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VACCINE PRODUCTION IN THE THIRD WORLD:

THE SEARCH FOR ALTERNATIVES

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VACCINE PRODUCTION IN THE THIRD WORLD: THE SEARCH FOR ALTERNATIVES

A) Vaccines for the Third World--Needs, Opportunities, and Options

1. The vital need for more and better vaccines in the Third World and the equally critical need for fresh approaches in developing, producing, and distributing these vaccines has been widely discussed in the international community in recent years. The argument was forcefully presented in an important article by Anthony Robbins and Phyllis Freeman in the November 1988 Scientific American. Robbins and Freeman began that article with this statement:

> Global immunization programs sponsored by the United Nations have made astonishing strides in the developing world during the past 25 years. Unfortunately this rapid forward movement is in danger of stalling. The loss of momentum would be tragic, given what has been achieved so far.[1/]

2. A similar assessment is offered by the recently initiated Dutch Biotechnology and Development Monitor:

> Global immunization programs sponsored by the United Nations have made considerable progress in the developing world during the

last 25 years. The Expanded Program of Immunization (EPI) of WHO and UNICEF is primarily targetted towards children, because they are the main victims of infectious diseases. In Africa, Asia and Latin America, acute respiratory infections (such as the pneumonias caused by Streptococcus and Hemophilu influenza) and dirrheal diseases (such as infections caused by rota virus, Shigella, vibrio cholera and certain types of E. Coli bacteria) annually kill some eight million children under the age of five. These infections, combined with other diseases, notably measles, malaria, tetanus, meningitis and typhoid fever kill an estimated 14 million children and disable many more.

The Institute of Medicine of the National Academy of Science of the United States in 1986 identified 19 priority infections for which new or vastly improved vaccines could feasibly be produced by 1996, from a scientific point of view (see Table 5). However, the obstacles to the development and distribution of the needed vaccines are many. <u>They are foremostly economic and political</u>.[2/]

3. What has been accomplished through international cooperation and the dedicated work of tens of thousands of doctors, nurses, and other public health workers on the ground throughout the Third World is truly impressive. Smallpox, a scourge of humankind throughout recorded history, was totally eradicated a

decade ago. In more recent years, mortality and morbidity rates have been very substantially reduced for six other major diseases--measles, diptheria, pertussis (whooping cough), tetanus, polio and tuberculosis. But these diseases still cause preventable death and disability for tens of millions of people, expecially children in the Third World. It is estimated, for example, that measles still kills two million children, or if we take the combined impact of infections and diseases mentioned in paragraph 2 above, 14 million children (not to mention the many more who are disabled) in developing countries every year.

4. In many ways, therefore, the struggle to develop, produce, and deliver new vaccines in the developing countries is focused on the needs of children because they are the main victims of the lack of effective vaccines. That struggle needs to be placed in the larger context of the global effort to protect the world's children, which was the subject of an important agenda-setting conference at Talloires, France, in March 1988 organized by the Task Force for Child Survival, a joint undertaking of five key organizations involved in this struggle (World Health Organization, UNICEF, United Nations Development Programme, World Bank, and Rockefeller Foundation). The conclusion of that conference, embodied in the "Declaration of Talloires", urged all those concerned--national governments, multilaterial development agencies, the UN, non-governmental organizations, and private and voluntary groups--to "accelerate progress to achieve universal childhood immunization by 1990" and to "assure the development of new vaccines and technology and their application...in developing countries."[3/] (The text of this Declaration is given in Appendix 1.)

5. Not only is there a need to increase production and distribution of

existing vaccines, in many cases improvements in the vaccines themselves are urgently required, a subject that is further discussed below. And of course there are still many diseases for which effective vaccines have yet to be developed, although it appears that we are on the threshold of breakthroughs in several instances.

6. The situation is summed up by the table and figures which follow. The first is a highly refined list of just ten priorities divided into two categories, North and South. However, it should be noted that at least three of the "Northern" priorities are also relevant to meeting health care needs in the South, underscoring the global nature of the struggle to develop, produce, and deliver new and improved vaccines.

Table 1

Priorities for New Vaccine Development

North	South
Hepatitis B	Streptococcus pneumoniae
Respiratory syncytial virus	Plasmodium spp.
Hemophilus influenzae b	Rotavirus
Influenza A and B	Salmonella typhi
Herpesvirus varicellae	Shigella spp.

Source: Kenneth S. Warren, "New Scientific Opportunities and Old Obstacles in Vaccine Development," Proceedings of the National Academy of Sciences, USA, December 1986 (Vol. 83), pp. 9275-9277, as quoted in New and Improved Vaccines," Biotechnology and Development Monitor, (Amsterdam: Department of International Relations

and Public International Law, University of Amsterdam, September 1989 (No. 1).

7. Another way of approaching the situation, focused in this instance on the health care needs of children, is reflected in Figures 1, 2, and 3 from the Task Force for Child Survival. These figures include both vaccines already used and more and more widely available in developing countries, such as measles, polio, and mumps as well as those in various stages of development such as malaria.

8. One of the truly remarkable exercises in global problem-solving is the already mentioned Expanded Programme on Immunziation (EPI) undertaken by the World Health Organization in collaboration with UNICEF. A recent report by the EPI Global Advisory Group sums up both what has been accomplished and what needs still to be done.

