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The evidence base for interventions to reduce mortality from vaccine-preventable diseases in low and middle-income countries

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The Evidence Base for Interventions to Reduce Mortality from Vaccine-Preventable Diseases in Low and Middle-Income Countries.

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Abstract

This paper is a synthesis of evidence on vaccine-preventable burden of disease, efficacy, cost-effectiveness and the potential to scale up immunization. It is also a collection of lessons learned. Immunization has already been scaled up substantially, reaching close to 80% coverage worldwide following the establishment of the Expanded Programme on Immunization (EPI) in the 1970's and the 1990 Universal Childhood Immunization initiative. Currently close to 100% of the world's children are being reached through the Polio Eradication Initiative.

Vaccines have been successful in greatly reducing the burden of disease due to diphtheria, pertussis, tetanus, polio and measles. However, measles, pertussis, hepatitis B and tuberculosis remain significant causes of death and disability. The total burden of disease in low and middle income countries that is preventable through full implementation of the six basic vaccines of the Expanded Programme on Immunization[1] stands at 1.6 million. If there were no vaccination, it is estimated that the burden of measles alone would be about ten times higher (see reference 64).

Vaccines in the EPI are cost-effective relative to other health interventions. The six traditional EPI vaccines have been shown to cost $25 per life healthy year of life gained.

The major constraint to scaling up in poor countries is the low capacity of the national health systems to plan, manage and deliver immunization services. Peripheral service delivery is particularly weak and limited in its reach. Financial resources are inadequate or not distributed optimally, resulting in significant lags in developing country uptake of new vaccines which are

[1] The basic six vaccines of the Expanded Programme on Immunization are those against tetanus, measles, pertussis, diphtheria, and polio. BCG is the sixth vaccine, which gives protection against childhood forms of tuberculosis.

highly cost-effective where indicated but which have higher price tags, such as vaccines against *Haemophilus influenzae* type b and hepatitis B.

Executive Summary

This paper is a synthesis of evidence on vaccine-preventable burden of disease, efficacy, cost-effectiveness and the potential to scale up immunization. It is also a collection of lessons learned. Immunization has already been scaled up substantially, reaching close to 80% coverage worldwide following the establishment of the Expanded Programme on Immunization (EPI) in the 1970's and the 1990 Universal Childhood Immunization initiative. Currently close to 100% of the world's children are being reached with polio vaccine through the Polio Eradication Initiative.

Vaccines have been successful in greatly reducing the burden of disease due to diphtheria, pertussis, tetanus, polio and measles. However, these still account for 1.6 million deaths in children under age 5, mostly in developing countries. New vaccines to prevent diarrheal disease and pneumonia are sought to bring down the death toll from these diseases, currently estimated at 1.8 million each in children under age 5. If there were no vaccination, it is estimated that the burden of measles alone would be approximately ten times higher (See reference 64).

The traditional vaccines being used in national immunization programmes are shown to be highly efficacious. Pre-licensure clinical trials and epidemiological assessments are the methods used to establish vaccine efficacy, either through demonstration of protection against disease, or through demonstration of an established immune response correlate of protection. Extensive research has established the efficacy of EPI vaccines against polio, measles, tetanus, pertussis, diphtheria, hepatitis B and Haemophilus influenzae type b (Hib) at rates between

75 and 100%. BCG is considered highly effective (75-86%) at preventing certain types of childhood tuberculosis. But protection against adult lung disease varies considerably.
New vaccines and technologies on the horizon most notably those providing protection against pneumococcus bacteria and rotavirus are nearing the end of the development pipeline.

These vaccines are cost-effective relative to other health interventions. The "EPI plus" (EPI vaccines with vitamin A and iodine supplementation) programme has been evaluated with results of $12-17 per healthy year of life gained while the six traditional vaccines have been shown to cost $25 per life healthy year of life gained. Measles vaccine is a particular bargain, preliminary results indicate a price tag of US$ 2-6 per discounted life-year gained. The paper briefly discusses particular issues in cost-effectiveness of scaling up coverage, and eradication or elimination programs.

The major constraint to scaling up in poor countries is the low capacity of the national health systems to plan, manage and deliver immunization services. Peripheral service delivery is particularly weak and limited in its reach, as demonstrated by coverage and dropout rates as a result of low access and utilization of vaccines.

Financial resources are inadequate or not distributed optimally, resulting in significant lags in developing country uptake of new vaccines which are highly cost-effective where indicated but which have higher price tags, such as Hib and hepatitis B.

Other constraints to scaling up include a decline in the amount of the traditional six EPI vaccines (BCG, DTP, measles and oral polio) being offered for tender to UN procurement mechanisms,

a rise in the price of some of these vaccines and a slow increase in the production of higher priced new vaccines and combinations, with a corresponding slow trend in price reduction.

Abbreviations

To be revised based on content of final version of paper.

BCG	*Bacille Calmette-Guérin vaccine against tuberculosis*
DALY	*Disability adjusted life year*
DTP	*(also referred to as DPT) diphtheria, tetanus, pertussis combination vaccine*
DT	*diphtheria-tetanus vaccine, for children*
ETEC	*enterotoxigenic Escherichia coli*
GAVI	*Global Alliance for Vaccines and Immunization*
GFCV	*Global Fund for Children's Vaccines*
GNP	*Gross National Product*
Hep B	*Hepatitis B vaccine*
Hib	Haemophilus influenzae *type b vaccine*
IU	*international units*
LPS	*lipopolysaccharide endotoxin of pertussis*
PAHO	*Pan American Health Organization*
PRP	*polyribosylribitol phosphate*
PT	*pertussis toxin*
QALY	*Quality adjusted life year*
Td	*preparation of diphtheria and tetanus toxoids with a low amount of diphtheria toxoid, for adolescents and adults*
TT2	*two doses of tetanus toxoid*
UNICEF	*United Nations Fund for Children*
WHO	*World Health Organization*

Aims of this paper

This paper aims to provide background on immunization as input for the synthesis report of Working Group 5 of the WHO Commission on Macroeconomics and Health. Working Group 5 is examining the potential to expand coverage of cost effective interventions that will make the most difference in improving the health status of the poor. The synthesis report is intended for the use of financial experts and macroeconomists who are not necessarily public health specialists.

The topic explored here is expansion of cost effective, essential immunization services to protect the poor against organisms that cause or have potential to cause the greatest burden of disease. Vulnerable people worldwide are the concern of this work, but special emphasis is placed on the needs of developing countries. We focus here on vaccines and related technologies that are already available or which are expected to be available in the near future.

The vaccines emphasized here are the ones that have the greatest potential to further decrease burden of disease by scaling up coverage. That is, the vaccines which address diseases that are causing a significant burden of disease and for which coverage can be further increased. Other background papers are focused on vaccine development to combat tuberculosis, malaria and HIV/AIDS, as well as costing the expansion of immunization. These topics are therefore not discussed here.

Guide for the reader

This paper is a synthesis of evidence on efficacy, cost-effectiveness and the potential to scale up immunization. It is also a collection of lessons learned as immunization has already scaled up substantially, reaching close to 80% coverage worldwide in 1990 as a product of the Universal

Childhood Immunization initiative, and currently coming close to reaching 100% of the world's children with polio vaccine through the Polio Eradication Initiative.

The table in section one summarises the existing burden of vaccine-preventable disease, showing the potential for further scaling up the intervention. The emphasis is on those diseases that cause the largest preventable burden.

The proven efficacy of the vaccines in current use is described in the second section. Immunization represents a good investment at least partly because it's based on very high quality scientific evidence.

Again, the emphasis is on those vaccines which can prevent the most burden of disease when coverage is scaled up. A table showing efficacy of the main vaccines of the Expanded Programme on Immunization (EPI) is supported by references to secondary sources. References to epidemiological assessments of vaccines are provided in Annex IV.
A short discussion is provided for vaccines against measles, pertussis, tetanus, hepatitis B and *Haemophilus influenzae* type b (Hib). Examples of the impact of measles and Hib vaccines are provided as figures, and a short case study on scaling up measles can be found in a text box.
A discussion of new vaccines and technologies on the horizon follows. Vaccines to protect against pneumococcus, rotavirus and shigella are discussed and a table is provided to illustrate the stage of development of these and other vaccines as well as vaccine presentations and delivery technologies.

Evidence on cost-effectiveness is presented in section five in tabular form together with an explanation of the key determinants of cost-effectiveness of vaccines and the measures used. A text box on herd immunity and cost effectiveness follows.

Section six moves on to an exploration of constraints to scaling up. The potential hurdles discussed include financial, supply, vaccine stability, vaccination delivery technologies and disposal, peripheral delivery capacity, monitoring and surveillance, and problems experienced by developing countries in accessing new technologies. Examples of problems in scaling up include the gap in uptake of hepatitis B and Hib vaccines between richer and poorer countries. Pricing issues are discussed as are the challenges to provide incentives for the production of traditional six EPI vaccines which may no longer meet manufacturer's criteria for profitability. Potential technical solutions like vaccine vial monitors are discussed, along with their own constraints.

The degree to which immunization services rely on peripheral delivery capacity (the health system) is the subject of section seven. The key elements required for successful delivery of immunization are identified and described.

This section also deals with the controversial issue of the impact of targeted disease control programmes like the Polio Eradication Initiative on the delivery of other health services.

Strategies for expanding immunization coverage and the number of vaccines in routine immunization services are expanded on in section eight. These strategies include expanding vaccine supply, strengthening immunization services, outreach, campaigns, accelerated vaccine introduction, and partnership building as typified by the Global Alliance for Vaccines and

Immunization (GAVI). Gaps in service delivery are identified and means of filling these gaps are proposed. Evidence is provided for both the scope to expand and the impacts of these strategies.

The paper concludes with the milestones for the future in terms of immunization coverage and vaccines to be introduced in the coming years. A brief summary of the potential effect on disease burden is provided.

Annexes provide additional information on immunization coverage, background on what vaccines are and how they work, using immunization for disease eradication or elimination, and epidemiological assessment of vaccine efficacy. Finally a historical background is provided to illustrate experience in scaling up immunization to date.

Methods

The published literature on vaccines and immunization is vast. This paper does not set out to review the literature but rather draws on secondary sources such as review papers and text books, primary sources and unpublished works in progress where relevant to lay out the key issues surrounding the expansion of immunization services for the poor.

1. Burden of vaccine-preventable disease

Mortality in low and middle-income countries from vaccine preventable disease is that which is preventable with current antigens or preventable with antigens on the horizon. Table 1 provides a summation of the evidence for various vaccine-preventable diseases.

Table 1. Numbers of deaths from selected vaccine-preventable conditions in low and middle income countries, 1998 (See reference 61)

Cause	Total deaths, in thousands	Percentage of total deaths from all causes
All Causes	45,897	100%
All communicable diseases, maternal and perinatal conditions and nutritional deficiencies	15,937	35%
(i) Childhood diseases-main cluster	1,640	3.6%
a. Measles	882	
b. Tetanus	409	
c. Pertussis	342	
d. Diphtheria	5	
e. Poliomyelitis	2	
(ii) Childhood diseases-other	3,814	8.3%
a. Acute lower respiratory infections in under age 5	1, 845	
b. Diarrhoeal diseases in under age 5	1,810	
Meningitis (all ages)	139	
d. Otitis media (all ages)	20	
(iii) Other diseases, mainly in adults	1,439	3.1%
a. Cirrhosis of the liver	653	
b. Liver cancer	563	
c. Cervical cancer	220	
d. Japanese encephalitis	3	

Immunization has been one of the most important successes in public health during the last 40 years. Starting from essentially zero coverage in the early 1970's, immunization has expanded dramatically so that in 1999, 74% of the target groups received maternal and child vaccines included in the Expanded Programme on Immunization. Currently, most infants in the world are covered by at least 6 basic antigens and newer vaccines are now being introduced at an accelerating pace. This rapid improvement in immunization services has resulted in significant declines in infant and child mortality rates.

Mortality from current antigens in use: WHO estimated that in 1998 there were an estimated 1.6 million deaths in low and middle-income countries from the childhood cluster of diseases that are preventable with the extended program on immunization vaccines (antigens against tetanus, Pertussis, diphtheria, and measles; Table 1). Most of these deaths occur among children under age 5, with measles causing about half of all deaths.

Mortality from antigens being developed shortly or in the introduction phase: A significant percentage of the 1.8 million deaths from acute respiratory infection and the 1.8 million deaths from diarrhea may also be prevented through vaccination. Stansfield et al (52) had estimated that about three-quarters of ARI was due to *Streptococcus pneumoniae* and *Haemophilus influenzae* (Hib) type b. Peltola's (49) recent comprehensive review of the Hib literature suggest that total Hib deaths in developing countries number about 500,000 per year of which 80% are due to ARI (in other words, Hib causes about 12% to 23% of total ARI deaths). Although Hib vaccine is a part of infant vaccination programmes in over 70 countries, it is still in the introduction phase. Randomized trials of antigens are the most direct method to measure the percentage of these conditions due to a specific agent. One such trial in Gambian infants found that Hib conjugate vaccine reduced severe pneumonia episodes by 21% (see reference 45), suggesting that this is the true contribution to ARI mortality. Experts agree that pneumococcus causes a larger proportion of pneumonia deaths in children than Hib, but similar direct estimates of the mortality from *Streptococcus pneumoniae* are not yet available[1]. Several ongoing trials of the pneumococcal conjugate vaccine will better help define its contribution to ARI mortality.

[1] (Coordinated Data Group of BOSTID Researchers. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries Rev Infect Dis. 1990 Nov-Dec; 12 Suppl 8:S870-88).

Diarrhoea is also a major killer and is caused by several agents. Using data from Martines et al (40) and projecting them on existing mortality totals, we estimate that rotavirus is responsible for about 30%, of deaths; *shigella* is responsible for about 27%, of deaths; typhoid is responsible for about 23%; enterogenic *E. Coli* is responsible for about 14% and cholera about 5% of deaths. Rotavirus has drawn most interest because of a possible vaccine (discussed below). A review of 43 epidemiological studies of diarrhea in Africa detected rotavirus in about a quarter of hospitalized or outpatient children (see reference 9). A hospital-based study in Bangladesh also found similar rotavirus detection rates, and found that those with the virus had more severe diarrhea (see reference 56).

Finally, vaccines against several chronic diseases are also possible. Hepatitis B vaccine protects against liver cancer and cirrhosis of the liver (see reference 32). Human papillomavirus, most often types 16 and 18 is a cause of most invasive cervical cancers, for which vaccines are being developed (see reference 46).

Mortality avoided due to vaccination: Current mortality reflects existing coverage with existing vaccines directed to these major causes. The actual mortality in the absence of vaccination is difficult to estimate directly. WHO's estimates suggest that prior introduction of measles vaccination, about 5.7 million people died each year from measles, and that by 1995, this had fallen by nearly nine-tenths (see reference 24).

WHO estimates from 1989 suggested that there were about 1.6 million measles death worldwide in 1990, with an additional 1.2 million deaths avoided. Neonatal tetanus deaths were estimated

at 0.75 million, with about 0.33 million additional deaths avoided. Pertussis deaths numbered 0.5 million, with about 0.4 million additional deaths avoided (see reference 60). Similarly, polio cases, which was once a major cause of morbidity have fallen from over 35,000 in 1988 worldwide to below 1,000 in 2000, mostly in pockets of South Asia and Africa. In contrast Peltola estimates that very few Hib deaths are being averted in developing countries due to low coverage with Hib vaccines.

Where Hib has been introduced, such as Latin America, Hib-related meningitis (which is a sensitive marker of Hib vaccine coverage) have fallen dramatically (Pan American Health Organization, Impact of Uruguay's introduction of the Haemophilus influenzae type b (Hib) vaccine. (See reference 16).

Total numbers of childhood deaths exceeded 10 million for the last two or so decades (see reference 3). Taking into account these numbers, and increasing levels of EPI coverage over the last 2 decades, it is likely that several tens of millions of deaths of children under 5 have been averted with increases in immunization. Thus it is no surprise that the childhood cluster of diseases are no longer in the top five list of childhood deaths, being replaced by a larger relative proportion from ARI, diarrhea and more recently by HIV/AIDS. These estimates of avoided mortality are broadly consistent with reported decreases in case-fatality rate and incidence for the major causes, as well as changes in the age distribution (see reference 10). Generally, with immunization, cases occur in older children and adults, and in more sporadic outbreaks.

For the purposes of this review, attention will be paid chiefly to the existing antigens against childhood conditions that cause the largest preventable burden of disease.

