectiveness of vaccination has been so dramatic as to prompt several countries, notably Finland, Sweden, and the United States, to set goals for eliminating the disease. Several factors, however, suggest that vaccination has still some way to go before elimination can be achieved and sustained.

- Outbreaks of mumps have continued to occur since the 1980s even in countries achieving high coverage rates with routine vaccination. More recently, large outbreaks occurred in the United Kingdom from 2004 to 2005 (*107*), in the United States in 2006 (*109*), and in the Republic of Moldova from 2007 to 2008 (*110*). All three outbreaks involved adolescents or young adults. In two of the outbreaks, most of the cases occurred in individuals who were believed to have received two doses of the MMR vaccine. This may suggest that immunity to the vaccine, which was thought to protect against mumps for at least 15 years, may start to wane much sooner. A first-line response to mumps outbreaks is mass vaccination of the entire population at risk. A second option under consideration by some countries using the two-dose schedule is to add a third dose, at least to control mumps outbreaks. The question then is whether mumps control would still be cost-effective. Developing a vaccine with a more durable protective efficacy is another option but achievable only in the much longer term.

- All of the mumps vaccines available internationally through the United Nations vaccine procurement system occasionally cause parotitis (1–2% of recipients), and very

occasionally, viral (aseptic) meningitis – a usually benign inflammation of the linings of the brain (*107*). The risk of aseptic meningitis following mumps vaccination varies widely according to vaccine strain, the manufacturer, the awareness and vigilance of health practitioners, and the intensity of surveillance (range: 1:11 000 recipients to fewer than 1:100 000 recipients (*108*)).

The future of global mumps control will thus hinge on how quickly and extensively the true public health burden of mumps will emerge from epidemiological research; how effectively the risk of mumps outbreaks and of vaccine-related side effects can be reduced; and, consequently, how many countries will know enough and have enough resources to consider routine mumps vaccination a worthwhile option.

Pertussis – too many children not being vaccinated, too many uncounted deaths

Pertussis, or whooping cough, is a disease of the respiratory system caused by infection with the bacterium *Bordetella pertussis*. The most characteristic symptom is a cough that occurs typically in spasms ending in a classic inspiratory whoop. In young infants, the only signs or symptoms may be cessation of breathing (apneoa) and blue colouring of the skin (cyanosis).

Complications arise in 5–6% of cases – the most serious and often fatal of them being bronchopneumonia and encephalopathy (*111*). Death from pertussis still occurs in industrialized countries (less than 1 per 1000 cases (*111*)), but more rarely than in developing countries (40 per 1000 infants, and 10 per 1000 in older children (*111*)). The global burden of the disease is difficult to estimate, given the paucity of surveillance data available. WHO's latest estimates put the annual number of cases worldwide as of 2004 at nearly 18 million, with about 254 000 deaths, of which 90% are in developing countries *(111, 4)*.

The first pertussis vaccine used the killed whole bacterium (whole cell) as the immune-stimulating antigen. It appeared in 1914 and became available in combination with diphtheria and tetanus antigens (DTP) in 1948 (*1*). Today, there are many whole-cell pertussis vaccines, some more effective and safer than others, and the variability depending mainly on the method of production (*111*). Fifteen safe and effective pertussis vaccines, usually in combination with tetanus and diphtheria vaccines, have been prequalified by WHO for international distribution through the United Nations procurement systems.

Adverse reactions related to whole-cell pertussis vaccines are frequent but mostly minor and self-limiting. In the mid-1970s, suspicions arose that whole-cell pertussis vaccines could very rarely cause serious complications, such as encephalopathy (*111*). Although no scientific studies have confirmed a link between whole-cell pertussis vaccines and encephalopathy, these suspicions caused enough public concern to fuel a search for a more purified, and presumably safer, vaccine.

The result was a non-whole-cell (acellular) pertussis vaccine, which first became available in Japan and later in other industrialized countries. Several acellular pertussis vaccines are currently available. Clinical trials suggest that the "best" whole-cell and acellular vaccines protect about 85% of recipients. Both are safe, although the acellular vaccine appears less reactogenic, i.e., less likely to produce fever or local reactions at the site of the injection (particularly among older age groups), than the whole-cell vaccine.

By the end of 2007, 46 of WHO's Member States had switched from whole cell to acellular vaccines (*41*). Most of these countries were in industrialized countries, where public sensitivity to rumour and even to the mild reactions to the whole-cell vaccine has been greater than in developing countries, and where the higher cost of the acellular compared to the whole-cell vaccine is less of a problem. An additional constraint on adoption of the acellular vaccines by developing countries is the fact that they have not acquired WHO prequalification status (largely because up to mid-2008 no manufacturer had the capacity to supply the developing country market). WHO expects a prequalified acellular vaccine to be available in the near future. However, more widespread use in developing countries will depend on country demand and secure financing.

In most countries, pertussis vaccination consists of three initial doses of the pertussis-containing DTP (the primary series) given at least one month apart to infants between six weeks and six months of age (*111*). In 1980, routine vaccination with three DTP doses was reaching about 20% of the world's infants *(41)*. By the end of 2007, the figure had risen to 81%. Determining the impact vaccination is making on the global burden of pertussis is difficult. Certainly, following widespread vaccination during the 1950s and 1960s, the industrialized world saw a more than 90% drop in pertussis cases and deaths (*111*). And certainly, numbers of cases reported annually to WHO dropped by 92% from about 2 million in 1980 to 162 000 by the end of 2007 – a drop consistent with the upward trend of vaccination coverage (*111*). But due to lack of adequate surveillance, reported cases of pertussis are believed to reflect less than 1% of the true incidence (*1*).

There is little doubt, though, that pertussis vaccination is preventing pertussis cases and deaths – nearly 38 million cases and 600 000 deaths in 2004, according to WHO estimates (*111*). What is less sure is its impact on circulation of the causative *B. pertussis* bacterium (*111*). High vaccine coverage rates in some industrialized countries are not preventing periodic outbreaks among adolescents and adults who remain susceptible to infection. Finland offers a striking example of this "epidemiological shift": with vaccine coverage reaching 98% of the infant population, the incidence of pertussis among adolescents doubled in the four years between 1995 and 1999 (*111*). Other industrialized countries are facing a similar trend. Compounding the problem is the likelihood of adolescents and adults acting as a source of infection for infants who have not been vaccinated by routine vaccination (*1*).

The primary purpose of pertussis vaccination is to prevent severe disease and death among infants and young children. To achieve this, at least 90% of the infant population should be receiving the primary three doses of DTP according to schedule. As of the end of 2007, 78 (40%) of WHO's 193 Member States had less than 90% coverage, and there were an estimated 24 million partially vaccinated or unvaccinated children in the world. WHO also recommends countries that have achieved a substantial reduction in pertussis incidence through infant vaccination to give a booster dose to all children one to six years after the primary series.

Future priorities for pertussis control include measures to improve disease surveillance and the consequent reliability of case reporting, particularly in the most severely affected (and often poorest) countries. Diagnosis of the disease is difficult and calls for laboratory facilities and expertise often lacking in the most affected countries. Research is under way to explore the possibility of developing diagnostic methods that could be used on a far wider scale to provide more accurate case reporting than is at present possible.

Pneumococcal disease – many deaths from many strains, many hopes from new vaccines

The bacterium *Streptococcus pneumoniae*, also known as the pneumococcus, is a leading cause of severe disease and deaths in children under five years old. According to unpublished WHO estimates, in 2000 there were 14.5 million episodes of severe pneumococcal disease and more than 800 000 deaths (of which 88 000 were HIV-related) among children in this age group. Children under five, people with depressed immune systems, smokers, and elderly people are among the population groups at highest risk of pneumococcal disease. The total number of annual deaths attributable to this bacterium, including adults and children, is about 1.6 million, according to WHO estimates (*112*).

