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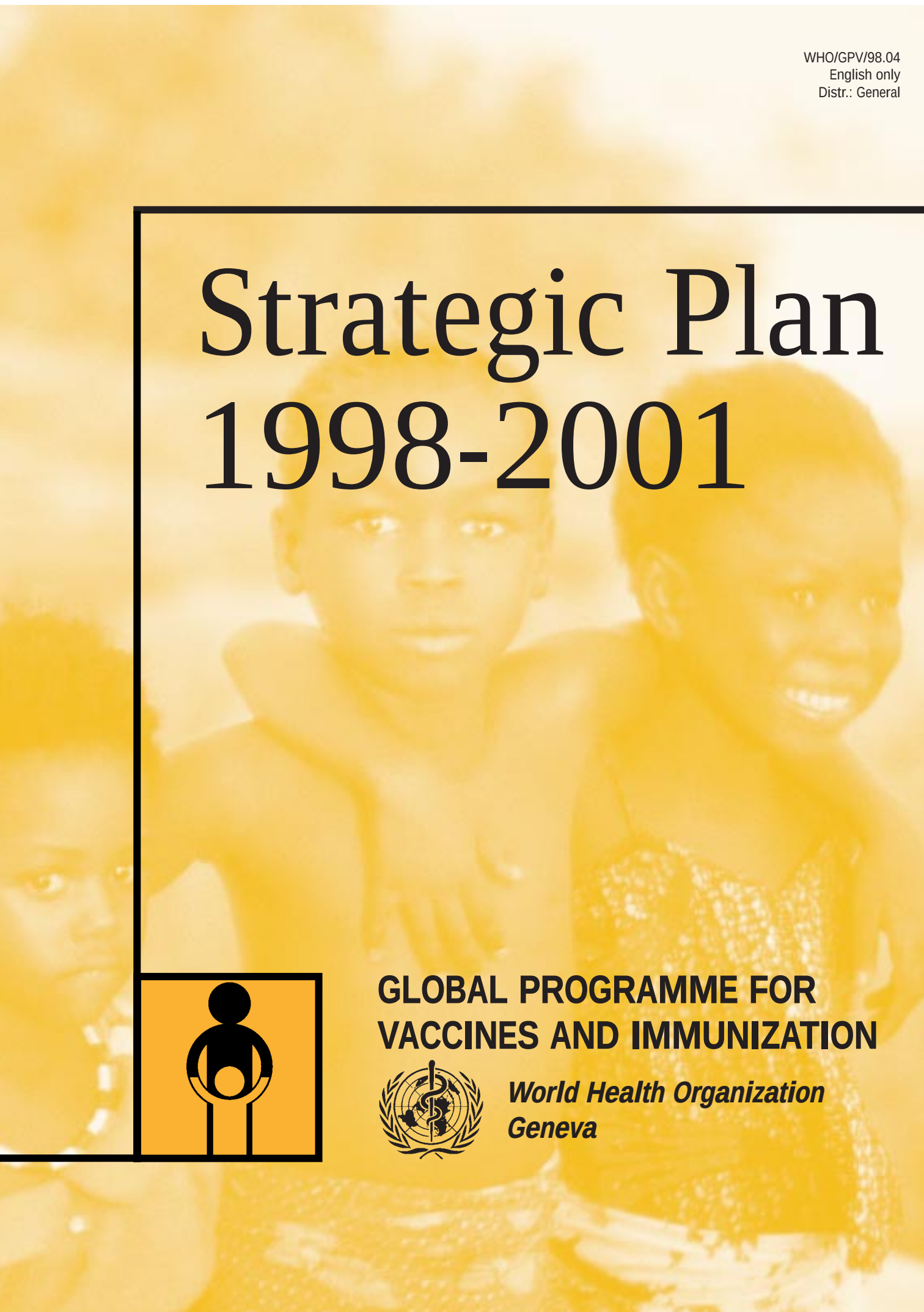

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION

World Health Organization
Geneva

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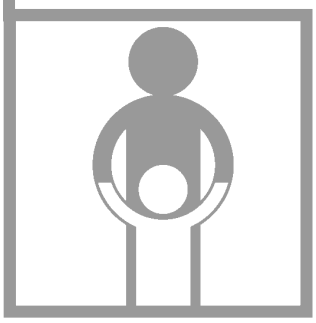

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION

World Health Organization
Geneva
1998

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ABBREVIATIONS

AEFIs	adverse events following immunization
AFP	acute flaccid paralysis
AFR	Regional Office for Africa
AMR	Regional Office for the Americas
ARI	accute respiratory infections
BCG	bacilles Calmette-Guérin (vaccine)
CCEE	Countries of Central and Eastern Europe
cDNA	complementary DNA
CFA	colonisation-factor antigens
CIGN	countries in greatest need
CILSS	Comité Inter-Etats de la Lutte contre la Sécheresse dans le Sahel
CPHA	Canadian Public Health Association
CTL	cytotoxic T lymphocytes
CVI	Children's Vaccine Initiative
DALY	disability-adjusted life year
DANIDA	Danish International Development Agency
DFID (UK)	Department for International Development and Cooperation
DHF	dengue haemorrhagic fever
DTP	diphtheria-tetanus-pertussis vaccine
ECBS	WHO Expert Committee on Biological Standardization
EHEC	enterohaemorrhagic *Escherichia coli*
EMC	Division of Emergency and other Communicable Diseases Surveillance and Control
EPI	Expanded Programme on Immunization
ETEC	enterotoxigenic *Escherichia coli*
EUR	Regional Office for Europe
EZ	Edmonston-Zagreb
FOS	Food Safety (WHO division)
GMP	good manufacturing practices
HB	hepatitis B
HBs Ag	hepatitis B surface antigen
HBV	hepatitis B vaccine
HBV3	third dose of hepatitis B vaccine
Hib	*haemophilus influenzae* type B
HIV	human immunodeficiency virus
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
IFNc	interfron c
Ig	immunoglobin (IgA*, IgD*, IgE*, IgG*, IgM*)
IPRs	intellectual property rights
JE	Japanese encephalitis
LPS	lypopolysaccharide
MECACAR	Middle East Caucasian and Central Asian Republics
MIP	meeting of interested parties
MSF	Médecins sans Frontières
NCAs	national control authorities
NCLs	national control laboratories
NIBSC	National Institute for Biologicals Standards and Controls

NIDs	national immunization days
NIH	US National Institutes of Health
NIS	newly independent states
NT	neonatal tetanus
OMNI	opportunities for micronutrient interventions
OMP	outer membrane proteins
OMV	outer membrane vesicles
OPV	oral polio vaccine
PDR	People's Democratic Republic
PIV3	parainfluenza virus type 3
PMS	postmarketing surveillance
PRP-T	polyribosyl-ribitol-phosphate-tetanus
rBS-WC	recombinant B subunit – whole cell
RIVM	Rijksinstutuut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment)
RSV	respiratory syncytial virus
SAGE	Scientific Advisory Group of Experts
SEAR	Regional Office for South-East Asia
SNIDs	sub-national immunization days
TGFb	transforming growth factor b
TNFa	tumor necrosis factor a
TRS	technical report series
TT	tetanus toxoid vaccine
TT2	two doses of tetanus toxoid vaccine
Ty21a	*Salmonella typhi* strain 21a
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VAD	vitamin A deficiency
VRD	Vaccine Research and Development Unit
VSQ	Vaccine Supply and Quality Unit
VVM	vaccine vial monitor
WPR	Regional Office for the Western Pacific
YF	yellow fever

THE STRATEGIC PLAN

— INTRODUCTION

THE Global Programme for Vaccines and Immunization (GPV) was established in March 1994. This Programme incorporated two existing programmes from the World Health Organization, the Expanded Programme on Immunization and the former Programme for Vaccine Development, and a new unit for Vaccine Supply and Quality was established. The Programme thus has terms of reference that span from basic vaccine research, through vaccine production and quality control, to helping ministries of health plan and manage their immunization services and control vaccine-preventable diseases.

This document is the third strategic plan for the Global Programme for Vaccines and Immunization. It covers the period 1998 to the year 2001 and describes the targets and indicators for the Programme for each main heading. The plan is compatible with the WHO-wide Activity Management System (AMS) and is reviewed and revised annually. A four-year strategic plan and a two-year budget will be produced every two years.

The strategic plan is written for three groups of people: the managers of the Programme itself, the Programme's contributors (be they financial contributors or contributors in time and effort) and WHO's administration.

The plan helps the Programme to be clear about its objectives and activities. It also opens the Programme to scrutiny and debate, encouraging broad discussion about its priorities and activities and how best they can be achieved.

The document has four sections:

- **Section one** describes briefly the Global Programme's mission, principal objectives, and priorities.
- **Section two** contains a summary of the Programme's planned costs, budgets, unmet needs for 1998-1999 and expected income for 1998.
- **Section three** contains a description of the progress made during 1994-1997, the achievements and constraints. Milestones and indicators are given – with funds needed, funds available and unmet needs. This information is repeated for each of the Programme's principal activities under three headings:
  - Self-sufficiency
  - Disease control
  - New vaccines
- **Section four** contains five annexes with details of the high priority countries for the different disease reduction activities.

GPV – THE GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION

— MISSION, STRUCTURE, OBJECTIVES AND PRIORITIES

The mission of the Global Programme for Vaccines and Immunization:

A world in which all people at risk are protected against vaccine-preventable diseases.

Sub-objectives	Main objectives		
	Self-sufficiency	Disease control	New vaccines
Filling the vaccine pipeline	Page 1	Page 27	Page 57
Global logistics and quality of vaccines	Page 2	Page 30	Page 113
National vaccine delivery	Page 9	Page 34	Page 116
Surveillance and other information systems	Page 23	Page 45	Page 117
Enabling functions	Page 123		

The table below presents the targets of the Programme under the 13 areas of work of the Global Programme for Vaccines and Immunization. The three main objectives are given at the top and the five sub-objectives are given on the left-hand side, the last row being the common "enabling functions".

Each cell in the grid contains a series of activities that are carried out by one or more of the three units of the Programme.

MAIN OBJECTIVES

The three main objectives of the Global Programme for Vaccines and Immunization, as outlined in the grid on the facing column, are:

SELF-SUFFICIENCY

All countries should become self-sufficient in their immunization programmes. This means independent of outside support for funding, management, technical assistance, vaccine supply, equipment, and training.

DISEASE CONTROL

All vaccine-preventable diseases included in the programme are monitored and controlled to a point where they are eradicated, eliminated, or cease to be a public health problem.

NEW VACCINES

New and improved vaccines are made available as soon as science, resources, and national programme management will allow.

SUB-OBJECTIVES

The five sub-objectives of the Programme are:

FILLING THE VACCINE PIPELINE

- ▷ Ensuring that the new vaccines and vaccination strategies that meet priority needs in developing countries are available for inclusion into country programmes, for example Hib vaccines or appropriate immunization schedules/target groups.
- ▷ Ensuring the development of new and improved vaccines for diseases with high global mortality and morbidity, for example vaccines against acute respiratory infections, tuberculosis and diarrhoeal diseases.
- ▷ Ensuring that new approaches to immunization with the potential to make vaccine delivery simpler, less expensive and more effective are developed, for example DNA vaccines or single-dose vaccines to replace multi-dose vaccines.

GLOBAL LOGISTICS AND QUALITY OF VACCINES

- ▷ Ensuring that all vaccines used in the Programme are of high quality when they leave the manufacturer.
- ▷ Ensuring that all vaccines are available at a price affordable to the buyers – be they donors or the country programmes themselves.
- ▷ Ensuring that there are adequate supplies of vaccine for the world and that the supplies are available to those who need them.
- ▷ Ensuring vaccines are provided in presentations that allow them to be used efficiently.

NATIONAL VACCINE DELIVERY

- ▷ Ensuring that countries have high-quality action plans for developing their immunization services.
- ▷ Ensuring that vaccines are of high quality and in adequate quantities at the point of use (i.e. an effective cold chain).
- ▷ Ensuring that other supplies (syringes, refrigerators, transport, etc.) are available, in working order, and can be maintained.

SURVEILLANCE AND OTHER INFORMATION SYSTEMS

- The development of effective surveillance and other information systems at national, regional, and global levels that can monitor in a timely manner changes in disease incidence, Programme performance, and progress towards programme goals.
- The development of high quality laboratory services for diagnosis.

ENABLING FUNCTIONS

These functions cut across the whole Programme and cannot be assigned to an individual unit. Therefore, they are typically functions for the Director's Office, though some are also performed at the level of the technical units. Examples include global administrative policies, seeking extrabudgetary funds, budgeting, and maintaining the strategic plan.

PRIORITIES OF THE GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION

The following list of 12 priorities has been extracted from World Health Assembly resolutions which together form the Programme's mandate.

- **Eradicate poliomyelitis by the year 2000:** eradication efforts should be pursued in ways which strengthen the development of the Expanded Programme on Immunization as a whole, fostering its contribution, in turn, to the development of the health infrastructure and of primary health care ***(WHA 41.28)***.
- **Increase coverage by 90%** in the context of comprehensive maternal and child health services ***(WHA 42.32).***
- **Reduce measles cases by 90%** compared with pre-immunization levels ***(WHA 42.32).***
- **Eliminate neonatal tetanus** ***(WHA 42.32).***
- **Integrate hepatitis B vaccine** into national immunization programmes ***(WHA 45.17).***
- **Introduce new or improved vaccines within routine national immunization services** as these become available for public health use ***(WHA 42.32).***
- **Assure the quality of vaccines** by obtaining information from countries importing vaccine, either in bulk or in final containers, on whether the national authority has certified that such vaccine and its manufacturer comply with the national and WHO requirements for manufacturing and control procedures ***(WHA 45.17).***
- Ensure the proper functioning of the cold chain and logistics system to maintain vaccine potency until the time of use ***(WHA 45.17).***
- **Strengthen financial mechanisms** that would permit the rapid integration of cost-effective new vaccines into national immunization programmes ***(WHA 45.17).***
- **Accelerate the development of new vaccines** against bacterial meningitis, acute respiratory infections, diarrhoeal diseases, dengue, tuberculosis and other communicable diseases ***(WHA 44.4).***
- **Develop improved vaccines against childhood diseases that could simplify immunization** schedules, that would require only one or two doses, that could be given earlier in life, and that could be combined in novel ways, reducing unit costs, bringing down drop-out rates and ensuring greater heat-stability and efficiency ***(WHA 44.4).***
- **Strengthen the system for epidemiological surveillance** of target diseases of the Expanded Programme on Immunization and other high priority diseases ***(WHA 45.17).***

STRATEGIC PLAN 1998-2001

— PLANNED COSTS

PLANNED COSTS, BUDGETS AND UNMET NEEDS

DEVELOPMENT OF THE 1998 AND 1999 PLANNED COSTS AND BUDGETS

Since 1995, GPV has adopted a management-by-objective policy in line with the World Health Organization's Ninth General Programme of Work: products and expected results have become the main consideration rather than the type of activity and resources available. The strategic plan developed by GPV for the period 1998-2001 is consistent with the planning and management process required by the World Health Organization, and the development of Plans of Action.

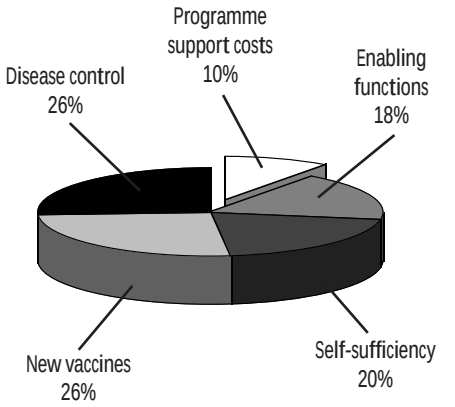
GPV strategic plan for 1998-2001 and the related planned costs, budgets and unmet needs for 1998 and 1999 were developed during the period September-November 1997, and entered by end 1997 in the management tool developed by the Organization to support these new management concepts (the Activity Management System). The 1999 budget will be revised at the end of 1998 to take into account variations in funds expected to be available for 1999. During the period September-November 1999, planned costs and budgets for 2000-2001 will be developed (and the present strategic plan revised for the period 2000-2003).

PLANNED COSTS AND BUDGET STATEMENTS FOR 1998 AND 1999

Table 1, page XV, and Table 2 , page XVI, provide, for 1998 and 1999 respectively, a summary of planned costs and budget statements by main objective and sub-objective, under each cell of the GPV grid. These tables also indicate unmet needs for each objective.

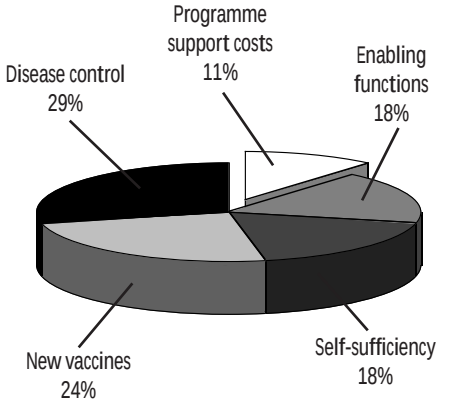
The GPV budget amounts to US$24 million in 1998, or a 16% increase over 1997 (US$20.7 million). GPV provisional budget for 1999 amounts to US$25.4. Figures 1 and 2 indicate the division of the GPV budgets by main objective, for 1998 and 1999 respectively.

Figure 1: Division of 1998 budget by main objective



Note: programme support costs are made available to WHO to contribute to the Special Account for Servicing Cost

Figure 2: Division of 1999 budget by main objective

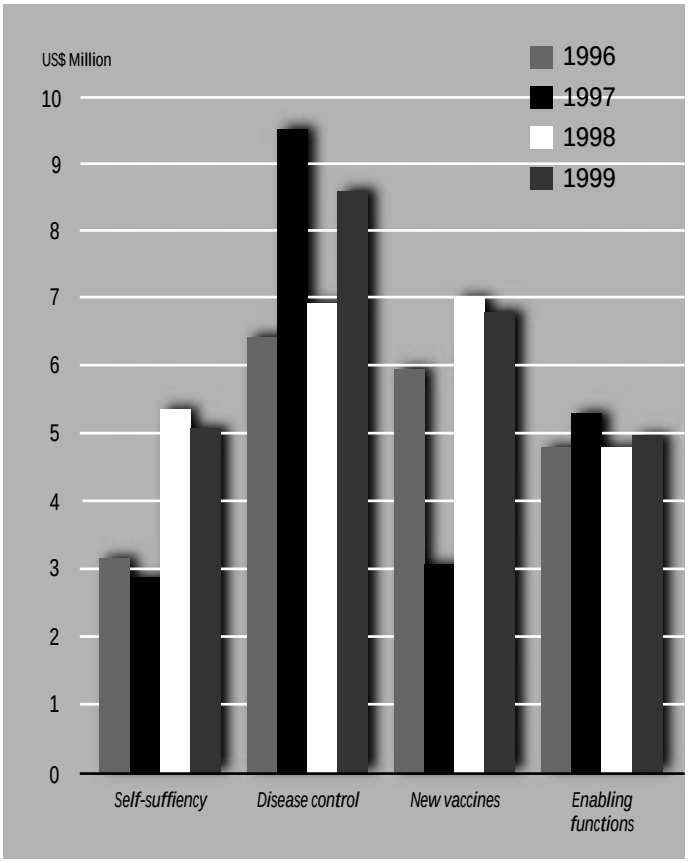


Note: programme support costs are made available to WHO to contribute to the Special Account for Servicing Cost

Figure 3 shows the evolution of amounts budgeted in 1996, 1997, 1998 and 1999, by main objective. The significant changes from one year to another in budgeted amounts are due to the combination of the following factors which are taken into account at the time the annual budget is finalized:

- ▷ The decision made by the Programme managers to focus human and financial resources to best meet the Programme priorities.
- ▷ Some donor-partners have informed the Programme of their decision to increase their contribution, and some new donor-partners have decided to support the Programme (the Goverments of Canada and Switzerland in 1997).
- ▷ Significant specified voluntary contributions are expected from some partners (e.g. self sufficiency in 1997 and 1998, and disease control in 1997 and 1999).
- ▷ Some partners suspended their support to the Programme (e.g. UNDP in 1997 for new vaccines, althought this support was ressumed in 1998).

Figure 3: Amounts budgeted by main objective (and enabling functions) 1996 -1999



UNMET NEEDS FOR 1998 AND 1999

Based on the evaluation of resources expected to be available in each year, unmet needs for 1998 should amount to US$8.3 million and to US$9.8 million for 1999. In 1998, 29% of the planned costs will not be covered; in 1999, 31%. Planned costs were carefully evaluated to avoid overestimating unmet needs.

The present comprehensive strategic plan was developed according to the targets set by WHO Member States through World Health Assembly resolutions (see page XI "Priorities"). The gap between planned costs and annual budgets for 1998 and 1999 indicate that additional resources should be made available to the Global Programme for Vaccines and Immunization through an increased commitment from the World Health Organization and other partners of the Programme, if objectives are to be achieved.

Table 1: Summary of planned costs, budgets and unmet needs for 1998, by main objective and sub-objective

1998

	Main objectives											
	Self-sufficiency				**Disease control**				**New vaccines**			
Sub-objectives	**US$**	Planned cost	Budget	Unmet needs	**US$**	Planned cost	Budget	Unmet needs	**US$**	Planned cost	Budget	Unmet needs
Filling the vaccine pipeline	Total	304 000	151 000	–153 000	Total	462 000	354 000	–108 000	Total	6 968 000	5 336 000	–1 632 000
Global logistics and quality of vaccine	Total	1 816 000	1 602 000	–214 000	Total	324 000	306 000	–18 000	Total	333 000	303 000	–30 000
National vaccine delivery	Total	2 385 000	1 708 000	–677 000	Total	7 273 000	5 068 000	–2 205 000	Total	41 000	35 000	–6 000
Surveillance and other information systems	Total	2 892 000	1 311 000	–1 581 000	Total	752 000	518 000	–234 000	Total	667 000	617 000	–50 000
Totals per main objective	Total	7 397 000	4 772 000	–2 625 000	Total	8 811 000	6 246 000	–2 565 000	Total	8 009 000	6 291 000	–1 718 000
					Enabling functions							
					Total	4 833 000	4 366 000	–467 000				
					Grand Totals 1998							
					Total	29 050 000	21 675 000	–7 375 000	***Total unmet needs***			
					PSC		2 313 000	–959 000	***PSC if unmet needs funded from voluntary contributions***			
					Grand total		23 988 000	–8 334 000	***Total unmet needs, inclusive of PSC***			

Table 2: Summary of planned costs, budgets and unmet needs for 1999 by main objective and sub-objective

1999

	Main objectives											
	Self-sufficiency				**Disease control**				**New vaccines**			
Sub-objectives	**US$**	Planned cost	Budget	Unmet needs	**US$**	Planned cost	Budget	Unmet needs	**US$**	Planned cost	Budget	Unmet needs
Filling the vaccine pipeline	Total	206 000	172 000	–34 000	Total	473 000	348 000	-125 000	Total	7 910 000	5 129 000	–2 781 000
Global logistics and quality of vaccine	Total	1 738 000	1 552 000	–186 000	Total	382 000	382 000	0	Total	286 000	248 000	–38 000
National vaccine delivery	Total	2 023 000	1 268 000	–755 000	Total	8 666 000	6 427 000	–2 239 000	Total	50 000	50 000	0
Surveillance and other information systems	Total	3 117 000	1 537 000	–1 580 000	Total	929 000	547 000	–382 000	Total	675 000	552 000	–123 000
Totals per main objective	Total	7 084 000	4 529 000	–2 555 000	Total	10 450 000	7 704 000	–2 746 000	Total	8 921 000	5 979 000	–2 942 000
					Enabling functions							
					Total	5 013 000	4 553 000	–460 000				
					Grand Totals 1998							
					Total	31 468 000	22 765 000	–8 703 000	***Total unmet needs***			
					PSC		2 675 000	–1 123 000	***PSC if unmet needs funded from voluntary contributions***			
					Grand total		25 440 000	–9 826 000	***Total unmet needs, inclusive of PSC***			

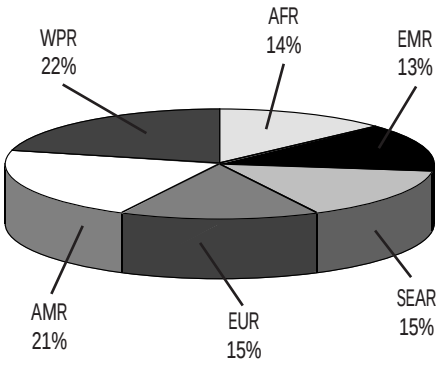
GPV 1998 DIRECT CONTRIBUTION TO THE REGIONS

Direct financial support will continue to be provided in 1998 by GPV to its counterparts in each regional office. A decision on this support for 1999 will be made at end 1998, when the resources expected to be available to the Programme can be estimated better.

This contribution comes in addition to:

- ▷ Resources (regular budget and extrabudgetary contributions) already available at the regional office levels.
- ▷ Funds made available by GPV units (Expanded Programme on Immunization, Vaccine Supply and Quality, and Vaccine Research and Development) to the regions.
- ▷ Expenditures directly supported by GPV budget for activities performed at the regional and country levels.

Figure 4: Division of GPV direct contribution to the WHO regions – 1998



In 1998, GPV's direct contribution to the regions amounts to US$2 million, 8% of its total budget (US$26 million). This contribution supports staff positions and activities. In 1997, the budgeted direct contribution from GPV to the regions was US$1.8 million, also 8% of its total budget (US$22.5 million). An average of 45% of unspecified funds available to the Programme is used by GPV for direct contribution to the regions annually. The distribution of this contribution between the regions is indicated by Figure 4.

The allocation of the funds between the regions was done on the basis of a systematic analysis of the regions' needs. Progress of each region in reaching the Programme's objectives was assessed and, taking into account commitments for staff salaries, an allocation was made with most support going to the regions that need it most.

The general increase in the level of extrabudgetary contributions, particularly to the regions (regional and country level) is much appreciated (Figure 5, page XVIII). However, the lack of unspecified funds recieved by headquarters (global and inter-level) limits the capacity of the Programme to continue to support the regions to the extent desirable.

EXPECTED INCOME

REGULAR BUDGET CONTRIBUTION TO IMPLEMENT THE 1998 AND 1999 BUDGETS

The regular budget contribution available to the Programme for the 1998-1999 biennium should be US$4.9 million for salaries and US$1.9 million for activities. Accordingly, 50% of this two-year allocation, or US$3.4 million, have been budgeted for each of these two years, for salaries and activities, in the hope that the Organization will not reduce these allocations.

EXTRABUDGETARY CONTRIBUTIONS RECEIVED IN 1996-1997 AND EXPECTED EXTRABUDGETARY CONTRIBUTIONS IN 1998 TO IMPLEMENT THE 1998 BUDGET

Besides WHO regular budget allocations, GPV funds its budget from extrabudgetary contributions made available by its partners at the global and interregional levels, regions and countries having the control of such contributions made available at the regional and country levels.

In 1997, all extrabudgetary contributions received for the Programme activities at all levels amounted to US$61 million:

- ▷ US$15 million at the global and interregional levels (funds available to GPV/HQ), and
- ▷ US$46 million at the regional and country levels (funds available to GPV counterparts in the regions and countries).

[Analysis done upon final closure of WHO accounts for the 1996-1997 biennium, at end March 1998].

Table 3, opposite, indicates all extrabudgetary contributions received in 1997 at the global and interregional levels, and so far in 1998 (31 March 1998).

Table 4, pages XX, provides similar information per region, at the regional and country levels.

Figure 5, below, shows financial support received by GPV, at all levels, in 1997.

Figure 6, page XXI, indicates the evolution of donor support to all levels of GPV since the creation of the Programme in March 1994.

Figure 5: GPV donor support in 1997 (all extrabudgetary contributions).
Final figures at March 1998, upon closure of WHO accounts for the 1996-1997 biennium.

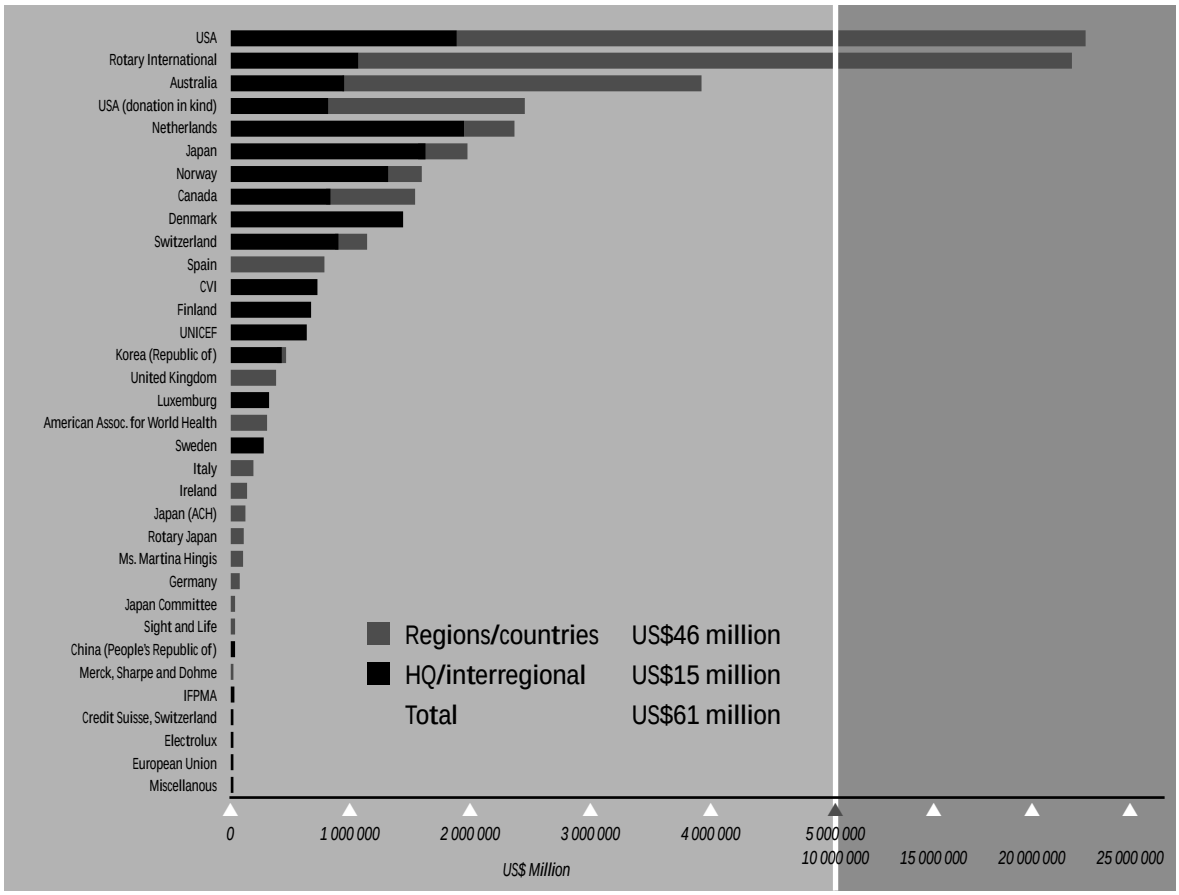


Table 3: All extrabudgetary contributions received in 1997 and in 1998 (as at 31 March 1998) – Global and interregional level

Source	1997	1998
	US$	US$
Unspecified	2 933 727	810 120
Designated (Unit)	3 772 598	1 381 086
Specified	8 337 457	5 207 358
Grand Total	**15 043 782**	**7 398 564**

Unspecified	1997	1998
	US$	US$
Australia	464 160	810 120
China (People's Republic of)	27 500	
Korea (Republic of)	353 823	
Miscellaneous	396	
Netherlands	245 475	
Norway	1 286 817	
Switzerland	555 556	
Sub-total	**2 933 727**	**810 120**

Designated (Unit)	1997	1998
	US$	US$
Credit Suisse Switzerland (EPI)	7 042	
Denmark (EPI)	1 354 532	
Electrolux (EPI)	3 776	
Netherlands (EPI)	1 319 077	
Rotary International (EPI)	8 807	
Australia (VRD)	464 160	
France (VRD)		163 934
Netherlands (VRD)	184 671	
Rockefeller Foundation (VRD)		775 000
Sweden (VRD)	217 971	42 152
UNDP (VRD)		400 000
Netherlands (VSQ)	211 053	
Miscellaneous	1 509	
Sub-total	**3 772 598**	**1 381 086**

Specified	1997	1998
	US$	US$
Canada	787 626	
CVI	630 000	
European Union	3 755	
Finland	587 438	
Hingis, Ms Martina		6 000
IFPMA	15 000	
Italy	132 890	
Japan	1 600 000	
Korea (Republic of)	20 000	
Luxemburg	293 800	
Rotary International	1 056 215	532 358
Switzerland	259 259	
Technet Consultation (several contributions)		19 460
UK		3 333 333
UNICEF	566 436	
USA	1 866 550	1 315 207
USA (donation in kind)	516 651	
Miscellaneous	1 837	1 000
Sub-total	**8 337 457**	**5 207 358**

Table 4: All extrabudgetary contributions received in 1997 and in 1998 (as at 31 March 1998) – regional and country level (excluding allocations from GPV headquarters)

AFR	1997	1998
	US$	US$
American Association for World Health	283 330	
Canada	730 398	
Hingis, Ms Martina	75 000	
Ireland	117 255	
Norway	36 357	
Rotary International	12 207 000	3 096 536
Sight and Life	30 000	
UK	332 800	
USA	14 769 289	1 118 700
USA (donation in kind)	1 067 258	
	29 648 687	**4 215 236**

AMR	1997	1998
	US$	US$
Merck, Sharpe and Dohme Int.	15 000	
Netherlands	400 000	
Spain	683 026	
USA	1 850 000	
	2 948 026	

EMR	1997	1998
	US$	US$
Rotary International	2 740 000	530 410
USA	212 298	423 750
USA (donation in kind)	341 171	
	3 293 469	**954 160**

EUR	1997	1998
	US$	US$
Germany	59 641	
Rotary International	335 200	84 074
Switzerland	296 296	
USA	385 323	274 025
USA (donation in kind)	109 594	
	1 186 054	**358 099**

SEAR	1997	1998
	US$	US$
Denmark		2 300 000
Norway	236 000	
Rotary International	1 189 975	572 800
USA	841 533	344 650
USA (donation in kind)	334 909	
	2 602 417	**3 217 450**

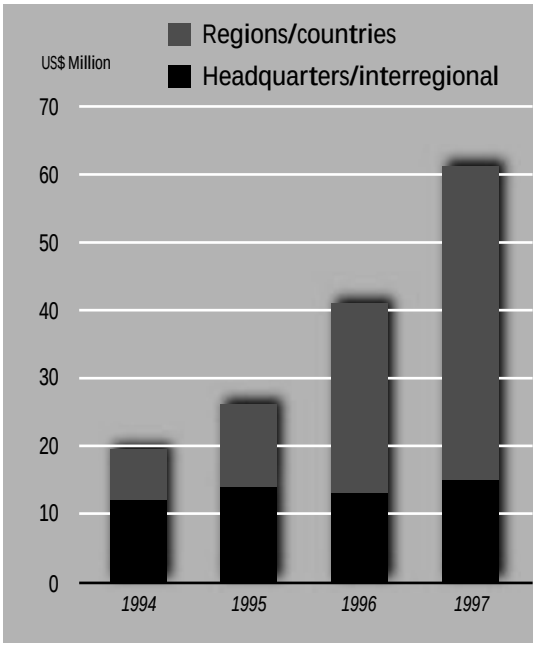
Table 4 continued

WPR	1997	1998
	US$	US$
Australia	3 009 512	147 620
Japan	384 100	
Japan (ACIH)	102 018	
Japan Committee	39 592	
Korea (Republic of)	25 000	
Rotary International	1 518 987	323 233
Rotary Japan	82 440	
USA	577 496	372 900
USA (donation in kind)	88 865	
	5 828 010	**843 753**

Laboratory network project	1997	1998
(All regions except AMR)	US$	US$
Rotary International	**461 979**	**14 524**

Grand Total	1997	1998
	US$	US$
AFR	29 648 687	4 215 236
AMR	2 948 026	
EMR	3 293 469	954 160
EUR	1 186 054	358 099
SEAR	2 602 417	3 217 450
WPR	5 828 010	843 753
Laboratory network project	461 979	14 524
	45 968 642	**9 603 222**

Figure 6: Evolution of donor support to all levels of GPV since 1994



CONTRIBUTIONS FROM THE CHILDREN'S VACCINE INITIATIVE

The Children's Vaccine Initiative (CVI) is a companion organization to the Global Programme for Vaccines and Immunization and has its own strategic plan (*The CVI Strategic Plan – Managing opportunity and change: a vision of vaccination for the 21st century,* CVI/GEN/97.04).