2. Vaccine efficacy

The emphasis in this section is on the existing vaccines that can make the most contribution to decreasing disease burden if scaled up. These are measles, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae* type b. The disease burden averted through hepatitis B vaccination is principally that due to adult mortality resulting from liver disease.

WHO has provided estimates of the efficacy and vaccine-induced immunity in its publication "Immunization Policy", 1996 (65). The following summary table on vaccine efficacy is taken from that document and supplemented with updated information[1].

[1] The efficacy levels reported here represent the performance of the vaccines of assured quality when they are stored and administered according to the manufacturer's specificactions. If vaccines are subjected to heat, or improperly administered, the efficacy would be expected to decrease.

Table 2 Vaccine Efficacy and vaccine-induced immunity

(Source: See references 65, 22 and 58)

Disease	Nature of vaccine	Vaccine Efficacy	Nature of protective antibodies and protective level of antibodies*	Duration of immunity after primary series	Comments
Childhood diseases – main cluster					
Measles[1]	Attenuated live virus	>90% at 12 months of age >85% at 9 months of age	Neutralizing antibody; 200 mlU/ml by neutralization test	Lifelong if boosted by wild virus; shorter when no wild virus circulating	Lower efficacy when maternal antibody present
Tetanus	Toxoid	>95% (>80% after 2 doses)	Antitoxin; 0.01 IU/ml by neutralization test	5 years	5 doses in adults provide over 20 yrs protection
Pertussis	Killed whole cell pertussis bacterium	Estimates vary widely; efficacy higher against severe disease (around 80% protection)	Immunity is probably provided by antibodies against different components of pertussis bacteria; which antibodies and what protective level are not known	Unknown; some evidence that it wanes with time	Lack immunological correlates of protection
Diphtheria	Toxoid	>87% (no data from developing countries)	Antitoxin; 0.01 IU/ml by neutralization test	Variable: probably around 5 years; longer in presence of natural boosting	Recent trades trends to lower antibody levels in adults because of less natural boosting

[1] Note that the protective effect of measles is enhanced with simultaneous administration of Vitamin A. Vitamin A is discussed further in the CMH Working Paper series Working Group 5 paper on nutrition, which is available on the CMH web site.

Disease	Nature of vaccine	Vaccine Efficacy	Nature of protective antibodies and protective level of antibodies*	Duration of immunity after primary series	Comments
Poliomyelitis	Attenuated live viruses of 3 types	>90% industrialized countries; 72-98%in hot climates; lower protection against type 3	Neutralizing antibody; detectable antibody thought to equal protection	Lifelong if boosted by wild virus; shorter when no wild virus circulating	Primary series may not give adequate protection in hot climates
Childhood diseases - other					
Pneumonia	Hib conjugate	93-100% after three doses	Antibody against PRP	Antibody levels decline over time after the primary infant series	
Tuberculosis	BCG Attenuated M.bovis	0-80% vs TB lung 75-86% vs meningitis and miliary TB; leprosy 20-80%	Not known; immunological response includes cell-mediated immunity.	Unknown; some evidence that immunity wanes with time	Reasons for varying efficacy multi-factorial
Other diseases – mainly in adults					
Hepatitis B	HBsAg	75-95%; efficacy higher against chronic carriage than against infection with the virus	Antibody to surface antigen 10mlU/ml		Efficacy lower if injected into gluteal muscle.

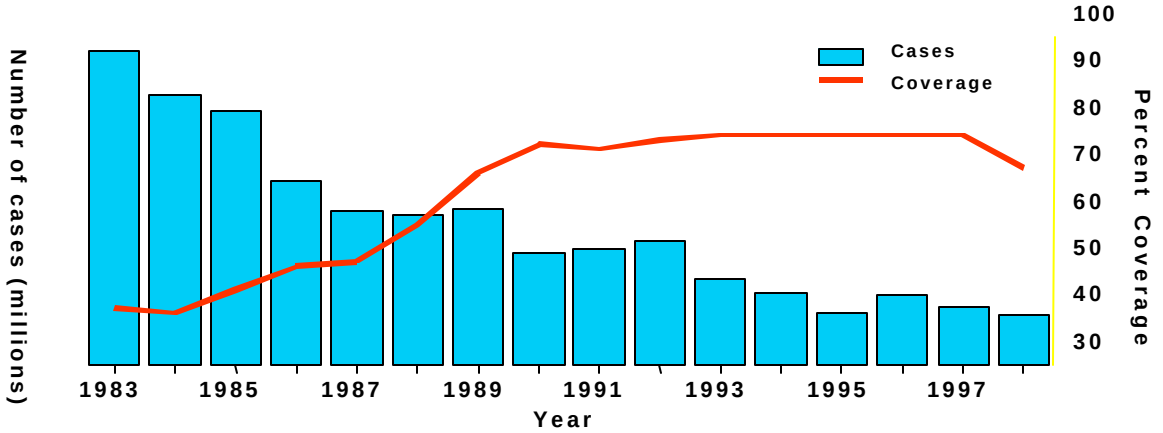
IU: international units of potency as determined in animal tests
* Best estimate of protective level of antibody when measured by neutralization tests: may not correlate well with other assays

Not only are the existing vaccines efficacious, they also benefit from very strong scientific evidence. For example, Hepatitis B vaccine has been subjected to double-masked, placebo controlled, randomized trials which provide the best possible scientific evidence for its efficacy. The existence of such evidence means that investments in these vaccines will, with a high degree of certainty, result in measureable improvements in health. The strong scientific basis for the efficacy of existing vaccines also allows the calculation of credible cost-effectiveness ratios.

Measles

Measles vaccines contain a live virus that has been attenuated through various means in order to make it safe. The efficacy of the vaccine when given at 9 months is about 85% and confers very long lasting protection against disease. The vaccines are more effective in older infants in whom there are no longer any maternal antibodies. At high levels of coverage, vaccination against measles can produce so-called herd immunity in which transmission in the community is blocked (see text box on herd immunity).

Reported global measles cases and measles vaccine coverage, 1983-1998



*Reported to WHO Headquarters, as of August 8, 1999

Text Box: Scaling up measles immunization reduces measles cases and deaths in Malawi

(excerpt from: see reference 64)

"Against the backdrop of low immunization coverage in Africa, Malawi has succeeded in boosting immunization coverage against measles from only 50% in 1980 to almost 90% today. As a result, the number of reported cases and deaths has fallen dramatically.

During 1999, only two laboratory-confirmed cases were reported. And, for the first time ever, no measles deaths. Yet only two years earlier, almost 7000 measles cases were reported and 267 deaths (although most cases go unreported and WHO estimates that nine times as many cases and almost five times as many deaths actually occurred.)

This turnaround has been achieved in one of the world's poorest countries. One in five of the population do not have access to health services, less than 50% have access to safe water, and only 3% have access to adequate sanitation. In 1998, life expectancy hovered at just below 40.

The first key step in reducing measles deaths in Malawi was a sustained increase in routine immunization coverage. This led to an encouraging sharp drop in measels cases and deaths. However, while epidemics have become less frequent, they still occur every 3-5 years – triggered by a build-up in the number of children who have not been immunized and by the vaccine's inherent 15% failure rate. In an epidemic in 1992, for example, 11 000 cases were reported. Then in 1998, Malawi launched a campaign to eliminate measles. The strategy, developed in the Americas, where measles has almost been eliminated, involves a 3-pronged attack to halt transmission of the virus: a nationwide immunization campaign usually targeting every child from nine months to 14 years ("catch-up"); sustained routine immunization coverage of at least 95% of children during the first year of life ("keep-up"); and nationwide campaigns every 2-5 years usually targeting children born after the initial catch-up campaign ("follow-up"). The aim is to ensure that few if any children slip through the immunization net.

In June 1998, a nationwide immunization campaign in Malawi targeting 4.7 million children from 9 months to 14 years succeeded in reaching over 90% of the target population. In addition, vitamin A supplements – which can prevent one in four child deaths from infectious disease – were given to all children aged six months to five years. The cost of the campaign – including delivery costs – was US$ 0.78 for every child vaccinated.

Malawi's success in reducing the death toll from measles has involved concerted efforts to train health workers, improve immunization safety (including vaccine quality assurance and injection safety) and strengthen disease surveillance and monitoring skills. A key factor has been the success of social mobilization campaigns in encouraging parents to immunize their children against measles. In some cases, community volunteers have helped organize door-to-door immunization or set up vaccination posts nearby to ensure that previously unreached children could be immunized.

Today, in an effort to prevent epidemics of measles, Malawi is continuing efforts to ensure that at least 95% of children are immunized during the first year of life and to identify populations where children are unimmunized and at high risk of continued transmission of the measles virus. These children will be targeted in the follow-up phase of the campaign."

Tetanus

Tetanus vaccine contains tetanus toxoid made from tetanus toxin inactivated with formaldehyde. It can be given alone to adult women, and is also given to children in various combinations with diphtheria, pertussis, hepatitis B and *Haemophilus influenzae* type b. Antibody-mediated immunity can be passed through the placenta to the fetus and thus provide protection against neo-natal tetanus. There is apparently no natural occurrence of immunity to tetanus as sub-lethal exposure to tetanus toxin does not seem to confer protection against future infection. Furthermore, tetanus occurs widely as spores and can be carried in the intestines of some animals. Therefore, there is no herd immunity or potential for eradication, and universal immunization is essential to prevent the negative consequences of tetanus infection.

Pertussis

There is no reliable measure of immunity to pertussis since it is difficult to determine the correlation between the levels of antibodies against specific pertussis antigens and level of protective immunity developed by animals or human subjects given the vaccine. Furthermore, the persistence of immunity to pertussis following the three primary doses of the combination vaccine diphtheria, tetanus, pertussis (DTP) is not well established. A Finnish study following an outbreak suggests that protection against pertussis conferred by the 3 doses given in infancy lasts for about one year, and protection following a fourth dose (booster) persists another 2 to 3 years (see reference 28).

Antibodies against pertussis pass through the placenta to the fetus. This is true of antibodies resulting from immunization of mothers as well as those resulting from natural immunity (see reference 7). However, these antibodies do not seem to confer protective immunity and a relatively large number of infants contract pertussis before the age of 6 months. Immunization schedules differ, but most countries give three doses of DTP between six weeks and eight months of age in order to immunize as soon as possible without risking that the vaccine components are neutralised by maternal antibodies.

Vaccines containing whole cell pertussis are made from killed *Bordetella pertussis* bacteria. They comprise the disabled toxoids as well as cell surface components called agglutinogens and a cell surface protein called filamentous hemagglutinin. Most of these components, as well as some others, elicit protective immune responses.

The pertussis lipopolysaccharide endotoxin (LPS) is the element of whole cell pertussis vaccine that is mainly responsible for significant adverse events. Therefore, a purified pertussis vaccine that does not contain this toxic element is attractive. Acellular pertussis vaccines typically contain different amounts of the other main components of pertussis that are known to provoke a protective immune response. As expected, most preparations of acellular pertussis vaccine made from purified sub-components of pertussis, but lacking LPS, produce fewer adverse reactions than the whole cell vaccine for the primary immunization doses.

Hepatitis B vaccine (Hep B)

Hepatitis B vaccine contains the hepatitis B surface antigen (HbsAg). This antigen may be made from the plasma of hepatitis B carriers or it can be manufactured through recombinant DNA technology. Therefore, although there are two forms of hepatitis B vaccine, they act by the same mechanism. Hepatitis B vaccine can be given at the same time as DTP. If there is a high rate of mother to child transmission at birth, a birth dose of hepatitis B alone is recommended, followed by at least two more doses of vaccine. Currently licensed vaccines are safe and result in greater than 95% protection against hepatitis B when given in childhood according to the recommended schedule.

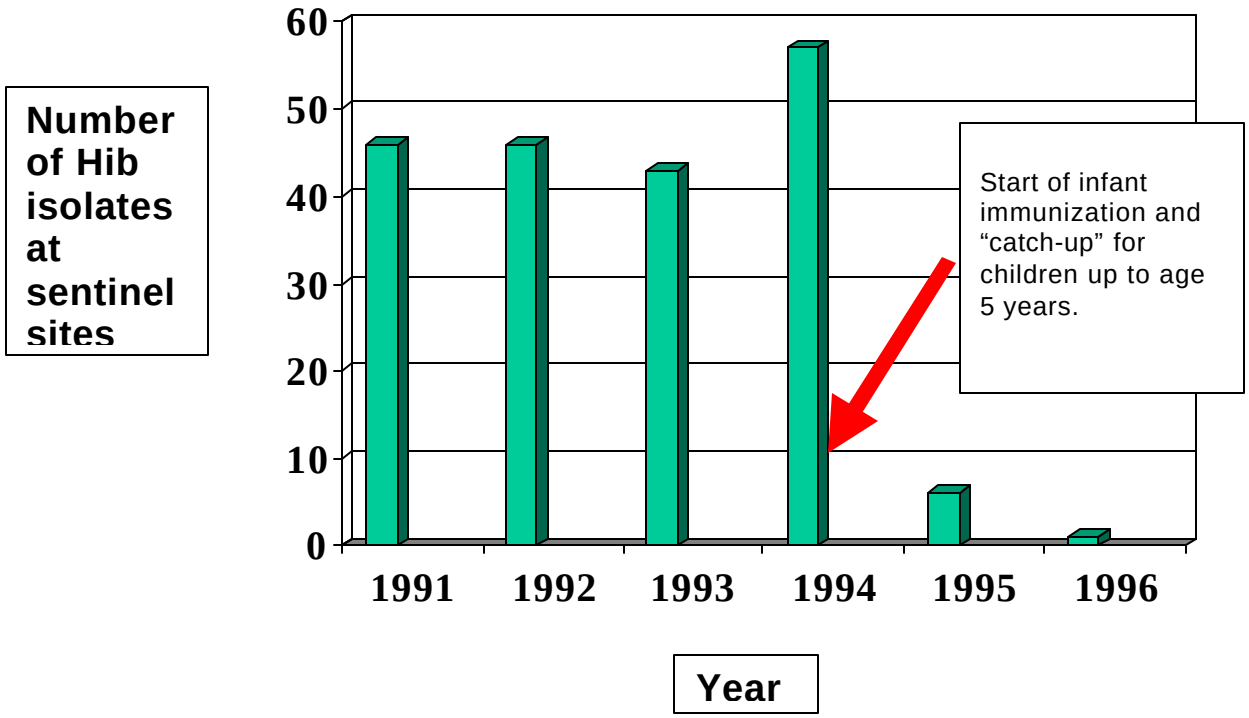
Haemophilus influenzae type b vaccine (Hib)

Vaccines against Hib are based on the type b polysaccharide (sugar), called polyribosylribitol phosphate or PRP. All in use now comprise the polysaccharide bonded (conjugated) to a protein in order to increase the efficacy of the vaccine when given to infants. The size of the polysaccharide, the type of protein linked to it and the form of the linkage vary among different vaccines. There are currently two Hib vaccines prequalified by WHO: oligosaccharide conjugate which is a group of about 20 PRP units linked to a safe form of diphtheria toxin; and a PRP-tetanus toxoid conjugate vaccine.

Figure 1 below shows the impact of vaccination against Hib in Uruguay as indicated by the number of Hib isolates at sentinel sites. Hib conjugate vaccines were introduced in 1994 with a "catch-up" campaign that included immunization of all children up to 5. Countries that do not conduct "catch-up" immunization of older children but only immunize infants do not experience such a rapid a decline, but eventually, over 2-3 years, the number of cases of Hib decreases (PAHO, 1999 (48)).

Figure 1: The impact of vaccination against Hib in Uruguay

(Source: see reference 48)



4. Vaccines and technologies on the horizon

The world's poorest regions are still suffering a heavy toll of premature death and disability from infectious diseases for which vaccines do not exist or else need to be improved. There are, however, reasons to be optimistic. Never have there been so many vaccines in various stages of development as now and the number of available vaccines stands to increase further.
Highly successful vaccines are available against *Haemophilus influenzae type b (Hib)* and *Streptoccocus pneumoniae.* The widespread use of Hib and pneumococcal vaccines would leave *Neisseria (N) meningitidis* and non-vaccine serotypes of pneumococci as the remaining causative agents of bacterial meningitis. In November 1999, the United Kingdom took the historic step of introducing serogroup C meningococcal conjugate vaccine (MenC) for the entire population under 18 years of age. Preliminary data suggest that this programme has been a great success, marked by a dramatic decrease in serogroup C meningococcal disease. Based upon the proven principals established for Hib, pneumococcal and serogroup C conjugate vaccines, manufacturers are currently developing vaccines for the prevention serogroup A, Y and W135 diseases.