In children, pneumonia accounts for about 95% of severe pneumococcal disease episodes and close to 90% of deaths due to the pneumococcus (other major causes of bacterial pneumonia include *Haemophilus influenzae* type b). Meningitis accounts for less than 1% of cases of severe pneumococcal disease in children, but is responsible for more than 7% of the deaths caused by pneumococcal infection. In addition, the pneumococcus can also cause sepsis, and other invasive diseases such as peritonitis, arthritis, and osteomyelitis.

The pneumococcus was first identified in the 1880s as the most common cause of pneumonia (*1*). By 1911, researchers began human tests of a crude whole-cell vaccine, made up of the whole pneumococcus, and by the mid-1940s, at least three vaccines had appeared. However, within a few years these had been withdrawn from the market for lack of commercial interest: physicians in industrialized countries favoured penicillin treatment (*1*).

Over the next four decades, however, it became clear that antibiotics were not making a large enough impact on reducing deaths from pneumococcal disease, and public health interest in pneumococcal vaccination revived. The early 1960s saw the advent of the first modern pneumococcal vaccines. These were "polysaccharide" vaccines, so-called because they targeted the sugar molecules (polysaccharides) making up the outer capsule, or coat, of the pneumococcus. At least 90 different types of the pneumococcus exist, each with a different capsular polysaccharide configuration. Less than 30 of these capsular types are commonly associated with human disease. In 1983, a polysaccharide vaccine became available, which contained 23 capsular polysaccharides – responsible for 85–90% of severe pneumococcal disease in industrialized countries (*112*). However, the vaccine had several shortcomings, the most serious being its inability to induce protective immunity in children under two years of age, the age group most affected by the disease.

The need for a better vaccine was clear. Researchers turned to conjugation technology (see Chapter 2). In the year 2000, a conjugate pneumococcal vaccine arrived on the market, which protected against the seven capsular types of the bacterium responsible for 65–80% of cases of severe disease in young children living in industrialized countries (*112*). However, this "7-valent" vaccine did not contain all the important serotypes responsible for severe pneumococcal disease in developing countries (*1*). Clinical trials of candidate conjugate vaccines containing 9 or 11 of the serotypes prevalent in developing countries conferred long-lasting protection in infants against invasive disease and pneumonia. One trial in the Gambia showed, in addition, a 16% reduction in deaths from all causes among children vaccinated with the "9-valent" vaccine. Although the

respective manufacturers decided not to seek licensure for these two vaccines, other formulations of the vaccine containing 10 and 13 serotypes are in the late stages of clinical testing and are likely to be on the market by 2009-2010 (*113*). In addition, other vaccine candidates, including conjugate vaccines as well as others based on protein antigens and some developed by emerging manufacturers, are in earlier stages of testing.

By mid-2008, the 7-valent conjugate vaccine was in use in more than 60 countries. Introduction of this or the newer vaccine in the poorest countries is expected to begin in 2009 through support from the GAVI Alliance. One analysis (*112*) has estimated that at current rates of DTP coverage, pneumococcal vaccines could prevent about 262 000 deaths a year in the 72 countries eligible for GAVI Alliance funding.

A substantial reduction in invasive pneumococcal disease and pneumonia has been seen in countries that have introduced conjugate vaccines. Within three years of conjugate vaccine introduction in the United States, invasive pneumococcal disease due to the pneumococcal serotypes in the vaccine had fallen by 94% in vaccinated children (*114*). In addition, unexpectedly large reductions in disease were seen in the unvaccinated population, including in elderly people, as a result of reduced transmission of the infection – a phenomenon referred to as "herd immunity". The total cases prevented in older children and adults through herd immunity in the United States were estimated to be twice as many as in the vaccinated age groups.

The mood in the vaccine community is decidedly optimistic over the potential for conjugate vaccines to improve child survival and thereby contribute to achievement of MDG 4.

With the availability of two effective vaccines that have great potential to control pneumonia – one of the major causes of sickness and deaths among children under five years old – there has been an increasing demand to scale up other interventions for pneumonia control along with vaccination. In the early months of 2007, WHO and UNICEF began laying the foundations for a Global Action Plan for Pneumonia Control (GAPP). The plan includes the use of vaccines but also better case management and the adoption of measures against indoor air pollution, malnutrition, and other factors that contribute to the public health burden of pneumonia (*115*).

An upsurge in funding for pneumococcal vaccines also reflects the renewed concern over pneumonia. Through an Advance Market Commitment (AMC) (see Chapter 4), in February 2007, five industrialized countries and the Bill & Melinda Gates Foundation pledged US$ 1.5 billion to accelerate the development and introduction of new

pneumococcal conjugate vaccines. The keenly awaited 10-valent and 13-valent vaccines should protect even more children against the infection, particularly in developing countries where the additional bacterial types covered by these candidate vaccines are prevalent. The outcome could be the saving of more than seven million children's lives between now and 2030.

Polio – a tough end-game

In 1988, polio was endemic in 125 countries and paralyzing an estimated 350 000 children every year (close to 1000 cases a day) (*25*). In that year, the World Health Assembly (WHA) passed a resolution calling for global eradication of the disease by 2000. An international partnership, the Global Polio Eradication Initiative (GPEI), came into existence to achieve that goal.

By the end of 2007, the disease had been eradicated in three of WHO's six regions – the Americas, Europe, and the Western Pacific – but not worldwide. At the end of June 2009, indigenous poliovirus remained endemic in only four countries, where 440 new cases had been reported in 2009 – Afghanistan (10 cases), Pakistan (20 cases), India (89 cases), and Nigeria (321 cases).

There were several reasons for the missed deadline. The mass vaccination campaigns necessary to stop polio transmission did not kick off in Asia and Africa until the mid-1990s. Driving the infection from densely populated urban areas in Egypt and India proved more difficult than had been anticipated. And vaccination was not reaching enough children among population groups on the move between the Afghanistan and Pakistan border.

More recently, in 2003, unfounded rumours that the oral polio vaccine (OPV) was being used to sterilize young girls brought polio immunization to a halt for 12 months in at least one northern Nigerian state, unleashing a nationwide polio epidemic and the transcontinental reinfection of 20 previously polio-free countries in Africa, Asia and the Middle East (*116*).

Among measures the GPEI took to deal with these setbacks was the introduction of new, faster diagnostic tests capable of providing more rapid identification of the specific poliovirus strain causing an outbreak or sustaining the endemic presence of polio infection in a given area. At the same time, the GPEI exploited the elimination of type 2 wild poliovirus by developing "monovalent" polio vaccines, designed to more rapidly provide protection against each of the two surviving poliovirus strains. Case control

studies carried out in India, Nigeria and Pakistan, as well as clinical trials in Egypt and India, demonstrated that the monovalent vaccines provided at least twice the protective efficacy provided by the traditional trivalent OPV, dose for dose.

In early 2007, the GPEI stakeholders launched an intensified eradication effort in which these diagnostic and vaccine tools – and tactics tailored to the specific challenges to reaching children in each of the remaining infected areas – were paired with intense high-level advocacy to ensure that children could be accessed in all remaining polio-infected areas. At the end of 2008, two advisory bodies to the WHO, the Strategic Advisory Group of Experts (SAGE) on immunization and the Advisory Committee on Polio Eradication (ACPE), concluded that the intensified eradication effort had demonstrated that the remaining technical, financial, and operational challenges to completing eradication could be overcome.

In India's Uttar Pradesh state, indigenous type 1 polio was interrupted for more than 12 months, and contingency plans were developed to address further the technical challenge of compromised OPV efficacy in that setting. Direct oversight by sub-national leaders in areas such as the Punjab in Pakistan, Bihar in India, and Jigawa in northern Nigeria overcame the operational challenges to raising OPV coverage to the levels needed to stop transmission in each of those settings. In addition, the application of new international guidelines on polio outbreak response rapidly stopped 45 of the 49 importations into "non-endemic" countries in 2007 and 2008. Meanwhile, GPEI donors and the affected countries demonstrated that the financial challenges could be addressed, by fully funding the US$ 1.4 billion needed for the 2007–2008 intensified eradication activities.