In 1997, specified extrabudgetary contributions made available to GPV through the Secretariat of the CVI amounted to US$630 000.

EVOLUTION OF UNSPECIFIED/DESIGNATED/SPECIFIED FUNDS

Based on past experience, indications from contributors and pledges, the Programme expects extrabudgetary contributions to amount to US$20.2 million in 1998 – in addition to the US$3.4 million regular budget allocation:

- US$5 million unspecified.
- US$3.8 million designated for one of the three GPV units (EPI, VRD or VSQ).
- US$11.4 million specified.

Figure 7, opposite, shows the evolution of unspecified and designated/specified extrabudgetary contributions available to GPV headquarters between 1994 and 1997:

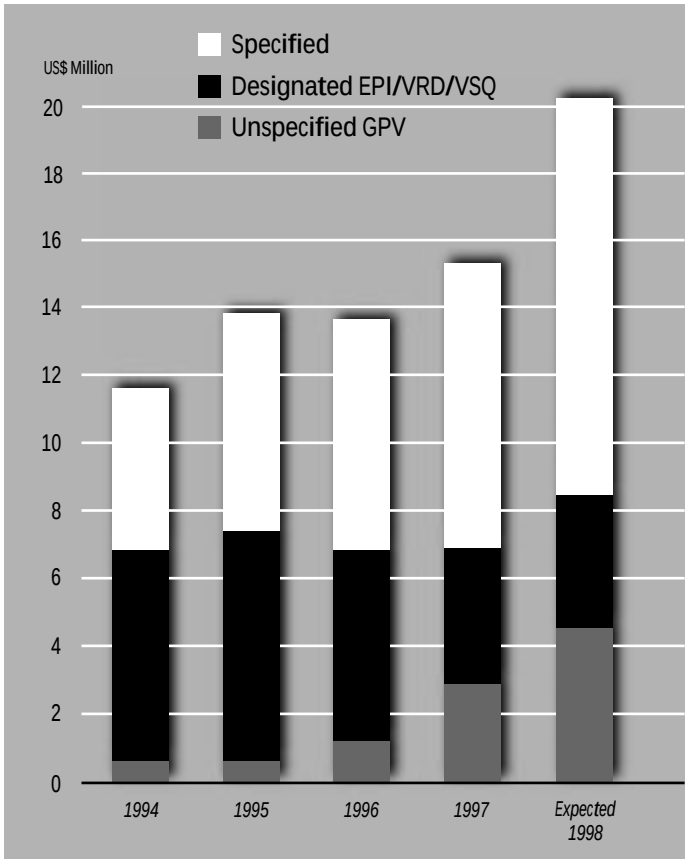
- In 1994 and 1995, the proportion of unspecified contributions received by the Programme for headquarters and interregional activities was stable (5% in both years). Unspecified contributions increased from 9% in 1996 to 19% in 1997, but still remain below the Programme's target of 50%. This increase was largely driven by the Government of the Netherlands which changed its contribution from "designated" to "unspecified" in 1997. This change was important as it enables the Programme to direct funds into priority areas of GPV work.
- However, in the same period, the proportion of designated contributions (for use by one of the three GPV units at headquarters) decreased steadily (53% in 1994, to 49% in 1995 and 41% in 1996), with a marked reduction to 25% in 1997. Simultaneously, specified contributions increased from 41% in 1994 to 56% in 1997.

- ▷ Over the four-year period (1994-1997), the total of unspecified and designated contributions remained stable, averaging US$6.9 million per year, while specified contributions increased from US$4.8 million in 1994 to US$8.6 million in 1997.
- ▷ Estimations for 1998 indicate that all extrabudgetary contributions should total US$20.2 million, of which US$ 5 million (25%) would be unspecified, US$3.8 million (19%) designated for one of the three GPV units, and US$11.4 million (56%) specified.

The trend shown in Figure 7 (below) indicates that unspecified contributions to the Programme increased while the unspecified but designated contributions to GPV's three units at headquarters declined. Furthermore, the specified contributions also increased.

The Programme, therefore, is still far from meeting its target of 50% unspecified voluntary contributions and will continue to seek a higher proportion of unspecified funds. The lack of unspecified funds makes it difficult to fund priorities that are less attractive to donors but still important for the Programme to reach its targets. It reduces management flexibility, since funds cannot effectively be allocated according to priorities set by the Programme.

Figure 7: All voluntary contributions received by GPV, 1994-1997: Global and interregional levels



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SELF-SUFFICIENCY

— FILLING THE VACCINE PIPELINE

Maximising efficiency of vaccine containers

UNTIL recently, over 50% of vaccine used in routine immunization was thrown away at the end of the day to avoid the risk of loss of potency due to possible exposure to heat. Once a multiple-dose vaccine vial had been taken out of a refrigerator or vaccine carrier and opened for use, there was no way of knowing whether it was still potent after several hours at a higher temperature. As a result, all partly used vaccine vials were thrown away at the end of the day. Additional doses were lost when the potency of the vaccine was in doubt after a breach in the cold chain. Further wastage occurred when the stated number of doses could not be obtained from the vaccine vial due to the inefficient design of the vial and stopper.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	284 000	130 000	–154 000
1999	185 000	150 000	–35 000

OBJECTIVE

- To reduce vaccine wastage to 10% or less without any negative impact on the effectiveness of the immunization programme, as measured by coverage.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

During 1994, it was estimated that 62% of vaccine was wasted. However, the introduction of improved forecasting techniques enabled immunization programmes to switch to smaller, more appropriate vial sizes. Meanwhile, laboratory and field studies confirmed the safety of using vaccine vials for multiple sessions, thereby eliminating the need to discard liquid vaccine at the end of each session. Then, in 1997, the first vaccine vial monitor (VVM) was introduced into the programme, making it easier for programmes to accept the use of liquid vaccines on subsequent days. However, many countries, especially those receiving donated vaccines, are not yet using appropriate vial sizes, nor have they adopted the multi-dose vial policy.

MILESTONES/TARGETS

By 1998:

- ▷ Vaccine vial monitors (VVMs) introduced on two vaccines – in addition to oral polio vaccine.
- ▷ Vaccine wastage for liquid vaccines reduced by 50%.

By 1999:

- ▷ VVMs introduced on remaining vaccines used in immunization programmes.

By 2000:

- ▷ Vaccines provided in containers that maximize efficiency.

INDICATORS

- ▷ Doses used per target population/doses shipped to programme (**Status:** as of December 1997, 57%).
- ▷ Number of vaccines used in immunization programmes with VVM (**Status:** as of December 1997, one vaccine).

SELF-SUFFICIENCY

— GLOBAL LOGISTICS AND QUALITY OF VACCINE

Procurement guidelines for new purchasers

As countries rely progressively less on donated vaccines, they need to acquire new techniques to purchase vaccines internationally. With different donors supporting new vaccines, international procurement is being undertaken by an expanding group of purchasers.

OBJECTIVE

- To ensure that all vaccines purchased internationally by agents meet specifications and standards of safety and efficacy recommended by WHO.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Explanatory reference documents have been prepared by VSQ. Major international donors have agreed to follow WHO guidelines when purchasing vaccines. International guidelines and training documents in general use have been amended to include WHO recommendations.

MILESTONES/TARGETS

By 1998:

- 95% of doses procured by international agencies according to established criteria.

INDICATORS

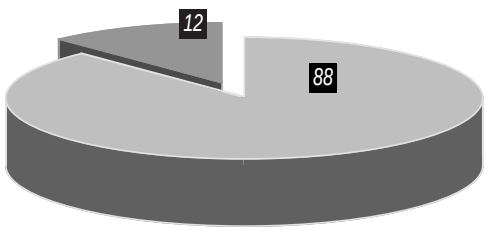
- Percentage of doses procured by international agencies using procurement standards (**Current status:** unknown).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	65 000	55 000	–10 000

Vaccine quality

THE quality of vaccines used in immunization programmes cannot be compromised. Through a published assessment system, VSQ prequalifies suppliers for international agencies which procure vaccines, including UNICEF and WHO. To date, there are 18 of these suppliers, and a total of 41 vaccines have been evaluated through this process. All suppliers will be re-evaluated on a regular basis.

Countries dependent on UN agency vaccine source with licensing criteria and postmarketing surveillance: 12/88



OBJECTIVE

- To ensure that all vaccines used in immunization programmes are safe and effective, with national mechanisms in place to ensure this. To guarantee a prompt response should vaccine quality problems occur.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The final responsibility for vaccine quality must rest with the government that is using the vaccines. VSQ has therefore defined: (a) six functions that should be performed by National Control Authorities in countries where vaccines are produced, and (b) those functions (dependent on vaccine source) which should be performed in countries where the vaccines are to be used. The definition of these six functions has determined VSQ activities to strengthen national control authorities: they include taking inventory of the functions, developing national control plans, and implementation of these national control plans through the Global Training Network.

The key achievements which have enabled progress in this area include: defining the six essential control functions, thus allowing an assessment of what countries are doing to safeguard vaccine quality; defining the concept of Known Good Quality based on the six essential control functions; developing national vaccine control plans in priority countries, using the six functions as a guide; and developing the Global Training Network to help implement national control plans.

The reassessment of prequalified suppliers on a two-year basis has been established. During 1997, half of the United Nations (UN) suppliers have been reassessed. Non-EPI vaccines are starting to be evaluated. Some have been assessed during 1997, including meningococcal A/C vaccines for use in emergency situations, which are now included in the evaluation process.

Through a policy statement on Vaccine Quality, published in 1996, VSQ has highlighted the central role of the National Control Authority in assuring vaccine quality. In 1996, 73% of the 725 million doses of DTP vaccine used throughout the world were of known good quality (i.e. they were controlled by a National Control Authority exercising all six essential control functions), compared with 54% in 1993. This indicator cannot be updated further until one key large country has strengthened its National Control Authority. Thus, only the number of countries in each vaccine source category will be monitored for the present. In 1996, 34 of 53 producing countries, 14 of 58 procuring countries, and 12 of 88 countries

In 1996, 73% of the 725 million doses of DTP vaccine used throughout the world were of known good quality (i.e. they were controlled by a National Control Authority exercising all six essential control functions), compared with 54% in 1993.

receiving vaccines from UNICEF were exercising necessary control functions appropriate to their vaccine source. To help in assessing the performance of the six control functions, indicators for the performance of each are being developed.

The Global Training Network was developed by VSQ in 1996 as a means of providing educational resources to vaccine control and production staff throughout the world. The Network consists of 10 training centres which offer instruction in priority areas using an approved syllabus and standardized documentation materials.

Global training network centres – courses and locations

More than 100 personnel from National Control Authorities (NCAs), National Control Laboratories (NCLs), and vaccine manufacturers have participated in the Global Training Network to date. Several of these trainees have successfully coordinated follow-up training at their own institutions. The Global Training Network will continue to support a variety of monitoring and follow-up activities to ensure that Network training is of the highest calibre and to measure its impact on the quality of vaccines world-wide.

MILESTONES/TARGETS

By 1998:

- ▷ All existing suppliers of vaccines to have been reassessed to ensure acceptability, in principle, for supply to United Nations agencies.
- ▷ All procuring countries to have developed licensing criteria and postmarketing surveillance systems.
- ▷ All procuring countries to have laboratory access for vaccine controls.
- ▷ 20 participants a year trained through the training network.

By 2000:

- ▷ 100% of countries to have NCAs.
- ▷ 100% of the vaccine used within the EPI to be of known good quality.
- ▷ Suppliers of Hib and other priority new vaccines to have been evaluated.
- ▷ Suppliers of new vaccine combinations to have been evaluated.

INDICATORS

- ▷ Percentage of doses of vaccine used meeting standards.
- ▷ Functions performed by National Control Authorities (NCAs) (**Status:** as of January 1998, 34 of 53 producing countries, 14 of 58 procuring countries, and 12 of 88 countries receiving vaccines from UNICEF were exercising necessary control functions appropriate to their vaccine source).
- ▷ Number of countries with NCAs (**Status:** as of January 1998, 57 of 199 i.e. 29%).
- ▷ Number of procuring countries with licensing and postmarketing surveillance (PMS) (**Status:** as of January 1998, 26 have licensing and 18 PMS).
- ▷ Number of procuring countries with laboratory access for vaccine controls (**Status:** as of January 1998, 18).
- ▷ Percentage of suppliers reassessed (**Status:** as of January 1998, 50%).
- ▷ Number of new suppliers assessed (**Status:** as of January 1998, 6).
- ▷ Number of vaccines assessed/reassessed (**Status:** proportion found acceptable, 37 of 41 (90%).
- ▷ Number of participants from priority countries completing training (**Status:** as of January 1998, see table below).

Proportion of doses of known good quality,1995 data

Vaccine	% Known good quality
DTP	73
OPV	79
Measles	81
Hepatitis B	70
Hib	100

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	1 024 000	820 000	–204 000
1999	1 041 000	651 000	–390 000

Training format	Subject area	Training centre	Number of trainees
Placements	Quality Control	RIVM	2
	Laboratory Quality Systems	NIBSC	1
Course	GMP	Mass Labs	8
Workshop	GMP	Follow-up in Thailand	137

Demand-forecasting for routine vaccines

To help countries more accurately forecast their vaccine needs, there is a need to establish a simple and useful tool for demand forecasting. In the past, this task was straightforward because it was based on historical-use data. However, changing patterns of vaccine usage, coupled with new vial sizes, updated immunization strategies, and efforts to reduce wastage have had an impact on the way in which vaccine demand is forecast. As a result, new tools will be developed for this purpose.

OBJECTIVE

- To develop a simple and useful tool for demand-forecasting to help countries improve the accuracy of national planning.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Assessments have been carried out in several countries to evaluate their performance since 1994 in demand-forecasting for routine vaccines and discussions held on demand forecasting methods. These methods should be integrated into a simple tool for demand-forecasting which countries can follow.

MILESTONES/TARGETS

By 1998:

- Countries' needs in demand-forecasting to be identified and simple and useful forecasting method under development.

By 2000:

- 50% of countries to be undertaking demand-forecasting with accuracy of 20%.

INDICATORS

Number of countries to cooperate in field testing the method selected by 1998.

LINKED TARGETS

Disease Control – Global logistics and quality of vaccine and New Vaccines – Global logistics and quality of vaccine

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	64 000	64 000	0
1999	44 000	44 000	0

Appropriate supply sources

As countries rely progressively less on donated vaccine, they will need to find new sources of vaccines through procurement activities. Some international agencies play a major role in vaccine procurement. However, these agencies are not following international standards in the procurement process. Guidelines for international procurement have now been developed and circulated. Failure to follow the principles embodied in these guidelines could lead to vaccines being made available to programmes that are not purchased from appropriately qualified sources, are not transported and distributed under conditions that will safeguard the quality, and may not meet appropriate specifications for national immunization programmes.

A major source of vaccine supply for national immunization programmes is locally produced vaccine. Unfortunately, the international community has encouraged many countries to produce vaccine without considering all the aspects needed for viable vaccine production. As a result, many production facilities fail to meet national needs, cannot invest in equipment and its maintenance, cannot update their production technologies, and – most importantly – cannot ensure the safety and efficacy of the product.

Some international agencies play a major role in vaccine procurement. However, these agencies are not following international standards in the procurement process.

OBJECTIVE

- To ensure that vaccines used within the programme are supplied by reliable producers supplying suitable products, which meet acceptable standards of safety and efficacy.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Training materials have been prepared to guide vaccine procurement agencies towards the selection of appropriate supply sources. An initial training workshop took place in Sri Lanka. Several other training workshops are in preparation, based on newly available materials.

MILESTONES/TARGETS

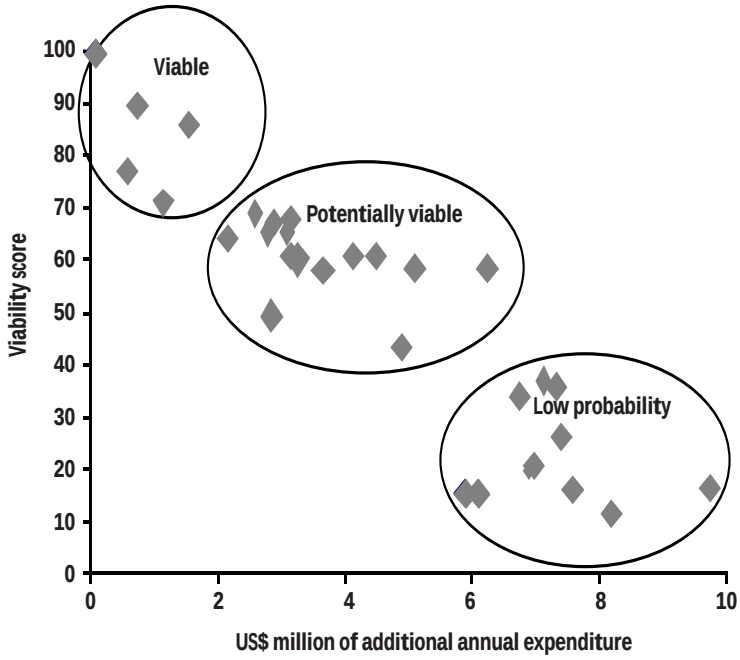
By 1998:

- ▷ Donors representing 80% of the available funds for support of vaccine production will be providing this support within the context of strategic plans which outline political, managerial, and technical inputs.
- ▷ 95% of doses obtained by international agency procurement using established criteria.

By 2000:

- ▷ All producers will meet international standards of viability and quality.

Viability ranking of local vaccine production



VSQ has developed a system to guide governments and donors on the complexity of vaccine production and the prospects for future viability of a facility. To ensure local production is a credible source of vaccine supply, donors and governments need to be encouraged to use these criteria when considering investment in local vaccine production. To date, of the 29 vaccine production facilities assessed using this procedure, which include most of the developing country public sector producers, only five (17%) achieved a Viability Score of greater than 70%.

In 1996, under pressure from the national immunization programme, several vaccine producers in India were dropped from the list of suppliers, and two shut down completely. Several other producers have decided to cease production, and others have suspended production indefinitely.

Many production facilities fail to meet national needs, cannot invest in equipment and its maintenance, cannot update their production technologies, and – most importantly – cannot ensure the safety and efficacy of the product.

INDICATORS

- Percentage of manufacturers with a viability score of 70% or more (**Status:** currently 17%).

LINKED TARGETS

Self-sufficiency – National vaccine delivery.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**245 000**	**245 000**	**0**
1999	**215 000**	**215 000**	**0**

SELF-SUFFICIENCY

— NATIONAL VACCINE DELIVERY

The quality of delivery is dependent upon technical, financial, and human resources. Improved quality will lead to higher coverage and thus, ultimately, to increased disease impact.

Coverage

IMMUNIZATION coverage remains a key programme indicator. As disease control makes progress towards eradication and elimination targets, the appropriate national body should be monitoring coverage levels by district to allow for more efficient use of resources and to identify areas at greatest risk or in greatest need.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	50 000	20 000	–30 000
1999	50 000	20 000	–30 000

OBJECTIVE

- Global DTP3 coverage of 90% with district level monitoring.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

At the global level, immunization coverage remains stable. Since 1992, 26 countries have achieved and sustained levels of infant DTP3 coverage of 80% or higher. In 1996, 73 countries (or 34% of all countries) achieved overall DTP3 coverage levels of at least 90%. An additional 28 countries reached DTP3 coverage levels of 80%-89%, while 20 countries remained below 50%; of these, 16 were in Africa. Of continuing concern are those 21 countries identified by GPV as being in greatest need. The average coverage for DTP3 in these countries was only 44% (range 20%-73%), a level which has remained below 50% since 1988, despite some improvements. Political instability and poor management are the key factors that hinder progress. At least 11 of these 21 countries are currently experiencing or have experienced major unrest in the recent past.

MILESTONES/TARGETS

By 1999:

- ▷ 80% of all countries monitoring immunization coverage by district for all vaccines used in immunization programmes.

By 2000:

- ▷ 90% global coverage.

INDICATORS

- ▷ Percentage of districts in each country with >80% coverage for DTP3 vaccine.
- ▷ National, regional, and global immunization coverage for each EPI vaccine.

STATUS AS OF DECEMBER 1996

Number of countries reporting DTP3 coverage by district for 1996:

Regional Office for the Americas (AMR): 20 of 47 countries gave data by district. Three of the 20 countries report DTP3 coverage over 80% in all districts. Two of the 20 countries achieved over 80% coverage in more than 80% of their districts.

Regional Office for South-East Asia (SEAR): All 10 countries except Thailand reported coverage data by district. In three countries the DTP3 coverage was over 80% in all districts, and four countries achieved over 80% coverage in more than 80% of their districts.

Regional Office for the Western Pacific (WPR): Data from districts were available from seven of 36 countries. None achieved greater than 80% DTP3 coverage in all districts, but three countries achieved more than 80% coverage in 80% of their districts.

No data were provided by Regional Office for Africa (AFR), Regional Office for Europe (EUR) or Regional Office for Eastern Mediterranean Region (EMR).

Reported regional and global coverage data, 1996

Region	BCG	OPV3	DPT3	HBV3	Measles	YF	TT2
AFR	70	54	54	62	56	39	34
AMR	97	93	86		86		
EMR	92	85	85	77	82		52
EUR	86	92	82	81	85		
SEAR	97	91	90	16	84		75
WPR	96	95	94	94	96		23
Global	90	84	82	77	81	39	47
Countries reporting	143	162	165	38	165	2	83

National planning

At national level, five-year EPI action plans should be prepared and updated annually, listing activities, costs, sources of funding, and unmet needs with the following components:

- Disease control, elimination, and eradication strategies and activities.
- Vaccine supply and financing, including plans for introducing new vaccines.
- Cold chain, logistics, and injection safety.
- Training, personnel, and other operational costs.
- Strengthening of information systems, including surveillance.
- Strengthening of laboratory services.
- Social mobilization.

Lessons learned from the polio eradication initiative have so far only been collected and analysed in a fragmented way. A more comprehensive review is required to identify and document each positive and adverse impact that the eradication process is having on basic health services. This would provide guidance for the design of future disease control and elimination strategies.

OBJECTIVE

- To ensure that all countries in greatest need have updated 5-year EPI plans.
- To carry out an evaluation of the impact of the polio eradication initiative on health services.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Of 21 countries in greatest need (CIGN), 16 are from the African region, for which data have not been available due to the evacuation of the WHO office from Brazzaville. During the above period, more than 50 % of the countries in greatest need have been through periods of civil unrest and war. In 1995, there were 9.4 million surviving infants in these countries, of which 18% (1.7 million) were living in countries which have updated EPI plans.

MILESTONES/TARGETS

By 1998:

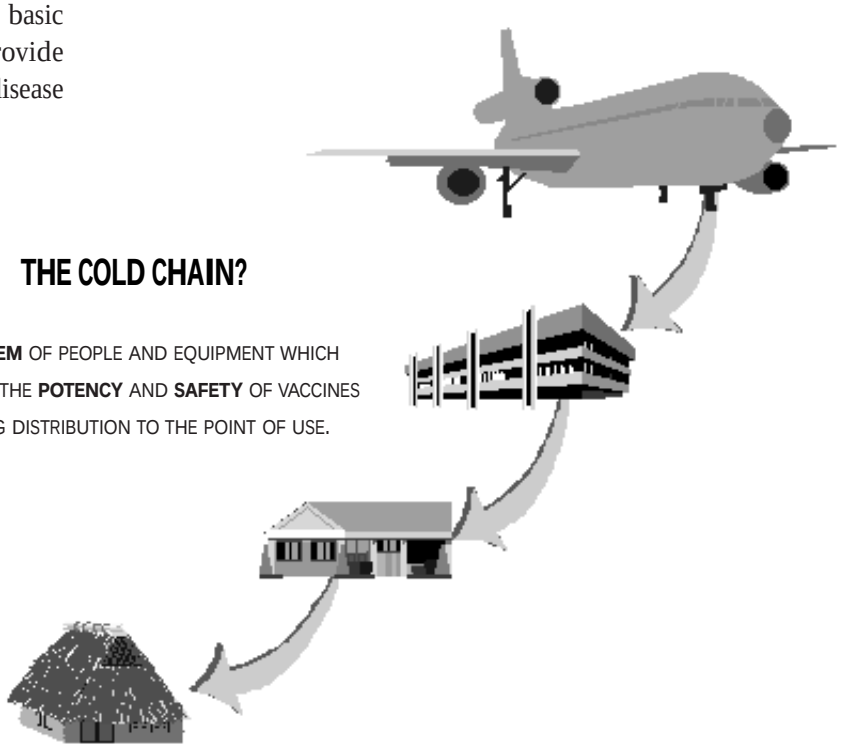
- Development of a framework comprising objectives and methodologies for the evaluation of the impact of the polio eradication initiative on health services.

By 1999:

- Action plans to be implemented in all countries.

By 2000:

- A comprehensive evaluation of the impact of the polio eradication initiative will have been conducted.



At national level, five-year EPI action plans should be prepared and updated annually, listing activities, costs, sources of funding, and unmet needs with the following components.

INDICATORS

- ▷ Percentage of countries with annually updated action plans.
- ▷ Number of regions with annually updated action plans.
- ▷ Availability of framework for polio impact on health services.
- ▷ Completion of evaluation of polio impact.

STATUS AS OF DECEMBER 1997

Afghanistan, Haiti, Laos, and Somalia have updated EPI workplans. Five African countries have prepared three-to five-year plans including specific actions to strengthen their logistics systems. Meanwhile, funding has been secured and terms of reference completed for the evaluation of the impact of polio eradication on health services.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	147 000	97 000	–50 000
1999	100 000	0	–100 000

Training

TRAINING is an essential component of all EPI activities. The aim is to improve the ability of regions and countries to be self-reliant in their training for immunization programmes. Country training needs have evolved over the past 15 years and vary greatly. The role of EPI/HQ is no longer that of a course organizer or training manual producer. EPI/HQ will provide: leadership and direction on policies, standards, guidelines, and essential information for field staff; develop generic reference materials to be incorporated into training materials by regional offices or countries; and ensure that relevant policies, guidelines, and information on EPI are introduced into basic training programmes. Training activities should be integrated, where possible, with those of other WHO programmes, and with other major external training providers.

OBJECTIVE

- ☐ Develop training plans for HQ and regional offices and decentralize training activities to regional offices.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The course for health workers, "Immunization in Practice", was revised and is supplied on disk, with accompanying hard copy, to each Region, so that the material can be adapted to local circumstances.

Because of the diversity of culture, health systems, and needs in the countries of Central and Eastern Europe (CCEE) and the Newly Independent States (NIS), a Steering Group was formed of experienced trainers from five countries, and from UNICEF and WHO, to revise the Russian language version of the Training Course for Mid-Level Managers.

MILESTONES/TARGETS

By 1998:

- ▷ Plans developed defining the respective roles of HQ and regional offices in relation to training functions and activities.

By 1999:

- ▷ Operational training activities decentralized to regional offices.

INDICATORS

- ▷ Existence of HQ and regional training plans.

STATUS AS OF DECEMBER 1997

The headquarters training plan has been elaborated, and training plans are available at AMR and EUR.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	131 000	45 000	–86 000
1999	120 000	30 000	–90 000

Targeted support

In countries in greatest need, chronic financial constraints limit the prospects for self-sufficiency in vaccine procurement and delivery. However, immunization has become an unquestioned priority in most countries and budget lines are gradually being established for service delivery and vaccine purchase. Most countries already finance all operational costs from internal sources.

GPV will increasingly target support to countries in greatest need and work with donor agencies and development banks to influence policy formulation and funding related to immunization services. Countries will be encouraged to establish separate budget lines for immunizations to promote sustainability. The health reform process, including decentralization, now under way in many of these countries will require changes in the management and structure of many national programmes. GPV will help facilitate this transition and assist countries in designing the most efficient service delivery strategy within the context of health reforms. This may include collaboration with the private sector and with health financing systems such as health insurance and social service mechanisms.

Immunization has become an unquestioned priority in most countries and budget lines are gradually being established for service delivery and vaccine purchase.

OBJECTIVE

- To target technical and financial assistance to countries according to their needs.
- To ensure that countries that can afford to pay for their own vaccines do so, freeing up funds that can be used to provide both new and existing vaccines for the world's poorest countries.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Most of the countries in greatest need are in Africa. However, data for these and other countries in Africa are not available due to the evacuation from Brazzaville of the WHO Regional Office for Africa in 1997. Earlier data show that while in 1990 only about 2% of the countries that fit Band A criteria were contributing financially to vaccine purchases, by early 1996, as many as 25% were meeting the WHO goals. About 70% of Band B countries were on target by 1996, compared to 40% in 1990, and Bands C and D had 90% compliance, up from 80%.

MILESTONES/TARGET

By 1998:

- 40% of countries in greatest need financing at least 20% of their vaccine requirements.
- All countries in greatest need (Annex 1), with the exception of war-torn countries, to have achieved at least 50% coverage with DTP3.

By 1999:

- 50% of countries in greatest need to have a budget line for immunization.
- 80% of all countries in greatest need to be financing at least 20% of their vaccine requirements.
- All countries in greatest need, with the exception of war-torn countries, to have achieved at least 70% coverage.

By 2001:

- All countries in greatest need to have a budget line for immunization.