Along the same line, a comprehensive vaccination strategy that tackles four-leading bacterial pathogens causing diarrhoeal diseases, is finally emerging. Several promising vaccine candidates, an oral recombinant vaccine against enterotoxigenic *E.coli*, subunit and live attenuated vaccines against the three main pathogenic strains of shigella, are at advanced stages of development; expanded roles for the current typhoid vaccines are being addressed and finally, several field trials of locally produced candidate vaccines against cholera are being carried out in Vietnam. The biotechnological revolution along with the increased knowledge about immune responses

allow the construction of “intelligent vaccines” that may challenge such “difficult” diseases as AIDS, malaria and TB.

Progressive introduction of hepatitis B immunization with its preventive effects on liver cancer, is paving the way for the introduction of new vaccines against other infection-related cancers such as those caused by *Helicobacter pylori* human papilloma viruses.

At the same time, future vaccines will have an increasing role beyond infancy, targeting other specific ages or occupational groups: vaccines against sexually transmitted diseases at adolescence or combined prevention of respiratory infections for elderly people. Finally, future vaccines will expand into chronic or autoimmune diseases.

Considerable effort has been made to develop vaccines capable of conferring a strong immune response over time – thereby eliminating the need for boosters. In a single-dose, an antigen would be delivered and released in a “programmed way”, mimicking a course of conventional vaccines that would otherwise require multiple doses. However, the fact that they are parenterally administered necessitates the presence of a health care professional. At the same time, it is anticipated that the majority of new vaccines that will be available by the year 2005 will be injectable and the number of immunization injections will increase to some 3.5 billion a year. Worryingly, unsafe injection practices may be spreading disease-hepatitis B and C, and HIV. Allegations regarding vaccine-related adverse effects that are not rapidly and effectively dealt with can undermine confidence in a vaccine and ultimately, may have dramatic consequences for immunization coverage and disease incidence.

Novel drying technologies, which incorporate antigens in inert, temperature-resistant solids, along with progress in the development of injection devices have the potential to change immunization programmes beyond recognition. Immunization via the oral route offers obvious advantages. Only a few vaccines, such as those against polio, cholera or typhoid fever, are licensed for oral administration. However, diverse antigen delivery systems are now being developed for the administration of non-living living and living vaccine antigens to mucosal surfaces and even protective vaccine antigens are being expressed in transgenic plants, which would then be administered as edible vaccines.

WHO's goal for the 21st century is to ensure success both in disease control and in delivering immunization services even in the most remote communities in the poorest countries of the world. To be successful, however, new vaccine designs are clearly needed both to remedy the limitations of existing immunization regimens and to allow for the development of new or improved vaccines.

New vaccines:

Pneumococcus (*Streptococcus pneumoniae*): the first vaccine licensed against *S. pneumoniae* was combination of polysaccharides derived from 23 serotypes. Unfortunately, this vaccine does not reliably protect the very young. The immune response of infants to this vaccine varies with serotype: the response of children to some serotypes may be protective; to others it is very poor. This vaccine may be most appropriate as boosters in children who have been primed with a (future) paediatric, e.g. conjugate vaccine.

Glycoconjugate vaccines represent the most advanced class of new paediatric vaccines against *S. pneumoniae*. Currently, The Wyeth-Lederle-Vaccines 7-valent pneumococcal conjugate vaccine has been be the first pneumococcal conjugate approved for use in the USA, based on satisfactory demonstration of efficacy, safety and manufacturing consistency. In addition, up to four manufacturers are undertaking clinical trials with products that include up to 11 serotypes, using different carrier proteins (tetanus toxoid, *N. meningitidis* type B OMP and mutant diphtheria toxin.). The serotypes included potentially cover about 70% of developing country serotypes. These vaccine candidates were shown to be safe and immunogenic in infancy after three doses. The pneumococcal glycoconjugates were modelled after the highly successful Hib conjugate vaccines. The latter eliminated meningitis and much of Hib pneumonia, but were not effective against mucosal surface infections in adults with chronic obstructive pulmonary disease. One of the open questions is to which degree "mucosal" diseases such as otitis media will be affected by pneumococcal glycoconjugates. Another important question is whether if replacement pneumococci occurs, this will present an equivalent risk of invasive disease as the ones eliminated.

Much work has been done on pneumococcal proteins because of their potential roles in control of pneumococcal disease. They may be used as vaccines in their own right, as protein carriers in glycoconjugate vaccines, as tools to study pathogenesis and as drug targets. A number of pneumococcal proteins are currently under pre-clinical evaluation as vaccine antigens (pneumolysoid, PspA, PsaA). Future vaccines may be a combination of these, perhaps alongside a conjugate vaccine.

Rotavirus: On July 16, 1999, rotavirus vaccination was halted in the U.S. after a period of only 9 months of routine immunization. About 1.5 million doses of vaccine were sold, and 800,000-900,000 children were vaccinated. There was an apparent increased risk of intussusception of 1.8 among vaccinated infants. Withdrawal of the vaccine in the U.S. led Wyeth-Lederle to discontinue production, leaving a void in programs to introduce the vaccine in Europe, Latin America and the developing world.

The void created by the loss of the rhesus vaccine is clearly being filled by two candidate vaccines from the multinationals (*i.e.* the bovine reassortment vaccine of Merck and the human monovalent vaccine of SKB-AVANT). These candidates are being tested in humans. Several candidate vaccines from local producers in developing countries may also prove useful. Finally, much remains to be learned about whether the newer vaccines might cause intussusception and whether they will work equally well for children in developing countries.

Shigella: Of the estimated 1.8 million children who die from diarrhoeal diseases each year in developing countries, a signficant percentage die from shigella diarrhoea. *S. flexneri* serotypes (serotype 2a is the most common) predominate as agents of endemic shigellosis. *S. dysenteriae* 1 (*Shiga* bacillus) has been an important cause of epidemic dysentery in Latin America, Asia, and Africa, beginning in the 1960's. There are currently no *Shigella* vaccines meeting U.S. or European standards of licensure, and there are few commercially supported vaccine development programs. In the coming year, six Asian countries will be conducting population-based *Shigella* epidemiology projects. I VI and the Lanzhou Institute of Biological Products are developing a program for evaluation of their *S. flexneri* 2a/*S. sonnei* bivalent hybrid vaccine in Chinese children. This bivalent vaccine is a licensed product in China, but the Chinese have no

paediatric experience with the vaccine. Among live attenuated vaccines, Phase 1 trials of the Institut Pasteur/Walter Reed Army Institute of Research *S. flexneri* 2a vaccine (SC602) being carried out by the International Center for Diarrheal Disease Research, Bangladesh (ICDDR, B). Other candidates including strains of both *S. flexneri* 2a and *S. dysenteriae* 1 have also entered in phase I clinical trials. Subunit vaccines such as a proteosome based candidate is at pre-clinical stage and a conjugate based vaccine against *S. dysenteriae* 1 have entered phase I clinical trials.

Serogroup A/C meningococcus: Countries within the meningitis belt suffer from devastating meningococcal epidemics, often in irregular cycles every 5-12 years. During an epidemic, attack rates are high in all age groups, including young adults who are in the prime of life. Polysaccharide (PS) vaccines against serogroups A, C, W135 and Y are currently available. These vaccines have shown to be safe, immunogenic and effective in controlling epidemics in all age groups during mass campaigns in Africa. However, their short duration of protection in young infants, immune depression in response to repeated vaccination with serogroup C PS and inability to confer herd immunity have precluded incorporation of these vaccines into routine immunization programmes. Therefore, in order to prevent and ultimately eliminate epidemic meningococcal disease in the African meningitis belt, WHO and the Bill and Melinda Gates Children's Vaccine Program at PATH (CVP), have created a partnership to accelerate the development, evaluation and introduction of serogroup A plus C meningococcal conjugate vaccine. The technology to produce a safe and effective meningococcal conjugates for Africa has been available for more than 10 years. Highly successful prototypes have been evaluated and have been shown to be highly immunogenic and to induce immunologic memory in African infants. Yet, these programs have been halted because serogroup A meningococcal disease is limited to persons in the poorest countries, and the returns on investment are perceived to be too

low. Different alternatives to establish a public/private sector partnership have been explored aiming at lowering costs and risks of product development and seeking incentives by creating a market, providing other economic rewards or removing economic deterrents. This public/private sector partnership could become a model for push-pull funding for other developing country market vaccines. At the same time, the partners are committed to seek the necessary resources to ensure procurement in sufficient volume to meet projected needs, and to carefully plan the introduction of the vaccine through mass and routine immunization programmes in synergy with other public health initiatives in Africa.

Table 3: Stages of development of new vaccines and technologies

PRODUCT		PREDOMINANT AREA OF ACTIVITIES						
			Preclinical studies		Clinical trials			
Pathogen	**Vaccines**	Epidemio-logical studies	Early	Late	Phase I	Phase II	Phase III	Phase IV post-licensure
Childhood diseases - other								
Pneumococcus	Polysaccharide Conjugates: 7-valent 9-11 valent Common Prot.	♦	 ♦	♦ ♦ ♦ ♦	♦ ♦ ♦	♦ ♦ ♦	♦ ♦ ♦	♦ ♦
Shigella	1.Live attenuated 2. Sub-unit: Proteosomes Conjugates	♦	♦ ♦ ♦	♦ ♦ ♦	♦ ♦	♦ ♦		
Rotavirus	Oral tetravalent Other Live, jennerian Merck-bovine reassortment SKB- human monovalent	♦ ♦	♦ ♦	♦ ♦	♦ ♦	♦ ♦	♦	♦withdrawn
Cholera[1]	O1 strain parenteral: inactivated *V.cholerae* O1 Oral: WC/rBS CVD103-HgR O139 strain: bivalent (01-0139), killed oral	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦	♦ not recommended ♦ limited use ♦ limited use

[1] Whereas there are several vaccines licensed against O1 strain (parenteral inactivated *V.cholerae* O1(not recommended anymore) and two oral vaccines, namely WC/rBS and CVD103-HgR) their use is limited to specific populations at risk. Cholera vaccination of high risk populations should be done pre-emptively only, in conjuction with other prevention and control measures. For vaccination of populations at immediate risk of cholera epidemics, the WC/rBS is currently recommended. No efficacy data exist for vaccines against the O139 strain.

PRODUCT		PREDOMINANT AREA OF ACTIVITIES						
			Preclinical studies		Clinical trials			
Typhoid[1]	1.Parenteral Vi Conjugate 2. Oral Ty21a Others	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦	♦ ♦ ♦	♦ limited use ♦ limited use
Enterotoxigenic E. coli (ETEC)	subunit vaccines; rCTB-CF live-attenuated; ETEC-cholera combo	♦	♦		♦	♦	♦	
Meningococcal Meningitis [2]		♦						
Serogroup AC	Polysaccharide Conjugate: -Bivalent -Tetravalent (including A,C, Y,W135)	♦		♦ ♦ ♦	♦ ♦ ♦	♦ ♦ interrupted	♦	♦ (limited use for control of epidemics)
Serogroup B	OMV-based Modified PS-Conjugate Others (Tbp, NspA, …)	♦ ♦ ♦	♦ ♦ ♦	♦ ♦ ♦	♦ ♦ ♦	♦	♦	♦ (limited use-control of epidemics)
Dengue	Live attenuated Chimeric	♦ ♦	♦ ♦	♦ ♦	♦ ♦	♦ ♦		
Other diseases, mainly in adults								

[1] Three vaccines are currently licensed (parenteral whole cell typhoid (poorly tolerated) Vi polysaccharide and oral Ty21a). These vaccines confer around 70% protection in older children and adults but protection for younger children is very limited. Therefore, no programme for prevention of typhoid fever by routine vaccination currently exist and their use is restricted for other targeted populations. At the same time, the development of a new generation of parenteral and oral typhoid vaccines are underway (results of an efficacy trial of a new conjugate vaccine in 2 year old children have been recently published in the NEngJMed 344:1263-1269),

[2] A bivalent serogroup A/C meningococcal conjugate vaccine has been evaluated in phase II and not phase III trials. However, please note that all manufacturers have abandoned their plans to develop a bivalent product for several reasons, including the perceived low returns on investment. Some manufacturers are now concentrating their efforts in developing quadrivalent conjugate vaccines (A, C, Y, W135) which will presumably be evaluated in phase II clinical trials soon.

Regarding serogroup B meningococcal Vaccines, the Cuban Finlay OMV-based vaccine has been licensed and more than 400 million doses have been administered, the majority in Latin America. However, this vaccine has some important drawbacks: protection is only short-term; as yet, there is little data on their protective efficacy in infants; and they show serosubtype specificity, which, given the antigenic diversity among serogroup B strains, limits their effectiveness. Thus, OMV vaccines are more appropriate for use as strain-specific "designer" vaccines against clonal outbreaks than for routine infant immunisation aimed at the prevention of endemic disease caused by diverse strains.

PRODUCT		PREDOMINANT AREA OF ACTIVITIES						
			Preclinical studies		Clinical trials			
HPV	VLP Others (DNA, etc)	♦	♦ ♦	♦ ♦	♦	♦		
Japanese Encephalitis	Inactivated SA14-14-2 live attenuated Chimeric JE-PIV	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦ ♦ ♦	♦ ♦	♦ limited use ♦ use in China
Vaccine delivery systems								
Controlled release	Microspheres		♦	♦				
Sugar-powder vaccine			♦	♦				
Transcutaneous immunization			♦	♦	♦			

5. Cost Effectiveness

Vaccination is repeatedly being quoted as one of the most cost-effective health interventions available to both developing and developed countries. There are two underlying reasons for its immediate cost-effectiveness:

It is a preventive measure. Prevention is generally considered more cost-effective than treatment due to the fact that future disease burden, which involves human suffering as well as utilization of health services, is avoided.

It is a relatively simple health intervention to deliver. Compared to other preventive measures, such as for instance promotion of safe water supply or food safety, delivery of vaccination is relatively uncomplicated due to a) a well-defined target group, b) contact with the health system is only needed at the time of delivery and c) the intervention does not require any major change in lifestyle.

Key determinants of cost-effectiveness

While vaccination as a principle is recognized as a cost-effective measure compared to other health interventions, caution should be taken in generalising across different vaccines and different epidemiological settings. Each type of vaccine must be assessed separately to determine its relative cost-effectiveness in any particular setting.

Key determinants of cost-effectiveness of a vaccine are:

1. Level of disease burden in the absence of vaccination. If there is only limited risk of contracting the disease, it is not likely to be cost-effective to vaccinate. One example is the yellow fever vaccine, which is only recommended as part of routine immunization services in countries at risk.

2. Costs of treatment of the disease relative to the costs of delivering vaccination, including costs of the vaccine. In certain settings, treatment may be more cost-effective than vaccination. Varicella is an example where a vaccine is available, but since the disease is not fatal and since it hardly requires any treatment, vaccination may not be the most cost-effective intervention in any setting.

Measures of cost-effectiveness

Different outcome measures are being used to assess the cost-effectiveness of vaccines, often determined by the availability of data on disease incidence and its associated effects. In developing countries this type of data is often not easily accessible.

For a comparison with other health interventions, outcome measures which include morbidity, such as a quality-adjusted life year (QALY) or a disability adjusted life year (DALY), are the most useful (for explanation of QALY and DALY see reference 13).

However, data on morbidity is time consuming to collect and the methodologies for its measurement have not yet been sufficiently elaborated upon for developing countries. Hence, in these countries there are only a few studies available where these outcome measures are used to assess the cost-effectiveness of vaccination.

The most common outcome measures in cost-effectiveness analysis of vaccination are deaths averted and/or discounted life years gained. Some studies present intermediate outcome measures in terms of cost per fully immunized child and/or cost per case prevented. However, since these measures are not directly comparable with other health interventions, they are not useful for decision making on overall resource allocations.

The evidence

In table 4 some of the available evidence on cost-effectiveness of selected vaccines in a number of developing countries is summarised. While there has been a considerable increase in the number of economic evaluations of vaccines and immunization services over the past decade, the evidence from developing countries is still too sporadic and unclear. There is generally agreement on the overall cost-effectiveness of immunization, due to the factors described above, but more work is still needed to determine the comparative cost-effectiveness of different vaccines against each other and compared to other interventions. First, more studies need to be carried out and secondly, the quality of studies must be improved.