The 2008 World Health Assembly proved a turning point in polio eradication. Member States called directly on polio-endemic countries to remove the remaining operational barriers to reaching children in all areas. Underpinning the WHA's resolution was the recognition that eradicating polio is an essential step towards meeting the MDGs. "Completing polio eradication," said WHO Director-General Dr Margaret Chan, "is essential to our credibility to deliver basic health interventions to over 80% of the world's children and to our capacity to achieve the MDGs."

Despite this progress, as of early 2009, efforts to interrupt wild poliovirus transmission globally faced considerable challenges. In Africa, a large outbreak of type 1 polio in northern Nigeria, where about 20% of children were still not being reached by vaccination, had spread to surrounding countries and threatened the entire region. In Angola, Chad, and the Democratic Republic of the Congo, outbreaks that started between 2003 and 2007 lingered on, further endangering children across the African continent. As a result, by the end of February 2009, an additional 11 countries were responding to importation-

associated outbreaks in West Africa and the Horn of Africa. In Asia, the key state of Uttar Pradesh in India was still struggling to stop a new type 1 outbreak following an importation in mid-2008 from neighbouring Bihar state. In Afghanistan and Pakistan, security was increasingly compromising access to children in parts of both countries, while oversight and accountability remained weak in other parts of the countries.

The humanitarian and financial benefits of interrupting wild poliovirus transmission globally, and then stopping the routine use of the oral poliovirus vaccines, are massive. The rare but substantive risks associated with continued OPV use after wild virus interruption account for the continuing occurrence of vaccine-associated paralytic polio cases (VAPP), and of outbreaks due to circulating vaccine-derived polioviruses (cVDPVs). The oral polio vaccine has itself caused polio outbreaks in nine countries due to cVDPVs, including in six that were previously free from the disease.

The GPEI is implementing an extensive programme of work to manage the long-term risks associated with continued use of OPV. The cornerstone of the risk management strategies is the eventual cessation of the use of OPV in routine immunization. In 2008, the WHA endorsed the concept of eventual OPV cessation and a strategy of bio-containment, surveillance, stockpile development, and outbreak response to manage the risks following eradication.

The WHA gave particular attention to the use of the inactivated polio vaccine (IPV). At a minimum, IPV will be needed in all countries that store poliovirus stocks. For other countries, which may perceive that the long-term polio risks warrant continued routine immunization, IPV will be the only option with which to do this, as it is the only vaccine which does not give rise to circulating vaccine-derived polioviruses and may be used safely in a post-eradication world. The GPEI is studying a range of approaches to establish "affordable" strategies for IPV use to achieve immunity at a cost similar to that achieved through OPV.

Rabies – a terrible but vaccine-preventable death

In most cases, the first symptoms of rabies in humans resemble those of influenza. Their onset, though, signals an almost inevitable, imminent death. As the virus begins to infest the central nervous system, the symptoms, in most cases, are anything but mild – anxiety, confusion, spasms, convulsions, agitation, delirium, and paralysis (*1*). Within a few days, coma and death from cardiac and respiratory arrest bring relief. Perhaps worst of all, the patient often remains conscious and aware of the body's relentless decline (*1*).

The disease is caused by a bullet-shaped "lyssavirus." In about two-thirds of cases (*1*), rabies runs a so-called "furious" course, marked by violent agitated movements of the body. A less dramatic form, "dumb" rabies, characterized by lethargy and paralysis, occurs in about a third of cases (*1*). In both forms, the outcome is invariably fatal within a few days although intensive medical care can delay, but not prevent, death (*1*). Only a very small number of people with symptomatic rabies have been known to escape death, and several of the survivors were left with neurological damage (*1*).

Worldwide, dogs are the main source of human infection. Transmission of the virus to a person occurs mainly through the bite, scratch, or lick of an infected (rabid) animal (transmission from human-to-human is rare). The virus in the animal's saliva enters the body and attaches to nerves close to the wound. Over an incubation period lasting typically two months (*117*), the virus travels up through the peripheral nerves to the brain (the closer the infective animal bite or scratch is to the head, the less distance the virus has to travel, and the shorter the incubation period (*1*)). In the brain, the virus takes up residence in nerve cells, out of sight of the person's immune system, starts replicating, and sets off the fatal sequence of symptoms.

During incubation of the disease, there is no test to indicate whether a person bitten by a rabid animal has in fact been infected, nor a way to determine whether the biting animal is rabid unless it is put to death and its brain examined in the laboratory. Nor is there any effective treatment for rabies after the onset of symptoms. However, highly effective vaccines exist, and when administered as soon as possible after exposure, the rabies vaccine gives the patient an almost 100% chance of surviving. Post-exposure treatment comprises – in addition to a series of vaccine shots – thorough cleansing and disinfection of the bite wound and, in severe cases of exposure, administration of anti-rabies immunoglobulins (a purified solution of anti-rabies antibodies taken from the blood of vaccinated people or horses). Every year, post-exposure prophylaxis (mostly the vaccine alone) is used in an estimated 10 million people (*117*), mostly in China and India (*117*). It is estimated that current levels of post-exposure prophylaxis prevent more than 250 000 deaths each year, mainly in Asia and Africa.

About 3.3 billion people live in the 100 or so countries where dog rabies is endemic (enzootic). A conservative estimate puts the annual number of rabies deaths occurring in Asia and Africa at 55 000. More than 60% of the total annual rabies deaths occur in Asia (the majority in India), and the rest occur mainly in Africa (*118*). Rabid dogs account for more than 98% of the deaths in people. Children aged 9 to 15 are the most common victims of dog bites. In industrialized countries and in most parts of Latin America and some Asian countries (e.g. Thailand), widespread use of a veterinary vaccine in domestic dogs, and measures to manage the dog population, have made human rabies a rare occurrence (*117*). Holding rabies in check, however, in both

industrialized and developing countries, is costing more than US$ 1 billion a year, at a minimum (*117*).

The first rabies vaccine was developed more than a century ago by Louis Pasteur in Paris (*1*). By 1910, Pasteur Institutes throughout the world were making this first, crude rabies vaccine that consisted essentially of dried nerve tissue taken from rabies-infected rabbits. Serious safety concerns over the vaccine, plus occasional failures, prompted a search for better vaccines.

Up until the late 1950s (*1*), several vaccines were developed. All, however, were made with rabies virus "grown" in animal nerve tissues. These nerve tissue vaccines, which are still in use in a few developing countries, have a number of drawbacks (*119*). The most serious is the fairly frequent occurrence of sometimes fatal neurological allergic reactions. The most inconvenient is their limited potency and the consequent need for a daily injection for up to 23 days (*117*). In the early 1960s, researchers succeeded in making a third-generation vaccine using rabies virus grown in a culture of human diploid cells (1, *117*). A fourth generation of rabies vaccines cultivated on various cell lines (e.g. primary chicken embryo fibroblasts, continuous cell lines such as vero cells), have since been developed and are produced today in very large quantities using fermentor technology. Modern cell culture vaccines are much more potent than nerve tissue vaccines. Devoid of animal nerve tissue, they are also much safer (*120*).

Cell culture vaccines have today replaced the older nerve-tissue vaccines in all industrialized countries and in most developing countries. Although they are primarily used for post-exposure prophylaxis, they are also recommended, at least in industrialized countries, for "pre-exposure" immunization in high-risk groups, such as laboratory staff, veterinarians, hunters, trappers, animal handlers, and travellers to areas with endemic rabies (*117*). Since 1991, WHO has repeatedly, with growing insistence, called on all countries to switch to the modern vaccines. Since then, 11 Asian countries, including India, and many Latin American countries, have made the switch. But the high cost of these vaccines (average US$ 50.00 for the five intramuscular doses needed), is an obstacle both for governments in the poorest countries when vaccines are provided free at rabies treatment centres, and also for individuals who have to pay for the vaccine themselves.

