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Global Alliance for Vaccines and Immunization

Fourth Board Meeting

Noordwijk, The Netherlands,
19 November 2000

GAVI Global Alliance for Vaccines and Immunization

Executive summary

Dr Gro Harlem Brundtland, Director-General of the World Health Organization and Chair of the GAVI Board, called the meeting to order. Dr Els Borst-Eilers, Deputy Prime Minister and Minister of Health, Welfare and Sport for the Netherlands, welcomed the Board to Noordwijk.

Agenda item 1. Status report of the Global Fund: projection of expenditures

Mr Jacques-François Martin, President of the Global Fund for Children's Vaccines, presented three financial scenarios representing low, intermediate and high projections for income and expenditures over the next five years (Annex 1).

The Board:

1.1 **Noted** that current Global Fund resources are sufficient to address the basic GAVI objectives but that more resources are needed for GAVI to meet all its goals.

1.2 **Endorsed** a conservative policy on expenditures so that financial commitments to countries will be consistent with available Global Fund resources.

1.3 **Welcomed** the announcement, made at the meeting by Dr Borst-Eilers, that the Government of the Netherlands will commit 250 million guilders (approximately US$ 100 million) to GAVI and the Global Fund over the next five years.

1.4 **Recognized** that the projections on expenditures do not take into consideration supply shortfalls among combination vaccines and that these shortfalls demonstrate GAVI's effect in generating demand for the vaccines and the need for long-term planning.

1.5 **Requested** that Mr Martin, in collaboration with the Working Group, further develop the three scenarios he described, providing specific recommendations on potential levels of support from the Global Fund and reporting back to the Board at its June 2001 meeting.

Agenda item 2. Country review process and recommendations for approval of second-round countries

Dr Viroj Tangcharoensathien, Chair of the Independent Review Committee, and Committee members Dr Maria Otelia Costales and Dr Abdallah Bchir, presented the outcome of the second review of country proposals to GAVI and the Global Fund. The report included country-by-country recommendations, overall policy considerations and suggestions for improving the process in future rounds (Annex 2).

The Board:

2.1 **Commended** the work of the Review Committee and its comprehensive and thoughtful responses to the country proposals.

2.2 **Approved** the recommendations of the Review Committee in regard to specific country proposals.

2.3 **Approved** the recommendation of the Review Committee that countries with less than 50% DTP3 coverage be eligible for Global Fund support to cover the provision of yellow fever vaccine to infants on a case-by-case basis.

2.4 **Recognized** the Review Committee's concern that high measles incidence, morbidity and mortality poses a serious challenge to the immunization programmes in many eligible countries (Annex 5).

2.5 **Confirmed** the need to maintain clearly-defined coverage eligibility criteria by which to assess country proposals and awards – for example, countries must have a minimum of 50% DTP3 coverage to qualify for support from the new and underused vaccine sub-account (except for yellow fever vaccine, as noted in para. 2.3 above).

2.6 **Agreed** to UNICEF's recommendation that the GAVI/Global Fund proposal form be revised to include banking details for the transfer of funds from the Global Fund Trust Account at UNICEF.

2.7 **Endorsed** the concept that support to immunization services in eligible countries (with <80% DTP3 coverage) would not end when countries reach 80%, but would continue for five years, as long as their coverage increases.

2.8 **Recognized** the need to identify ways for the Global Fund to support low-income countries, such as Cuba, with relatively strong health and immunization systems, in order to meet the GAVI milestone of 80% coverage in all districts in 80% of countries.

2.9 **Requested** UNICEF and WHO to develop a draft GAVI strategy relating to countries in complex states of emergency (the draft to be submitted to the GAVI Board for consideration by 1 March 2001).

2.10 **Requested** the Task Force on Country Coordination to develop a draft GAVI strategy on capacity-building in countries (the draft to be submitted to the GAVI Board for consideration by 1 March 2001).

Agenda item 3. Task Force on Research and Development: terms of reference and composition

Dr Peter Wilson, consultant to the Task Force on Research and Development (R&D), presented a summary of the composition, objectives, strategies and goals of the task force.

The Board:

3.1 Approved the composition of the R&D Task Force which assures a range of expertise in vaccinology and immunology, provided that the recommendation in para. 3.4 below is addressed. The task force comprises:

- three co-chairs – from WHO, industry and academia, and
- five members from different geographical regions.

3.2 Endorsed the advisory role that the task force will play in the process of identifying and supporting the GAVI research and development agenda. The task force will:

- identify highest priority research gaps and make recommendations to the GAVI Board;
- provide technical support to implementing partners in:
  - identifying key barriers and strategies to address research and development gaps;
  - evaluating alternative project structures; and
  - setting up a research and development agenda and timetable;
- monitor adherence to an agreed-upon agenda and timetable.

3.3 Approved the recommendation of the task force that GAVI should focus initially on three vaccine products: pneumococcal, rotavirus and meningococcal A (or A/C). These products, described in the presentation (Annex 3), were picked from a larger list because they satisfied all or most of the following criteria:

- there is either no currently-registered vaccine, or the existing vaccine has drawbacks that severely limit its utility;
- the vaccine has a high potential impact; and could significantly reduce morbidity and mortality in children and/or adults;
- a high probability of success in short/medium term use of the vaccine;
- the vaccine has a potential for improving immunization systems;
- the vaccine fills a strategic gap, i.e., no other effort is currently focusing on it;
- there is a lack of other, non-vaccine solutions (preventative or curative).

3.4 Endorsed the proposal outlined in the presentation that the task force, in consultation with the GAVI Working Group and others in the research community, would seek to identify up to three promising fields of research on new technologies and systems for improving immunization services. Similar criteria as those used for vaccine product selection would be used to identify the under-addressed research fields, which may include:

- proven strategies for reaching the hard-to-reach, including the application of lessons learned from polio eradication;
- improved information technology (IT) infrastructures for better management of immunization services;
- development of new technologies – including 'low-tech' devices – for increasing immunization and injection safety, reducing the need for a cold chain, and/or other tools that could improve efficiency.

3.5 Recognized that the current composition of the task force does not include experts in the area of applied and operational research, and encouraged the task force to add two to four appropriately qualified individuals to support this research area.

3.6 Requested the task force to provide the Board with its recommendations on candidate projects to support immunization services, at the latest by the Board's next meeting in June 2001.

Agenda item 4. Improved immunization systems, products and technologies: GAVI project development agendas

Dr Mark Kane, the Gates Children's Vaccine Program at PATH, presented a proposal from the Working Group to use the current GAVI structure to develop a team approach to addressing the GAVI research priorities.

The Board:

4.1 Approved the basic principles outlined in the paper, confirming that current efforts to help countries introduce new and under-used vaccines and increase basic immunization coverage should remain GAVI's top priorities, and that human resources should not be shifted away to satisfy new research agendas.

4.2 Endorsed the priority project areas as identified:

- three vaccine-related projects:
  - to assure the availability, affordability and use of pneumococcal conjugate vaccines for the developing world within seven years; Dr Borst-Eilers pointed out the possible need to develop simpler and less expensive vaccines than the candidate vaccines currently under development;
  - to assure the development, availability and use of a safe, effective and affordable rotavirus vaccine for the developing world within seven years;
  - to assure the development, availability and use of an affordable meningococcal A or A/C conjugate vaccine for the "meningococcal belt" in Africa within five years;
- up to three non vaccine-related projects, such as research to improve immunization systems and technologies (specific project recommendations to be provided by the R&D Task Force).

4.3 Urged the Working Group to work with the appropriate task forces and consult with those in the public and private sectors already engaged in the three vaccine-related project areas to identify:

- the gaps that need to be addressed to move products from their current pre-licensed state to being fully developed, manufactured and delivered to children in developing countries;
- the lead partners that will be responsible for developing project proposals.

4.4 Endorsed the proposed steps the task forces need to take immediately in order to contribute their expertise to vaccine-related project development agendas.

4.5 Requested the Working Group and the task force(s) concerned to jointly report back to the Board regarding the development of project organization and financing, before the next Board meeting (June 2001).

4.6 Accepted the responsibility of reviewing the refined project agendas approving fully developed proposals for implementation.

4.7 Recommended that the Global Fund use the third sub-account to address the specific bottlenecks constraining the rapid development and availability of priority products or technologies. If approved by the Fund Board, the Working Group would work closely with the Executive Committee of the Fund to develop the criteria for drawing on the third sub-account.

Agenda item 5. Collaboration with specific disease programmes

Dr Bruce Aylward, WHO, presented the current status of the Polio Eradication Initiative, outlining the status of polio eradication since 'acceleration', challenges to the 2001-2005 Strategic Plan, lessons that might be applicable to GAVI, and GAVI/polio synergies. Mr Michel Zaffran, WHO, presented the new draft strategy on reducing measles mortality, prepared jointly by WHO, UNICEF and the US Centers for Disease Control and Prevention.

The Board:

5.1 Reaffirmed its previously stated objective that "it is of high priority for GAVI that the mortality from measles (presently 900 000 children's deaths per year) is brought down by reaching every child with measles vaccine."

5.2 Requested the Working Group to consult with partners and develop a combined paper outlining the strategies for integrating GAVI objectives into the polio eradication and measles initiatives (including cost-benefit analyses of the different strategies). The paper, to be presented for discussion at the Board's June 2001 meeting, should:

- propose a framework and time-line for the transition of human resources, surveillance capacity and physical infrastructure of the polio eradication initiative to support the broader GAVI agenda;
- consider the possibility of adopting joint milestones for GAVI, polio and measles;
- consider the use of polio performance indicators for countries receiving support from the Global Fund;
- explore new opportunities for integration of vitamin A supplementation and other practical health interventions into routine immunization activities.

Agenda item 6. GAVI Secretariat: progress, plans, income, expenditures and budget for 2001–2002

Dr Tore Godal, GAVI Executive Secretary, presented a summary of the Secretariat's income and expenditures to date, and a proposed budget for 2001-2002.

The Board:

6.1 Urged its partners to make their contributions to the Secretariat in a timely manner.

6.2 Approved the proposed budget, in principle, but questioned whether estimated expenditures actually represented projected needs, or were a reflection of projected income.

6.3 Recommended that, because of its increasing workload, the Secretariat change its currently vacant post for an administrative staff member from half-time to full-time, regularize the contracts of its short-term staff, and consider adding a limited number of additional staff as needs arise.

"In-camera" session

During the members-only 'in-camera' session, the Board:

(1) Noted that the procedures on the turnover of Board members, as outlined in the GAVI Guiding Principles document, are ambiguous. The Board emphasized that selection of new members is a consultative process based on nominations coming from the constituencies.

(2) Urged the Executive Secretary to consider extending his contract with the GAVI Secretariat beyond its current ending date of 30 June 2001. Considering that the GAVI Board Chair will change as of 1 July 2001, Dr Brundtland and Ms Carol Bellamy – the respective current and future Board Chairs – will confer on the details and time-frame of the contract extension.

Agenda

1. Status Report of the Fund: projections of expenditures
   (Mr Jacques-François Martin, President of the Global Fund for Children's Vaccine)

2. Country review process and recommendations for approval of second-round countries *(Dr Viroj Tangcharoensathien, Chair of the Independent Review Committee)*

3. Terms of reference and composition of the Task Force on Research and Development *(Dr Peter Wilson, consultant)*

4. Improved immunization systems, products and technologies: A proposal on the evolution of GAVI *(Dr Mark Kane, Bill & Melinda Gates' Children's Vaccine Program; Ms Amie Batson, The World Bank)*

5. Collaboration with specific disease programmes:

   - Global Polio Eradication Initiative
     (Dr Bruce Aylward, World Health Organization)
   - Reducing measles mortality
     (Mr Michel Zaffran, World Health Organization)

6. The GAVI Secretariat *(Dr Tore Godal):*

   - progress and plans;
   - finance: income, expenditures and budget for 2001–2002;
   - staff.

7. Other matters

8. "In-camera" session

List of annexes

Annex 1

Status report of the Global Fund: Projections of expenditures

Jacques-François Martin
President of the Global Fund for Children's Vaccines

Presentation on agenda item 1

This annex comprises a slide presentation, prepared and presented by Mr Jacques-François Martin, President of the Global Fund for Children's Vaccines, on low, intermediate and high projections for income and expenditures projections over the next five years.

Global Fund for Children's Vaccines
Meeting of the Board

November 19, 2000
Noordwijk - The Netherlands

The Global Fund for Children's Vaccines

Base of calculations

❶ They are on line with GAVI targets.
❷ Base 1999 for DPT3 coverage is the WHO/UNICEF consensus on a country-per-country basis.
❸ A linear projection has been considered for the improvement of DPT3 coverage towards the GAVI targets. The progress is however quicker when the baseline is lower.
❹ The share value is US$ 20.
❺ Prices of vaccines are kept constant over the five years at current levels.
❻ The Fund is paying for all new vaccines used.

The Global Fund for Children's Vaccines

Projected revenues (1)

(as of 1 November 2000)

	US$
▪ Bill & Melinda Gates Foundation	750 million
▪ United States of America	50 million
▪ Norway	125 million
▪ United Kingdom	5 million
Total	**930 million**

The Global Fund for Children's Vaccines

Projected revenues (2)

(if all contributions are consistent)

	US$
▪ Bill & Melinda Gates Foundation	750 million
▪ United States of America	250 million
▪ Norway	125 million
▪ United Kingdom	25 million
Total	**1150 million**

The Global Fund for Children's Vaccines

Revenues	2000	2001	2002	2003	2004	2005	TOTAL US$
If contributions are not recurrent:							
• Gates	325	150	150	125	--	--	750
• USA	--	50	-	--	--	--	50
• Norway	--	25	25	25	25	25	125
• UK	--	5	--	--	--	--	5
TOTAL	**325**	**230**	**175**	**150**	**25**	**25**	**930**
Recurrent contributions							
• Gates	325	150	150	125	--	--	750
• USA	--	50	50	50	50	50	250
• Norway	--	25	25	25	25	25	125
• UK	--	5	5	5	5	5	25
TOTAL	**325**	**230**	**230**	**205**	**80**	**80**	**1.150**

The Global Fund for Children's Vaccines

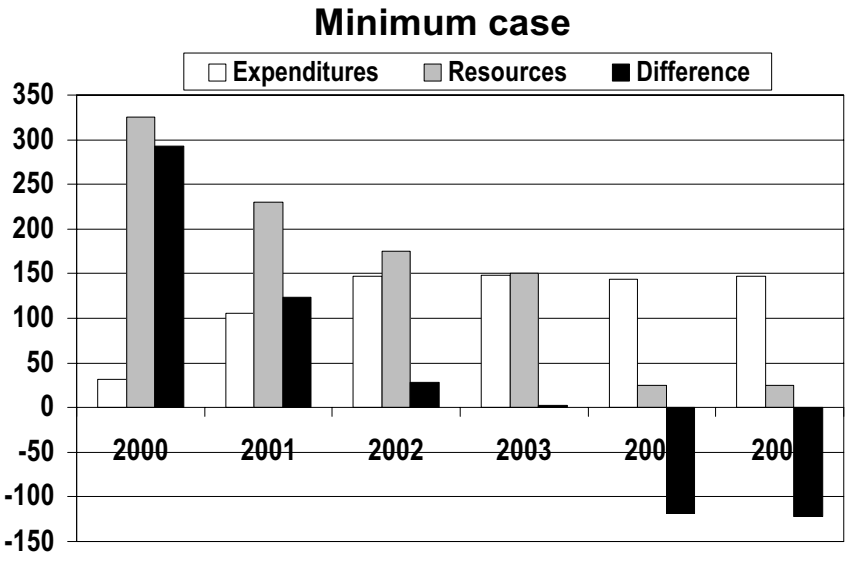
	Minimum (US$) (1)
Infrastructure	189 million
Vaccines	504 million
TOTAL	**693 million**

(1) Current eligibility.

The Global Fund for Children's Vaccines

Minimum case	2000	2001	2002	2003	2004	2005	TOTAL
Expenditures							
* Infrastructure	4	40	56	43	30	20	193
* Vaccines	28	66	91	105	114	127	531
TOTAL	32	106	147	148	144	147	724
Resources							
* Minimum	325	230	175	150	25	25	930
Difference	+293	+124	+ 28	+ 2	-119	-122	+ 206
* Accumulated		417	+445	+447	+ 328	+206	

The Global Fund for Children's Vaccines



The Global Fund for Children's Vaccines

	Minimum [1] (US$)	Intermediate [2] (US$)
Infrastructure	189 million	257 million
Vaccines	504 million	504 million
TOTAL	**693 million**	**761 million**

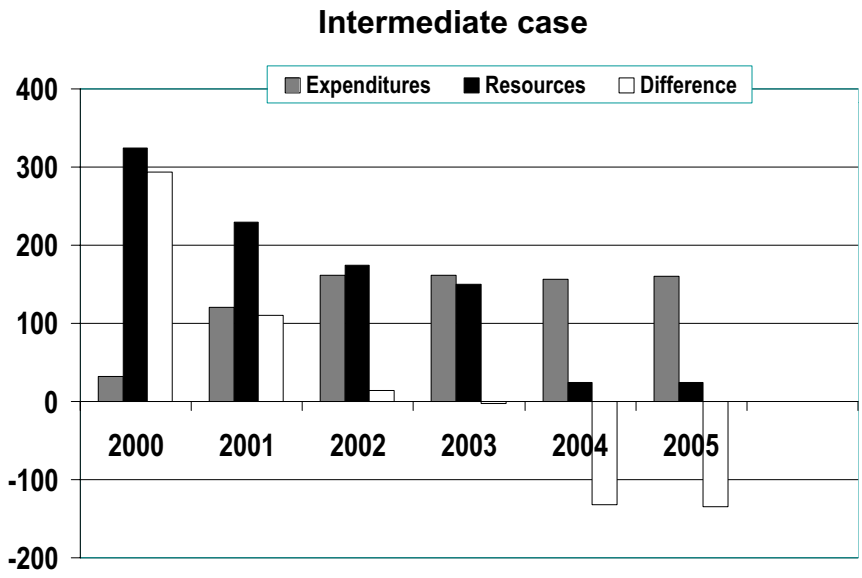
[1] Current eligibility.

[2] Current eligilibily, plus China, India, Indonesia for infrastructure only.

The Global Fund for Children's Vaccines

Intermediate case	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**TOTAL**
Expenditures							
* Infrastructure	4	54	70	57	43	33	261
* Vaccines	28	66	91	105	114	127	531
TOTAL	**32**	**120**	**161**	**162**	**157**	**160**	**792**
Resources							
* Minimum	**325**	**230**	**175**	**150**	**25**	**25**	**930**
Difference	**293**	**110**	**14**	**-12**	**-132**	**-135**	**+138**
* Accumulated		403	+417	+405	+273	+138	

The Global Fund for Children's Vaccines



The Global Fund for Children's Vaccines

	Minimum (1) (US$)	Intermediate (2) (US$)	Maximum (3) (US$)
Infrastructure	189 million	257 million	257 million
Vaccines	504 million	504 million	1241 million
TOTAL	**693 million**	**761 million**	**1498 million**

(1) Current eligibility.

(2) Current eligibility, plus China, India, Indonesia for infrastructure only.

(3) Current eligibility, plus China, India, Indonesia for infrastructure and products.

The Global Fund for Children's Vaccines

Maximum case (in US$)

Expenditures	1.498	1.498
Resources	930 (1)	1.150 (2)
Gap	568	348

(1) If contributions are not recurrent.
(2) If current contributions are recurrent.

The Global Fund for Children's Vaccines

	Minimum (1)	**Intermediate (2)**	**Maximum (3)**	**Maximum exposure (4)**
Infrastructure	189 million	257 million	257 million	632 million
Vaccines	504 million	504 million	1241 million	1538 million
TOTAL (US$)	**693 million**	**761 million**	**1498 million**	**2170 million**

(1) Current eligilibity.
(2) Current eligibility plus China, India, Indonesia for infrastructure only.
(3) Current eligibility plus China, India, Indonesia for infrastrucutre and products.
(4) If all countries reach 100 % coverage.

The Global Fund for Children's Vaccines

Remarks

1. It is extremely difficult to predict how quickly the 71 poorest countries will be able to increase their coverage in a sustainable manner.
2. There is no consideration of any catch-up activity (yellow fever, conjugate Meningococcus A or even measles)
3. The limit of US$ 1000 GNP per capita has something arbitrary.
4. The share value at US$ 20 can be questioned in remote and/or low density areas.

The Global Fund for Children's Vaccines

Third sub-account

Innovative products, technologies and processes

Minimum per year	US$ 20 million
Maximum per year	US$ 50 million

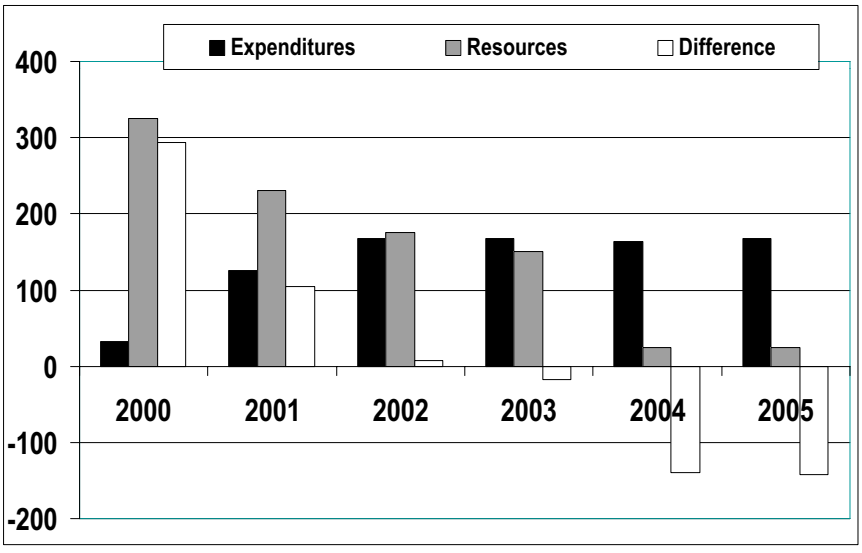
The Global Fund for Children's Vaccines

Minimum case with the third sub-account at US$ 20 million per year

	2000	2001	2002	2003	2004	2005	TOTAL (US$)
Expenditures							
* Infrastructure	4	40	56	43	30	20	189
* Vaccines	28	66	91	105	114	127	531
* Sub-account 3		20	20	20	20	20	100
TOTAL (US$)	32	126	167	168	164	167	824
Resources							
* Minimum	325	230	175	150	25	25	930
Difference	293	104	+8	-18	-139	-142	+106
* Accumulated		+397	+405	+387	+248	106	

The Global Fund for Children's Vaccines

3rd sub-account at US$ 20 million



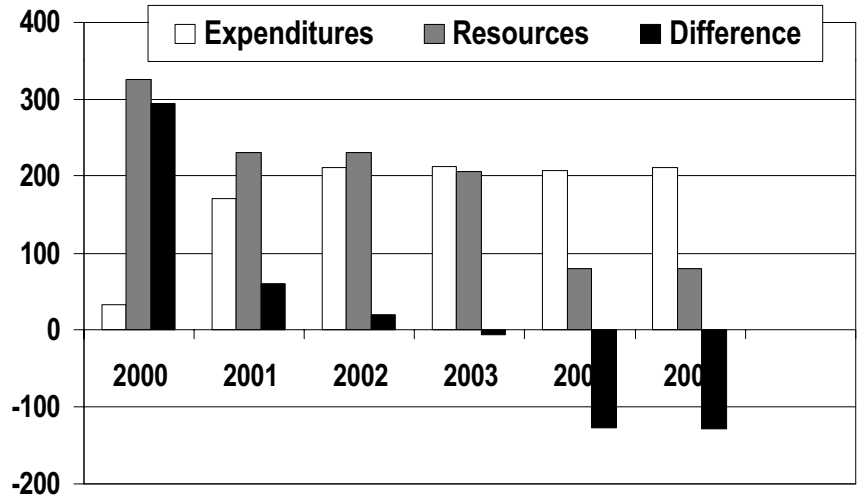
The Global Fund for Children's Vaccines

Intermediate case: recurrent revenues plus 3rd sub-account at 50 million US$ per year

	2000	2001	2002	2003	2004	2005	TOTAL (US$)
Expenditures							
* Infrastructure	4	54	70	57	43	33	261
* Vaccines	28	66	91	105	114	127	531
* 3rd sub-account	--	50	50	50	50	50	250
TOTAL (US$)	32	170	211	212	207	210	1.042
Resources							
* Recurrent	325	230	230	205	80	80	1.150
Difference	293	60	19	-7	-127	-130	108
* Accumulated		353	372	365	238	108	

The Global Fund for Children's Vaccines

Sub-account at 50 million US$



The Global Fund for Children's Vaccines

Conjugated meningococcus A

Hypothesis

African meningitis belt

- 80 % coverage
- infants
- 3 doses — 33 million doses
- 15 % wastage
- 2 US$ per dose — US$ 66 million
-

If catch-up — 150 million doses

- 1 - 29 years of age
- 80 % coverage — 145 million doses
- 10 % wastage
- 1 dose — US$ 290 million

Source WHO - L. Jodar

The Global Fund for Children's Vaccines

Hib

Countries in Asia and the former USSR	US$ 84 million per year
China, India, Indonesia	US$ 240 million per year

The Global Fund for Children's Vaccines

Yellow fever

Routine immunization	US$ 7 million per year
Catch-up	US$ 33 million

Source WHO - M. Zaffran

The Global Fund for Children's Vaccines

Additional options

Class One	**Per year**	**Catch-up**
Conjugated meningococcal A	66	290
Hib (Asia)	84	p.m
Yellow fever	7	33
TOTAL	157	323

The Global Fund for Children's Vaccines

	Minimum case	Intermediate	Maximum case
Expenditures			
* Infrastructure			
* Vaccines	189	261	257
* 3rd sub-acc.	531	531	1.241
	100	250	250
TOTAL	824	1.042	1.748
Resources	**930**	**1150**	**1150**
Difference	**+ 106**	**+108**	**-598**

Additional options

	Per year	Catch-up
Conjugated Meningococcal A	66	290
Hib (Asia)	84	p.m.
Yellow fever	7	33
TOTAL (US$)	157	323

The Global Fund for Children's Vaccines

Conjugated pneumococcal vaccine

Hypothesis

- Birth cohort 46 million
- 80 % coverage
- 3 doses
- 10 % wastage
- US$ 10 per dose

Annual costs US$ 1214 million

Annex 2

Country review process and recommendations

This document was provided as a basis for the Board to formulate its second request to the Global Fund. It comprises a three-part report:

- a summary of the Review Committee's recommendations,
- estimates of the resulting financial commitments, and
- a summary of the recommendations and responses to each country's proposal.

The list of members of the Independent Review Committee is included as an appendix to this annex.

Report of the Independent Review Committee, second-round of country proposals

1. Summary report

The second round of reviews of country proposals requesting support from GAVI and the Global Fund took place in Geneva from 2-10 November 2000.

A total of 19 countries submitted new proposals in this round but, as two proposals were incomplete, 17 proposals were reviewed. In addition, three countries that received conditional approval for introduction of new and under-used vaccines in the first round – Bhutan, Côte d'Ivoire, and Pakistan – submitted the requested information in time for it to be incorporated into this second round. Recommendations on these proposals are also included in this report.

The Review Committee consists of nine people (see Appendix to Annex 2 below). One member, Dr Nafo-Traore, the Health Minister of Mali, was unable to participate in this round due to official duties.

The review took eight full working days, as compared to five days in the previous round. This, as well as the addition of two reviewers, made it possible for each proposal to be assessed by three reviewers. The presentations and recommendations were then discussed with the full group. All recommendations reflect the consensus of the group.

For this round, more time was scheduled between the receipt of proposals and the beginning of the review. This enabled staff at WHO and the GAVI Secretariat to have a preliminary look at the data and to check for consistency. In addition, comments on the country proposals from WHO, UNICEF and the Gates Children's Vaccine Program (CVP) were received and shared with the Committee. This step, as well as the revisions to the proposal forms based on the experience of the first round, resulted in more complete and thorough information and facilitated a better review process.

There were five possible outcomes for each proposal. As with the first round, the reviewers split their decisions between the two sub-accounts (immunization services; new and under-used vaccines). This round elicited two decision categories that had not emerged during the first round: outright approval, and not eligible/not approved. There are now five categories:

1) Approval.

2) Approval with clarifications.

3) Conditional approval; final approval to be given only when the proposal can satisfactorily meet conditions. Applications with conditional approval will be assessed again by the Review Committee and subsequently forwarded to the Board for approval.

4) Re-submission; this implies a new proposal and subsequent review process.

5) Not eligible/not accepted.

1.1 Recommendations on country proposals

Decisions on each application were taken by consensus among the reviewers. Table 1 summarizes the Review Committee's recommendation to the Boards of GAVI and the Global Fund.

