Advances and challenges for the expanded programme on immunization

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Over 3 million deaths from measles, neonatal tetanus and pertussis are prevented by vaccination each year. In the Americas, poliomyelitis has been eliminated, and measles is close to elimination. Globally, reported poliomyelitis incidence has declined by over 80% since 1988.

Strategies have evolved from strengthening routine childhood immunization services, to establishing disease surveillance and defining specific activities for disease control and elimination. Efforts to ensure the supply and quality of vaccines are underway. New vaccines against major pathogens will be licensed soon. Some of these will be used for groups other than mothers and infants, requiring re-definition of the ‘EPI target groups’.

Despite global successes, in 1995, six of the world’s most populous developing countries reported coverage levels below 70% and coverage is below 50% in several African countries. Immunization programmes will need to be tailored to the level of economic and health systems development of a country. Industrialized countries must offer sustained support to expand immunization programmes in ways that strengthen health systems in developing countries.

Over 3 million deaths from measles, pertussis and neonatal tetanus are estimated to be averted each year by vaccination. In 1995, measles vaccination was estimated to have reduced measles-associated mortality worldwide by 88% from the pre-vaccination levels of 5.7 million deaths per year. Poliomyelitis has been eradicated from the Americas and the goal to eradicate wild polio virus from the world is well on its way.

Despite these successes, the recent resurgence of diphtheria, increasing spread of yellow fever in Africa, and continuing high morbidity and mortality from hepatitis B, measles, pertussis and neonatal tetanus in low income countries emphasize the need for continued support for vaccination programmes. At the same time, new vaccines against major infectious diseases are becoming available, bringing new challenges for the Global Expanded Programme on Immunization (EPI).
Current disease control goals of the global EPI are that by the year 2000, poliomyelitis will be eradicated; neonatal tetanus will be eliminated (incidence rate less than 1 case per 1000 live births in all districts); measles mortality and morbidity will be reduced, respectively, by 95% and 90% from the pre-immunization era, and new hepatitis B virus carrier incidence will be reduced by at least 80% (adapted from Ninth General Programme of Work, 1996–2001, World Health Organization, Geneva). In this paper, the strategies used to pursue and monitor these goals are reviewed, achievements are summarized, and challenges facing the EPI are discussed.

### Strategies for routine immunization

The World Health Organization (WHO) recommends that the primary childhood vaccination series in developing countries include Bacille Calmette-Guerin (BCG) and oral polio vaccine (OPV) at birth; OPV and diphtheria-tetanus-pertussis (DTP) vaccines at 6, 10 and 14 weeks of age, and measles vaccine at 9 months of age. In countries where perinatal transmission of hepatitis B (HBV) is important, HBV vaccination should commence at birth. In countries where HBV transmission is predominantly in childhood, the vaccine is recommended at the time of each DTP dose. In countries endemic for yellow fever, YF vaccine is recommended at the time of measles vaccination.

The number and frequency of booster doses depends on the epidemiological patterns of diseases in a particular country, the level of health services infrastructure and resources, and the relative priority of boosters compared, e.g. to introduction of new vaccines into the primary vaccination schedule. The importance attached to booster doses has increased in recent years because of the resurgence of diphtheria. Booster doses of DTP are recommended in the second year of life and, where disease is documented among school children, a further dose is recommended at school entry.

To prevent neonatal tetanus, in countries where most women of childbearing age were not immunized as children, or lack documentation of such vaccination, a 5-dose TT programme for women of childbearing age is recommended (Table 1). In future, increasing numbers of women of childbearing age will have documentation of prior receipt of TT-containing vaccines, and adult women will need fewer booster doses of TT.