At the moment very few studies adhere to appropriate analytic techniques, such as those described (see reference 13 and 57). In 1993, the World Bank concluded that the traditional EPI vaccines together with hepatitis B vaccine, yellow fever and vitamin supplements ("EPI plus") is among the most cost-effective health interventions for developing countries, ranging from US$ 12-17 per DALY gained in low income countries and US$ 25-30 per DALY gained in middle income countries (table 4). Other interventions with comparable cost-effectiveness include school health programmes, tobacco and alcohol control, vector control and STD prevention.

Results from a number of subsequent studies confirm that certain vaccines, especially measles vaccine, is a highly cost-effective intervention. In a recent study from Bangladesh, (see reference 57) conclude that the current measles immunization programme prevents around 1,048 deaths a year. When this is compared to total costs of delivering the vaccine, costs per discounted life years gained amount to as little as US$ 14.39.

The evidence on the cost-effectiveness of new and underused vaccines (such as Hib and hepatitis B) will be discussed in the section below on scaling up immunization services.

Table 4: Cost-effectiveness ratios of vaccination in a selection of developing countries

Vaccine	Country	Year	Vaccination strategy	CE measure	Source
Childhood diseases – main cluster					
EPI Plus (DTP, polio, BCG, Hep.B, yellow fever, vitamin A and iodine supplements)	Low income countries	1990	Routine infant immunization	US$ 12-17 per DALY gained	Reference 66
BCG, DTP, OPV and measles	Guinea	1994	Routine infant immunization	US$ 25 per life year saved	Reference 30
MMR	Guyana	1997	Routine infant immunization	Benefit/cost ratio: US$ 38.8	Reference 31
Measles	Developing countries with average age of infection at 2 years	1999	Expanding routine infant immunization coverage from 50% to 80%	US$ 2.53-5.06 per discounted life-year gained *(preliminary results)*	Reference 14
Measles	Bangladesh	1999	Routine infant immunization	US$ 288 per death prevented US$ 14.39 per life years gained	Reference 57
Childhood diseases – other					
Hib	South Africa	1995	Routine infant immunization	Benefit/cost ratio: US$ 1.29-1.43	Reference 29
Hib	Chile	1993	Routine infant immunization	Benefit/cost ratio: US$ 1.66	Reference 38
Hib	Developing countries with high mortality	1999	Routine infant immunization	US$ 480 per discounted life-year gained *(preliminary results)*	Reference 14

Hib	Africa	2000	Routine infant immunization	US$ 21-22 per life years gained	Reference 42
Other diseases, mainly in adults					
Hepatitis B	Bangladesh	1998	Routine infant immunization	US$ 4,809 per death prevented	Reference 4
Hepatitis B	Developing countries with high HBV prevalence	1999	Routine infant immunization	US$ 219 per discounted life-year gained *(preliminary)*	Reference 14
Hepatitis B	Low-income countries with HBV prevalence less than 2%	2000	Routine infant immunization	US$ 42-59 per life years gained	Reference 42
Hepatitis B	Low-income countries with HBV prevalence greater than 8%	2000	Routine infant immunization	US$ 8-11 per life years gained	Reference 42

Text Box: Herd immunity and cost effectiveness
(Sources: EDI, 1996; Plotkin & Orenstein, 1999 (51)

Live viral vaccines such as oral polio and measles vaccines actually prevent infection by a disease from occurring. Therefore, in the absence of an environmental reservoir of disease, they can be used to reduce the amount of circulating virus. If a high enough proportion of the population is vaccinated, transmission of disease can be stopped. This means that if the disease is imported by an infected person, almost all of the people they expose to the virus will be protected from infection and there will be no further transmission of the disease. An unvaccinated person in this environment will stand very little chance of being exposed to the virus, and therefore is protected by the vaccination status of the others. A similar effect is shown when inactivated or toxin-derived vaccines reduce the transmission of a disease or of the toxic form of an organism. This reduction in the rate of disease transmission is known as "herd immunity". Herd immunity is defined as a greater decrease in disease burden following immunization than would be expected due to the effects of vaccination on individuals alone.

The level of vaccination coverage required to achieve herd immunity varies with the efficacy of the vaccine and the ease with which the disease can be spread from one person to another. For example, because it is so easy to spread measles and because the efficacy of the measles vaccine is approximately 85-90%, very high levels of measles vaccine coverage must be reached before herd immunity is achieved. Herd immunity against polio is achieved at 80% oral polio vaccine coverage in the Netherlands where sanitation and hygiene conditions are good. However an outbreak in Myanmar in 1979 demonstrated that 97% coverage with oral polio vaccine is necessary to achieve herd immunity where sanitary conditions favour the spread of polio through the fecal-oral route. Similar high coverage requirements were demonstrated in Senegal, Morocco and in the Dominican (see reference 53).

Herd immunity cannot be achieved with certain vaccines which have little effect on transmission, such as BCG and tetanus. Given the reservoir of tetanus in soil and animals, and given the fact that the tetanus vaccine is a toxoid which protects against toxic effects but not against infection, the tetanus vaccine does not result in reduced transmission at high coverage levels.

Several of the essential vaccines confer herd immunity. Herd immunity has been demonstrated for pertussis vaccine (see reference 15), oral and inactivated polio vaccines (see references 51 and 53), typhoid (see reference 37) and yellow fever (see reference 44). High levels of coverage with diphtheria vaccine also seem to reduce transmission of the toxic form of diphtheria (see reference 21). Herd immunity is also recognised at high levels of coverage with measles vaccines and with *Haemophilus influenzae* type b (see references 17 and 18).

Because of herd immunity, outbreaks can be prevented before reaching 100% coverage. Therefore, it can be more cost effective to vaccinate at high levels of coverage rather than at moderate levels. Even though the level of effort per child is greater at levels of coverage approaching 100%, these high coverage levels actually prevent outbreaks of disease even among the unimmunized in the community. So the reduction of disease burden per child

immunized is greater at the high levels of coverage that confer herd immunity.

Cost-effectiveness of scaling up

Immunization services can be scaled up in two ways. Firstly, by expanding immunization coverage of vaccines already recommended by the national immunization system and secondly, by introducing new and/or underused vaccines into the system.

While some information is available on the cost-effectiveness of introducing new vaccines (see table 4), very little work has been done on the cost-effectiveness of increasing immunization coverage. Since coverage is a function of demand, infrastructure and the motivation of local officials and health care workers, accurate and generalisable information is difficult to estimate. It is however generally assumed that when a certain level of coverage has been achieved, the marginal costs of delivering immunization to the last part of the population increases with the coverage level. That is, the last percents of the population are considered relatively more difficult to reach than those already being covered and these services are therefore more costly. However, on the other hand it would be possible to provide examples of diseases with a higher incidence rate and a more severe impact among poor and un-reached populations compared to the relatively privileged part of the population who have more easy access to health services. This is the case for diseases related to acute respiratory infections (ARI). For populations without easy access to health services it is likely that immunization would provide a relatively high benefit in terms of reduced disease burden. However, since ARI in many cases can be treated with relatively cheap antibiotics, vaccination with a relatively expensive vaccine, might not be cost-effective for populations with access to health services.

The following circumstances have been quoted as reasons for low or stagnating immunization coverage in developing countries:

1. Drop-outs – if children immunized against some diseases do not turn up for later immunizations.
2. Missed opportunities – if children who need immunization are seen periodically in health care settings, but providers miss the opportunity to immunize them.
3. Lack of geographical access – if a child lives in an unreasonable travel distance to the immunization service and health workers do not travel to the village to conduct immunization services.
4. Never reached – if people never use the health services for other reasons than lack of geographic access. One reason could for instance be user fees that deter people from approaching the health system.
5. Programmatic issues – people avoid immunization because of long waits, inconvenient hours, or after seeking immunization they sometimes find that there is no vaccine in stock at the clinic, and they do not return.

For estimating the cost-effectiveness of expanding coverage, the most successful strategies to obtaining this must be identified for the country in question and the associated costs estimated. Cost-effectiveness estimates can then be generated by comparing the costs to predicted decrease in disease burden. This work is in progress among GAVI partners.

Immunization services can also be scaled up by introducing new or underused vaccines, such as hepatitis B and Hib vaccines. Quite a few studies are available on the cost-effectiveness of introducing hepatitis B vaccine into national immunization programmes, but most of these are from developed countries (see references 19 or 23). For less developed countries, the cost-effectiveness of hepatitis B vaccine has not yet been appropriately addressed. A study from Bangladesh (see table 1) demonstrates that introducing hepatitis B vaccine will give a cost-effectiveness ratio between US$ 873 and US$ 1,178 per death prevented, depending on the carrier fatality rate.

Cost-benefit analysis on Hib vaccination from South Africa and Chile demonstrate a benefit-cost ratio higher than one, indicating that introduction of the vaccine into the routine immunization system is cost-saving. However, more studies from different settings are needed to make overall conclusions on this vaccine.

Cost-effectiveness of elimination and eradication

Small pox was the first disease to be eradicated by vaccination. The eradication programme lasted a total of 13 years (1967-1979) and ended up costing about US$ 300 million (see reference 20). Savings resulting from the eradication of smallpox, however, save hundreds of millions of dollars per year. Polio is well on its way to be eradicated. The programme started in 1988 and it is hoped that no more polio cases will occur after year 2005.

Eradication programmes pose specific challenges for cost-effectiveness studies. Since the benefits of an eradication programme are likely to be infinite, the cost-effectiveness ratio for such programmes will be near zero regardless of the cost in the numerator. Compared to other

interventions that have finite costs and benefits, and thus non-zero cost-effectiveness ratios, eradication programs will appear much more attractive (see reference 2). However, it is generally assumed that benefits occurring today are more valuable than benefits occurring in the future and reflect this dominating preference for the presence, researchers discount benefits as well as costs in their analysis. Overall results are consequently very sensitive to the choice of discount rate.

Strategies for the elimination of measles are currently being implemented in the regions of the Americas and Europe. However, an analysis that takes future costs and benefits into account, eradication of the disease might be more cost-effective than elimination. In regions where elimination has been achieved, it will be necessary to maintain a very high level of vaccination coverage (at least 95%) to avoid epidemics arising from imported cases. High levels of coverage can in certain areas only be achieved by carrying out immunization campaigns, which are known to be relatively costly.

6. Constraints to scaling up:

Financial barriers to vaccine introduction

Until recently there has been more than a decade of lag time between the introduction of a new vaccine in the developed world, and its uptake in developing countries. Hepatitis B vaccine was introduced twenty years ago and many countries still have not introduced it into their routine immunization programmes. These countries represent about half of the world's children. Hib vaccine was introduced in 1990 but only about 20% of the target population receives it. The maps in figures 2 and 3 below show that richer countries have incorporated the relatively

expensive hepatitis B and Hib vaccines into their infant immunization programmes well ahead of poorer countries, where Hib causes deadly pneumonia and hepatitis B kills adult carriers.

Figures 2 and 3 global status of Hib and hepatitis B immunization
(Source: see reference 12)

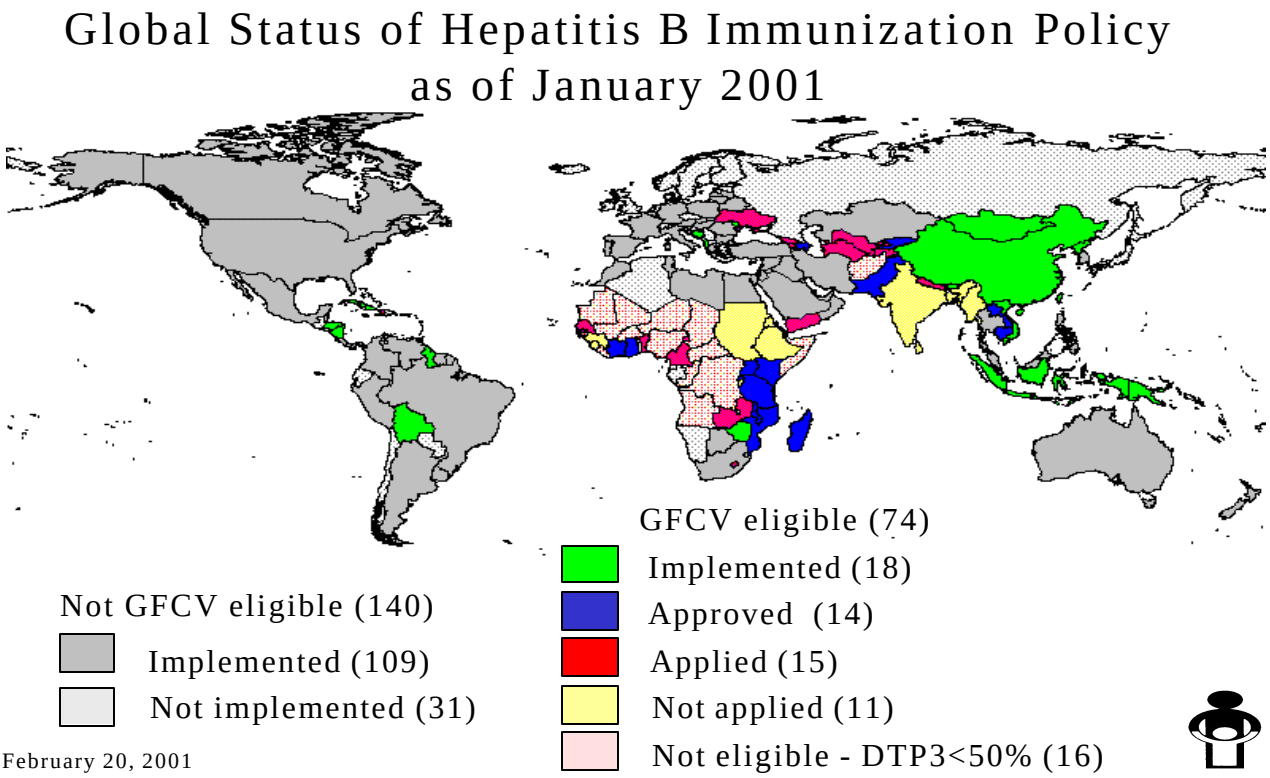
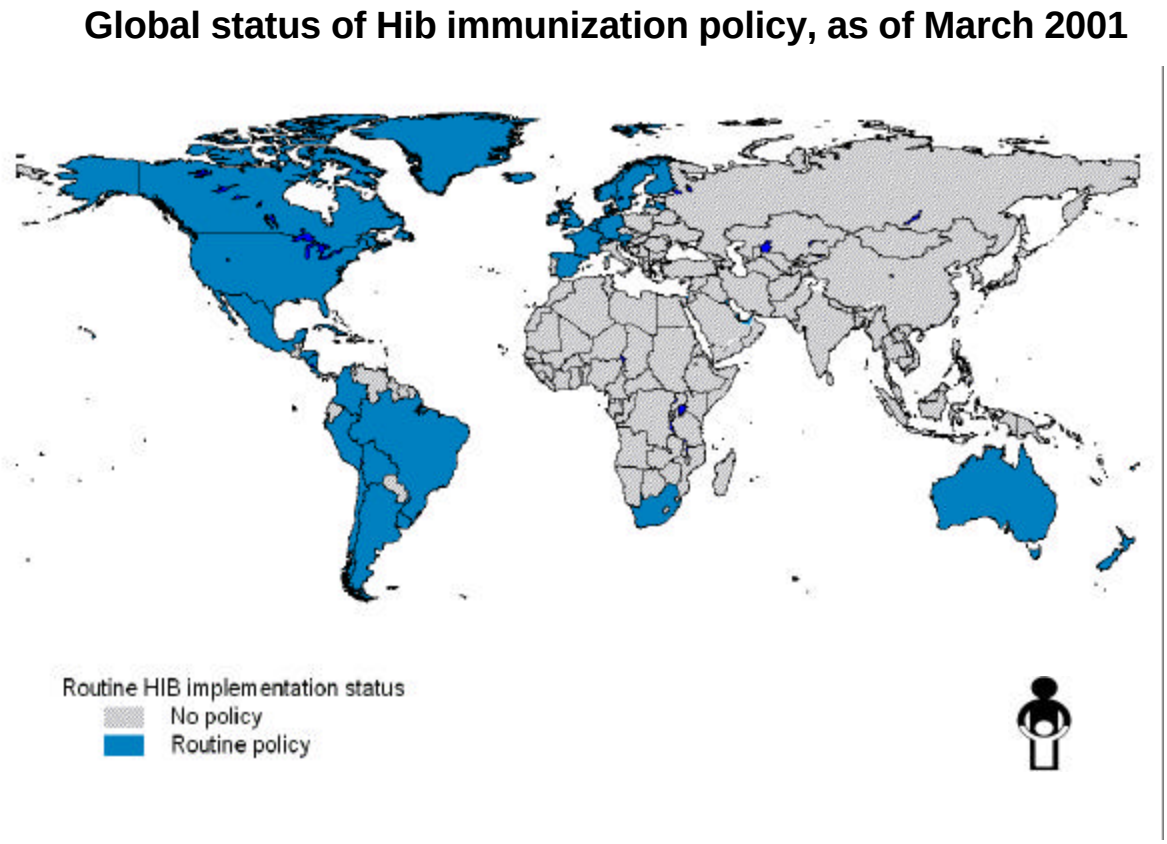