Table 1: Summary recommendations

Country	Sub-account for immunization services	Sub-account for new and under-used vaccines
Second-round proposals		
Albania	-	Conditional approval
Armenia	Approved with clarifications	hepB: conditional approval Hib: re-submission
Azerbaijan	Approval with clarifications	Approval with clarifications
Burkina Faso	Conditional approval	Not eligible
Cuba	-	Not accepted
Gambia	-	Re-submission
Haiti	Approval with clarifications	Re-submission
Honduras	Not eligible	-
Lesotho	Re-submission	Re-submission
Liberia	Approval with clarifications	-
Rwanda	-	Approval with clarifications
Sao Tomé	Approval	Re-submission
Sierra Leone	Conditional approval	Not eligible
Uganda	Approval	Approval
Uzbekistan	Re-submission	Re-submission
Viet Nam	-	Conditional approval
Zambia	Conditional approval	Re-submission
Conditional approvals from first round		
Bhutan	-	Approval with clarifications
Côte d'Ivoire	-	Approval
Pakistan	-	Approval

1.2 Recommendations on policy issues

During the course of the deliberations, the Review Committee took note of several policy and technical issues. Suggestions to GAVI on how to address these issues included the following:

(a) Support to countries in complex emergency situations

Background: A substantial proportion of children live in countries in conflict, post-conflict or in otherwise complex emergency situations. The context for each of these countries varies greatly and it is generally difficult for them to meet the current eligibility criteria for the new and under-used vaccines sub-account. There are also technical problems related to the measurement of DTP3 coverage, especially in countries with significant displaced or mobile populations.

As the Global Fund is structured to provide time-limited support to countries that demonstrate fundamental capacity for provision of immunization and health services, it would not be appropriate to revise eligibility criteria.

Recommendation: Each country in conflict has its own specific needs and issues. The Review Committee therefore urges GAVI to develop a strategic approach for these countries, bearing in mind that partners at the country level, including non-governmental organizations (NGOs) and bilateral agencies, must take a lead in assisting the countries.

(b) Yellow fever vaccine

Background: Yellow fever has long been recommended for routine immunization in high-risk countries. However, little progress has been made due to lack of funds; many of the most high-risk countries have the weakest health infrastructure. Yellow fever epidemics are therefore frequent in high-risk countries, leading to outbreak-control measures, emergency campaigns and mop-up operations.

Recommendation: The Review Committee recommends that GAVI consider, on a country-by-country basis, lowering the minimum DTP3 coverage eligibility criteria. In addition, the committee was concerned that the recently published GAVI vaccine product catalogue does not include yellow fever vaccine and recommends that the catalogue be revised as soon as possible to include this under-used vaccine.

(c) Countries producing sub-standard EPI vaccines

Background: Some countries produce their own EPI vaccines that do not meet the WHO standards for safety, quality and efficacy.

Recommendation: The Review Committee urges GAVI to enforce the WHO/UNICEF policy on safety of vaccines so that by 2003, all vaccine-producing countries that receive support from GAVI/the Global Fund, must also produce EPI vaccines that meet WHO standards and certification of vaccine production.

(d) Sustainability of financing

Background: GAVI has adopted the policy that the Global Fund should not replace existing funding for vaccine and immunization. However, many countries find long-term planning difficult, with donors' decisions on funding often varying from year to year.

Recommendation: The Review Committee recommends that the GAVI Board urge partners at global and country level to develop multi-year financial commitments. In addition,

national inter-agency coordinating committees (ICCs) should be requested to monitor annual trends of financial contributions by the partners at country level.

1.3. Other recommendations

In addition to the above policy issues, the Review Committee has some general recommendations to improve the overall quality of future country proposals. While the revised forms resulted in better proposals, many countries submitted applications with arithmetical errors and internal inconsistencies. In addition, some countries requested vaccine presentations that do not currently exist, or for which they are not eligible.

(a) Information dissemination

GAVI partners need to improve the systems for dissemination of basic information to countries and to the consultants who are sent to work with countries. Specifically, information about available vaccines, eligibility requirements for these vaccines, and immunization schedules needs to be better disseminated.

(b) Sample proposals

One basic strategy for improving future proposals would be to distribute, with the approval of the countries in question, samples of good components of their proposals. The Review Committee found excellent examples among the proposals submitted – for example, a resource mobilization plan from Uganda, a plan for the introduction of hepatitis B from Azerbaijan, a safe-injection plan from Viet Nam, and a multi-year plan from Honduras.

(c) Immunization safety

The importance of immunization safety was discussed at length. Countries should be requested to develop a national policy on injection safety including vaccine quality issues, if they don't already have one. Built-in systematic reporting of international vaccine arrival and problems related to accidental freezing of vaccines are other issues that require attention.

1.4 Recommendations on application forms and guidelines

The review of technical issues led to the following suggestions for further improvement of the application form and guidelines, if possible without increasing their total length:

- Provide a statement on the recommended proposal development process including the nature of ICC participation;
- Insert space for countries to include a summary of the key indicators the ICC will monitor;
- Include a separate table to calculate wastage rate and provide the formula to calculate the wastage factor from the wastage rate;
- Insert, in all appropriate locations, the statement that requested coverage figures applies to "children before the age of 12 months";
- Provide a formula to calculate the drop-out rate;
- Introduce a section in the form, to correspond to section in the guidelines on capacity-building;

- Provide a formula for calculating syringe needs;
- Indicate more clearly that catch-up immunization and campaigns are not supported;
- Be more explicit regarding the provision of auto-disable syringes for reconstitution of lyophilized vaccines.

2. Estimates of financial commitments of second round recommendations

Table 2: Countries recommended for approval – US$
(this implies immediate financial commitment)

	Sub-account for immunization services		**Sub-account for new and under-used vaccines**	
Countries	November 2000: first instalment [1]	October 2001: 2nd instalment	For 2001 (procurement in first quarter 2001)	For 2002 (procurement in 2nd quarter 2001)
1. Sao Tomé	5 000	5 000	-	-
2. Uganda	455 000	455 000	-	4 155 000
Conditional approvals from first round				
3. Côte d'Ivoire	-	-	702 000	1 732 000
4. Pakistan	-	-	223 000	4 363 000
Sub-total (US$)	**460 000**	**460 000**	**925 000**	**10 250 000**
Grand total (US$)				**12 095 000**

Table 3: Countries that received a recommendation for approval with clarification – US$
(this implies future financial commitment; to be verified in the clarification process)

	Sub-account for immunization services		**Sub-account for new and under-used vaccines**	
Countries	November 2000: first instalment [1]	October 2001: 2nd instalment	For 2001 (procurement in first quarter 2001)	For 2002 (procurement in 2nd quarter 2001)
1. Armenia	76 000	76 000	-	-
2. Azerbaijan	16 000	16 000	80 000	228 000
3. Haiti	272 000	272 000	-	-
4. Liberia	306 000	306 000	-	-
5. Rwanda	-	-	-	4 373 000
Conditional approval from first round				
6. Bhutan[2]	-	-	-	-
Sub-total (US$)	**670 000**	**670 000**	**80 000**	**4 373 000**
Grand total (US$)				**6 021 000**

[1] The calculation of funds for investment is based on targets for the period ending December 2001; divided into two equal instalments for December 2000 and October 2001.

[2] Bhutan has requested support for the year 2003.

3. Summary of detailed recommendations by the Independent Review Committee for each of the country proposals

Recommendation on:	Albania
Conditional approval:	Vaccines: Conditional approval for hepB and Hib vaccine provided that Albania can: • provide a financial plan for the whole EPI (to ensure that donors do not withdraw from the current funding, GAVI will not replace current funding for hepB vaccine); • delay the plan to introduce Hib vaccine until early 2002 (when a DTP-Hib combination is likely to be available); • check cold-chain capacity requirements and protection from freezing.
Not eligible:	GAVI will not fund MR and MMR.
Recommendation on:	**Armenia**
Approval with clarifications:	Immunization services: For Armenia to be eligible for this sub-account, the reviewers will accept a figure of 63.4% and recommend that the GAVI Board approves the proposal, provided Armenia can provide clarification on: • the baseline coverage for children under 12 months of age; • the 2001 target of children under 12 months of age (not the whole birth cohorts); • the target for subsequent years (2002-05) – for the calculation of awards.
Conditional approval:	Vaccines: Conditional approval for hepB vaccine provided that Armenia can: • provide a five-year financial plan for the whole EPI (to ensure that donors do not withdraw from the current funding, GAVI will not replace current funding for hepB vaccine); • recalculate targets of hepB vaccine to be consistent with children immunized by DTP; • present justifications on the request for single-dose hepB vaccine and its implications on cold-chain capacity; • provide a plan to introduce and integrate new vaccine into routine EPI operations, including training requirements, logistics, cold-chain capacity and requirements, especially when single-dose hepB

Armenia *(continued)*	
	is envisaged; experience could be based on operations since November 1999. GAVI also requests Armenia to provide: • more information on current hepB vaccine coverage and wastage rates; • estimates on the number of births and infant deaths in 2000-2005.
Re-submission:	Vaccines: the Review Committee recommends that the proposal for Hib vaccine be resubmitted once there is ample evidence of the disease burden of *Haemophilus influenzae* pneumonia and/or meningitis and taking into account that: • for a prompt submission of applications, the survey planned for 2003 should be carried out earlier; • an introduction plan for Hib vaccination is crucial.
Not eligible:	GAVI will not fund MMR.
Recommendation on:	Azerbaijan
Approval:	Immunization services and vaccines: Approved, with clarification required on: • how to increase target of DTP3 from 74% to beyond 80%; • how to maintain the cold chain, especially on the peripheral level; • when the cold chain assessment in relation to arrival of vaccine will be done; and • who will finance the cold chain.
Recommendation on:	Burkina Faso
Conditional approval:	Immunization services: Conditional approval when the country can: • provide information on immunization safety plan and sharps waste-disposal; • provide details of financial sustainability and a resource mobilization plan; • estimate figures on surviving children; • set up a realistic target of children to be immunized.
Not eligible:	Vaccines: Burkina Faso is not eligible as DTP3 coverage does not achieve 50%. The country may resubmit when

Burkina Faso *(continued)*	
	DTP3 reaches 50%, in which case plans on safety of injections, sharps waste-management and the introduction of new vaccines should be strengthened.
Recommendation on:	Cuba
Not eligible:	Vaccines: Cuba is self-reliant in the area of vaccination with funding from the national government and Mexican Rotary. It is against GAVI's general principles to replace existing funding so the proposal is not accepted, despite the fact that Cuba is eligible. The performance of Cuba's health systems is very good, ranking 37 in the *World Health Report 2000*.
Recommendation on:	Gambia
Re-submission:	Vaccines: The Committee suggests re-submission, taking into account the following suggestions to: • use a new application form which includes a multi-year plan, a safety of injections plan, immunization assessments, immunization policy, plans for the introduction of new vaccines, assessments of hepB, Hib and yellow fever vaccinations; • strengthen the ICC membership and its functions; • draw up plans on resource mobilization and sustainability; • note the current funding by two major donors (hepB funded by Italian Aid and Hib by Pasteur Merieux). GAVI will not replace existing funding sources.
Recommendation on:	Haiti
Approval with clarifications:	Immunization services: Approved, with clarifications required on: • vaccine safety; • reduction in vaccine wastage rates; • a realistic target of increase coverage; • recalculation of vaccine needs; • strengthening of the ICC functions; • analysis of cold-chain capacity and safe storage of vaccines.
Re-submission:	Vaccines: The Committee recommends resubmission in six or more months with a revised time-frame for introducing new vaccines. The immunization system is still frag-

Haiti (continued)	
	ile and needs a careful plan for this. In revising the proposal, it should be noted that: • GAVI hepB vaccine is not provided for health care workers and medical students; yellow fever vaccine is not provided for travellers; • GAVI will not provide measles vaccine; • pentavalent liquid 10-dose vials do not exist; • the second choice, monovalent Hib and hepB, could over-stretch a fragile system.
Not eligible:	MR vaccine is not eligible.
Recommendation on:	Honduras
Not eligible:	Immunization services: The country is not eligible because it has a DTP3 coverage of 95% with >80% coverage in all areas; this is well above the eligibility criteria. GAVI will not provide support for the mop-up activities which Honduras plans in order to reach >90% coverage in the remaining 84 municipalities. Honduras has an extremely high performance in immunization and is self-sufficient in all antigens.
Recommendation on:	Lesotho
Re-submission:	Immunization services and vaccines: The application should be resubmitted, taking into account the following suggestions to: • strengthen the ICC to include other partners who will participate in the proposal resubmission and other ICC activities; • conduct a comprehensive immunization assessment; • develop a multi-year strategic plan (based on the results of the comprehensive immunization assessment) to include plans for the introduction of hepB, safe-injection practices, wastage reduction and sustainability; members of the ICC should participate in these activities; • seek technical assistance to work with the ICC and in-country local partners to conduct the comprehensive assessment and draw up the multi-year plan.

Recommendation on:	Liberia
Approval with clarifications:	Immunization services: Approved, with clarification required on: • how to accelerate coverage from 23% (Dec 1999) to 60% in 2001 (13 months); • plans to reduce drop-out and vaccine wastage rates.
Recommendation on:	**Rwanda**
Approval with clarifications:	Vaccines: Rwanda has a good performance record in accelerating its immunization coverage; it has resubmitted a sound plan in time for this second review and is eligible for the new and under-used vaccines sub-account (DTP3 63%). The Review Committee recommends approval with clarification on the following: • implications of new vaccines on cold-chain capacity; • a realistic financing source to replenish cold chain equipment; • a sustainable financial plan (not detailed); • mobilization of resources; • how activities will be financed in 2001.
Recommendation on:	**Sao Tomé**
Approval: Re-submission:	Immunization services: Approved. Vaccines: Re-submission is recommended, taking into account the following suggestions to: • strengthen the ICC; • strengthen the EPI services; • develop a detailed plan for the introduction of new vaccines to include targets, wastage, plans for cold chain, sustainability and monitoring ; • identify technical assistance to increase government capacity to manage immunization services.
Recommendation on:	**Sierra Leone**
Conditional approval:	Immunization services: The Committee approves the proposal provided the country can: • set a target which is more realistic than that proposed; • strengthen the ICC with competent members who will be effective and involved in operations;

Sierra Leone *(continued)*	
	• provide a complete plan for improving coverage and injection safety, including operational aspects and the reduction of drop-outs; • provide a complete plan for the reduction of wastage; • find new partners and technical assistance for EPI management, focusing special attention on immunization safety, the cold chain, logistics, waste disposal and a strategy to improve coverage and disease surveillance.
Not eligible:	Vaccines: • The country is not eligible for the new and under-used vaccines sub-account because of its <50% DTP3 coverage, but it is welcome to re-submit if special criteria for countries in armed conflict are developed by the GAVI Board in the future. • The request for meningococcal meningitis vaccine is not eligible. GAVI does not support outbreak control or emergency preparedness but aims rather to strengthen immunization systems as part of the overall development of a country's health system.
Recommendation on:	Uganda
Approval:	Immunization services: approved Vaccines: approved
Recommendation on:	Uzbekistan
Re-submission:	Immunization services: Uzbekistan will be eligible if recent and reliable figures on DTP3 coverage are less than 80% (card plus recall by 12 months of age from survey data). If this is so, re-submission is recommended, with a clear indication on the target number of children to be immunized. Vaccines: Uzbekistan will be eligible if recent and reliable figures on DTP3 coverage are above 50% (card plus recall by 12 months of age from survey data). If this is so, re-submission is recommended with the provision of more information on: • experience with hepB vaccine; • vaccine management; • injection safety; • immunization schedule review;

Uzbekistan (continued)	
	• vial-size; • plans to prevent vaccine freezing; • plans for sustainable financing of immunization; • ensuring the use GAVI hepB vaccine for infants; • the linkage of hepB vaccine introduction with recommendations generated by immunization assessments. The Committee suggests that, to allow adequate time for preparing the proposals, the Ministry of Health should takes at least six months before re-submitting to both sub-accounts.
Recommendation on:	Viet Nam
Conditional approval:	Vaccines: Viet Nam is eligible for this sub-account but the Committee recommends that the GAVI Board should provide conditional approval for hepB vaccine until the country can meet the conditions outlined below: • to comply with GAVI policy on auto-disable supports, the Government of Viet Nam should cover the cost of auto-disable or disposable syringes for the portion of hepB vaccines financed by the government; • Viet Nam should provide an explicit strategic plan to expand and integrate hepB vaccine into the routine immunization programme, including information on cold-chain requirements, training of health workers, social mobilization and logistics (the information provided in section 5 of the proposal is too general); • provide a realistic target for hepB coverage; the proposed plan to achieve 100% coverage is too ambitious. • justify the vial sizes (1, 2 and 10 dose-vials) to accommodate cold-chain capacity; • produce a plan for monitoring safety of production with plans to achieve WHO standards by a time-frame that satisfies WHO. GAVI also requests the country to provide more information on: • the current DTP and hepB wastage rates; • the conflicting figures for the numbers of surviving infants (given in tables 1 and 4 of the proposal);

Viet Nam *(continued)*	
	• when the time-frame for cold chain support from the Government of Luxembourg materializes, including resource mobilization (section 5 and table 1-2 in Annex 1 of the Viet Nam proposal).
Recommendation on:	Zambia
Conditional approval:	Immunization services: The Committee recommends conditional approval when recent and reliable figures on DTP3 are less than 80% (card plus recall by 12 months of age from survey data).
Re-submission:	Vaccines: The Committee considers this plan should be resubmitted, with stronger information provided on the following points: • the ICC; • timing and presentation of hepB and Hib; • plan of introduction (pentavalent vaccine); • logistic and cold-chain capacity. A safe-injection plan and sharps waste management is important.

Conditional approvals from first round

Recommendation on:	Bhutan
Approval with clarifications:	Vaccines: The Committee noted with satisfaction that Bhutan meets the conditions provided in the first round review, but still needs clarification on some points, including: • targets, • whether the auto-disable syringes will be supported by DANIDA or financed by the government (disposable syringes could be an interim measure).
Recommendation on:	Côte d'Ivoire
Approval:	Vaccines: approved
Recommendation on:	Pakistan
Approval:	Vaccines: approved

Appendix to Annex 2

List of members of the Independent Review Committee

1. Dr Sam Adjei, Deputy Director-General, Ghana Health Services, Accra, Ghana
2. Dr Caroline Akim, Programme Manager, Expanded Programme on Immunization, Ministry of Health, Dar es Salaam, Tanzania
3. Dr Abdallah Bchir, Professor, Department of Community Medicine, School of Medicine, Monastir, Tunisia
4. Dr Maria Otelia Costales, Country Representative, AVSC International, Manila, Philippines
5. Dr Merceline Dahl-Regis, Chief Medical Officer, Ministry of Health, Nassau, Bahamas
6. Dr Alenka Kraigher, Epidemiologist, Institute of Public Health, Ljubljana, Slovenia
7. Dr Fatoumata Nafo-Traoré, Minister of Health, Bamako, Mali
8. Dr Robert Steinglass, Immunization Team Manager, BASICS, Washington DC, USA
9. (Chair) Dr Viroj Tangcharoensathien, Health Systems Research Institute, Bangkok, Thailand

Annex 3

Task Force on Research and Development

Discussion and background documents on agenda item 3

Annex 3 comprises:

- Annex 3a: Terms of reference of the GAVI Task Force on Research and Development. Drawn up by the newly-appointed members of the task force, the terms of reference reflect the Board's desire to identify projects which:
  (a) are high-impact and readily-achievable; and
  (b) allow the various GAVI public and private sector partners to forge new bonds to achieve their specific research and development objectives.
- Annex 3b: Issues and opportunities for consideration by the GAVI in addressing its research and development objectives. A background paper prepared by Dr Myron Levine for the Board's discussion on the terms of reference of the task force.
- Annex 3c: The role and goals of the R&D Task Force, a slide presentation prepared and presented by Dr Peter Wilson

Annex 3a

Terms of reference of the GAVI Task Force on Research and Development

(prepared by the members of the GAVI R&D Task Force)

1. Mission

The job of the task force is to catalyse action in research and development (R&D) in support of GAVI's overall objectives. The task force should, in particular, support the attainment of GAVI objectives 3 and 4, namely:

- Objective 3: Accelerate the development and introduction of new vaccines and technologies.
- Objective 4: Accelerate research and development efforts for vaccines needed primarily in developing countries.

The task force will seek the most effective ways to mobilize the knowledge, resources and assets of the GAVI partners, and to coordinate the efforts to achieve these objectives for a limited number of finite, selected projects.

The ultimate goals of the task force are to:

- reduce mortality and morbidity in developing countries from diseases for which either no vaccine is currently available or existing vaccines have important drawbacks that severely limit their usefulness, and
- improve the safety and performance of immunization services through research and development initiatives.

In carrying out its responsibilities, the task force will concentrate on "push" initiatives that involve promoting appropriate research and development activities that reduce the risk or cost of development. However, various approaches will be needed to promote and develop a project, and push-and-pull (e.g., market-led strategies) may become difficult and perhaps unnecessary to differentiate. In many instances, the strategies that reduce costs and investment risks may need to be complemented by strategies that increase the likelihood that reliable markets will come to exist for the product, thereby encouraging industrial investment. There will be a need to coordinate with other task forces, notably the Financing Task Force that will be concentrating on "pull" strategies.

2. Specific objectives and goals

The specific objectives of the task force will be to catalyse action and coordinate global initiatives for:

- a limited number of disease-specific programmes which can most effectively contribute to the task force's ultimate goals; and
- development of a limited number of new technologies that will improve safety, effectiveness, utility or performance of immunization in developing countries.

However, it is anticipated that the task force will consider certain activities and goals when designing and coordinating the specific projects, namely:

- strengthening capacity in developing countries;
- promoting private/public sector partnerships in research and development, and involving the private sector in research and development initiatives in developing countries;
- conducting applied field research to assess the effectiveness of vaccines on disease burden;
- conducting operational research to improve effectiveness, safety and delivery of immunization;
- fostering pilot-lot production capacity in developing countries;
- improving the information technology (IT) infrastructure for better management of immunization in developing countries;
- establishing forums for policy dialogue and information sharing, e.g., regulatory requirements in developing countries.

3. Project selection

It is recommended that the task force focus initially on:

- three disease-specific projects;
- up to three new technologies.

In the initial stage of the task force's operations, the portfolio of projects will focus on high impact, near-term projects that have a high probability of success. Through these projects the task force will lay the foundation for more difficult longer-term projects that will follow in a second stage. These later projects will then be more easy to promote and implement as the path will already have been laid, mechanisms tried and established, capacity for research and development in developing countries improved to handle the more difficult projects, and partnership and funding models developed.

4. Disease-specific projects

The criteria for choosing the disease-specific projects will be based upon:

- considering only diseases for which there is either no currently registered vaccine or for which the existing vaccines have notable drawbacks that severely limit their public health usefulness (for example, the existing vaccines that are not yet immunogenic in infants whose age group is an epidemiological target for vaccination);
- high potential impact – disease mortality rate:
  - paediatrics,
  - adults;
- high potential impact: disability-adjusted life years (DALYs);
- high probability of success in a short/medium time-frame – that is, introduction into disease control in 5-10 years time – focusing on the scientific and technical feasibility;
- magnitude of the strategic gap: little else being done about the disease?
- non-availability of alternative solutions to managing the disease;
- good potential for changing/improving the immunization system for the future;
- capacity-building;
- promoting behavioural or system changes;
- high programme feasibility:
  - can it be done with the tools and infrastructure available?
  - political commitment.

The recent questionnaire sent to various GAVI partner representatives produced the following list of candidate vaccines for consideration:

HIV/AIDS
malaria
tuberculosis
Streptococcus pneumoniae
rotavirus
Neisseria meningitidis groups A & C
Shigella
respiratory syncytial virus (RSV)

Evaluation of these vaccine candidates against the criteria shows that they all score highly against at least one of the criteria. The task force recognizes that a high priority lies in HIV/AIDS and malaria. However, given the massive global effort focused on these projects worldwide, the task force recognizes that it can do little to push them more at this point in time. Furthermore, the task force recognizes that, even if these vaccines become available, there is

no infrastructure to efficiently put them into public health use. The task force will therefore initially focus on vaccines that have a lower technical risk (such as those for which proof of concept has been demonstrated). Success with these vaccines will alleviate the burden of important diseases in developing countries but will also build the infrastructures for efficient delivery of vaccines that will come later, such as HIV, tuberculosis and malaria.

Taking an overall view that incorporates all the criteria, it is recommended that the task force focus its initial efforts on the following vaccines:

Streptococcus pneumoniae
Rotavirus
Neisseria meningitidis group A (which may be approached either as a monovalent group A, a bivalent group A/C or a quadrivalent group A/C/Y/W135 vaccine)

Once the pathway has been laid by work on these vaccines, attention could turn to the more difficult candidates, such as HIV, malaria or tuberculosis.

5. New technologies

The task force will seek out and evaluate new technologies that will improve safety, effectiveness, utility or performance of immunization in developing countries. Unlike vaccines, there is no readily available or easily prepared list to evaluate, and it will be the task force's responsibility to initiate a suitable process to identify candidate technologies.

The same broad criteria for evaluating vaccine candidates would be used for new technologies, but with different parameters:

- potential impact upon safety, effectiveness, access, utility or performance of immunization in developing countries;
- high probability of success in a short/medium time-frame;
- need/strategic gap – is anybody doing anything in this area?
- non-availability of alternative solutions to address the problem;
- potential for changing/improving the immunization system for the future:
  - capacity-building;
  - programmatic feasibility.

Preference would be given to research and development on new technologies being conducted in developing countries. The two areas of technology suggested for initial focus are:

a) increasing access to immunization and safety of vaccines and vaccination – for example, the introduction of pre-filled, monodose vaccine-administrative devices;

b) improving management of immunization services and disease surveillance – for example, information technologies and simplified immunological assays.

Information technologies are already widely used by the commercial sector in developing countries but are seldom applied to the management of immunization services within ministries of health. Yet communications and data transfer are critical to the effective and efficient tracking of immunization performance and to surveillance of disease.

6. Role and method of operation

6.1 The Board

The Board will consider projects in two stages:

a) initial approval of project areas for development of proposals, based on task force recommendations;

b) approval of fully developed project proposals for implementation.

6.2 The R&D Task Force and the Working Group

The role of the task force is to identify worthwhile projects, plan and catalyse research and development action on the projects, and coordinate and monitor the resulting activities. There will be three stages to each project, with a distinct role for research and development at every stage:

a) Identification stage: Identifying possible candidate projects, evaluating them against agreed criteria, and recommending to the GAVI Board those projects to be taken forward for action.

b) Planning stage: Identifying the key research and development gaps and planning how to address them, evaluating alternative ways to structure the project, and co-ordinating and facilitating input from different partners. This will also involve close coordination with other GAVI task forces. The delineation of responsibilities between different task forces in each project will be done by the Working Group, which will have responsibility for coordinating the different activities required to plan and structure each project.

c) Implementation stage: Projects will be undertaken and pursued to completion by an implementing GAVI partner (or a consortium of partners). The task force will monitor the implementation to assess adherence to the agenda and time schedule of the research and development activities.

6.3 The implementing partner

The development and implementation of a full project proposal to the Board will be the responsibility of the implementing partner (to avoid conflict of interest, preferably not a Board Member).

Appendix to Annex 3a

List of members of the GAVI Task Force on Research and Development

1. [Co-Chair] Professor Myron M. Levine, Director of the Center for Vaccine Development of the University of Maryland School of Medicine, Baltimore MD, USA
2. [Co-Chair] Dr Rino Rappuoli, Vice President for Vaccine Research of Chiron Vaccines, Milano, Italy
3. [Co-Chair] Dr Yasuhiro Suzuki, Executive Director of Health Technology and Pharmaceuticals of the World Health Organization, Geneva, Switzerland[1]
4. Dr Fred Binka, Director of the Navrongo Health Research Centre, Ministry of Health, Navrongo, Ghana
5. Dr Punnee Pitisuttithum, Principal Investigator, Vaccine Trial Center, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
6. Dr Rosanna Lagos, Coordinator, Centro para Vacunas en Desarrollo, Chile (CVD-Chile); Hospital Roberto Del Rio, Santiago, Chile
7. Professor Barry Bloom, Dean, School of Public Health, Harvard University, Boston MA, USA
8. Sir Gustav Nossal, Professor Emeritus, Department of Pathology, University of Melbourne, Melbourne, Australia

[1] The senior WHO staff member in charge of vaccine research (IVR Coordinator) will serve as Secretary to the R&D Task Force.

Annex 3b

Issues and opportunities for consideration by the GAVI in addressing its research and development objectives

(Dr Myron M. Levine[1], Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD 21201)

1. GAVI comes on the scene

The final quarter of the 20th century saw many advances and achievements in the area of vaccines and immunization. Among the most notable were the eradication of smallpox, the elimination of poliomyelitis from several regions of the world and significant strides towards the ultimate goal of global eradication, the establishment of an infrastructure – the Expanded Programme on Immunization (EPI) – to deliver a series of basic vaccines to infants throughout the developing world, and application of the powerful tools of modern biotechnology to develop new and improved vaccines. In great part, these achievements can be directly attributed to various agencies and interested parties that worked together in coalitions and alliances with common goals. The Smallpox Eradication Programme and the Polio Eradication Initiative represent examples in which other agencies joined a lead agency (in these two instances, the World Health Organization) to work in unison towards achieving a common agenda. One coalition, the Task Force for Child Survival, that included UNICEF, WHO, UNDP, the World Bank and the Rockefeller Foundation, was instrumental in achieving impressively high levels of immunization coverage through the EPI, during the period 1984 through 1990. A subsequent coalition with many of the same major partners, the Children's Vaccine Initiative (CVI), which was born in 1991 following the 1990 World Summit for Children, advocated the development of simpler, more practical immunization *(1, 2)*. The CVI envisioned a future in which single-dose, combination vaccines would be available to immunize very young infants by non-parenteral routes.