INDICATORS

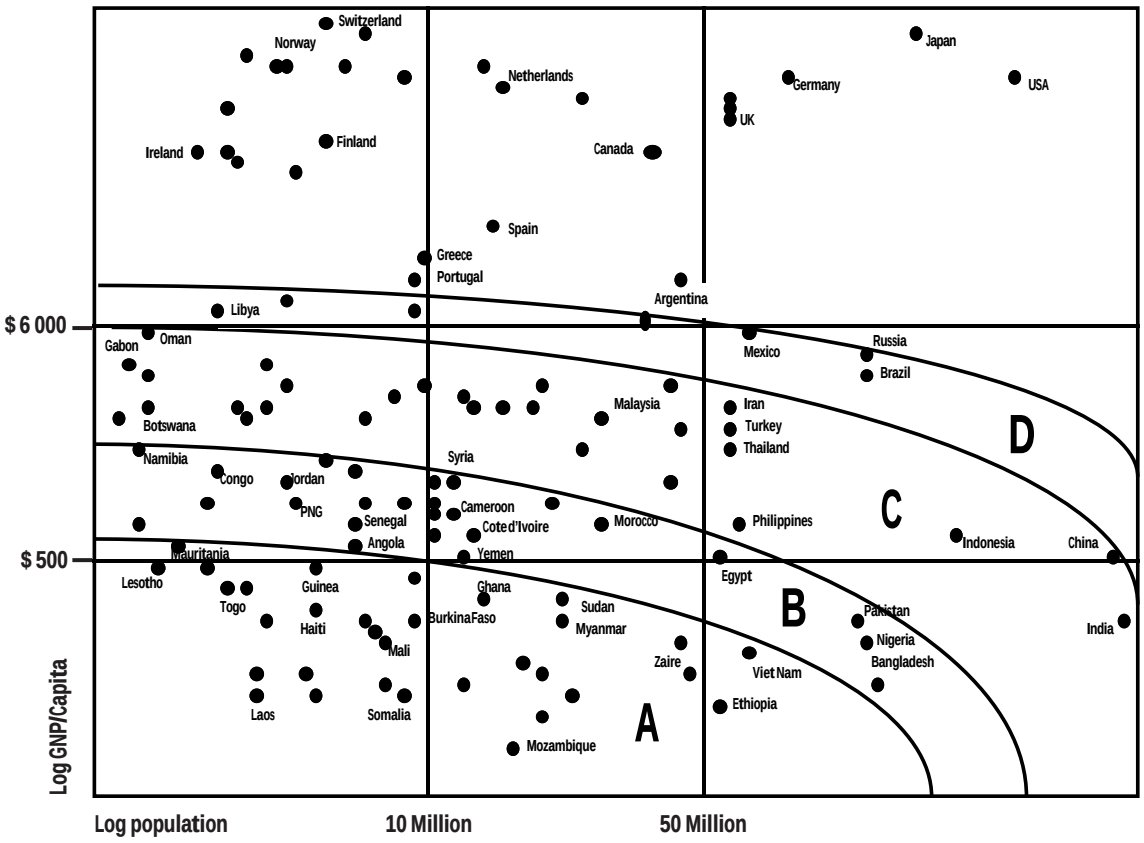
- Number of countries in greatest need with budget line for immunization.
- Percentage of vaccine needed for routine programmes that is financed through national budgets (**Status:** not available for 1996).
- DTP3 coverage in countries in greatest need, apart from war-torn countries (**Status:** not yet available for 1996).

STATUS AS OF OCTOBER 1997

Djibouti finances 100% of its vaccines, while Laos finances 0%. In Africa, all CILSS countries, including those countries in greatest need (Burkina Faso, Chad, Mali, Mauritania, Niger), have entered an agreement with the European Union whereby a line for the purchase of vaccines used in immunization programmes is being established in the national budget. No data are available for other African countries or for Afghanistan, Haiti, and Somalia.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	143 000	103 000	–40 000
1999	135 000	35 000	–100 000

Sustainable vaccine supply, global targeting strategy



A Financial support
B Finance/service gradual hand-off
C Self sufficient
D Rapid independence

Availability and quality of resources at point-of-use

IMMUNIZATION services rely on the availability and quality of resources such as cold chain equipment, vaccines, injection and sterilization equipment, as well as the correct use of these supplies and equipment. In the countries in greatest need, cold chain equipment that was financed at the launch of the EPI is now ageing. External funding is probably needed to replace it within the next five years.

The introduction of vaccine vial monitors (VVMs) on oral polio vaccine vials is probably the single most important event in the vaccine cold chain since the EPI was launched in the 1970s. VVMs enable health staff to ensure that vaccine is not heat damaged at the point of use, and to exploit the true stability of vaccines currently available. VVMs also make it possible for countries to ascertain the reliability of the vaccine delivery and cold chain system and to document their quality.

OPV vial with vaccine vial monitor

OBJECTIVE

- To ensure that vaccines of good quality are available in sufficient quantity at the point of use and that they are administered safely.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

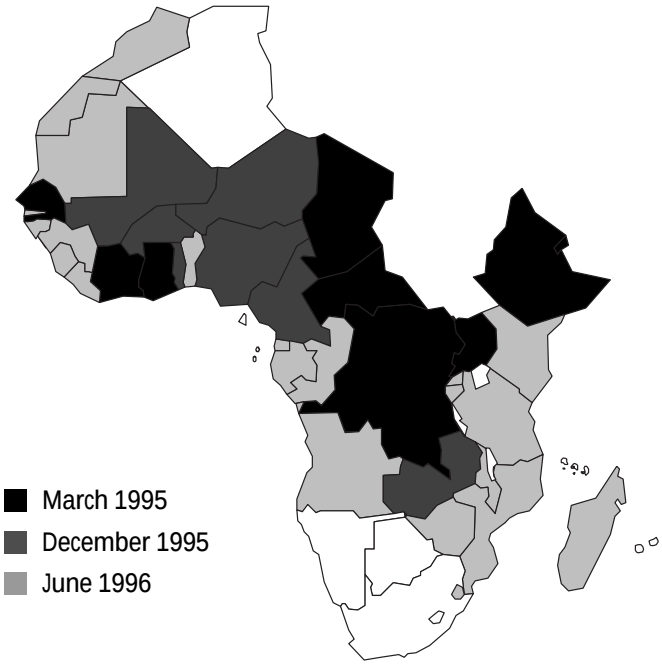
During 1996 and 1997, training on the use of VVMs was conducted in a large number of countries and proved to be an easy process. Impact studies initiated in Nepal, Mozambique, Tanzania, and Viet Nam to collect information on wastage rates and vaccine handling have so far yielded limited data. Additional studies are under way in Bhutan, South Africa, and Yemen. During the first year of introduction, one of the OPV manufacturers systematically supplied a VVM which did not meet WHO specifications and changed colour too fast. This situation was uncovered only at the beginning of 1997, and large quantities of Oral Polio Vaccine (OPV) had to be replaced in several countries. Because of this problem and the delay in data collection, no recommendation could be made on the introduction of VVMs on other vaccines used in immunization programmes. Therefore this target has been postponed until 1999.

VVM card prepared for the National Immunization Days in Yemen

A logistics project for Africa was designed to identify material and management problems relating to the logistics of immunization programmes and to launch the necessary activities and fund-raising needed to solve these problems. Started in Ghana in March 1995, this project has been extended to 16 African countries, each group of four countries being assigned a WHO expert logistician. Funded by United State Agency for International Development (USAID), the Department for International Development and Cooperation, United Kingdom (DFID, UK), and Danida, the project has achieved slow, but steady progress. In 1997, six countries had conducted rapid assessments of injection practices.

In 1997, over 1 billion injections were given through national immunization programmes or special immunization campaigns in developing countries. However, immunization injections represent less than 10% of the total injections delivered. Unsafe injections are a potential hazard placing patients, health workers and the general community at risk of serious diseases. The situation in countries in greatest need is more acute that in other countries because supply shortages increase the risk of unsafe injection practices.

Logistics project in the WHO African Region



Safety boxes for the disposal of used syringes and needles

Incineration of a safety container with used reringes

Auto destruct syringe

In an effort to tackle the problem of unsafe injections, three WHO programmes (the Division of Emerging Diseases Surveillance and Control, the Division of Emergency and Humanitarian Action, and the Global Programme for Vaccines and Immunization), together with the Programme and Supply Divisions of UNICEF, signed a joint policy statement (WHO/EPI/LHIS/97.04). This recommends that adequate supplies of non-reusable autodestruct syringes and safety boxes are automatically provided along with high quality vaccine for all mass immunization campaigns, including measles control operations (the so-called "bundling policy").

MILESTONES/TARGETS

By 1998:

- ▷ VVMs introduced on two EPI vaccines (in addition to oral polio vaccine).

By 1999:

- ▷ Funding for the replacement of cold chain equipment secured in all countries in greatest need.
- ▷ Injection safety assured in all countries in greatest need.
- ▷ All emergency and elective mass immunization campaigns to be planned in line with the "bundling strategy".
- ▷ A good quality cold chain documented in all countries in greatest need.

By 2000:

- ▷ VVMs introduced on remaining EPI vaccines.

The introduction of vaccine vial monitors (VVMs) on oral polio vaccine vials is probably the single most important event in the vaccine cold chain since the EPI was launched in the 1970s.

INDICATORS

- Percentage of countries where VVMs have been introduced.
- Percentage of countries with no vaccine stockouts at the national levels.
- Percentage of countries with a safe injections component in their Action Plan and which have implemented a budget for the procurement and supply of syringes, needles, safety boxes, and sterilizers.
- Percentage of countries in greatest need (Annex 1) with all funding secured for the replacement of cold chain equipment.

STATUS AS OF DECEMBER 1997

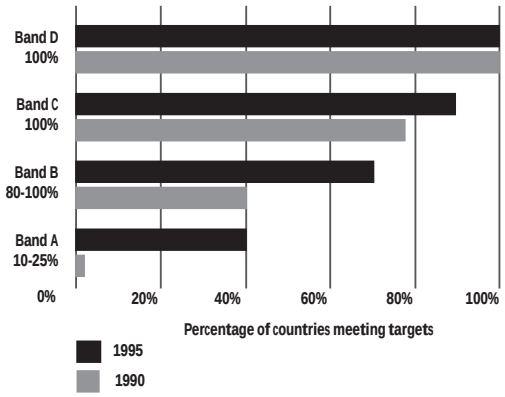
- VVMs have been introduced on oral polio vaccine in more than 80 countries.
- Vaccine stockouts have been reported from Bangladesh, PDR Korea, and Thailand. No data are available from African countries.
- The "bundling policy" was adopted for all mass immunization campaigns for the control of epidemic meningitis conducted in Africa in 1997. It was also successfully implemented for measles campaigns in Chad, Democratic Republic of Congo (formerly Zaire), and Fiji.
- Plans for injection safety have been implemented in Haiti and Laos but not in Afghanistan, Djibouti, or Somalia. Of the African countries targeted by the logistics project, six have conducted rapid assessments of injection practices, and four have made – or are making inventories of their equipment and transport on which to base estimates of needs over the next five years. Five countries have prepared three-to five-year plans including specific actions to strengthen their logistics systems.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	976 000	559 000	–417 000
1999	820 000	332 000	–488 000

Vaccine self-sufficiency

WHILE many of the VSQ targets are monitored at the global level, self-sufficiency can only be monitored at the national level. To be successful in the long term, national immunization programmes must not only protect lives now, but must be able to continue to expand national efforts, independent of outside donor support. Only when a country has taken on responsibility for the programme is the introduction of new vaccines possible. Donors need to act in a coordinated fashion, directing aid to countries according to their need and encouraging countries of intermediate wealth to take responsibility for paying for both existing and new vaccines. Self-sufficiency targets have been set for countries, which takes into account each country's relative wealth and population, and thus its ability to pay.

Progress sustainability targets (1990-1995) % = Target



67% of all countries and 25% of countries in greatest need are meeting their self-sufficiency targets.

OBJECTIVE

- To encourage countries that can afford to pay for their own vaccines to do so.
- To make countries independent of outside support for funding, technical assistance, vaccine supply, and training.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Governments have made continuous progress in taking on the responsibility for financing their immunization programmes and vaccine supply. Today, 67% of all countries and 25% of countries in greatest need are meeting their self-sufficiency targets. In addition, WHO is developing a new training system to strengthen each country's ability to procure quality vaccine in a reliable, competitive fashion.

MILESTONES/TARGETS

By 1998:

- ▷ Self-sufficiency goal for 80% of countries throughout the world.
- ▷ 40% of countries in greatest need to be financing at least 20% of their vaccine requirements, with collaboration from EPI.

By 1999:

- ▷ 80% of the countries in greatest need to be financing at least 20% of their vaccine requirements, with collaboration from EPI.

By 2001:

- ▷ Self-sufficiency goals to be sustained by 90% of all countries for priority vaccines.

INDICATORS

- ▷ Percentage of countries meeting self-sufficiency targets for "traditional" vaccines.
- ▷ Percentage of vaccine needed for routine programmes that is financed through national budgets.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	18 000	18 000	0
1999	14 000	14 000	0

International procurement of vaccines

As countries approach self-sufficiency and rely less on donated vaccine, they will need to acquire new techniques to purchase vaccines internationally. Without these techniques, national costs could increase, vaccine availability could be reduced and quality compromised. Procurement guidelines have been developed and circulated by VSQ, to assist countries in buying their own vaccines.

OBJECTIVE

- To ensure that all countries are able to purchase vaccines at low cost from reliable sources with suitable specifications and meeting acceptable standards of safety and efficacy.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

International guidelines and training documents have been amended to include WHO recommendations. Assessment of procurement systems in the Gulf States as a model for other group purchases. Four-country procurement training workshop held in Sri Lanka.

MILESTONES/TARGETS

By 1998:

- Effective procurement systems to be available for all countries procuring vaccines.

INDICATORS

- Percentage of countries using procurement standards (**Status:** not yet monitored).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	109 000	109 000	0
1999	94 000	94 000	0

Vaccine donation policy

FOR countries that still receive donations, it is important that each has a policy to deal with these, to ensure that donated vaccines are of good quality and are consistent with national policy. In 1996, the Drug Action Programme published guidelines on donations of pharmaceutical products, which had the same aim.

OBJECTIVE

- To ensure that donated vaccines are of good quality and are consistant with National policy.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

In 1997, VSQ published a policy document on Vaccine Donations (WHO/VSQ/97.05). This was also published in the *Essential Drugs Monitor* to obtain a wider audience.

Vaccine donations were discussed in regional meetings in the South East Asia and Eastern Mediterranean Regions. These regions, together with the African Region, have developed regional donations policies.

After reviewing progress, VSQ has determined that major efforts in 1998 will be targeted to: strengthening National Control Authorities in those countries likely to receive vaccine donations (generally the same as those which receive vaccine through UN agencies); and promoting the Good Donation Policy among vaccine donors.

MILESTONES/TARGETS

By 1998:

- All countries to have outlined a mechanism to deal with vaccine donations.
- Major vaccine donors to have been contacted regarding Good Donations Policy.

By 2000:

- All countries receiving vaccines from UN agencies to have in place the two Critical Control Functions needed.

INDICATORS

- Number of countries with guidelines on donations (**Status:** not yet monitored).

Maximizing efficiency of vaccine use

NOT all countries have implemented policies that lead to the most efficient use of the vaccines they buy. As a result, vaccine wastage is high and costly.

OBJECTIVE

- To reduce the wastage of vaccine to 10% or less without any negative impact on the effectiveness of the immunization programme as measured by coverage.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

During 1994, it was estimated that 62% of vaccine was wasted. However, as a result of new forecasting techniques, immunization programmes were able to switch to smaller, more appropriate vial sizes. Meanwhile, laboratory and field studies confirmed the safety of using vaccine for multiple sessions – thereby eliminating the need to discard liquid vaccine at the end of each session. The introduction of temperature-controlled vaccine vial monitors (VVMs) into the programme in 1997, made it easier for programmes to accept the use of liquid vaccines on subsequent days. Despite these advances, many countries, especially those receiving vaccines as a donation, do not yet use appropriate vial sizes and have not adopted the use of the multi-dose vial policy.

MILESTONES/TARGET

By 1998:

- Vial-opening rules adopted by countries in which children represent 25% of the total population.

INDICATOR

- Number of countries adopting vial opening rules.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	10 000	10 000	0

S SELF-SUFFICIENCY — SURVEILLANCE & OTHER INFORMATION SYSTEMS

Surveillance

EFFECTIVE disease surveillance that is both efficient and action oriented is critical to guide disease control activities, monitor programme performance, and target resources efficiently. Information on immunization coverage reflects programme efficiency and access to services. Information on programme activities and resources is necessary to ensure injection safety and vaccine delivery at the periphery. In summary, the following information "package" is needed to manage immunization programmes, monitor programme performance, and ensure safety:

- Key programme indicators (e.g. disease surveillance data, immunization coverage, process/performance indicators);
- Implementation status of key activities (e.g. training, supplemental activities, supervision/ evaluations);
- Resources:
  - human
  - financial
  - equipment (e.g. cold chain equipment/vehicles)
  - commodities (e.g. vaccines/ injection materials);
- Demographic data;
- Policies (immunization schedules, immunization policies, surveillance policies).

While surveillance performance has improved in all regions, more improvements are urgently needed.

OBJECTIVE

- To introduce standardized, efficient, and action oriented information systems for all EPI diseases.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Over the past year, WHO/HQ has developed and published recommended surveillance standards that include case definitions, type of surveillance needed, data elements to collect, analyses, and use of data for decision-making. A prototype software was developed to monitor coverage and incidence as well as surveillance and programme performance. Workshops have been held in several WHO regions to improve data management and field surveillance. In 1997, surveillance reference materials were finalized and made available as hard copy and on diskette for adaptation to local conditions. Over the past three years, the amount of technical assistance provided to countries has increased dramatically in the form of surveillance assessments, designated personnel, training, and consultants. While surveillance performance has improved in all regions, more improvements are urgently needed.

MILESTONES/TARGETS

By 1999:

- ▷ Standardized and efficient information systems for EPI target diseases operational in 50% of countries, and surveillance data directly linked to disease-control goals and activities.
- ▷ Information systems for EPI in 50% of countries to include a complete package of programme indicators, activities, resources, demographic data, and policies.
- ▷ Available technologies to maximize the efficiency of data management and transfer appropriately exploited in 50% of countries .

By 2001:

- ▷ Standardized and efficient information systems for EPI target diseases to be operational in 75% of countries, and surveillance data to be directly linked to disease control goals and strategies.
- ▷ Information systems for EPI in 75% of countries to include the complete information package (surveillance

The challenge of strengthening surveillance and other information systems for immunization programmes is to:

- Standardize and minimize data collection by clearly defining data needed for action;
- Ensure adequate resources (human, financial, equipment, supplies) for surveillance activities;
- Address the logistical challenges involved in collecting essential information and specimens;
- Ensure good management and efficient transfer of data;
- Strengthen capacity for analysing and using data at national and subnational levels.

New information and communication technologies are rapidly emerging that make data management and transfer easier and more efficient. These technologies should be appropriately exploited at all levels. Support from proficient laboratories with good data management is also critical so that laboratory information can be used to guide strategies. Good teamwork is essential among laboratory, EPI, surveillance, and clinical staff in order that appropriate information can be collected and used effectively for public health action.

Effective disease surveillance that is both efficient and action-oriented is critical to guide disease-control activities, monitor programme performance, and target resources efficiently.

data, indicators, activities, resources, demographic data, and policies).

- ▷ Available technologies to maximize the efficiency of data management and transfer appropriately exploited in 75% of countries.

INDICATORS

- ▷ Percentage of countries managing the complete package of EPI information.
- ▷ Percentage of countries achieving targets of surveillance performance indicators (Annex 2).
- ▷ Percentage of countries managing and transferring EPI data electronically according to standards defined by the WHO Regional Office.

STATUS AS OF DECEMBER 1996

Completeness of monthly reporting of EPI targets from district to national level:

AMR: all 47 countries comply.

EMR: 14 (61%) of 23 countries comply. Three of the countries which do not reach the 80% mark are CIGNs (Afghanistan, Djibouti, Somalia).

SEAR: 7 (70%) of 10 countries comply.

No data were provided from EUR, WPR, or AFR.

Regular written feedback (quarterly):

AMR: 47 countries (100%) comply.

EMR: 0 countries comply.

SEAR: 8 countries (80%) comply.

No data were provided from EUR, WPR, or AFR.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	987 000	735 000	–252 000
1999	1 112 000	996 000	–116 000

Availability of laboratory services

LABORATORY services are an essential element of disease surveillance. A network of proficient laboratories is critical to the achievement of polio eradication and certification, as well as for yellow fever and measles control.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**1 905 000**	**576 000**	**–1 329 000**
1999	**2 005 000**	**541 000**	**–1 464 000**

Laboratory services are an essential element of disease surveillance.

OBJECTIVE

- Availability of a Global Network of fully accredited laboratories using WHO recommended techniques, methods and reagents.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

To support surveillance and the detection of poliovirus, a Global Polio Laboratory Network was set up and now operates in each WHO region. The network provides virological laboratory support to all countries. The Network currently consists of 67 National Laboratories, 14 Regional Reference Laboratories and 6 Specialized Reference Laboratories. To ensure the quality of the network, an annual accreditation programme was initiated in 1997 and will be completed for all National and Regional Laboratories by April and August 1998 respectively.

MILESTONES/TARGETS

By 1999:

- All countries to have access to a WHO-accredited laboratory for polio surveillance.
- All critical laboratories within the polio laboratory network to attain and sustain their accreditation status.
- Establishment of a database of wild polioviruses by geographic origin.
- At least 85% of laboratories to be exploiting existing technologies for efficient data management and transfer.
- All countries in the measles elimination phase to have access to appropriate laboratory support.

By 2001:

- All critical laboratories within the polio laboratory network to be sustaining their accreditation status.
- A database of major measles virus families by geographic origin to be established and regularly updated.
- A strain bank of measles viruses to be established.
- All laboratories within the EPI laboratory network to be exploiting existing technologies for efficient data management and transfer.

INDICATORS

- ▷ Existence of a global wild poliovirus database by geographic origin.
- ▷ Percentage of laboratories within the polio laboratory network that have maintained their accreditation status.
- ▷ Percentage of laboratories within the network that are managing and transferring data electronically.

STATUS AS OF JANUARY 1998

Data not available until the network completes the accreditation process in April and August 1998.

SELF SUFFICIENCY – US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Maximizing efficiency of vaccine containers	284 000	130 000	–154 000	185 000	150 000	–35 000
Procurement guidelines for new purchasers	65 000	55 000	–10 000			
Vaccine quality	1 024 000	820 000	–204 000	1 041 000	651 000	–390 000
Demand forecasting for routine vaccines	64 000	64 000	0	44 000	44 000	0
Appropriate supply sources	245 000	245 000	0	215 000	215 000	0
Coverage	50 000	20 000	–30 000	50 000	20 000	–30 000
National planning	147 000	97 000	–50 000	100 000	0	–100 000
Training	131 000	45 000	–86 000	120 000	30 000	–90 000
Targeted support	143 000	103 000	–40 000	135 000	35 000	–100 000
Availability and quality of resources at point of use	976 000	559 000	–417 000	820 000	332 000	–488 000
Vaccine self-sufficiency	18 000	18 000	0	14 000	14 000	0
International procurement of vaccines	109 000	109 000	0	94 000	94 000	0
Vaccine donation policy						
Maximizing efficiency of vaccine use	10 000	10 000	0			
Surveillance	987 000	735 000	–252 000	1 112 000	996 000	–116 000
Availability of laboratory services	1 905 000	576 000	–1 329 000	2 005 000	541 000	–1 464 000
Global coordination	1 239 000	1 186 000	–53 000	1 149 000	1 407 000	258 000
Total workplans	**7 397 000**	**4 772 000**	**–2 625 000**	**7 084 000**	**4 529 000**	**–2 555 000**
Programme support costs*		497 000	–341 000		536 000	–332 000
Grand total		5 269 000	–2 966 000		5 065 000	–2 887000

*On voluntary funds only

DISEASE CONTROL

— FILLING THE VACCINE PIPELINE

Measles control: development of new formulations of the current measles vaccine for alternative route of administration

MASS campaigns are becoming increasingly popular in countries as key methods of measles control. The development of an easily-administered vaccine for use in a campaign is therefore a priority.

OBJECTIVE

- To develop a new formulation of vaccine to help facilitate mass immunization campaigns.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The main approaches for development of new formulations of measles vaccine were identified in 1997. Three research projects are currently under way.

MILESTONES/TARGETS

By 1998:

- Selection and support of research projects.

By 2000:

- Preclinical evaluation of candidate vaccines in monkey model.

By 2000:

- Development of network of laboratories with monkey facilities.

By 2001:

- Clinical evaluation of candidate vaccines.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	279 000	232 000	–47 000
1999	290 000	237 000	–53 000

Aerosol measles vaccine

AEROSOL vaccination could make it easier to carry out mass campaigns of immunization against measles. The objective of the project is to measure the immune response in children immunized with measles vaccines administered by aerosol route or subcutaneously.

OBJECTIVE

- To complete testing of aerosol measles vaccine.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The study involves children from 20 primary schools in Durban, South Africa. Preliminary results show considerable potential of EZ measles vaccine administered by aerosol route.

MILESTONES/TARGETS

By 1998:

- ▷ Immunogenicity study in South Africa conducted.

By 1999:

- ▷ Evaluation of results completed.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	45 000	44 000	–1 000
1999	45 000	32 000	–13 000

Neonatal tetanus elimination – development of simpler-to-deliver tetanus vaccines

CONTROL of neonatal tetanus was identified as a primary target for the EPI. Despite substantial advances in the control of the disease, the need to repeatedly inject the tetanus toxoid vaccine over several months is a factor which is somehow hampering successful achievement of a sufficient level of maternal immunity to protect the neonates from the disease. The drop-out rates from individuals receiving a first dose but not successive doses in developing countries can be as high as 70%, which demonstrates a major problem for full immunization. It is obvious that a single-dose vaccine against neonatal tetanus able to fully immunize at the first health-care contact of a pregnant woman would stretch immunization coverage to both low compliant and difficult to reach populations. In addition, it would also represent a good model to be applied to a number of childhood vaccines requiring multiple doses such as DTP and hepatitis B.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	116 000	56 000	–60 000
1999	117 000	57 000	–60 000

OBJECTIVE

- To develop and evaluate a single-dose vaccine against tetanus

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Three approaches were identified as ways to develop single – or reduced – dose regimes for vaccines: a live-vector (*Salmonella*); an adjuvant (polyphosphazene); and a controlled-release system, consisting of polymeric microparticles that release the antigen in a programmed way. The model antigen was tetanus toxoid, but other antigens were also used. These projects are today at different stages of pre-clinical and Phase I clinical evaluation. Emphasis was given to the controlled-release vaccines. The first stages of this project encountered stability problems that resulted in a loss of immunogenicity of the toxoid in the microspheres.

Attempts to solve this problem were made by (a) an additive that will protect and stabilize; (b) particles with improved design to achieve the desired release profile; (c) an accepted adjuvant as excipient combined with one-dose of tetanus toxoid-containing microspheres. Single doses of current improved formulations have shown to induce similar immune responses as at least two doses of conventional vaccines.

MILESTONES/TARGETS:

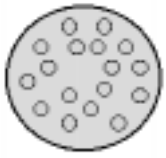
By 1998:

- Preclinical studies completed.

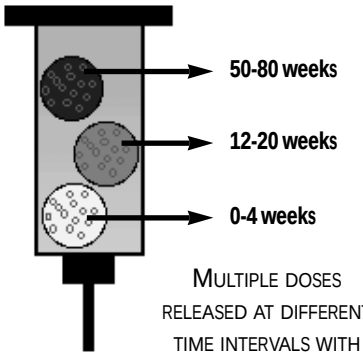
By 1999:

- Clinical studies initiated.

Single-dose controlled release vaccines



MICROSPHERES CAN BE PRODUCED SUCH THAT THEY ENCAPSULATE PROTEIN ANTIGENS.



MULTIPLE DOSES RELEASED AT DIFFERENT TIME INTERVALS WITH ONLY ONE SHOT.

D DISEASE CONTROL — GLOBAL LOGISTICS AND QUALITY OF VACCINE

The supply system, based on demand, supply, and financing considerations, as described under Self-sufficiency, will serve to deal with specific disease control strategies as well.

Supply system for emergency needs

VACCINE supplies issued for emergencies are subject to the same problems as those for routine use. However, in an emergency all issues must be resolved immediately. With the Division of Emergency and other Communicable Diseases Surveillance and Control (EMC), VSQ is developing the foundations of an emergency vaccine supply system, based on lessons learned from dealing with vaccine supply for disease control activities and problems encountered in recent emergency situations. Such a system will include a method for ascertaining and aggregating demand, for assessing available vaccine production capacity, development of a vaccine stockpile of high quality, and designating responsibility for a coordinated vaccine financing, procurement, and distribution system.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	14 000	14 000	0
1999	14 000	14 000	0

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Long term financial mechanism is established with a revolving fund mechanism.

MILESTONES/TARGETS

By 1998:

- ▷ Extended supply system to meet other emergency needs.
- ▷ A financial system in place to meet emergency needs for vaccine.
- ▷ Cost of stockpile to have been estimated and funds raised.
- ▷ All "traditional" donors to have been approached.

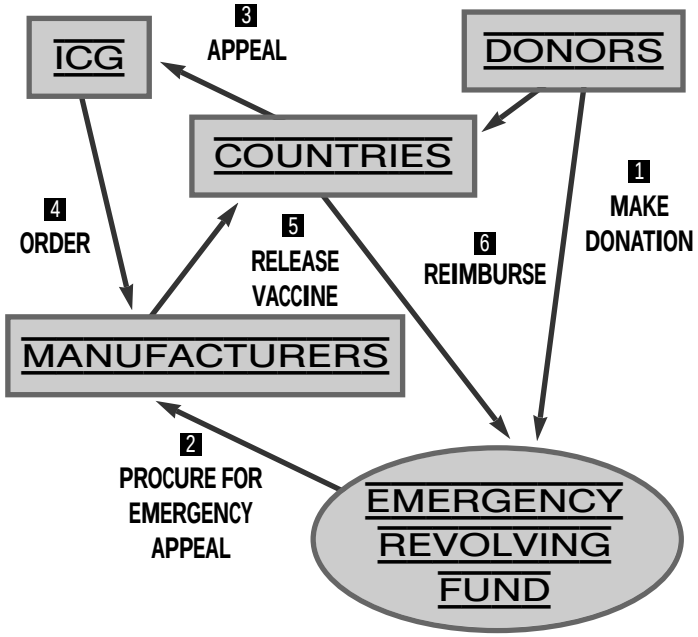
INDICATORS

Percentage of emergencies for which adequate quantities of vaccines are available.

CURRENT STATUS

Not yet monitored.

An emergency preparedness fund



Demand-forecasting for accelerated immunization activities

In all accelerated immunization activities, knowledge of the aggregated global demand is essential to ensure that vaccines are available on demand.

OBJECTIVE

- For vaccines newly introduced into the programme, to make adequate global demand forecasting using models to ensure supply. For vaccines already in the programme, to help countries improve the accuracy of national planning.

1994-1997, PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Models for forecasting demand for newly introduced vaccines are now under discussion. More data and information are needed to improve the reliability of these models.

MILESTONES/TARGETS

By 1998:

- For vaccines newly introduced into the programme, global vaccine demands to be known within 20% of global demand.
- For vaccines already in the programme, countries' needs in demand-forecasting method to have been identified and a simple, useful forecasting tool to be under development based on needs in the field.

INDICATORS

- Number of countries identified to cooperate in the field testing of the new forecasting method.
- Doses forecasted and doses supplied.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	12 000	7 000	–5 000
1999	39 000	12 000	–27 000

Maximising efficiency of vaccine containers

DURING National Immunization Days (NIDs) with oral poliomyelitis vaccines (OPV), vaccines are handled in a non-routine manner. The use of vaccine vial monitors (VVMs) on all vials would assure the quality of vaccines at the point of use during NIDs and routine immunization activities. VVMs are now on all doses of OPV supplied by UNICEF. Countries obtaining vaccines by other means should also have access to VVMs.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	18 000	5 000	–13 000
1999	18 000	15 000	–3 000

OBJECTIVE

- To reduce the wastage of vaccine to 10% or less without any negative impact on the effectiveness of the immunization programme as measured by coverage.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Evaluation of OPV droppers currently in use has shown that the number of doses from a twenty-dose vial may be as low as 15 doses. This reduction in expected doses depends on the design of containers, the practices of the user, and the temperature of the vaccine. Studies have identified the variables than can affect the efficiency of the dropper and some of these can be controlled. Modest changes in design are expected to halve the number of wasted doses. This will not only save money but also help improve the accuracy of forecasting and certainty of supply.

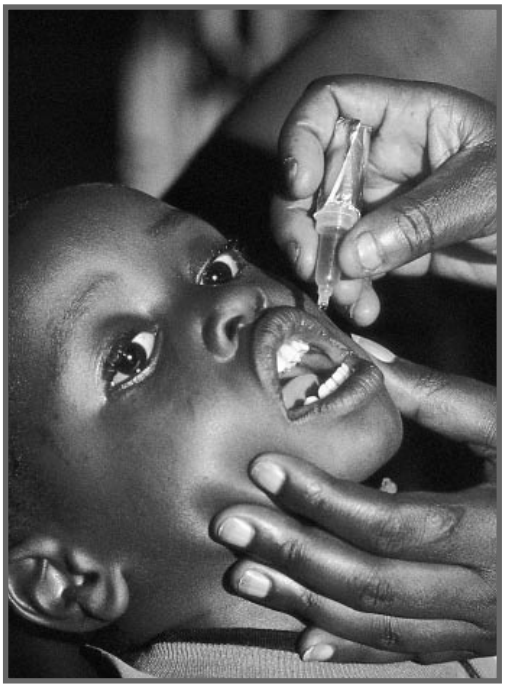
MILESTONES/TARGETS

By 1998:

- Dropper efficiency improved from 80% to 90%.

INDICATORS

- Vaccine wastage during NIDs.
- Number of local OPV producers supplying OPV with VVMs.



Transgenic mice as a model for routine screening of oral polio vaccine (OPV)

THE monkey neurovirulence test adopted by WHO in 1982 has proved to be a reproducible assay. However, for several reasons, including ethical concerns, the high cost of monkeys, and the potential danger of exotic diseases, there is a need to replace monkeys with another animal species in the OPV neurovirulence test.

OBJECTIVE

- To improve biological control of OPV.

1994-97 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two stages of the WHO collaborative study involving OPV manufacturers and national control agencies, demonstrate a good correlation between monkey and transgenic mice neurovirulence tests.

MILESTONES/TARGETS

By 1999:

- ▷ Submission of proposals to WHO Expert Committee on Biological Standardization (ECBS).
- ▷ Revision of Requirement by ECBS.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	155 000	155 000	0
1999	185 000	154 000	–31 000

D DISEASE CONTROL

— NATIONAL VACCINE DELIVERY

The achievement of targeted levels of disease control for the EPI diseases requires specific strategies that are tailored to the disease and its epidemiology. For each EPI disease, such strategies have been elaborated, promoted, and translated into action through activities implemented by regional offices and national staff.