Figure 3
(Source: see reference 12)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

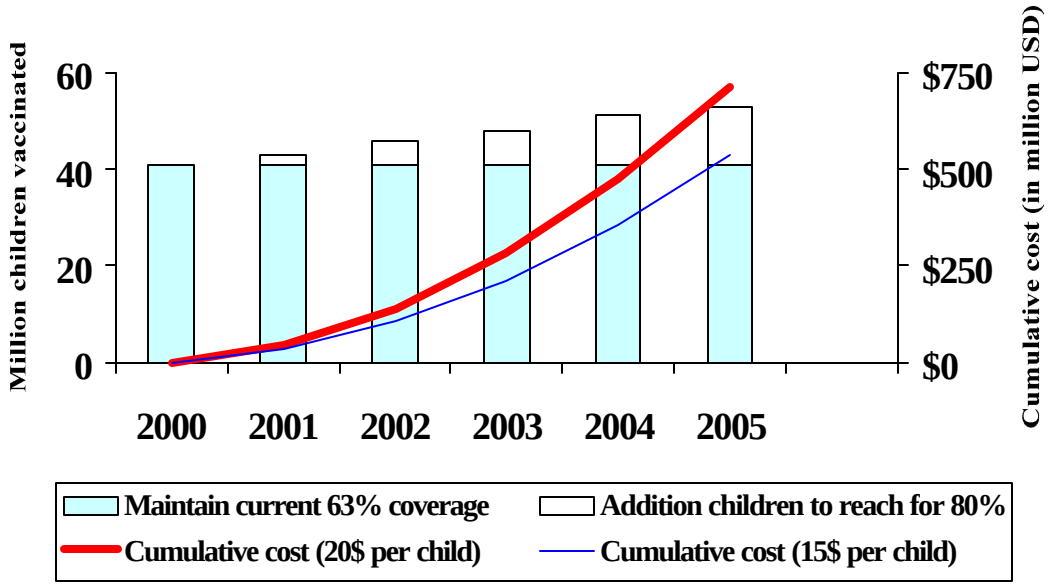
Clearly, the higher prices of relatively new vaccines are one of the barriers to their adoption. Despite the cost-effectiveness of interventions like yellow fever vaccination, the absolute cost of vaccinating every infant in a birth cohort can seem overwhelming to beleaguered Ministries of Health. This phenomenon of so-called "sticker shock" has slowed the introduction of vaccines against yellow fever, Hib and hepatitis B.

Bulk procurement mechanisms have brought prices for some newer vaccines into the affordable range where there is excess production capacity in the industry. For example, the Pan American Health Organization (PAHO) revolving fund vaccine purchase mechanism engineered a price drop from a high of US$8.50 per dose of Hib vaccine in 1998 to US$2.18 or 2.60 per dose depending on formulation at the end of that same year (see reference 48). However, this downward price pressure has the risk of dampening the incentives to produce new vaccine products for the developing country markets.

Beyond vaccine price, the cost of delivering vaccines and upgrading the associated infrastructure and management capacity can be daunting. Figure 4 below illustrates the cost of scaling up immunization coverage from current levels to 80% in 43 of the world's poorest countries that do not currently have 80% coverage of children with three doses of DTP. The cost is estimated at US$535-713 million to reach 35.7 million additional children over the five years from 2000 to 2005 (Source: Vaccine Assessment and Monitoring Team, WHO). This does not include the cost of expanding the number of antigens from the basic EPI six (BCG, DTP, measles and polio).

[1] PAHO. Introduction of Hib Vaccine in the Americas: Lessons Learned. PAHO EPI Newsletter, April 1999; 21(2): 4-5.

Figure 4 The cost of improving immunization coverage from current levels to 80% by 2005 in countries with GNP per capita under US$1000 (Source: Vaccine Assessment and Monitoring team, Department of Vaccines and Biologicals, World Health Organization, 2000).



Constraints to supply

The trend towards privatisation of state run enterprises over the past decades has affected public sector vaccine producers. An ever-increasing percentage of vaccines used in public health programmes are produced in the private sector. These private sector manufacturers are often subdivisions of larger pharmaceutical companies, which have themselves been subject to consolidation recently. There are now relatively few vaccine manufacturers, although there is growth in the number of developing country suppliers. For example, as of February 2001 there were only 21 suppliers world-wide pre-qualified to provide vaccines to UN procurement mechanisms. Many of these are developing country manufacturers that produce only one or two pre-qualified vaccines. The five-component vaccine providing protection against diphtheria,

pertussis, tetanus, hepatitis B and *Haemophilus influenzae* type b is produced by only one pre-qualified supplier. To some extent this is simply the result of chance.
(Source: Access to Technologies Team, Department of Vaccines and Biologicals, WHO).

The outcome of this consolidation and privatisation is increasing pressure on vaccine producers to maximize profit in the use of research and development resources as well as of manufacturing capacity. Redirection of manufacturing capacity has meant that production of existing vaccines barely keeps pace with demand. Demand for combination vaccines combining DTP with Hep B far outstrips supply and will continue to do so well into the next decade (Source: UNICEF Supply Division). In the case of oral polio vaccine, vaccine production has failed to meet demand. Reasons for the shortage of oral polio vaccine include production problems and the unforeseen huge increase in demand (demand was forecast by WHO, but the forecast did not have credibility without guaranteed purchase).

The complex processes involved in producing a vaccine, the high capital requirements for vaccine production and the long and stringent regulatory hurdles are barriers to new vaccine development and to development of existing vaccines. As a result of these factors, from a public health perspective, inadequate investment is being made in new vaccines against diseases of the poor, and inadequate volumes of some vaccines are being produced. As the time lag between a decision to increase production and the supply of vaccine to the market can be up to five years, public health initiatives and demand projections must be signalled to industry early. The graph in figure 5 below indicates the dropping trend since 1993 in the amounts of DTP vaccine being offered in response to UNICEF tenders and figure 6 illustrates the precarious supply of oral polio vaccine (Source: UNICEF Supply Division).

Figure 5: **Dropping amounts of DTP available for UNICEF purchase**
(Source: UNICEF Supply Division)

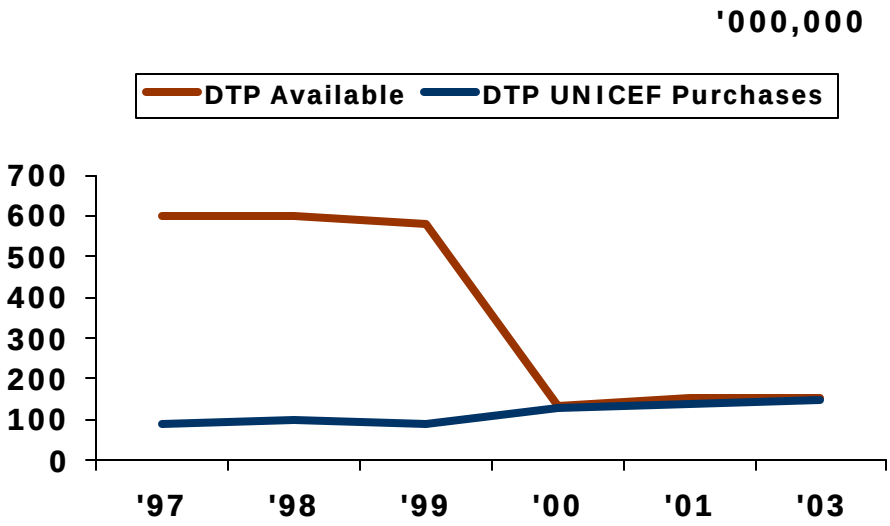
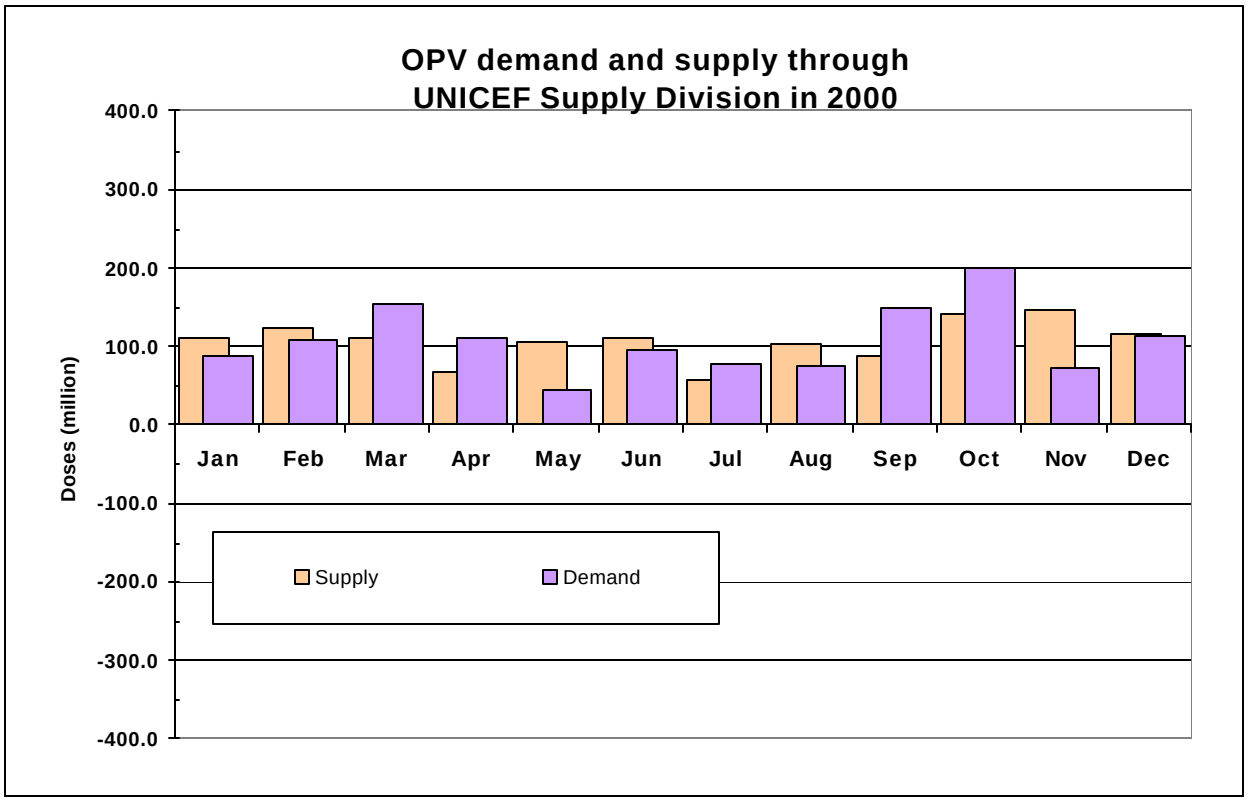


Figure 6 Oral polio vaccine demand and supply, 2000
(Source: UNICEF Supply Division)



Vaccine quality

Supply also depends on the enforcement of quality standards by national regulatory authorities. Vaccines purchased by UNICEF and WHO bulk procurement mechanisms are produced by manufacturers whose products are pre-qualified. Pre-qualification means that the quality of these vaccines is assured. An important part of this multi-stage quality assurance process is the work of the national regulatory authority in the country of production. The functioning of the national regulatory authorities is assessed by WHO. Countries that do not have a fully functioning national regulatory authority cannot supply vaccine through the UN system.

Therefore, quality and safety considerations have a very significant impact on worldwide supply. (However, there are both producing and purchasing countries in which vaccine quality and safety considerations are not given a high priority.)

Vaccine stability

The ability to expand delivery of vaccines beyond the current coverage level often depends on outreach services. When outreach requires complex or lengthy transportation through difficult terrain, where conflict has destroyed infrastructure or where equipment is ageing or in need of repair, rapid transport and refrigeration may not be available. Heat stable vaccines are therefore a key technology for extending coverage. Vaccine vial monitors are part of the solution. Vaccine vial monitors (VVMs) are small detectors stuck to the label of a vial of vaccine. These detectors change colour according to the temperature they have been exposed to and according to the length of time they have been stored at a given temperature. They can be calibrated so that they change colour when the vaccine in the vial is exposed to sufficient heat to inactivate it. They have proven themselves in the field in the polio eradication initiative by preventing wastage and extending outreach beyond the cold chain. Their use is being extended to other vaccines. However, vaccines still rely on a "cold chain" of cold rooms, refrigerated transport and cold boxes in order to retain their potency to the point of service delivery. The development and maintenance of this cold chain is dependent on management and good governance as well as technical know-how.

Vaccination technologies and disposal

Injection is technically difficult for untrained people, uncomfortable for babies and their mothers, and has the potential to be unsafe if injection equipment is not sterile. Unsafe injection practices also pose a danger to health workers. The AIDS pandemic has heightened the concerns surrounding injection safety. Furthermore, syringes and needles are expensive and bulky. Alternatives to injection, such as oral vaccines or alternative delivery technologies would make vaccination easier, faster, less expensive and safer. These advantages would greatly facilitate the expansion of immunization to the unreached and increase its cost effectiveness.

Peripheral delivery capacity

The peripheral delivery capacity is critical to the expansion of immunization. In order to carry out this delivery function, the health system needs to have the capacity to make rational policy decisions on immunization strategies including outreach and the introduction of new vaccines, to obtain safe and effective vaccines, to store and transport them according to prescribed conditions, to carry out social mobilisation, to plan effectively at all levels, to carry out programme monitoring, surveillance to investigate suspected cases of vaccine-preventable disease and adverse events following immunization, and to deliver high quality immunization services at all levels of the health system, including outreach. Any deficit in these capacities will have a negative impact on immunization services and will limit the potential to expand immunization to higher levels of coverage or to include more vaccines.

Monitoring and Surveillance

Surveillance of acute flaccid paralysis is essential to the success of the polio eradication initiative and tremendous efforts have been put into building the detection, sample transport and laboratory analysis capacities required. Successful polio surveillance networks have been established in zones of active warfare and in the most remote areas. Other disease surveillance efforts are beginning to "piggy-back" on to the polio networks. Integrated surveillance in over half of the countries of Africa embraces measles, neonatal tetanus, cholera and meningitis. Monitoring of immunization coverage continues to be a significant challenge as it depends on several elements of peripheral service delivery and central managerial and technical capacity. Accurate monitoring and surveillance data are essential for good management of service delivery and for early warning of outbreaks. As an indicator of the weaknesses in this area, the table below illustrates the constraints in the availability of data (see reference 5). This analysis includes industrialised countries.

Table 6: Number of countries for which immunization coverage data are available for five or more years during the period 1990-98 (see reference 5).

Vaccine	Number of countries for which immunization coverage data are available for five or more years during the period 1990-98 (n=215)	Number of countries with data as a percentage
Hepatitis B	39	18%
Tetanus	90	42%
BCG	160	74%
Measles	190	88%
Oral polio	190	88%
DTP	191	89%

An analysis of the difference between reported coverage data for routine immunization and the results of immunization coverage surveys showed that a difference of 30 percentage points was not unusual (see reference 5). However, there can also problems with the accuracy of survey data which result in point estimates with confidence intervals, and administrative coverage data tend to underestimate as well as overestimate coverage. Underestimation is a result of poor reporting, a large private sector or poor census data which overestimates the denominator of the coverage calculation.[1]

[1] The best approach to solving this problem is to strengthen routine monitoring and to use surveys every three to five years to validate routine monitoring results.

Hurdles in accessing new technologies

Because immunizations are given to millions of healthy children, any new technology to be used in immunization is subject to a very high degree of testing to assure safety and efficacy. Therefore, new product development is lengthy and difficult. There are four major hurdles for any new technology to overcome before it can be recommended by WHO for incorporation into immunization programmes and provided through UNICEF or WHO procurement mechanisms:

1. In the case of vaccines or vaccine delivery devices, the product and its manufacturing process must satisfy national regulatory agency requirements for safety and efficacy.
2. In the case of vaccines or vaccine delivery devices, the national regulatory agency in the country of production must meet WHO assessment standards.
3. The product must be cost effectiveness in comparison with alternatives.
4. There must be evidence of significant disease burden (in the absence of immunization) in the target population to justify a new vaccine introduction, or there should be evidence that the technology solves a serious operational problem.