Both the Task Force on Child Survival and the CVI made important contributions to protect the health of children globally. However, within a few years of their founding, the effectiveness of each was found to be somewhat limited by the absence of certain constituencies *(3, 4)*. In the waning years of the 20th century three glaring gaps became apparent:

1) EPI coverage had stagnated globally from the peak coverage reached circa 1990 and had even began to fall in certain areas;

2) some relatively new vaccines that were routinely being given to infants in industrialized countries (such as *Haemophilus influenzae* type b conjugate and hepatitis B) were not being expeditiously introduced for routine use in developing countries;

3) inadequate resources were being channelled to develop vaccines of particular importance for populations in developing countries.

It is against the above background that the Global Alliance for Vaccines and Immunization (GAVI) came into existence, as various traditional partners (such as WHO, UNICEF, the

[1] Dr Levine is a member of the GAVI Working Group and Co-Chair of the GAVI R&D Task Force.

World Bank, the Rockefeller Foundation, national governments and bilateral agencies) teamed with new partners, including industry and the Bill and Melinda Gates Foundation, to forge a novel alliance to address the perceived gaps and weaknesses *(5)*. It was hoped that GAVI would invigorate the commitment of all relevant agencies and partners to provide safe and effective vaccines for immunization of all the world's children. The process that gave birth to GAVI included formative meetings in Washington in March 1998, Bellagio in March 1999 and Seattle in June 1999, an internal launch within the United Nations agencies in New York in October 1999 and a worldwide launch in January 2000 (during the World Economic Forum).

2. How GAVI works

GAVI is not an implementing agency. Rather, it is a consortium of partners that includes important implementing agencies. For the running and financing of immunization programmes and the production of vaccines, these include, national governments, WHO, UNICEF, the World Bank, the Bill and Melinda Gates Foundation and bilateral agencies and the vaccine industry. Implementers of vaccine research and development activities include many governmental, academic and philanthropic institutions, biotechnology companies, the vaccine industry and certain international agencies such as WHO.

In practical terms, GAVI functions in three main ways to shrink the identified gaps. One is to increase synergy and cooperation among the various partners so that they can accomplish tasks and achieve objectives that would otherwise be unattainable or that would take much longer to accomplish. An invaluable tool to achieve synergy among the different GAVI partners is through work of task forces. Second, since each partner contributes to GAVI in the way it deems most appropriate, an implementing partner may strengthen itself in order to better address an important gap or to undertake a critical task identified by GAVI. The third instance is an exceptional one wherein the GAVI partners agree to the need for a special new resource, the best example being GAVI's Global Fund for Children's Vaccines.

3. GAVI's objectives

GAVI has promulgated five specific objectives, two of which specifically encompass research. The five objectives are to:

1) Improve access to immunization services.

2) Expand the use of existing cost-effective vaccines.

3) Accelerate the development and introduction of new vaccines.

4) Accelerate research and development efforts for vaccines and related products specifically needed by developing countries, particularly vaccines against HIV/AIDS, malaria and tuberculosis.

5) Make immunization coverage an integral part of international development efforts.

4. Economics and vaccine development

There is increasing recognition of the fundamental role that economic factors play in driving the development of specific vaccines and in the setting of vaccine development priorities within industry *(6)*. Table 1 summarizes four generic categories of vaccines in relation to whether or not there exist credible markets for the vaccine in industrialized countries.

Table 1: Four generic categories of vaccines in relation to disease burden and the reliability of markets

Category of vaccine	Developing countries		Industrialized countries		Examples
	Disease burden	Current markets	Disease burden	Current markets	
Global market vaccines	large	small	large	large	Hib conjugate; HepB; acellular pertussis
Industrialized market vaccines	small	small	large	large	Lyme disease
Impeded vaccines	large	small	large	large	RSV; Group A *S. pyogenes*
Developing market	large	small	small	small	malaria; typhoid; *Shigella*

The existence of an industrialized country market increases the odds that there will accrue a fair return on the enormous investments that must be made to develop a vaccine to the point of licensure and to scale-up manufacture to achieve the volume necessary for commercial availability*(7)*. In contrast, heretofore, developing country markets have proven to be less certain and of lower profitability.

Whereas the diseases against which "global market vaccines" are directed exhibit a substantial burden among populations in both industrialized and developing areas of the world, the anticipated industrialized country market overwhelmingly drives the development of such vaccines. Nevertheless, the public health need for these vaccines in the developing world is generally more compelling because of the greater frequency of severe clinical syndromes and fatalities. Examples, of licensed "global market vaccines" include the *Haemophilus influenzae* type b conjugates and hepatitis B vaccines. Important global market vaccines that are not yet licensed but that are in advanced development include 9-valent and 11-valent *Streptococcus pneumoniae* conjugate vaccines and several new candidate rotavirus vaccines.

During the past two decades, two categories of vaccines have languished in development, albeit for quite different reasons. One category, "developing market vaccines", aims to prevent diseases for which the burden is prominent in developing country populations but little if any risk is posed for individuals in industrialized countries (unless they travel to developing areas). Examples include vaccines against certain bacterial diseases (e.g., *Shigella* and enterotoxigenic *Escherichia coli* infections, cholera, typhoid fever, group A meningococcal infections and tuberculosis), viral diseases (e.g., dengue fever, hepatitis E) and parasitic infections (e.g., malaria, leishmaniasis and schistosomiasis). The fact that industrialized country markets are either lacking or limited to travellers provides little incentive for industry to invest in the development of these vaccines. The term "developing market vaccines" not only reflects that these are particularly targeted for use in developing countries but also conveys the notion that the GAVI partners will have to stimulate non-traditional markets for these vaccines in the less developed world.

"Impeded vaccines" would almost certainly have substantial markets in industrialized countries if they were shown to be safe and effective but certain scientific, ethical or public perception obstacles raise the risk that they might not reach product licensure and commer-

cialization. As a consequence, such vaccines are generally lower priority for investment by the vaccine industry. The legacy from experiences with earlier generations of respiratory syncytial virus (RSV) and M protein-based Group A *S. pyogenes* vaccines that either caused severe adverse events or resulted in immunopathology when vaccinees were exposed to the wild type pathogen in the course of clinical trials *(8)* has stifled the pace of development of more modern vaccine candidates *(9-12)*.

5. Accelerating the development and introduction of new vaccines

5.1 Global market vaccines

Even though candidate global market vaccines expeditiously enter clinical trials in industrialized country populations, driven by the desire of industry to get them licensed and marketed in industrialized countries in the shortest possible time, the clinical trials that are specifically necessary to demonstrate their safety, efficacy and practicality in developing country populations are often inordinately delayed or not undertaken at all. This is regrettable because the target clinical disease for these vaccines is often much more severe and lethal in the developing versus the industrialized world. For example, in industrialized countries, where there is little mortality from rotavirus disease, the goal of vaccination is to prevent gastroenteritis episodes that result in hospitalizations and visits to health-care providers, and that lead infants and toddlers to be excluded from day care (and their parents to be absent from work). In contrast, in the developing world many deaths, as well as many hospitalizations, are attributed to diarrhoeal dehydration caused by rotavirus *(13, 14)*.

Similarly, the interest in pneumococcal vaccines for use in the infant population in industrialized countries has historically been driven in great part by an ultimate goal of preventing otitis media, whereas in the developing world the aim of a new pneumococcal vaccine is to prevent deaths and hospitalizations from invasive disease and pneumonia.

5.2 Impeded and developing market vaccines

A few impeded vaccines and developing market vaccines are high public health priorities because they aim to prevent infections that contribute substantially to global mortality and vaccine candidates are either already in clinical trials or such trials are imminent. These include, in particular, vaccines to prevent RSV, *Shigella* and enterotoxigenic *Escherichia coli* (ETEC).

By fostering the clinical trials needed to demonstrate the safety, efficacy and practicality of a few high priority global market vaccines, impeded vaccines and developing market vaccines in populations in developing countries, the alliance partners can expedite the speed at which GAVI achieves its research and development objectives. This will require close collaboration and coordination among the major GAVI partners and will necessitate the active participation of many other partners that have expertise in undertaking research (in particular, clinical trials in developing countries).

6. Selecting global market, impeded and developing market vaccines for accelerated development and introduction

6.1 Factors to be considered

Multiple factors need to be taken into account in selecting vaccines that should be targeted for accelerated development *(7)*. Table 2 summarizes the various relevant parameters that must be considered in choosing which vaccines – global market, impeded or developing

market vaccines – should have their development accelerated by a concerted effort of the GAVI partners.

Arguably, extra weight should be given to vaccines that will prevent infectious diseases that are major causes of mortality. Figures 1 and 2 (published by the World Health Organization) show the most important causes of infectious disease burden – presented as disability adjusted life years (DALYs) – and of infectious-disease mortality worldwide in 1998.

It is clear that acute respiratory infections and diarrhoeal diseases constitute the two most important infectious disease killers of children under five years of age, of which the vast majority of deaths occur within the developing world. Although many etiologic agents can cause respiratory infections and diarrhoeal disease, a small number of agents are collectively responsible for the vast majority of deaths and hospitalizations from severe disease. The most important pathogens of endemic respiratory infection disease include *Streptococcus pneumoniae*, RSV, and *Haemophilus influenzae* type b. Indeed, vaccine probe studies in Africa and Latin America have convincingly demonstrated the importance of *Haemophilus influenzae* type b as a cause of severe pneumonia *(15, 16)*. Of lesser importance are some other bacterial pathogens, para-influenza viruses and adenovirus. During pandemics (and some epidemics) influenza becomes an important cause of respiratory disease mortality in young children (and in the elderly).

6.2 Respiratory infection vaccines in clinical development

A realistic expectation is that more than 75% of invasive pneumococcal disease and pneumococcal pneumonia may be prevented in immunized populations if the 9-valent and 11-valent pneumococcal conjugate vaccines that are currently being evaluated in several large-scale clinical trials in the developing world prove to be efficacious. One large-scale trial (in the Gambia) is addressing the efficacy of a 9-valent pneumococcal conjugate vaccine in preventing mortality; several trials are evaluating the efficacy of 9-valent and 11-valent vaccines in preventing pneumonia (Chile, Gambia, the Philippines, South Africa); and several trials (in Chile, Gambia, South Africa) are assessing the efficacy of the vaccine in preventing invasive pneumococcal disease. Two efficacy trials are also under way in special populations in industrialized countries (native Americans in the United States of America and Bedouins in Israel) that manifest many features of developing countries including a high incidence of invasive pneumococcal disease.

Several candidate RSV vaccines are in clinical trials. Since these are "impeded vaccines" the clinical trials in infants are moving at a cautious pace for bioethical reasons *(17)*. Even greater caution will have to be exercised in the step of initiating clinical trials in young infants in developing countries.

Influenza, which occurs in seasonal epidemics and undergoes frequent antigenic drifts every one to three years and pandemic-associated shifts every 10-30 years, is an elusive vaccine-preventable infection. Although antigenic variation remains the Achilles heel of all influenza vaccines, nevertheless, an important new development is the advent of a trivalent cold-adapted attenuated intranasal vaccine that showed a high level of efficacy in a field trial *(18)*. This nasal spray vaccine has proved to be practical for administering vaccine to children in developing – as well as industrialized – country settings *(19)*.

One would anticipate that, in the future, if immunization with vaccines to prevent pneumococcus, Hib and RSV disease could be widely implemented, the global childhood mortality burden from respiratory infections would be diminished by >50% and overall child mortality will be reduced by circa 15%.

Table 2: Various factors that must be taken into consideration in selecting certain vaccines for accelerated development

Disease burden
1. The magnitude of the disease burden: mortality; short-term morbidity; long-term morbidity.
Other public health issues
2. The public perception of the disease and the need for its control. 3. Whether alternative public health measures are available to prevent infection. 4. Whether an effective treatment exists. 5. Whether the prevalence of antimicrobial resistance in the pathogen is high or increasing. 6. Whether the disease has the potential to cause epidemics and pandemics (emerging/re-emerging infection). 7. Whether vaccination could regionally eliminate the disease. 8. Whether herd immunity would promote regional elimination of the disease.
Likelihood of return on private investment
9. Whether the projected rate of return on the private industrial investment will be comparable to other potential (competing) investments. 10. Whether travellers from industrialized countries could benefit from the vaccine, thereby creating a small but higher projected rate of return market.
Development and evaluation issues
11. Whether the science is sufficiently mature to generate rational vaccine candidates (is enough known about the microorganism, the human immune response to the agent and correlates of immunity?). 12. Complexity of the microbe. 13. Whether vaccine candidates are already in clinical trials or are imminent for transition to clinical trials. 14. Whether there exists the possibility of adverse consequences of which we are aware *a priori.* 15. Ease of design and performance of Phase III vaccine efficacy trials. 16. Ease of manufacture. 17. Concerns for deleterious non-target effects (e.g., survival in environment, hazard to unborn child of a pregnant individual or immunocompromised host, infection of non-human animals). 18. Whether the vaccine can be easily transported in the field (e.g., need for cold chain). 19. Whether the vaccine can be combined or concomitantly delivered with other vaccines through existing immunization services. 20. Whether the vaccine has characteristics that are particularly attractive for use in developing countries such as non-parenteral (e.g., mucosal or transcutaneous) administration, an immunization schedule that requires only 1-2 doses, and effectiveness in infants.
Implementation issues for a specific vaccine
21. Ease of manufacture. 22. Concerns for deleterious non-target effects (e.g., survival in environment, hazard to unborn child of a pregnant individual or immunocompromised host, infection of non-human animals). 23. Whether the vaccine can be easily transported to the field (e.g., need for cold chain). 24. Whether the vaccine can be combined or concomitantly delivered with other vaccines through existing immunization services. 25. Whether the vaccine has characteristics that are particularly attractive for use in developing countries such as non-parenteral (e.g., mucosal or transcutaneous) administration, an immunization schedule that

6.3 Relevant diarrhoeal disease vaccines in clinical development

A few enteropathogens, led by rotavirus, ETEC and *Shigella*, account for the majority of severe diarrhoeal disease and mortality in infants and young children worldwide *(20-23)*. Whereas deaths from rotavirus and ETEC are mainly consequent to diarrhoeal dehydration, deaths from *Shigella* dysentery are predominantly caused by complications other than dehydration *(23, 24)*, making *Shigella* mortality largely refractory to the benefits of oral rehydration *(23)*.

In pre-licensure trials in Finland, the USA, and Venezuela, a Rhesus tetravalent re-assortant rotavirus vaccine conferred a high level of efficacy in preventing more severe forms of rotavirus diarrhoea *(25-28)*. For approximately one year this vaccine was routinely administered to infants in the USA but this practice was discontinued when post-licensure surveillance revealed an association between administration of this vaccine and the occurrence of intussusception *(29-32)*. Since such an association has not been demonstrated with diarrhoeal infection caused by wild type human rotavirus *(33)*, other manufacturers are moving ahead with clinical development of other rotavirus vaccine candidates. One such vaccine (being developed by SmithKline Beecham) consists of an attenuated human strain of rotavirus *(34)*. The other (which is being developed by Merck) is a quadrivalent bovine re-assortant vaccine *(35)*. Another candidate vaccine that is moving towards clinical trials is an Indian rotavirus vaccine based on a "naturally attenuated" nursery strain *(36)*.

Conferring broad-spectrum protection against *Shigella* is a daunting task because immunity is related to serotype and there is extensive antigenic heterogeneity; there are 39 serotypes and sub-types, of which many are of epidemiological importance *(23)*. Thus, like pneumococcal vaccines, *Shigella* vaccines must be multivalent. Vaccine targets must include *S. dysenteriae* 1 (Shiga's bacillus, which causes epidemics and pandemics of severe disease), all or most of the 15 *S. flexneri* serotypes and sub-types (which are the main agents of endemic disease in developing countries), and *S. sonnei* (the main cause of traveller's shigellosis) *(23)*.

There are four leading candidate *Shigella* vaccines in clinical trials. One is a parenteral vaccine consisting of O-polysaccharides of *Shigella* conjugated to a carrier protein *(37, 38)*. Another is a non-living vaccine (given orally or intra-nasally) that consists of *Shigella* lipopolysaccharide non-covalently linked to group B *Neisseria meningitidis* outer membrane protein vesicles (proteosomes) *(39)*. The two other candidates are live oral vaccines that consist of genetically engineered attenuated strains of *Shigella* with attenuation based on the inactivation of selected virulence genes *(40, 41)*. Although, heretofore, clinical trials with these vaccines have been limited to monovalent or at most bivalent prototypes, clinical trials with multivalent formulations are planned.

Two ETEC vaccines are in clinical trials. By far the most advanced in development is a non-living vaccine consisting of five inactivated fimbriated ETEC strains that together express the most common ETEC fimbrial colonization factor antigens against which immunity is directed *(42, 43)*. This inactivated bacterial mixture is formulated in combination with the B subunit of cholera toxin (which stimulates antitoxin that cross reacts with the ETEC heat-labile enterotoxin elaborated by a proportion of wild type strains). The other ETEC vaccine, that is just entering clinical trials, is a multivalent live *Shigella*/ETEC hybrid vaccine. It consists of a mixture of five attenuated *Shigella* strains (serotypes *S. dysenteriae* 1, *S. flexneri* 2a, *S. flexneri* 3a, *S. flexneri* 6 and *S. sonnei*) *(44, 45)*, each expressing two ETEC fimbrial antigens and a mutant heat-labile enterotoxin *(46, 47)*.

If clinical trials of candidate rotavirus, ETEC and *Shigella* vaccines in infants and children in developing countries demonstrate their safety and their efficacy in preventing diarrhoeal disease, and if widespread use of such vaccines could be implemented, one would expect a marked diminution to ensue in the global mortality burden due to diarrhoeal disease.

A non-diarrhoeal enteric infection that is an important cause of mortality, as well as morbidity, is typhoid fever caused by *Salmonella enteric* serovar typhi. The widespread prevalence in South and South-East Asia and the Middle East of *S. typhi* that exhibit resistance to the most important – previously useful – oral antibiotics, has rekindled interest in improved vaccines to prevent typhoid fever *(48-50)*. Several attractive candidate vaccines are in clinical trials. A Vi polysaccharide conjugate vaccine is being evaluated in a Phase III efficacy trial in Viet Nam *(51)*. An attenuated *S. typhi* strain that shows promise as a single-dose live oral vaccine is in Phase II trials and is progressing towards a Phase III trial *(52, 53)*; two other attenuated strains have been evaluated in Phase I clinical trials *(54, 55)*.

6.4 Epidemic Group A meningococcal disease in sub-Saharan Africa

Within the countries that comprise the "meningococcal belt" there is a high public perception of the importance of meningococcal disease and local public health authorities have expressed their strong interest in having an improved vaccine for disease control *(56, 57)*. A quadrivalent meningococcal conjugate vaccine containing groups A, C, Y and W-135 conjugates is under development, as is a bivalent A-C conjugate. One solution in the future would be for GAVI to provide eligible countries with these multivalent meningococcal vaccines through the Global Fund for Children's Vaccines. However, the bivalent and quadrivalent conjugates will be more expensive per dose than a monovalent group A conjugate vaccine. Therefore, another approach is to develop a monovalent group A conjugate as a developing market vaccine. This is highly feasible since an immunologic correlate of protection exists (serum bactericidal antibody), the immunogenicity of some candidate group A conjugates has already been established *(58)*, and the technology to scale-up production can be adapted from experience with the licensed group C conjugate vaccines that are currently being used in the United Kingdom (assuming that the appropriate partnerships can be arranged). Together, these features make the accelerated development of a group A meningococcal conjugate a plausible and achievable goal. WHO has already taken significant strides to explore such a project.

7. Accelerating research and development efforts for vaccines and related products specifically needed by developing countries, particularly vaccines against HIV/AIDS, malaria and tuberculosis

7.1 Technical feasibility

A fundamental concept in vaccinology is that of "low-hanging fruit" versus "high-hanging fruit" among vaccines. Quite aside from any question of disease burden or finances, some vaccines are technically achievable and readily amenable to expedited clinical development because the pathogenesis of the causative agent is understood, there is little antigenic heterogeneity, protective human immune responses are recognized and no impediments preclude the performance of Phase I, II and III clinical trials. From the purview of technical feasibility, such vaccines are "low hanging fruit". Unfortunately, many of the most-needed developing market vaccines, such as a malaria vaccine, an improved tuberculosis vaccine and an AIDS vaccine, represent daunting and complex "high-hanging fruit" vaccine-development projects.

7.2 Synergistic mechanisms to "pull-and-push" the development of priority vaccines

With respect to three vaccines particularly needed by the developing world, AIDS, malaria and a new tuberculosis vaccine, the GAVI partners are trying to expedite research and development simultaneously from two distinct but synergistic avenues. GAVI's Financing Task Force is seeking ways to create strong market incentives, so-called "pull mechanisms", that will encourage industry to invest in research and development on these vaccines. In contrast, the pre-R&D Task Force began to address "push mechanisms" that rely on public sector actions and public sector/private industry collaborations to progress candidate vaccines through the phases of clinical development by directly contributing to allaying the costs of pilot-lot production and of performing clinical trials. For industry, these actions serve to diminish the overall financial risk of a vaccine development project. An important preliminary to being able to foster "push" mechanisms is to prepare an inventory of the global infrastructure (particularly in the public sector) that is available to perform vaccine development activities, and to identify components that need to be strengthened.

Some relevant components of the vaccine development infrastructure that can be manipulated as "push" mechanisms include:

- facilities that can prepare pilot-lot formulations of various types of vaccines (including different candidate malaria, AIDS and tuberculosis vaccines);
- sites in developing countries that can perform Phase I, II and III clinical trials;
- vaccine industry facilities in developing countries that can undertake large-scale production of some developing market vaccines that may be of little interest to vaccine manufacturers in industrialized countries.

In conjunction with the GAVI pre-R&D Task Force, several GAVI implementing partners, including the intercluster Vaccine Research Initiative of the World Health Organization (in particular, the Department of Vaccines and Biologics) and the Rockefeller Foundation, have been involved in compiling these inventories. The pre-R&D Task Force concluded that if ways could be found to economize the performance of clinical trials, while still adhering to the harmonized rules of Good Clinical Practice, this would constitute a particularly useful "push" mechanism.

7.3 Synergy and communication between GAVI task forces

Arguably, "push" mechanisms can most expeditiously speed the development of a candidate vaccine to the point of licensure. On the other hand, "pull" mechanisms offer the best chance that a newly licensed vaccine will in fact be introduced into public health programmes in developing countries and used in a sustainable manner. By maintaining close liaison, the GAVI Financing Task Force and the R&D Task Force can maximize the potential synergy of the two approaches.

7.4 Adding value

The nascent R&D Task Force must recognize that there already exist various international committees, advisory groups, non-governmental entities and consortia specifically devoted to expediting the development and testing of vaccines for AIDS, malaria and tuberculosis. Moreover, well-organized periodic international meetings are convened to exchange information and monitor the progress of research for each of these vaccines and their diseases.

Accordingly, for the task force to play a constructive, value-added role that avoids duplication, it should address the cross-cutting issues, obstacles and impediments common to the development of all three of these vaccines. Some cross-cutting examples include:

- capacity-building to perform pre-licensure clinical trials in developing countries and to undertake post-licensure effectiveness evaluations;
- increasing access to preparation of pilot-lot formulations; resolving intellectual property barriers to collaboration if they exist;
- extending the targets of vaccine research in developing countries beyond infants.

Considering the characteristics of certain AIDS and tuberculosis vaccines and recognizing that the mortality burden from AIDS and tuberculosis falls mainly among adults, it is likely that teenagers and adults will be the targets of future immunization programmes. Yet experience in carrying out extended vaccine trials and in mounting sustained immunization programmes in these age groups in the developing world is limited. Nevertheless, some positive experiences have been garnered, as with school-based field trials and immunization programmes with typhoid vaccines *(59-62)*.

8. Making immunization safer, more practical and logistically simpler

In developing countries, the practicalities and logistics of maintaining immunization services are demanding and the infrastructure is often fragile. Immunization coverage can be increased and subject compliance enhanced if the characteristics of new or improved vaccines or their modes of administration can decrease the number of health care contacts needed, diminish the stringency of cold-chain requirements, or make the administration of vaccine simpler.

Ideally, future vaccines should:

- be administered by non-parenteral (mucosal or trans-cutaneous) routes;
- require only one dose (or at most two doses) to elicit protection;
- be capable of immunizing very young infants (< 3 months of age);
- be available in formulations already combined with multiple other vaccines or combinable with other vaccines at the moment of administration;
- exhibit temperature stability to minimize (or perhaps even eliminate) the stringency of cold chain requirements.

By and large, the vaccine industry in industrialized countries is not aggressive in making substantial investments to develop vaccines that exhibit these characteristics because they are not critical for marketing in established industrialized country markets. The one exception is parenteral combination vaccines. Industry has invested enormously in preparing and testing combination parenteral vaccines to minimize the number of inoculations infants must receive to become fully immunized. Since most (albeit not all) of these combinations are directed towards industrialized country markets, the most ambitious hexavalent combinations contain antigens (e.g., acellular pertussis, inactivated polio) that are not relevant for use in developing countries.

Since the development of vaccines with the above characteristics (with the exception of combinations) is largely an orphan area of vaccine research – but one of immense impor-

tance to immunization in developing countries – the GAVI partners would do well to foster research in this broad area *(63)*. Several platform technologies have been developed in recent years that hold much theoretical potential to achieve the kinds of non-parenteral, multi-antigen combination vaccines that would be particularly useful for immunizing populations in developing countries. These include DNA vaccines *(64-66)*; bacterial live vector vaccines *(67, 68)* which can deliver DNA vaccines as well as expressed protein and polysaccharide antigens *(60-71)*, viral live vector vaccines *(72, 73)*, potent mucosal adjuvants that greatly enhance the immune response to mucosally delivered antigens *(74-77)*, replicons *(78)*, and some generic non-living antigen delivery systems *(39, 79)*.

9. The role of surveillance in vaccine research and development

Epidemiologic surveillance plays a fundamental role in vaccine research, as well as in disease control. The systematic collection of disease burden data helps direct vaccine development, allows sites to be prepared where field trials of efficacy of vaccines can be efficiently undertaken, and enables post-licensure assessments of vaccine effectiveness. The global microbiologic and epidemiologic infrastructures that allow these surveillance data to be gathered need strengthening. Moreover, for some vaccines of high interest to GAVI, such as Hib and pneumococcal conjugates, enormous gaps exist in our knowledge of disease burden caused by these pathogens in certain geographic areas (e.g., China and some other parts of Asia).

Surveillance is also a key to evaluating the performance of immunization services. Heretofore, assessments of the effectiveness of routine immunization programmes in developing countries have been mainly based on immunization surveys that estimate vaccine coverage. Yet from the epidemiologic perspective, this is only one component of the effectiveness of programmes. Ideally, the ability to undertake surveys that actually verify (in a practical, non-invasive way) immunoconversion following vaccination and quantify the prevalence of individuals of selected ages who possess protective titres of specific antibodies, together with the capacity to reliably measure the incidence of vaccine-targeted diseases, would greatly improve assessments of how well immunization services are performing. In individuals old enough to have teeth, technology currently exists to collect oral fluid (that contains gingival-crevicular fluid) to measure serum-derived IgG antibodies *(80-86)*. This provides a non-invasive, practical way of sampling serum antibodies without collecting blood. In the USA, a commercial test kit for diagnosis of HIV infection based on the detection of specific antibodies in oral fluids has been licensed for several years and has proven to be robust (87). Further research, development and field evaluation of technological advances such as these can help GAVI to further address its research and development objectives.

10. Vaccine safety

The very success of several vaccines in controlling disease in industrialized countries creates a situation where rare adverse reactions attributed to efficacious vaccines are increasingly becoming the focus of anti-vaccination groups and public controversy. In recent years, in a number of industrialized countries, some of the most important vaccines in the public health armamentarium have become the focus of strong criticism and negative publicity. This happened with whole-cell pertussis vaccines in the USA and some European countries in the 1970s and 1980s. More recently, the safety of vaccines for measles and measles/mumps/rubella has been impugned in the absence of credible incriminating scientific data *(88-90)*. Of late, the timing of infant immunization with DPT and Hib conjugate has been accused of an association with Type I diabetes *(91-93)*.

The information revolution leads issues that appear in the industrialized world to surface increasingly quickly in the developing world. The same may become true for vaccine safety issues. On the other hand, in the search for solutions to developing world problems, real safety issues sometimes arise. An example is the apparent increase in mortality among female children immunized at six months of age (i.e., three months below the usual WHO-recommended age) with high titre measles vaccine *(94-98)*. It therefore behoves the GAVI partners to increasingly consider safety issues in all aspects of the agenda that GAVI will follow in addressing its research and development agenda.