Polio eradication

In 1988, the World Health Assembly set a goal of global eradication of polio by the year 2000. While the eradication initiative is based on achieving and maintaining high routine immunization coverage, three additional strategies are recommended for all endemic or recently endemic countries. These strategies involve: conducting two rounds of National Immunization Days (NIDs) annually; implementation of effective acute flaccid paralysis (AFP) surveillance, including laboratory investigation of all cases; and, once wild poliovirus circulation is reduced to focal

OBJECTIVE

- To eradicate polio by the year 2000.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Final victory in the war against polio is close, with wild poliovirus transmission now restricted primarily to the Indian subcontinent and West and Central Africa. In the Western Pacific Region, where polio was widespread until recently, no wild poliovirus was detected for the last ten months of 1997, despite excellent surveillance; in China, no indigenous wild poliovirus has been found for over three years. In 1997, breakthroughs were also achieved in many high priority countries in other parts of the globe. They included Egypt, where the polio high-transmission season passed with very few reported cases involving wild polioviruses. In the European Region, only seven polio cases were reported, the lowest number ever, with wild poliovirus found only in south eastern Turkey.

Intensive eradication activities continued on the Indian subcontinent, until now the largest remaining reservoir of wild poliovirus. India reported a dramatic decline in cases following two National Immunization Days (NIDs) during which more than 120 million children were immunized over a few days. Elsewhere, temporary truces were negotiated in countries in conflict, including Afghanistan, so that children on both sides could be immunized. NIDs have now been conducted in all polio-endemic countries in Africa apart from the Democratic Republic of Congo (formerly Zaire), Liberia, Sierra Leone. During 1997, more than 420 million children were immunized globally during NIDs and sub-national immunization days (SNIDs). The number of countries which have conducted NIDs or sub-NIDs (SNIDs) increased to 117 by the end of 1997.

Wherever possible, immunization efforts have been planned so that neighbouring countries synchronize their NIDs. This increases the impact of NIDs and helps ensure that migrant populations in border areas are also reached. A total of 257 million children under five years were immunized during coordinated NIDs between December 1996 and January 1997 in the WHO South-East Asia Region (Bangladesh, Bhutan, India, Myanmar, Nepal, Thailand), Western Pacific Region (China, Viet Nam) and Eastern Mediterranean Region (Pakistan).

geographic areas, house-to-house "mopping up" immunization to interrupt the last chains of transmission. At all stages of the initiative efforts are needed to establish or maintain high routine immunization coverage. Once circulation of wild poliovirus has been interrupted, high immunization coverage with polio vaccine and high quality AFP surveillance is critical for regional and global certification.

The programmatic priorities of the eradication initiative at the global level are: to implement or improve the quality of NIDs; to establish effective AFP surveillance in all countries which are currently or have recently been endemic for polio; to ensure all diagnostic specimens are processed in WHO-accredited laboratories; to begin the process of certification through independent Regional Certification Commissions; and to secure sufficient resources to ensure that these tasks are accomplished with maximum efficiency and all due speed. Given the progress of the eradication initiative to date, WHO/HQ is also beginning the process of establishing action plans and research agendas to address the issues of containment of polioviruses and the eventual cessation of polio immunization worldwide.

Almost 60 million children were immunized in the third year of "Operation MECACAR" during March and April 1997 as part of synchronized NIDs involving 18 countries in the European and Eastern Mediterranean Regions. NIDs conducted in Africa in 1997 benefited greatly from the continent-wide initiative, "Kick Polio out of Africa", launched by President Mandela of South Africa in 1996. In the Western Pacific, large 'mopping-up' immunization activities targeted the last remaining reservoir of wild poliovirus in Cambodia and the Mekong delta area of Viet Nam.

The global impact of eradication activities was reflected in a further drop in reported cases. As of 1 February 1998, the preliminary total number of confirmed polio cases reported in 1997 was approximately 2 500, compared to 35 000 cases reported in 1988, when the global eradication goal was set.

Despite the progress to date, the eradication initiative continues to face a number of significant challenges, the most important of which include: securing the resources necessary to fully implement the eradication strategies in countries which are politically isolated and/or affected by conflict; improving surveillance worldwide to accurately and rapidly identify wild poliovirus transmission; and maintaining the necessary political commitment in both endemic and polio-free countries to achieve the goal of eradication by the year 2000.

MILESTONES/TARGETS

By 1998:

- ▷ All endemic countries to have conducted at least one round of high quality NIDs reaching > 80% of the target population.
- ▷ All endemic countries to have established Acute Flaccid Paralysis (AFP) surveillance with at least 60% of countries demonstrating high quality surveillance.
- ▷ Specimens from every case of AFP investigated by an accredited laboratory.
- ▷ Wild poliovirus transmission interrupted in the European and the Western Pacific regions and indigenous transmission of wild poliovirus ceased in Northern and Southern Africa and the Middle East.
- ▷ Strategic plan developed for the safe handling and eventual disposal of poliovirus stocks.
- ▷ Finalization of the research agenda for eventually stopping immunization.

By 2000:

- ▷ At least three years of high quality NIDs (six rounds) implemented in all high-risk countries in the African, Eastern Mediterranean, and South-East Asia Regions.

Final victory in the war against polio is close.

- ▷ All countries meeting the surveillance criteria needed for eventual certification.
- ▷ Wild poliovirus transmission stopped in all countries.
- ▷ The Western Pacific Region and the European Region certified as polio-free.
- ▷ Wild poliovirus stocks identified worldwide and safe handling procedures in place.
- ▷ A plan and strategy for stopping polio immunization defined.

INDICATORS

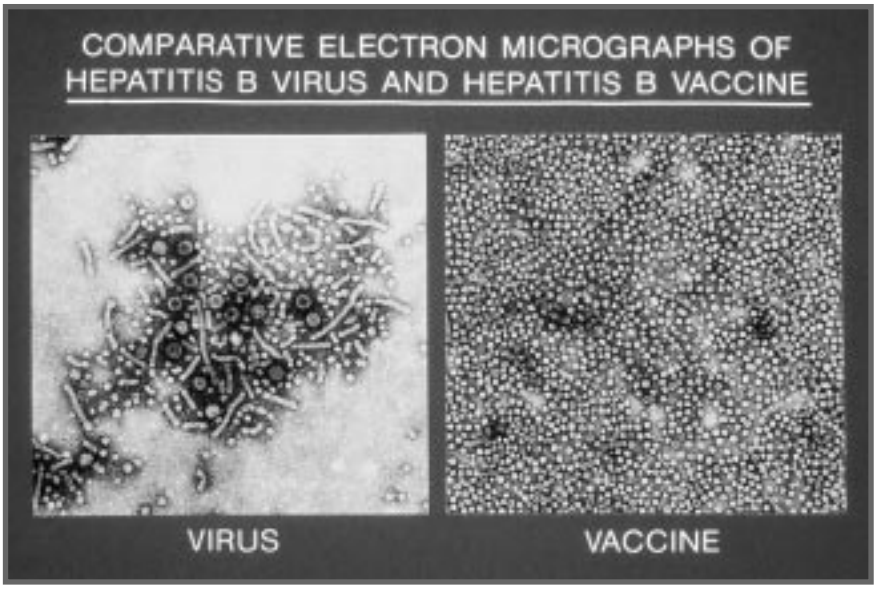
- ▷ Number of polio cases reported by country, region, and worldwide.
- ▷ Number of wild polioviruses reported by country, region, and worldwide.
- ▷ Percentage of countries achieving the key AFP surveillance indicators (Annex 2).
- ▷ Number of Global Polio Network laboratories which are fully accredited.
- ▷ Number of regions and countries certified as polio-free.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	3 921 000	2 337 000	–1 584 000
1999	3 095 000	2 134 000	–961 000

STATUS

1997 Reported polio cases (as of April 1998):

AFR:	219
AMR:	0
EMR:	1 023
EUR:	7
SEAR:	2 118
WPR:	9
Global:	**3 376**



Measles control

STRATEGIES to strengthen measles control have to be tailored to the level of measles control reached. Countries with limited measles control (i.e. those in the "control phase") should focus on improving routine coverage and ensuring proper case management, particularly in high-risk areas, to reduce measles mortality. In addition, accelerated immunization activities should be targeted in areas of high measles morbidity and mortality, particularly densely populated peri-urban areas.

Countries with advanced measles control (i.e. those in the outbreak prevention phase) should strive to maintain high coverage, continue to focus on high-risk populations, and provide supplementary measles immunization to prevent potential measles epidemics due to an accumulation of susceptibles.

Measles outbreak prevention activities should be implemented in polio-free countries to ensure continued political and financial commitment so that the established infrastructure and momentum gained from polio eradication activities can be sustained for use in future measles eradication initiatives. One region (AMR) is already committed to the elimination of measles and to preventing importation of the virus by the year 2000. The major progress achieved so far of the Region of the Americas has increased global interest in the future eradication of measles. An additional region, EMR, has set a goal of measles elimination by the year 2010.

OBJECTIVE

- To control measles disease to levels where it no longer represents a public health problem.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The number of reported measles cases is down from 4.2 million in 1980 to 0.8 million in 1996. However, the number of reported cases is an underestimate. The disease still accounts for 10% of global mortality from all causes among children under five years of age. In 1996, just 21 countries accounted for 80% of all measles cases reported, of which 16 were in Africa, which accounted for 62% (446 000) of the global total of reported cases that year.

Forty countries (accounting for only 1% of the global population) reported zero measles cases in 1996, compared with 12 countries in 1990. Most of them are in the Region of the Americas (23), the Western Pacific Region (9), and the African Region (4).

Of the six WHO regions, the most significant progress in measles control was achieved in the Region of the Americas. In 1996 in that region, implementation of the current elimination strategies resulted in the lowest number of measles cases ever reported (2 109 cases). During 1993-1996, a total of 49 countries conducted a one-time immunization campaign ("catch up") to interrupt measles transmission, administering approximately 166 million doses of measles vaccine to children under 18 years of age (93% of the target population). Approximately 142 million of those doses were administered in the Americas. In addition, 29 countries in the Americas conducted at least one follow-up campaign where measles persisted after the initial campaign. In 1997, in the Americas, there were renewed measles activities, mainly in Brazil, involving young adults who had not been immunized.

MILESTONES/TARGETS

By 1999:

- 25% of countries to be reporting zero indigenous measles cases.
- 25% of countries with adequate measles control to have developed activities to prevent measles outbreaks.
- In addition to the Region of the Americas and the European Region, the setting of a goal for measles elimination by the Western Pacific Region, the Gulf and the Maghrebien countries.

Measles still accounts for 10% of global mortality among children under five years of age.

By 2001:

▷ A decision taken on a global measles eradication goal.

INDICATORS

▷ Percentage of countries with no indigenous measles cases reported.

STATUS AS OF DECEMBER 1996

22 % of countries report zero indigenous measles cases (27 in AMR, 2 in SEAR, 11 in WPR, 2 in EUR, 4 in AFR).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	688 000	657 000	–31 000
1999	726 000	625 000	–101 000

Neonatal tetanus elimination

NOT all countries are at equal risk of neonatal tetanus (NT). Twenty-five countries (Annex 3) contribute 90% of the global NT burden, estimated at 400 000 cases annually. Even within countries, NT cases tend to cluster according to local risk factors related to delivery practices, umbilical cord care, and access to health care.

OBJECTIVE

- Eliminate neonatal tetanus and maintain elimination from all countries (except those affected by conflicts).

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

By the end of 1996, more than 40 million women living in high-risk areas had been immunized with tetanus toxoid. This included 10 million women in high-risk counties of China, four million in 10 000 high-risk villages in Indonesia, and one million in Viet Nam. In addition, 340 000 women were immunized in door-to-door activities in Pakistan. With WHO and Canadian Public Health Association (CPHA) support, seven African countries (Burkina Faso, Côte d'Ivoire, Gambia, Mali, Niger, Nigeria, and Tanzania) initiated the high-risk approach in selected priority districts.

A technical meeting to review progress towards NT elimination and elimination strategies was held in Geneva on 24-26 April 1997. The meeting was instrumental in raising regional and country commitment towards the NT elimination goal and its sustainability. It confirmed the effectiveness of existing strategies and stressed the urgency for the 52 countries which have not yet eliminated NT to implement the high-risk approach. This involves three rounds of immunization with tetanus toxoid vaccine (TT), using auto-destruct syringes, targeted to all women of childbearing age in all high-risk areas of those districts which have not eliminated NT. To ensure the sustainability of NT elimination, the meeting also stressed the need for countries which have achieved the goal to introduce school-age boosters of diphtheria/tetanus vaccine (DT) or of tetanus vaccine with a reduced dose of diphtheria vaccine (Td).

Achieving the global goal of neonatal tetanus elimination by the year 2000 will necessitate a renewed commitment from the African Region and external financial support to immunize 60 million women of childbearing age in high-risk areas over the next 3 years.

MILESTONES/TARGETS

By 1999:

- ▷ All countries (except those affected by conflicts) to have eliminated and documented the elimination of neonatal tetanus by district.

By 2001:

- ▷ All countries (except those affected by conflicts) to be maintaining neonatal tetanus elimination.

INDICATORS

- Percentage of countries that have eliminated neonatal tetanus according to WHO criteria.
- In each of the 25 priority countries (Annex 3), the percentage of high-risk districts attaining coverage with two doses of tetanus toxoid (TT2+) of at least 80% among women of childbearing age.

STATUS AS OF DECEMBER 1997

- Percentage of high-risk districts where women of childbearing age have on average two doses of tetanus toxoid vaccine (TT2+): not available in the information system at HQ level.
- **Priority countries:** 10 countries (Afghanistan, Bangladesh, Burkina Faso, Côte d'Ivoire, Indonesia, Mali, Nepal, Pakistan, Sudan, Yemen) out of the 25 priority countries have prepared a three-year plan with a major emphasis on the high-risk approach.
- **Countries which have eliminated NNT:** 102 countries (64% of developing countries) have eliminated NNT. Of those that have not eliminated the disease, 25 account for 90% of cases.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	724 000	478 000	–246 000
1999	537 000	316 000	–221 000

Hepatitis B control

THE Expanded Programme on Immunization (EPI) and the World Health Assembly have called for all countries to include hepatitis B vaccine in their national immunization programmes by 1997. WHO's Ninth General Programme of Work calls for a 80% reduction in the incidence of new hepatitis B carriers in children by the year 2000.

As of October 1996, 83 countries had included hepatitis B vaccine in their national immunization programmes and 52 countries are reporting immunization coverage for the third dose of hepatitis B vaccine (HBV3). While most countries have introduced hepatitis B vaccine countrywide, some countries are phasing the vaccine into all areas over several years, and some countries are delivering hepatitis B vaccine outside their national immunization programme. The coverage of hepatitis B vaccine should be no less than the coverage of DTP.

Many countries with high disease burden and strong programmes have been forced to delay the introduction of hepatitis B vaccine because of their inability to afford the vaccine. Using a targeting strategy, the neediest, highest priority countries (measured by HBsAg greater than 5%, DTP3 coverage greater than 70%, and financial need in bands A and B) could be supported by roughly US$20 to $25 million a year in external financing. Focusing donor resources to the neediest countries can maximize the impact of external funds and ensure that cost-effective vaccines continue to be available.

OBJECTIVE

- To make the price of hepatitis B vaccine affordable to the neediest countries, and rapidly introduce hepatitis B vaccine into national immunization programmes.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

By January 1998, more than 90 countries had included hepatitis B vaccine in their routine national immunization programme, and another 13 are planning to add the vaccine during 1998. These countries account for approximately 47% of births and 67% of chronic hepatitis B carriers. It is estimated that the global coverage of HB vaccine is about 35%. Studies from many countries where the disease is highly endemic now show a marked decrease in the prevalence of HBV carriers in immunized cohorts of children, usually to below 1%. A direct reduction in liver cancer in immunized cohorts of children has already been demonstrated in Taiwan.

A number of new producers of HB vaccines have been approved for UN agency purchase, and a significant reduction in prices (down to US$0.50 - $1.00 per paediatric dose in developing countries) is already occurring, due to increased competition – allowing more countries to obtain the vaccine. Combination vaccines containing a hepatitis B component have been licensed, including DTP-hepatitis B vaccines containing both whole cell and acellular pertussis components, and a combined Hib-HB vaccine in the USA. Use of combination vaccines will allow some countries to add HB vaccine without the need for additional injections. More effort should now be given to financing the introduction of hepatitis B vaccine into Band A and B countries.

MILESTONES/TARGETS

By 1998:

- ▷ 50% of the financing of hepatitis B vaccine in priority band A and B countries assured.
- ▷ 50% of countries which have introduced hepatitis B vaccine to be reporting HBV3 coverage equal to their DTP3 coverage.
- ▷ 50% of countries to have included hepatitis B vaccine in their national immunization programme.

By 1999:

- ▷ 80% of the financing of hepatitis B vaccine for priority band A and B countries to be assured.
- ▷ 80% of countries which have introduced hepatitis B vaccine to be reporting HBV3 coverage equal to their DTP3 coverage.

By January 1998, more than 90 countries had included hepatitis B vaccine in their routine national immunization programme, and another 13 are planning to add the vaccine during 1998.

- ▷ 80% of countries to have included hepatitis B vaccine in their national immunization programme.

INDICATORS

- ▷ Percentage of countries that have introduced hepatitis B vaccine as part of the national immunization programme.
- ▷ Percentage of countries reporting HBV3 coverage equal to their DTP3 coverage.
- ▷ Percentage of priority countries in bands A and B for which financing for hepatitis B vaccine is assured.

STATUS AS OF DECEMBER 1997

A total of 90 countries have introduced hepatitis B vaccine in their national immunization programme. Meanwhile, 18 countries are reporting HBV3 coverage equal to their DTP3 coverage and a further eight countries are within 5% of this goal. Among priority countries in bands A and B, 31% have secured financing for hepatitis B vaccine.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	568 000	366 000	–202 000
1999	705 000	409 000	–296 000

Other diseases and micronutrient supplementation

RESURGENCE of epidemics of other EPI diseases reflects the changing epidemiology of certain diseases as a result of immunization efforts, inadequate implementation of strategies, or inappropriate strategies. In many instances, remedial action is needed to strengthen the programme, improve logistics and management, or target efforts in areas at high risk or with poor programme performance. There is currently a need to improve disease control in certain regions of the world, particularly for yellow fever.

Meanwhile, WHO and UNICEF have jointly adopted the goal of elimination of vitamin A deficiency and its consequences by the year 2000. In countries with clinical and sub-clinical vitamin A deficiency (Annex 5), EPI will ensure that vitamin A is administered through routine immunization services to women and children, as part of supplementary immunization activities, and whenever children are treated for measles.

Only nine of the 34 at-risk countries have ever included yellow fever in their immunization programmes.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Yellow fever remains a public health problem in tropical and subtropical areas of Africa and South America. In 1996-97, four countries in West Africa experienced outbreaks. In 1996, Ghana reported 27 cases and five deaths and Benin reported 48 cases and 37 deaths in a first outbreak, and 38 cases and 28 deaths in a second outbreak the same year. In 1997, a case of yellow fever was confirmed in Northern Liberia which led to a large scale immunization campaign among refugees who were being repatriated from Guinea.

Two countries in South America reported outbreaks in 1996-1997. Bolivia had 30 cases and 21 deaths and Colombia reported four confirmed cases. The reason for the continuing outbreaks may be the over-reliance on "fire-fighting" immunization campaigns instead of focusing on routine immunization programmes and planning epidemic prevention strategies.

Although it has been recommended since 1988 that yellow fever vaccine be included in the routine infant immunization schedule of the EPI, only nine of the 34 at-risk countries have ever done so. Moreover, during 1996, only one country, Côte d'Ivoire, officially reported yellow fever coverage data (53%). WHO will hold an international technical meeting in early 1998 to review the lack of progress and make practical recommendations for improving efforts to prevent yellow fever.

The current policy on vitamin A is to promote its administration through three programme activities: routine immunization; supplementary immunization, such as NIDs, urban measles mass campaigns, and tetanus toxoid campaigns; and treatment of measles cases. This policy takes advantage of the similar target groups for immunization and vitamin A, and the low cost and ease of administration of vitamin-containing capsules. With backing from the Scientific Advisory Group of Experts (SAGE), a major initiative was launched during 1997 to implement these policies. Strong support has been received from other WHO Programmes , including the Nutrition Programme and the Integrated Management of Childhood Illness, as well as from other partners involved with vitamin A administration, including the Micronutrient Initiative, UNICEF, and Opportunities for Micronutrient Interventions (OMNI). Over the next two years, a number of countries will be identified which have populations suffering from vitamin A deficiency, and they will be offered support in their efforts to administer vitamin A through immunization services.

WHO and UNICEF have jointly adopted the goal of elimination of vitamin A deficiency and its consequences by the year 2000.

MILESTONES/TARGETS

By 1999:

- ▷ 80% of countries at risk of yellow fever outbreaks (Annex 4) to have included yellow fever vaccine in their national immunization programmes.
- ▷ All countries with clinical vitamin A deficiency (VAD) to have written plans of action for administering vitamin A through immunization services.

By 2001:

- ▷ 80% of countries at risk of yellow fever outbreaks (Annex 4) reporting yellow fever vaccine coverage equal to measles vaccine coverage.
- ▷ All countries with clinical VAD to be administering vitamin A during immunization services.
- ▷ All countries with sub-clinical VAD to have written plans of action for administering vitamin A through immunization services.

INDICATORS

- ▷ Percentage of countries at risk of yellow fever outbreaks (Annex 4) with yellow fever vaccine in their national immunization programme.
- ▷ Percentage of countries at risk of yellow fever outbreaks (Annex 4) reporting yellow fever vaccine coverage at least equal to measles vaccine coverage.
- ▷ Percentage of VAD countries administering vitamin A through immunization services.

STATUS AS OF DECEMBER 1997

Among at-risk countries, 29% have yellow fever vaccine in their immunization programme, but no at-risk country is reporting yellow fever vaccine coverage equal to measles vaccine coverage.

Among countries with known vitamin A deficiency, only 5% are administering vitamin A through their immunization programme.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	1 336 000	1 194 000	–142 000
1999	3 565 000	2 890 000	–675 000

D DISEASE CONTROL — SURVEILLANCE & OTHER INFORMATION SYSTEMS

Surveillance for measles

THE development of measles surveillance should evolve with the degree of measles control in a country. In countries with limited measles control, surveillance should monitor measles incidence trends and identify high-risk areas. As good measles control is achieved, surveillance data should describe the changing epidemiology of measles, identify population at risk, provide enough information to predict epidemics, and eventually pave the way for measles elimination. In the advanced measles elimination phase, intensive surveillance is needed to identify susceptible populations and identify any source of infection or importation.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	20 000	0	–20 000
1999	20 000	0	–20 000

OBJECTIVE

- Establish an effective and action-oriented measles surveillance system.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The creation of an effective measles surveillance system remains a major challenge in most industrialized and developing countries. Measles is not even a notifiable disease in some industrialized countries including Austria, France, Germany, and Japan. And even in countries where measles is a notifiable disease, there is substantial under-reporting of cases, and information on the age and immunization status of cases is not routinely collected.

Surveillance needs to be strengthened as a crucial component of accelerated measles control efforts. It is needed to evaluate the impact of the strategies and to monitor the build-up of susceptibles in a population.

The Region of the Americas has substantially improved measles surveillance. Forty three (91%) countries in the Americas are now reporting weekly, standardized case-based data with laboratory confirmation for measles.

MILESTONES/TARGETS

By 1998:

- Data on age group and immunization status for 30 % of the measles cases to be reported by all countries.

By 2000:

- Data on age group and immunization status for 80% of the measles cases to be reported by all countries.

INDICATORS

- Percentage of reported measles cases with information on age and immunization status.

STATUS AS OF DECEMBER 1997

AMR: 100%
EMR: 26%
SEAR: 60%
No data were provided from WPR, EUR, or AFR.

Surveillance for neonatal tetanus

SURVEILLANCE does not provide a complete picture of the incidence of neonatal tetanus (NT) because many cases are never reported. There is a need for more sensitive NT surveillance and for monitoring of other key indicators to assess the status of NT elimination and identify areas at high risk for the disease. Other key indicators include the proportion of clean deliveries, coverage with at least two doses of tetanus toxoid (TT2+), and the proportion of infants protected at birth against NT. Since NT tends to cluster, surveillance and indicator data need to be monitored by district. Retrospective hospital record reviews or active surveillance for NT should be conducted in key hospitals of 25 priority countries (Annex 3) to ensure that at least those cases seen in major hospitals are not missed and that appropriate actions are taken. In the same 25 priority countries, community surveillance should be considered in areas where NT cases are often never seen for treatment at a health facility.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	10 000	0	–10 000
1999	10 000	10 000	0

OBJECTIVE

- To establish effective and action oriented surveillance for neonatal tetanus.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The number of estimated NT deaths occurring globally has decreased by 42%, from 470 000 in 1990 to 275 000 in 1996. During 1996, 20 countries contributed to 82% of the global disease burden. There is evidence of some improvements in surveillance for NT in all WHO regions through more complete reporting by district, hospital record reviews, and active surveillance for NT cases. However the vast majority (95% of cases) are still not reported. Priority is given to complete reporting of NT cases from health facilities and use of all information available from existing health information systems to complement NT surveillance data. High risk areas can usually be identified through information available at the local level, and all resources should therefore be used to provide a protective dose of tetanus toxoid to women of childbearing age in these areas. Any suspected cases of NT in low risk areas (i.e. where NT should not occur) should be investigated.

MILESTONES/TARGETS

By 1999:

- Among all 25 priority countries for NT elimination, retrospective hospital record reviews to be conducted at least once annually, or active surveillance conducted to ensure that at least all cases occurring in major hospitals are notified through the routine reporting system.
- NT cases reported in countries/districts where NT has been eliminated to be investigated and supplementary immunization carried out.

INDICATORS

- Among the 25 countries at risk (Annex 3), the percentage conducting retrospective hospital reviews at least once annually or active surveillance in major hospitals (i.e. those likely to admit NT cases).
- Percentage of NT cases investigated in countries (districts) which have eliminated NT.

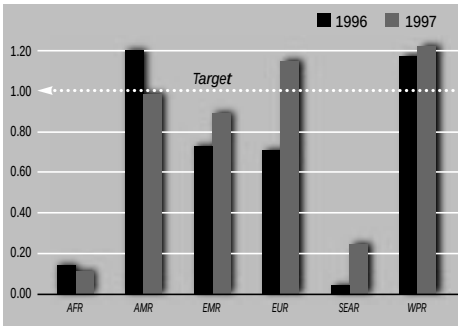
STATUS AS OF JANUARY 1998

No information available.

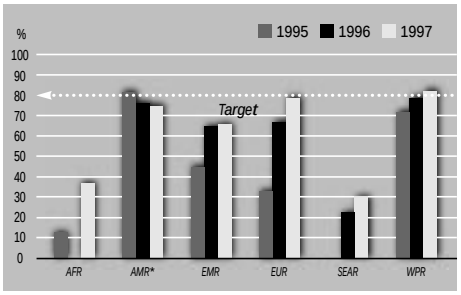
Surveillance for polio eradication

EFFECTIVE acute flaccid paralysis (AFP) surveillance is a key strategy for polio eradication to track wild poliovirus circulation, monitor performance, and provide evidence for polio-free certification. AFP surveillance should be established in all countries, involving immediate case investigation, stool specimen collection, and laboratory confirmation in a WHO-accredited laboratory.

Annualised non-polio AFP rate per 100 000 children under 15 years of age by WHO region, 1996 and 1997



Percentage of AFP cases with 2 specimens collected by WHO region, 1995-1997



OBJECTIVE

- To establish effective AFP surveillance.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

As the number of reported cases decreases and virus transmission is interrupted in increasingly large areas, high quality surveillance becomes essential to trace and detect wild poliovirus wherever it may still circulate, and to provide evidence for certification. Surveillance systems to report all cases of acute flaccid paralysis and to test for the presence of wild poliovirus are now established in most endemic and recently endemic countries. Meanwhile, AFP surveillance performance based on the two standard performance indicators has improved in all WHO regions.

MILESTONES/TARGETS

By 1999:

- All countries to have achieved the targets of standard indicators for AFP surveillance performance required by the Global Commission for the Certification of Poliomyelitis Eradication.

INDICATORS

- Non-polio AFP rate per 100 000 children aged under 15 years.
- Percentage of AFP cases for which two adequate specimens were collected.

STATUS AS OF JANUARY 1998

All regions have shown an improving trend between 1996 and 1997 for both indicators. The following two figures below show the number of countries per region achieving the performance targets.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	70 000	70 000	0
1999	70 000	70 000	0

New approaches for detection of polioviruses

Virus surveillance is critical to the eradication of polio. To ensure the highest quality virus surveillance, the WHO Laboratory Network needs new or improved methods for rapid and accurate detection of wild-type polioviruses in clinical and environmental samples.

OBJECTIVE

- To develop new tests for detection of wild-type polioviruses.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A new test was developed, and successfully field tested, for the detection of polioviruses in mouse cells (L20B) expressing the poliovirus receptor. At present, the test is being transferred to the WHO Laboratory Network for use in monitoring the circulation of poliovirus. Meanwhile the development of two other tests is under way, with promising results.

MILESTONES/TARGETS

By 1998:

- Development and introduction of methods to detect any wild polioviruses.

By 2001:

- Use of new tests for surveillance of circulation of polioviruses.

BUDGETARY COMMENTS

Common with New approaches for measles global surveillance, see page 52.

Surveillance for adverse events following immunization

VACCINE and injection safety is critical for every national immunization programme since the occurrence of adverse events following immunization (AEFIs) can seriously undermine a programme's credibility. Most serious AEFIs are related to programmatic errors rather than vaccine quality. Nevertheless, surveillance for AEFIs should also provide pertinent information for a National Control Authority (in case of vaccine quality problems).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	0	0	0
1999	10 000	10 000	0

OBJECTIVE

- To establish an effective and action oriented surveillance system for AEFIs.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

During 1997, sporadic reports of AEFIs were received from various countries. In one reported incident in 1997, 21 children died after 70 children were given insulin instead of DTP vaccine. Elsewhere, two Newly Independent States in Eastern Europe (NIS) reported cases of children becoming seriously ill following immunizations. In both cases, the vaccines were shown to be of acceptable quality. In one of the incidents, it was clearly confirmed that contamination of the vaccine had occurred during or after its reconstitution. It is therefore likely that these unfortunate events were all due to programmatic errors.

As a result of reports received in 1996 and 1997, WHO and UNICEF have joined forces to review the quality of service delivery in NIS countries to identify where problems occur in the distribution and delivery chain. Activities initiated in 1997 will be reviewed at the end of 1998. Meanwhile, the EPI field guide for managers on surveillance of AEFIs has been revised and printed in English and French.

MILESTONES/TARGETS

By 1999:

- 80% of countries to have established surveillance for serious adverse events following immunization according to WHO standards and guidelines.

INDICATORS

- Percentage of countries that have established surveillance for serious adverse events.

STATUS AS OF DECEMBER 97

AMR : 27 countries (56%);
EMR: 1 (4%);
SEAR: 6 (60%);
WPR : 8 (22%).
No data were provided from EUR or AFR.

Surveillance for yellow fever

YELLOW fever outbreaks are occurring with increasing frequency among the 34 African countries at risk (Annex 4). One of the key strategies for yellow fever control is the rapid detection of outbreaks and implementation of emergency immunization measures. Rapid outbreak detection requires detection and immediate investigation of all suspected cases, collection of the appropriate specimens, and processing of specimens in a proficient laboratory. Once an outbreak is confirmed in an area, the priority for surveillance is the detection of yellow fever cases in neighbouring areas.

OBJECTIVE

- To establish, in all at-risk countries, a routine system for the rapid detection of outbreaks of yellow fever to enable control measures to be taken.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Training courses on yellow fever laboratory procedures have been conducted for several African countries at risk, and there is a need to ensure continued laboratory proficiency as well as the availability of adequate reagents and other laboratory supplies. However, increased efforts are needed to improve field surveillance (detection, notification, specimen collection, and dispatch). This will require designated personnel, training, specimen collection kits, and improved logistics for surveillance.

MILESTONES/TARGETS

By 1999:

- Ten of the 34 at-risk countries to be collecting specimens from at least 50% of suspected cases during non-outbreak periods.

By 2001:

- Twenty of the 34 at-risk countries to be collecting specimens from at least 50% of suspect cases during non-outbreak periods.

INDICATORS

- Percentage of suspect cases from which specimens were collected (during non-outbreak periods).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	20 000	10 000	–10 000
1999	40 000	10 000	–30 000

New approaches for measles global surveillance

GLOBAL control of measles infection requires the development of new tools for laboratory confirmation of measles infection, and the creation of a system for the molecular typing of measles virus isolates from different geographical areas.

RAPID AND SIMPLE TEST FOR DETECTION OF ANTI-MEASLES IGM ANTIBODIES

The development of simple tests for diagnosis of measles infection that can be used in a primary health care setting is important for rapid differentiation of measles from a number of other skin-rash diseases (e.g. dengue, rubella).

OBJECTIVE

- Laboratory confirmation of measles in primary health care setting.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Recombinant proteins of measles virus as antigens have been prepared. Two projects are in progress to develop tests that should meet WHO requirements for simple and rapid tests.

MILESTONES/TARGETS

By 1998:

- Development of reference reagents.

By 1999:

- Evaluation of two prototypes in WHO Reference Laboratories.

By 2000:

- Field trials initiated.

MOLECULAR BIOLOGICAL SYSTEM FOR DIFFERENTIATION OF MEASLES VIRUS

Use of molecular epidemiological techniques is important for understanding the transmission of measles virus throughout the world. Moreover, studies on genetic and antigenic variability of measles virus strains provide information on the possible role of the variability of measles virus strains in the efficacy of immunization with the existing vaccine.