Even when all these criteria are met, a problem may evolve on post-licensure trial that convinces a manufacturer, a national immunization programme or a national regulatory authority to withdraw the product rather than risk even a very low level of adverse effects[1].

[1] This occurred recently in the case of a vaccine against rotavirus which caused a very low incidence of potentially fatal but treatable adverse effect. The manufacturer voluntarily withdrew the product and debate continues over whether the vaccine should still have been offered for use in developing countries where many children die for lack of vaccine.

7. Degree of dependence on health system and health system impacts of scale up

The three elements affecting immunization services are immunization operations, the health system, and the external environment. The following table shows the elements of immunization operations, the health system and the external environment that have an impact on scaling up immunization and that in turn would be affected by a scaling up effort.

Table 7: Health system, immunization operations and external elements affecting immunization services and upon which scaling up immunization will have an impact

1	Immunization operations *The activities that promote the organization and implementation of immunizations*	Immunization service delivery the strategies and activities involved in giving vaccinations Disease surveillance measurement of disease incidence record keeping, and reporting laboratory testing Logistics delivery of vaccines and other equipment to the place of use transport cold chain waste disposal Vaccine supply and quality forecasting vaccine needs procurement of vaccines vaccine utilization monitoring Advocacy and communications immunization education and promotion social mobilization advocacy
2	Health system *The activities that primarily promote, restore, or maintain health*	Stewardship policy making, regulation, standard setting. planning collecting and using information coordination with sectors and stakeholders outside the health system, and with development partners evaluation Service provision infrastructure drug supply Resource generation training and education working conditions Financing budgeting, identifying funding sources, collecting revenues, tracking expenditures. cross-cutting sues ~ *integration of services* ~ *decentralisation* public/private mix (provision and financing)
3	External environment *refers to any elements outside the health system that have an impact on services*	Forces and trends – Geographic political, e.g. economic, e.g. ~ macro-economic reforms social, e.g. ~ decentralisation ~ self-sufficiency technological. Expectations & needs of stakeholders the public politicians development partners competitors and collaborators, e.g. ~ private practitioners ~ the education sector

Targeted disease control impact on the delivery of other health services

In 1997, Taylor, Cutts and Taylor (54) made the assertion that polio eradication is not a high priority for developing countries, doesn't necessarily contribute to health system development, and is mainly to the financial benefit of industrialised countries. A rebuttal appeared in the same edition of the American Journal of Public Health by Sutter and Cochi (53). The war of words continued in that journal until July 1998 (see references 35 and 54) and the impacts of targeted disease control programmes such as polio eradication on the capacity to deliver other health services have been hotly debated ever since. Clearly this is a controversial issues, but recent evidence has shed more light on the real impacts of targeted programmes, as elaborated below. Table 8 (see reference 41) lays out the potential opportunities and threats posed by eradication and elimination activities.

Table 8: Key elements of health systems and examples of the opportunities and threats presented by the implementation of disease eradication or elimination programmes (Source: see reference 41)

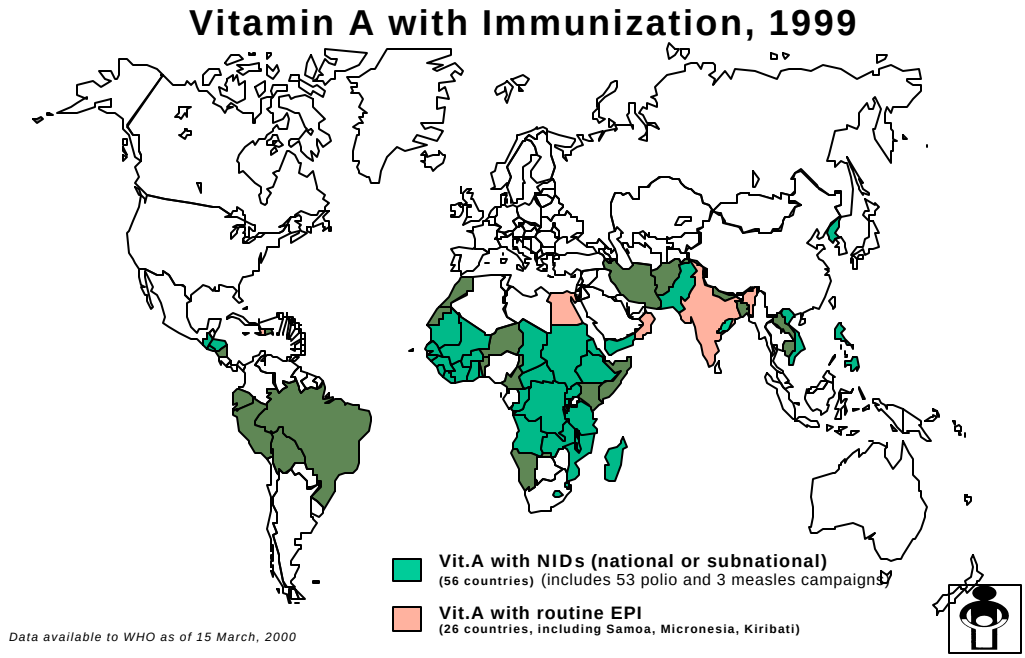
	Examples of the impact of eradication/elimination activities	
Health system element	Potential opportunities	Potential threats
Health policy regulatory and strategic planning function	Policy: strengthening of national health policy development	Strategic planning: compromising local decision-making
	Stakeholders: increased transparency and broadened commitment to health	Imposition of external priorities
Institutional arrangements	Management systems: systematic introduction of targets and indicators	Management process: risk of establishing parallel structures
	Decentralisation: mechanisms for delegating authority to districts	
Financial resources: mobilisation and use	Resource mobilisation: improved advocacy and mobilisation mechanisms	Fund-raising and resource allocation: diversion of scarce financial resources
	Private sector resources: expanded role of private sector in public health	
Human resources: number, mix and quality	Incentive schemes: introduction of performance-based incentive models	Human resources: diversion of personnel as opposed to increasing productivity
	Training: coordination of strong training component with national plans	Uncoordinated in-service training
Service management and delivery	Access to services: increased access and utilization of health services	Service delivery: disruption of routine service delivery
	Surveillance: establishing surveillance as a key tool in disease control	

Field studies in Tanzania, Nepal and Lao People's Democratic Republic examined the impact of polio eradication activities on major health system areas, the policy context, organisational capacity, service delivery, training and supervision and social mobilisation. Special attention was given to investigating impacts on infrastructure, finance and human see reference 43). Organisational capacity was affected by interruptions due to polio activities, but was positively affected by the associated training, for example in planning. The initiative brought with it significant investment in the cold chain (refrigerators, cold rooms). Financing was found to be largely additional and money was not drained from the routine immunization programme or other health sector budgets for polio. This was also found to be true in a study of the impact of polio eradication on the financing of routine immunization in Bangladesh,
Cote d'Ivoire and Morocco (see reference 36).

It was found that polio eradication has the biggest positive benefit where it is building new capacity where none existed. Where a peripheral health service delivery system exists and is functional, polio eradication activities have more potential to be disruptive to training or supervision schedules (see reference 43). However, most of these negative impacts could be averted through coordinated planning. Rarely, competing schedules for events that can only be held in one season may create competition between initiatives for time. Similarly, positive impacts could be sought through establishing clear objectives to strengthen peripheral service delivery capacity through the polio eradication initiative.

For example, political contacts made between health service staff and political figures for national immunization day promotion should be exploited for other health aims.

A meeting at the World Health Organization in December of 1999 reviewed the results of these and other studies of polio eradication impacts. The meeting participants concluded that although there were no grave negative impacts, there were significant missed opportunities for positive synergies. These could be brought about by better planning linked to an explicit monitoring framework including specific targets and objectives. It was recommended that indicators and an oversight committee be established to insure improvement in country level and global performance in this critical area (see reference 12).



Text Box: Impediments to scaling up measles control in West and Central Africa

In a follow up study of measles control activities in West and Central Africa, November 2000, six impediments to smooth planning and implementation of the programme were identified.

1. Decreasing or stagnant routine coverage in the context of poor or still inadequate health systems.

2. Although the surveillance system infrastructure seems to be good in many countries, the aggregated data requested at the central level and invited from different projects or programmes means that trend analysis (age vaccination status of cases) has only a limited validity and there is little integration.

3. More time and greater precision is called for in planning measles mass campaigns, but also more reliable epidemiological data is required to guide implementation and evaluation. More countries (such as Burkina Faso, Cameroon and Mali) are now able to provide such data.

4. In many countries vitamin A supplementation is still not undertaken during routine vaccination. Key indicators to assess vitamin A supplementation efforts and their impact must be identified and tested at the national and district levels.

5. Even when data on case management for measles are available, they tend to be of poor quality. The Polio Eradication Initiative needs to liaise with Integrated Management of Childhood Illness (IMCI) to experiment with case-management algorithms and assess their impact.

6. These problems stem directly from poor management at all levels, the lack of resources and the absence of strategies for effective sustainability.

Text box: Immunization and health sector reform

Immunization is becoming less of a "vertical" programme and the delivery of immunization is more than ever integrated with the delivery of other health services. There are a number of reasons for this.

Firstly, health systems are changing. Health reforms mean that the health systems in which immunization services operate are changing, with significant changes in the health system structure, the location of authority and responsibility, and the mix of public and private participation.

Secondly, the environment health systems operate in is changing. Health sector reforms are often a result of a changing external environment related to things like demographic changes ('health in transition'), other epidemiological changes, changes in the macro-economic situations and policies, and the changing role of the public sector.

Thirdly, new vaccines and technologies are available. As new vaccines and technologies are introduced, it becomes more important to assess the readiness of existing services to introduce and sustain them.

Fourthly, disease control goals must be met. Polio eradication, neonatal tetanus elimination, yellow fever and measles control goals need new strategies, or improvements to old strategies.

This means one must assess the capacity of existing health systems to determine if new disease control strategies can be implemented.

However experience with health sector reform to date has shown that some elements of immunization services should remain centralised even in a reformed system. These are the formulation of national policies, standards and guidelines, vaccine procurement, national level monitoring, surveillance and reporting, and operational research on topics such as optimal outreach strategies.

8. Strategies for scaling up immunization services

Scaling up immunization requires:

assuring vaccine supply,

strengthening routine immunization services, including surveillance and monitoring, particularly to under-serviced populations

accelerating ongoing disease control efforts

accelerating the introduction of new vaccines and

building new partnerships

1. Assuring vaccine supply

Strategies to expand supply include determining potential capacity through meetings with manufacturers, compiling a database of global production capacity for strategic vaccines like oral polio vaccine, and for technical processes like freeze drying which is required for measles vaccine. Enhancing production capacity involves determining the potential of contract manufacturers, providing market-based incentives, subsidies and support to research and development, and promoting viable vaccine production in developing countries.

One of the Global Fund for Children's Vaccines strategies (GFCV) is to send a signal to industry showing that there is effective demand for vaccines for the poor. New procurements strategies guiding purchases by the GFCV are aimed at obtaining a fair, affordable price for the poorest countries while maintaining a profitable market to encourage further investment in vaccine R&D and production capacity (see reference 59).

Scaling up immunization to meet the needs of the poor will require more of this kind of financial incentive for new vaccine development as well as for maintaining and increasing the production capacity of currently available vaccines. One option is to step-up partnerships for sharing technology with manufacturers in developing countries where there is a fully functional national regulatory agency that can ensure quality and safety.

Technology transfer raises questions of intellectual property protection. A significant amount of "know how" is needed in order to produce a vaccine. This know-how is not communicated through process or product patents. For this reason, compulsory licensing is unlikely to be an effective means of transferring vaccine production capacity. Moreover, there is convincing evidence that patent protection does not represent one of the most significant barriers to vaccine supply (Mercer Management Consulting, 1995; CVI Secretariat Survey, 1997, as quoted by Roy Widdus, Global Forum for Health Research).

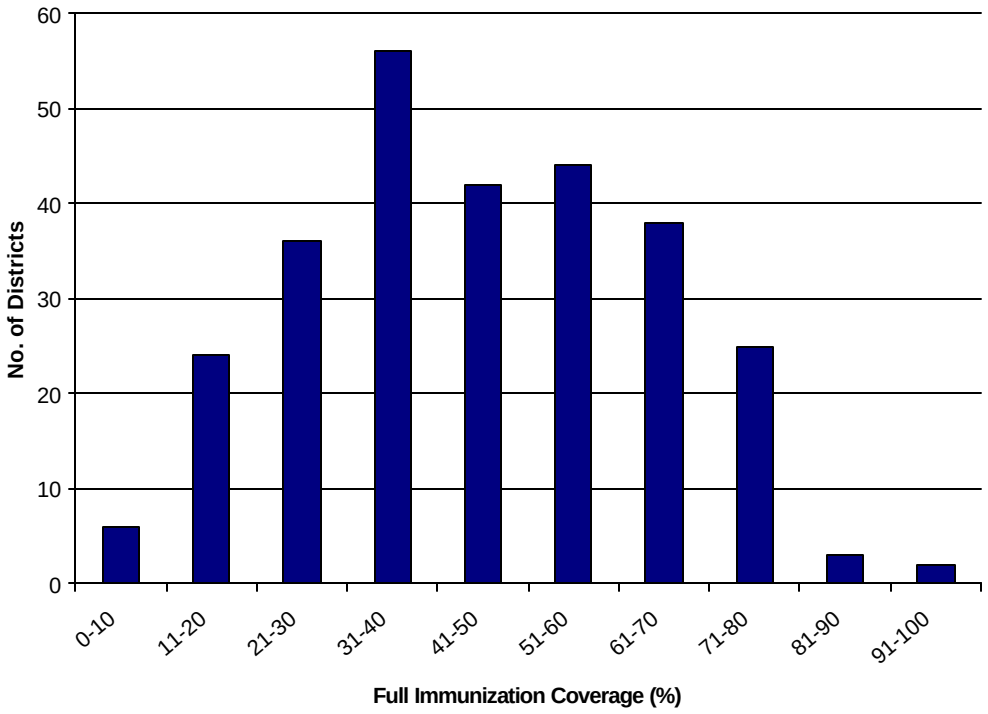
Vaccine quality must be ensured through strengthening national regulatory authorities, continuing to provide a mechanism for pre-qualifying products for purchase by UN procurement agencies, providing training in procurement to those responsible in developing countries, estimating demand in order to send a signal to manufacturers, and technical assistance to national vaccine supply planning.

2. Strengthening immunization services

The global goal for immunization is to achieve 80% coverage in all districts in 80% of all countries by 2005.

Key constraints faced by national immunization programmes are 1) lack of access to services, 2) poor planning, management and supervision and 3) low health staff performance. Reaching every child with immunization requires a considerable expansion of current immunization delivery capacity as well as better quality health statistical data for surveillance and monitoring. Currently there is a considerable heterogeneity among districts in terms of immunization coverage (see Figure 5 below.)

Figure 5: Histogram of District Level Immunization Coverage in 8 Poorly Performing States in India, 1999 RCH Household Survey



The large disparity among districts suggests that there is a large scope for improving coverage even when resources are constrained. It also suggests that management, motivation and accountability are critically important aspects of improving coverage. The same pattern is evident between countries. Malawi for instance has much higher coverage than Kenya. So, similar prospects apply.

Outreach

Immunization already reaches nearly 80% of the world's children. However, the children who are not immunized are by definition among the world's most ill served by social services. The imperative to expand access can be leveraged and strengthened by combining immunization with other essential health services and sustainable livelihood interventions. The Sustainable Outreach Services package comprises periodic visits to remote communities to deliver a basket of interventions chosen in consultation with those communities. This basket may contain micronutrient supplementation, pre-natal care, and curative therapy against parasites and veterinary interventions as well as immunization.

National immunization days for polio eradication often combine polio vaccination with the administration of vitamin A to promote child survival and prevent blindness. Immunization is also a key component of the holistic approach for Integrated Management of Childhood Illness (IMCI) which promotes complete care of the child at every contact he or she has with the health system.

Outreach must include new strategies to increase utilisation of existing services in population that do not use these. Advocacy and community involvement are key strategies to enhance the coverage in these sections of society, notably the urban slum dwellers. NGO's play an important role in these communities and their activities should be strengthened and expanded.

Campaigns

Accelerating ongoing disease control programmes often require a campaign strategy to reach the last child.