11. Marshalling resources to pursue the GAVI research objectives

It is expected that certain of the implementing GAVI partners that are involved in research will be able to increase or to redirect funding to specifically support some of the priority projects cited. In addition, the GAVI Governing Board can be solicited to recommend that financial resources be released through Window #3 (the Research and Development Window) of the Global Fund for Children's Vaccines to allow expedited performance of clinical trials in developing countries of rotavirus, pneumococcal conjugate, RSV, Shigella and ETEC vaccines (and perhaps also of group A meningococcal and typhoid vaccines).

Support for clinical trials of new respiratory and diarrhoeal disease vaccines will build new capacity in developing countries (and will strengthen existing capacity) for performing clinical trials of malaria, tuberculosis and AIDS vaccines. In addition, if the GAVI R&D Task Force determines that some of the gaps identified through surveys initiated by the Pre-Task Force require strengthening (e.g., facilities to prepare pilot-lot formulations, access to such facilities and sites to perform clinical trials), this will have to be addressed by the GAVI partners.

Whereas there are many needs, worthy goals and multiple potential solutions to address GAVI's broad objectives, resources are limited. There must thus be focus and priorities must be established. If a coherent strategy can be evolved with specific goals and timelines, some future donors may wish to contribute specifically to Window #3 of the Global Fund for Children's Vaccines to support activities that will allow GAVI's research and development objectives to be achieved. Alternatively – or in addition – some donors may contribute directly to certain implementing partners (that are identified as being the most suitable to undertake specific vaccine research and development activities) so that targeted high priority research activities can be expedited.

12. Large-scale production and supply of high priority vaccines

Even if increased resources allow the safety, efficacy and practicality of several high priority vaccines to be demonstrated in clinical trials in target populations in developing countries, and even if funds become available for the purchase of these vaccines for eligible countries, making sustainable arrangements for the production of these vaccines in quantities necessary for the developing world will be a complex undertaking. The experience with the Rhesus reassortant rotavirus vaccine, which was withdrawn after being routinely used in the US infant cohort for less than one year, leaves a legacy that will further complicate both decision-making and timing. It may be imagined that, henceforth, for some vaccines, international agencies and industry will exert caution before taking the decision to invest large amounts of capital in the construction of production facilities to produce vaccine for the developing world.

One option to alleviate this potential impasse to new vaccine introduction will be to invite, early on, the involvement of developing country vaccine industry to take significant respon-

sibility for the additional production needed to make the new vaccines available for the developing world. In instances where intellectual property for the vaccines in question belongs to industrialized country "big pharma" companies, suitable arrangements will have to be made among the parties to honour that property. It is anticipated that the Financing and R&D Task Forces respectively, with the input of various GAVI partners, will be able to devise ways to overcome the various legal and technical hurdles and allow such transfers of technology and capacity-building to proceed. It is envisioned that this will take place, in particular, in those developing countries that have a strong vaccine industrial base (e.g., Brazil, China, India, Indonesia).

13. A way forward: a strategy for GAVI to begin to address its research and development objectives

Having outlined many of the dilemmas, obstacles and options that GAVI faces in deciding how to address its research and development objectives, the following courses of action are proposed as a way to begin to move forward:

- Priority should be given by the GAVI partners to foster research and development of vaccines against diseases that constitute major causes of mortality among children (e.g., respiratory infections, diarrhoeal diseases, malaria, measles) and adults (respiratory infections, AIDS, tuberculosis) in the developing world.

- Priority should be given to fostering the accelerated development of candidate global market vaccines that currently exist, such as new rotavirus vaccines and 9-valent and 11-valent pneumococcal conjugate vaccines.

- Priority should be given to foster the accelerated development of a few highly feasible ("low-hanging fruit"), developing market vaccines. Prime candidates include group A meningococcal conjugate, new typhoid vaccines, *Shigella* and ETEC vaccines.

- Once the results of clinical trials in infants in industrialized countries demonstrate the safety of new RSV vaccine candidates, the GAVI partners should foster the accelerated development of these impeded vaccines in developing country infants.

- The development of the above-mentioned vaccines, as well as vaccines against AIDS, malaria and tuberculosis, should be accelerated by "push" mechanisms that will reduce the financial risk to industry of eventually assuming the downstream development, scale-up and production of these vaccines. "Push" mechanisms should include access to pilot-lot formulation for promising vaccine candidates, direct support for clinical trials, strengthening the infrastructure for the performance of field trials on the efficacy of various vaccines (particularly AIDS, malaria and tuberculosis) in developing countries, and brokering partnerships to resolve intellectual property obstacles.

- GAVI's R&D Task Force should coordinate closely with the Financing Task Force that will be stimulating the development of priority vaccines by "pull" mechanisms that create credible markets.

- The GAVI partners should advocate and support research and development of vaccines and vaccine technologies that increase safety, enhance practicality

(e.g., non-parenteral administration, fewer doses, temperature stability, combinability with other vaccine antigens) and efficacy (ability to immunize young infants, long duration of protection).

- In its research and development agenda, GAVI should encourage strict attention to relevant issues of vaccine safety.
- Emphasis should be placed on strengthening surveillance activities that will allow improved measurement of the disease burden from specific vaccine-targeted infectious diseases, improved microbiologic confirmation of infections, measurements of the immune status of populations using field-applicable, non-invasive methodologies.
- GAVI should promote the transfer of technology and capacity-building so that developing country vaccine industry in relevant countries can increasingly assume responsibility for providing the additional production needed to make certain new vaccines available for the developing world.

Figure 1: Burden of disease – all ages;
disability adjusted life years (DALYs) lost in 1998 due to infectious diseases

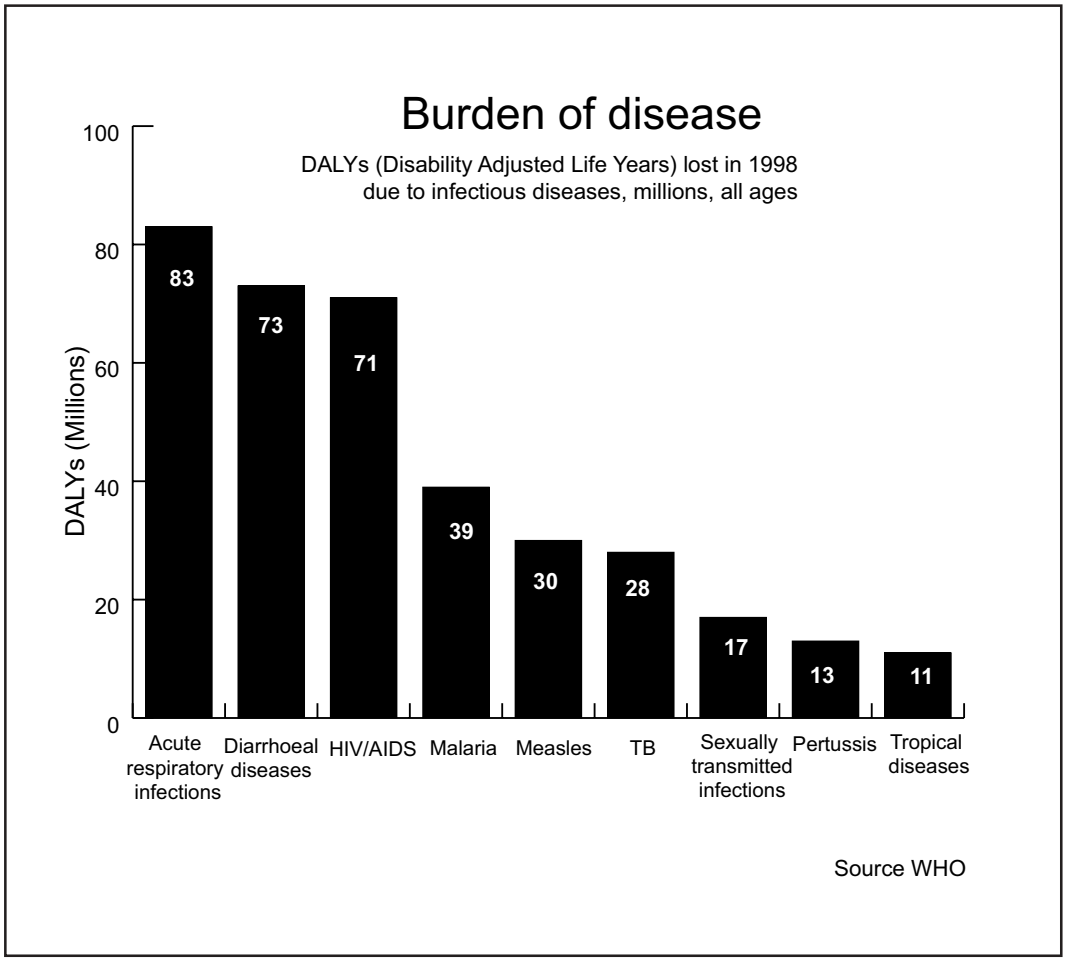
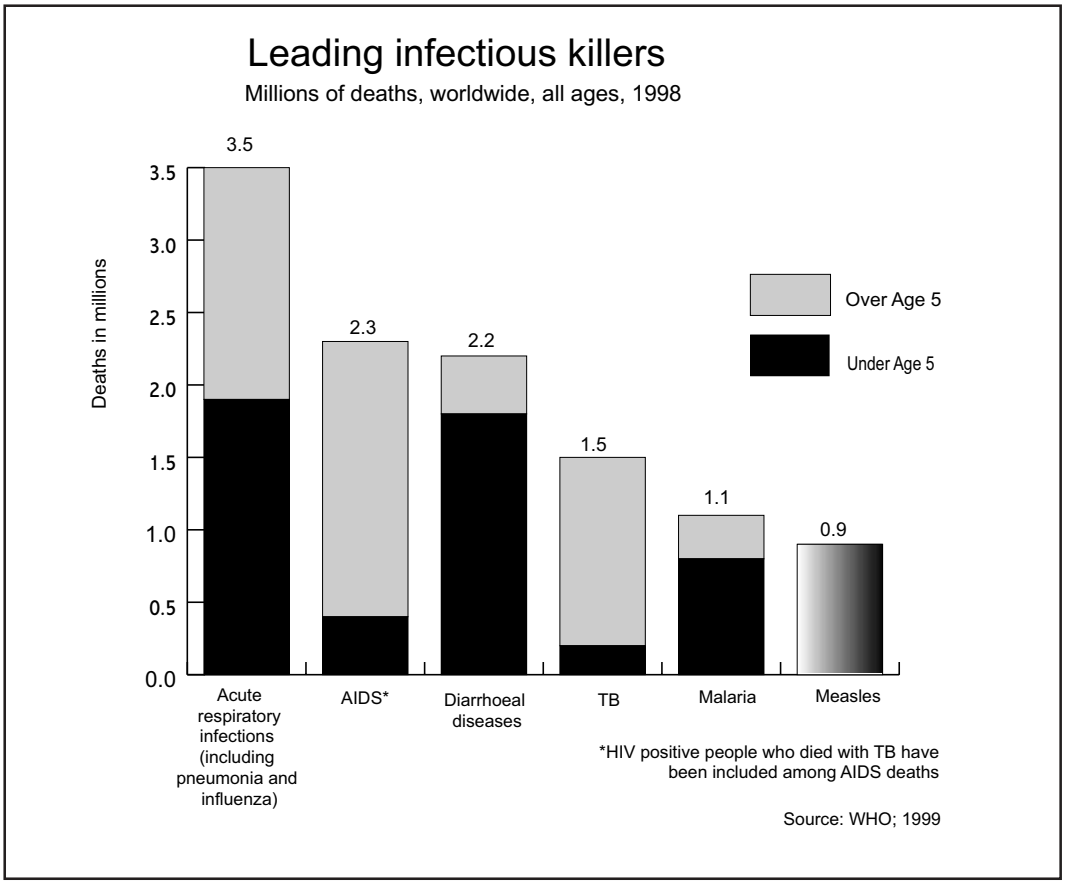


Figure 2: Leading infectious killers, worldwide, all ages, 1998



References

1. Robbins, A., Freeman, P., and Powell, K.R. 1993. International childhood vaccine initiative. *Pediatr.Infect.Dis.J.* 12:523-527.

2. Robbins, A. and Freeman, P. 1991. Children's Vaccine Initiative. *Lancet* 338:1006-1007.

3. Muraskin, W. 1996. Origins of the Children's Vaccine Initiative: the political foundations. *Soc.Sci.Med.* 42:1721-1734.

4. Muraskin, W. 1998. In *The politics of international health.* The Children's Vaccine Initiative and the struggle to develop vaccines for the Third World. State University of New York Press, Albany. 1-258.

5. Godal, T. 2000. Viewpoint: immunization against poverty. *Trop.Med.Int.Health* 5:160-166.

6. Batson, A. 1998. Win-win interactions between the public and private sectors. *Nat.Med.* 4:487-491.

7. Levine, M.M. and Levine, O.S. 1997. Influence of disease burden, public perception, and other factors on new vaccine development, implementation, and continued use. *Lancet* 350:1386-1392.

8. Kapikian, A.Z., Mitchell, R.H., Chanock, R.M., Shvedoff, R.A., and Stewart, C.E. 1969. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. *Am.J.Epidemiol.* 89:405-421.

9. Peter, G., des Vignes-Kendrick, M., Eickhoff, T.C., Fine, A., Galvin, V., Levine, M.M., Maldonado, Y.A., Marcuse, E.K., Monath, T.P., Osborn, J.E. et al. 1999. Lessons learned from a review of the development of selected vaccines. National Vaccine Advisory Committee. *Pediatrics* 104:942-950.

10. Fulginiti, V.A., Eller, J.J., Sieber, O.F., Joyner, J.W., Minamitani, M., Meiklejohn, G. 1969. Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. *Am.J Epidemiol.* 89:435-448.

11. Chin, J., Magoffin, R.L., Shearer, L.A., Schieble, J.H., and Lennette, E.H. 1969. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. *Am.J Epidemiol.* 89:449-463.

12. Massell, B.F., Honikman, L.H., and Amezcua, J. 1969. Rheumatic fever following streptococcal vaccination. Report of three cases. *JAMA* 207:1115-1119.

13. Vesikari, T. 1997. Rotavirus vaccines against diarrhoeal disease. *Lancet* 350:1538-1541.

14. Glass, R.I., Bresee, J.S., Parashar, U.D., Holman, R.C., and Gentsch, J.R. 1999. First rotavirus vaccine licensed: is there really a need? *Acta Paediatr.Suppl* 88:2-8.

15. Lagos, R., Valenzuela, M.T., Levine, O.S., Losonsky, G.A., Erazo, A., Wasserman, S.S., and Levine, M.M. 1998. Economisation of vaccination against Haemophilus influenzae type b: a randomised trial of immunogenicity of fractional-dose and two-dose regimens. *Lancet* 351:1472-1476.

16. Mulholland, K., Hilton, S., Adegbola, R., Usen, S., Oparaugo, A., Omosigho, C., Weber, M., Palmer, A., Schneider, G., Jobe, K. et al. 1997. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 349:1191-1197.

17. Karron, R.A., Wright, P.F., Crowe, J.E., Jr., Clements-Mann, M.L., Thompson, J., Makhene, M., Casey, R., and Murphy, B.R. 1997. Evaluation of two live, cold-passaged, temperature-sensitive respiratory syncytial virus vaccines in chimpanzees and in human adults, infants, and children. *J.Infect Dis.* 176:1428-1436.

18. Belshe, R.B., Mendelman, P.M., Treanor, J., King, J., Gruber, W.C., Piedra, P., Bernstein, D.I., Hayes, J., Kotloff, K., Zangwill, K. et al. 1998. Efficacy of trivalent live attenuated intranasal influenza vaccine in children. *N.Eng.J.Med.* In press.

19. King, J.C., Jr., Lagos, R., Bernstein, D.I., Piedra, P.A., Kotloff, K., Bryant, M., Cho, I., and Belshe, R.B. 1998. Safety and immunogenicity of low and high doses of trivalent live cold-adapted influenza vaccine administered intranasally as drops or spray to healthy children [In Process Citation]. *J.Infect Dis.* 177:1394-1397.

20. Huilan, S., Zhen, L.G., Mathan, M.M., Mathew, M.M., Olarte, J., Espejo, R., Khin Maung, U., Ghafoor, M.A., Khan, M.A., and Sami, Z. 1991. Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries. *Bull.Wld.Hlth.Org.* 69:549-555.

21. Black, R.E., Merson, M.H., Huq, I., Alim, A.R.M.A., and Yunus, M. 1981. Incidence and severity of rotavirus and *Escherichia coli* diarrhoea in rural Bangladesh. *Lancet* I:141-143.

22. Cunliffe, N.A., Kilgore, P.E., Bresee, J.S., Steele, A.D., Luo, N., Hart, C.A., Glass, R.I. 1998. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. *Bull.Wld.Hlth.Org.* 76:525-537.

23. Kotloff, K.L., Winickoff, J.P., Ivanoff, B., Clemens, J.D., Swerdlow, D.L., Sansonetti, P.J., Adak, G.K., and Levine, M.M. 1999. Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies. *Bull.Wld.Hlth.Org.* 77:651-666.

24. Bennish, M.L. 1991. Potentially lethal complications of shigellosis. *Rev.Infect Dis.* 13 Suppl 4:S319-24.

25. Rennels, M.B., Glass, R.I., Dennehy, P.H., Bernstein, D.I., Pichichero, M.E., Zito, E.T., Mack, M.E., Davidson, B.L., and Kapikian, A.Z. 1996. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines – report of the National Multicenter Trial. United States Rotavirus Vaccine Efficacy Group. *Pediatrics* 97:7-13.

26. Santosham, M., Moulton, L.H., Reid, R., Croll, J., Weatherholt, R., Ward, R., Forro, J., Zito, E., Mack, M., Brenneman, G. et al. 1997. Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations [see comments]. *J Pediatr.* 131:632-638.

27. Joensuu, J., Koskenniemi, E., Pang, X.L., and Vesikari, T. 1997. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. *Lancet* 350:1205-1209.

28. Perez-Schael, I., Guntinas, M.J., Perez, M., Pagone, V., Rojas, A.M., Gonzalez, R., Cunto, W., Hoshino, Y., and Kapikian, A.Z. 1997. Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. *N.Engl.J.Med.* 337 :1181-1187.

29. Abramson, J.S., Baker, C.J., Fisher, M.C., Gerber, M.A., Meissner, H.C., Murray, D.L., Overturf, G.D., Prober, C.G., Rennels, M.B., Saari, T.N. et al. 1999. Possible association of intussusception with rotavirus vaccination. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics* 104:575.

30. Rennels, M.B. 2000. The rotavirus vaccine story: a clinical investigator's view. *Pediatrics* 106:123-125.

31. 1999. Centers for Disease Control and Prevention. Withdrawal of rotavirus vaccine recommendation. *JAMA* 282:2113-2114.

32. 1999. Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine – United States, 1998-1999. *JAMA* 282:520-521.

33. Rennels, M.B., Parashar, U.D., Holman, R.C., Le, C.T., Chang, H.G., and Glass, R.I. 1998. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. *Pediatr.Infect Dis J* 17:924-925.

34. Bernstein, D.I., Sack, D.A., Rothstein, E., Reisinger, K., Smith, V.E., O'Sullivan, D., Spriggs, D.R., and Ward, R.L. 1999. Efficacy of live, attenuated, human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. *Lancet* 354:287-290.

35. Clark, H.F., Offit, P.A., Ellis, R.W., Eiden, J.J., Krah, D., Shaw, A.R., Pichichero, M., Treanor, J.J., Borian, F.E., Bell, L.M. et al. 1996. The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. *J Infect Dis* 174 Suppl 1:S73-S80.

36. Cunliffe, N.A., Das, B.K., Ramachandran, M., Bhan, M.K., Glass, R.I., Gentsch, J.R. 1997. Sequence analysis demonstrates that VP6, NSP1 and NSP4 genes of Indian neonatal rotavirus strain 116E are of human origin. *Virus Genes* 15:39-44.

37. Cohen, D., Ashkenazi, S., Green, M.S., Gdalevich, M., Robin, G., Slepon, R., Yavzori, M., Orr, N., Block, C., Ashkenazi, I. et al. 1997. Double-blind vaccine-controlled randomised efficacy trial of an investigational *Shigella sonnei* conjugate vaccine in young adults. *Lancet* 349:155-159.

38. Ashkenazi, S., Passwell, J.H., Harlev, E., Miron, D., Dagan, R., Farzan, N., Ramon, R., Majadly, F., Bryla, D.A., Karpas, A.B. et al. 1999. Safety and immunogenicity of *Shigella sonnei* and *Shigella flexneri* 2a O-specific polysaccharide conjugates in children. *J.Infect Dis.* 179:1565-1568.

39. Lowell, G.H. 1997. Proteosomes for improved nasal, oral or injectable vaccines. In *New Generation Vaccines*. M.M.Levine , Woodrow, G.C., Kaper, J.B., and Cobon, G.S., editors. Marcel Dekker, New York. 193-206.

40. Kotloff, K.L., Noriega, F.R., Samandari, T., Sztein, M.B., Losonsky, G.A., Nataro, J.P., Picking, W.D., Barry, E.M., and Levine, M.M. 2000. *Shigella flexneri* 2a Strain CVD 1207, with Specific Deletions in virG, sen, set, and guaBA, Is Highly Attenuated in Humans. I*nfect Immun* 68:1034-1039.

41. Coster, T.S., Hoge, C.W., VanDeVerg, L.L., Hartman, A.B., Oaks, E.V., Venkatesan, M.M., Cohen, D., Robin, G., Fontaine-Thompson, A., Sansonetti, P.J. et al. 1999. Vaccination against shigellosis with attenuated *Shigella flexneri* 2a strain SC602. *Infect.Immun.* 67:3437-3443.

42. Savarino, S.J., Brown, F.M., Hall, E., Bassily, S., Youssef, F., Wierzba, T., Peruski, L., El-Masry, N.A. , Safwat, M., Rao, M. et al. 1998. Safety and immunogenicity of an oral, killed enterotoxigenic *Escherichia coli*-cholera toxin B subunit vaccine in Egyptian adults. *J.Infect.Dis.* 177:796-799.

43. Savarino, S.J., Hall, E.R., Bassily, S., Brown, F.M., Youssef, F., Wierzba, T.F., Peruski, L., El-Masry, N.A. , Safwat, M., Rao, M. et al. 1999. Oral, inactivated, whole cell enterotoxigenic Escherichia coli plus cholera toxin B subunit vaccine: results of the initial evaluation in children. PRIDE Study Group. *J.Infect.Dis.* 179:107-114.

44. Noriega, F.R., Liao, F.M., Maneval, D.R., Ren, S., Formal, S.B., and Levine, M.M. 1999. Strategy for cross-protection among *Shigella flexneri* serotypes. *Infect.Immun.* 67:782-788.

45. Levine, M.M. 2000. Immunization against bacterial diseases of the intestine. *J.Pediatr.Gastroenterol.Nutr.* In press.

46. Noriega, F.R., Losonsky, G., Wang, J.Y., Formal, S.B., and Levine, M.M. 1996. Further characterization of ΔaroA, ΔvirG *Shigella flexneri* 2a strain CVD 1203 as a mucosal *Shigella* vaccine and as a live vector vaccine for delivering antigens of enterotoxigenic *Escherichia coli*. *Infect.Immun.* 64:23-27.

47. Koprowski, H., Levine, M.M., Anderson, R.J., Losonsky, G., Pizza, M., and Barry, E.M. 2000. Attenuated *Shigella flexneri* 2a vaccine strain CVD 1204 expressing colonization factor antigen I and mutant heat-labile enterotoxin of enterotoxigenic *Escherichia coli*. *Infect Immun* 68:4884-4892.

48. Ivanoff, B. and Levine, M.M. 1997. Typhoid fever: Continuing challenges from a resilient bacterial foe. *Bull.Inst.Pasteur* 95:129-142.

49. Bhutta, Z.A., Naqvi, S.H., Razzaq, R.A., and Farooqui, B.J. 1991. Multidrug-resistant typhoid in children: presentation and clinical features. *Rev.Infect.Dis.* 13:832-836.

50. Rowe, B., Ward, L.R., and Threlfall, E.J. 1997. Multidrug-resistant *Salmonella typhi:* a worldwide epidemic. *Clin.Infect.Dis.* 24 Suppl 1:S106-9.

51. Kossaczka, Z., Lin, F.Y., Ho, V.A., Thuy, N.T., Van Bay, P., Thanh, T.C., Khiem, H.B., Trach, D.D., Karpas, A., Hunt, S. et al. 1999. Safety and immunogenicity of Vi conjugate vaccines for typhoid fever in adults, teenagers, and 2- to 4-year-old children in Viet Nam. *Infect Immun* 67:5806-5810.

52. Tacket, C.O., Sztein, M.B., Losonsky, G.A., Wasserman, S.S., Nataro, J.P., Edelman, R., Pickard, D., Dougan, G. , Chatfield, S.N., and Levine, M.M. 1997. Safety of live oral *Salmonella typhi* vaccine strains with deletions in htrA and aroC aroD and immune response in humans. *Infect.Immun.* 65:452-456.

53. Tacket, C.O., Sztein, M.B., Wasserman, S.S., Losonsky, G., Kotloff, K.L., Wyant, T.L., Nataro, J.P., Edelman, R., Perry, J., Bedford, P. et al. 2000. Phase 2 Clinical Trial of Attenuated *Salmonella enterica* Serovar Typhi Oral Live Vector Vaccine CVD 908-htrA in U.S. Volunteers. *Infect Immun* 68:1196-1201.

54. Hohmann, E.L., Oletta, C.A., Killeen, K.P., and Miller, S.I. 1996. phoP/phoQ-deleted *Salmonella typhi* (Ty800) is a safe and immunogenic single-dose typhoid fever vaccine in volunteers. *J Infect Dis* 173:1408-1414.

55. Tacket, C.O., Kelly, S.M., Schodel, F., Losonsky, G., Nataro, J.P., Edelman, R., Levine, M.M., and Curtiss, R., III. 1997. Safety and immunogenicity in humans of an attenuated *Salmonella typhi* vaccine vector strain expressing plasmid-encoded hepatitis B antigens stabilized by the ASD balanced lethal system. *Infect.Immun.* 65:3381-3385.

56. Peltola, H. 2000. Emergency or routine vaccination against meningococcal disease in Africa? *Lancet* 355:3.

57. Miller, M.A., Wenger, J., Rosenstein, N., and Perkins, B. 1999. Evaluation of meningococcal meningitis vaccination strategies for the meningitis belt in Africa. *Pediatr.Infect Dis J* 18:1051-1059.

58. Campagne, G., Garba, A., Fabre, P., Schuchat, A., Ryall, R., Boulanger, D., Bybel, M., Carlone, G., Briantais, P., Ivanoff, B. et al. 2000. Safety and immunogenicity of three doses of a *Neisseria meningitidis* A + C diphtheria conjugate vaccine in infants from *Niger. Pediatr.Infect Dis J* 19 :144-150.

59. Bodhidatta, L., Taylor, D.N., Thisyakorn, U., and Echeverria, P. 1987. Control of typhoid fever in Bangkok, Thailand, by annual immunization of school children with parenteral typhoid fever. *Rev.Infect.Dis.* 9:841-845.

60. Levine, M.M., Ferreccio, C., Black, R.E., Germanier, R., and Chilean Typhoid Committee. 1987. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. *Lancet* 1:1049-1052.

61. Ferreccio, C., Levine, M.M., Rodriguez, H., and Contreras, R. 1989. Comparative efficacy of two, three, or four doses of Ty21a live oral typhoid vaccine in enteric-coated capsules: a field trial in an endemic area. *J.Infect.Dis.* 159:766-769.

62. Levine, M.M., Ferreccio, C., Abrego, P., Martin, O.S., Ortiz, E., and Cryz, S. 1999. Duration of efficacy of ty21a, attenuated salmonella typhi live oral vaccine. *Vaccine* 17 Suppl 2:S22-S27.

63. Levine, M.M. and Dougan, G. 1998. Optimism over vaccines administered via mucosal surfaces. *Lancet* 351:1375-1376.

64. Liu, M.A. 1998. Vaccine developments. *Nat.Med.* 4:515-519.

65. Huygen, K. 1998. DNA vaccines: application to tuberculosis. *Int.J Tuberc.Lung Dis* 2:971-978.

66. Ferreira, G.N., Monteiro, G.A., Prazeres, D.M., and Cabral, J.M. 2000. Downstream processing of plasmid DNA for gene therapy and DNA vaccine applications. T*rends Biotechnol* 18:380-388.

67. Galen, J.E., Gomez-Duarte, O.G., Losonsky, G.A., Halpern, J.L., Lauderbaugh, C.S., Kaintuck, S., Reymann, M.K., and Levine, M.M. 1997. A murine model of intranasal immunization to assess the immunogenicity of attenuated *Salmonella typhi* live vector vaccines in stimulating serum antibody responses to expressed foreign antigens. *Vaccine* 15:700-708.

68. Barletta, R., Snapper, S., Cirillo, J., Connell, N., Kim, D., Jacobs, W., and Bloom, B. 1990. Recombinant BCG as a candidate oral vaccine vector. *Res.Microbiol.* 141:931-940.

69. Darji, A., Guzman, C.A., Gerstel, B., Wachholz, P., Timmis, K.N., Wehland, J., Chakraborty, T., and Weiss, S. 1997. Oral somatic transgene vaccination using attenuated *S. typhimurium*. Cell 91:765-775.