Applying the recommended immunoglobulin component of the post-exposure regimen is also an obstacle for many poorer countries because of its cost (average US$ 50.00 for a purified horse derived product) and limited availability worldwide. Currently on average only 1% of people infected or presumed to be infected with the rabies virus receive immunoglobulin.

To increase the supply of immunoglobulin, manufacturers in developing countries are being encouraged to produce purified equine immunoglobulin. An alternative to immunoglobulin is also being sought. One approach showing promise in animal studies is the use of a "cocktail" of at least two monoclonal, or highly specific, antibodies that can neutralize most commonly circulating rabies viruses.

One way of reducing the cost of the modern cell culture vaccines is by using the intradermal, instead of the standard intramuscular, route of vaccine administration. Intradermal injection is as effective and as fast-acting as intramuscular injection and requires a much smaller volume of vaccine – up to 60% less than for vaccines administered by the standard intramuscular route (*117*). This tactic is being successfully used in India, the Philippines, Sri Lanka, and Thailand. In India, intradermal administration has brought the cost of a full vaccination regimen down from US$ 81.00 to about US$ 13.00 (*1*).

The use of routine preventive pre-exposure vaccination has been considered for children living in countries where they have high risk of infection from rabid animals. Preliminary clinical studies in Thailand and Viet Nam have shown that it produces a high immune response in the vaccinated children. One economic analysis showed that use of pre-exposure vaccines becomes cost-effective in areas where 20–30% of children are bitten by dogs over a year (*1*).

Global eradication of rabies is not an option, given the large number of animal species providing a large and diverse reservoir for the causative virus. Elimination of the human disease caused by dog rabies has been widely achieved by eliminating rabies in dogs through the use of effective veterinary vaccines. It takes vaccination coverage rates of 75–80% to achieve this outcome. The Bill & Melinda Gates Foundation and WHO are together supporting dog rabies control projects in some poorer countries, with the aim of demonstrating the cost-effectiveness of dog rabies as a means to eliminate human rabies and thereby drastically reduce the need for human post-exposure prophylaxis.

Rotavirus – vaccines set to prevent half a million child deaths a year

Discovered in 1973, rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world (*1, 121*). Virtually all children under three years of age are infected in both industrialized and developing countries (*1, 121*). Most disease episodes consist of a mild attack of watery diarrhoea, accompanied by fever and vomiting (*1*). In about 1 in every 75 cases, however, the infection produces severe,

potentially fatal dehydration (*1*). Globally, more than two million children are hospitalized for rotavirus infections every year (*122*). According to WHO 2004 estimates, 527 000 children under five years old die every year from rotavirus disease. Nearly two-thirds of these deaths occur in just 11 countries, with most – 23% of total rotavirus deaths – in India (*121*).

Work on developing a vaccine to prevent rotavirus disease began in the early 1980s and culminated in August 1998 with the licensure in the United States of the first rotavirus vaccine, Rotashield™. Nine months later, after more than 600 000 children had received the vaccine, the manufacturer withdrew it from the market: several cases of bowel intussusception (severe bowel blockage caused by the bowel telescoping into itself) had occurred, supposedly associated with administration of the vaccine. The vaccine community was dismayed. In 2000, voicing the opinion of many vaccinologists at the time, Dr Ciro de Quadros, then Director of the Division of Vaccines and Immunization at PAHO, believed "it would take at least a decade to get new rotavirus vaccines". In fact, it took only six years: by the end of 2006, two new-generation rotavirus vaccines, made by multinational companies, had appeared on the market. Meanwhile, other vaccine producers, including some in developing countries (notably, China, India, and Indonesia) had been working on several vaccine candidates, of which at least six, as of mid-2008, were in the advanced stages of the R&D pipeline.

Before receiving regulatory approval for human use, the two new vaccines had to prove not only their efficacy but, more importantly given the fate of the first rotavirus vaccine, their safety in much larger studies. In trials conducted in industrialized and developing country settings, each involving more than 60 000 participants, the new vaccines protected 85–98% of vaccinated infants from severe rotavirus disease (*123, 124, 125*). Both vaccines were found to be safe and are now WHO-prequalified (*123, 124, 125*).

Optimism over these new vaccines is, however, tempered by the need for further large-scale trials – particularly in the poorest developing countries – before they can be considered universally applicable. Both are live oral vaccines and may prove less effective in developing countries with higher child mortality than in industrialized countries. This was the case with other live oral vaccines, such as those against polio, cholera, and typhoid. Several of these trials are being completed in 2009 and will provide the necessary data for WHO to review its recommendations for introduction of these vaccines in Africa and Asia.

Cost is another issue. In 2008, the new vaccines cost between US$ 16.00 and US$ 17.00 per fully immunized child when bought by the PAHO Revolving Fund for use

in Latin America – almost a tenth of the price on the private United States market but still too expensive for the poorest countries with the highest rotavirus mortality rates in other regions. One rotavirus vaccine that is manufactured, licensed, and has been in wide use in China since 2000, sells for about US$ 16.00 a dose to the private sector in China (it has not yet requested WHO prequalification status for international use). Of course, for the 72 countries within the GAVI Alliance purview, cost may not be a major issue, at least in the short term. In the longer term, the costs of sustaining rotavirus vaccination may prove difficult for some countries.

Rubella – eliminating a threat to the unborn

Rubella, or German measles, was first noted in the mid-19th century as a mild disease involving little more than a skin rash. However, its ability to cause congenital defects – cataracts, heart disease, and deafness, to mention three – became evident in the 1940s. And it was not until the early-1960s, during a rubella epidemic in the United States, that the full range of congenital abnormalities making up the "congenital rubella syndrome" (CRS) was revealed to the world.

The United States rubella epidemic caused 12.5 million cases of rubella, including more than 2000 cases of brain inflammation (encephalitis) and 20 000 cases of CRS in newborns. Of these newborns, more than 8000 were deaf, some 3600 were both deaf and blind, and nearly 2000 were mentally retarded (*1*). There were more than 2000 deaths, as well as over 6000 spontaneous and 5000 induced abortions. The world awoke to the dramatic reality of CRS, and the quest for a vaccine began.

By 1970, several rubella vaccines were available. Before the end of the decade, one (using the so-called RA 27/3 rubella virus strain) emerged from the pack as offering a high degree of safety and efficacy in protecting children against mild (or "acquired") rubella (*1*). Given to women of childbearing age, the vaccine gives 95–100% protection for at least 15 years against the risk of having a baby with CRS (*1, 126*).

By 1996, 65 countries, accounting for 12% of babies born in that year, were using the vaccine in their national immunization programmes (*71*). By the end of 2007, the rubella vaccine was being used nationally in 125 countries, accounting for 31% of births worldwide (*71*).

WHO recommends that all countries where CRS has been identified as a major public health problem should use the vaccine. Moreover, where logistically feasible, they should do so in conjunction with measles elimination activities (*126*). Linking up with the Measles Initiative makes sense, given the availability of combined measles-rubella vaccines and

the compatibility of the two administration schedules. Indeed, most countries using the rubella vaccine administer it as part of the MMR vaccine, given in two doses, the first at 12–18 months of age and the second later in childhood. However, in most developing countries, rubella vaccine has not been included in the national immunization schedule because of lack of information on the burden caused by rubella, increased cost, and the concern that if high coverage (>80%) cannot be achieved and maintained, the risk of CRS may increase due to a shift in rubella susceptibility to older age groups including women of childbearing age.

Elimination of CRS, i.e. stopping indigenous (or endemic) transmission of the rubella virus that causes the disease, is possible. It calls for a strategy to ensure high levels of immunity through vaccination among children, adolescents, and young adults (both women of childbearing age and men). For poorer countries, this strategy may not be affordable, but on the other hand, caring for people with CRS is costly. Cost-benefit studies in developed as well as developing countries have shown that where coverage rates exceed 80% and rubella vaccination is combined with measles vaccination, the benefits of rubella vaccination outweigh its cost (of US$ 0.60 a dose) (*127*).