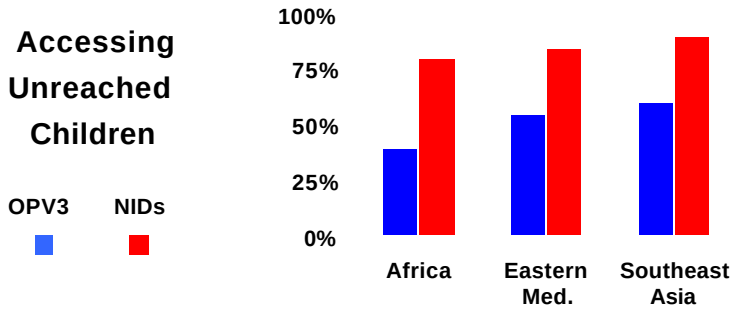
Campaigns, including national immunization days and sub-national immunization days are an important tool in bringing immunization coverage levels up in a short time. Campaigns are a key pillar of the polio eradication initiative and they were used extensively, along with routine immunization, to reach universal immunization coverage targets in the 1980s. They are also a key strategy to achieve the goal of reducing measles mortality by 50 by 2005 and to eliminate maternal and neonatal tetanus by 2005.

Campaigns are extremely effective at reaching the unreached. For example, in China two national immunization days held a week apart in 1993 resulted in the immunization of 83 million children and contributed to bringing the number of polio cases down from 5,000 in 1990 to zero in 1995 (see reference 65). Coordinated immunization days in the Middle East, Caucasus, and Central Asian Republics (MECACAR) and separately in West Africa (WACAR) have resulted in epidemiological and advocacy advantages offered by immunizing simultaneously on both sides of national borders.

India's polio eradication effort is a stunning example, with over a hundred and forty million children vaccinated in one day resulting in dramatic decreases in polio incidence, even in the poorest states. West Africa's coordinated immunization days in 2000 were the biggest peacetime event ever held in Africa. Figure 6 below illustrates the number of children reached through routine immunization with three doses of oral polio vaccine (OPV3) and through polio immunization campaigns called national immunization days (NIDs).

Reaching the unreached is a constant challenge. Initiatives such as polio eradication have taken extreme measures to reach every child. Cease-fires have been negotiated by the United Nations secretary-general to allow the vaccination of children. Outreach programmes are delivering vaccine on the backs of camels and in dugout canoes. Vaccine-preventable disease surveillance programmes air lift samples out of war zones to neighbouring countries for laboratory analysis.

Figure 6 Accessing unreached children through national immunization days
(Source: Polio Eradication Initiative, Department of Vaccines and Biologicals, WHO, 2000).



Campaigns can galvanise a community, promote solidarity, give health workers a sense of achievement and a “can do” attitude, attract new financial and in-kind resources to immunization and breed a culture of prevention. Campaigns can also be the cutting edge of health services, providing not only immunization but also other interventions such as micronutrient supplementation to communities that are otherwise completely unserved with basic social services. In 1999, adding vitamin A supplementation to polio national immunization days is estimated to have saved 242,000 lives.

However, campaigns are difficult and time-consuming to organise, they may divert resources from routine health services. They can also tend to be top-down and perceived as imposed from outside the system. National immunization days constitute a tremendous outlay of energy from all participants and can be exhausting for immunization programme staff. Campaigns result in a one-time dip in disease incidence rates, which can only be maintained through intensified routine immunization or regular campaigns.

In summary, campaigns are a powerful, effective device that can be used to rapidly increase coverage and promote equity. However, they are difficult and expensive, can be perceived as top-down or imposed by outside interests, and the results are not sustainable except through further campaigns or upgraded routine services.

Text box: Lessons learned from expanding immunization and from the polio eradication initiative

The experience gained from scaling up immunization from 1974 to 1990, from eradicating smallpox and from the ongoing efforts to establish GAVI and to eradicate see reference 10) can be applied to scaling up other interventions. In summary, the ten most important lessons to be learned are the following:

- Win over a high level devoted champion who will secure political support from decision-makers (eg: James Grant of UNICEF).
- Form broad coalitions in support of scaling up (Eg: Task Force for Child Survival, GAVI). Make sure ALL key stakeholders are represented. Explicitly foster alliances between unlikely partners such as industry and the public sector.
- Devote substantial resources to development of training materials, training, and capacity building, with an emphasis on supervision. Use training for one technique or programme to refresh knowledge of others where appropriate.
- Provide operational support and advocacy at all levels and combine efforts with other programmes where feasible.
- Build in strong surveillance and reporting systems. Combine surveillance and routine supervisory visits with those of other programmes or disease control initiatives where appropriate.
- Ensure rational financial planning and full use of all proven, appropriate financial mechanisms. Use financial incentives to support rational decision-making, sound management, coordination (eg: inter-agency co-ordinating committee) and as seeds to generate sustainable financial plans (eg: GFCV).
- Set realistic targets and hold people accountable for meeting them.
- Make specific plans to ensure that the initiative will contribute to health system development.
- Use targeted programmes (eg: campaigns and outreach) to raise coverage quickly, reach the unreached and increase equity, but build routine services for sustainability. Use the high visibility of campaigns to troubleshoot and solve administrative and technical bottlenecks that affect routine services as well.
- Be sensitive to the impact of the initiative on the health system and safeguard against negative impacts on other programmes and opportunity costs of diverting resources. Plan ahead to minimize negative impacts and share plans early with other health programmes.

Planning, management, supervision and staff performance.

Scaling – up immunizations require careful problem analysis and planning of activities.
A common assessment tool has been developed by WHO which is currently recommended for all developing countries. The assessment tool details the key functions of the immunization service as well as those of essential health system components that contribute to the delivery of immunization, surveillance and monitoring (see reference 12).

The assessment leads to multi-year planning using a systematic approach. Multi-year plans now form a general basis for national immunization programmes and are a prerequisite for applications to the GFCV, as is the assessment. This ensures a broad application of these tools in the poorest countries since the majority of these have – or intend to – apply for financial support from the Fund.

Microplanning at the district level is an essential element in translating multi-year plans into activities at the local level. It is an essential component of all accelerated disease control initiatives and in expanding outreach or conducting campaigns.

Supervision of activities at and beyond the district level requires skills as well as means. Providing transport and developing logistics management capacity is essential.

The performance of health staff partly depends upon efficient supervision but many health systems are unable to support – and pay – their health staff properly. Improvement in this area is therefore often contingent upon civil service and health systems reforms. However, progress could be made by testing and introducing performance based district health systems mirroring a model introduced by GAVI where financial support is depending upon outcome performance measured in terms of increased coverage.

The improvement in the performance of health staff at all levels is recognised as key. Capacity building is therefore among the highest priorities in strengthening immunization services aiming at both national management, district leadership and service providers. Capacity building must go beyond the health system at large and extend into communities to ensure that advocacy and community involvement become integrated strategies in service delivery by both government and NGO services.

A sub-group of members from the GAVI Task Forces (Advocacy, Country Coordination and Financing) have developed a capacity building strategy aimed at significantly enhancing the ability of national immunization programmes (NIPs) to increase and maintain access to immunization services, decrease the burden of vaccine-preventable diseases, and expand the use of safe and cost-effective vaccines. Special attention is given to safety and quality; consistency with national health sector goals; identifying funding shortfalls; and progressing towards self-reliance to identify and generate resources. Also essential is the systematic management of knowledge to retain work experiences and disseminate expertise throughout the organization.

This strategy describes a conceptual framework wherin the health systems functions as defined in the World Health Report 2000 (see reference 63) of stewardship, creating resources and financing are seen to bolster the operations of the immunization programme. More specifically, Management (stewardship), Strengthening Human and Institutional Resources (creating resources) and Financing are outlined as the foundation upon which the five operational components of a service delivery programme (service delivery, supply and quality, logistics, surveillance and advocacy & communications) are built. Based on universally recognised management principles, a five step approach has been defined for capacity building in countries: benchmarking, assessment, planning, implementation and monitoring and evaluation. The first step will be to pilot this approach in several countries..

3. Accelerated disease control

Three global goals have been defined:

- The certification of polio eradication by 2005
- The elimination of maternal and neonatal tetanus (MNT) by 2000
- Reduction of measles mortality by 50% by 2005

Polio eradication is well underway. Cases have been reduced to a minimum since the eradication goal was set in 1988. The eradication strategies will leave behind an infrastructure upon which scaling up can be based. It includes a large number of immunization staff trained in appropriate applications of strategies. Accelerated disease control activities are guided by effective case-based surveillance and the polio initiative has established a highly effective surveillance infrastructure with a global laboratory network that can be utilised by other disease control

initiatives. It is expected that transmission can be stopped within a few years and the polio infrastructure can thus serve a broader immunization agenda with a very short time horizon. The largest gain in mortality reduction in the short-term can be achieved by the focusing on measles control. The current goal is to prevent an additional app. 450.000 deaths annually by 2005. This will require campaign strategies to ensure that every child is immunized against measles twice. This is the "best buy" available among current vaccines. The global measles strategic plan estimates that this will require app. 900 million USD. Accelerated measles control is an intervention, using available technology and infrastructure that can contribute the largest gain in reduction of child mortality and morbidity in the short-term.

Elimination of maternal and neo-natal tetanus will lead to an additional app. 300.000 deaths prevented when targeting high-risk areas. Both polio eradication activities and routine immunization can be combined with delivery of vitamin A in deficient childhood populations it is estimated that this lead to a prevention of 240.000 deaths in year 2000. An expansion of vitA delivery to include it in all routine immunizations would greatly enhance the impact of the intervention.

4. Accelerated Vaccine Introduction

Milestones established are:

- By 2002 80% of countries with adequate delivery systems will introduce HepB vaccine and by 20007 all countries.

- By 2005 80% of the poorest countries with high disease burden and adequate delivery systems will have introduced Hib vaccine.

The strategy for universal childhood immunization launched in the late 70s aimed at vaccinating all the world's children with six vaccines: polio, measles, diphtheria, pertussis, tetanus and BCG (see historical background section in annex). Although this effort was largely successful, vaccines introduced since then have not been adopted at an acceptable rate in developing countries. For example, by year 2000 most of sub-Saharan Africa and the Newly Independent States of the former Soviet Union had not introduced Hepatitis B vaccine despite its use for more than a decade in the Americas and Europe and a long-standing WHO recommendation for its inclusion in routine EPI worldwide.

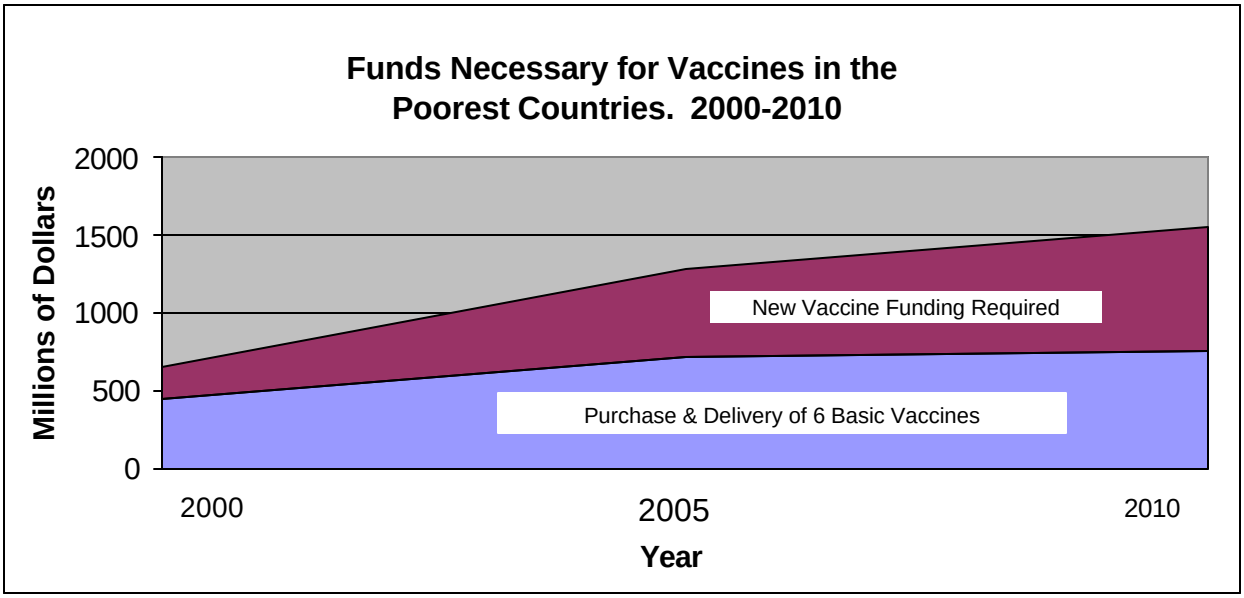
The slow uptake of these newer vaccines is due to several factors and the strategy to accelerate uptake reflects this. The strategy that is being adopted involves ensuring a high quality, global supply of new vaccines, decreasing the financial barriers to the introduction of new vaccines, developing tools, materials and methods to support decision making on immunization, and the delivery of technical resources and training to support new vaccine introduction.
An example of a decision-making tool is provided in the text box on introducing a new vaccine.

The Global Fund for Children's Vaccines (GFCV) has a subaccount dedicated to financing the introduction of new vaccines in low-income countries. This strategy involves financing the first few years of vaccine supply and providing technical support to assure long term sustainable financing of the newly introduced vaccines.

Figure 7 below shows the financing needed to purchase new and underused vaccines such as hepatitis B and Hib in countries with GNP per capita under US$1000 over a ten-year period. This does not include the cost of service delivery.

Figure 7: Funds necessary for vaccines in the poorest countries

(Source: GAVI, 1999).



Text box: Introducing a new vaccine

Table 9 Factors affecting inclusion of a vaccine in a national EPI programme (Source: see references 16 and 17)

Priority of the disease	Morbidity and mortality from the disease Age-specific attack rates Availability of other interventions for its control
Characteristics of the vaccine	Immunogenicity Efficacy Duration of immunity Interaction with other antigens Safety/adverse reactions Dose Route of administration Storage Thermostability Potential for combination with other antigens
Programmatic feasibility	Ability to reach the target population before the age of maximum risk Potential contact points with target population (health services, schools, etc.) Cost of alternative strategies
Vaccine supply	Global production adequate? Technology transfer to developing countries possible? Affordability

5. Partnerships

The polio eradication initiative is led by a strong and successful partnership with WHO, UNICEF; ROTARY and CDC, Atlanta as core partners. A number of other partners have joined hands especially in terms of funding. The partnership has proved that resource mobilisation and advocacy can generate new funds and political commitment beyond all expectations. The polio initiative has spearheaded a unique collaborative mechanism at the country level, the Inter-Agency Coordination Committees (ICC). The ICC gets partners together around national planning and resource mobilisation. It prevents duplication of efforts and strives to ensure longer-term funding and sustainability of polio activities. The ICC mechanism is currently being expanded to a broad immunization agenda, through the GFCV application process.

A measles alliance has recently been formed which aims at enhancing advocacy, political commitment and funding for measles control. The alliance is based on a global strategic plan endorsed by all partners.

In order to address the slowdown in progress towards universal coverage a Global Alliance for Vaccines and Immunization (GAVI) has been formed with a broad membership. GAVI's high level board met for the first time in 1999. Its mission: “to save children’s lives and protect people’s health through the widespread use of vaccines, with a particular emphasis on developing countries.” GAVI provides a long-range strategic focus for its members and ensures that a strong voice can advocate for immunization in dialogues and debates on health sector reform and in broader development discussions, for example, the mechanisms of debt relief.

Strategies to expand coverage in terms of both the number of children vaccinated and the number of antigens given to each child are being developed through this alliance in several task forces established by the Alliance. Task forces chaired by partner agencies and representatives of key constituencies have been convened on finance, country coordination including capacity building, advocacy and research and development. These task forces bring together partners to coordinate work plans and push forward action towards reaching GAVI milestones. GAVI is not an organisation in itself but an alliance that strives to enhance the efforts by each of the alliance partners.

At the regional level a new coordination mechanism has emerged, the Regional working groups. This group brings together partners that operate through regional structures, notably WHO and UNICEF. They help coordinate technical support to countries, enhances advocacy and streamline policies and strategies so that they are adapted to regional requirements.

GAVI has attracted substantial new resources to catalyse action towards its goals through the Global Fund for New Vaccines (GFCV). The GFCV, supported by generous private and public contributions, is an independent mechanism that disburses financing according to recommendations from the GAVI Board. The GFCV controls annual cash flows measuring in the hundreds of millions of dollars. These funds are used strategically to provide incentives for programme assessment, long-range planning, partner coordination at country level, introduction of new and under-used vaccines, immunization safety, and improvement of immunization services as measured by increases in the number of children immunized. An application to GFCV requires that countries recently have assessed their immunization services, that they have developed multi-year plans and that they have a functioning ICC.