70. Pasetti, M.F., Anderson, R.J., Noriega, F.R., Levine, M.M., and Sztein, M.B. 1999. Attenuated ΔguaBA *Salmonella typhi* vaccine strain CVD 915 as a live vector utilizing prokaryotic or eukaryotic expression systems to deliver foreign antigens and elicit immune responses. *Clin.Immunol.* 92:76-89.

71. Anderson, R., Pasetti, M.F., Sztein, M.B., and Levine, M.M.N.F.N. 2000. ΔguaBA attenuated *Shigella flexneri* 2a strain CVD 1204 as a *Shigella* vaccine and as a live mucosal delivery system for fragment C of tetanus toxin. *Vaccine* 18:2193-2202.

72. Lubeck, M.D., Natuk, R., Myagkikh, M., Kalyan, N., Aldrich, K., Sinangil, F., Alipanah, S., Murthy, S.C., Chanda, P.K., Nigida, S.M., Jr. et al. 1997. Long-term protection of chimpanzees against high-dose HIV-1 challenge induced by immunization. *Nat.Med.* 3:651-658.

73. Gonin, P., Oualikene, W., Fournier, A., and Eloit, M. 1996. Comparison of the efficacy of replication-defective adenovirus and Nyvac poxvirus as vaccine vectors in mice. *Vaccine* 14:1083-1087.

74. Rappuoli, R., Pizza, M., Douce, G., and Dougan, G. 1999. Structure and mucosal adjuvanticity of cholera and *Escherichia coli* heat-labile enterotoxins. *Immunol.Today* 20:493-500.

75. Douce, G., Giannelli, V., Pizza, M., Lewis, D., Everest, P., Rappuoli, R., and Dougan, G. 1999. Genetically detoxified mutants of heat-labile toxin from *Escherichia coli* are able to act as oral adjuvants. *Infect Immun* 67:4400-4406.

76. Partidos, C.D., Pizza, M., Rappuoli, R., and Steward, M.W. 1996. The adjuvant effect of a non-toxic mutant of heat-labile enterotoxin of *Escherichia coli* for the induction of measles virus-specific CTL responses after intranasal co-immunization with a synthetic peptide. *Immunology* 89:483-487.

77. Agren, L.C., Ekman, L., Lowenadler, B., and Lycke, N.Y. 1997. Genetically engineered nontoxic vaccine adjuvant that combines B cell targeting with immunomodulation by cholera toxin A1 subunit. *J.Immunol.* 158:3936-3946.

78. Davis, N.L., Caley, I.J., Brown, K.W., Betts, M.R., Irlbeck, D.M., McGrath, K.M., Connell, M.J., Montefiori, D.C., Frelinger, J.A., Swanstrom, R. et al. 2000. Vaccination of macaques against pathogenic simian immunodeficiency virus with Venezuelan equine encephalitis virus replicon particles. *J Virol.* 74:371-378.

79. Gluck, R., Mischler, R., Durrer, P., Furer, E., Lang, A.B., Herzog, C., and Cryz, S.J., Jr. 2000. Safety and immunogenicity of intranasally administered inactivated trivalent virosome-formulated influenza vaccine containing *Escherichia coli* heat-labile toxin as a mucosal adjuvant. *J Infect Dis* 181:1129-1132.

80. Emmons, W. 1997. Accuracy of oral specimen testing for human immunodeficiency virus. *Am.J Med.* 102:15-20.

81. George, J.R. and Fitchen, J.H. 1997. Future applications of oral fluid specimen technology. *Am.J Med.* 102:21-25.

82. Gallo, D., George, J.R., Fitchen, J.H., Goldstein, A.S., and Hindahl, M.S. 1997. Evaluation of a system using oral mucosal transudate for HIV-1 antibody screening and confirmatory testing. OraSure HIV Clinical Trials Group. *JAMA* 277:254-258.

83. Brown, D.W., Ramsay, M.E., Richards, A.F., and Miller, E. 1994. Salivary diagnosis of measles: a study of notified cases in the United Kingdom, 1991-3 [see comments]. *BMJ* 308:1015-1017.

84. Behets, F.M., Edidi, B., Quinn, T.C., Atikala, L., Bishagara, K., Nzila, N., Laga, M., Piot, P., Ryder, R.W., and Brown, C.C. 1991. Detection of salivary HIV-1-specific IgG antibodies in high-risk populations in Zaire. *J Acquir.Immune.Defic.SynDr* 4:183-187.

85. Nokes, D.J., Nigatu, W., Abebe, A., Messele, T., Dejene, A., Enquselassie, F., Vyse, A., Brown, D., and Cutts, F.T. 1998. A comparison of oral fluid and serum for the detection of rubella-specific antibodies in a community study in Addis Ababa, Ethiopia. *Trop.Med.Int.Health* 3:258-267.

86. Nokes, D.J., Enquselassie, F., Vyse, A., Nigatu, W., Cutts, F.T., and Brown, D.W. 1998. An evaluation of oral-fluid collection devices for the determination of rubella antibody status in a rural Ethiopian community. *Trans.R.Soc.Trop.Med.Hyg.* 92:679-685.

87. U.S.Department of Health and Human Services. 1996. FDA approves first HIV home test system. *HHS News* 96-100.

88. Wakefield, A.J., Murch, S.H., Anthony, A., Linnell, J., Casson, D.M., Malik, M., Berelowitz, M., Dhillon, A.P., Thomson, M.A., Harvey, P. et al. 1998. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 351:637-641.

89. Thompson, N.P., Montgomery, S.M., Pounder, R.E., and Wakefield, A.J. 1995. Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 345:1071-1074.

90. Chen, R.T. and DeStefano, F. 1998. Vaccine adverse events: casual or coincidental? *Lancet* 351:611-612.

91. Classen, J.B. and Classen, D.C. 1999. Association between type 1 diabetes and Hib vaccine. Causal relation is likely [letter; comment]. *BMJ* 319:1133.

92. Classen, J.B. and Classen, D.C. 1999. Immunization in the first month of life may explain decline in incidence of IDDM in The Netherlands. *Autoimmunity* 31:43-45.

93. Classen, J.B. and Classen, D.C. 1999. Public should be told that vaccines may have long term adverse effects. *BMJ* 318:193.

94. Aaby, P., Samb, B., Simondon, F., Whittle, H., Seck, A.M., Knudsen, K., Bennett, J., Markowitz, L., and Rhodes, P. 1991. Child mortality after high-titre measles vaccines in Senegal: the complete data set. *Lancet* 338:1518-1519.

95. Aaby, P., Samb, B., Simondon, F., Knudsen, K., Seck, A.M., Bennett, J., and Whittle, H. 1993. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am.J.Epidemiol.* 138:746-755.

96. Aaby, P., Samb, B., Simondon, F., Knudsen, K., Seck, A.M., Bennett, J., Markowitz, L., Rhodes, P., and Whittle, H. 1994. Sex-specific differences in mortality after high-titre measles immunization in rural Senegal. *Bull.Wld.Hlth.Org.* 72:761-770.

97. Holt, E.A., Moulton, L.H., Siberry, G.K., and Halsey, N.A. 1993. Differential mortality by measles vaccine titer and sex. *J.Infect.Dis.* 168:1087-1096.

98. Halsey, N.A. 1993. Increased mortality after high titer measles vaccines: too much of a good thing. *Pediatr.Infect.Dis.J.* 12:462-465.

Annex 3c

Slide presentation on the role and goals of the Task Force

(Prepared and presented by Dr Peter Wilson, GAVI consultant)

GAVI R&D Task Force
Terms of Reference

Presentation to the GAVI Board

19 November

GAVI Global Alliance for Vaccines and Immunization

Members of the R&D Task Force

Co-Chairs	
Academia	Dr Myron Levine
Industry	Dr Rino Rappuoli
WHO	Dr Yasuhiro Suzuki
Members	
Ghana	Dr Fred Binka
USA	Dr Barry Bloom
Chile	Dr Rosanna Lagos
Australia	Sir Gustav Nossal
Thailand	Dr Punnee Pitisuttithum

GAVI Global Alliance for Vaccines and Immunization

Slide presentation on roles and goals of the R&D Task Force *(continued)*

The responsibility of the R&D Task Force is to:

Catalyse action in support of GAVI's overall Objectives 3&4:

- Accelerate the development and introduction of new vaccines and technologies
- Accelerate R&D efforts for vaccines needed primarily in developing countries

Effectively mobilize, in support of these R&D efforts, the:

- Knowledge
- Resources
- Assets – tangible and intangible of the GAVI partners

GAVI Global Alliance for Vaccines and Immunization

Specific goals of the R&D Task Force

Catalyse action and coordinate global initiatives for:

- A limited number of **disease-specific programmes** which can most effectively contribute to the Task Force's ultimate goals

- Development of a limited number of **new technologies** which will improve safety, effectiveness, utility or performance of immunization in developing countries

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Slide presentation on roles and goals of the R&D Task Force *(continued)*

Sub goals & activities

Capacity-building in developing countries, e.g.

- Improve the IT infrastructure for better management of immunization services
- Involve the private sector in R&D initiatives
- Foster pilot lot production capacity

Conduct research in developing countries

- Applied field research to assess the effectiveness of vaccines on disease burden
- Operational research to improve effectiveness, safety and delivery of immunization services

Promote private/public sector partnerships

Establish forums for policy and information sharing

GAVI Global Alliance for Vaccines and Immunization

Criteria for selection of projects

Over-riding: No currently registered vaccine,
Or existing vaccine has drawbacks which severely limit its utility

- High potential impact
- High probability of success in short/medium term
- High programme feasibility
- Potential for improving immunization system
- Strategic gap
- Non-availability of alternative solutions

GAVI Global Alliance for Vaccines and Immunization

Slide presentation on roles and goals of the R&D Task Force *(continued)*

Project selection

The first stage projects will pave the way for more difficult projects in the future

Initial focus:
- 3 disease-specific projects;
- Up to 3 new technologies.

- High impact;
- Near-term;
- High probability of success.

Lay the path, establish mechanisms, build capacity, develop partnership and funding models

Second stage
More difficult projects

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Candidate diseases

HIV/AIDS

Malaria

Tuberculosis

Streptococcus pneumoniae

Rotavirus

***Neisseria meningitidis* A (and C)**

Shigella

Respitory syncytial virus (RSV)

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Slide presentation on roles and goals of the R&D Task Force *(continued)*

Evaluation of the candidate diseases against the criteria

The R&D Task Force evaluated each of the diseases against the criteria.
The results can be grouped into 3 disease categories.
"H" indicates the category scoring highest for that criteria.

Criteria	HIV/TB/ Malaria	Pnuemo/ Rota / Men A/C	Shigella/ RSV
Potential impact – adults	H		
– paediatric		H	
Probability of short-term technical success		H	
Program feasibility		H	
Capacity-building/change initiation		H	
Needs gap (who else)			H

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New technologies

The R&D Task Force will seek out and evaluate candidate technologies which will improve the following aspects of immunization in developing countries:

- Safety
- Effectiveness
- Utility
- Performance
- Access

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Slide presentation on roles and goals of the R&D Task Force *(continued)*

Method of choice of new technologies

1. Seek out candidate technologies
   - Seek proposals through partners' network
   - Public advertisement
2. Convene meeting of experts
3. Evaluate candidates versus criteria
4. Proposal to the Board

Suggested technology areas of initial focus:

1. Those that will increase access to immunization and safety of vaccination
2. Those that improve immunization services and disease surveillance

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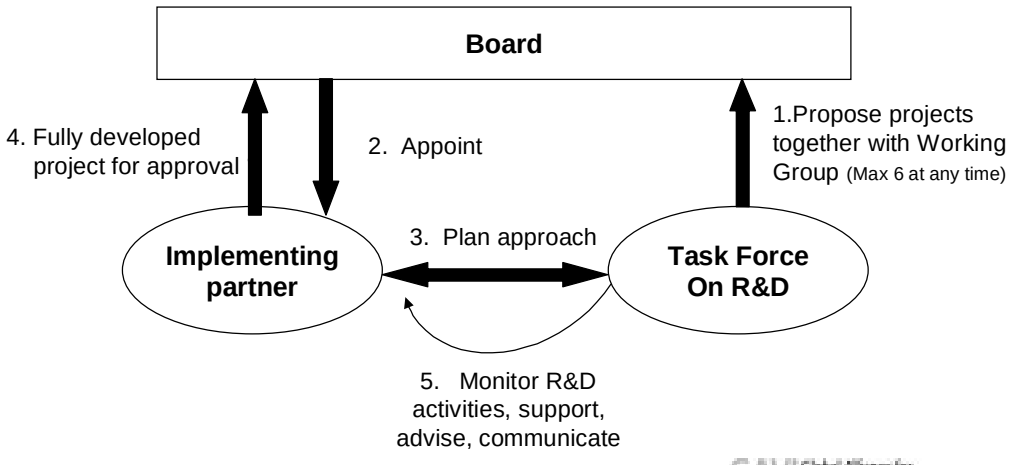
Role of the R&D Task Force in relation to the Board and implementating partner



GAVI Global Alliance for Vaccines and Immunization

Slide presentation on roles and goals of the R&D Task Force *(continued)*

Summary

Goals :	Catalyse action & coordinate global initiatives for: 3 disease-specific projects, 3 new technologies	
Sub-goals:	Capacity-building & research, public/private partnerships Policy dialogue & information sharing	
Criteria:	High impact, near-term, high probability of success	
TF's role in Projects:	Project identification: Planning: Implementation:	Primary Catalysing support Monitoring and support
Projects:	Pneumo, Rota, Men A/C New technologies – still to be determined	

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Role of R&D Task Force in the 3 project stages

Role focuses on R&D projects and the R&D aspects of those projects

Identification	Identify *highest priority* candidates Evaluation Recommend projects to Board
Planning	Jointly work with implementing partner to: Identify key R&D gaps/barriers Plan how to address gaps/barriers Evaluate alternative project structures Set up R&D agenda & timetable
Implementation	

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Slide presentation on roles and goals of the R&D Task Force *(continued)*

Goals of the R&D Task Force

- Reduce mortality and morbidity in developing countries from diseases for which there is either no currently available vaccine or the existing vaccines have important drawbacks that severely limit their usefulness

- Improve the safety and performance of immunization services through R&D initiatives

Coordination of responsibilities with other task forces

Push initiatives:	Mainly R&D Task Force
Pull initiatives	Mainly Task Force on Finance

Sometimes difficult & unnecessary to differentiate

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Criteria for choice of new technologies

Similar criteria to that used for disease-specific projects:

- Potential impact – safety, effectiveness, access, utility, performance
- High probability of success – short/medium time-frame
- Need/strategic gap
- Non-availability of alternative solutions
- Potential for changing/improving the immunization system for the future
- Programmatic feasibility
- Preference to R&D on technologies being conducted in developing countries

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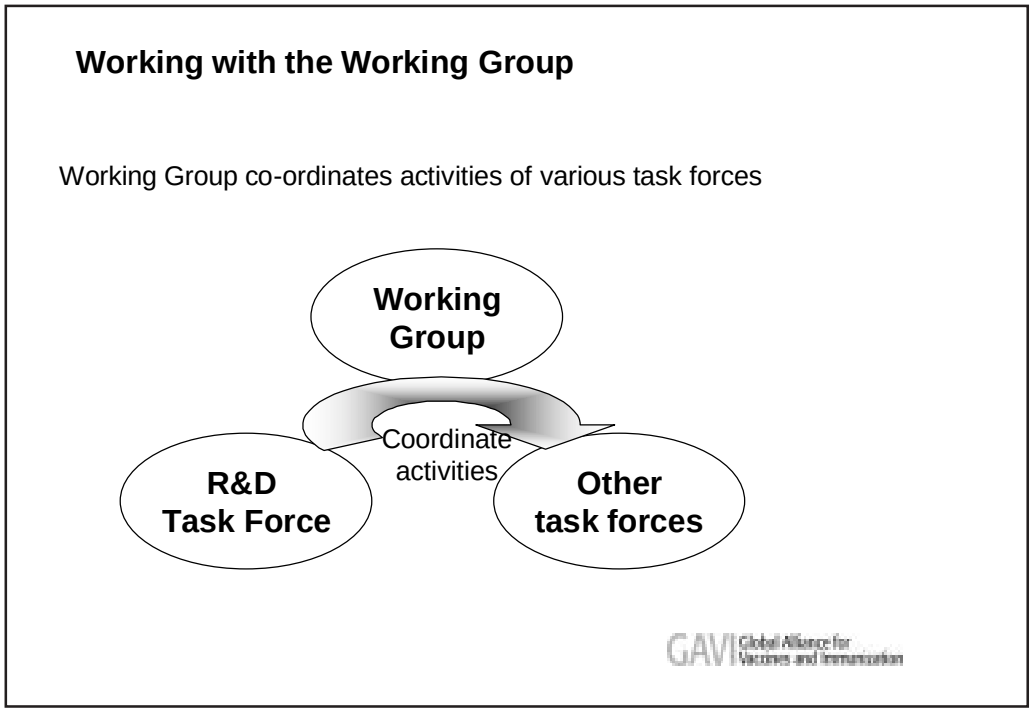
Slide presentation on roles and goals of the R&D Task Force *(continued)*



Annex 4

Improved immunization systems, products, and technologies

Discussion material on agenda item 4

This annex comprises:

- Annex 4a: Improved immunization systems, products, and technologies: a proposal on the evolution of GAVI – Developed by the GAVI Working Group and presented by Dr Mark Kane, the proposal outlines areas of research that could benefit from a GAVI-wide approach. The Board was requested:
  (a) to consider the principles outlined and to work with the Global Fund on the use of the third sub-account to address specific bottlenecks, and
  (b) to endorse the selection of the three vaccine products for development into full proposals.
- Annex 4b: A slide presentation on a Financing Task Force to provide financial expert support to GAVI product objectives, prepared and presented by Ms Amie Batson, World Bank

Annex 4a

Improved immunization systems, products and technologies: a proposal on the evolution of GAVI

(Prepared by the GAVI Working Group)

Introduction

As GAVI moves into its second year, it is perhaps useful to stop for a moment and take stock of what we have accomplished, what gaps still remain, and where we are going in the next 5-10 years. Clearly, the first year of GAVI was one of the most exciting – and exhausting – years in the memory of those who are devoted to public health immunization. Thanks to the generosity of partners, particularly the Gates Foundation, we have established the Global Fund, giving us some money "in the bank". We have also established processes for working better with governments in developing countries and have mobilized the "political will" to significantly impact the gaps of access to immunization and the introduction of important new and under-used vaccines. The hard work is ahead of us as we try to improve immunization access in the poorest countries of the world. In addition, while the bulk of our efforts over the last year have focused on the 74 poorest countries, we recognize the need to devote more of the GAVI partners' time and attention toward the problems, needs and solutions of middle-income countries.

Although the access to immunization and the introduction of new and under-used vaccine "gaps" are beginning to be addressed by the concerted efforts of governments and partners, we have a great deal more work to do to support these efforts. We need to strengthen many aspects of country-level immunization systems with better management, reaching the unreached, and the introduction of new technologies including new vaccines. In addition, we need to define how GAVI will address the third gap – enabling research and development into new vaccines and technologies that primarily benefit the developing world. If we had effective vaccines for HIV/AIDS, malaria and tuberculosis tomorrow, we would face monumental problems with sustainable financing and delivery of these products. The GAVI process is the primary tool for developing the financing mechanisms and strengthening the delivery systems needed for the future. At the same time, these projects represent excellent opportunities for capacity-building, both for research and for the strengthening of services.

As proposed by Mr Jean-Jacques Bertrand and Dr Timothy Cooke at the Oslo GAVI Board Meeting, we believe that the most effective approach that GAVI could make to address the "three gaps" would be to define a small number of specific projects with the goal of expediting the availability of the highest priority vaccines and delivery technologies, and ensuring the implementation of the improvements to infrastructure that we would like to see in the next 5-10 years.

The evolution of GAVI

A useful way to conceptualize this evolution is to highlight GAVI's objectives and the technical and financial contributions that the Global Fund and partners are making toward these goals (as shown in Figure 1). The left-hand column shows the current products being supported by the Global Fund and the current status of immunization programmes. The right-hand column shows the progress the GAVI partners expect to see in 5-10 years. Governments, foundations, bilaterals, agencies, the private sector and others are all contributing funds and/or people to move our shared agenda forward. Some of the resources are channelled through the Global Fund's sub-account for new and under-used vaccines which finances hepatitis B, Hib, yellow fever vaccines and auto-disable syringes in the poorest countries. If we are successful, in 5-10 years these products will have become routine components of the immunization system, with sustained financing by the countries themselves, partners, or other financing mechanisms as appropriate. In 5-10 years the community should be ready to support the widespread introduction of the next generation of new vaccines such as pneumococcal conjugate, rotavirus, and meningococcal A or A/C conjugate vaccines. This transition will not occur spontaneously: it will require planning, work, and resources that no single partner or small consortium can achieve. It will require a GAVI-level effort.

To take one example: the pneumococcal conjugate vaccine currently in clinical trials in developing countries has the potential to be one of the most important vaccines ever developed, in terms of reduction of morbidity and mortality. However, because the vaccine includes 9 to 11 different serotypes, it will be the most expensive vaccine ever developed; there will be essentially 9 or 11 Hib vaccines in each vial. How will the public sector be able to afford this vaccine? The answer to this question will be the biggest challenge to GAVI in the future. We need to begin work on this issue now, when manufacturers are planning production capacity and pricing for it. The potential commitment of governments, partners and the Global Fund to guarantee a market for this vaccine can be a powerful tool to influence industry to invest in adequate production capacity and to offer an affordable price for it. Only a GAVI-level effort could achieve this.

While the GAVI partnership is focused on strengthening the vaccine infrastructures in all developing countries, the first year has focused primarily on the poorest countries. Currently, immunization coverage in these countries is about 60%, vaccine wastage is about 60%, and fewer than 60% of injections for immunizations are known to be safe. If we are successful, in 5-10 years immunization coverage will be at least 80%, wastage will be about 10% and all immunization injections will be safe. Again, this will not happen spontaneously: no single partner, on its own could achieve the level of planning, work, and investment needed. The new and under-used sub-account of the Global Fund provides performance-based investment to the poorest countries for infrastructure.

Dramatic improvements in immunization coverage will require improved management and logistics and innovative strategies to reach currently unreached populations. This may involve new applications of information technology, novel ideas on outsourcing logistics and transportation, and development of new outreach strategies based on what we have learned from polio eradication. Making immunizations safer and reducing wastage will require innovative approaches such as moving to monodose safe injection devices (such as Uniject). Exciting evidence points to the possibility of making vaccines so stable that refrigeration may be unnecessary, greatly expanding the reach and efficiency of immunization systems. New technologies will be needed to meet these goals and there is currently a shocking paucity of human and financial resources devoted to these issues.

Proposal for GAVI Projects

We propose that the GAVI Board select a small number of vaccines, technologies and implementation issues for GAVI Projects. These projects would be prioritised, based on their importance to countries and the added value that a GAVI-level effort would bring in assuring their rapid and successful completion. By focusing on a small number of near-term products and technologies, GAVI can harness the expertise represented in the task forces, focusing on specific GAVI Projects in addition to the more general tasks. The selection of near-term products also enables the GAVI partners to validate the impact of new push-and-pull strategies which have been widely discussed, setting the stage for the implementation of new mechanisms to support future products, like vaccines against HIV/AIDS or malaria.

Project "Agendas" and implementation

In accordance with the GAVI approach, the Working Group proposes that each product or technology project be implemented and managed by the GAVI partners with particular expertise in the appropriate field. Accelerating a new product requires a variety of special efforts to streamline the development steps, the production scale-up, the purchase of the product and, ultimately, its introduction into country programmes. The multi-disciplinary nature of these projects will require the expertise of many partners as well as the expertise represented on all four GAVI task forces. It is proposed that the lead partner will convene a small core group of experts to develop a " Project Agenda" which will identify and attempt to address the most important issues currently blocking rapid development, scale-up, purchase, introduction, and delivery of the specific product or technology. This will include activities which, as appropriate, create demand, assess disease burden, determine efficacy, identify appropriate introduction strategies, develop and provide appropriate training, ensure adequate production capacity, and provide incentives for private investment in making the product available and affordable. These agendas will be shared work plans that identify the tasks that need to be done, whether they are being adequately addressed, who is responsible for doing them, how much funding is needed, and the source of funding. The project leader will provide regular progress reports to the GAVI Board.

The GAVI task forces and several partners have given considerable thought to how they can support the future of immunization. The R&D Task Force has prepared terms of reference that reflect the approach found in this proposal. They have undertaken a wide consultative process to identify priority vaccine products. Based on this process, the Working Group recommends that the first three GAVI Projects be to:

1) Assure the availability, affordability and use of pneumococcal conjugate vaccines for the developing world within five years.

2) Assure the development, availability and use of a safe, effective and affordable rotavirus vaccine for the developing world within seven years.

3) Assure the development, availability and use of an affordable meningococcal A, A/C or quadravalent conjugate vaccine for the "meningococcal belt" in Africa within five years.

Several partners, including the private sector, have already made considerable commitments to these products. WHO has already prepared position papers on global use of pneumococcal conjugate and rotavirus vaccines. It is therefore a matter of urgency to explore how a GAVI-wide effort can add a powerful new dimension to increase the probability that these important new vaccines will be available and affordable for the developing world.

We propose that the Board considers one to three additional GAVI Projects related to improved immunization systems and technologies, as described above. If the GAVI Board approves this proposal, the R&D Task Force and the Working Group will convene a sub-group to prepare specific proposals for these additional GAVI Projects. The sub-group will include experts on immunization delivery systems and technologies.

The Financing Task Force (FTF) has already begun to identify a process to help implement financing "push-and-pull" strategies such as investment in production capacity and implementing a means to "guarantee" the future purchase of products. The FTF will also continue to develop and promote the implementation of cross-cutting financing issues such as tiered pricing, the role of purchase funds, and the potential for World Bank grants or low-cost credits. The FTF will focus exclusively on financing issues, relying on the other task forces for activities supporting the science, demand creation and introduction of products. The FTF proposes to establish a small sub-group on financing issues with an advisory group of global financing experts who are not in the immunization community. The advisory group will give recommendations to the FTF and, ultimately, the GAVI Board on the structure of financial plans proposed by product teams, the viability of new mechanisms and the gaps in the financial thinking. This group might, for example, include a creative venture capitalist, a partner from McKinsey & Co. (a respected management consulting firm), or a responsible party for the debt-relief financing.

The Advocacy Task Force will be charged with helping to create demand for the new products in developing countries and with global partners. They will help package and share information with key national, regional and global decision-makers.

The Task Force on Country Coordination is home to those with the most experience on programmatic issues and will consider the programmatic impact of introduction of pneumococcal, rotavirus and meningococcal A vaccines. Programmatic issues will be the most difficult for meningococcal A vaccines since the disease occurs primarily in the poorest-performing countries. This task force also consists of individuals and partners with the greatest experience in strengthening immunization systems, reaching the unreached, management, and logistics including cold chain, transportation, and injection safety. Their input will be critical in developing the additional GAVI Projects.

Project financing: the role of the Global Fund

Financial support for the activities identified on the Project Agendas will primarily come from partners. However, it is anticipated that many of the large financing needs for new products and technologies may not be compatible with traditional funding routes. Large investments in development or production capacity and/or the guarantee of future purchases (which may be identified as critical strategies for the implementation of the product agendas) may require new, more flexible, financing mechanisms It is proposed that the third sub-account of the Global Fund, as well as other possible mechanisms, be used as a flexible source of funds to finance public-private investment or market based strategies which address the specific bottlenecks constraining the rapid development and availability of priority products or technologies. Criteria will be established to identify the high priority investments or uses of this sub-account, and safeguards will be established to ensure that the third sub-account will not replace traditional sources of funding or become a "slush fund" for any task force or partner. The Working Group would like to work with the Executive Committee of the Global Fund and the GAVI Board to develop specific GAVI policies that will outline the best use of funds from the Global Fund for Children's Vaccines in support of Project Agendas.

Summary

This proposal describes a process by which GAVI can most effectively move into the future by investing human and financial resources into several GAVI Projects that draw on the wealth of skills of the different partners and represented in the task forces. Through teams led by different partners, GAVI will facilitate the development of shared Project Agendas that focus the partners and task forces on critical next steps to accelerate the development, availability, affordability and use of priority new products and technologies. The task forces which already draw together partners or specific skills in research and development, finance, advocacy and country implementation will help to organize the support for the shared product goals, filling gaps that may exist currently.

The Board is asked to:

- approve the three proposed projects;
- approve the process outlined in this paper;
- accept the responsibility of reviewing the progress against these Project Agendas;
- recommend to the Global Fund that the third sub-account will be used to address the specific bottlenecks constraining the rapid development and availability of priority products or technologies;
- propose to develop further, with the Executive Committee of the Fund, a process that will define more precisely the criteria for drawing on the third sub-account.