Delivery sites for vaccination range from fixed sites to mobile teams. Fixed sites include health centres and health posts that offer a range of primary health care (PHC) activities, and/or curative services. Utilization
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Table 1  Tetanus toxoid immunization schedule for women of childbearing age

<table>
<thead>
<tr>
<th>Dose</th>
<th>When to give</th>
<th>Expected duration of protection</th>
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</thead>
<tbody>
<tr>
<td>TT 1</td>
<td>At first contact or as early as possible in pregnancy</td>
<td>None guaranteed</td>
</tr>
<tr>
<td>TT 2</td>
<td>At least 4 weeks after TT 1</td>
<td>1-3 years</td>
</tr>
<tr>
<td>TT 3</td>
<td>At least 6 months after TT 2</td>
<td>5 years</td>
</tr>
<tr>
<td>TT 4</td>
<td>At least 1 year after TT 3 or during subsequent pregnancy</td>
<td>10 years</td>
</tr>
<tr>
<td>TT 5</td>
<td>At least 1 year after TT 4 or during subsequent pregnancy</td>
<td>All childbearing years</td>
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</table>

is higher when sites are easily accessible, have minimal administrative barriers, and also provide good quality curative care and an adequate supply of essential drugs. Wherever vaccinations are offered, it is vital to use all opportunities to administer vaccines. For this, the immunization status of all children in the target age group should be screened routinely and immunization provided to eligible children and mothers. Health workers should be taught which are true and which are false contra-indications, and supervisors should monitor compliance with recommendations, for example using the EPI training module on missed opportunities.

In areas progressively further from a health facility, regular outreach services from the nearest health facility or district centre, or mobile teams (which involve stay of at least one night in a distant village) are used. Outreach and mobile services may be scheduled throughout the year, or in annual campaigns or ‘pulses’. Pulse campaigns are planned at district level and conducted by local staff and village health workers or volunteers. Where possible, the pulses are timed for the months preceding the seasonal peaks of diseases such as measles. Advantages include easier management of vaccines, fuel and equipment in a relatively concentrated period of activity, in areas where year-round outreach activities are hard to maintain.

The role of national mass campaigns in the EPI has been debated. Experience with campaigns that were conducted with the sole purpose of raising immunization coverage rapidly was often poor. Such campaigns were seen as being imposed on countries or districts by donors, interrupting other health services and increasing donor dependency. Increases in coverage were short lived in countries such as Guinea, Ghana and Senegal, and the quality of vaccination was low in some campaigns. In contrast, in the region of the Americas, where they have been a major component of disease eradication programmes, they are implemented effectively with predominantly local funding. Campaigns are now used in most countries as a strategy within a long-term plan of action to improve disease control or eradication rather than a short-term measure to increase coverage (see below).
No single strategy is likely to be appropriate for all circumstances and all diseases. The choice of strategy should depend upon the epidemiology of the disease, the characteristics of the vaccine, the facilities available, the accessibility of the population, their cultural attitudes and practices and the socio-economic level and health systems context of the country. There is a need for continued capacity building for national and district-level managers to select strategies that are appropriate for their own context.

**Disease elimination/eradication initiatives**

In 1985, the region of the Americas adopted a goal of eradication of poliomyelitis from the Western Hemisphere by the year 1990\(^\text{20}\). Three years later, the 41st World Health Assembly ratified the goal of global eradication by the year 2000\(^\text{21}\). The last case of poliomyelitis due to wild virus in the Americas occurred on 23 August 1991, in Peru.

To achieve polio eradication, National Immunization Days (NIDs) are recommended, in which all children in the target age, usually under 5 years, receive OPV during a short period with the aim of displacing the wild virus from communities by the mass circulation of the vaccine virus. Once transmission is reduced only to focal areas, ‘mopping up’ operations, consisting of door to door vaccination are conducted in areas at risk. Every case of acute flaccid paralysis (AFP) is investigated, and stool specimens are collected from cases and contacts for viral isolation\(^\text{20}\).

The region of the Americas has adopted a measles eradication goal, and a global goal is under consideration\(^\text{22}\). In the measles eradication strategy, initial mass ‘catch-up’ campaigns, targeting the age group where most susceptibles have accumulated (1–15 years in the Americas), are used. To prevent resurgence of measles, programmes must sustain high routine vaccination coverage of infants, and conduct periodic supplemental campaigns when susceptibles (comprising unvaccinated persons and vaccine failures) accumulate. Surveillance of suspected measles cases with laboratory confirmation of cases is another key element of the strategy\(^\text{23}\).