OBJECTIVE

- Use of molecular epidemiology to support measles control.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Molecular epidemiological techniques have been developed for comparative analysis of measles viruses isolated from different geographical areas, and a WHO bank of measles virus isolates established. Further studies should be encouraged for collection of new strains of measles virus from different regions.

MILESTONES/TARGETS

By 1998:

- Selection of research project.

By 1999:

- Isolation of strains from different countries.

By 2000:

- Testing and use of the system.

New approaches for detection of polioviruses (page 48) and measles global surveillance:

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	223 000	158 000	–65 000
1999	335 000	159 000	–176 000

Serologic methods to evaluate tetanus immunity

SEROLOGIC methods to assess tetanus immunity in women of childbearing age have received little attention. Few laboratories can carry out the labour-intensive and relatively expensive methods which this currently involves. Nevertheless, limited serosurveys may be useful for countries with highest estimated numbers of cases of neonatal tetanus, especially where there are problems in assessing tetanus toxoid coverage for women of childbearing age. The goal of this project is thus to develop a rapid diagnostic test to assess protection against tetanus. Preliminary inquiries indicate good potential feasibility of developing cheap, rapid, field-based methods to assess tetanus immunity.

OVERALL OBJECTIVE

To develop a rapid diagnostic test for assessing protection against tetanus which can be used within the strategies for elimination of neonatal tetanus.

TETANUS SEROLOGIC STUDIES

OBJECTIVE

- To demonstrate the usefulness of serological data in monitoring tetanus immunization.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A small-scale pilot survey has been conducted in the Central African Republic.

MILESTONES/TARGETS

By 1998:

- ▷ Serological survey completed and data analysed.

By 1998:

- ▷ Larger scale serological study initiated using Lot Quality Approach.

TETANUS ANTITOXIN DIAGNOSTIC TEST

OBJECTIVE

- To design a rapid diagnostic test to assess the status of tetanus immunity.

MILESTONES/TARGETS

By 1998:

- ▷ Expert meeting, selection of projects.

By 1999:

- ▷ Testing in reference laboratories.

By 2000:

- ▷ Field testing.

By 2001 or later:

- ▷ Commercial development of the test.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	99 000	69 000	–30 000
1999	106 000	69 000	–37 000

Operational research related to immunization strategies: Define optimal measles immunization strategies

MASS immunization campaigns against measles have become an important operational tool for measles elimination strategies. Therefore, it is increasingly important to examine the epidemiological impact of measles vaccine delivery by mass campaign, with the aim of developing a model that will predict the appropriate intervals between measles vaccine campaigns and identify target groups to immunize.

OBJECTIVE

- To develop a predictive mathematical model of measles vaccine delivery by mass campaigns to optimize immunization strategies.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A country has been identified which has an appropriate historical set of measles epidemiology data that permits the development of a mathematical model. The study has been commissioned and two mathematical models developed. Models await their validation with the completion of the serosurvey.

MILESTONES/TARGETS

By 1998:

- Measles serosurvey completed.

By 1999:

- Validation of mathematical model.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	42 000	32 000	–10 000
1999	54 000	32 000	–22 000

DISEASE CONTROL – US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Measles control – New formulations	279 000	232 000	–47 000	290 000	237 000	–53 000
Aerosol measles vaccine	45 000	44 000	–1 000	45 000	32 000	–13 000
Neonatal tetanus elimination – Simpler to deliver vaccine	116 000	56 000	-60 000	117 000	57 000	–60 000
Supply system for emergency needs	14 000	14 000	0	14 000	14 000	0
Demand forecasting for accelerated immunization activities	12 000	7 000	–5 000	39 000	12 000	–27 000
Maximum efficiency of vaccine containers	18 000	5 000	–13 000	18 000	15 000	–3 000
Transgenic mice as a model for routine screening of OPV	155 000	155 000	0	185 000	154 000	–31 000
Polio eradication	3 921 000	2 337 000	–1 584 000	3 095 000	2 134 000	–961 000
Measles control	688 000	657 000	–31 000	726 000	625 000	–101 000
Neonatal tetanus elimination	724 000	478 000	–246 000	537 000	316 000	–221 000
Hepatitis B control	568 000	366 000	–202 000	705 000	409 000	–296 000
Other diseases and micronutrient supplementation	1 336 000	1 194 000	–142 000	3 565 000	2 890 000	–675 000
Surveillance for measles	20 000	0	–20 000	20 000	0	–20 000
Surveillance for neonatal tetanus	10 000	0	–10 000	10 000	10 000	0
Surveillance for polio eradication	70 000	70 000	0	70 000	70 000	0
Surveillance for adverse events following immunization				10 000	10 000	0
Surveillance for yellow fever	20 000	10 000	–10 000	40 000	10 000	–30 000
New approaches for detection of polioviruses & New approaches for measles global surveillance	223 000	158 000	–65 000	335 000	159 000	–176 000
Serologic methods to evaluate tetanus immunity	99 000	69 000	–30 000	106 000	69 000	–37 000
Define optimal measles immunization strategies	42 000	32 000	–10 000	54 000	32 000	–22 000
Global coordination	451 000	362 000	–90 000	470 000	449 000	–20 000
Total workplans	**8 811 000**	**6 246 000**	**–2 565 000**	**10 450 000**	**7 704 000**	**–2 746 000**
Programme support costs*		695 000	–333 000		980 000	–350 000
Grand total		6 941 000	–2 898 000		8 684 000	–3 096 000

*On voluntary funds only

NEW VACCINES

— FILLING THE VACCINE PIPELINE

INTRODUCTION OF NEW VACCINES

A major goal for EPI is the gradual introduction of new vaccines. This process will be based on the need for each vaccine, a careful analysis by EPI of each candidate vaccine, and the feasibility of its introduction. Introduction of new vaccines will require a flexible approach which takes into account the geographical variations of disease burden for certain diseases as well as their epidemiology. Surveillance standards and methods for the diseases prevented by these new vaccines will need to be defined and implemented.

OVERALL OBJECTIVE

To introduce new vaccines into EPI.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

In 1997, the GPV SAGE issued recommendations on how and when Hib vaccine should be introduced into national immunization programmes.

MILESTONES/TARGETS

By 1999:

- ▷ All regions to have prepared a plan for the introduction of new vaccines into EPI.
- ▷ 50% of countries to have prepared a plan for the introduction of new vaccines into EPI.

INDICATORS

- ▷ Number of regions with a plan for introducing new and improved vaccines.

STATUS AS OF DECEMBER 1997

Only the Region of the Americas has a plan for the introduction of new vaccines.

See budgetary comments on page 59.

Introduction of Hib conjugate vaccines

Haemophilus influenzae type b (Hib) conjugate vaccines have been introduced into routine immunization programmes with outstanding results, nearly eliminating Hib disease in over 20 countries. The 1997 SAGE recommended their use as appropriate, depending on national capacities and priorities. Wider use of the vaccine involves addressing a number of issues, including burden of disease, pricing, and selection of appropriate vaccine combinations and presentations. EPI is evaluating the introduction of these vaccines in a number of countries to identify any problems, developing guidelines for introduction, and encouraging regional plans for the introduction of Hib vaccines.

OBJECTIVE

- To introduce Hib vaccine into the immunization programmes of all countries where HIB disease burden has been established to be a public health priority.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

In most countries where appropriate studies have been done, *Haemophilus influenzae* type b (Hib) disease is the leading cause of childhood bacterial meningitis, and a major cause of pneumonia in children. Over 25 countries now routinely use Hib conjugate vaccines in national infant immunization programmes. In countries where these vaccines have been used routinely, cases of Hib meningitis and other serious forms of Hib disease have decreased by over 95%. However, it is estimated that more than 400 000 children a year die from Hib disease, mainly in the developing world. In 1997, the SAGE recommended that the safe and effective Hib conjugate vaccines should be included in infant immunization programmes, depending on national capacities and priorities. They also recommended that where the burden of Hib disease is not known, efforts should be made to identify the burden to enable rational decisions to be made on the use of the vaccine. Meanwhile, in a joint collaborative effort, GPV and CVI are helping countries assess the burden of Hib disease; addressing technical issues involved in the introduction of Hib vaccines; and obtaining Hib conjugate vaccines at affordable prices.

MILESTONES/TARGETS

By 1998:

- A protocol to be implemented in five countries to monitor the early introduction of Hib vaccine and a report prepared on the findings.
- Guidelines to be produced on introducing Hib conjugate vaccines into national immunization programmes.

By 1999:

- Regional plans for introducing Hib conjugate vaccines to be completed.
- Vaccine prices for Hib to be differential to a point where they are affordable.
- In countries using Hib vaccine, coverage with Hib3 to be equal to DTP3 coverage.

INDICATORS

- Number of countries which have introduced Hib conjugate vaccine into their national immunization programme.
- Level of infant coverage with a third dose of Hib conjugate vaccine.

STATUS AS OF DECEMBER 1997

25 countries have introduced Hib vaccine into their national immunization programme.

BUDGETARY COMMENTS FOR TWO PRODUCTS

- *Introduction of new vaccines.*
- *Introduction of Hib conjugate vaccines.*

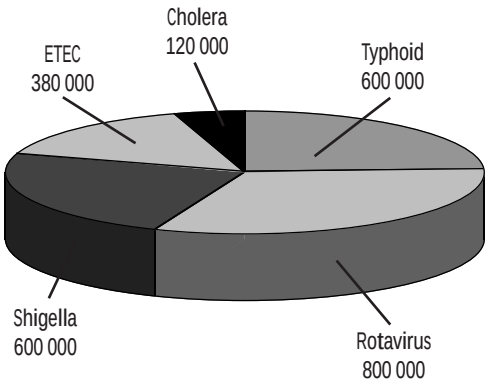
	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	487 000	452 000	–35 000
1999	353 000	278 000	–75 000

VACCINES AGAINST DIARRHOEAL DISEASES

Diarrhoeal diseases kill around 2.5 million children below five and rank second among all causes of disease burden worldwide (about 7%). Five diseases, cholera, enterotoxigenic E. coli *diarrhoea, typhoid fever, dysenteria and rotavirus diarrhoea are responsible for most of the deaths.*

A comprehensive vaccination package directed against diarrhoeal and other enteric diseases is becoming increasingly conceivable.

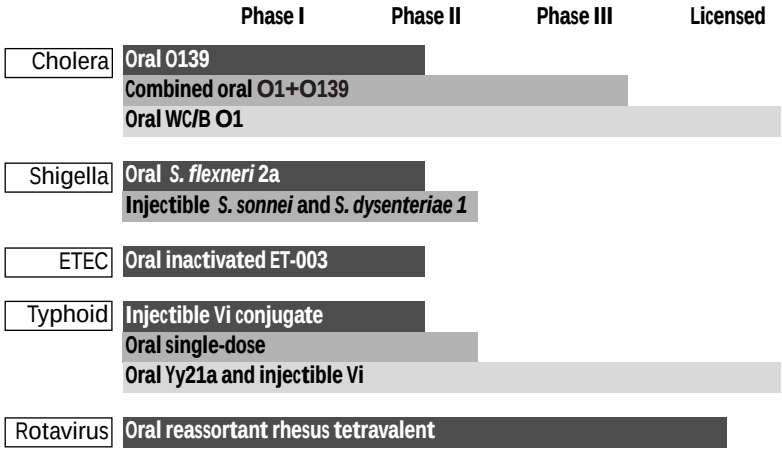
Mortality due to diarrhoeal diseases



Annual mortality: 2.5 million

Newborns who are not breastfed are eight times more likely to die from diarrhoeal diseases than breast-fed newborns. Low birth weight, undernourishment and lack of maternal education all increases children's vulnerability. Unsafe water and sanitation, and poor personal hygiene are important risk factors for diarrhoeal diseases. Preventive measures that assure clean water and hygiene should be encouraged and highly implemented. But this is not enough, additional preventive interventions, such as vaccines, need to be developed and introduced. For the first time, a comprehensive vaccination package directed against diarrhoeal and other enteric diseases is becoming increasingly conceivable.

Vaccines against diarrhoeal and other enteric diseases: Priority is given to the development of vaccines against shigellosis and rotavirus diarrhoea.



Vaccines against shigella diarrhoea

It is estimated that each year almost 600 000 children die from shigella diarrhoea in developing countries. The worldwide incidence of the disease is about 200 million cases. In developing countries, the major burden of shigella infection is among children 1-4 years of age, and all age groups during shigella dysentery epidemics. For more than 15 years, epidemics of dysentery caused by *Shigella dysenteriae* type 1(Sd1) have been regularly affecting Central African countries.

OVERALL OBJECTIVE

To accelerate the development and evaluation in developing countries of candidate shigella vaccines with the ultimate goal of introducing them in high risk areas

NEW APPROACHES FOR ACCELERATING SHIGELLA VACCINE DEVELOPMENT

OBJECTIVE

- In order to increase the pool of available live shigella vaccine candidates, several attenuation approaches will be supported. First, a wild type mutant of *Shigella flexneri* able to synthesize non-toxic lipopolysaccharide (LPS) will be prepared. Should the new LPS be atoxic, it will be added to the currently available vaccine candidates (SC602 and SC599).
- Second, the development of shigella strains with an altered invasive (IpaB) protein will be explored in order to generate mutants that are invasive but not cytotoxic.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The development of the wild type mutant of *Shigella flexneri* able to synthesize non-toxic lipopolysaccharide (LPS) is a new project.

Regarding the developent of strains with altered IpaB protein there has been difficult to select isolates more invasive than cytotoxic. A new experimental design to better screen the IpaB clones using gentamicin will be evaluated.

MILESTONES/TARGETS

By 1998:

- Selection of invasive isolates for the altered IpaB strain.

By 1999:

- *In vivo* and *in vitro* pathogenesis assays of non-toxic LPS evaluated.
- Selection of non-cytotoxic IpaB mutants.

By 2000:

- Development of non-toxic LPS mutant strains.

SHIGELLA DISEASE BURDEN

The assessment of the disease burden attributed to shigella will provide policy makers and manufacturers with more accurate data on the importance of introducing vaccination programmes against shigellosis.

OBJECTIVE

- To obtain data on the shigella disease burden.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS:

Bibliographic collection on shigella disease-burden estimates is under way as a basis for establishing surveillance systems and conducting disease-burden studies in specific countries.

MILESTONES/TARGETS

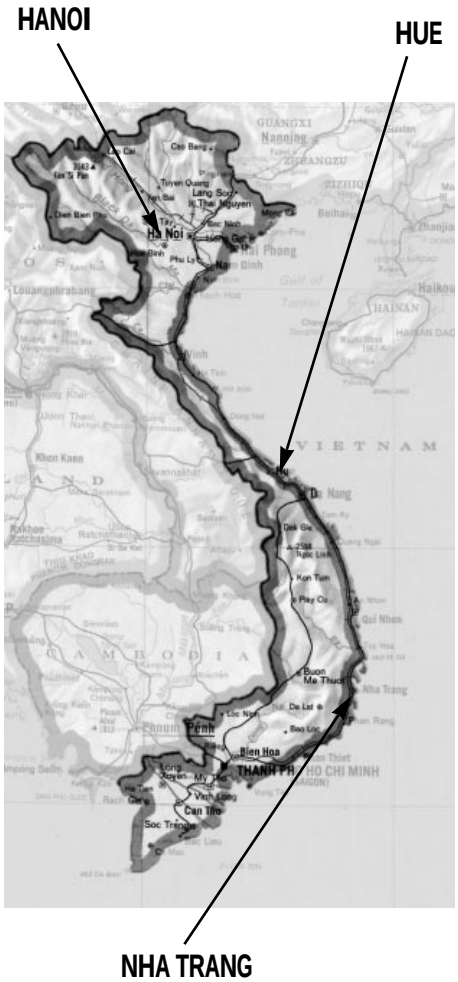
By 1998:

- ▷ Bibliography-based document prepared.
- ▷ Disease burden studies initiated in ten countries.

By 1999:

- ▷ Studies completed.

Possible sites to conduct clinical trials



PHASE I AND II TRIALS OF CANDIDATE SHIGELLA VACCINES

OBJECTIVE

- ☐ To evaluate oral and injectable candidate vaccines against shigellosis in phase I and II clinical trials.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The first site visit has been carried out in Viet Nam to determine shigella serotypes in circulation and assess laboratory facilities.

MILESTONES/TARGETS

By 1998:

- ▷ Vaccine testing areas selected.
- ▷ Protocol established.

By 2000:

- ▷ Phases I and II clinical trials completed.

SHIGELLA CANDIDATE VACCINES: EFFECTIVENESS TRIALS

OBJECTIVE

- ☐ To provide several types of information needed for rational policy decisions about the introduction of shigella vaccines:
  - ▷ Assessment of vaccine performance in the heterogeneous target population and under the ordinary conditions of a public health programme.
  - ▷ Measurement of the marginal improvement conferred by vaccination over other existing intervention tools to control shigella diarrhoea.

- ▷ Evaluation of the impact of vaccination on practical outcomes of public health importance, analysed from the outset of a vaccine programme and in the entire target population.

MILESTONES/TARGETS

By 2000:

- ▷ Vaccine testing areas identified.
- ▷ Protocol established.

By 2001:

- ▷ Trials ongoing.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	214 000	177 000	–37 000
1999	231 000	194 000	–37 000

Vaccines to prevent diarrhoea due to rotavirus

ROTAVIRUS diarrhoea is estimated to cause 600 000 to 870 000 deaths each year, primarily among children in developing countries, and is responsible for 6% of all deaths among children less than five years old. In both developed and developing countries, rotavirus infects all children early in life and accounts for one-third of hospitalizations for diarrhoea. Children in developing countries develop illness earlier in life, and are infected all year-round. Other differences in rotavirus epidemiology between developed and less developed countries include the presence of greater strain diversity (particularly in Brazil and India), the common occurrence of mixed infections and of infections with multiple rotavirus strains (20-30% of infections in some countries), and the possibility for a alternative modes of transmission.

If 80% efficacy were achieved, as current studies seem to show, the estimated cost-effectiveness of a rotavirus vaccine would be excepcionally high: around US$ 10 per disability-adjusted life year (DALY) averted. Since more than one candidate is already in an advanced stage of development, the likely pay-off is high, the time frame short and the investment requirement relatively low.

OVERALL OBJECTIVE

To introduce the existing rotavirus vaccine in the EPI routine immunization schedule and develop additional new candidates.

DEVELOPMENT OF NEW GENERATION OF VACCINES AGAINST ROTAVIRUS

Several important approaches towards the development of new generation of vaccines against rotavirus that complement existing candidates will be initiated. They include the development of candidates based on DNA, recombinant technologies which include virus-like particles expressed in transgenic plants and attenuated strains through reverse genetics. At the same time, immunogenicity of live or inactivated rotavirus using the microencapsulation technique will be evaluated.

OBJECTIVE

- To develop a new generation of rotavirus candidate vaccine as viable alternatives to the existing candidates

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Good immune responses and levels of protection have been shown with a VP4,VP6 and VP7 DNA-based vaccine in a mouse model. At the same time, attempts to express VP2, VP4,VP6 and VP7 in potato leaves are showing mixed results with good expression levels for VP6 but no expression for the other three proteins.

MILESTONES/TARGETS

By 1998:

- ▷ Good immune responses obtain for each viral protein (VP4,VP6 and VP7) tested individually and combined with plasmids encoding for cytokines such as IL-5 and IL-6.

By 1999:

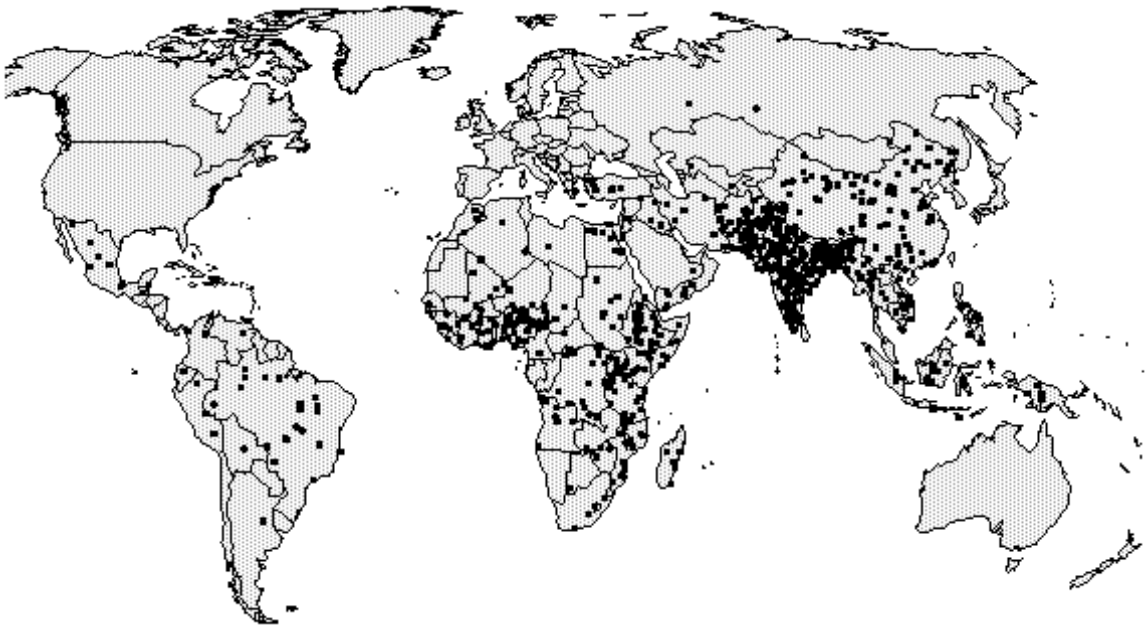
- ▷ Good expression levels for VP2, VP4 and VP7 in potato leaves.

By 2000:

- ▷ Oral DNA formulations coated in gold particles to be delivered by gen gun prepared.
- ▷ Protective efficacy of rotavirus candidate vaccine based on transgenic plants evaluated.

If 80% efficacy were achieved, as current studies seem to show, the estimated cost-effectiveness of a rotavirus vaccine would be excepcionally high: around US$ 10 per DALY averted.

Estimated global death distribution due to rotaviral infection (each dot = 1000)



EPIDEMIOLOGICAL STUDIES THAT ASSESS THE BURDEN OF DISEASE AND PREVALENCE OF STRAINS IN DEVELOPING COUNTRIES

A plan for training scientists from many countries to build-up a network of scientists.

Surveillance systems to estimate the burden of rotavirus diarrhoea and to monitor circulating rotavirus strains will be necessary for several reasons: (1) to establish baseline disease estimates to monitor the effect of vaccine introduction; (2) to detect and to explain potential vaccine failures; (3) to develop cost-effectiveness models; (4) to detect strains potentially not covered by vaccination; and (5) to convince policy-makers of the importance of rotavirus vaccination programmes.

OBJECTIVE

- To establish standard surveillance of diarrhoea due to rotavirus and strain characterization both at national and global levels.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Standard guidelines for surveillance of rotavirus strains are being produced. A laboratory in South Africa has been identified to determine the epidemiology of the VP7 serotypes and the VP4 genotypes of human rotavirus strains circulating in the sub-continental African Region (Cameroon, Kenya, South Africa, Zambia and Zimbabwe). The protocol includes a plan for training scientists from many countries to build-up a network of scientists.

MILESTONES/TARGETS

By 1998:

- ▷ Guideline surveillance for countries established.

By 2000:

- ▷ Regional surveillance network established.

By 2001:

- ▷ Uniform methods for strain characterization established.
- ▷ Estimates of national and global disease completed.

CLINICAL TRIALS IN DEVELOPING COUNTRIES TO ESTABLISH THE IMMUNOGENICITY EFFICACY AND EFFECTIVENESS OF THE EXISTING ROTAVIRUS CANDIDATE VACCINE

A number of small phase II trials should be conducted in settings where no trials have been performed using current vaccines in order to ensure an immune response comparable to those observed in studies where the vaccine has proven to be effective. These studies should be completed quickly, so that the demonstration of vaccine efficacy and effectiveness, as shown by the introduction of vaccine programmes in developed countries could go ahead in developing countries, and vaccine introduction could be expedited.

OBJECTIVE

- □ To conduct a number of immunogenicity and efficacy trials in selected settings from Africa, Asia and Latin America.
- □ To conduct effectiveness trials which will expedite the introduction of rotavirus vaccines into the EPI.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	1 058 000	900 000	–158 000
1999	532 000	276 000	–256 000

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Several candidate sites were identified and trials are either ongoing or ready to start in Bangladesh, Brazil, China, Guinea Bissau, India, Venezuela and Viet Nam.

MILESTONES/TARGETS

By 1999:

- ▷ Immunogenicity studies conducted.

By 2000:

- ▷ Vaccine efficacy trials in Africa and Asia completed.

By 2001:

- ▷ Vaccine effectiveness trial to assess the impact of the candidate vaccine in the routine EPI schedule conducted.

New strategies for accelerating cholera vaccine development

CHOLERA – one of the oldest scourges suffered by man – is still responsible for 120 000 deaths affecting over 5.5 million people every year. Over a fifth of the deaths occur in children under five. In 1991 there were more cases of cholera and more countries affected by the disease than in any other year on record.

Limitations of the old parenteral cholera vaccines prompted the Twenty-sixth World Health Assembly to abolish the requirement of the International Health Regulations for a certificate of vaccination against cholera. Now, several new types of cholera vaccine have been developed and are being evaluated for safety and efficacy. Thus, the cholera vaccine programme will be focusing on evaluating existing candidate vaccines and assessing combination of *vibrio cholerae* O1 and O139 serogroups in one vaccine.

OVERALL OBJECTIVE

To have a safe, effective, cheap, and easy-to-administer cholera vaccine for use in mass immunization campaigns.

The recent availability of efficacious oral cholera vaccines has led to renewed interest to prevent outbreaks in situations with high cholera incidence such as refugee camps.

VACCINATION STRATEGIES AGAINST CHOLERA IN REFUGEE CAMPS

Refugee camps are periodically affected by outbreaks of cholera which, apart from high rates of morbidity, generates panic in the population, hampering in turn other health care activities.

In the past injectable cholera vaccines have been rejected because of low efficacy and too short duration of protection. The recent availability of efficacious oral cholera vaccines has led to renewed interest to prevent outbreaks in situations with high cholera incidence such as refugee camps.

OBJECTIVE

- To assess the feasibility and acceptability of administration of oral cholera vaccine in an established refugee camp.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A cost-effectiveness analysis of the use of recombinant B subunit-whole cell (rBS-WC) vaccine in Sub-Saharan refugee settings, was conducted collaboratively by investigators from Epicentre, MSF, the U.S. National Institutes of Health, and the University of Maryland. The analysis was performed for a hypothetical refugee camp with 50 000 persons, in which the costs and outcomes were compared for alternative interventions in which appropriate rehydration therapy for cholera is introduced pre-emptively or reactively, and in which mass immunization with rBS-WC is given, in addition to one of these therapeutic strategies, either pre-emptively or reactively.

If the cost per dose of this vaccine were to drop below US$ 0.20, pre-emptive mass immunization would become a cost-effective adjunct to pre-emptive therapy and, if the cost were to drop below US$.16 per dose, this combined strategy would be predicted to prevent more deaths and to cost less than pre-emptive therapy *per se*.

MILESTONES/TARGETS

By 1998:

- ▷ Research project on the use of rBS-WC in an actual refugee setting.
- ▷ Report completed.

Cholera disease outbreaks in 1995

BIVALENT CHOLERA VACCINE EFFECTIVENESS STUDY

A locally produced cholera vaccine has proved to be safe and effective, and a large effectiveness study is now under way in Viet Nam to evaluate the public health interest in using this vaccine for controlling diarrhoea due to cholera.

OBJECTIVE

- To evaluate bivalent O1 + O139 cholera vaccine in Viet Nam.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two pre-tests were conducted of the lot vaccine to be used in the trial, the first in adults and the second in children. The vaccine showed four-fold or greater sero-conversion rates in more than 80% of those vaccinated. The vaccine and a placebo have been administered to 320 000 people in 30 communes.

MILESTONES/TARGETS

By 1998:

- Phase II study completed.

By 2001:

- Phase III trial completed.

O139 CHOLERA VACCINE CLINICAL PHASE I STUDY

In October 1992, a new epidemic strain of *vibrio cholerae* emerged in Bangladesh and India, and it has since been classified as *vibrio cholerae* O139 Bengal.

OBJECTIVE

- To initiate evaluation of new O139 cholera vaccines in developing countries, using Thai volunteers.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The pathogenic O139 reference strain has been prepared by the US National Institutes of Health (NIH).

MILESTONES/TARGETS

By 1998:

- Availability of O139 pathogenic strain.

By 1999:

- Dose-escalation study completed.

CHOLERA O1 VACCINE EFFECTIVENESS STUDY

In countries where the water facilities and sewage disposable are inadequate, the use of cholera vaccines to control the disease will be evaluated.

OBJECTIVE

- To assess the benefit of including cholera vaccination in a country where the disease is endemic.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	204 000	164 000	–40 000
1999	238 000	174 000	–64 000

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Contacts has been made with the health authorities in Peru and Comores Island, which is anticipating a new outbreak of cholera.

MILESTONES/TARGETS

By 1998:

- Vaccine testing areas identified.
- Protocol established.

By 2000:

- Effectiveness trial completed.

New tools to prevent diarrhoea due to enterotoxigenic and enterohaemorrhagic *E. coli* (ETEC and EHEC)

In developing countries diarrhoeal disease caused by ETEC is responsible for an estimated 400 000 deaths a year among children under five – almost 10-20% of the global total of deaths from diarrhoeal disease in this age group. The disease is poorly reported and detailed surveillance data are difficult to obtain. ETEC is the most common cause of diarrhoea in developing countries – accounting for an estimated 400 million cases a year. The pathogen is also the leading cause of travellers' diarrhoea.

In 1982, *E.coli* O157:H7 which belongs to the enterohaemorrhagic *E.coli* group, was recognized as a human pathogen for the first time and since then, has been a steadily increasing cause of foodborne illness worldwide. Recently, there has been unprecedented, large outbreaks of *E.coli* O157:H7 in Japan and Scotland.

OVERALL OBJECTIVE

To move new ETEC and EHEC vaccines into the public health armamentarium available in developing countries.

ASSESSMENT OF CURRENT STATUS OF ETEC AND EHEC VACCINES

Both live and inactivated oral vaccine candidates have been developed against ETEC and decisions to expedite their evaluation and introduction in high risk populations will be discussed. WHO is particularly worried about bloody diarrhoea as a potential cause of morbidity and mortality among children in developing countries. The proportion caused by *E.coli* O157:H7 strain and other EHEC strains remain largely unknown. Recent workshops held in Geneva and Baltimore during 1997 have focused primarily in developing recommendations for surveillance, outbreak investigation, control and prevention. However, an in-depth discussion on whether efforts are needed to develop a vaccine against EHEC and which should the features of a potential vaccine be, is still lacking.

OBJECTIVE

- To organize a meeting on ETEC and EHEC vaccine development.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Contacts have been made with authorities in Japan to organize this meeting. A draft Agenda with a list of participants has been submitted to the WHO Division of Emerging and other Communicable Diseases Surveillance and Control (EMC), WHO Unit for Food Safety (FOS) and Japan authorities.

MILESTONES/TARGETS

By 1998:

- ▷ Meeting report completed.

ETEC VACCINE CLINICAL PHASE II TRIAL IN EGYPT

A Phase II vaccine trial of an ETEC candidate vaccine is due to begin in 1998 in Egypt, following the completion of serological and epidemiological studies.

OBJECTIVE

- Clinical evaluation of the safety and immunogenicity of ETEC vaccine in Egypt.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Enrolment has been completed but immunization has been delayed for several months.

MILESTONES/TARGETS

By 1998:

- ▷ Enrolment completed.
- ▷ Immunization under way.

By 1999:

- ▷ Study completed.

IMMUNOGENICITY AND EFFICACY TRIALS OF A NEW RECOMBINANT ETEC VACCINE IN EGYPT

A candidate vaccine consisting of a mixture of recombinant cholera toxin B subunit (rBS) and CFA-producing, formalin-activated ETEC whole cells, has reached an advanced stage of development. It has been administered in one-, two- or three-dose regimens, without induction of significant side-effects, to approximately over 500 adults and children in Bangladesh, Sweden, the United States, and now will be evaluated for immunogenicity and efficacy in Egypt. It is expected to protect against 80% of the current pathogenic strains.

OBJECTIVE

- □ To evaluate the immunogenicity and efficacy of an ETEC candidate vaccine in Egypt.

MILESTONES/TARGETS

By 1999:

- ▷ Phase II study initiated.

By 2000:

- ▷ Phase II study completed.

By 2001:

- ▷ Phase III clinical trial initiated.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	98 000	53 000	–45 000
1999	68 000	48 000	–20 000

New approaches for controlling typhoid fever by using Vi polysaccharide vaccine

Salmonella typhi, the etiologic agent that causes typhoid fever, affects 16 million people claiming at least 600 000 lives every year. As salmonella is becoming increasingly resistant to drugs, a new effective vaccine seems, more than ever, an utmost priority.

Two safe and effective vaccines are currently licensed and available. The oral Ty21a and of parenteral Vi polysaccharide vaccines are very well-tolerated and confer a good level of protection in school age children that lasts several years; these observations should make these vaccines amenable to use in school-based immunization programmes.

OVERALL OBJECTIVE

To prepare for the introduction of typhoid fever vaccine in settings where the disease is an important public health problem (endemic areas and refugee camps).

The oral Ty21a and of parenteral Vi polysaccharide vaccines are very well-tolerated and confer a good level of protection in school age children that lasts several years; these observations should make these vaccines amenable to use in school-based immunization programmes.

VI VACCINE EFFECTIVENESS STUDY

In view of this large, favorable experience in school-age children, the lack of uptake and use of either Ty21a or Vi for school-based immunization programs in typhoid endemic areas is disappointing. One would like to see one or more countries undertake demonstration projects based on school immunization with these vaccines. Vi vaccine will soon be under production in Viet Nam, where it will be used for controlling typhoid fever. An effectiveness study of the vaccine will be carried out in one province of Viet Nam.