Figure 1: Evolution of GAVI and the Global Fund

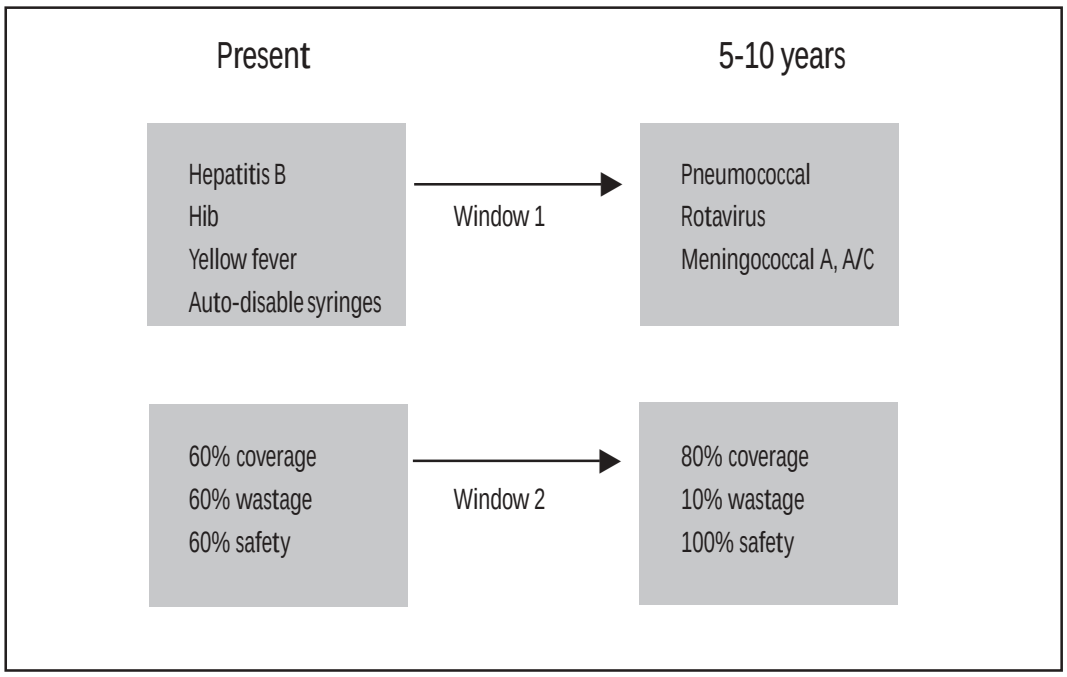
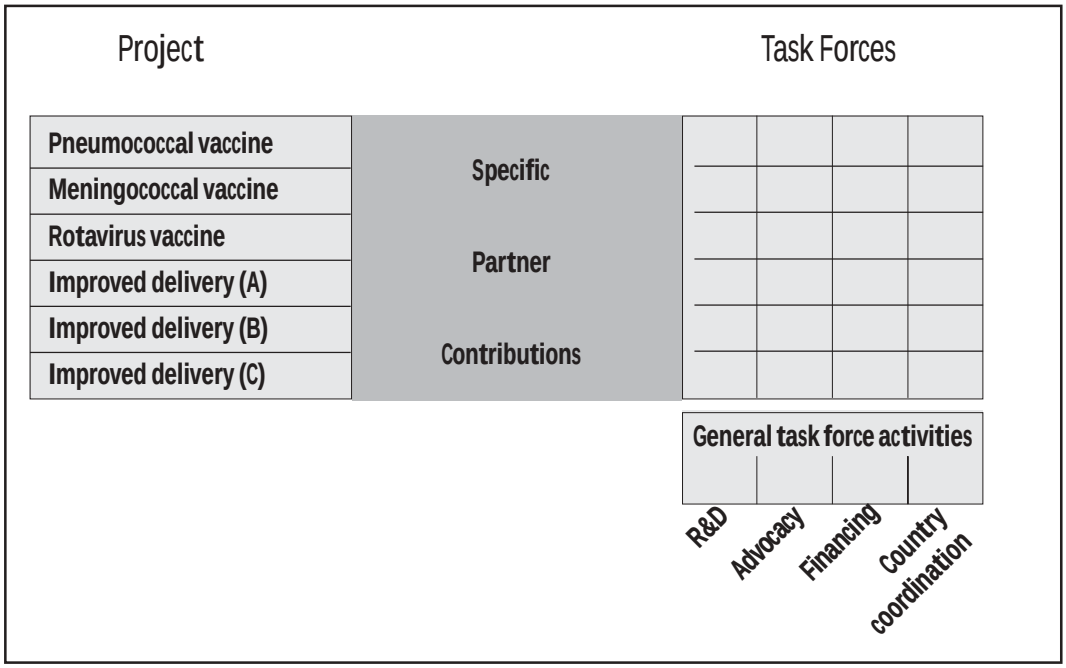


Figure 2: Contributions to Project Agendas



Annex 4b

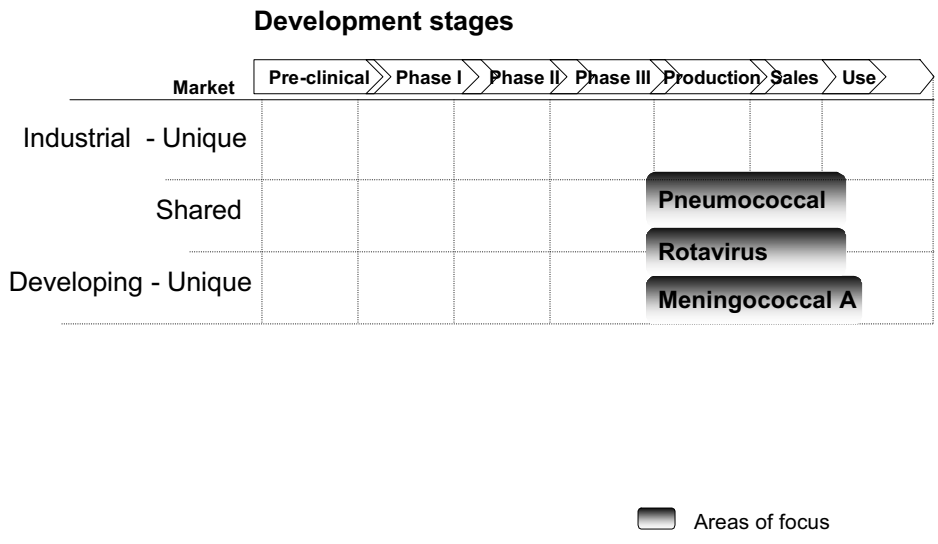
Financing Task Force (FTF) contribution to GAVI product objectives

(Slide presentation by Ms Amie Batson, The World Bank)

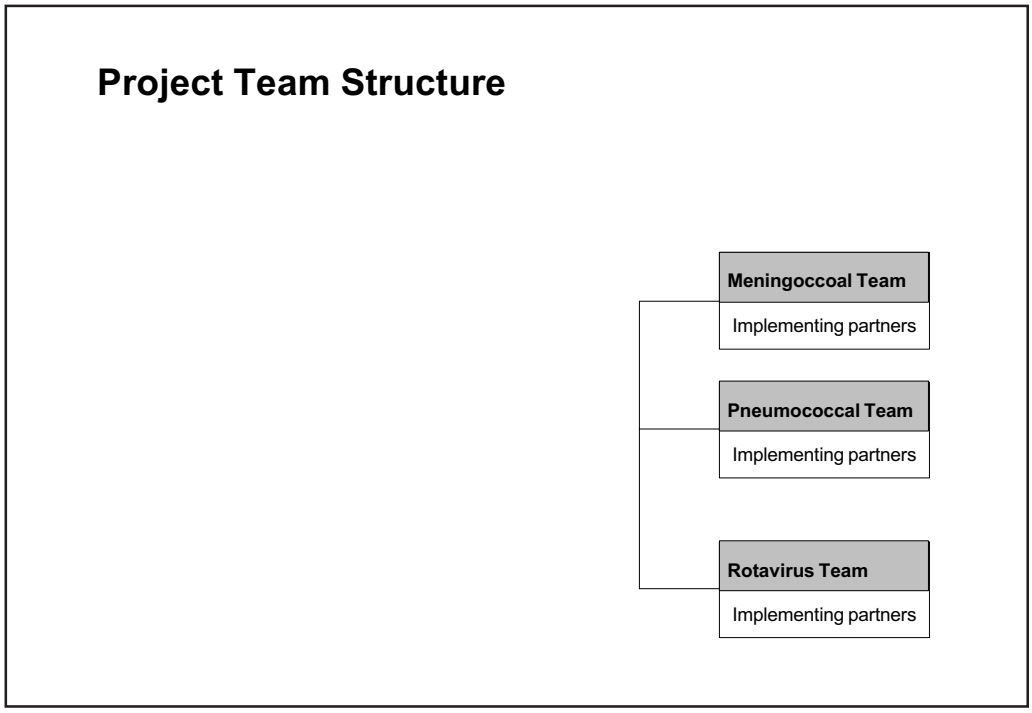
GAVI and FTF Objectives

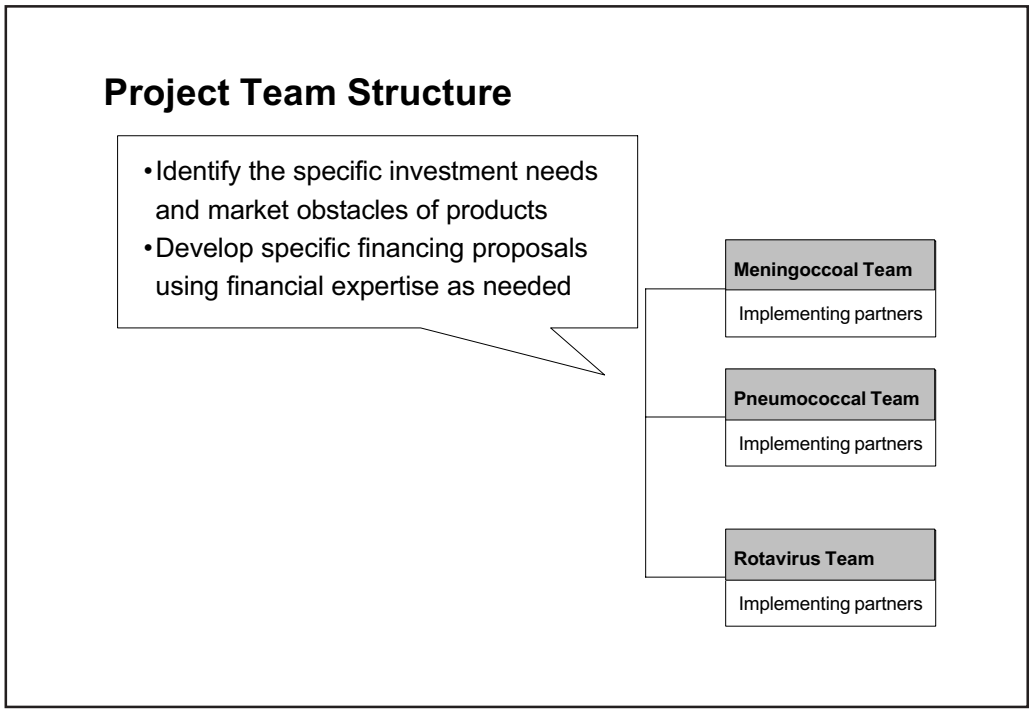
- Overarching objective
  - Accelerate the development, scale-up and introduction of three new vaccines
- FTF objective
  - Validate the practicality and effectiveness of investment and market-based strategies
    - Identify and address implementation issues
    - Assess the value-added compared to traditional mechanisms
    - Explore generic investment and financing issues
    - "Pave the way" to address AIDS, malaria and TB vaccines

FTF Project Focus



Slide presentation on Financing Task Force *(continued)*





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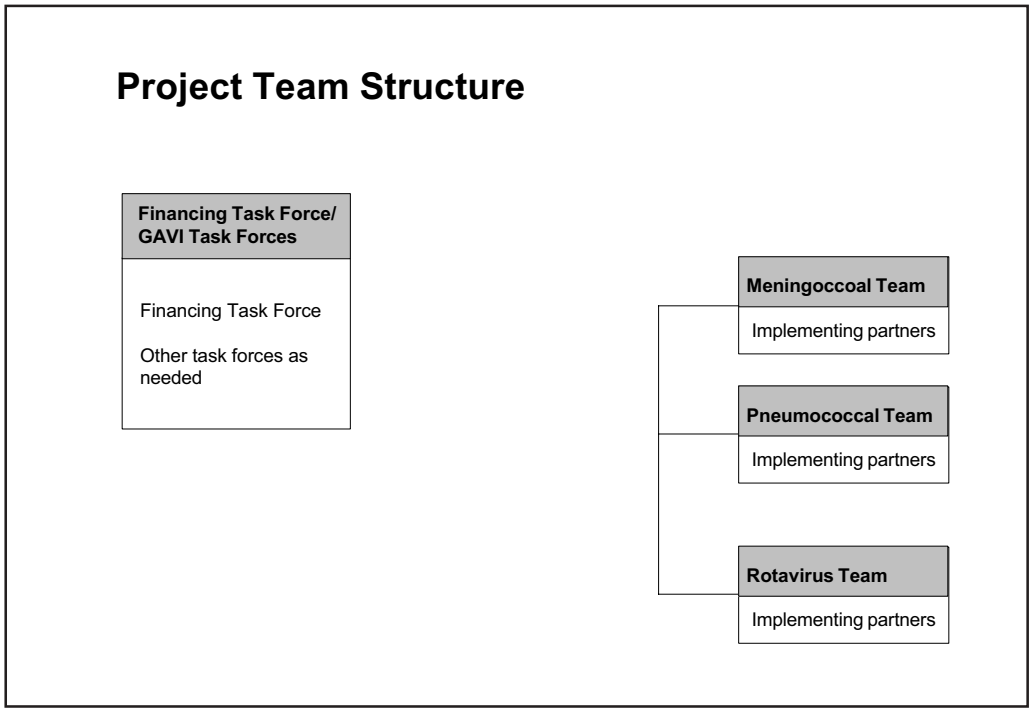

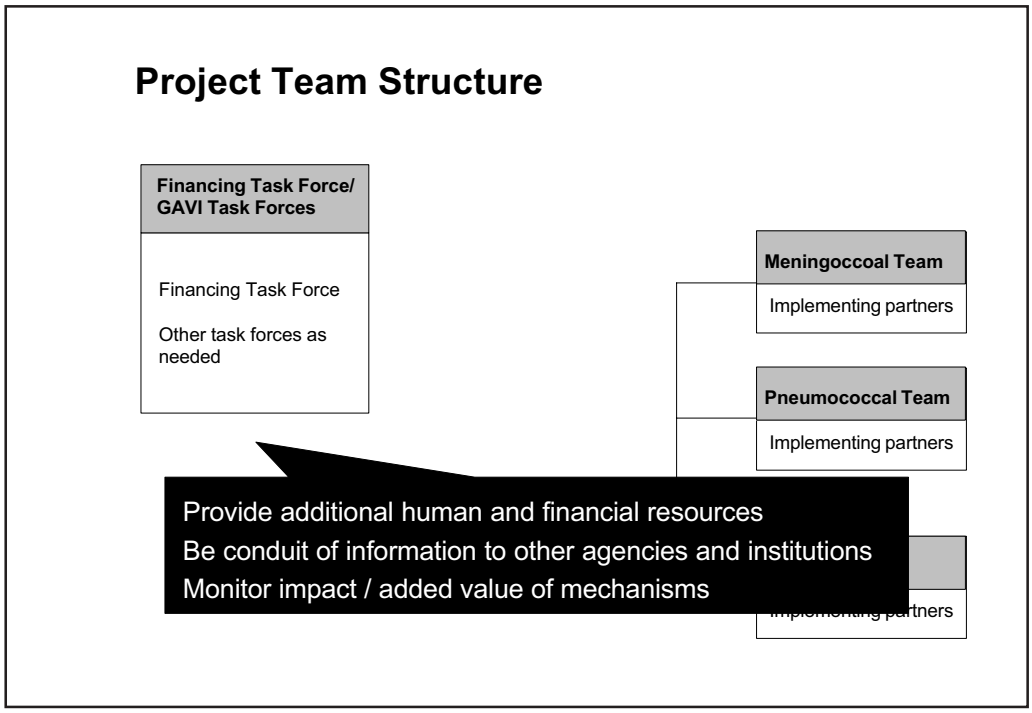

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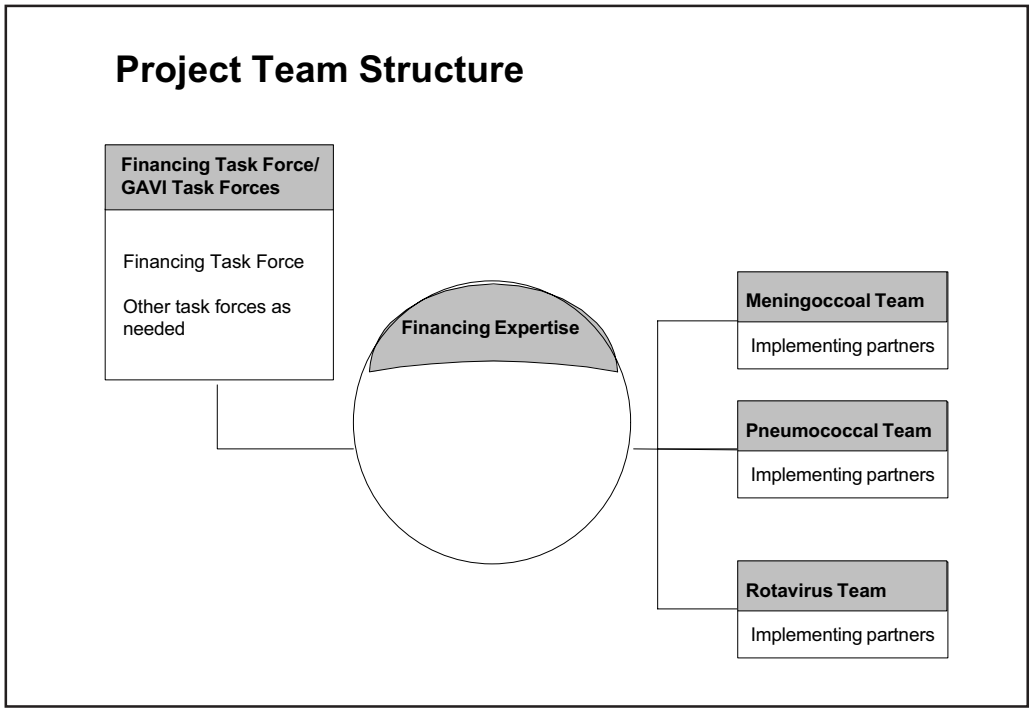
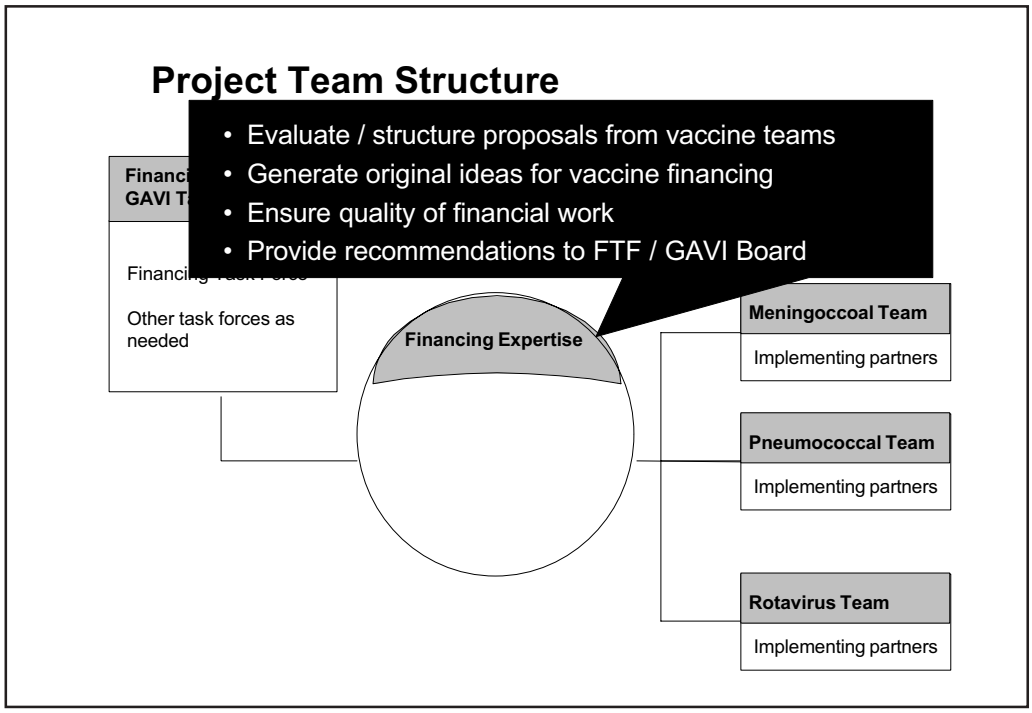
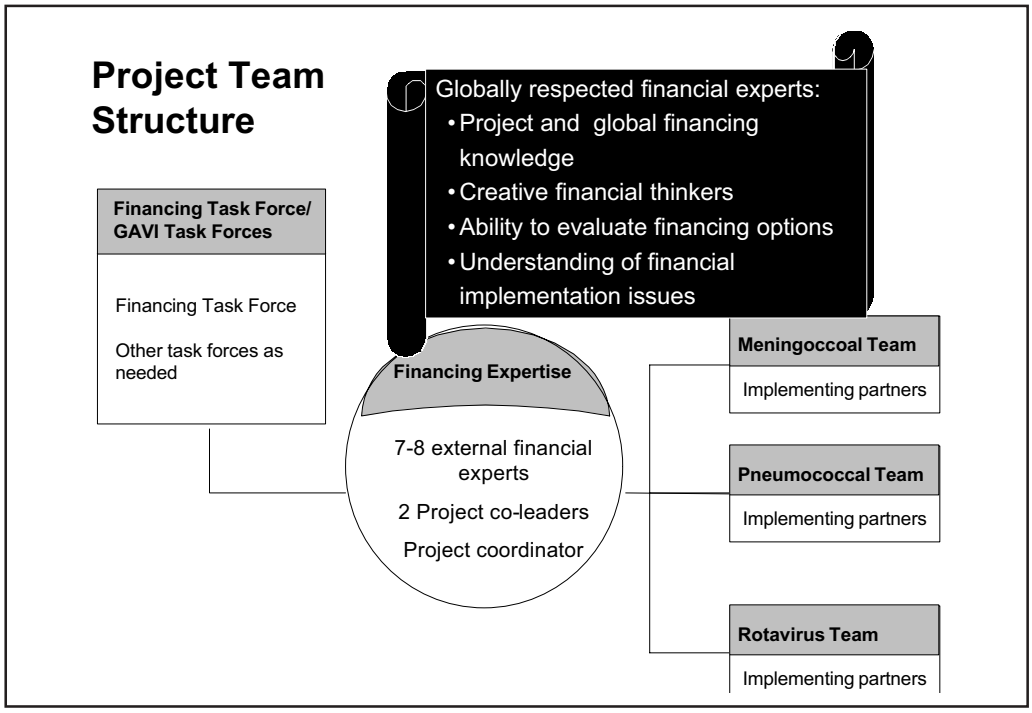
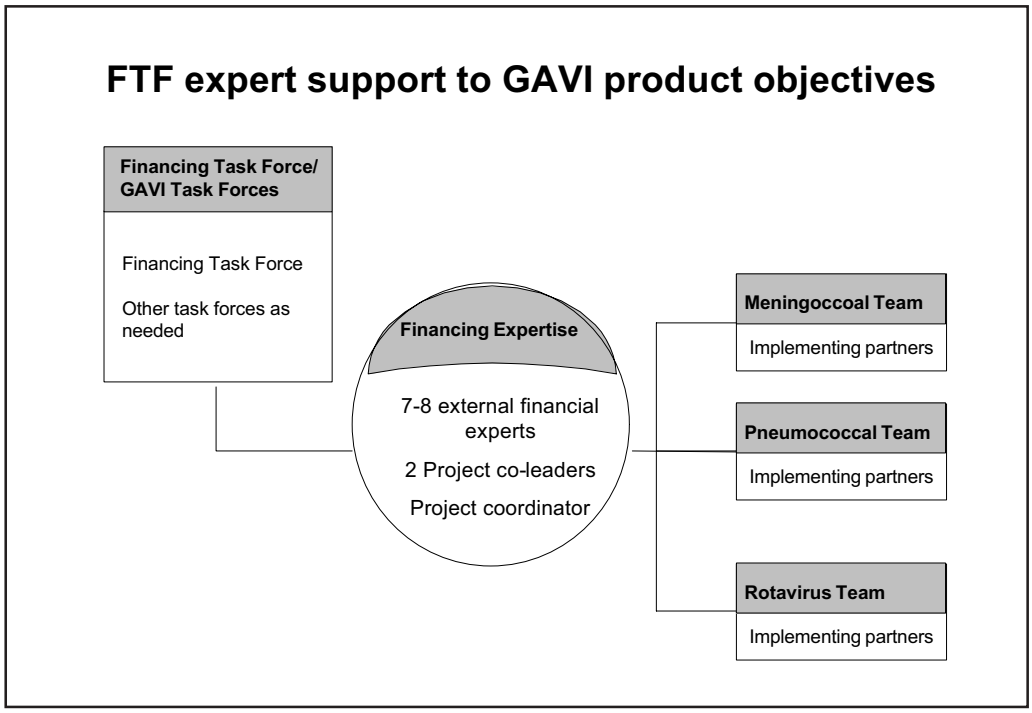




Slide presentation on Financing Task Force *(continued)*





Annex 5

Collaboration with specific disease programmes

Background material on agenda item 5

This annex comprises:

- Annex 5a: Reducing childhood mortality by reaching every child with measles vaccine – A paper prepared by WHO and UNICEF as a basis for the Board's discussions on:
  (a) reaffirming its objective to reduce measles mortality,
  (b) consulting with partners on proposals to incorporate sustainable measles mortality reduction into GAVI's overall strategic objectives, time-frame and work plan, and
  (c) presenting an overall plan, including a cost-benefit analysis of different strategies, to the Board at its June 2001 meeting.
- Annex 5b: The Global Polio Eradication Initiative – A slide presentation by Dr Bruce Aylward, WHO.
- Annex 5c: Reducing measles mortality and improving child survival – A slide presentation by Mr Michel Zaffran, WHO.

Annex 5a

Reducing childhood mortality by reaching every child with measles vaccine

(Prepared by WHO and UNICEF)

1. The magnitude of the problem

Children under five years of age account for 30% of the total burden of disease in poor countries[1] . Measles is a major childhood killer in developing countries and accounts for around 888 000 deaths a year. This represents approximately 9% of the deaths in children less than five years of age in developing countries.

Measles remains the leading cause of childhood vaccine-preventable deaths worldwide. It represents 40% of the estimated two million deaths due to childhood vaccine-preventable diseases. In 1999, in 15 countries (mainly in sub-Saharan Africa and Asia) over 50% of newborn infants were not protected with measles vaccine.

Failure to deliver at least one dose of measles vaccine to all infants remains the primary reason for the high measles morbidity and mortality. Measles immunization is one of the most cost-effective interventions available.

2. Strategies to achieve sustainable measles mortality reduction

Sustainable measles mortality reduction can be achieved by implementing the following strategies:

1) More than 90% routine vaccination coverage (in each district and nationally) with at least one dose of measles vaccine administered at nine months of age or shortly thereafter.

2) Ensuring the provision of a second opportunity for measles vaccination for all children (through campaigns or routine immunization that will help reduce the proportion of the population susceptible to infection below the threshold at which the disease remains endemic.

3) Establish an effective surveillance for measles disease incidence and monitoring of vaccination coverage.

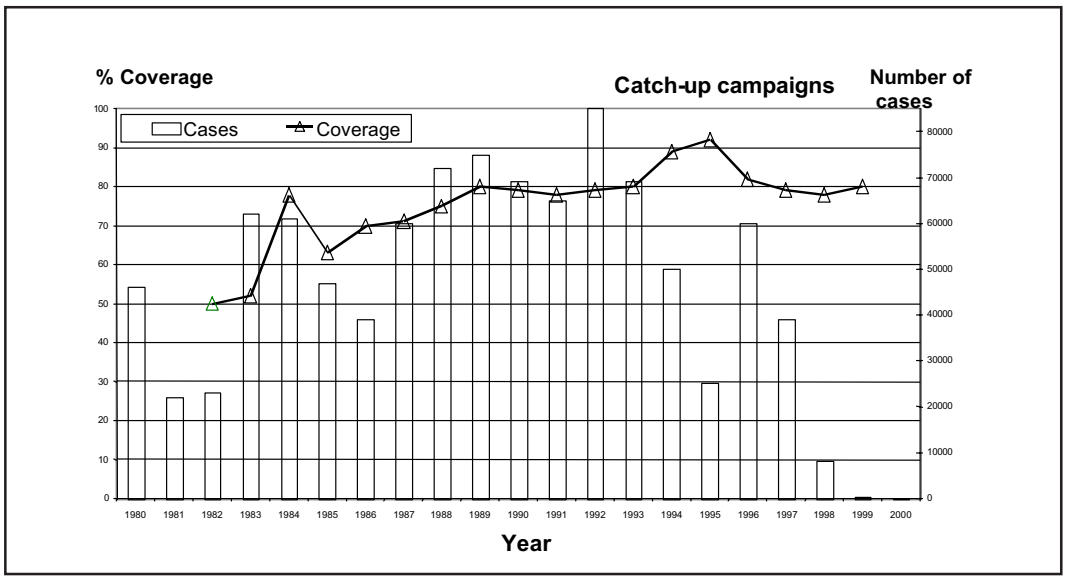
In addition, strategies include provision of vitamin A supplements to children through immunization contacts and improved management of measles cases, as well as adequate treatment of complications. These strategies have been successfully implemented in a number of countries as documented by recent epidemiological information (Figure 1).