Another disease, neonatal tetanus (NT) has been targeted for elimination (defined as a reduction in the incidence of NT to less than 1 per 1000 live births in all districts of the world). The recommended strategies include routine immunization of pregnant women with TT, immunization of all women of childbearing age in high risk areas, improvement of clean delivery and hygienic cord care practices and effective NT surveillance.
### Table 2 Selected indicators and methods to monitor the EPI

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Commonly used methods</th>
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<tr>
<td>Immunization coverage</td>
<td>Routine reports on number of vaccine doses administered to 0–11 month olds, compared to birth cohort</td>
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<tr>
<td>Median age at receipt of vaccines</td>
<td>Coverage surveys using the EPI cluster sampling method</td>
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<tr>
<td>Dropout between DTP1/OPV1 and measles vaccines (indicator of effectiveness of tracking activities)</td>
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<tr>
<td>Missed opportunities for vaccination</td>
<td>Comparing DTP and OPV coverage</td>
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<tr>
<td>Cold chain quality</td>
<td>Supervision; use of temperature records and cold chain monitors</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Routine reports of abscesses, lymphadenitis, unusual or severe events, with lot numbers of vaccines administered</td>
</tr>
<tr>
<td>Target disease incidence &amp; mortality</td>
<td>Outbreak investigations (e.g. lymphadenitis)</td>
</tr>
<tr>
<td>Age-specific levels of susceptibility</td>
<td>Surveillance from routine notification systems ± sentinel sites</td>
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<tr>
<td></td>
<td>Laboratory reports of confirmed cases</td>
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<tr>
<td></td>
<td>Outbreak investigations</td>
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<td></td>
<td>Special surveys</td>
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<tr>
<td>Costs per fully immunized child</td>
<td>Serological surveillance or special surveys (used at more advanced stages of immunization programmes)</td>
</tr>
<tr>
<td>Cost per dose administered (e.g. in NID)</td>
<td>Monitoring administrative financial and budgetary data</td>
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<td></td>
<td>Periodic costing studies</td>
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### Monitoring and evaluation

The EPI has developed indicators and methods to monitor programme performance, coupled with operational research to identify and solve problems (Table 2).

Programme quality should be monitored through regular supervision and periodic operational research. Health facility-based studies combining exit interviews with mothers, interviews with providers, and observation using check-lists, are used to evaluate timeliness of vaccination, drop-out rates, and missed opportunities among children and mothers who attend vaccination sites, and to assess provider knowledge and practices. Inexpensive surveys of households near to health facilities can be used to investigate reasons for failure to use accessible vaccination services.
There is increasing recognition of the importance of adverse events that occur because of programme failure. In some cases vaccine caused side-effects because it was reconstituted with the wrong diluent. Elsewhere, contaminated needles or syringes were used, or dangerous drugs were mistakenly administered instead of vaccines. Outbreaks of lymphadenitis have occurred after BCG vaccination, following a change in strain of vaccine and/or problems in intradermal injection technique. To detect such adverse events, every country should report cases of abscesses, and unusual or severe events such as septicaemia or death, that are temporally related to vaccination. Clinics and vaccine stores should note the manufacturer, lot number and expiry date of each vaccine received.

In addition to monitoring the coverage and quality of vaccination programmes, reasons for non-vaccination or incomplete vaccination should be investigated through a mixture of qualitative and quantitative methods. Distance to vaccination sites, waiting times, availability of curative services, and cost affect utilization. Characteristics such as low parental educational level, recent migration, and large family size can be used to identify families at risk of under-vaccination. Door-to-door canvassing can increase uptake among such groups. The involvement of communities and local leaders in promoting immunization, planning immunization services and informing families about the availability of vaccination services is important.

Disease surveillance was a crucial component of the smallpox eradication programme and poliomyelitis elimination in the Americas, but it remains one of the weak links in the EPI. Methods of surveillance vary depending on the stage of the programme and the resources available. Surveillance is complemented by outbreak investigations. Substantial effort is currently being invested in improving surveillance, through development of training materials, conduct of workshops, and provision of laboratory and communications support, not just for EPI but also for diseases of epidemic potential. Public health programmes and services are automating the management and analysis of surveillance data, using computers to enhance the timely and systematic collection of data, its consolidation, analysis, evaluation and feedback.