Use of the rubella vaccine has eliminated CRS in a number of countries (e.g. Cuba, the English-speaking Caribbean countries, Sweden, and the United States). Successful use of the vaccine has also prompted the WHO Regions of the Americas and Europe – the two WHO regions with the highest rubella vaccine coverage rates in young children – to target rubella for elimination by 2010.

As for eradication, rubella, like measles, fulfils the biological criteria for an eradicable disease: only humans maintain transmission of the virus, accurate diagnosis is possible, and transmission has already been interrupted in large geographical areas (*128*). And if eradicating two diseases with a single blow is the aim, the combined measles-rubella vaccine is there to make the operation feasible. Two unanswered questions, though, point to potential stumbling blocks: will there be sufficient political will to mount and maintain a two-disease eradication effort? And will it be possible to bring sustained vaccination to communities lacking access to basic health services or isolated by conflict? The end-game struggles of the polio eradication initiative are instructive in this respect. Meanwhile, country-by-country elimination of rubella and congenital rubella syndrome is surely a worthwhile first step, and more and more countries are taking it.

Tetanus, neonatal and maternal – victory in sight

Tetanus is characterized by muscle rigidity and painful muscle contractions caused by a toxin – one of the most potent ever identified – released by the bacterium *Clostridium*

tetani. The spores of this bacterium are present throughout the world in soil. A person is infected when the spores enter the body via dirt or soil through a scratch or open wound. Neonatal tetanus, which is the most common form of the disease in developing countries, is primarily caused by infection of the umbilical cord stump in babies delivered in unhygienic conditions. It is most prevalent among the poorest, most neglected population groups that have little or no access to medical care. In the late 1980s, tetanus was estimated to be causing more than a million deaths a year, of which about 790 000 were newborn infants.

Prevention of tetanus is possible and inexpensive. The tetanus toxoid vaccine is one of the most effective, safest, and least costly vaccines on the market. Its discovery, subsequent development and initial use, at least in industrialized countries, date from the first half of the 20th century.

In 1989, the public health community officially declared neonatal tetanus a target for elimination, defined as an incidence of less than one case per 1000 live births in all districts. At that time, 90 countries had not yet reached the elimination target (*129*). Vaccination of women before or during pregnancy with at least two doses of the vaccine was the main strategy to be used to reach the target. Antibodies produced by the vaccine protect not only the mother but also the foetus and, for up to two months, the newborn child. Vaccination was combined with efforts to increase the proportion of births taking place in hygienic conditions and to reduce harmful traditional practices at home births.

By 1995, 27 of the 90 countries had eliminated neonatal tetanus. In the 63 remaining countries, most cases were occurring in poor, hard-to-reach communities. To accelerate elimination efforts, a "high-risk approach" was adopted that aimed to reach out to these "high-risk communities". This new approach called for mass immunization campaigns, delivering three sequential doses of vaccine to all women of childbearing age in the high-risk communities. Education about providing hygienic conditions for births was also part of the strategy.

The new approach paid off. By 2000, 135 countries had eliminated neonatal tetanus (*28*) and annual deaths from the disease had fallen to an estimated 200 000 – a 75% drop from the 790 000 deaths in 1988 (*28*). Ninety percent of these 200 000 deaths were occurring in just 27 countries, mostly in South Asia and sub-Saharan Africa. WHO, UNICEF, and the United Nations Population Fund (UNFPA) decided to launch a more vigorous attack on tetanus, both neonatal and, in a new development, also maternal tetanus. In fact, an estimated 15 000–30 000 women were dying every year from tetanus contracted during or shortly after pregnancy. This maternal and neonatal tetanus (MNT) elimination partnership also set a new deadline, 2005, for achieving elimination – a

deadline which, however, was to prove too optimistic. By the end of 2008, 12 of the 58 remaining countries with neonatal tetanus had achieved elimination in all districts (see Fig. 12).

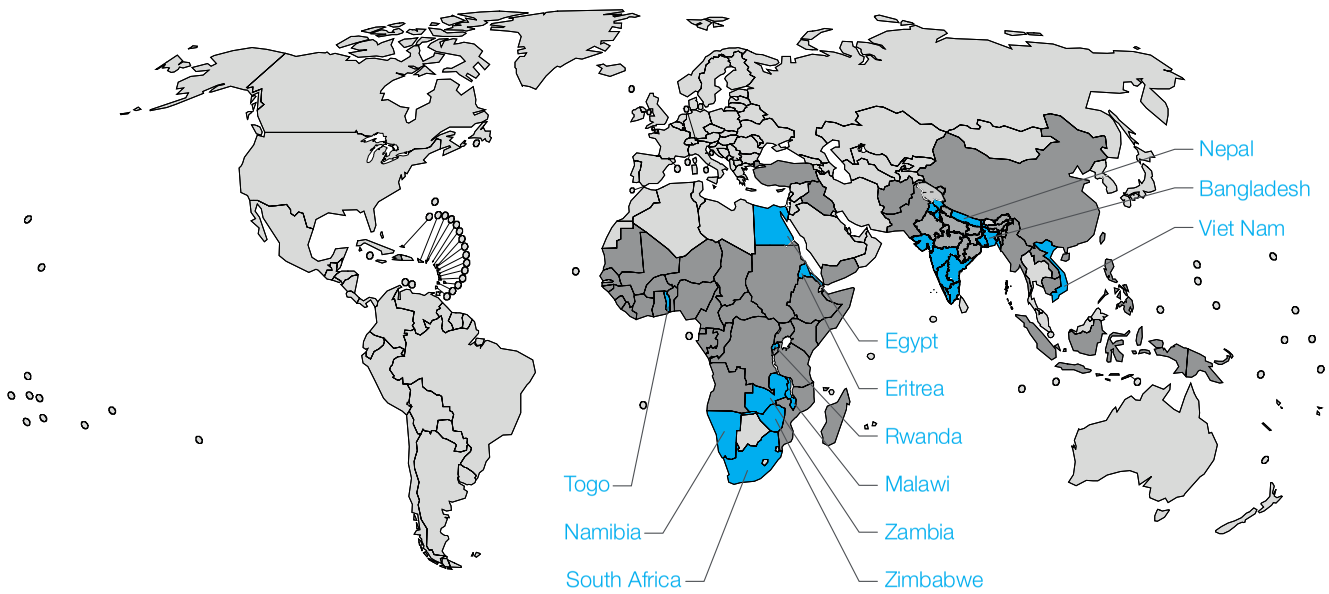
The MNT elimination partnership estimates that – with sufficient funding – by the end of 2010, only 10 countries will still be in the grip of the disease and that by 2012, all countries will have reached the ultimate target. Their confidence is based on the impetus that tetanus elimination efforts have been gathering since 2000, and also from the influx of funds – US$ 160 million – the partnership has received since 2000, mostly through UNICEF and the GAVI Alliance, to finance its activities.

Confidence is, however, tempered by hurdles still to be overcome. One is the need for funding over the 2008–2012 period. A second is the lack of solid data on which to base disease estimates: less than 10% of cases are being reported, according to survey findings. Disease surveillance clearly needs a major boost.

As for the longer-term future, will the momentum created by elimination of neonatal and maternal tetanus be sustained? *Clostridium tetani* is, and will always be present in nature, and its spores are extremely resistant to destruction. If future generations are to live without the threat of a catastrophic resurgence of the disease, tetanus experts estimate that routine immunization coverage in all countries must reach and stay at 80% of women of childbearing age in all districts and that at least 70% of births must take place in hygienic conditions. If countries succeed in reaching most people with booster doses in school-age, adolescence, and early adulthood, not only would MNT remain eliminated, but protection against tetanus would be life-long (*131*). Several countries are taking steps in that direction, by offering tetanus vaccines in school-based immunization programmes and in activities such as mother and child health days or immunization weeks.