Long-term commitment is required to achieve and maintain the measles mortality reduction goal. To achieve major impact within the next few years, it is important to ensure that

[1] EIP/WHO, based on 1999 estimates.

the 20[2] countries that represent 85% of the global measles mortality will have resources to plan, implement and monitor a three to five year strategic plan to achieve and sustain the measles mortality reduction targets.

Figure 1: Reported measles cases and vaccine coverage, Southern African countries, 1980-2000



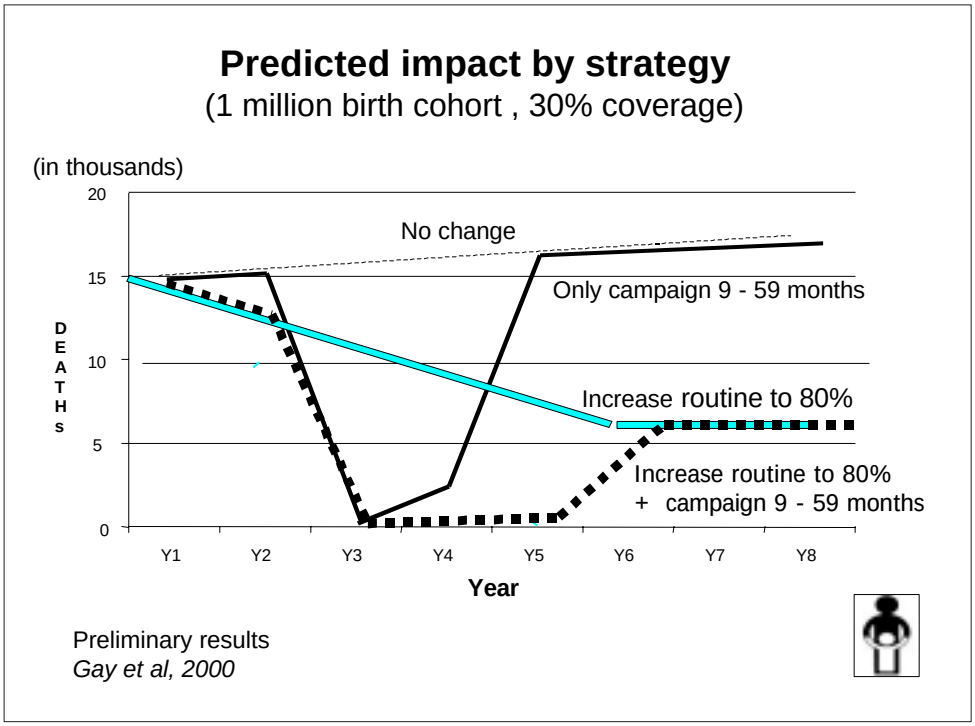
Recent assessments of the expected impact of different strategies to reduce measles mortality have highlighted the importance of increasing measles routine coverage as a way to achieve sustainable reduction in measles mortality. Moreover, these assessments have shown that countries could benefit earlier from reduction in measles deaths if increments in routine measles coverage are combined with epidemiologically designed high coverage mass campaigns. The dramatic reduction in mortality achieved with a mass measles campaign alone is short-lived if not accompanied by improvements in routine coverage (Figure 2). GAVI's aim to ensure that 80% of the developing countries have routine coverage of at least 80% in all districts by 2005 is an essential first step in reducing the burden of measles. However, even at 80% routine coverage, measles will remain a significant cause of morbidity and mortality.

Poor measles control in certain industrialized countries (in Europe and Japan) means that a huge global reservoir will continue to exist and threaten efforts to control the disease in Africa and elsewhere in the developing world. Measles control efforts in these countries therefore need to be strengthened to improve population immunity and measles surveillance.

[2] Using the WHO Vaccine and Biologicals model: four countries (the Democratic Republic of the Congo, Ethiopia, India and Nigeria) contribute to 50% of the estimated global measles mortality. The provisional lists of countries includes: 1) African Region: Burkina Faso, Democratic Republic of the Congo, Ethiopia, Ghana, Mali, Mozambique, Niger, Nigeria, Tanzania, Uganda; 2) Eastern Mediterranean Region: Afghanistan, Pakistan, Somalia, Sudan, Yemen; 3) South-East Asia Region: Bangladesh, India, Indonesia, Myanmar.

Figure 2: Effectiveness of strategies for reducing measles mortality

An illustrative example considers options for improving measles control in a typical developing country with 30% routine measles vaccination coverage and an initial birth cohort of 1 000 000. With no improvement in the vaccination programme, deaths from measles will gradually increase, in line with the population. Increasing routine coverage from 30% to 80% over five years produces a sustainable 65% reduction in measles deaths after year five, but prevents approximately 30% of deaths in the first five years.



Conducting a mass vaccination campaign produces a dramatic reduction in deaths but this impact is not sustained for long if routine coverage remains at 50%. The mass campaign, conducted at the beginning of year two, is assumed to vaccinate 90% of the target age-group, with the pessimistic but, in many circumstances, realistic assumption that the 10% missed by the campaign are all children who were previously unvaccinated. A combination of improved routine coverage and a mass vaccination campaign produces an immediate impact and a sustained reduction in measles deaths. The positive interaction between improved routine coverage and a campaign is also illustrated by the resulting increase in the duration of the time impact of the campaign, as the rate of input of new susceptibles into the population is reduced by higher routine coverage.

3. Conclusions

- Measles is the leading cause of childhood vaccine-preventable diseases. This disease burden can be prevented using available vaccine and current strategies.
- GAVI's efforts to improve performance of immunization programmes in developing countries will be a critical first step in reducing measles mortality.
- Concerted efforts are needed both to address the specific challenge of reducing measles mortality and to develop immunization services that can support effective delivery of interventions. Additional resources will be needed to support countries in meeting these challenges.

4. Proposed action points for consideration by the GAVI Board

Based on the above information, a recommendation is made to the GAVI Board to:

- Reaffirm its objective to reduce measles mortality, stated as follows: "It is of high priority for GAVI that the mortality from measles (presently 900 000 children's deaths per year) is brought down by reaching every child with measles vaccine"[3] ;
- Request the Working Group to consult with partners and propose ways to incorporate sustainable measles mortality reduction into the GAVI plan on strategic objectives and time-frame and to present an overall plan (including cost-benefit analysis of different strategies) to the Board at its June 2001 meeting.

[3] *GAVI, Immunize every child* – GAVI strategy for sustainable immunization services, February 2000.

Annex 5b

Global Polio Eradication Initiative

(Dr Bruce Aylward, World Health Organization)

Global Polio Eradication Initiative

GAVI Board Meeting

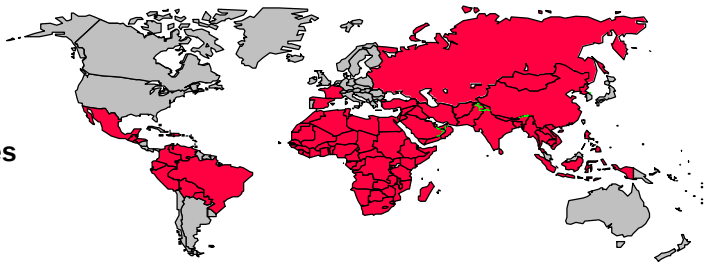
19 November 2000

Noordwijk

Pre-acceleration progress

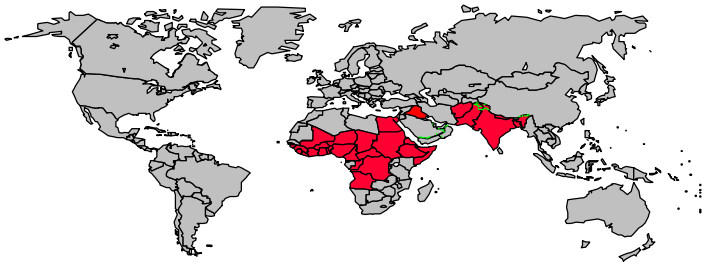
1988

350 000 cases



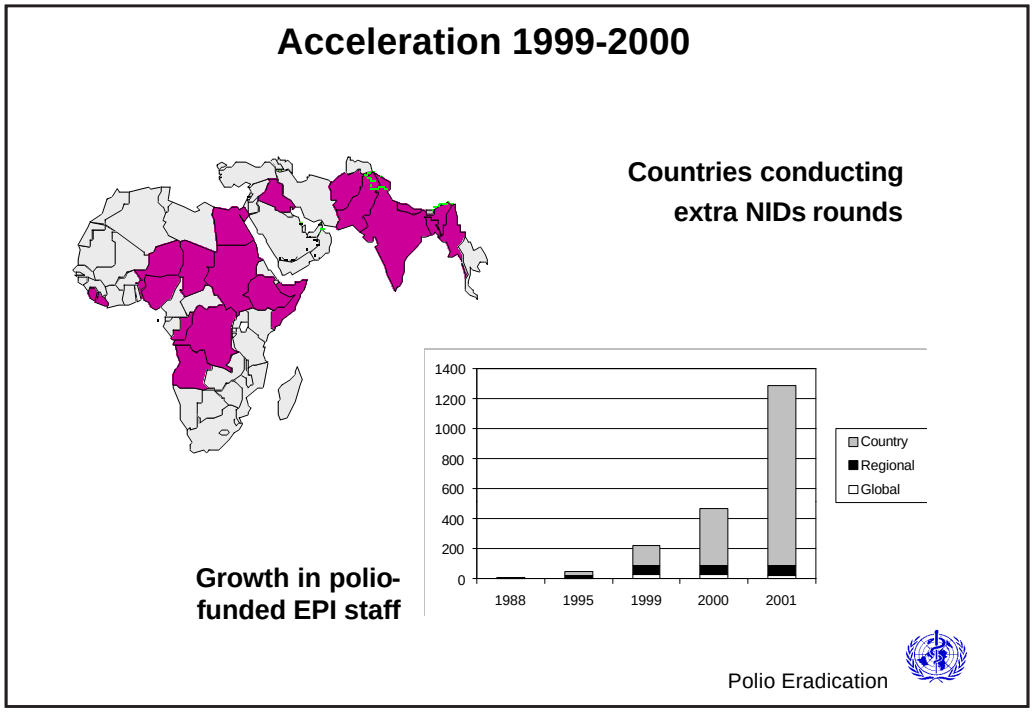
1999

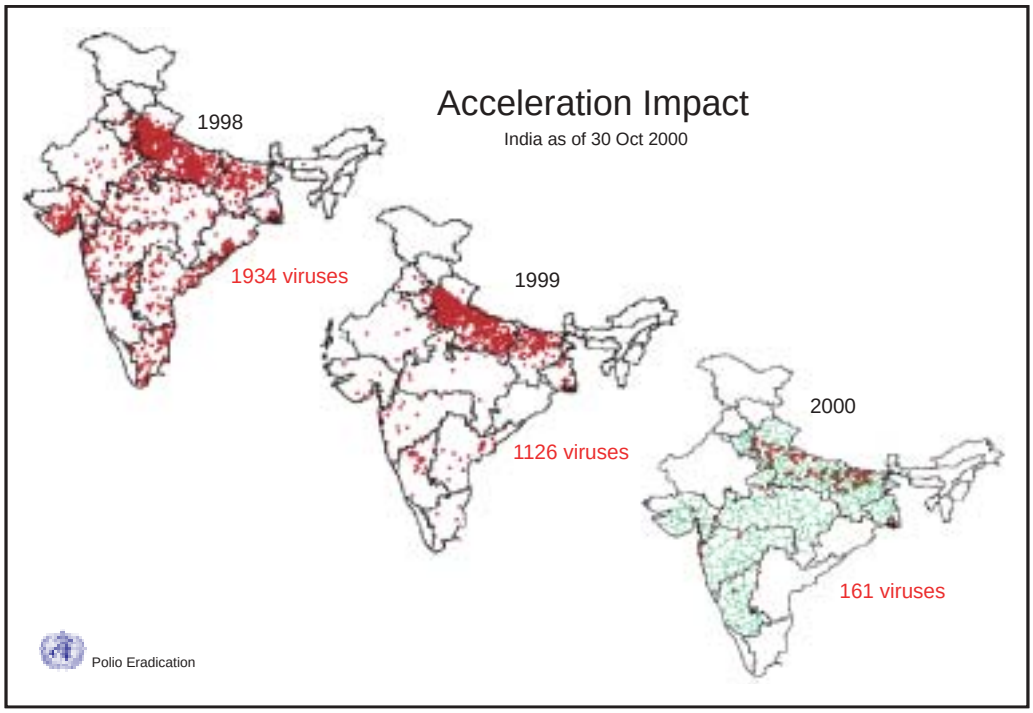
7 094 cases



Polio Eradication

Slide presentation on Global Polio Eradication Initiative *(continued)*





Slide presentation on Global Polio Eradication Initiative *(continued)*

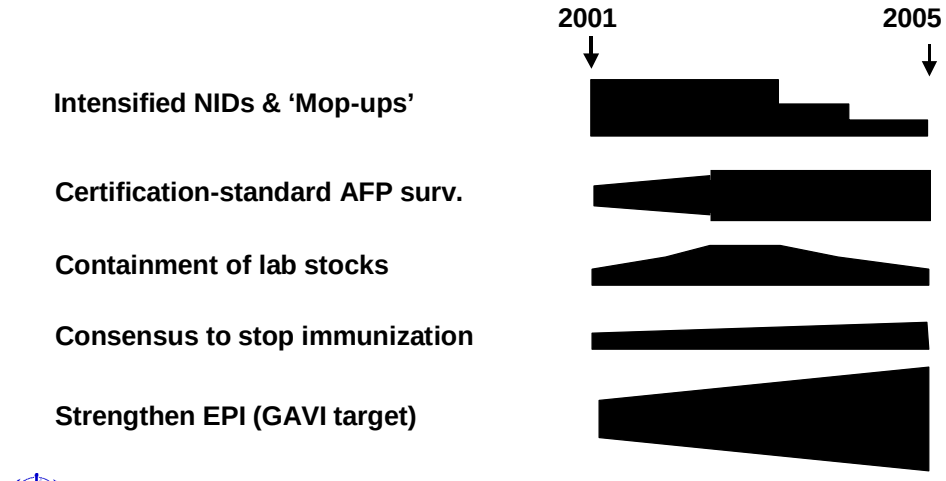
Acceleration impact

	1999	2000
Paralysis (AFP):	**16 035**	**19 320**
Polio cases:	**3 317**	**1 530**

Note: Global data as of 30 Oct each year.

Polio Eradication

Strategic plan



Polio Eradication

Slide presentation on Global Polio Eradication Initiative *(continued)*

Targets and priorities

Targets	**end-2000:**	**< 20 countries**
	24 months:	**0 countries**
Priorities	**Pakistan, Afghanistan, N. India**	
	Nigeria, DR Congo, Angola,	
	Horn Africa	
Emphasis	**House-to-house immunization**	

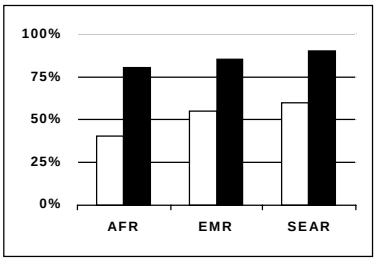
Polio Eradication

Lessons learned

Service delivery

Accessing unreached children

OPV3 ☐ **NIDs** ■



Endemic Areas

Integrating Vit A & EPI

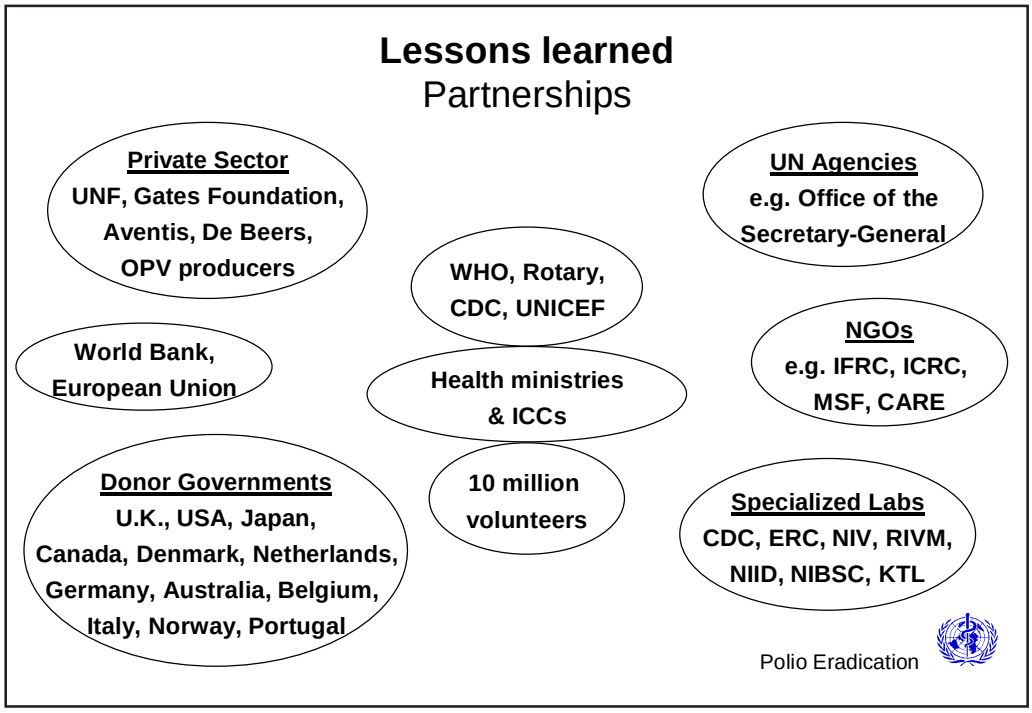
NIDs	*Deaths averted*
1998	*169 000*
1999	*242 000*

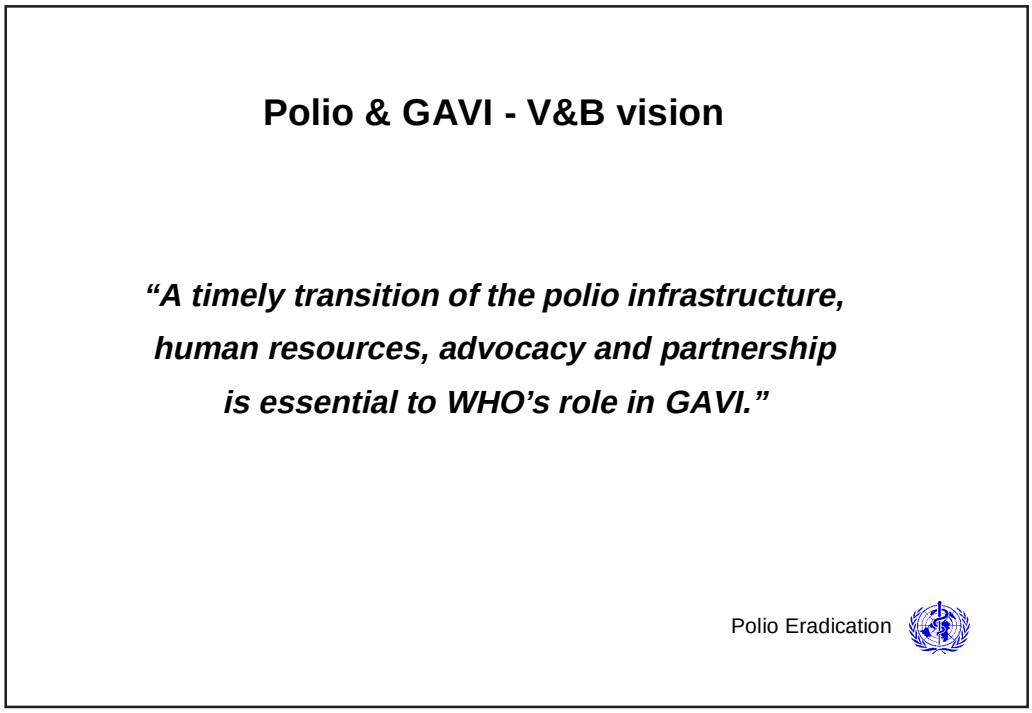
Integrating surveillance

Disease	*AFR countries*
Measles/NT	*86%*
Cholera/Mening.	*60%*

Polio Eradication

Slide presentation on Global Polio Eradication Initiative *(continued)*

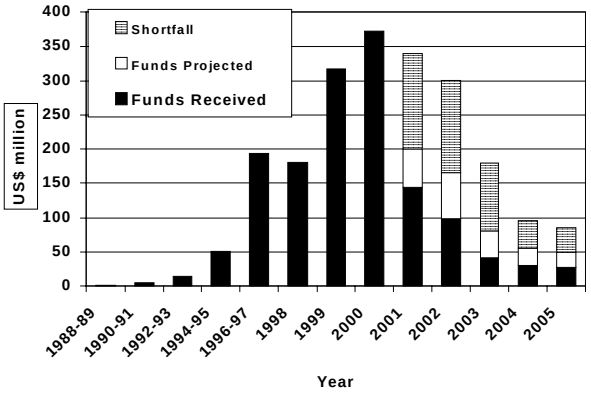




Slide presentation on Global Polio Eradication Initiative *(continued)*

Polio Eradication Challenges

1. **Accessing all children**
2. **Funding the US$ 450m gap**
3. **Sustaining commitment**



Polio Eradication

What Polio brings to GAVI

Human resources

(e.g., staff in GFCV-eligible countries)

Immunization infrastructure

(e.g., replaced >30% of AFRO cold chain)

Management capacity

(e.g., vaccine, ICC, sustainable outreach)

Polio Eradication

Slide presentation on Global Polio Eradication Initiative *(continued)*

What GAVI brings to Polio

International advocacy

(e.g., GAVI communications; fundraising)

National planning

(e.g., multi-year plans include polio)

Sustaining national commitment

(e.g. GFCV application review process)

Polio Eradication

Annex 5c

Reducing measles mortality – improving child survival

(Mr Michel Zaffran, World Health Organization)

Reducing measles mortality

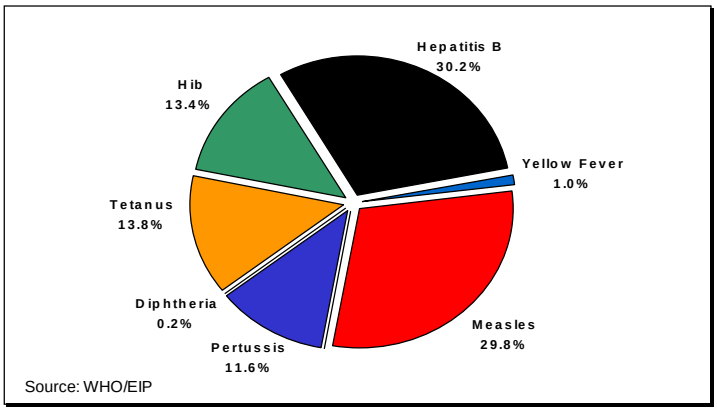
Improving

child

survival

GAVI Board Meeting, 19 Nov 2000

Globally : 3 million vaccine-preventable deaths

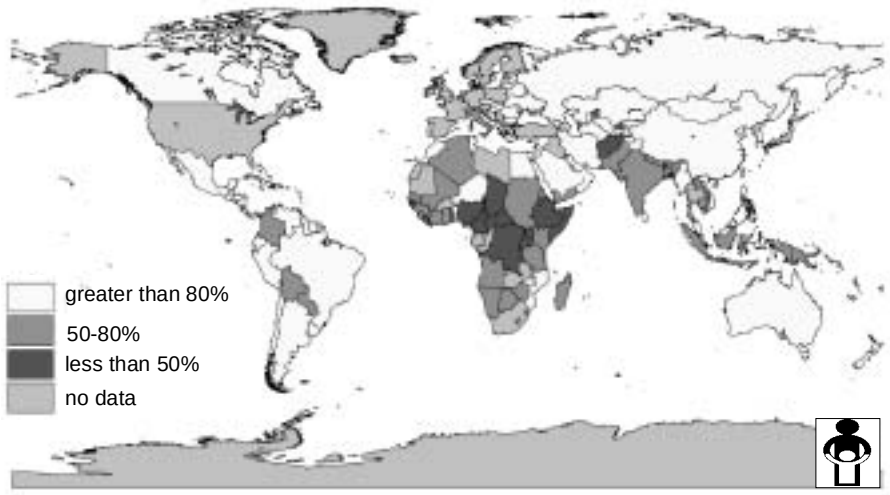


Source: WHO/EIP

888 000 deaths
9% of overall childhood mortality
40% of vaccine-preventable disease mortality

Slide presentation on reducing measles mortality *(continued)*

Reported coverage with measles vaccine, 1998

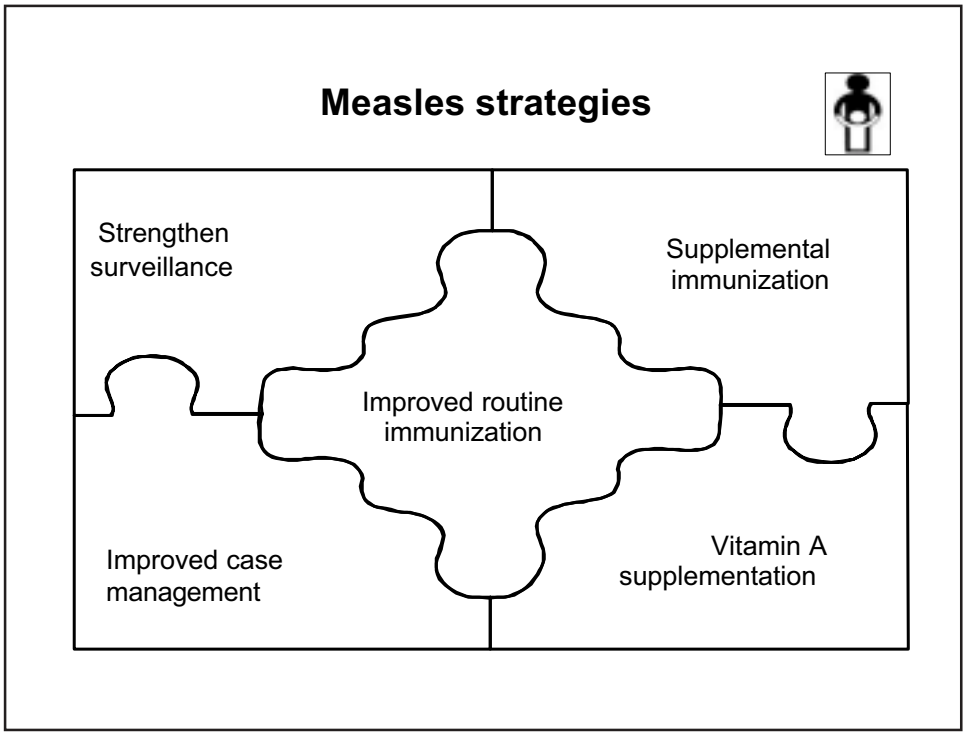


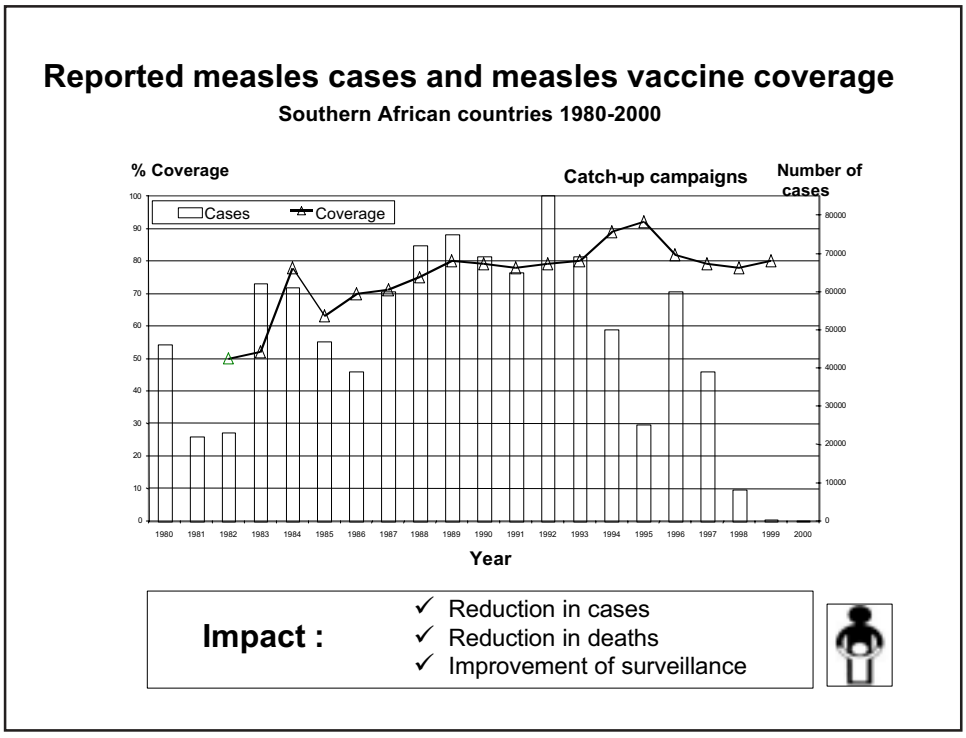
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers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

Facts

- **Measles kills** nearly one million children every year. All deaths could be prevented.
- **Measles immunization is cost-effective :** (US$ 2.5 - 6.2 per life-year gained to increase coverage from 50 to 80%)
- **Under-utilization** of measles vaccine remains the primary reason for the high measles mortality
- **High immunization coverage** ($\geq$ 90 %) is required to achieve and maintain a high level of measles control

Slide presentation on reducing measles mortality *(continued)*

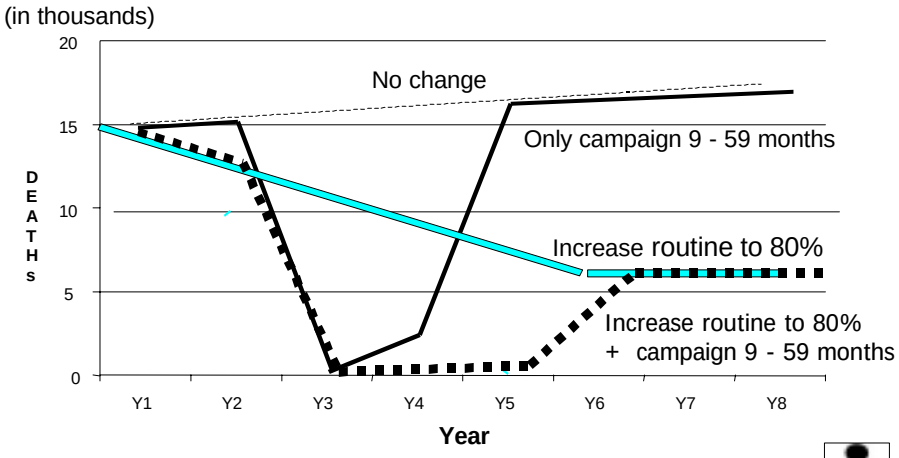




Slide presentation on reducing measles mortality *(continued)*

Predicted impact by strategy

(1 million birth cohort , 30% coverage)



Preliminary results
Gay et al, 2000

GAVI and measles

- **GAVI milestone** : by 2005 : 80% of developing countries should have routine coverage of at least 80% in all districts :
  - essential first step in reducing the burden of measles.
- However, **even at 80% routine coverage** measles will remain a significant cause of morbidity and mortality.