Laboratories play an essential role in the surveillance of most vaccine-preventable diseases, particularly once disease incidence decreases and clinical diagnosis may become less reliable. For the poliomyelitis eradication programme, WHO has set up a global polio laboratory network capable of detecting wild poliovirus. A similar network is being prepared for measles laboratory diagnosis worldwide and for yellow fever in the 33 countries of Africa endemic for yellow fever. For new candidates for inclusion in the programme such as *Haemophilus influenzae* type B (Hib) and conjugate pneumococcal vaccines, which
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protect against diseases with less specific clinical manifestations, laboratory support in surveillance will also be essential.

With the rapid growth of enzyme linked immunoassay (EIA) techniques, often in kit form, serological surveillance may be more widely used in future. The detection of virus-specific antibody in saliva has been reported and further development of this assay could greatly facilitate field surveys. Randomised age-structured serosurveys can provide useful background information by which to compare subsequent profiles of herd immunity, for example, of measles, rubella and polio.

Data from clinical and laboratory-based surveillance systems can be used to develop and validate mathematical models of disease transmission. Models are used to describe the dynamics of infections in populations, to predict changes induced by a vaccination programme, to explore the effects of different vaccination policies, to compare different delivery strategies, and to explore thresholds for elimination or eradication of infections from populations.

Last, but not least, it is important to assess the costs of immunization programmes. The EPI developed costing guidelines in 1979 and subsequently developed spreadsheet software (EPICOST) to support costing studies. The average cost of fully immunizing a child (cost per FIC) in low-income countries in studies from 1979–87 was US$ 13, excluding technical assistance (1987 US$ rate), and US$15 if technical assistance was included. For all strategies, personnel costs accounted for the largest proportion, with supervision and management the second largest cost. Vaccines represented approximately 10% of all costs. In general, costs per FIC decreased as the number of children immunized increased, but the marginal costs are likely to increase when trying to reach the last 15–20% of infants.

Economic analyses have helped to show problems in the process of disbursing funds, including irregular and delayed receipt of donor funds; poor accountability; over-centralization of management of funds so that there is no access to funds for running costs at health centre level; non-standardization of payments for daily allowances between different vaccination strategies and/or between agencies. Monitoring the process of utilization of resources and establishing transparent and co-ordinated systems for accountability of donors as well as government health services could greatly improve efficiency.

Summary of achievements

For over 20 years, the EPI programme has helped to create a global consensus on disease prevention and immunization.
developed effective training programmes and modules for peripheral health workers, mid-level and senior-level managers. A series of clear guidelines on immunization practices were developed, and the strong field-base of the EPI enabled WHO to update and clarify these guidelines to resolve questions raised by health workers. Guidelines were followed up by supervision and monitoring through programme reviews and *ad hoc* studies using simple protocols. Extensive innovative work was conducted to develop and standardize appropriate cold chain and injection technology and simple methods for monitoring its use in the field.

The pragmatic and field-based approach of the EPI, with its continuous cycle of planning, conducting applied research on priority problems, disseminating guidelines, monitoring closely all aspects of the programme and feeding back on progress, have benefited industrialized countries as well as developing countries. Survey tools such as the EPI cluster sample, missed opportunity, and cold chain monitor surveys have enabled peripheral health workers to evaluate their own programmes. They have been modified for use in richer countries, and for a wide range of public health programmes.

**Challenges**

The EPI has shown remarkable progress throughout the world, but there are now several potentially competing demands for expansion. Coverage of existing vaccines needs to be increased, particularly in sub-Saharan Africa. Additional activities are being promoted to eliminate or eradicate diseases. The quality and safety of vaccines and injections must be ensured, and countries are being encouraged to become self-sufficient in vaccine procurement and/or supply. A range of new vaccines is being developed and licensed. There may be tension between global priorities (e.g. disease eradication) and local priorities (e.g. introduction of new vaccines), and careful evidence-based decision-making will be necessary.