Figure 12

Status of elimination of maternal and neonatal tetanus



MNT eliminated prior to 1999

MNT not eliminated *(46 countries)*

MNT eliminated during 2001-2008 *(12 countries and 15 states in India*: Andhra Pradesh, Chandigarh, Goa, Gujarat, Haryana, Himachal Pradesh, Karnataka, Kerala, Lakshadweep, Maharashtra, Pondicherry, Punjab, Sikkim, Tamil Nadu and West Bengal)*

**India is the only country with sub-national validation of MNT elimination*

Source: (130)

Tuberculosis – waiting for a better vaccine

The first and only vaccine ever used to protect against tuberculosis is the *Bacille Calmette-Guérin* (BCG) vaccine, developed at the Pasteur Institute in Paris and first used in 1921. Since the 1950s, when routine BCG immunization against tuberculosis began in many countries, more than four billion people are believed to have received the vaccine worldwide *(1)*. By 1990, 81% of the world's newborn infants were receiving the vaccine. By the end of 2007, BCG coverage had climbed to 89%. In Europe and North America, several countries where the incidence of reported tuberculosis had dropped to below 25 cases per 100 000 have ceased routine BCG immunization.

That is the good news. The not-so-good news is that over the past two decades the burden of tuberculosis has followed an upward curve that peaked in 2004 with 8.9 million new cases (up from 8 million in 1997) and approximately 1.46 million deaths (*4*). The advent of HIV/AIDS in the 1980s, with its ability to lower natural protection against latent infections, including tuberculosis, has contributed to the escalation of tuberculosis cases: globally, about 15% of tuberculosis cases occur in people with HIV/AIDS, but in some countries with high HIV incidence rates, the proportion can be as high as 50–60%, as in Mozambique, South Africa, and Zimbabwe (*132*).

By contrast, estimates of both incidence and mortality rates in 2007 (*132*) suggest that the disease may be on the verge of a downswing. But despite worldwide use of BCG over the past three or four decades, and despite the availability since the early 1990s of an inexpensive highly effective treatment strategy ("DOTS"), tuberculosis is still a leading cause of disease and death. The inability to control this disease has been called "a colossal failure of public health" (*1*).

For the vaccine community, the mood is one of frustration over the lack of evidence that BCG consistently protects against pulmonary tuberculosis. Some studies have found a high degree of protection; others none at all. By contrast, evidence from several trials has consistently shown that BCG gives strong protection against tuberculosis in infants and young children (*1*). Tuberculous meningitis and disseminated (miliary) tuberculosis – the two most common and most severe forms of extrapulmonary tuberculosis – occur in about 25% of children with tuberculosis and are rapidly fatal without treatment (*1*). BCG is protective against these forms of tuberculosis in 64–78% of recipients (*1*).

However, there is no empirical evidence that high coverage of a population with BCG vaccination lowers the incidence of these severe forms of tuberculosis in infants and young children. The problem is that tuberculosis in children is very difficult to diagnose and often remains undetected. The disease is so rapidly fatal, that diagnosis can only

be attempted in the earliest stages of the disease. But at that stage, the symptoms are not specific, x-rays show no evidence of disease, and tuberculin skin tests are negative in about 40% of cases (*1*). Under-reporting and poor record-keeping compound the difficulty of gathering incidence or mortality data.

Given this situation, many health officials wonder if vaccination with BCG at birth is worth the effort and cost. A recent analysis (*133*) suggests that it is. BCG costs US$ 2–3 per dose. Given to more than 100 million infants in 194 countries in 2002, the vaccine would have prevented more than 40 000 cases of tuberculous meningitis and miliary tuberculosis in children under five years of age. The cost, worldwide, would have been US$ 200 or less per healthy life year gained, using the disability-adjusted life year (DALY) measure. In the WHO African Region, South-East Asia Region, and Western Pacific Region, where the incidence of tuberculosis and BCG coverage are highest, the analysis showed BCG to be a cost-effective intervention against severe childhood tuberculosis – almost as cost-effective as short-course chemotherapy – costing US$ 50 per DALY gained. In the few industrialized countries where BCG is still used routinely despite a low risk of infection, the cost per DALY gained amounts to several thousand dollars. Such countries, the research team speculates, may be better off replacing routine BCG vaccination by vaccination of only high-risk population groups, such as health workers and others at risk of exposure to the infection. This has, in fact, long been the strategy adopted by several countries, including the United Kingdom and the Netherlands.

To most tuberculosis experts, it is clear that a new, more consistently effective vaccine is needed that protects not only against the disease in childhood but against pulmonary tuberculosis in adults. Several candidate vaccines are in early-stage clinical trials and are being tested for safety, immunogenicity, and early indicators of efficacy (*134, 135*).

Typhoid fever – vaccines ready and waiting

Typhoid fever, also known as enteric fever, is caused by one of the most virulent bacteria to attack the human gut. Commonly spread via contaminated water and food, the causative bacterium, *Salmonella typhi*, thrives in unsanitary conditions, particularly where clean water is lacking. Through the gut, the organism infects the bloodstream, altering brain function in some cases, and often resulting in death. Before the advent of antibiotics, the symptoms of typhoid fever – typically, persistent high fever, abdominal pain, malaise, and headache – usually lasted several weeks and in many cases culminated in death.

Today, in industrialized countries, typhoid fever has ceased to be a problem, thanks to improved hygiene and a clean water supply. In developing countries, however, it is still

very much a problem. In 2004, WHO estimated the global typhoid fever disease burden at 21 million cases annually, resulting in an estimated 216 000–600 000 deaths per year, predominantly in children of school age or younger. The majority of this burden occurs in Asia (*136*). In a comprehensive study relating to the incidence of typhoid fever in five countries in Asia, it was reported that incidence in highly-endemic countries is similar in children 2–5 years of age as in school-aged children 5–15 years of age and adolescents (*137*).

Typhoid fever was discovered as a distinct disease entity in the 1880s. At that time, its hold on industrialized countries had begun to slacken in the face of improved sanitation. Cases still occurred though, often in outbreak situations, and among high-risk population groups, such as migrant groups. The continued occurrence of the disease and the fear engendered by its high mortality rate – 10–20% of infections resulted in death *(1)* – combined to fuel the search for a cure and a means of prevention. A cure came in the form of antimicrobial drugs; prevention in the form of vaccines.

Early research produced two vaccines made from the entire (whole-cell) bacterium. One became available in the 1890s, the second in 1952. Both protected about 65% of recipients. However, the frequency and severity of the adverse effects they caused dissuaded many countries from using them. These shortcomings, combined with drug treatment failures, which had escalated in previous years as a result of increasingly widespread resistance to antibiotic therapy, intensified the quest for a more effective vaccine.

Before the end of the 20th century, two new-generation typhoid vaccines had entered the scene. One, named "Ty21a" and first licensed in 1983, is given in three to four oral doses (*136*) and consists of a live but genetically modified *S. typhi* strain (*138*). The second, named "Vi" and licensed in 1994, is given by injection and consists of a sugar molecule (polysaccharide) located on the surface of the bacterium (*138*). In clinical trials and early field use, the duration of efficacy of both vaccines varied to some degree. Moreover, no evidence of efficacy has been reported in children under two years of age. On a positive note, both vaccines are licensed, internationally available, and safe, and both are effective enough not only to reduce the incidence of typhoid fever in endemic areas but also to control outbreaks.

Price was initially thought to be a barrier to adoption of the vaccines by developing countries. However, several manufacturers in developing countries now quote prices of about US$ 0.50 for the Vi vaccine in multi-dose vial presentations for use in public health programmes, and the main producer of Ty21a is offering a discounted price for the poorest countries. Moreover, typhoid vaccines have now been accepted by the GAVI Alliance as a possible candidate for future financial support.

In 2008, WHO reiterated its earlier recommendations that the new vaccines be used for routine immunization – alongside active strategies to improve hygiene and sanitation – in countries or areas (such as deprived urban areas) where typhoid fever is endemic. In most of these countries, vaccination will be confined to high-risk population groups, such as school-age and preschool-age children, particularly in areas where antibiotic-resistant strains of *S. typhi* are prevalent. WHO also recommends use of the new vaccines for the control of outbreaks (*136*). Which of the two vaccines a country chooses depends on the capacity, logistics, and cultural context of its immunization programme. Very few countries still use the whole-cell vaccine: those that do should, according to WHO, switch to one of the new-generation vaccines (*136*).