OBJECTIVE

- To evaluate the effectiveness of Vi typhoid fever vaccine in Viet Nam.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A site has been selected in Hue, Viet Nam.

MILESTONES/TARGETS

By 1998:

- ▷ Study site selected.
- ▷ Protocol written.

By 2000:

- ▷ Effectiveness trial initiated.

VI VACCINE EVALUATION IN ENDEMIC AREA WITH POTENTIAL RISK OF OUTBREAKS

The increased number of typhoid fever cases reported in Uzbekistan during the last few years highlights the potential for a major epidemic in this country. Epidemiological studies have shown that increased incidence is likely to be related to the use of water in Uzbekistan which originates from open reservoirs in neighbouring Tajikistan. In Uzbekistan, distribution of purified water to the whole population is not feasible. Although other public health measures known to prevent the person-to-person spread of typhoid fever will be initiated, based on previous experience in the region, it is the opinion of experts that control of a potential epidemic of multi-drug resistant typhoid strains will need complementary interventions as well. Therefore, a demonstration study to evaluate the value of immunization with either oral Ty21a or Vi for school-based immunization programs is now planned for the Samarkand and Dijzak regions in Uzbekistan.

OBJECTIVE

- To evaluate the impact of Vi vaccination on typhoid fever during an outbreak. Vaccination against typhoid fever could offer an effective alternative for controlling the disease during an outbreak until water and sewage facilities could be improved or repaired.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A site has been selected in Uzbekistan with the approval of health authorities.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	64 000	39 000	–25 000
1999	101 000	57 000	–44 000

MILESTONES/TARGETS

By 1998:

▷ Study site selected.

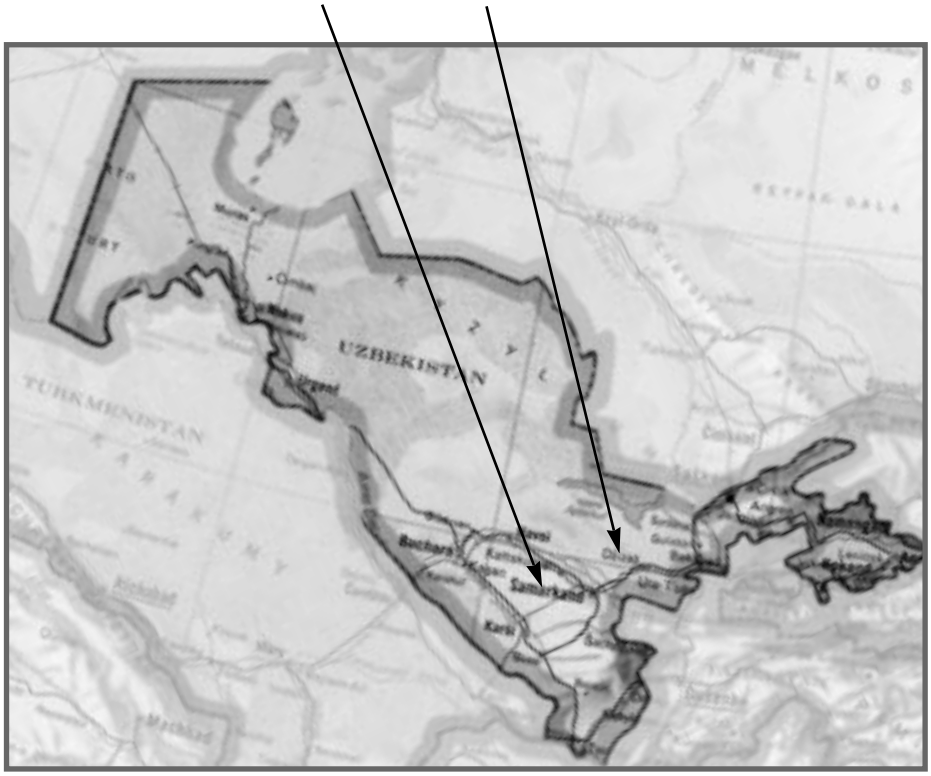
By 1999:

▷ Protocol prepared.

By 2001:

▷ Study completed.

SAMARKAND AND DJIZAK REGIONS



VACCINES AGAINST DISEASES WITH REGIONAL IMPORTANCE: DENGUE AND JAPANESE ENCEPHALITIS

The wealth and complexity of knowledge that has emerged after two decades of progress in the field of microbial genetics is already being applied to the development of new/improved vaccines against dengue and Japanese encephalitis, arthropod borne viral infections endemic in many parts of the world.

Biotechnological approaches to develop a new dengue vaccine

DENGUE is the most important arthropod-borne viral infection of humankind. The last twenty years have witnessed a significant increase in epidemic activity, an expansion in geographic distribution, continuous transmission of multiple dengue virus serotypes, and emergence of dengue haemorrhagic fever (DHF) in previously unaffected areas. Every year there are about 60 million cases of dengue disease. The principal factors underlying this expansion include: changes in human demography, particularly urbanization; a covariate increase in vector mosquito *(Aedes aegypti)* density; and hyperendemic transmission of multiple dengue serotypes required for immune sensitization and the pathogenesis of DHF.

OVERALL OBJECTIVE

Development of candidate dengue vaccines for rapid integration into clinical trials.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Several approaches are under investigation including multivalent combinations of live-attenuated dengue viruses that generate full protection against infection, attenuation of the parental DEN4 clone for use as a vaccine vector and development of a cDNA clone of yellow fever virus for vaccine production. Recombinant live vector systems and DNA-based vaccines have also been used as novel approaches against dengue. The characterization of the immunological factors involved in the protective response induced by poxvirus and alphavirus vectors encoding flavivirus antigens are in an advance stage of development.

Finally, a subunit approach to vaccination, employing various expression vectors to generate defined polypeptide segments of the flavivirus polyprotein has continued to receive considerable attention. However, the immunogenicity of these candidate vaccines has not yet been evaluated.

MILESTONES/TARGETS

By 1998:

- ▷ Selection and support of research projects.
- ▷ Preparation of draft requirements for live dengue vaccine.

By 1999:

- ▷ Preparation of flavivirus infectious clone-derived vaccine under GMP.
- ▷ Development of standardized test for dengue virus neutralization to be used in clinical trials of dengue vaccines.

By 2000:

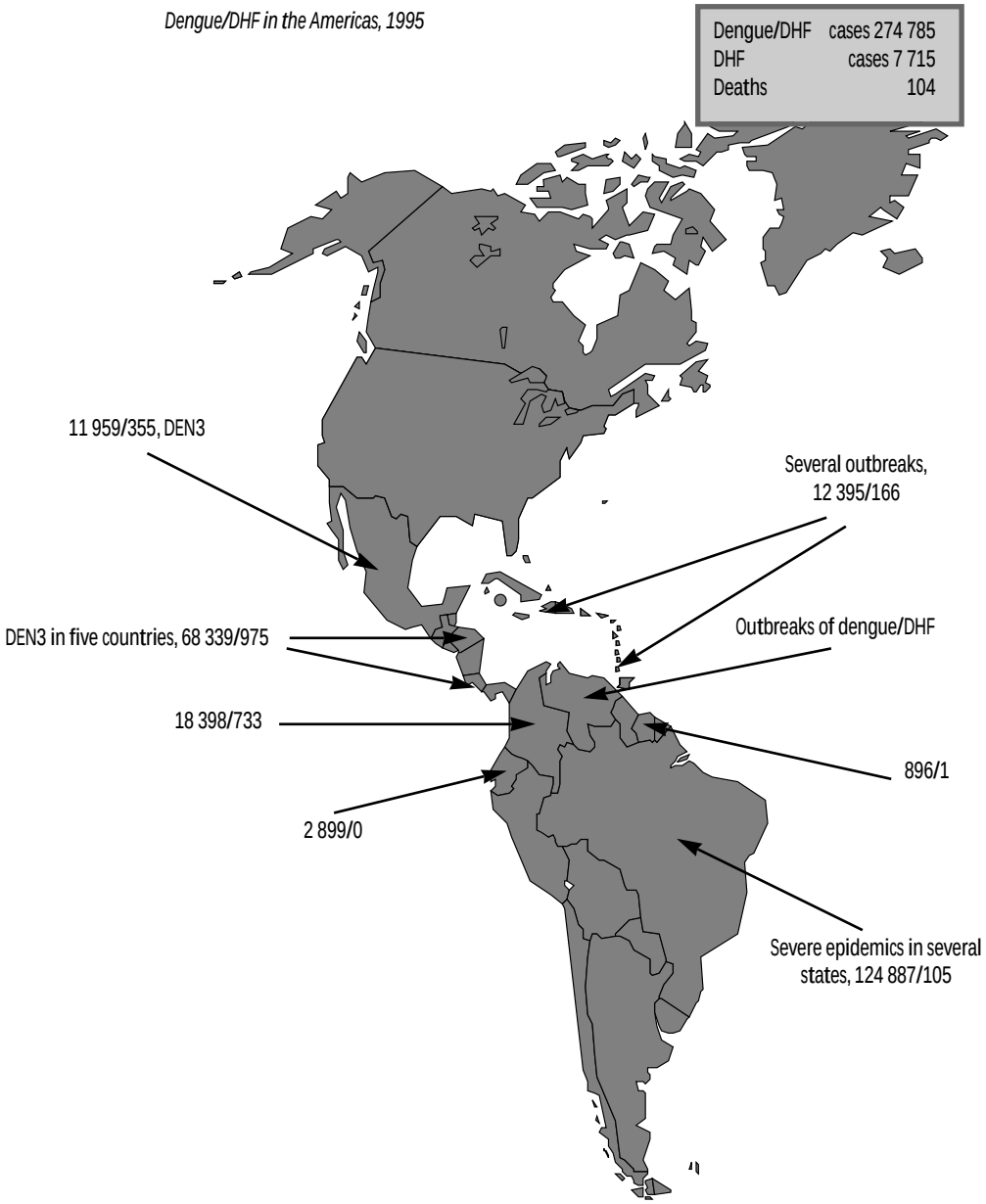
- ▷ Preclinical evaluation of candidate vaccine in animal models.

By 2001:

- ▷ Clinical evaluation of vaccine candidate.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**308 000**	**276 000**	**–32 000**
1999	**298 000**	**245 000**	**–53 000**

Dengue/DHF in the Americas, 1995



Development of new Japanese encephalitis vaccine with improved immunogenicity

An inactivated virus vaccine was developed in Japan over 20 years ago and has been successfully used there. The vaccine was licensed for use by travellers and military personnel in the United States in 1992 and is also used on a limited scale in India, Korea, and Taiwan. In only one country – Thailand, in 1995 – has it been added to the EPI schedule. Since this vaccine is currently too expensive to be used extensively in many of the worst affected countries, research and development of new more affordable candidates are needed.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	185 000	27 000	–158 000
1999	167 000	152 000	–15 000

OVERALL OBJECTIVE

To improve tools for the control of Japanese encephalitis.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two new candidate vaccines against Japanese encephalitis have been developed: a vaccine comprising a chimeric yellow fever/Japanese encephalitis virus, and a DNA vaccine including different combinations of genes that encode to specific viral proteins. However, the immunogenicity and safety of these candidate vaccines have not yet been evaluated in animals.

MILESTONES/TARGETS

By 1998:

- ▷ Selection of research project.

By 1999:

- ▷ Preclinical evaluation of candidate vaccines.

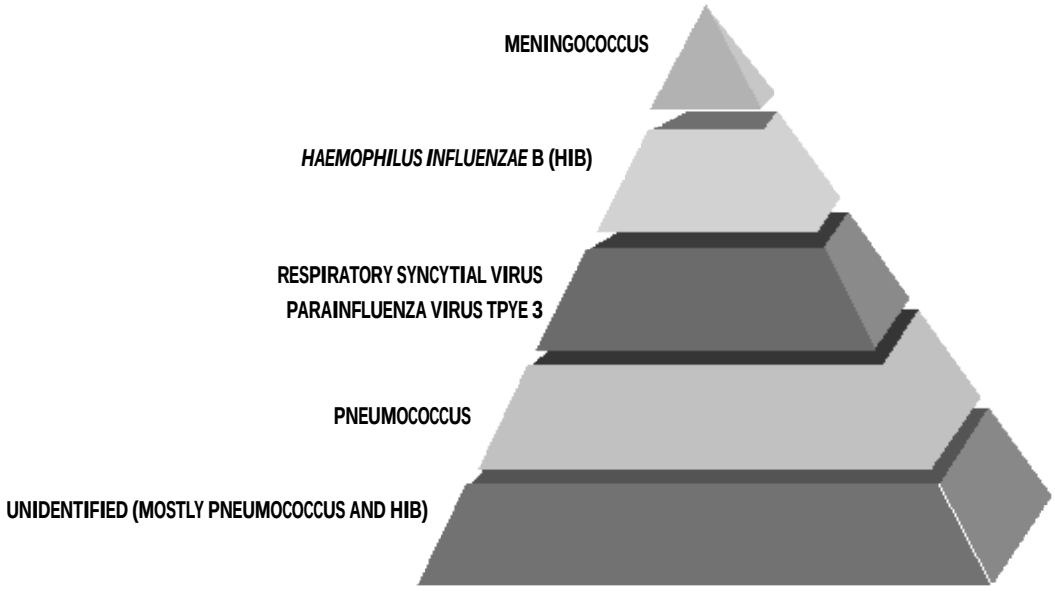
By 2001:

- ▷ Clinical evaluation of one vaccine in clinical trial.

VACCINES AGAINST ACUTE RESPIRATORY INFECTIONS AND MENINGITIS

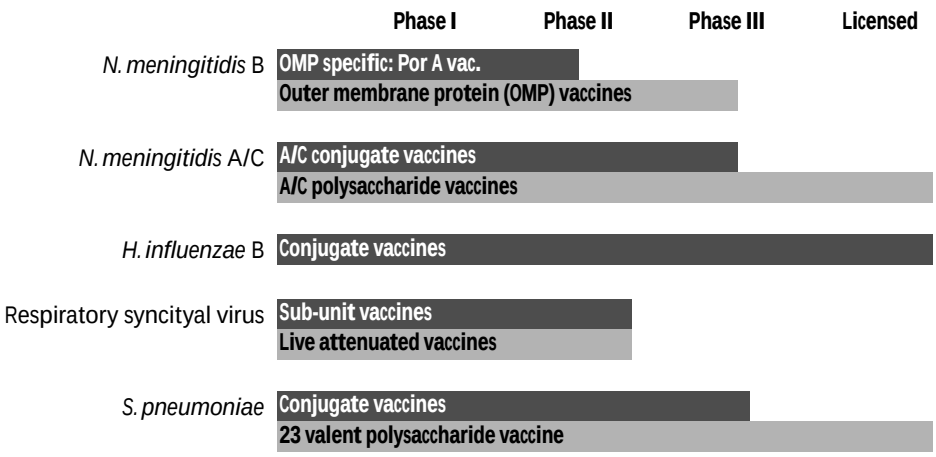
Globally acute respiratory infections remain the most important cause of paedriatic mortality, accounting for about 3 million deaths each year. This clinical entity is related to multiple etiologic agents; as yet, however, their attributable participation in the total burden of disease is still undetermined.

Acute respiratory infection and meningitis – over 3 million deaths



We can now envisage an integrated vaccination strategy against acute respiratory infections (ARI) which would address the complexity of this group of diseases through the combined prevention of its most frequent causes.

A "vaccination package" against respiratory infections and meningitis



VACCINES AGAINST BACTERIAL PNEUMONIA AND MENINGITIS: HAEMOPHILUS, PNEUMOCOCCAL AND MENINGOCOCCAL VACCINES

A safe and effective protein-polysaccharide conjugate vaccine against disease caused by Haemophilus influenzae *type b (Hib) is now in use in most industrialized countries. However, its use in developing countries has been limited by the high cost of the vaccine and lack of understanding of the disease burden. Of the three main groups of* Neisseria meningitidis *(meningococcus) which cause meningitis, two (groups A and C) are suitable for conjugate vaccine development along similar lines, and this is being pursued by several companies. For reasons of both safety and immunogenicity, the third (group B) probably requires a different, protein-based approach. Finally, the development and evaluation of vaccines against pneumococcI is showing good progress. The most advanced pneumococcal polysaccharide conjugate vaccines have now reached a stage of development similar to where the Hib conjugate vaccines were 10 years ago, with large, phase III trials just starting.*

OVERALL OBJECTIVE

The development of a family of vaccines to prevent pneumonia and meningitis due to the three common bacterial causes, *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*.

Vaccines against *Haemophilus influenzae* type b (Hib)

COST is a major barrier to the widespread introduction of Hib vaccine in the developing world. The current cost of Hib vaccines is US$3-5 per dose or $9-15 per child immunized. Thus, strategies should be designed to reduce the costs of Hib immunization programmes. Decreasing antigen dose in the vaccine formulation may result in lower costs without adversely affect vaccine efficacy. Further, alternative administration strategies including multidose vials, and liquid versus lyophilized vaccine preparations will have to be addressed. Finally, ongoing research is aiming at the development of an entirely synthetic Hib conjugate vaccine comprising Polyribosyl-Ribitol-Phosphate (PRP) linked to a tetanus toxoid peptide which could potentially be easier for quality control issues as well as economic scale-up capacity than products dependent on bacteriologic methods.

AVAILABILITY OF LOW COST *HAEMOPHILUS INFLUENZAE* TYPE B CONJUGATE VACCINATION

OBJECTIVE

- To develop a less expensive Hib vaccination strategy for developing countries.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Ongoing discussions with manufacturers have confirmed their intention to apply differential pricing, which would probably result in a cost of between US$1 and $2 per dose. Meanwhile, a study in Chile has shown that the dose of PRP-T can be reduced to a third or less without any reduction in immunogenicity.

MILESTONES/TARGETS

By 1999:

- Completion of Phase II studies exploring low cost vaccination regimens.

By 2001:

- Completion of effectiveness study of two-dose regimen.

INDICATOR

Current cost of three doses of Hib conjugate vaccine for a child in a developing country.

BUDGETARY COMMENTS

Common with vaccines against meningococcal menigitis, see page 80.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	222 000	217 000	–5 000
1999	200 000	154 000	–46 000

Vaccines against meningococcal meningitis

Neisseria meningitidis and *S. pneumoniae* have since the introduction of *H.influenzae* type b conjugate vaccines, become the commonest causes of bacterial meningitis in the world. All countries suffer from endemic meningococcal disease, primarily in children under the age of five, at an annual attack rate of around 1 to 3/100 000 of the population. In addition, some countries, predominantly – but not exclusively – in the developing world, suffer from occasional or even regular epidemics of meningitis. Epidemics involve attack rates from about 10/100 00 to as high as 400-600/ 100 000 per year and have often been caused by group A strains. Serogroup B and C strains are most prevalent during endemic periods, but they have also been responsible for outbreaks and epidemics in reduced scale.

OVERALL OBJECTIVE

To develop new, improved vaccines and vaccination strategies against meningococcal meningitis serogroups A, B, C.

BUDGETARY COMMENTS

Common with vaccines against *Haemophilus influenzae* type b (Hib), see page 79.

Recombinant techniques to "tailor make" OMP vaccines against several serosubtypes of N. meningitidis *B have been developed and will be evaluated to prevent outbreaks.*

AVAILABILITY OF A SAFE AND EFFICACIOUS MENINGOCOCCAL GROUP B VACCINE

Although group A strain is the principal causes of epidemic bacterial meningitis in the meningitis belt in Africa and China, group B and C meningococcal meningitis, generally associated with sporadic disease, have been recognized as the commonest cause of meningitis in industrialized countries causing limited outbreaks as those reported in Brazil (1989), Chile (1986, 1993), Cuba (1982-1984), or Norway (mid-1970s).

OBJECTIVE

- To develop a safe and effective meningococcal group B vaccine.

1994-1997 PROGRESS, ACHIEVEMENTS AND CONSTRAINTS

The two most dominating strategies in the development of vaccines against *N. meningitidis* group B, are first, to increase the immunogenicity of the normally poorly immunogenic group B capsule polysaccharide, by conjugating it with protein carriers or by modifying its structure prior to conjugation. The second strategy is in the application of the protein based or subcapsular approaches. Investigators have focused on the use of serogroup B meningococcal outer membrane vesicles (OMV) as potential candidate vaccines. Two clinical trials have been conducted in Chile and Iceland using OMV vaccines developed in Cuba and Norway, with mixed results. In Finland an animal model is being evaluated to measure protection. Recombinant techniques to "tailor make" OMP vaccines against several serosubtypes of B have been developed and will be evaluated to prevent outbreaks. Plans are under way to evaluate this in the current New Zealand epidemic.

Major epidemics of meningococcal meningitis serogroup B, 1970-1997

MILESTONES/TARGETS

By 1998:

- ▷ Comparative pre-clinical assessment of different subcasular approaches for the development of candidates vaccines which are not serosubtype specific.
- ▷ Development of outer membrane vesicle or outer membrane protein class 1 (Por A) specific protein based vaccines starts against a defined serosubtype for outbreak control.

By 1999:

- ▷ Clinical evaluation of outer membrane vesicle or Por A specific protein based vaccines starts against a defined serosubtype for outbreak control.

By 2001:

- ▷ Phase III trial of one outer membrane vesicle or Por A specific protein based meningococcal group B candidate vaccine.

AVAILABILITY OF A SAFE AND EFFICACIOUS MENINGOCOCCAL GROUP A/C CONJUGATE VACCINE

Serogroup A meningococcus has historically been the main cause of explosive epidemics especially in the so-called "meningitis belt" in sub-Saharan Africa, from Ethiopia in the east to Senegal in the west. However, the disease is now reported to be spreading further afield in Africa – affecting countries outside the meningitis belt – possibly as a result of climate change and increasing population movements. Today, an estimated 357 million people are at risk in Africa, where case fatality rates range from 8% to 20%. Serogroup C, like serogroup A, has been responsible for large outbreaks in Brazil (1972-74), Northern Nigeria (1975), or Viet Nam (1977-78). Currently licensed vaccines against serogroups A and C are based on purified capsular polysaccharides. However, in view of the deficiencies in immunogenicity to elicit a sustained antibody response in children below two years old, new candidates which covalently couple the polysaccharide with a protein carrier molecule are currently being developed.

OBJECTIVE

- □ To develop a safe and effective meningococcal A/C conjugate vaccine for use in the meningitis belt of Africa.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A Phase II study is under way in Niger to evaluate the safety and immunogenicity of a meningococcal A/C conjugate vaccine. There is concern at the reluctance of some manufacturers to include group A in their conjugate vaccine.

MILESTONES/TARGETS

By 1999:

- ▷ Completion of a Phase II study of a meningococcal A/C conjugate vaccine involving African infants.

By 2001:

- ▷ Agreement on requirements for vaccine licensure.

OPTIMAL STRATEGY FOR THE USE OF MENINGOCOCCAL A/C POLYSACCHARIDE VACCINE FOR THE MENINGITIS BELT OF AFRICA

Continuing severe meningococcal epidemics in Africa have prompted calls for routine use of existing polysaccharide vaccines within the EPI. However, controversy persists regarding the effectiveness of group A polysaccharide vaccine in infancy.

OBJECTIVE

- □ To identify the optimal strategy for the use of meningococcal polysaccharide vaccine in Africa.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Recent Phase II studies of meningococcal conjugate vaccines in the Gambia and Niger have included groups receiving polysaccharide vaccine. However, these studies do not adequately evaluate a two-dose regimen of meningococcal A vaccine in infancy.

MILESTONES/TARGETS

By 1999:

- ▷ Completion of Phase II studies to resolve the role of meningococcal A polysaccharide vaccine in infancy.

Development and evaluation of a safe and effective vaccine against pneumococcal pneumonia

WHILE *Streptococcus pneumoniae* (pneumococcus) can cause disease at any age, children are worst affected. It is estimated that 1-2 million child deaths each year are due to the pneumococcus – as many as 30% of them in the first three months of life, and many in children with other problems such as malnutrition or HIV infection. Protein-polysaccharide conjugate vaccines have been developed, which cover the most important 9-11 of the 90 serotypes of pneumococci. These vaccines are now due to undergo formal evaluation in developing countries.

It is estimated that 1-2 million child deaths each year are due to the pneumococcus – as many as 30% of them in the first three months of life, and many in children with other problems such as malnutrition or HIV infection.

OVERALL OBJECTIVE

To evaluate the use of a pneumococcal conjugate vaccine in developing countries.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two companies have now produced pneumococcal conjugate vaccines in advanced stages of development and one is in Phase III trials. Plans have been developed for the evaluation of both vaccines in developing countries. At least two such trials will be started in 1998.

MILESTONES/TARGETS

By 1998:

- ▷ First Phase III pneumococcal conjugate vaccine trial under way in a developing country.

By 1999:

- ▷ Second and third pneumococcal conjugate vaccine trials under way.

By 2001:

- ▷ Completion and analysis of first Phase III pneumococcal conjugate vaccine trial in a developing country.

DEMONSTRATION OF THE EFFECTIVENESS OF EARLY INFANT OR NEONATAL PNEUMOCOCCAL CONJUGATE IMMUNIZATION

Even if pneumococcal conjugate vaccines prove to be highly effective, this will not reduce the significant proportion of pneumococcal illness that occurs in infants under three months of age. To address this group, studies of vaccine use in early infancy are planned.

OBJECTIVE

- □ To evaluate alternative regimens of pneumococcal conjugate vaccination in very young infants in developing countries.

1994-1997 PROGRESS, ACHIEVEMENTS AND CONSTRAINTS

Unpublished data suggesting that neonatal use of one of the Hib conjugate vaccines (PRP-OMP) resulted in the induction of tolerance will be reviewed at a meeting early in 1998 to review plans for work in this field.

MILESTONES/TARGETS

By 1998:

- ▷ Identification of sites and completion of proposals for studies.

By 2000:

- ▷ Completion of Phase II studies.

DEMONSTRATION OF THE SAFETY AND EFFECTIVENESS OF MATERNAL PNEUMOCOCCAL VACCINATION

Immunization of pregnant women to protect the newborn has been employed with great effect for the prevention of neonatal tetanus. Maternal immunization with PRP-T Hib conjugate vaccine in the Gambia did not affect the subsequent response of the infants to the same vaccine. Therefore, the same strategy should be tested as a means of protecting newborns from pneumococcal disease.

OBJECTIVE

- □ Completion of a Phase III trial of maternal pneumococcal immunization in a developing country.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two important studies of this strategy have been published from Bangladesh and the Gambia. Four further studies have been completed and are awaiting sample analysis. In 1997, WHO undertook an analysis of existing studies with a special emphasis on safety aspects.

MILESTONES/TARGETS

By 1998:

- ▷ Agreement at a meeting of experts on strategies to be undertaken.

By 1999:

- ▷ Identification of a site and start of a Phase III trial on maternal pneumococcal immunization.

By 2000:

- ▷ Trial initiated.

DEMONSTRATION OF THE SAFETY AND IMMUNOGENICITY OF PNEUMOCOCCAL VACCINATION OF HIGH-RISK INFANTS

Certain groups of infants and adults are at high risk for pneumococcal disease and will require special consideration for vaccination.

OBJECTIVE

- To complete Phase II trials in a developing country of pneumococcal conjugate vaccination in infants with malnutrition, HIV infection, and sickle cell disease.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The South African pneumococcal conjugate vaccine trial has been designed to determine the efficacy of the vaccine in HIV-infected infants.

MILESTONES/TARGETS

By 2000:

- ▷ Completion of safety and immunogenicity study of pneumococcal conjugate vaccination in infants with HIV disease.
- ▷ Completion of safety and immunogenicity study of pneumococcal conjugate vaccination in infants with malnutrition.
- ▷ Completion of safety and immunogenicity study of pneumococcal conjugate vaccination in infants with sickle-cell disease.

IDENTIFICATION OF A PNEUMOCOCCAL COMMON PROTEIN CANDIDATE VACCINE FOR FIELD EVALUATION IN DEVELOPING COUNTRIES

At best pneumococcal conjugate vaccines will prevent invasive disease and possibly carriage associated with the serotypes included in the vaccine and related groups. This would still leave other serotypes which may continue to cause disease, possibly with greater frequency than before. Thus, while the focus is currently on the conjugate vaccines, they will not provide complete protection against all pneumococcal disease on their own. Common protein vaccines offer a means of avoiding that problem by targeting conserved protein epitopes.

OBJECTIVE

- To develop a common protein pneumococcal vaccine.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

For the past several years, research has been promoted towards the development of a pneumococcal vaccine based on common pneumococcal proteins. As yet, three proteins (pneumolysin, pneumococcal surface protein A and pneumococcal surface adhesin) have emerged as promising candidates. The eventual role of these vaccines may be to complement the conjugate vaccine.

MILESTONES/TARGETS

By 1999:

- First Phase II trial of a pneumococcal protein vaccine under way involving children in a developing country.

By 2001:

- Identification of a site for a Phase III pneumococcal common protein vaccine trial in infants.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	1 846 000	1 541 000	–305 000
1999	2 519 000	1 772 000	–747 000

VACCINES AGAINST VIRAL LOWER RESPIRATORY TRACK DISEASE: RESPIRATORY SYNCYTIAL VIRUS AND PARAINFLUENZA VIRUS TYPE 3

Respiratory syncytial virus and parainfluenza virus type 3 are responsible for about 30% of viral respiratory tract disease leading to hospitalization of infants and children. For this reason there is a need to develop effective vaccines against these viruses. Since these viruses cause severe lower respiratory tract disease in early infancy, vaccines must be effective in the presence of maternally derived antibodies. To date several strategies for immunization against disease caused by these viruses have been explored. A coordinated effort to expedite the preclinical evaluation of the newly developed candidate vaccines and their testing in human subjects is urged.

OVERALL OBJECTIVE

To improve global control of infections caused by respiratory syncytial virus and parainfluenza virus type 3.

Development of vaccines against Respiratory Syncytial Virus (RSV)

RESPIRATORY syncytial virus (RSV) is estimated to cause about 900 000 deaths a year – mainly in infants and young children. The virus is highly contagious and most children throughout the world are infected during the first two years of life. Previous infection does not protect against subsequent reinfection with the virus. In the industrialized countries RSV is the largest single cause of lower respiratory tract infections in young infants. In the United States alone the disease is responsible for about 91 000 hospitalizations a year and 4 500 deaths – mainly in children under one. In developing countries, treatment costs are often not affordable. There is therefore an strong case for R&D to develop new intervention tools.

Vaccine development has been hampered by the unexpected and severe reactions to the experimental formalin-inactivated vaccine in the 1960s. Since then vaccine testing has been largely restricted to animal models and to a lesser extent to seropositive adults and children.

OBJECTIVE

- To develop new safe and effective vaccines against RSV and accelerate their introduction in developing countries.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Coordination of research on the development of RSV candidate vaccines has been carried out through WHO research meetings and through distribution of reference reagents from the WHO Bank of RSV strains. Two candidate vaccines have been developed and submitted for evaluation in clinical trials: live attenuated viruses and subunit vaccine. There is now a need to assess the demand for RSV vaccine in developing countries.

MILESTONES/TARGETS

By 1998:

- Evaluation of progress in Phase I clinical trials.

By 1999:

- An international meeting to be held on needs and requirements for RSV vaccines in developing countries.

By 2000:

- Evaluation of results of Phase I trials.
- Initiation of study in developing countries on needs for RSV vaccines.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	74 000	69 000	–5 000
1999	56 000	89 000	16 000

Development of vaccines against parainfluenza type 3 virus (PIV3)

PARAINFLUENZA type 3 virus is an important cause of severe viral lower respiratory tract disease in infants and young children. However, no vaccine is available to protect against this virus.

OBJECTIVE

- To improve control of diseases caused by PIV3.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Coordination of research in the development of PIV3 candidate vaccines has been carried out through WHO research meetings and through the distribution of reference reagents from the WHO Bank of PIV3 strains. Two vaccines have been developed and submitted for evaluation in clinical trials: cold-passage mutants of human PIV3 and bovine PIV3 strains.

MILESTONES/TARGETS

By 1998:

- Evaluation of progress in clinical trials.

By 1999:

- International meeting on the need for PIV3 vaccines in developing countries.