**Coverage**

Immunization coverage is a key indicator of access to and utilization of immunization services. In spite of continuous efforts to raise immunization coverage, since 1990 global figures for EPI vaccines have levelled off at around 80% for infants (Fig. 1), and considerable disparity remains both between and within countries (Fig. 2). Average coverage of DTP-3 in the African region has not yet reached 60%. To
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Fig. 1 Expanded Programme on Immunization coverage 1980–1996. Data before 1984 are estimated: (a) up to 2 years of age; (b) tetanus toxoid (mothers). Figures kindly provided by the World Health Organization Global Programme for Vaccines and Immunization.

improve coverage in the lowest income countries, long-term, co-ordinated and reliable investment by national governments and donors is required.

Two vaccines have been recommended for inclusion in the EPI for several years, but are still not widely used. Hepatitis B results in more than 1 million deaths every year, worldwide. The high effectiveness of the vaccine has been demonstrated by dramatic reductions in the carrier rate in immunized cohorts of children. In Taiwan, 10 years after implementation of a mass vaccination programme, a fall in the annual incidence of hepatocellular carcinoma in children aged 10–14 years has already been documented. However, introduction of universal HBV vaccination globally has been determined more by the economic status of the country than by its disease burden (Fig. 3). A minority of the 33 African at-risk countries include yellow fever vaccine in their EPI, and The Gambia is the only country to achieve high coverage and impact on disease. In 1994 and 1995, outbreaks of yellow fever were reported in six African countries.

Eradication

Substantial progress has been achieved towards the goal of global eradication of poliomyelitis. Reported OPV-3 coverage in 1996 was over 80% in all regions except Africa, where it was 60%. By the end of 1996, only 17 endemic countries in the world had not yet conducted NIDs (15 of these were in Africa). AFP surveillance is now conducted in 126 (86%) of the 146 recently or currently endemic countries. However,
Fig. 2 1996 immunization coverage (%) with three doses of DTP in infants. Figures kindly provided by the World Health Organization Global Programme for Vaccines and Immunization.
Fig. 3  Hepatitis B vaccine: Universal Immunization Policy. Figures kindly provided by the World Health Organization Global Programme for Vaccines and Immunization.
such surveillance is still in its infancy in the southeast Asia and African regions, and requires substantial strengthening. A total of 3,997 cases of poliomyelitis were reported globally in 1996, with declines in all WHO Regions. Activities will concentrate increasingly on countries affected by civil conflict and those with the weakest health service infrastructure. The total external funding support required for the period 1997–2005 is estimated at over US$ 1000 million.

Regions which have already eradicated poliomyelitis are adopting new eradication goals. Measles eradication is theoretically possible because there is no known animal reservoir and measles vaccine is highly effective. In practice, the high infectivity of measles makes it difficult to eradicate, because more than 90% (and possibly more than 95%) of the population must be immune in order for incidence to decline towards zero. Despite encouraging progress in the Americas, questions remain about the selection of the most appropriate strategies for measles control/eradication in different countries, the ability to ensure safe injection practices, and the feasibility and cost of reaching high enough coverage for eradication in the poorest countries. The marginal cost-benefit of aiming for eradication rather than control needs to be assessed. Lastly, the effects of an eradication programme on social development need to be considered.

Improving vaccine supply, quality and injection safety

The increasing demand for vaccines generated in part by additional mass vaccination activities for disease eradication has highlighted the need to ensure a sustainable supply of adequate quantities of vaccines. Strategies include targeting donor assistance for vaccine purchase to the smaller, poorer countries, while the larger countries, particularly those with higher income/capita, are encouraged to produce their own vaccines. Revolving funds, in which countries contribute funds in local currency to funds supported by international agencies such as UNICEF to procure vaccines, are also promoted.

There is heightened awareness of the need to monitor vaccine quality. In a review of 43 vaccine-producing countries conducted by the Children's Vaccine Initiative (CVI), only 21 had appropriate control functions in place. Failure to meet WHO minimum standards of purity of diphtheria and tetanus toxoids was documented for 10% of producers assessed and tetanus toxoids from 8 manufacturers had low potency values.

The most important areas of technology transfer for developing countries are those relevant to achieving and maintaining Good Manufacturing Practice standards in vaccine production, establishing
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independent and credible national quality control laboratories, and instituting national (or perhaps regional, if necessary) regulatory capability. Another priority area is ensuring safe injection practices. In 1994, the WHO reported that up to one-third of immunization injections in 4 of its 6 Regions were unsterile, carrying the risk of iatrogenic infections including fatal septicaemia, and transmission of bloodborne pathogens. EPI has had a long-standing policy of ‘a single sterile needle and a single sterile syringe should be used with each injection’ and is continuing to develop and evaluate alternative injection technologies, such as autodestruct syringes and jet injectors, to minimize the risk of unsafe injection practices.