Meanwhile, third-generation typhoid vaccines are in the pipeline. One is a Vi conjugate vaccine that protects about 85% of recipients, according to late-stage clinical trials, and appears to be effective in children under two years of age. A second candidate vaccine, further back in the R&D pipeline, is, like Ty21a, a live attenuated vaccine but, unlike Ty21a, can be given in a single oral dose.

Vaccine scientists point out, though, that these newer typhoid vaccines have still several years to go before reaching the market. Action against the daily toll of disease and death from typhoid fever in endemic populations is needed now and, although current new-generation vaccines may not be perfect, they are available to meet that need.

Varicella and herpes zoster – a single virus that can linger for a lifetime

Varicella, commonly known as chickenpox, is caused by the varicella-zoster virus (a member of the herpesvirus family), which was first identified in 1952 (*139*). The same virus, when reactivated from a latent state in nerve cells causes another disease – herpes zoster, or shingles. In most populations, varicella is a disease of children, and herpes zoster a disease of elderly people. However, the epidemiology of disease can vary, especially in tropical countries where infection and varicella may occur more often in older age groups. The hallmark symptom of varicella is an itchy rash, consisting of blister-like vesicles. Seventeenth century medical documents describe chickenpox as a mild form of smallpox (*139*) but in 1767 the English physician William Heberden showed that the two diseases are distinct (*1*).

The varicella-zoster virus only infects humans. It spreads from person-to-person through direct contact, or from the virus being sneezed or coughed into the air or released from the vesicles on the skin. Generally, varicella is a mild disease. However, complications, which can sometimes be severe, occur in about 10% of cases, mostly in adolescents

and adults (*139*) (who are 30–40 times more likely than children to die from severe complications (*139*)). The most common, and sometimes life-threatening, complications of varicella are bacterial infections of the skin, which can occasionally become severe through spread to contiguous or distant parts of the body (*1*). Other bacterial infections (pneumonia, or infection of the bones or bloodstream), neurological conditions (uncontrollable muscle movement or brain inflammation), and inflammatory conditions (of the liver, kidneys, heart, or testicles) are prominent on the list of complications from varicella (*139, 1*). In pregnant women, the infection can cause congenital limb foetal abnormalities, brain damage, and death. However, babies born to women who have immunity to varicella receive their mother's anti-varicella antibodies and are protected against the infection for about a month after birth (*139*). Varicella infection itself induces lifelong immunity to chickenpox in virtually everyone whose immune system is working normally (*139*).

Box 22

Herpes zoster – the same virus, a different disease

In 10–20% of children infected with varicella, the virus takes up residence in nerve cells, where it lies dormant for several decades, until a lowering of the host's immune defences (as a result of ageing, disease, or immunosuppressive treatment) allows it to awaken, begin replicating, and precipitate herpes zoster disease, or shingles as it is commonly known (*139*). In the United States alone, 43 million people are believed to be at risk of herpes zoster (*1*).

Herpes zoster is characterized by a painful blistering rash along the distribution of the infected nerve cells (*139*). In many elderly people the rash and pain subside and resolve completely in a few weeks. In about 15% of patients, though, pain and numbness in the area of the rash can last for weeks or months. The pain can be severe and highly disabling, both physically and mentally (*1*). Itching, which may fluctuate from mild to intense, adds to the person's discomfort (*1*).

In addition, 8–15% of people suffer permanent neurological damage, impaired vision, or problems of bowel or bladder function (*1, 139*). Elderly people and immunocompromised people run the highest risk of developing herpes zoster. Since the same virus causes varicella, people with herpes zoster constitute a source of varicella outbreaks among unvaccinated children and other non-immune population groups.

Treatment with antiviral drugs is effective if started soon after the onset of herpes zoster. However, accurate diagnosis at that stage of the infection is difficult and in most cases antiviral treatment is begun too late to be of optimal benefit (*1*).

In 2005, a vaccine against herpes zoster was licensed for use in people over 60 years of age. It contains at least 14 times the amount of virus as the varicella vaccine (*1*). Its protective efficacy, though, varies with the recipient's age, falling from 64% in the 60–69 year age group to 41% in the 70–79 year age group, and 18% in the 80–89 year age group (*1*). Some herpes zoster experts believe younger age groups – such as people in their 50s, who account for almost 20% of herpes zoster cases – could benefit from the vaccine (*1*). Two factors, though, militate against its widespread adoption by developing countries: price (the vaccine currently costs about US$ 150 a dose in industrialized countries), and the low public health priority of herpes zoster in relation to the many other serious diseases that ravage these countries.

Little is known about the burden of varicella in developing countries (*139*). However, in 2006, an estimate based on the incidence of varicella in industrialized countries gave a total worldwide estimate of 90 million cases a year (*1*).

Treatment for varicella consists of antiviral drugs, which are expensive and work only when used early in the course of infection. It is generally reserved for people at risk of severe disease. Vaccination is the only way to protect whole communities and populations from varicella, and possibly from herpes zoster. A safe and effective vaccine against varicella has been available in several formulations since the mid-1970s (*139*), and in 2005, a combination measles-mumps-rubella-varicella vaccine also came on to the market. The single-antigen (i.e. containing varicella virus only) vaccine has been administered to millions of children, adolescents, and adults in many countries (*1*). In children, a single dose produces anti-varicella antibodies in about 95% of recipients and protects them against the disease (*139*). Furthermore, at least 90% of people given the vaccine within three days of being exposed to the virus are protected against developing the disease (*139*). In those who develop disease after vaccination, it is much milder than in unvaccinated individuals.

The effectiveness and cost-effectiveness of the vaccine have prompted several industrialized countries in Asia, Europe, and North America to adopt it in their routine child immunization programmes (*139*). In 1995, the United States became the first country to adopt the vaccine into its routine immunization programme (*1*) and by 2002 saw a 74–92% drop in child deaths from varicella and an 88% drop in hospitalizations due to the disease (*1*). The use of the vaccine has also been shown to be cost-effective in the United States (*139*). Some epidemiologists believe that widespread routine administration of the varicella vaccine in children could eventually lead to the virtual disappearance of the disease.

In general, most developing countries have other diseases associated with high disease burden and deaths that need to be given higher priority than varicella. Where varicella represents a sizeable public health and socioeconomic problem, countries may consider routine varicella immunization. However, immunization programmes must reach at least 85–90% of children as lower coverage rates could theoretically shift the target of the virus from young children to older children and adults.

Yellow fever – defusing a bomb waiting to explode

Yellow fever is a viral haemorrhagic fever caused by a virus transmitted to humans and non-human primates by the bite of a mosquito. After a few days of being bitten by an infected mosquito, sub-clinical infection, non-specific illness, or influenza-like symptoms can develop. The latter can culminate in the vomiting of blackish blood, one of the two hallmark symptoms of the disease (*1*). A few days later, in about 15% of cases, bleeding occurs from several sites, accompanied by painful convulsions and failure of several organ systems, notably the liver, kidneys, and heart (*1*). This stage is also marked by jaundice – the second hallmark symptom – which colours the skin a deep yellow. About 20–50% of people with severe disease die from the disease. Children and elderly people run the greatest risk of death from yellow fever.

Yellow fever was a major scourge in the 18th and 19th centuries in colonial settlements in the Americas and West Africa. The discoveries (in 1900) that mosquitoes were responsible for transmission and that the disease was preventable by vector control, as well as the development of vaccines (in the 1930s), have reduced both the fear associated with the disease and its medical impact. In 1940, mass vaccination of 25 million people in French-speaking West and equatorial Africa led to the virtual disappearance of yellow fever. However, inadequately immunized populations and urbanization set the stage for the disease to re-emerge.