By 2000:

- Evaluation of results of Phase II trials.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	12 000	12 000	0
1999	72 000	11 000	–61 000

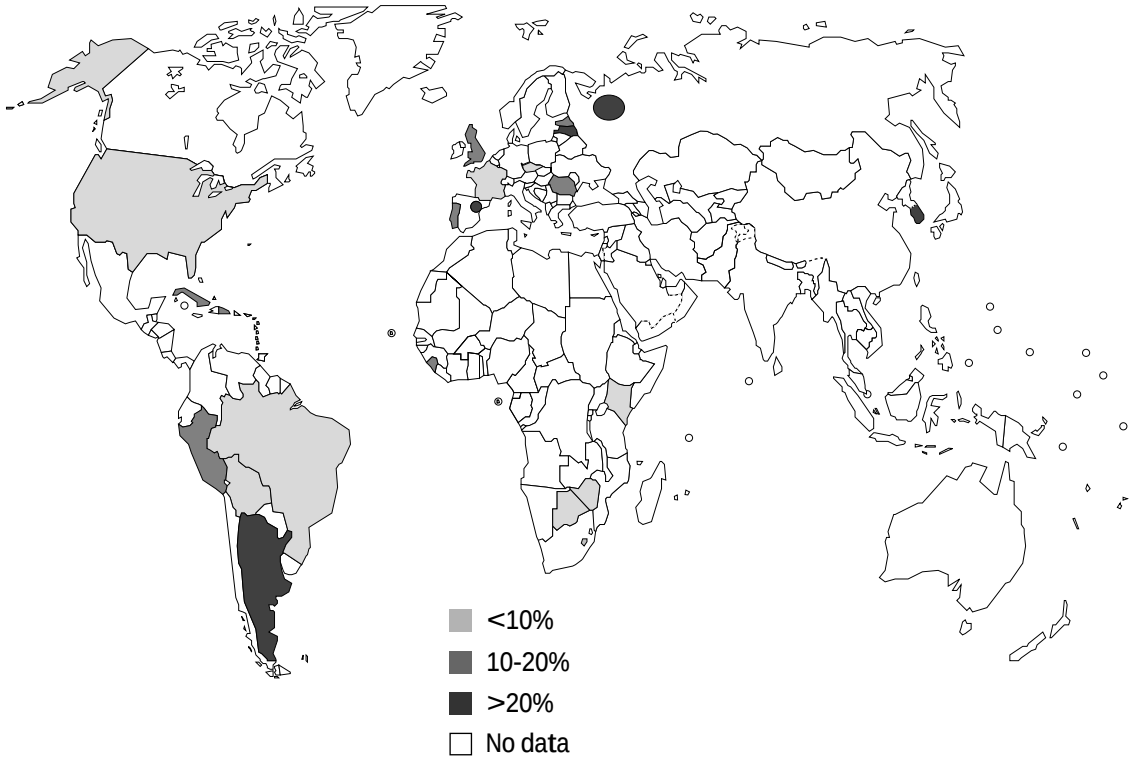
VACCINES AGAINST TUBERCULOSIS (TB)

Tuberculosis (TB), often considered a 19th century disease, kills more people than any other infectious disease. The estimated 3 million deaths a year, including almost 300,000 children under the age of 15, exceed the 2.1 million annual deaths attributed to malaria and the 2.5 million deaths for all diarrhoeal diseases combined. More women die from TB than from all maternally related causes. One-third of the World's population is infected with Mycobacterium (M.) tuberculosis, and of that one-third, approximately 15 million have the active disease. TB patients who stop taking antibiotics before they are cured continue to infect others and also risk developing and spreading multi-drug-resistant strains of the bacteria that are becoming increasingly difficult to treat. More than 50 million people are believed to have already been infected with TB drug-resistant strains. Health workers and other contact groups are highly vulnerable to untreatable forms of the disease. The efficacy of BCG in the prevention of severe disease in children is generally recognized. However, the impact of BCG vaccination on adolescent and adult TB is highly variable and generally rather poor. Therefore, the development of a new tuberculosis vaccine, more efficient than BCG, is needed to tackle the threat of TB permanently. Initial priority will be given to testing of post-exposure vaccines.

OVERALL OBJECTIVE

To translate recent progress in fundamental research into new and more efficient vaccines for the prevention of tuberculosis.

Prevalence of acquired MDR-TB in countries and regions surveyed, 1994-1997
(WHO/IUATLD global project on anti-TB drug resistance surveillance, 1997)



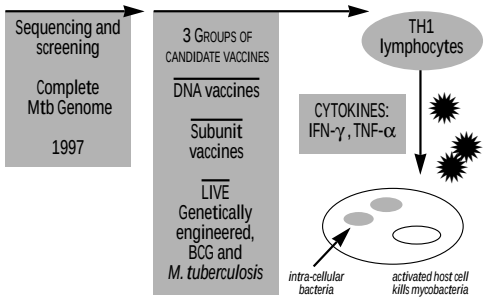
NEW APPROACHES TOWARDS TB VACCINES

More than 50 million people are believed to have already been infected with TB drug-resistant strains.

In recognition of the need for a forum for all the different parties (national and international organizations, vaccine manufacturers, regulatory authorities, the scientific community) who participate in the development of new TB vaccines, a GPV Working Group for the Development of New Tuberculosis Vaccines was established. This group designed a comprehensive strategic plan aimed at filling the gaps currently existing in the development of TB vaccines, from strategic research to human clinical testing. The group will maintain contact with industry and regulatory agencies, and will ensure that research activities are coordinated on a global basis.

Four different types of vaccine candidates for TB have been developed: modified BCG, rationally attenuated *M. tuberculosis*, protein subunit vaccines, and nucleic acid vaccines. However, antigens or antigen combinations which induce protection superior to BCG remain to be experimentally defined. Strategic research on TB is urgently required in two areas: highly innovative approaches towards the definition of protective antigens, antigen combinations, and antigen-adjuvant combinations; and the development of immune parameters for potential for use as immunological markers of protection.

Tuberculosis – from genomic sequence to effective vaccines



OBJECTIVE

- To conduct at least 10 highly innovative studies and to identify lead candidate vaccines and markers of protection.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A major breakthrough in antigen definition was the development of methods to screen the entire mycobacterial genome for protective antigens, using nucleic acid vaccination technology in animal models.

MILESTONES/TARGETS

Development of a new tuberculosis vaccine, more efficient than BCG, is needed to tackle the threat of TB permanently.

By 1998:

- ▷ Innovative projects identified and studies initiated.
- ▷ New vaccine candidates characterized.

By 1999:

- ▷ Immunological markers of protection identified.

CLINICAL TRIAL PROTOCOLS FOR NEW TB VACCINES

Until recently it was assumed that a new TB vaccine would be given to newborn infants not previously exposed to the virus. However, post-exposure vaccination is now considered a more feasible option for clinical testing, particularly since it would not involve withdrawal of BCG from a part of the trial population and it may considerably shorten the duration of Phase III clinical trials.

OBJECTIVE

- To establish a protocol for Phase II and III clinical trials.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The concept of post-exposure TB vaccine trials (testing in BCG-vaccinated, or sub-clinically infected individuals) was developed. Current efforts focus on identification of potential sites, infrastructure requirements, and the elaboration of clinical testing protocols.

MILESTONES/TARGETS

By 1998:

- Concept of post-exposure vaccination established.
- Protocol for comparative Phase II trials developed.
- Protocol for Phase III trials developed.

ANIMAL TESTING OF NEW TB CANDIDATE VACCINES

Before preclinical evaluation of TB vaccine candidates in animals can begin, there is an urgent need to: enlarge the network of laboratories capable of testing TB vaccine candidates under standardized conditions; develop standard protocols for post-exposure vaccination of experimental animals; and develop a standardized animal model – for example, a primate model – which is phylogenetically closer to man than the current guinea pig and mouse models.

OBJECTIVE

- To develop a standardized and validated post-exposure guinea pig and primate model and at least one lead candidate for post-exposure vaccination.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Guinea pig, mouse, and rabbit models for testing TB vaccine candidates under pre-exposure conditions were standardized and validated during the period under scrutiny. However, these now need to be adapted to model the post-exposure TB vaccine testing paradigm which, in the meantime, has been developed for clinical trials in humans.

MILESTONES/TARGETS

By 1998:

- ▷ Development of a standard protocol for pre-clinical testing of vaccine candidates.

By 1999:

- ▷ Establishment of an international network of laboratories.

By 2000:

- ▷ Identification of lead candidates for post-exposure vaccination.

RAPID TEST TO ASSESS PROTECTIVE IMMUNITY AGAINST TB

Identification of immunological markers of protection against TB would be particularly useful given the anticipated long duration of clinical trials of candidate vaccines. Furthermore, the availability of a rapid field test of preliminary indicators of protection in humans would give decision-makers the confidence needed to embark on lengthy and costly Phase III clinical trials of a new TB vaccine.

OBJECTIVE

- □ To develop a field-applicable skin-test and cytokine assays to monitor vaccine-induced protection against TB .

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The search for immunological markers of protection yielded valuable information on the differential distribution of certain cytokines (e.g. IFNg, TNFa, TGFb) in treated as well as untreated TB patients. However, this progress has yet to be turned into a simple field tool for measurement of a correlate of protection. Therefore, Vaccine Research and Development Unit (VRD) has established a global network of laboratories for the validation of immunological markers of protection.

MILESTONES/TARGETS

By 1998:

- ▷ Establishment of standard protocol.

By 1999:

- ▷ Establishment of a network of laboratories for development and validation of tests.

By 2001:

- ▷ Validation of tests and assays in vaccinated individuals.

TB CANDIDATE VACCINE TRIAL

CURRENT, rapid progress in the development and pre-clinical testing of TB vaccine candidates – especially the non-living versions, such as protein subunit and nucleic acid vaccines – suggests that at least one candidate vaccine will be available by the year 2000 or soon after.

OBJECTIVE

- □ To evaluate post-exposure candidate vaccines in Phase II/III clinical trials.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A working group has been established for the preparation of clinical trials, and a paper on vaccination strategies has been prepared. Identification of potential trial sites and drafting of trial protocols has been initiated.

MILESTONES/TARGETS

By 2001:

- ▷ At least one post-exposure vaccine candidate in clinical Phase II/III trials.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	620 000	435 000	–185 000
1999	733 000	474 000	–259 000

VACCINES AGAINST INFECTION-RELATED CANCERS

The causal link between the development of cancer and infectious agents has already been established for many years, opening the way to producing vaccines against them. It is estimated that around 15.6% (1 450 000 cases) of the worldwide incidence of cancer in 1990 was attributed to infectious agents, primarily: Helicobacter pylori *(stomach cancer), human papilloma virus (cervix cancer), and hepatitis B and C (liver cancer).*

Vaccines against infection-related cancers

NEW VACCINES ?

STOMACH CANCERS ■ 55% attributable to *heliobacter pylori*	**496 000**	*Year* ***2001 (?)***
LIVER CANCERS ■ 60% attributable to Hepatitis B ■ and 24% to Hepatitis C	**285-400 000** **113 000**	✔ *Year* ***2010 (?)***
CERVIX CANCERS 89% attributable to human papillomaviruses (HPV) ■ 60% attributable to Hepatitis B	**416 000**	*Year* ***2001 (?)***

There already is one extremely efficient vaccine in use in the EPI – the hepatitis B vaccine – which protects against chronic hepatitis that leads to liver cancer. It is estimated that 300 000 to 500 000 cases of liver cancer connected to hepatitis B infection occurs every year. Vaccines against Helicobacter pylori *and human papilloma virus are at advances stages of development. If successful, they have the potential to prevent around 900 000 cases of cancer.*

OVERALL OBJECTIVE

To coordinate and facilitate the development and evaluation of vaccines against *Helicobacter pylori* and human papilloma virus.

Vaccine against *Helicobacter pylori* Infection

OVER recent years, evidence has emerged of a causal link between *H. pylori* infection and stomach cancer. The relative risk of cancer associated with infection varies from 1.5 to 6, leading to 500 000 cases annually. Preliminary studies suggest that a vaccine against *H. pylori* infection is feasible. The project will be pursued jointly with the International Agency for Research on Cancer (IARC) in Lyon.

OBJECTIVE

- To initiate clinical evaluation of candidate vaccines.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

New project.

MILESTONES/TARGETS

By 1998:
- ▷ Designation of collaboration centre.
- ▷ Technical review meeting.

By 1999:
- ▷ Identification of lead candidates.

By 2001:
- ▷ Participation in clinical evaluation.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	57 000	11 000	–46 000
1999	77 000	31 000	–46 000

Vaccines against cancer caused by human papillomavirus (HPV)

HUMAN papillomavirus is considered to be the most important risk factor in the development of cervical cancer, the second most important cancer in women worldwide. A vaccine against HPV is currently unavailable.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	12 000	11 000	–1 000
1999	62 000	22 000	–40 000

OBJECTIVE

- To develop a candidate vaccine against HPV.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Work is under way to identify and designate two WHO Collaborating Centres for reference and research in relation to vaccines against cancer caused by human papillomavirus.

MILESTONES/TARGETS

By 1998:
- ▷ Designation of WHO Collaborative Centres.
- ▷ Evaluation of current status of problem.

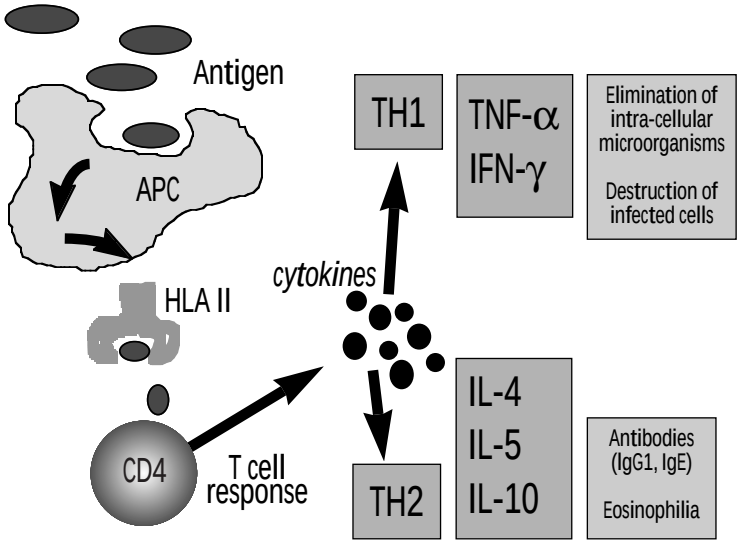
By 1999:
- ▷ Plan of activity.

By 2001:
- ▷ Selection and support of research project.

NEW VACCINATION APPROACHES TO INDUCE PROTECTIVE RESPONSES

*Increased knowledge acquired over the last few years of the molecular mechanisms of immune responses has allowed researchers to design vaccines with the ability to selectively elicit humoral and/or cellular responses. Selective polarisation of vaccine-induced immune responses can now be achieved to generate the effector cells (e.g. cytotoxic T lymphocytes) a major role in fighting intracellular pathogens, such as tuberculosis or viruses. Interestingly, as shown in the figure below, T-helper cell responses can also be selectively polarized toward the so-called Th-1 or Th-2 types of responses. Th-1 type is accompanied by a production of substances (cytokines) such as interleukin 2, tumor necrosis factor (TNF)-*a *and interferon-*c *which also play a major role in the defence against viral, intracellular bacterial or parasitic infections.*

Modulation of T-helper cell response through vaccination



Nucleic acid vaccines

A new technology to immunize has been developed that implies the administration of DNA encoding for the desired antigens. It works by inducing the *in vivo* production of proteins containing the protective epitopes of the corresponding pathogen but avoiding the risks of the pathogen itself. The exogenously administered DNA (with selected key antigens inserted in a plasmid) will "use" the material in our cells needed for the production of the desired vaccine, in its native conformation, therefore mimicking closely the parts of the micro-organism needed for the induction of the immune response, but avoiding at the same time its harmful effects.

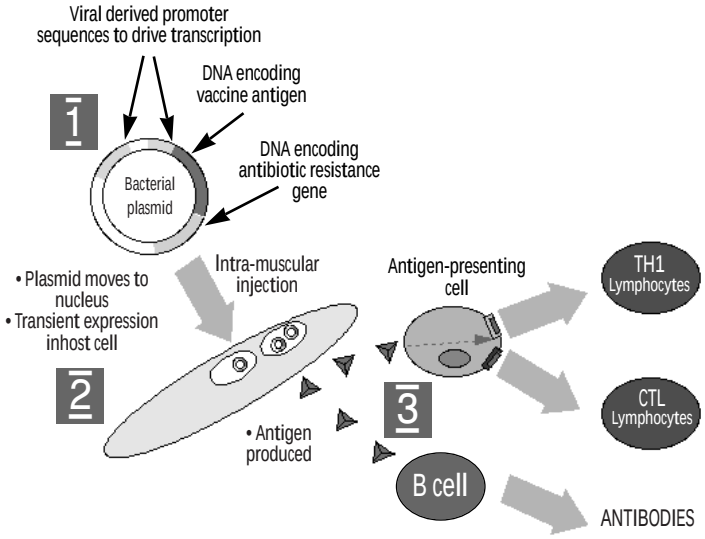
This is a simple to develop technology, which can produce stable, inexpensive vaccines, that allows the combination of several vaccines and is supposed to be an optimal way to induce not only protective antibodies but the right cellular response when required. Concerns remain on its long-tern safety side.

The exogenously administered DNA (with selected key antigens inserted in a plasmid) will "use" the material in our cells needed for the production of the desired vaccine.

OVERALL OBJECTIVE

The goals are to assess the potential and limitations of this technology in general, as well as to explore its potential for mucosal immunization.

DNA vaccines



PHASE I TRIALS OF DNA VACCINES

An analysis is needed to assess the performance of this new kind of vaccination in man by comparing the results of several trials of candidate vaccines.

OBJECTIVE

- To analyse the safety and immunogenicity of DNA vaccines tested in man (Phase I trials).

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The Steering Committee on New Vaccination Approaches has had a long-standing interest in nucleic acid vaccines and has supported some of the original projects in this area. Two international meetings were organized and the proceedings were published in two special issues of Vaccine: volumes 12 and 16 in 1994, and volumes 8 and 15 in 1997. WHO Guidelines were also generated: *Guidelines for Assuring the Quality of DNA Vaccines* (TRS 872).

MILESTONES/TARGETS

By 1999:

- ▷ Meeting on safety and immunogenicity held.
- ▷ Report available.

MUCOSAL DELIVERY OF DNA VACCINES

In order to administer this new type of vaccines through mucosal surfaces (oral, nasal or vaginal) it is necessary to design and adapt different vaccine delivery methods to DNA administration.

OBJECTIVE

- □ To complete preclinical studies of a method(s) for mucosal DNA immunization.

MILESTONES/TARGETS

By 1998:

- ▷ Preclinical studies ongoing.

By 2001:

- ▷ An appropriate method to deliver DNA vaccines to mucosal surfaces evaluated in animal models and ready for clinical evaluation in human volunteers.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	210 000	81 000	–129 000
1999	206 000	126 000	–80 000

New adjuvants and carriers

THERE exist today a series of new products (adjuvant, carriers) which have the ability to improve the immunogenicity of a given vaccine. They can also reduce both the number of doses and the amount of antigen per dose in a cost-effective way.

OVERALL OBJECTIVE

To identify candidate adjuvants and carriers for selected antigens.

COMBINATION OF DTP AND LOW DOSE HIB-T

Combination of certain antigens can help a given formulation to have an increased potency while using a reduced amount of antigen, which can result in turn in a reduced vaccine price.

OBJECTIVE

- To reduce the amount of antigen(s) in selected combination vaccines.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A formulation with reduced dose Hib-T component of a DPT-Hib vaccine is being developed and the preclinical testing has almost been completed.

MILESTONES/TARGETS

By 1999:

- ▷ Preclinical studies completed.

By 2000:

- ▷ Clinical evaluation started.

VIRUS-LIKE PARTICLES TO DEVELOP A VACCINE AGAINST HEPATITIS C

It has been shown that the development of chimeric virus-like particles bearing main antigens of pathogenic organisms are able to induce strong cellular and humoral responses against them.

OBJECTIVE

- To develop and assess pre-clinically the potential of virus–like particles against (VLPs) hepatitis C.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The virus-like particle (VLP) is based on the ability of the hepatitis delta virus large antigen to interact with the hepatitis B surface antigen (HBsAg) to result in the packaging of the former into the HbsAg. It is expected that the construction of chimeric proteins which combines Hepatitis C core proteins with Hepatitis delta large antigen protein will result in the induction of immune responses when packaged as a virus like particle within the HbsAg.

MILESTONES/TARGETS

By 1999:

- ▷ A new formulation developed and preclinical testing completed.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**67 000**	**67 000**	**0**
1999	**92 000**	**67 000**	**–25 000**

Evaluation of different strategies to immunize neonates

THE immature immune system of the neonates does not necessarily respond by the same mechanisms than its adult counterpart. Antibody and cellular responses are not always easy to induce or they are not the appropriate in quality or quantity. Understanding the mechanisms that govern these responses and having the right tools to modify them so as to make them effective early on would be a tremendous advantage when developing vaccines for this population target group. Newborns (animal models) can be immunized by using strategies that directly address the function of specific cell subsets.

OBJECTIVE

- To compare different immunization strategies (DNA, live vectors) in animal models that determine the optimal induction of immune responses in newborns (T-helper 1, T-helper 2, and B cell responses).

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A study has been carried out using an animal model to compare the different responses in newborns and adults to different antigens and different delivery systems/type of vaccines. The results indicate that early immunization with DNA induces a comparable response in newborns to that of adult mice when other systems fail to do so.

MILESTONES/TARGETS

By 2000:

- Pre-clinical comparison of different immunization strategies assessed.
- Delineation of immunological mechanisms in the newborn.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	114 000	74 000	–40 000
1999	157 000	97 000	–60 000

Application of selected technologies to HIV/AIDS vaccines

THE efforts worldwide to develop an efficient vaccine against this new disease have been enormous and yet, no vaccine exists today for preventive or therapeutic use. The difficulty with the viral charactetistics and with the definition of correlates of protection has hampered a faster development and, although a number of candidates have been moved to advanced clinical testing, results in general are quite disappointing. There are therefore good reasons to further apply new approaches to try to find good ways to induce protection or even to modulate the course of the disease.

OVERALL OBJECTIVE

The goal is to test selected novel immunization approaches to develop new HIV/AIDS vaccines. This effort is jointly undertaking with UNAIDS. Studies have been selected on the basis of promising preliminary data and because they represent less explored ones in the very large field of AIDS vaccine research.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A meeting was organized in 1997 to decide on priorities. BCG-vectored and mucosal DNA-based approaches for new HIV/AIDS vaccines have been selected. Cytotoxic T-lymphocytes (CTL) mapping to identify critical epitopes for new candidate vaccines will be undertaken. Several projects have already been initiated.

BCG-VECTORED AIDS VACCINE

Among an array of possible live vectors to be used as carriers of HIV antigens, BCG seems to induce neutralizing antibodies in animal models and its potential to be used as an AIDS vaccine needs to be further explored in order to accommodate several antigens.

OBJECTIVE

- To develop and evaluate BCG-vector candidate(s).

MILESTONES/TARGETS

By 1998:

- At least one preclinical study completed.

By 1999:

- Phase I trials initiated.

MUCOSAL DNA VACCINES AGAINST HIV/AIDS

Despite a number of HIV/AIDS DNA vaccines have been delivered parenterally, little has been done for their mucosal delivery due to the special methodology required. Mucosal surfaces would be an optimal induction sites, as a good stimulation immune responses at this level would greatly contribute to protect against this disease.

OBJECTIVE

- To define a method(s) of mucosal DNA immunization against HIV/AIDS.

MILESTONES/TARGETS

By 1999:

- Preclinical studies completed.

By 2000:

- Phase I trials initiated.

IDENTIFICATION OF HIV CTL EPITOPES

Some CTL epitopes have been identified but further work is needed to identify the most important ones in the different clades

OBJECTIVE

- To identify optimal CTL epitopes for protection against HIV/AIDS.

MILESTONES/TARGETS

By 1999:

- Assessment of the best antigenic CTL epitopes.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	218 000	175 000	–43 000
1999	298 000	218 000	–80 000

IMPROVEMENT OF VACCINE ADMINISTRATION: DEVELOPMENT OF NEW DELIVERY SYSTEMS

Most vaccines currently in use today could be administered in a simpler, safer and sometimes even less costly way. These improvements would help tremendously to increase coverage and facilitate immunization campaigns. Reducing the number of doses required to fully immunize, increasing thermostability, administering vaccines through the nose or the mouth are some examples of possible ways to facilitate the delivery; selected projects and activities in those areas are being supported.

Single-dose vaccines

THE goal is to simplify vaccine administration through reducing the number of contacts needed to fully immunize an individual. One way is to develop a single-dose tetanus vaccine as a model and eventually apply the technology to other antigens.

Most vaccines currently in use today could be administered in a simpler, safer and sometimes even less costly way.

OBJECTIVE

- To assess several technologies for single-dose vaccines in preclinical and clinical trials (Phase I/II) using tetanus toxoid as a model, and to assess the application of these technologies to other antigens.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

For the development of single-dose vaccines, tetanus toxoid was chosen as model because its potential use in the elimination of neonatal tetanus and the inherent physico-chemical advantages of the molecule. For further details on the progress, achievements and constraints of this area please refer to "neonatal tetanus elimination-development of simpler-to-deliver tetanus vaccines" within the section Disease control – Filling the vaccine pipeline.

MILESTONES/TARGETS

By 1998:

- ▷ Preclinical studies completed.

By 1999:

- ▷ Clinical studies initiated.

By 2000:

- ▷ Application of this technology to other antigens (diphtheria and pertussis) initiated.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	169 000	49 000	–120 000
1999	529 000	79 000	–450 000

Mucosal immunization

THERE has been a long-standing interest among vaccine developers in understanding the mechanisms of induction of immune responses induced at the mucosal level or systemic responses induced through mucosal routes. The last aspect, the fact that if a vaccine is appropriately designed, can induce protective humoral and cellular responses when administered through the mouth or the nose (the only two mucosal sites with practical value for immunization) is the focus of our efforts to make a vaccine simpler to deliver. Rather than using syringes and needles, the use of oral or nasal vaccine can have a number of advantages, from the point of view of safety, logistics, acceptability, etc.

OVERALL OBJECTIVE

To assess the potential of selected living (eg *Salmonella*) and non-living (eg adjuvants, particles) carriers to induce the desired systemic immmune responses and to improve oral and nasal antigen delivery. Emphasis is being given to approaches that are in advanced preclinical or phase I trials.

ADJUVANTS FOR MUCOSAL IMMUNIZATION

Adjuvants (coming from the latin *adjuvare* which means help) are used to increase or modulate the cellular or humoral immune responses to an antigen. A modern vaccinology approach speculates that, irrespective of the desired effector response that a vaccine must elicit in order to confer protective immunity, these responses can be achieved by vaccines administered via mucosal surfaces, mainly oral and nasal routes. Mucosal adjuvants would therefore be used to help vaccines administered by these routes elicit the appropriate responses. A number of molecules have been identified that "help" immune responses following mucosal co-administration of vaccine antigens.

OBJECTIVE

- To conduct several studies (preclinical and clinical) on different mucosal adjuvants/delivery formulations for oral and nasal routes as well as on living systems for the oral route.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Funding has been provided to different adjuvant systems for oral or nasal immunization, with an emphasis on cholera toxin derivatives. Recently, efforts have focused on identifying the most promising adjuvants for these routes and assuring their potential for inducing systemic (as well as local) immune response in man. Comparative studies among different adjuvants or other systems have become a goal. In an effort to catalyse this advance, both NIH and WHO are joining efforts to coordinate studies and move quickly the most promising candidates to human trials.

MILESTONES/TARGETS

By 1998:

- ▷ Technical review conducted.
- ▷ Selection and commission of projects.

By 1999:

- ▷ Preclinical and clinical assessment of the best adjuvants and living systems for human use initiated.

By 2000:

- ▷ Comparative Phase I trials initiated, phase II trials ongoing.

MUCOSAL DELIVERY OF NON-LIVING CARRIERS: OUTER MEMBRANE VESICLES (OMV)

Soluble outer membrane vesicles (OMVs) have been previously used as vaccines against meningococcal meningitis serogroup B. It is now understood that OMVs can also act in combination with other antigens as a potent adjuvant.

OBJECTIVE

- To conduct a Phase I trial with meningococcal serogroup B OMV vaccine administered nasally.
- To assess the potential suitibality of OMVs as adjuvants for candidate vaccines.

MILESTONES/TARGETS

By 1998:

▷ Phase I trial completed.

By 2001:

▷ Adjuvant effect of OMVs assessed pre-clinically and clinically.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	248 000	143 000	–105 000
1999	308 000	183 000	–125 000

Live vectors

THE use of live vectors (bacterial or viral) consists in the insertion of foreign genes of a given pathogen in the genome of an organism (the vector) with the aim to induce a better response to the pathogen, an stronger or longer lasting response, as part of the immune response to the recombinant organism. Emphasis is being placed in the use of these vectors for mucosal delivery as well in addressing the effects of repeated immunization with the same vector carrying but different antigens on subsequent immunizations.

OBJECTIVE

- To assess the utility of live vectors (*Salmonella*, BCG, and herpes) for mucosal delivery.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Numerous projects have been supported on the use (advantages and limitations of the system, improvement of the constructs for optimal antigen expression) of *Salmonella* as a vector. Most of them have been completed and provide the basis for the optimal use of this vector, while others are ongoing or have entered Phase I trials. In addition, a number of projects have been supported dealing with live vectors for parenteral use, including the concomitant expression of several antigens as well as immunomodulators, like citokynes.

MILESTONES/TARGETS

By 1999:

- At least one preclinical study completed (*Salmonella*, BCG, and herpes).
- Clinical studies initiated (BCG).

By 2001

- Clinical evaluation ongoing.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	97 000	87 000	–10 000
1999	107 000	107 000	0

Plant-based technology for vaccines

SINCE the early 1980's, it has been possible to genetically alter many plant species by the stable introduction of foreign DNA (transgenic plants). Nowadays the list of potential candidate plants to be transformed contains over 60 different species and is constantly growing. The expression of antigenic proteins in plants has three major components: (1) creation of DNA expression vector which will drive the synthesis of one or more foreign proteins when introduced into plant cells; (2) analysis of gene expression resulting from plant transformation with these vectors; (3) evaluation of the immunogenicity.

OBJECTIVE

- To assess the potential of plant expression systems to produce oral vaccines.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

To date, attempts to engineer plants for vaccine production include potatoes, tobacco plants and bananas. Research has been supported aiming at developing protein expression vectors for plant transformation to drive the synthesis and accumulation of selected antigens in plant tissues to levels that may cause a desired level of immune responses in two projects: in the first one, researchers are attempting to express each of the four major proteins (VP2, VP4, VP6, VP7) of rotavirus serotypes individually in potato leaves, in order to assess the capacity of plant cells to accumulate each VP and, in the second project, a study to develop hepatitis B transgenic plant- based vaccine has been initiated.

MILESTONES/TARGETS

By 1998:

- ▷ Preclinical studies initiated.

By 2001:

- ▷ Potential of this technology as a vaccine production system or ultimately, as a tool to develop edible vaccines assessed.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	82 000	72 000	–10 000
1999	122 000	72 000	–50 000

Parenteral administration of vaccines as solids

THE scale of immunization programmes is expected to rise dramatically in the next century as the number of vaccines increases and as mass disease control operations are implemented. Success will depend on the streamlining of the vaccine delivery system, on eliminating the cold chain, and on achieving rapid "zero-risk" injections. Advances in the vaccine and the injection device industries offer the potential for direct injection of vaccines (in the form of heat-stable dry powders) delivered safely and at low cost.

Novel drying technologies, which incorporate antigens in inert, temperature-resistant solids, together with progress in the development of injection devices, have the potential to change immunization programmes beyond recognition. The transition from unstable liquid formulations or freeze-dried vaccines to dry powders will also allow the vaccine to be formulated in the same form and the same volume in which it is to be administered. Some manufacturers are focusing their efforts on development of injection devices to administer solid vaccines parentally without trauma. More importantly, in view of the one billion immunization injections given in the developing world each year, these devices will deliver the vaccine without any possibility of contamination or cross-infection in the field. Neither of these technologies would generate contaminated sharps for disposal, nor would they be re-used.

OBJECTIVE

- To develop vaccines in a form that is stable and ready-to-use (monophasic) and new devices to deliver them.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Powder vaccines, developed through a trehalose-based drying and stabilizing technology, are already being tested in animals and occasionally in humans. However, additional research is still needed. Extensive safety and immunogenicity studies need to be performed in various animal models. Meanwhile, comparative assessment of different delivery systems (intradermal, sub-cutaneous and intra-muscular) for known vaccines are needed before new antigens can be tested.

MILESTONES/TARGETS

By 1998:

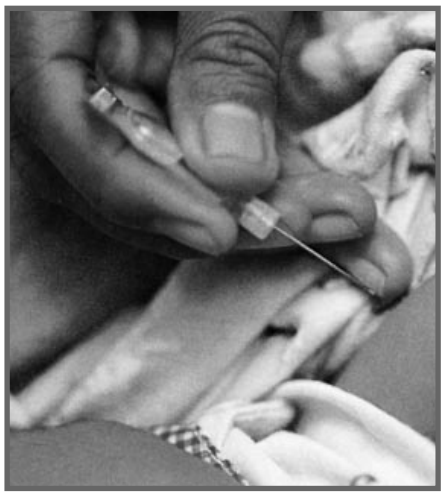
- ▷ A new generation of jet injectors tested in the laboratory and in the field for safety and available for routine and mass immunization.
- ▷ Survey of existing technology conducted.

By 1999:

- ▷ Preclinical studies that investigates the feasibility, safety and efficacy of model vaccines presented and injected as solids initiated.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	146 000	72 000	–74 000
1999	227 000	72 000	–155 000

Pouch and needle



STANDARDIZATION AND MONITORING OF GPV VACCINE TRIALS AND THEIR METHODS: GPV REGISTRY OF VACCINE FIELD TRIALS

Over recent years, involvement of the Global Programme for Vaccines and Immunization in vaccine trials has increased considerably and is expected to increase even further in the future. A registry of planned, ongoing, and completed vaccine trials supported by GPV and its predecessor programmes is essential to track studies and compare methodologies, to identify field sites, and to predict resource needs for future studies. A review document is prepared and annually updated.

OBJECTIVE

- To prepare and disseminate a regularly updated GPV registry of vaccine trials.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The first GPV vaccine trial registry was issued in 1996 (WHO/GEN/96.01) and listed a total of 50 WHO-supported vaccine trials.

MILESTONES/TARGETS

Annual updates.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	12 000	12 000	0
1999	17 000	12 000	–5 000

— GLOBAL LOGISTICS AND QUALITY OF VACCINE

The systems in place to meet the demand, supply, and financing of current vaccines will be a basis on which to develop systems for the introduction of new vaccines. VSQ will be active in these three areas. A first major priority will be to develop financing systems for these new vaccines. A second priority will be to ensure high quality sources of vaccines. This will entail communication with major commercial manufacturers who are developing, or have already developed the technology, and will require knowledge of the technology and the intellectual property agreements involved. It will also require the development of strategies for technology transfer to qualifying developing country manufacturers.