Introduction of additional vaccines

A number of effective vaccines are available but not yet included in the EPI, while still more are near to licensure. *H. influenzae* type b (Hib) vaccine is a highly effective vaccine against a major pathogen. In The Gambia, it had an efficacy of over 90% against invasive Hib disease, and significantly reduced the incidence of radiologically-defined pneumonia by 21% (95% CI, 4.6–34.9%) since pneumonia is estimated to underlie 18% of deaths in developing countries, the development of mechanisms to make Hib vaccine affordable to children in the poorest countries is a major challenge for the international health community.

Rubella vaccine has been used for almost 30 years in industrialized countries. A review completed for the WHO in 1995 showed that 7 developing countries have documented rubella outbreaks with congenital rubella syndrome (CRS) incidence rates as high as those in industrialized countries pre-vaccination. All 7 countries now have national rubella vaccination policies. Although 28% of developing countries already include rubella vaccine in their national immunization programmes, many countries need further data urgently to determine the relative priority to give to control of CRS.

Lower respiratory infections and diarrhoeal diseases were among the top four causes of death worldwide in 1990; therefore, vaccines that are under development against these diseases have immense potential to improve health status. Some new vaccines will be licensed for the existing EPI target groups, *e.g.* rotavirus vaccine, conjugate pneumococcal and meningococcal vaccines; some will be targeted at adolescents, *e.g.* herpes virus vaccines, HIV vaccines, and others will be indicated for persons of all ages, *e.g.* dengue, malaria. This means that the ‘EPI target groups’ will need to extend beyond pregnant women and infants, giving further impetus to the drive to strengthen PHC through the EPI.
Conclusions

Immunization programmes have spearheaded the development of public health worldwide. Through immunization, over 3 million deaths are averted each year. Health professionals around the world have been trained to use a range of simple tools to plan, manage and monitor their programmes. Nevertheless, the context in which immunization programmes operate has changed markedly over the last decade, and programmes will need to respond innovatively to these changes.

Healthcare absorbs an increasingly large share of global resources. In 1990, average per capita expenditure on health care was about US$ 1500 in industrialized countries, yet official development assistance has declined to US$ 0.3 per capita, its lowest level in real terms for 25 years. Developing countries spent an average of only US$ 41 per capita, and many of the poorest countries spent less than US$ 5. Sizable sums of public money are spent on tertiary level hospitals, while access to basic health services remains low in many rural and dispersed communities. Implementation of health programmes is becoming increasingly decentralized, thus the role of Ministries of Health and international agencies is changing to one of advice, policy-making and advocacy. The increasing involvement of the private sector in health care raises challenges for co-ordination, standardisation and quality control of interventions.

To meet these challenges, the trend towards inequitable use of global resources must be reversed. Measles continues to cause approximately half a million deaths per year in sub-Saharan Africa, and 16 of the 26 countries that account for 90% of globally estimated cases of NT are in Africa. Coverage for routine childhood immunizations and TT is below 50% in much of western and Central Africa, where the PHC infrastructure is still weak. Campaigns can reach communities that lack access to routine services, but donors must be convinced to invest not only in campaigns but also in strengthening the physical, human and managerial infrastructures in those countries. Polio NIDs are being implemented even in low income countries, but AFP surveillance lags behind, and the implementation of national campaigns in countries affected by civil conflict is a major challenge. Hepatitis B vaccine, which was to have been introduced in all highly endemic countries by 1997, is available in only a minority. Immunization services, which are already highly cost-effective, will become increasingly so as new vaccines are developed which can be delivered using the same contacts. Despite decades of sustained progress through development and targeted health interventions, 5 of the 10 leading causes of death are still communicable or perinatal disorders. Mobilizing governments in industrialized countries to help developing countries profit fully from vaccines is a major challenge for public health professionals throughout the world.
Acknowledgements

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