There are thus structures in place at global, regional and national level that effectively can support major scaling-up operations.

Conclusions: scaling up, milestones, and strategies

A number of global immunization goals have been set for the next decade.

- The World Health Assembly has set: The certification of polio eradication for 2005.

- Major partners have agreed on a global reduction of measles deaths by 50 % in 2005 and x % by 2010. This goal is expected to be endorsed by member states at the World Health Assembly in 2002.

- The UN Special session for Children in September 2001 is expected to endorse a target of 80% coverage in all countries.

This will underpin the milestones for immunization that have been agreed on by the partners of the Global Alliance for Vaccines and Immunization which are as follows:

- By 2002, 80% of countries with adequate delivery system will introduce Hepatitis B vaccine, and by 2007, all countries will have introduced the vaccine.

- By 2005, 80% of developing countries will have routine immunization coverage of at least 80% in all districts. (All countries will reach 80% coverage in all districts by 2015.)

- By 2005, 50% of poorest countries with high burden of disease and adequate delivery systems will have introduced Hib vaccine.

- By 2005, the vaccine efficacy and burden of disease will be known for all regions for rotavirus and pneumococcal vaccines, and mechanisms identified to make these vaccines available to the poorest countries.

According to calculations by the GAVI (1999) a concerted effort to introduce new vaccines to combat acute respiratory infection, (Hib and pneumococcal conjugate vaccines), could reduce associated mortality by 10% by year 2005, saving 300,000 lives a year. By year 2010, 800,000 lives per year could be saved using these vaccines. By 2020, 1.5 million lives could be saved every year through the use of Hib and pneumococcal vaccines. Introducing new vaccines against diarrhea, (rotavirus and shigella) would reduce mortality in children from 2.5 million deaths a year by 250,000 a year by 2005. Six hundred thousand lives per year could be saved by 2010 and 900,000 lives saved per year by 2010. The impact of HepB immunization would not been seen within the next decade as the benefits of this vaccine accrue in adulthood.

Implementation of the global measles plan would save approximately 450,000 lives per year by 2005 and close to 800.000 by 2010. MNT elimination would add app. 300.000 lives saved (incl. mothers) to this figure.

All told, if GAVI milestones are reached and further expanded beyond 2005, well over 2.5 million lives per year could be saved by 2010.

In order to achieve these targets, scaling up immunizations by increasing coverage through strengthened routine services, outreach and campaigns; accelerating ongoing disease control initiatives especially measles control, accelerating introduction of new and underused vaccines and by advocacy and political commitment. Better management of immunization services and capacity building is key as is decreasing financial barriers.

Strategies for accelerated disease control must be expanded against high-burden diseases with the application of lessons learned through polio eradication initiatives and by maintaining the infrastructure developed by the initiative for a broader immunization agenda.

The development of vaccines against major diseases must be accelerated especially focusing on those products that are closest to licensing. A combination of push and pull strategies is needed to ensure this goal.

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Annex I: What are vaccines and how do they work?

What are vaccines?

Vaccines are biological products designed to imitate infection by a particular disease-causing organism in order to trick the body into mounting a defence. The body builds a specific defence in response and this "practice" helps the body to mount a more effective defence against the real disease in future.

Some vaccines contain live viruses, which are weakened (attenuated) to make them safe. Other vaccines contain inactivated or killed viruses or bacteria or inactivated forms of the toxins they produce. Still others contain only certain parts of the disease organism derived through purification or through recombinant DNA technology. In the future, vaccines may be developed that contain DNA only.

Vaccines containing live virus include measles, oral polio and yellow fever. These viruses are attenuated, but they can still multiply inside the body. This means that less material is required in the vaccine itself. Fewer vaccinations may be required to reach high levels of immunity, and the safe form of the virus may be transmitted to others so that they also become immunized. However, vaccines containing live viruses may cause more severe adverse effects.

Vaccines containing killed viruses or bacteria or sub-components of these organisms may be safer but also somewhat less effective than live vaccines. This is because a small amount of live

vaccine can multiply in the body to produce a significant effect and the introduction of a live vaccine can follow the natural infection pathway. Killed vaccines require more material per vaccination, and they may require a longer series of vaccinations in order to reach high levels of immunity. Vaccines containing purified sub-components of disease-causing organisms can be designed to cause fewer adverse events than whole cell versions, but they also tend to be more difficult to produce. That can make them more expensive.

Most vaccines are sensitive to heat and have to be kept under controlled temperature conditions. Since they are given to large numbers of children in order to prevent disease, vaccine quality and immunization safety are extremely important and have to be safeguarded at every stage of the immunization process.

How vaccines work:

From the moment of birth, every human body is constantly under attack by countless foreign organisms and substances. To defend itself, the body has a sophisticated system of defence called the immune system. Some parts of this system are active immediately from birth, whereas others require an activation step or "priming" that includes exposure to an invading agent. One of the immune system's front lines of defence comprises specialised white blood cells and proteins, including antibodies, which are produced by some of those cells. These cells and antibodies confer specific immunity against particular invading agents. This specific defence requires priming by exposure to an infecting agent. The infecting agent can be mimicked with a vaccine. This safe mimicry of infection and subsequent priming of the immune system to mount a defence against a disease-causing organism is the process of vaccination.

Following vaccination, the immune system responds by mounting a defence against the invading substance. The defence entails multiplying the number of the body's disease fighting cells and antibodies which match the infecting particles. The first time the immune system encounters an attacker, the defence response takes about 10 days to turn fully on. This recruitment of a precisely matched defence "primes" the immune system so that when a real infection by that organism occurs, the immune system recognises and remembers its attacker and calls into action the specific matching defence team that has been bolstered through immunization. The second time the immune system meets the attacker; the response is faster, stronger, and last longer. Subsequent exposures of the immune system to the same attacker further strengthen and quicken the response. The body's reaction to the vaccine in mounting a specific immune response refered to as seroconversion as antibodies appear in the blood serum. To reach high levels of immunity, more than one vaccination with the same vaccine may be necessary.

The elements of vaccines that induce immune reactions are called antigens. A disease organism such as a virus or bacterium may have several parts that can cause an immune reaction. Some antigens provoke stronger immune reactions than others do. This difference between antigens affects the efficacy of the vaccines that contain them.

Typically, big bulky antigens, such as repeating polysaccharide (sugar) subunits, induce only weak protection against future infection and this protective effect is particularly poor in people aged less than two years. Antigens of this type are called T-independent antigens because they don't require the action of specialised white blood cells called T cells in order to stimulate

multiplication of specific antigen-neutralising antibodies. To make these antigens work better in vaccines, they are mixed with other substances that stimulate immune responses. These substances are called adjuvants and include such things as aluminum salt. However, even with adjuvants, T-independent antigens don't usually make good vaccines for infants.

By contrast, some antigens, particularly proteins, must first interact with T cells before antibodies against them can multiply. These are called T-dependent antigens, and among there are some that can induce strong immunity in infants. In order to make T-independent antigens work well in infants, polysaccharide antigens can be linked to protein antigens. This linking process is called conjugation. Typical proteins used for conjugation include tetanus toxoid and diphtheria toxoid. These are inactivated forms of the tetanus and diphtheria toxins and they are also used by themselves in vaccines against tetanus and diphtheria.

Annex II: Using immunization to eliminate or eradicate diseases

(Sources: see references 61 and 62.)

The last case of smallpox was diagnosed in 1978. Since then the world has been free of the disease. Polio is the next disease to be eradicated through immunization. Other goals set by WHO and its partners include the elimination of measles in the Americas and of neonatal tetanus worldwide.

Elimination of a disease is the reduction to zero of the incidence of a specific disease in a defined geographical area as a result of deliberate efforts. Elimination of a disease does not mean that the risk of the disease is zero, so continued interventions are required to prevent the re-emergence of the disease.

Eradication of a disease is the permanent reduction to zero of world-wide incidence of infection caused by a specific agent as a result of deliberate efforts. As a result of eradication, no interventions are needed for further prevention of the disease. One example of disease eradication is smallpox.

Diseases can be eliminated as public health problems through strong control measures. For example, neonatal tetanus can be eliminated as a public health problem through immunization of pregnant women and mothers. However, because tetanus spores are present in dirt and are carried by animals, tetanus cannot be eradicated through immunization programmes.

Diseases that can be eradicated through immunization are those that are transmitted only through human carriers, and for which there is no environmental reservoir. Furthermore, the vaccine must prevent infection with the agent, not just provide protection against the negative effects of infection. For example, diphtheria vaccine provides protection against the toxic form of diphtheria but does not prevent people from carrying the diphtheria organism. Yellow fever vaccine is a live virus vaccine that confers long term protection, but there is an environmental reservoir of the disease in monkeys, so the virus cannot be eradicated. Diseases for which there are long term carriers are also very difficult to eradicate. Eradication may be practical where immunization confers lifelong protection against the disease. This is most likely to be true in the case of live vaccines such as those against smallpox, polio and measles.

A programme of work for eradication by immunization could be the following
(based on the polio eradication strategy):

1. Use eradication to strengthen and expand routine immunization services.
2. Conduct effective and high-quality national immunization days and door-to-door ("mop up") campaigns to interrupt disease transmission.
3. Develop and sustain certification-standard surveillance and laboratory systems that can rapidly identify disease-infected areas.
4. Ensure laboratory containment of stocks of disease organism.
5. Develop a consensus strategy to stop immunization after certification of eradication.

Key strategic considerations for disease eradication by immunization are:

- Securing access to all children, including those in conflict-affected countries and areas.

- Ensuring adequate financial resources from the public and private sectors to meet needs.

- Maintaining political commitment world-wide.

Annex III: Vaccine Efficacy in epidemiological assessment

Vaccine efficacy in a population that is regularly exposed to the infecting organism can be difficult to determine. People who have antibodies against the organism may have developed them from exposure to the disease, rather than from vaccination. Certain population groups, such as those taking other medications or those infected with HIV, may react differently to the vaccine than the carefully chosen pre-licensure clinical trial subjects. Therefore, epidemiologic assessment of vaccines is of particular interest. Orenstein and his colleagues (1998 (47)) have reviewed the literature on epidemiologic assessment and the following table sets out the sources of proof of efficacy through field trials for several of the vaccines discussed in this paper according to Orenstein supplemented with some more recent sources.

Disease	References for epidemiologic assessments of associated vaccines
Measles	Ten studies (see reference 47)
	One study (see reference 17)
Diphtheria	One study reviewed in (see reference 17)
Polio	Four studies (see reference 47)
Pertussis	Twenty-six studies (see reference 47)
	Secondary source for comprehensive review of pertussis efficacy: (see reference 6)
Pneumococcal disease	Four studies (see reference 47)
Meningococcal disease	Two studies (see reference 47)
Haemophilus influenzae type b	One study (see reference 47)
Japanese encephalits	(see references 55 and 33)
Tuberculosis	Twelve studies (see reference 47)
	Four studies (see reference 17)

Annex IV: Historical backround

Historical Background: From 5% to 80% coverage with EPI

To a great extent, the scaling up of immunization occurred in the period from 1974 which witnessed the birth of the Expanded Programme on Immunization (EPI) of WHO, and 1990, the year of the World Summit for Children. Stimulated by the success of the smallpox eradication initiative, massive expansion of immunization was envisaged. During this period, coverage of the world's children with vaccination against six major childhood diseases went from less than 5% to a reported 80% (see reference 34). An estimated 3 million deaths per year are prevented through this huge effort involving a broad range of stakeholders from multinational pharmaceutical companies to governments, private donors, non-governmental Organizations, UN agencies, health workers, community level volunteers and mothers of babies. This was achieved through the establishment of a "culture of prevention" and involved massive investment in training, infrastructure and social mobilisation.

EPI strategy 1974-1990

Early EPI strategy was determined partly by experience gained through the ongoing smallpox eradication initiative as well as through a feasibility study in Ghana in 1976. The six basic EPI vaccines, BCG, measles, polio, diphtheria, pertussis and tetanus, were chosen on the basis of burden of disease and cost effectiveness.

Universal child immunization (UCI) with these six vaccines was declared as a target for 1990 by the World Health Assembly in 1977, the same year as the last case of smallpox.

James Grant, the Executive Director of UNICEF during this period, took on this mission single-mindedly and pressed world leaders to provide the necessary political commitment. Immunization coverage began to increase in the late 70s with accelerated growth in coverage occurring between 1984 and 1990.

The timeline of progress in raising coverage entailed the following steps:

1974: the successful progress towards smallpox eradication inspired the establishment of the expanded programme on immunization.

1977: A World Health Assembly resolution called for universal childhood immunization against six diseases of public health importance. That same year, work on expanding immunization involved development of an EPI operations manual, seminars on EPI for senior public health officials in all WHO regions, the first course for EPI managers from 19 countries, and the introduction of routine monitoring and EPI information systems including software for monitoring coverage, surveillance and cold chain. The following year systematic national programme reviews were initiated using joint national and international teams. Material was also developed for a cold chain and logistics training course. In 1979 a training course was developed for mid level managers. Up through the early 80s, additional materials developed on equipment, training and supervision. By 1982 over 9500 people had been trained in some aspect of EPI.

Technical advances were also made in the late 70s. For example, ice-lined refrigerators were designed for use in the “cold chain” to keep heat-sensitive vaccines like OPV stable and to avoid

freezing the frost-sensitve DPT. These refrigerators stayed cold during periods of unstable electricity supply. Kerosene refrigerators were also developed. WHO specifications were established for EPI equipment and testing laboratories were established. Information was published in Product Information Sheets. This effort was followed in the 80s by the development of special syringes which resisted breakage, and steam sterilisers for safe injections. vitamin A was considered for addition to campaigns in the late 80s, and yellow fever vaccine was recommended for addition to the basic EPI package of six vaccines in 33 African countries with high disease burden.

Political commitment continued to drive the process of expansion. In 1984: the Task Force for Child Survival was born through the efforts of Rockefeller Foundation together with WHO, UNICEF, the World Bank, UNDP (64) and representatives of developing countries, public health specialists and development experts. This Task Force coordinated enhanced support for EPI. UNICEF stepped up operational support and advocacy at all levels. The World Health Assembly in 1988 passed a resolution to eradicate polio. By 1990, virtually 80% immunization coverage was achieved, and there was a shift to an emphasis on the quality and sustainability of programmes. Continuing the political momentum was the World Summit for Children held in 1990; the largest ever gathering of heads of state. Goals were confirmed for polio eradication by 2000, neonatal tetanus elimination by 1995 and the reduction of measles mortality and morbidity by 95% and 90% respectively by 1995.

By 1994, nearly 300 national EPI programme reviews and coverage surveys had been conducted and the Americas were certified as polio-free. The early nineties saw hepatitis B recommended for incorporation into the basic EPI package worldwide and vitamin A was incorporated into

polio national immunization days in many countries. The last known case of polio in the European region was diagnosed in 1998. By the turn of the century, polio transmission was interrupted in close to 90% of countries and the Western Pacific region was certified as polio-free.

Throughout EPI expansion, operational research was ongoing to overcome epidemiological and technical obstacles to expansion, to determine the optimum immunization schedule in the developing country context, and to determine the safety of immunizations in the context of high HIV prevalence. Feedback on EPI performance and policy is provided through a variety of mechanisms. Besides the annual WHO Global Summary on Vaccine-Preventable Diseases, feedback is provided through the WHO Weekly Epidemiological Record, periodic EPI updates and annual Technet meeting reports. Global policy is set by WHO which is advised by a Strategic Advisory Group of Experts (SAGE). Progress has been phenomenal. The effect of the EPI programme has been to shift vaccine-preventable diseases out of the top 5 infectious disease killers. Had a vaccine not been developed and used against smallpox, that disease would now be killing millions of people every year.

However, a stagnation and in some cases a decrease in immunization coverage in many countries was observed in the 1990s, and the use of newer or higher price tag vaccines such as Hib, Hep B and yellow fever is still much lower than it should be. As a result of low uptake of newer, more expensive vaccines and the lack of a commercially attractive new vaccine market in the developing world, little effort has been expended on developing new vaccines against big killers like tuberculosis, malaria and HIV/AIDS. Furthermore, there are significant regional disparities in coverage levels and in the number of antigens offered through the national

immunization programmes. Some of the problem is financial, some is technical, some is political and some is managerial.