Demand forecasting for new vaccines

One of the keys to rapid introduction of new vaccines is to provide manufacturers with data on timing and the size of projected demand as early in the life cycle as possible. This information allows them to make investment and plant sizing decisions which can bring down vaccine production costs and thus affect prices. It is also necessary to ensure the early availability of these new vaccines.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	85 000	85 000	0

OBJECTIVE

- To accelerate the introduction of new vaccines through providing manufacturers with advance estimates of market size.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Initial estimates based on needs have often turned out to be little more than wish lists. Meanwhile, examination of instances of early introduction of new vaccines in a number of countries has so far failed to provide a blueprint on how to introduce a new vaccine into a programme. Vaccines needed by countries with strong programmes are often not introduced even when the price drops. Key factors in the introduction process have been identified but their relative importance is not yet understood.

MILESTONES/TARGETS

By 1998:

- Establishment of a credible global forecasting system to estimate global demand for new vaccines.

INDICATORS

- Number of doses demanded/doses predicted.

Financing mechanisms for new vaccines

THE introduction of new vaccines at affordable prices requires considerable cooperation among immunization partners. Negotiating prices requires a commitment for financing. A previous target, "Structure of a Global Vaccine Fund will have been designed and donor agreement obtained", has been altered to allow exploration of several types of financing mechanisms that can secure financing for these new products.

Controlled price tiering of vaccines so that the lowest prices are reserved for countries, dependent on donor support, is one way to minimize the amount of donor dependence for new vaccine introduction. However, manufacturers are reluctant to offer heavily differential pricing on new vaccines because this threatens their high-profit market. Strategies are needed which protect the high-profit markets for the producer while, at the same time, making the same vaccines available to the neediest countries at affordable prices.

OBJECTIVE

- To secure financing mechanisms for introducing newly developed vaccines into national immunization programmes in the neediest developing countries.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The concept of differential pricing system has been understood by the vaccine industry.

MILESTONES/TARGETS

By 1998:

- Price of new vaccines to be differential in the same way as existing vaccines.

INDICATORS

- Percentage of countries which introduce new vaccines into their immunization programmes.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	10 000	10 000	0

Availability of new vaccines

THE availability of new products depends to a great extent on the financing strategies in place, as well as on pricing and access to technology for qualifying local producers. Understanding the cost structure of vaccine production for these new technologies will facilitate negotiations with manufacturers. Study of intellectual property rights limiting access to technologies will be important in activities with local producers. Study of production capacity linked to demand and financing is also essential. All these VSQ activities will be needed to ensure the achievement of the primary target for new vaccine introduction, the rapid availability of high-quality new vaccines to immunization programmes. No new vaccines have yet been recommended.

OBJECTIVE

- To make new high quality vaccines available to immunization programmes.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

To make high quality vaccines available to countries, VSQ has worked out assessments of acceptability in principal of those new vaccines already licensed. In addition, VSQ has embarked on discussions with other concerned groups, both within and outside WHO, on activities to promote technology access in ways that support intellectual property rights (IPRs) while still promoting affordability.

MILESTONES/TARGETS

By 2001:

- Within five years of a recommendation on the use of a new vaccine, it will be available to national immunization programmes.

INDICATORS

Time required from licensing to widespread use of a new vaccine.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	124 000	94 000	–30 000
1999	166 000	76 000	–90 000

Financing mechanisms

THE primary constraint to the introduction of new vaccines is financing. Realistic planning to take responsibility for ensuring vaccine financing is critical to new vaccine introduction.

OBJECTIVE

- To ensure financing mechanisms are in place for introducing new vaccines into national immunization programmes.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The concept of controlled differential pricing has not had a significant impact on the pricing of new vaccines. Although some countries have introduced new vaccines into their immunization programme, many countries still cannot afford to do so.

MILESTONES/TARGETS

By 1998:

- Agreement reached on tiering of royalties for new vaccines.

By 2000:

- 90% of priority countries to have adequate financing to introduce the recommended new vaccines.
- Prior to introduction of a new vaccine, every country to have assured, with the help of EPI, funding for the first five years.

INDICATORS

- Percentage of countries introducing a new vaccine.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	11 000	6 000	–5 000
1999	19 000	6 000	–13 000

NEW VACCINES

— SURVEILLANCE & OTHER INFORMATION SYSTEMS

Haemophilus influenzae type b disease burden assessment

DESPITE their proven effectiveness, the introduction of Hib conjugate vaccines has been slow in many developing countries. Lack of reliable, population-based data on disease incidence is a prime cause for the delay in introducing the vaccine.

A standard tool for measuring disease burden due to Hib infection was developed by VRD, and will now be used for pilot studies at selected field sites. Data from these studies are expected to help facilitate the introduction of the vaccine.

OBJECTIVE

- To make available age-stratified data on the incidence of Hib disease.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A "Generic protocol for population-based surveillance of *Haemophilus influenzae* type b" (WHO/VRD/GEN/95.05) has been developed. Four sites have been selected and disease burden studies initiated.

MILESTONES/TARGETS

By 1998:

- Interim results available from four study sites.
- Identification and preparation of 1-2 new sites.

By 1999:

- Final results available from four studies.

By 2000:

- Final results available from 1-2 additional sites.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	185 000	195 000	10 000
1999	216 000	153 000	–63 000

Approaches to assess local disease burden due to congenital rubella syndrome (CRS)

SINCE the last review of the global rubella situation by EPI in 1991, at least six countries have reported outbreaks of rubella. A global review paper has been prepared, summarizing experience from the 1990s. Retrospective and prospective methods for assessing the burden of congenital rubella syndrome (CRS) should now be developed through field studies.

FIELD METHOD TO ASSESS THE LOCAL DISEASE BURDEN DUE TO CRS

OBJECTIVE

- To establish a validated surveillance tool to assess disease burden due to CRS.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Two global review papers on the burden of disease from CRS and vaccination against rubella in developing countries have been published in the *Bulletin of the World Health Organization*, 1997, 75 (1) 55-68 and 69-80.

MILESTONES/TARGETS

By 1998:

- ▷ Three different CRS surveillance methods to be established.

By 1999:

- ▷ Data analysed and disease transmission mathematically modelled.

CONGENITAL RUBELLA SYNDROME MODELLING

OBJECTIVE

- To design and validate a mathematical model that predicts the impact of private sector vaccination on congenital rubella syndrome.

MILESTONES/TARGETS

By 1998:

- ▷ Compilation of empirical data from several sites.
- ▷ Establishment of a predictive mathematical model.

By 1999:

- ▷ Validation.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	129 000	96 000	–33 000
1999	83 000	100 000	17 000

Disease burden due to respiratory syncytial virus (RSV)

RESPIRATORY SYNCYTIAL VIRUS (RSV) infection is a major cause of childhood morbidity and mortality. RSV vaccines are still under development, but should become available in the near future. Rapid introduction of a vaccine requires knowledge of the burden of the disease. As very limited data are available on RSV disease incidence in developing countries, a number of epidemiological studies will be conducted at selected sites. Such standardized data on disease incidence should facilitate the rapid introduction of future vaccines into immunization programmes.

OBJECTIVE

- To obtain age-stratified data on disease burden due to RSV.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

A "generic protocol to examine the incidence of lower respiratory infection due to RSV in children less than five years of age" has been commissioned and a field test version was released in November 1996. Six sites, five of them in Africa, have been selected to conduct population-based RSV disease burden studies based on the generic protocol. A preparatory workshop has been held in South Africa for participants of the disease burden studies.

MILESTONES/TARGETS

By 1998:

- Training workshop conducted and studies initiated.

By 1999:

- First year interim results from 4-5 study sites.

By 2000:

- Second year final results from 4-5 study sites.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	343 000	316 000	–27 000
1999	366 000	289 000	–77 000

Surveillance of diseases for new vaccines

SURVEILLANCE and other forms of monitoring will be needed for the diseases prevented by new and improved vaccines. Surveillance standards, methods, guidelines, and performance indicators must be developed.

OBJECTIVE

- To establish an effective surveillance system for diseases for when new vaccines are being introduced.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

By the end of 1997, 25 countries had introduced Hib vaccine into their national immunization programmes. Surveillance data from these countries have demonstrated a spectacular decrease in the incidence of invasive Hib disease. During 1997, WHO developed recommended surveillance standards for countries introducing Hib vaccine to assess its impact and monitor the performance of Hib surveillance.

MILESTONES/TARGETS

By 1998:

- Surveillance standards, methods, and performance indicators established for rubella.
- Development of guidelines for establishing effective surveillance for Hib disease.
- Countries introducing Hib to have established surveillance to monitor impact.

INDICATORS

- Existence of written standards for surveillance and surveillance performance indicators for rubella.
- Existence of guidelines for establishing Hib surveillance.
- Number of countries using Hib vaccine which have established surveillance for Hib disease.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	10 000	10 000	0
1999	10 000	10 000	0

NEW VACCINES – US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Introduction of new vaccines	487 000	452 000	–35 000	353 000	278 000	–75 000
Vaccines against shigella diarrhoea	214 000	177 000	–37 000	231 000	194 000	–37 000
Vaccines to prevent diarrhoea due to Rotavirus	1 058 000	900 000	–158 000	532 000	276 000	–256 000
New Strategies for accelerating cholera vaccine development	204 000	164 000	–40 000	238 000	174 000	–64 000
New tools to prevent diarrhoea due to ETEC and EHEC	98 000	53 000	–45 000	68 000	48 000	–20 000
New approaches for controlling typhoid fever by using Vi polysaccharide vaccine	64 000	39 000	–25 000	101 000	57 000	–44 000
Dengue vaccine	308 000	276 000	–32 000	298 000	245 000	–53 000
Development of new Japanese encephalitis vaccine	185 000	27 000	–158 000	167 000	152 000	–15 000
Vaccines against Hib and meningococcal meningitis	222 000	217 000	–5 000	200 000	154 000	–46 000
A safe and effective vaccine against pneumococcal pneumonia	1 846 000	1 541 000	–305 000	2 519 000	1 772 000	–747 000
Vaccines against respiratory syncytial virus (RSV)	74 000	69 000	–5 000	56 000	89 000	33 000
Vaccines against parainfluenza type 3 virus (PIV3	12 000	12 000	0	72 000	11 000	–61 000
Vaccines against TB	620 000	435 000	–185 000	733 000	474 000	–259 000
Vaccine against *Helicobacter pylori* infection	57 000	11 000	–46 000	77 000	31 000	–46 000
Vaccines against cancer caused by HPV	12 000	11 000	–1 000	62 000	22 000	–40 000
Nucleic acid vaccines	210 000	81 000	–129 000	206 000	126 000	–80 000
New adjuvants and carriers	67 000	67 000	0	92 000	67 000	–25 000
Neonatal vaccination strategies	114 000	74 000	–40 000	157 000	97 000	–60 000
Applicationof selected technologies to AIDS/HIV vaccines	218 000	175 000	–43 000	298 000	218 000	–80 000
Single-dose vaccines	169 000	49 000	–120 000	529 000	79 000	–450 000
Mucosal immunization	248 000	143 000	–105 000	308 000	183 000	–125 000
Live vectors	97 000	87 000	–10 000	107 000	107 000	0
Plant-based technology for vaccines	82 000	72 000	–10 000	122 000	72 000	–50 000
Parenteral administration of vaccines as solids	146 000	72 000	–74 000	227 000	72 000	–155 000

NEW VACCINES – US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
GPV Registry of vaccine field trials	12 000	12 000	0	17 000	12 000	–5 000
Demand forecasting for new vaccines	85 000	85 000	0			
Financing mechanisms for new vaccines	10 000	10 000	0			
Availability of new vaccines	124 000	94 000	–30 000	166 000	76 000	–90 000
Financing mechanisms	11 000	6 000	–5 000	19 000	6 000	–13 000
Hib disease burden assessment	185 000	195 000	10 000	216 000	153 000	–63 000
Approaches to assess local disease burden due to CRS	129 000	96 000	–33 000	83 000	100 000	17 000
Disease burden due to RSV	343 000	316 000	–27 000	366 000	289 000	–77 000
Surveillance of diseases for new vaccines	10 000	10 000	0	10 000	10 000	0
Global coordination	288 000	263 000	–25 000	291 000	335 000	44 000
Total workplans	**8 009 000**	**6 291 000**	**–1 718 000**	**8 921 000**	**5 979 000**	**–2 942 000**
Programme support costs*		745 000	–223 000		697 000	–381 000
Grand Total		7 036 000	–1 941 000		6 676 000	–3 323 000

*On voluntary funds only

—ENABLING FUNCTIONS

"Enabling functions" comprise a set of secondary objectives which describe targets that are common to all primary objectives. They thus cut across the three primary objectives of self-sufficiency, disease control, and new vaccines.

Enabling functions are shared by all units in GPV and the GPV Director's office. While all units are expected to contribute to meeting the objectives, the Director's office will coordinate the activities and monitor the achievements.

GPV ENABLING FUNCTIONS

Adequate level of funding

THE Global Programme for Vaccines and Immunization depends on a high proportion of extra-budgetary funding. The WHO regular budget contribution had been more or less stable since the programme was established, until it was cut by a total of 57% during 1996 as part of cutbacks throughout the Organization. During 1997, the regular budget accounted for 18% of global and interregional funds, and 55% of regional and country funds.

OBJECTIVE

- To ensure that the Programme's existing and prospective donor partners have all the information they need to be confident to support the Programme. These are typically the Governments of the Organisation for Economic Cooperation and Development (OECD) countries but they also include nongovernmental organizations, foundations, and to a smaller extent private sector industry.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The Programme's extrabudgetary income has tripled during this four-year period (from US$15 million to US$45 million). The greatest increase has been in the WHO regions and countries where the increase has been six-fold (from US$3 million to US$18 million).

MILESTONES/TARGETS

By the end of each calendar year GPV should:

- ▷ Achieve its revenue target at the global level and for the global contribution to the regional offices.
- ▷ Have an appropriate cash reserve to ensure continuity of the Programme into the next year.
- ▷ Achieve a 10% increase in the "donor base" of the Programme.
- ▷ Hold a Meeting of Interested Parties (MIP).
- ▷ Improve contact with donor partners.

By 1998:

- ▷ GPV should be actively supporting the Interagency Coordination Committees at the regional level.

INDICATORS

- An increase in the number of donors attending the Interagency Coordinating Committee Meetings for EPI (**Status:** not known. This figure will be made available during 1998).
- An increase in the number of financial contributors to the programme at global and regional levels (**Status:** a 10% increase during 1997, with the addition of four new contributors).
- Revenue targets reached at each level by the end of each financial year (**Status:** as of December 1998, achieved in Geneva and in all regions).
- The Programme's cash reserve will be kept within the "Goldthorpe Range" (**Status:** achieved in 1997).
- Six-monthly review of awareness of donor contacts, to take place in June and December 1998 (**Status:** all donors and potential donors are contacted informally, more frequently than every six months).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	621 000	576 000	–45 000
1999	659 000	611 000	–48 000

Adequate promotion and coordination

GOOD support from the international community for vaccine research and immunization services depends on a high level of knowledge of the Programme's successes and failures.

In future, the Strategic Plan will be produced each two years, for a period of four years.

OBJECTIVE

- To ensure that the important news from the Programme – both good and bad – reaches the people who need to know about it, particularly the Programme's donor partners, and that all promotion activities are closely co-ordinated with the activities of the Children's Vaccine Initiative.
- To ensure that the public, health professionals, and national decision makers are well informed about all vaccines of public health importance.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

During this period, the Programme has developed yearly budgets, programme reports, financial reports, a "rolling" five-year strategic plan and, most recently, a set of programme-wide priorities. In future, the Strategic Plan will be produced each two years, for a period of four years, to coincide with the WHO two-year budget cycle.

MILESTONES/TARGETS

By the end of each calendar year:

- ▷ GPV to have produced a report on the previous year's activities.

By the end of each alternate calendar year (odd numbered):

- ▷ GPV to have an up-to-date strategic plan for four years and a budget for the following two years.

By the end of 1998:

- ▷ In association with the University of Bergen, the production of four new position papers and four new information-base papers covering four priority vaccines for global health.
- ▷ Revision of the existing position papers and information papers.

By the end of 1999:

- ▷ Establishment of a procedure to continue the production of further position and information-base papers to include all vaccines of public health importance – especially those of key importance for developing countries.

INDICATORS

- ▷ Annual updates of the Programme budget (**Status:** completed for 1997).

- ▷ Strategic Plan updated at the end of each odd numbered year, i.e. December 1999 (**Status:** completed for the period 1998-2000).
- ▷ Production of position papers and information-base papers and their revisions (**Status:** as of December 1998, seven position papers and two information-base papers completed).
- ▷ Existence of a plan to continue production of position papers and information-base papers.
- ▷ Production of an annual Programme Report that follows the principal objectives of the Programme (**Status:** as of March 1998, on target).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	861 000	796 000	–65 000
1999	928 000	844 000	–84 000

Production of high-quality documents

THE documents of the Global Programme for Vaccines and Immunization are its public face.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**199 000**	**189 000**	**–10 000**
1999	**211 000**	**200 000**	**–11 000**

OBJECTIVE

- To ensure that documents are accurate, with high graphic standards, produced in several languages, and readily available. The documents should be widely distributed to the people who use them and not to those who do not.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

The GPV document centre currently produces about 60 new or revised documents each year and keeps stock of approximately 500 documents in English and 300 in other languages. A permanent presence has also been established on the World Wide Web: **(http://www.who.ch/gpv-documents/).**

MILESTONES/TARGETS

By 1998:

- Existing mailing lists stratified to ensure targeted mailings.
- Existing "Send" software refined to allow analysis of mailings.
- Implementation of a billing policy for documents sent to organizations that can afford to pay for them.
- Development of a method for pro-active mailings to ensure that GPV documents are reaching all those who need them.
- Elimination of "dead" stocks of documents.

By 1999:

- Analysis of needs for document distribution in the regional offices and availability of services that have been developed by GPV, Geneva.

INDICATORS

- Existence of targeted mailing lists and pro-active mailings (**Status:** as of December 1998, 9 000 names in English and French.)
- Existence of an analysis of mailings and size of income from billings (**Status:** as of December 1998, limited analysis and billing income small).
- No "dead" stocks.

Trained personnel available (WHO staff and associated people)

DURING 1997, 227 people worked in the GPV worldwide and these people need to be kept up to date with current programme policies and with the latest management and public health thinking. A programme of staff retraining was established in 1996. In addition, there are many thousands of workers in other international organizations and NGOs who work with the Programme. These people also need to be kept up to date with the Programme's changing policies, strategies, and activities.

A programme of staff retraining was established in 1996.

OBJECTIVE

- To ensure that all GPV staff have access to in-service training and all other interested individuals have access to regular briefings, and that the training is carefully targeted to the needs of the individual and those of the Programme.

1994-1997 PROGRESS, ACHIEVEMENTS, AND CONSTRAINTS

Since the launch of the GPV's study leave programme in 1996, 20 people (9% of the total staff) have undergone training in areas including epidemiology, management, computer skills, languages, accounting, development studies, and vaccine quality assurance.

MILESTONES/TARGETS

By 1998:

- A plan completed by the GPV Director's Office, and revised annually, for training GPV personnel, consistent with WHO policies.

INDICATORS

- Existence of both a plan and the level of its implementation (**Status:** as of December 1998, 20 out of 22 applications for study leave were funded).
- Extension of posts (including associate professional officers) filled and vacant (**Status:** as of December 1998, 28 vacant posts i.e. 11%, of which half are posts for Associate Professional Officers).

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	166 000	125 000	–41 000
1999	164 000	134 000	–30 000

Efficient and effective computing tools

GOOD computing tools are essential in today's working environment to keep pace with the demands of the health community. The improvements in technology can be applied to collect and disseminate information more efficiently, accurately, and consistently. Better information will contribute to better decision-making by the Programme and its partners, and wider acceptance of its policies.

Good computing tools are essential in today's working environment.

OBJECTIVE

- To ensure that all GPV staff have access to a wide range of up-to-date, reliable, efficient, and effective computing hardware and software and that all staff are well trained in their use.

MILESTONES/TARGETS

Every year:

- ▷ Software applications and systems previously introduced in headquarters to be maintained or improved.
- ▷ Possibilities of automation of work processes reviewed and prioritized.

By 1998:

- ▷ Software applications to be in place in GPV to monitor the following:
  - financial data from grants to implementation;
  - technical progress against the indicators in the strategic plan;
  - track research projects;
  - country information on immunization coverage and disease incidence;
- ▷ Headquarters staff to have remote access to the GPV network.

By 1999:

- ▷ 80% of GPV headquarters staff to be equipped with the tools and skills needed to produce effective presentations.
- ▷ 80% of GPV staff who travel to be equipped with the tools and skills to connect to the GPV network.
- ▷ GPV information to be internationally accessible by a two-way process with a user-friendly interface.
- ▷ GPV network to be uniform with WHO's networking environment.

INDICATORS

- ▷ Number of applications and services that are actively used in headquarters. There are currently 11 services and applications in place. These are the hotline service, portable equipment loans, standard workstations upgrade and maintenance, server maintenance and backup, training and seminars, group scheduling and “bulletin board “ service, address system, staff database, and maintenance of Internet pages, activitiy management system, and EPI data access.

- ▷ Percentage of GPV staff capable of producing effective presentations (**Status:** 29%).
- ▷ Percentage of GPV staff who connect to the GPV networkwhile offsite (**Status:** 1%).
- ▷ Percentage of computers with the WHO-recommended configuration (**Status:** zero).
- ▷ Number of information areas accessible two-way on the Internet with a user-friendly interface (**Status:** zero).
- ▷ Existence of an annual review of work processes and its possible automation.
- ▷ Existence of stated software packages.

	Funds needed (Planned cost) US$	Funds available (Budget) US$	Unmet needs US$
1998	**193 000**	**193 000**	**0**
1999	**204 000**	**204 000**	**0**

GPV – ENABLING FUNCTIONS

US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Adequate level of funding	621 000	576 000	–45 000	659 000	611 000	–48 000
Adequate promotion and coordination	861 000	796 000	–65 000	928 000	844 000	–84 000
Production of high-quality documents	199 000	189 000	–10 000	211 000	200 000	–11 000
Trained personnel available (WHO staff and associated people)	166 000	125 000	–41 000	164 000	133 000	–31 000
Efficient and effective computing tools	193 000	193 000	0	204 000	204 000	0
Support to LEG and VRD/VSQ/EPI	119 000	82 000	–37 000	126 000	86 000	–40 000
Total workplans	**2 159 000**	**1 961 000**	**–198 000**	**2 292 000**	**2 078 000**	**–214 000**
Programme support costs*		187 000	–26 000		260 000	–28 000
Grand total		2 148 000	–224 000		2 338 000	–242 000

*On voluntary funds only

EPI – ENABLING FUNCTIONS

US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Management	948 000	948 000	0	991 000	1 022 000	31 000
Communication and advocacy	327 000	252 000	–75 000	342 000	252 000	–90 000
Total workplans	**1 275 000**	**1 200 000**	**–75 000**	**1 333 000**	**1 274 000**	**–59 000**
Programme support costs*		77 000	–10 000		85 000	–8 000
Grand total		1 277 000	–85 000		1 359 000	–67 000

*On voluntary funds only

VRD –ENABLING FUNCTIONS

US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Development and implementation of fund-raising strategies	108 000	59 000	–49 000	91 000	60 000	–31 000
Development and yearly update of communication strategies	88 000	42 000	–46 000	90 000	43 000	–47 000
Development of a systematic approach for prioritization and resource allocation & technical and operational monitoring of activities	138 000	118 000	–20 000	146 000	118 000	–28 000
Global coordination	421 000	338 000	–84 000	417 000	361 000	–56 000
Total workplans	**755 000**	**557 000**	**–199 000**	**744 000**	**582 000**	**–162 000**
Programme support costs*		32 000	–26 000		36 000	–21 000
Grand total		589 000	–225 000		618 000	–183 000

*On voluntary funds only

VSQ –ENABLING FUNCTIONS

US$

Products	Funds 98 needed (Planned cost)	Funds available (Budget)	Unmet needs 1998	Funds 99 needed (Planned cost)	Funds available (Budget)	Unmet needs 1999
Leadership, obtain support, VSQ database, and VSQ management	378 000	383 000	5 000	365 000	340 000	–25 000
Global coordination	266 000	266 000	0	279 000	279 000	0
Total workplans	**644 000**	**649 000**	**5 000**	**644 000**	**619 000**	**–25 000**
Programme support costs*		79 000	1 000		81 000	–3 000
Grand total		728 000	6 000		700 000	–28 000

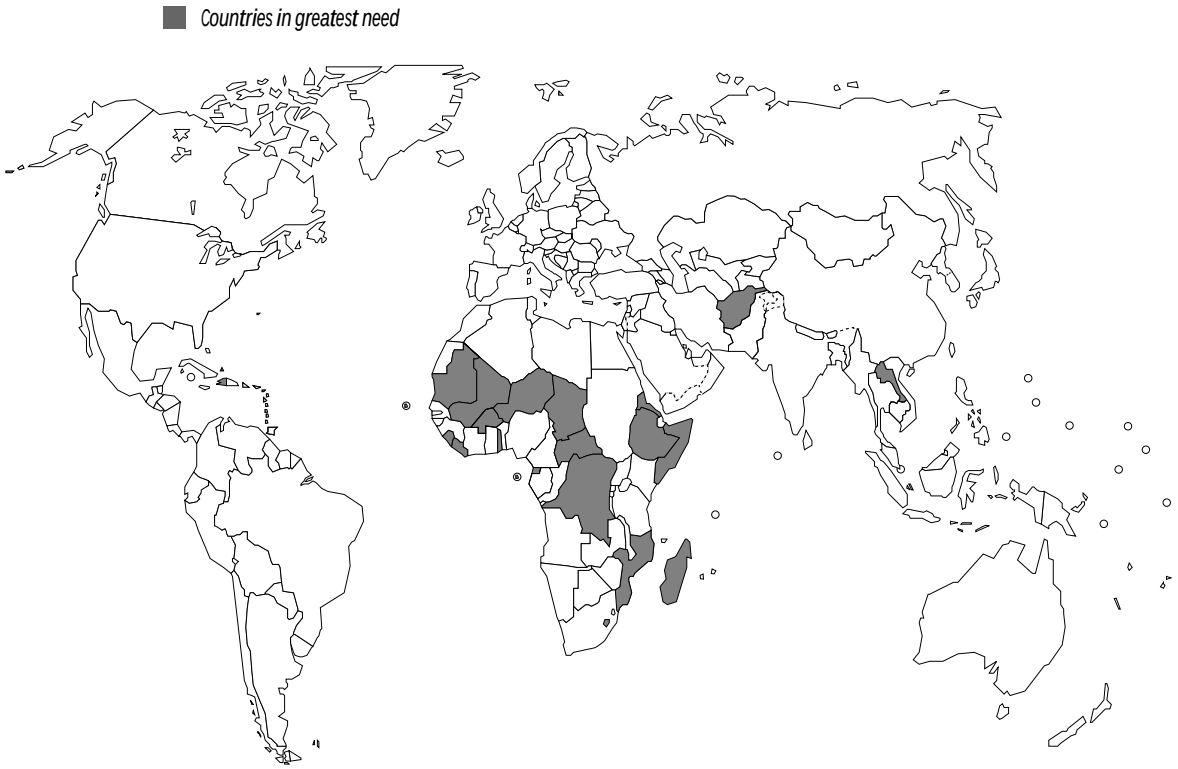
*On voluntary funds only

ANNEX 1

COUNTRIES IN GREATEST NEED

Countries in greatest need are currently classified as those countries that have DTP3 coverage levels below 70% and which are placed in band A (see page 15).

Countries in greatest need:
Afghanistan, Burkina Faso, Burundi, Central African Republic, Chad, Democratic Republic of Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Haiti, Laos, Lesotho, Liberia, Madagascar, Mali, Mauritania, Mozambique, Niger, Sierra Leone, and Somalia).



ANNEX 2

KEY SURVEILLANCE PERFORMANCE INDICATORS

1. Completeness of reporting (i.e. # of reports received/# of reports expected)
   (target: > 90%).

2. Non-polio acute flaccid paralysis (AFP) rate per 100 000 children aged <15 years
   (target: > 1).

3. AFP cases for which 2 adequate specimens were collected within 14 days of paralysis onset
   (target: > 80%).

4. Accreditation status as part of the polio laboratory network
   (target: achieved/maintained).

5. Reported measles cases for which age and immunization status were recorded
   (target: > 80%).

6. Suspect yellow fever cases for which specimens were collected during non-outbreak periods
   (target: > 50%).

7. Regular feedback that includes EPI data and surveillance performance to sub-national levels
   (target: provided on at least a quarterly basis).

ANNEX 3

PRIORITY COUNTRIES FOR NEONATAL TETANUS ELIMINATION

Angola, Bangladesh, Burkina Faso, Cambodia, Cameroon, Chad, China, Côte d'Ivoire, Democratic Republic of Congo, Ethiopia, Ghana, Guinea Bissau, India, Indonesia, Liberia, Mali, Mauritania, Mozambique, Nepal, Niger, Nigeria, Pakistan, Senegal, Somalia, and Sudan.

ANNEX 4

COUNTRIES AT RISK FOR YELLOW FEVER OUTBREAKS

Angola, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Sao Tome & Principe, Senegal, Sierra Leone, Somalia, Sudan, Togo, Uganda, United Republic of Tanzania.

ANNEX 5

COUNTRIES WITH KNOWN VITAMIN A DEFICIENCY

WHO region	Clinical	Subclinical			No data available	VAD under control – no likely problem
		Severe	Moderate	Mild		
AFRICA	Angola Benin Burkina Faso Cameroon Chad Ethiopia Ghana Kenya Malawi Mali Mauritania Mozambique Niger Nigeria Rwanda Togo Uganda United Rep. of Tanzania Zambia Zimbabwe	Burundi Cape Verde Congo Côte d'Ivoire Gambia Lesotho Senegal South Africa	Botswana Namibia Sierra Leone	Madagascar	Algeria Central African Republic Comoros D. R. Congo Equatorial Guinea Eritrea Gabon Guinea Guinea-Bissau Liberia Mauritius Sao Tome & Principe Seychelles Swaziland	
AMERICAS	Dominican Republic Haiti	Brazil Colombia El Salvador Guatemala Mexico Nicaragua Peru	Belize Bolivia Ecuador Honduras	Guyana Panama	Argentina Cuba Dominica Paraguay Puerto Rico* Suriname Uruguay Venezuela	Antigua & Barbuda Bahamas Barbados Canada Chile Costa Rica Grenada Jamaica St. Kitts & Nevis St. Lucia St. Vincent & the Grenadines Trinidad & Tobago United States of America
SOUTH-EAST ASIA	Bangaldesh Bhutan India Myanmar Nepal Sri Lanka	Indonesia	Thailand		Maldives Mongolia	Democratic Peoples Republic of Korea

*Associate Member

WHO region	Clinical	Subclinical			No data available	VAD under control – no likely problem
		Severe	Moderate	Mild		
EUROPE				Israel Romania Turkey Uzbekistan	Albania Armenia Azerbaijan Belarus Bosnia & Herzegovina Bulgaria Croatia Czech Republic Estonia Georgia Hungary Kazakhastan Kyrgyzstan Latvia Lithuania Malta Republic of Moldova San Marino Slovakia Slovenia Tajikistan The former Yugoslav Rep. of Macedonia Turkmenistan Ukraine Yugoslavia	Austria Belgium Denmark Finland France Germany Greece Iceland Ireland Italy Luxembourg Monaco Netherlands Norway Poland Portugal Russian Fed. Spain Sweden Switzerland U.K. of Great Britain & Northern Ireland
EASTERN MEDITTERANEAN	Iraq Somalia Sudan Yemen	Afghanistan Pakistan	Djibouti Iran (Islamic Rep. of) Oman	Jordan Lebanon Libyan Arab Jamahiriya Saudi rabia Syria Arab Rep. Tunisia	Egypt Kuwait Morocco Qatar United Arab Emirates	Bahrain Cyprus
WESTERN PACIFIC	Cambodia Kiribati Marshall Islands Micronesia (Fed. States of) Papua New Guinea Philippines Solomon Islands Vanuatu Viet Nam	Lao P.D.R.	China Malaysia		Cook Islands Nauru New Zealand Niue Tonga Tokelau* Tuvalu	Australia Brunei Darussalam Fiji Japan Rep. of Korea Samoa Singapore

The Global Programme for Vaccines and Immunization, established by the World Health Organization in 1994, defines its goal as "a world in which all people at risk are protected against vaccine-preventable diseases". The Programme comprises three units:

Expanded Programme on Immunization
Vaccine Research and Development
Vaccine Supply and Quality

The *Expanded Programme on Immunization* focuses on the prevention of selected childhood diseases and, through support to national immunization programmes, aims to achieve 90% immunization coverage of children born each year. Its goals are to eradicate poliomyelitis from the world by the year 2000, reduce measles deaths and incidence, eliminate neonatal tetanus as a public health problem and introduce hepatitis B vaccine in all countries.

Vaccine Research and Development supports and promotes research and development associated with the introduction of new vaccines into the Expanded Programme on Immunization. This includes research and development of new vaccines, improvement of immunization procedures and support to epidemiological studies.

Vaccine Supply and Quality ensures adequate quantities of high quality, affordable vaccines for all the world's children, supports the efforts of governments to become self-reliant as regards their vaccine needs, and assists in the rapid introduction of new vaccines.

The *Global Programme for Vaccines and Immunization* produces a range of documents, audiovisual materials and software packages to disseminate information on its activities, programme policies, guidelines and recommendations. It also provides materials for group and/or individual training on topics ranging from repair of health centre equipment to curricula guidelines for medical schools, nursing colleges and training of vaccine quality control personnel.

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