Today, yellow fever remains an endemic and epidemic disease affecting thousands of people in tropical Africa (33 countries) and South America (11 countries and territories) (*140*), and is a continued threat to people who travel to these regions without vaccination. An estimated 200 000 cases and 30 000 deaths (*141*) occur every year worldwide. About 90% of cases and deaths occur in Africa (*141*), where more than 600 million people are at risk of infection (*141*). In South America, about 60 million people live in endemic areas (*1*). Outbreaks may affect urban populations, with the infection spreading by mosquitoes from human-to-human. Yellow fever also occurs in jungles, where it exists as an animal (epizootic) disease, spread by mosquitoes from monkey-to-monkey and, accidentally, to humans.

Travellers, too, are at risk of yellow fever. Every year, an estimated nine million people travel from non-endemic to endemic areas and about three million of these travellers may be going to places where outbreaks are raging (*141*). Only 10–30% of travellers to these "danger zones" are vaccinated, according to one estimate (*141*). The International Health Regulations require travellers to or from endemic countries, to carry a valid vaccination certificate (*1*).

No specific treatment exists for yellow fever. Vector control targeting the mosquito responsible for transmitting the disease, has its limits. Hence, vaccination is the single

most effective means of obtaining protection against yellow fever. The 17D vaccine is both highly effective and safe, conferring a high degree of protective immunity for at least 30–35 years (and probably for a lifetime). The vaccine is highly cost-effective as it confers long-term immunity in an infant for an estimated US$ 0.01 a year.

In 1988, WHO and UNICEF proposed a two-pronged vaccination strategy that is still the universally recommended approach to controlling yellow fever. It is designed to create a high level of protective immunity in at-risk populations, to sustain that level from generation to generation, and, ultimately, to eliminate yellow fever as a public health problem. One prong of the strategy is the integration of the vaccine into the national childhood immunization programmes of countries at risk of epidemics (*141*). The second prong is the use of mass vaccination campaigns to protect susceptible older age groups (*141*) and populations threatened by imminent or incipient outbreaks. In addition, the strategy calls for vector control measures; for use of the vaccine to battle ongoing outbreaks; and for strengthening disease surveillance which is critical for outbreak detection and control, and for programme monitoring.

Implementing the strategy has been slow. Of the 33 endemic countries in Africa, 22 had adopted the vaccine in their national immunization programmes by the end of 2007, up from eight countries in 2000. The GAVI Alliance provided support to the poorest endemic countries. However, according to data reported by WHO and UNICEF, the proportion of children vaccinated with the yellow fever vaccine in the 33 African countries had reached an average of only 50% by the end of 2007.

Poor disease surveillance, resulting in gross underestimation of the disease burden, has been a key deterrent to the implementation of the WHO-recommended vaccination strategies. One reason is that the signs and symptoms of yellow fever are similar to those of other diseases, such as malaria, influenza, and typhoid fever (*141*). Surveillance must therefore be backed up by a network of laboratories capable of accurate diagnosis (*141*).

Another deterrent is an "insecure" vaccine supply. Approximately 30 million doses a year (*1*) are provided by manufacturers for the African market. Yet, to meet demand for enough vaccine to implement the WHO-UNICEF strategy would require an estimated 40 million doses plus at least 6 million doses to respond to outbreaks.

At US$ 0.71 a dose (on the developing country market), the cost of the vaccine has been an additional deterrent for many countries. However, the support of the GAVI Alliance has made it possible for the GAVI-eligible countries to adopt the vaccine.

These three deterrents – surveillance, vaccine supply, and price – are likely to become less critical, at least for the poorest countries at highest risk of yellow fever: the GAVI

Alliance has been supporting the introduction of yellow fever vaccine into routine infant immunization since 2002. In addition, it has supported an emergency vaccine stockpile since 2003. More recently, the GAVI Alliance has approved a request from WHO, UNICEF and other members of the Yellow Fever Initiative to provide about US$ 100 million for control of yellow fever in Africa. The money would be spent over five years mainly on providing vaccines for preventive campaigns in 12 endemic African countries within the GAVI Alliance mandate, and also for responding to outbreaks in any GAVI-eligible country at risk in the event of outbreaks.

In South America, yellow fever vaccination has been ongoing for at least three decades. Up to 1991, mass vaccination campaigns were carried out every five years in the endemic countries of the region (*1*). Since 1998, integration of the yellow fever vaccine within national child immunization programmes has become the norm (*1*). By the end of 2007, the average reported vaccine coverage had reached 86% for these countries (*1*). One concern in the region is the movement of unvaccinated people from coastal areas, where vaccination is not carried out, to the more inland endemic areas. Another is resurgence and spread of the urban form of the disease as a result of the recent re-invasion of the continent by the urban-dwelling mosquito vector (*1*).

For Africa and South America, the ongoing circulation of the yellow fever virus remains a time-bomb waiting to explode. The new funding being provided to endemic African countries for yellow fever vaccines and vaccination, and the high levels of vigilance and surveillance in South American countries, should keep the bomb from exploding. But it is still ticking. With escalating international air travel providing a mechanical vector for the mosquito and the virus, and with the lack of adequate immunity in many populations (a single case of infection can cause a massive outbreak in the presence of the mosquito responsible for transmitting the disease), the bomb could explode, disseminating the virus well beyond its current hunting grounds.

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Annex 1. Global immunization profile

Population data in thousand[1]	2007	2006	2005	2004	2003	2000	1990	1980
Total population	6'659'040	6'580'921	6'502'983	6'425'275	6'347'724	6'113'437	5'279'007	4'439'786
Live births	135'590	134'985	134'397	133'865	133'418	132'820	136'793	123'711
Surviving infants	128'816	128'120	127'440	126'816	126'275	125'369	128'148	114'051
Pop. less than 5 years	628'7210	625'407	622'797	620'980	619'905	620'422	629'747	545'390
Pop. less than 15 years	1'843'756	1'841'906	1'841'380	1'842'270	1'844'242	1'846'856	1'724'575	1'566'771
Female 15-49 years	1'718'802	1'698'386	1'677'375	1'655'843	1'633'781	1'564'554	1'314'119	1'058'498
Number of reported cases								
Diphtheria	4'273	3'978	12'735	10'069	6'781	11'625	23'864	97'774
Measles	280'771	373'941	601'232	509'734	680'454	852'937	1'374'083	4'211'431
Mumps	407'787	643'078	619'062	654'216	334'063	544'093	-	-
Pertussis	161'861	119'916	135'326	244'989	110'854	190'476	476'377	1'982'384
Polio	1'385	2'021	2'032	1'258	784	2'971	23'366	52'795
Rubella	196'506	252'340	267'366	308'219	321'180	671'286	-	-
Rubella (CRS)	225	63	37	88	99	181	-	-
Tetanus (neonatal)	6'086	8'376	9'918	9'318	9'028	16'943	25'293	13'005
Tetanus (total)	19'867	14'646	15'980	13'772	12'857	21'242	64'378	114'248
Yellow fever	265	356	588	1'344	672	684	4'336	144
Percentage of target population vaccinated by antigen *based on WHO-UNICEF estimates TT2plus and YFV are based on reported coverage*								
BCG	89	88	86	84	83	81	81	16
DTP1	90	89	88	87	85	85	88	30
DTP3	81	81	79	77	75	73	75	20
HepB3	65	60	56	50	46	32	1	-
Hib3	26	22	21	20	19	14	-	-
MCV	82	81	79	77	75	72	72	16
Pol3	82	82	79	77	76	74	75	21
TT2plus	71	69	66	59	61	62	55	9
YFV	51	48	42	35	31	26	4	0

Most countries have standard recommendations regarding which vaccines should be offered and at what ages they should be given. In general, vaccines are recommended for the youngest age group at risk of developing the disease whose members are known to respond to the immunization without adverse effects.

Unless otherwise specified, data are provided by Member States through the WHO-UNICEF Joint Reporting Form and WHO regional offices.

[1)] Source: (*6*)

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