Slide presentation on reducing measles mortality *(continued)*

Reducing measles deaths

- **Improve coverage and quality of routine immunization services in all countries**
- **Ensure a second opportunity for measles immunization (supplemental or routine)**
- **Establish effective surveillance for measles disease**

Strategic options

Total financial resources needed to reduce measles deaths 2001-2005 (US $ millions)

Stratum	Routine	Supplemental	Surveillance	Total
Top 20 countries	430	260	65	755
Other *high child-mortality* countries	470	275	70	815
Selected countries in elimination stage	90	220	55	365
Total	**990**	**755**	**190**	**1935**

Slide presentation on reducing measles mortality *(continued)*

Proposed next steps

❶ Reaffirm commitment to reduce measles mortality as stated in Davos :

"It is of high priority for GAVI that the mortality from measles is brought down by reaching every child with measles vaccine."

Source: Immunize Every Child, 2000

Proposed next steps

We need :

- Ways in which GAVI can incorporate sustainable measles mortality reduction in its overall strategic objectives;
- Overall plan, time-frame and work-plan (including impact and cost-benefit analysis of different strategies and monitoring of progress).

❷ Request the Working Group to consult with partners and to report at the June GAVI Board meeting.

Annex 6

The GAVI Secretariat

Discussion document on agenda item 6:

- The GAVI Secretariat: the first year (1999-2000) – This discussion document outlines the main activities of the GAVI Secretariat during its first year and provides a report on:
  (a) expenditures,
  (b) the financial outlook for 2000,
  (c) budget projections, and
  (d) the staffing situation. In accordance with the GAVI Guiding Principles, it is the responsibility of the GAVI Board to approve the Secretariat budget.

GAVI Secretariat: the first year (1999-2000)

Major activities

Over the past year the GAVI Secretariat:

1) Facilitated the overall development of the Alliance, from its conception in Seattle in July 1999 to the development of policies and priorities, to being fully functional in 2000.

2) Coordinated development and supported operations of the GAVI Board; organized four meetings (Davos, Oslo, New York and Noordwijk), including the preparation of documentation and meeting reports; organized regular Board teleconferences to address topical issues.

3) Supported the GAVI Working Group; this included arranging weekly teleconferences and five face-to-face meetings.

4) Worked with the GAVI Working Group and partners to develop criteria for the assessment of proposals from countries to the Global Fund for Children's Vaccines; finalized and revised guidelines and application forms.

5) Developed a process for the review of country proposals; worked with the GAVI Working Group to identify and screen members for an Independent Review Panel, and organized two reviews in Geneva, in July and November 2000; managed the initial promotion of the Global Fund proposal process to countries and partner agencies; monitored the process of country applications.

6) Contributed to the functioning of GAVI task forces, especially on research and development and advocacy.

7) Supported fund-raising efforts for the Global Fund for Children's Vaccines; met with congressional/parliamentary/political staff and donor agency representatives in Europe and the USA; secured international support for the Global Fund.

8) Worked with a freelance editor to develop, launch and maintain the GAVI website (www.vaccinealliance.org).

9) Worked with a freelance editor to create a new quarterly electronic newsletter, *Immunization Focus*, a policy, research and news periodical on GAVI issues and concerns; three issues were produced in 2000.

10) Organized the first GAVI Partners' Meeting, held in Noordwijk, the Netherlands, in collaboration with the Dutch Government.

GAVI challenges and priorities: years two and three (2001-2002)

In the first year of the Alliance, the main challenges for the GAVI partners were to set policy and develop structures. In its second year, the main challenges will be implementation and monitoring of efforts, especially in relation to support from the Global Fund for Children's Vaccines to countries. In addition to supporting countries prepare proposals for the Global Fund, GAVI partners will be called upon to provide technical assistance and build capacity in countries already being funded to strengthen their immunization services and introduce new and under-used vaccines.

In addition, GAVI partners will need to reflect on how countries in political crises or complex emergencies, such as civil war, can best be supported to improve their immunization programmes. Task force activities relating to financial and managerial sustainability, and advocacy at country level, are expected to be critical.

The activities of the GAVI Secretariat in its second and third years will continue to focus on providing support to the Board, Working Group and task forces, and facilitating communication between the partners. The Secretariat will also focus on coordination of efforts so that countries are supported throughout the proposal process – from the submission of proposal to verification of coverage data, progress reports and in-depth reviews.

Table 1, below, outlines the schedule of principal activities needed to support the work of the Global Fund.

Table 1: Estimated time-frame of support to countries [1]

Activities requiring support [2]	Number of countries to be supported				
	2000	2001	2002	2003	2004
A. Preparation of GAVI proposal					
EPI assessment	8	2			
Develop multi-year plan	13	3			
Develop plan for introduction of new vaccines	14	3			
Develop GAVI proposal	4				
B.Projected number of proposals approved	27	27 12	8		
C.Monitoring implementation					
Verification of data (of previous year)		27	39	8	
Inception report		27	39	8	
Progress report			27	39	8
Mid-term, or in-depth review			27	39	8
Building capacity for managerial and technical sustainability [3]	• • • •	—	—	—	—
Implementing sustainable financing plan [4]	• • • • • • • • • • • • • •	—	—	—	—

1 Preliminary draft based on available information and contacts with an in-country GAVI partner in 61 of the 74 countries.
2 Consolidation of incomplete information on 6 November 2000.
3 To be supported by the R&D Task Force and the Task Force on Country Coordination.
4 To be supported by the Financing Task Force .

GAVI Secretariat: 1999-2000 expenditures and 2001-2002 budget

In accordance with the Rules and Regulations of GAVI's Host Organization, UNICEF, the proposed GAVI budget will cover two calendar years, as outlined in Figure 1 below and the Tables 2-5.

Figure 1: Staffing situation

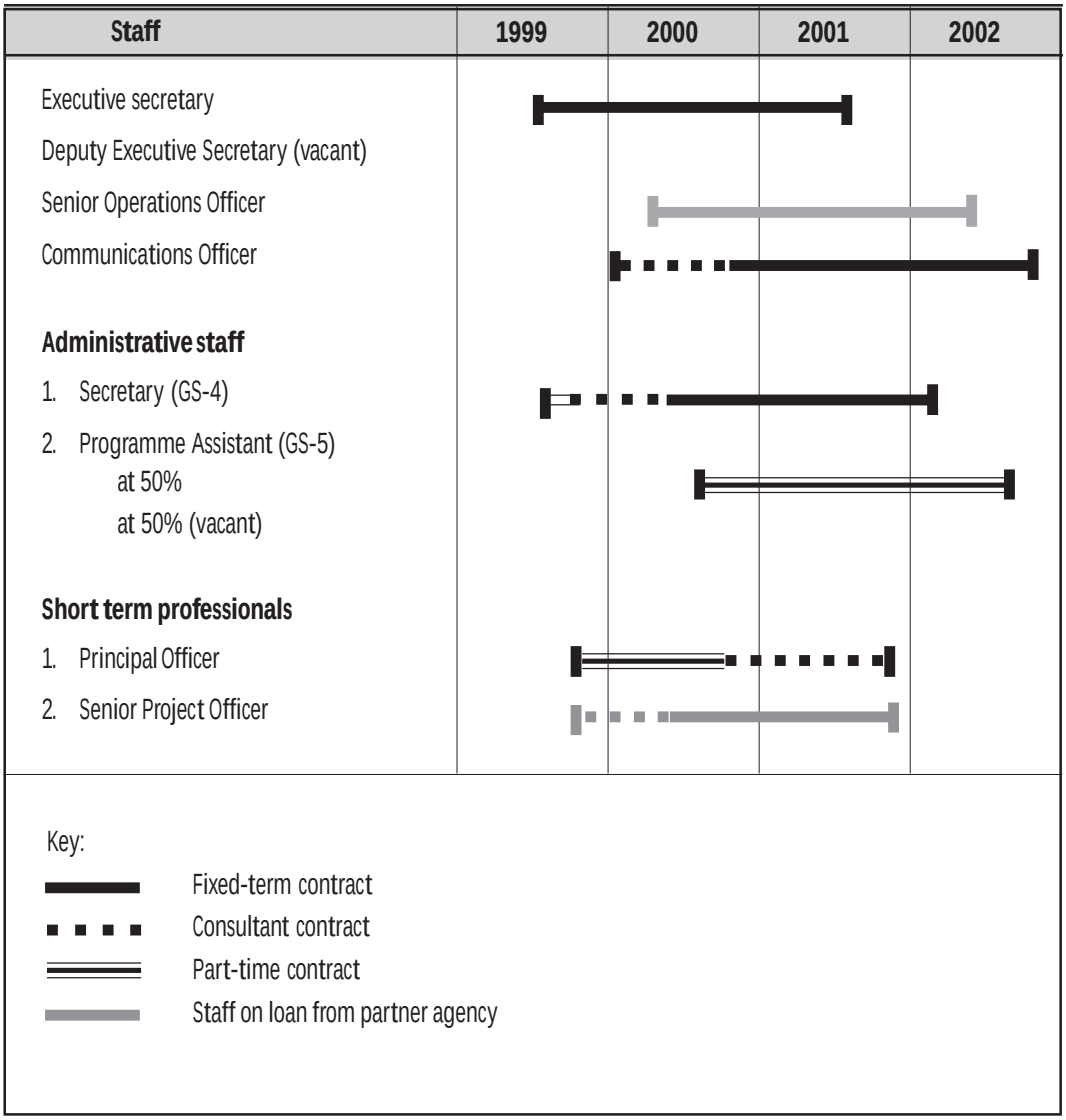


Table 2: Income and projected income (US$)
for budget period 1 July 1999 to 31 December

	GAVI Board Member	1999	2000	Total	Paid [1]	To be paid
1	UNICEF	150 000	300 000	450 000	170 000	280 000
2	The World Bank	150 000	300 000	450 000	300 000	150 000
3	WHO	150 000	300 000	450 000	300 000	150 000
4	The Bill & Melinda Gates Foundation/ PATH/Children's Vaccine Program (CVP)[2]	150 000	300 000	450 000	450 000	0
5	OECD 1 (Canada)	150 000	300 000	450 000	0	450 000
6	OECD 2 (the Netherlands)	--	300 000	300 000	0	300 000
7	OECD 3 (to be elected)	--	--	--	--	0
8	Low Income Country 1 (Bhutan)	--	--	--	--	0
9	Low Income Country 2 (to be elected)	--	--	--	--	0
10	OECD Industry (IFPMA)	150 000	300 000	450 000	290 000	160 000
11	Developing country industry	--	--	--	--	0
12	Foundations (Rockefeller)	150 000	300 000	450 000	500 000	0
13	Research and Development (NIH)	150 000	300 000	450 000	0	450 000
14	Technical Health Institution (vacant)	--	--	--	--	0
15	NGO (Currently CVP)[2]	--	150 000	150 000	150 000	0
	Total (US$)	**1 200 000**	**2 850 000**	**4 050 000**	**2 160 000**	**1 940 000**

[1] US$ 1 870 000 was received by 30 September 2000.
[2] Contribution paid in full, up to 30 June 2001.

Table 3: Analysis of expenditures versus approved budget (US$)
as of 30 September 2000

Budget category	1999	2000	Total	Requisitions [1]
IP Staff	353 682	750 372	1 104 054	248 753.52
Support staff	48 022	99 915	147 937	54 000.00
Equipment maintenance/operating costs	71 368	27 184	98 552	76 986.66
Travel	50 000	100 000	150 000	192 876.67
Task forces	300 000	750 000	1 050 000	643 198.56
Meetings and contractual work	200 000	400 000	600 000	536 692.97
Total (US$)	**1 023 072**	**2 127 471**	**3 150 543**	**1 752 508.38**

[1] This includes recorded expenditures amounting to US$ 1 415 935.03.

Table 4: Projected income (US$) for the budget period, 1 January 2001 to 31 December 2002

GAVI Board Members	2001	2002	Total
1 UNICEF	300 000	300 000	600 000
2 The World Bank	300 000	300 000	600 000
3 World Health Organization	300 000	300 000	600 000
4 The Bill & Melinda Gates Foundation	300 000	300 000	600 000
5 OECD 1	300 000	300 000	600 000
6 OECD 2	300 000	300 000	600 000
7 OECD 3	300 000	300 000	600 000
8 Low-income country 1	n/a	n/a	n/a
9 Low-income country 2	n/a	n/a	n/a
10 OECD industry	300 000	300 000	600 000
11 Developing country industry	n/a	n/a	n/a
12 Foundations	300 000	300 000	600 000
13 Research and development	300 000	300 000	600 000
14 Technical health institutions	300 000	300 000	600 000
15 Non-governmental organizations	300 000	300 000	600 000
Total (US$)	**3 600 000**	**3 600 000**	**7 200 000**

Table 5: Proposed expenditures (US$) for the budget period, 1 January 2001 to 31 December 2002

Budget line		2001	2002	Total	% per category
1.	**Staff & operating costs**				
1.1	Professional staff	607 304	634 424	1 241 728	17.25%
1.2	Support staff	143 356	149 134	292 490	4.06%
1.3	Short-term professionals & consultants	445 840	464 942	910 782	12.65%
1.4	Operating costs (including equipment and maintenance)	80 000	90 000	170 000	2.36%
1.5	Travel	200 000	200 000	400 000	5.56%
2	**Task forces**	600 000	300 000	900 000	12.50%
3.	**Meetings, reviews & associated costs**				
3.1	Reviews of country proposals	270 000	180 000	450 000	6.25%
3.2	Verifications	360 000	360 000	720 000	10.00%
3.3	Mid-term reviews[1]		1 080 000	1 080 000	15.00%
3.4	Workshops	100 000	120 000	220 000	3.06%
3.5	Partners' meeting		600 000	600 000	8.33%
3.6	Contractual work including website	100 000	115 000	215 000	2.99%
	Total (US$)	**2 906 500**	**4 293 500**	**7 200 000**	**100.00%**

[1] 40K per review might not be sufficient.

Annex 7

Other matters

Discussion documents on other matters

Annex 7 comprises documents produced for information only:

- Annex 7a: GAVI Board policy on vaccines of limited supply – Produced by the GAVI Working Group, this document outlines the main points of consensus reached by the GAVI Board on the allocation of scarce combination vaccines during its 4 October 2000 teleconference.
- Annex 7b: GAVI in-kind donation policy

Annex 7a

GAVI Board policy on vaccines of limited supply

The GAVI Board will authorize the procurement of yellow fever, hepatitis B (hep B) and *Haemophilus influenzae* type B (Hib) vaccines for countries through the new and under-used vaccine sub-account of the Global Fund for Children's Vaccines (the Global Fund).

Early country demand for vaccines through the Global Fund has been enormous. In the short-term (until 2003), the supply of certain combination vaccines will not meet the expected demand. This document outlines the allocation process for vaccines in limited supply.

1. Current vaccine supply situation

At this time, the GAVI Board recognizes the following vaccine supply situation:

- Yellow fever vaccine: There may be shortages of some presentations of yellow fever vaccine in the short-term.
- Monovalent hepB and Hib: There are sufficient monovalent hepB and Hib vaccines to meet the current demand.
- Combinations with hepB and/or Hib: The supply of combination vaccines with hepB and/or Hib offered to UNICEF for the Global Fund will not be sufficient to meet anticipated demand through 2003.

2. GAVI policies on allocation of vaccines in limited supply

The following considerations will govern the allocation of vaccines among countries. These considerations will be applied in a manner consistent with previously established GAVI and Global Fund policies.

2.1 Yellow fever vaccine

In the event that there is a shortage of some presentations of yellow fever vaccine, priority for introduction will be established according to risk level as specified in Table 1.

3. Combination vaccines

Preliminary indications from the first round of procurement and evolving-country data indicate that demand for selected combination vaccines, and in particular DTP-hep B, will outstrip supply until 2003.

Table 1: Priority countries for yellow fever vaccine

Group	Risk level	Characteristics	Countries (in order of priority)[1]
Group 1	Highest risk	Recent large epidemics; high number of reported cases; densely populated; many epidemics.	Nigeria, Cameroon, Kenya, Liberia, Mali, Burkina Faso, Senegal, Benin, Ghana, Guinea, Cote d'Ivoire, Niger, Sierra Leone, Togo
Group 2	Medium risk	Epidemic and/or reported cases in the past; this includes countries that have already included yellow fever into routine EPI and have good measles coverage.	Angola, Gabon, Mauritania, Central African Republic, Chad, Congo, Equatorial Guinea, Ethiopia
Group 3	Lower risk	No reported epidemics or, at least, not in the last 20 years.	Sudan, DR Congo, Eritrea, Rwanda, Burundi, Gambia, Guinea, Bissau, Tanzania, Uganda, Cape Verde, Sao Tome, Somalia

[1] Additional countries will be added based on input from the Pan American Health Organization.

The GAVI Board has determined that all combination vaccines in limited supply will be allocated as follows:

- Countries with DTP3 coverage of 50% will have first priority for combination vaccines, if such vaccines are requested by the respective government, in collaboration with the major partners on the Inter-Agency Coordinating Committee (ICC).
- Countries with DTP3 coverage of 51% would have second priority, those with DTP3 coverage of 52% would have third priority, and so on (See Table 2).
- Coverage will be based upon DTP3 as reported on the 1999 WHO-UNICEF Joint Reporting Form.
- For the 13 countries that received approval for proposals in July 2000, DTP3 coverage data will be taken from their proposal documents which reflect the signed endorsement of the data by the governments and ICC partners at country level.

In providing combination vaccines to those countries with weaker immunization systems (as defined by the DTP3 coverage rate), the GAVI Board recognizes that those countries with weak immunization systems are also those that have the greatest programmatic and safety considerations to overcome and the least flexibility in introducing new vaccines. The burden of introducing new vaccines and the consequent challenges to the immunization programme, including the need for training and the additional cold chain and logistics requirements, are minimized through the use of combination vaccines. Furthermore, vaccines given in combination necessitate fewer injections per child, thereby minimizing the risk of adverse injection events and enhancing safety.

In adopting this policy of allocation of all vaccines in limited supply, the GAVI Board affirms the following:

- A specific vaccine formulation or presentation will only be introduced where there will be sufficient quantity to meet a country's total projected needs. This commitment extends to countries that decide to introduce new vaccine in a phased programme.
- Countries with large birth cohorts (those that will require on the order of 50% of the available doses) will be strongly encouraged to introduce monovalent vaccine. The Fund will not provide combination vaccines to those countries at this time (e.g., based on the available supplies of DTP-hep B the Global Fund will not be able to provide this vaccine to Pakistan and Bangladesh at present).
- Given that the introduction of monovalent vaccines will pose additional challenges for immunization delivery systems, countries that introduce monovalent vaccines will receive priority for GAVI partner-supported training and technical assistance.
- The supply of combination vaccine is expected to increase substantially from 2004. Additional supplies will be allocated according to the GAVI policy outlined above. Countries that have recently become eligible for support for vaccines from the Global Fund by increasing their national DTP3 coverage rate to at least 50% will be included in the allocation of new supplies. The GAVI Board will also review the vaccine allocation policy and guidelines for countries with large birth cohorts at this time.

4. Time-frame of introduction of combined vaccines

If a country is likely to substantially delay introduction of a combined vaccine, beyond the end of 2001 or to a point in time when available combined vaccines would not be used efficiently, the GAVI Board directs the UNICEF Supply Division to reallocate vaccines to countries requesting them sooner, thereby ensuring that available supplies are fully utilized.

Table 2: Priority for combination vaccines

In accordance with GAVI Board policy, countries with 50% DTP3 coverage in 1999 and a birth cohort that will not require on the order of 50% of the available doses for 2001,2002, or 2003, have initial priority for combination vaccines, with availability to countries with higher coverage as supplies permit.

	Country	1999 % DTP3 coverage		Country	1999 % DTP3 coverage
1	Uganda	54	27	Guyana	83
2	Papua New Guinea	56	28	Malawi	83
3	Lao PDR	56	29	Solomon Islands	86
4	Eritrea	56	30	Bolivia	87
5	Cote d'Ivoire	56	31	Gambia, The	87
6	Rwanda [1]	57	32	Korea, DPR	87
7	Madagascar	57	33	Armenia	88
8	Pakistan[2]	59	34	Bhutan	88
9	Senegal	60	35	Sudan	88
10	Haiti	61	36	Nicaragua	90
11	Guinea-Bissau	63	37	Bosnia & Herzegovina	90
12	Burundi	63	38	Mongolia	90
13	Lesotho	64	39	Benin	90
14	Kenya	64	40	Zambia	92
15	Cambodia	65	41	Azerbaijan	93
16	Bangladesh [2]	69	42	Viet Nam	93
17	Yemen	72	43	Cuba	94
18	Sao Tome	73	44	Tajikistan[3]	94
19	Mozambique	73	45	Honduras	95
20	Ghana	73	46	Moldova	97
21	Myanmar	75	47	Albania	97
22	Comoros	75	48	Turkmenistan	99
23	Tanzania	76	49	Kyrgyzstan	99
24	Nepal	76	50	Sri Lanka	99
25	Georgia	80	51	Ukraine	99
26	Zimbabwe	81	52	Uzbekistan	99

[1] May not apply until 2002.
[2] Birth cohort that will require approximately 50% of the available doses and is not eligible for combination vaccines in limited supply.
[3] 1998 figures given for DTP3 coverage.

Table 3: Countries not currently eligible
for new and under-used vaccine sub-account of the Global Fund,
September, 2000

Country	1999% DTP3 coverage
1. Congo, Democratic Republic of	15
2. Somalia	18
3. Mauritania	19
4. Niger	21
5. Nigeria	21 (1998)
6. Ethiopia	21
7. Sierra Leone	22
8. Liberia	23
9. Djibouti	23
10. Central African Republic	28
11. Congo, Republic of	29
12. Angola	29
13. Chad	33
14. Afghanistan	37
15. Burkina Faso	37
16. Guinea	46
17. Togo	48
18. Cameroon	48
19. Mali	48

Annex 7b

GAVI in-kind donation policy

Several manufacturers have indicated an interest in donating vaccines to GAVI, "bundled" together with auto-disable syringes and safety boxes. The proposed guidelines on a GAVI donation policy are as follows:

- Vaccines, together with auto-disable syringes and safety boxes, may be offered at no cost to UNICEF Supply Division as part of a procurement on behalf of GAVI, on the condition that other supplies of the same type are purchased at a set price (referred to as "free goods" offers). The cost of the total quantity in the offer will be taken as the weighted average price per unit (total cost divided by the total units received). All offers will be evaluated on the basis of UNICEF rules and regulation on procurement.
- Stand-alone donations of vaccines and the above supplies can be made through the Global Fund for Children's Vaccines, which has 501(c) 3 tax status under the tax laws of the United States.
- Donated vaccines will be directed to countries that have received approval, through the GAVI review process, for country support from the Fund. The allocation will be coordinated with the allocation of procured vaccines and related supplies.
- The active participation of the vaccine producer will be strongly encouraged, particularly in the areas of shipment, distribution, training and capacity-building for the safe use of vaccines. UNICEF Supply Division can provide guidance on technical matters related to donations of vaccines and injection materials, such as appropriate labelling, packaging of products and shipping instructions,.
- All vaccines should be pre-qualified by WHO for procurement by United Nations agencies; all auto-disable syringes and safety boxes should meet WHO specifications.
- The in-kind donations to GAVI, described above, are for new and under-used vaccines. Currently, these include vaccines for Hib, hepatitis B and yellow fever as well as combination vaccines or the antigens.

Annex 8

List of participants

(4th GAVI Board meeting, November 2000)

GAVI Board Members

1. Host: Dr Els Borst-Eilers, Deputy Prime Minister and Minister of Health, Welfare and Sport, The Netherlands
2. Chair: Dr Gro Harlem Brundtland, WHO Director-General, and GAVI Chair, Geneva
3. Mr David Alnwick, UNICEF, New York, USA
4. Mr Jean-Jacques Bertrand, Aventis Pasteur, Paris, France
5. Dr Yves Bergevin, CIDA, Canada
6. Dr Tim Evans, Rockefeller Foundation, New York USA
7. Mr William Gates Sr., Bill & Melinda Gates Foundation, Seattle, USA
8. Dr Mark Kane, Bill & Melinda Gates' Children's Vaccine Program, Seattle, USA
9. Dr John LaMontagne, NIH, Bethesda, USA
10. Mr Chris Lovelace, The World Bank, Washington, USA
11. Dr Lyonpo Sangay Ngedup, Ministry of Health and Education, Thimphu, Bhutan
12. Mr André Roberfroid, UNICEF, New York, USA
13. Dr Lomamy Shodu, Ministry of Child Health Department, Harare, Zimbabwe
14. Dr Yasuhiro Suzuki, WHO, Geneva, Switzerland

GAVI Working Group

15. Ms Amie Batson, The World Bank, Washington, USA
16. Dr Tore Godal, GAVI, Geneva, Switzerland
17. Ms Jackie Keith, Wyeth-Ayerst Labs, Pennsylvania, USA
18. Dr Steve Landry, USAID, Washington, USA
19. Dr Myron Mike Levine, University of Maryland, Baltimore, USA
20. Mr Jacques-François Martin, President, The Global Fund for Children's Vaccines, Lyon, France
21. Dr Suomi Sakai, UNICEF, New York, USA
22. Mr Michel Zaffran, WHO Geneva, Switzerland

Observers

23. Mr Bruce Aylward, WHO, Geneva, Switzerland
24. Mr Christian Falkowski, European Commission, Belgium
25. Prof. Jan Holmgren, University of Goteborg, Sweden
26. Mr Steve Jarrett, UNICEF, New York, USA
27. Mr Charles Lyons, United States Fund for UNICEF, New York, USA
28. Dr Julian Lob-Levyt, DFID, United Kingdom

29. Dr Bjorn Melgaard, WHO, Geneva, Switzerland
30. Dr Sigrun Mogedal, State Secretary, Oslo, Norway
31. Mr Terry Peel, Edington, Peel & Associates, Washington, USA
32. Dr Gordon Perkin, The Gates Foundation, Seattle, USA
33, Dr Peter Wilson (consultant), United Kingdom
34. Dr David Nabarro, WHO, Geneva, Switzerland

GAVI Secretariat

35. Mr Umberto Cancellieri
36. Ms Lisa Jacobs
37. Dr Ivone Rizzo
38. Mr Bo Stenson

The Netherlands

39. Professor Kees Lucas
40. Ms Monique Middelhoff, Ministry of Health
41. Mr Jacob Waslander, Permanent Mission of the Netherlands, Geneva

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