> Immunization services which were virtually nonexistent in developing countries in 1974 now cover half the children of the world with a dose of measles vaccine (generally by early in their second year of life) and cover 60% of children reaching their first birthday with a third dose of polio or DPT vaccines and over 60% with BCG vaccine. As a consequence, the EPI now prevents over 1.9 million deaths from measles, whooping cough and neonatal tetanus and some 240,000 cases of poliomyelitis in developing countries each year.
>
> Yet the daily tragedy of vaccine-preventable death and disability

Figure 1

CHILDHOOD VACCINES IN ROUTINE GLOBAL USE IN YEAR 2000

- Measles
- Polio**
- DPT
- Mumps
- Rubella
- Rotavirus
- Hepatitis B
- Hepatitis A
- Hemophilus influenzae
- Pneumococcus

** Excluded if eradication goals met

Source: The Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University.

Figure 2

OTHER CHILDHOOD VACCINES IN YEAR 2000 AVAILABLE TO COUNTRIES IN NEED

- BCG
- Meningococcus
- Yellow Fever
- Japanese Encephalitis B
- Typhoid
- Shigella
- Cholera
- Leprosy

Source: The Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University.

Figure 3

POSSIBLE NEW VACCINES IN YEAR 2000

- Malaria
- Herpes 1 and 2
- Shistosomiasis
- Dengue
- RSV (Respiratory Syncytial Virus)
- Streptococcus (Group B)

Source: The Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University.

continues. Each year, nearly three million children die, over 200,000 are paralysed and some 150,000 are blinded from these diseases. Immunization levels need to be raised further, aiming to reach levels of at least 80% for all children of the world by 1990 and of at least 90% by the year 2000, in the context of comprehensive maternal and child health services. This will require continued effort, particularly in improving the management of immunization services.

Immunization schedules need to be simple, effective and epidemiologically appropriate. Screening for the need for immunization should occur with every contact with the health services, and all unimmunized women and children should either be immunized at that contact or referred for immunization. Screening by hospital staff and other health workers who provide curative services is especially needed and represents a step toward more general integration of curative with preventive care.[4/]

9. The current status of these efforts and what remains to be achieved is indicated in Tables 2, 3, and 4. It is clear from these numbers that, notwithstanding what has been accomplished, much remains to be done. And these tables, of course, reflect the situation in the six major diseases mentioned above. There are many others that need also to be addressed in the years ahead.

10. Another picture of this situation is provided in Table 5, which identifies and ranks 19 diseases in terms of their impact on infant mortality.

Table 2

Protection of Young Children and Pregnant Women in Developing Countries Through Immunisation for Six Major Diseases

As of December 1988

Country[1]	Newborns surviving to 1 year of age (millions)	Cumulative percentage of infants		Immunisation coverage (%)				
				Children less than 1 year of age				Pregnant women
				BCG	DPT III	Polio III	Measles	Tetanus II
		%		%	%	%	%	%
1. India[a]	22.58	25		72	73	64	44	58
2. Indonesia[a]	5.15	31		74	61	62	55	29
3. Nigeria[b,c]	4.50	36		37	21	21	24	17
4. Bangladesh[b]	4.15	40		14	9	8	6	7
5. Brazil[b]	4.07	45		88	57	90	55	62
6. Pakistan[b]	4.03	49		72	62	62	53	27
7. Mexico[b]	2.68	52		71	62	97	54	42
8. Ethiopia[b,c]	1.99	55		27	16	6	13	7
9. Islamic Republic of Iran[b]	1.98	57		56	74	74	76	12
10. Philippines[b,c]	1.83	59		92	73	73	68	49
11. Viet Nam[b]	1.78	61		68	61	75	60	...
12. Egypt[b]	1.78	63		72	81	81	86	12
13. Thailand[b]	1.44	64		61	48	47	34	38
14. Turkey[b]	1.41	66		34	71	70	50	...
15. Zaire[b]	1.29	67		54	36	36	39	25
16. South Africa	1.28	69		...	...	...	...	...
17. Burma[b]	1.17	70		45	23	13	14	24
18. Kenya[b,e]	1.13	71		86	75	75	60	37
19. United Republic of Tanzania[b,d]	1.07	73		94	81	65	88	54
20. Republic of Korea[b]	0.95	74		95	85	93	95	...
21. Sudan[b]	0.84	75		46	29	29	22	12
22. Algeria[b,e]	0.90	76		85	66	66	50	...
23. Colombia[b]	0.88	77		80	58	82	50	6
24. Morocco[b]	0.85	78		87	78	78	76	33
25. Argentina[b,c]	0.75	78		91	75	85	81	...
Total 25 countries	70.63	78		63	58	58	46	35
Other developing countries	19.46	22		61	48	48	46	25
Sub-total, developing countries (excluding China)	90.09	100	82	63	55	56	48	33
China[b,e]	19.84		18	85	75	77	77	...
Total, developing countries (including China)	110.03		100	67	60	60	52	27
Total, industrialized countries	18.11			58	66	66	76	...
Global total	128.14			66	60	61	55	23

Notes: See next page

Notes for Table 2

1 Developing countries ranked by numbers of surviving infants

(a) 1988 coverage data

(b) 1987 coverage data

(c) 1986 coverage data

(d) 1985 coverage data

(s) Survey data

*) Children up to 60 months of age

... No information available

The six major diseases and the vaccines are tuberculosis (BCG), diptheria, pertussis (whooping chough), tetanus (DPT), polio, and measles. The figures in Roman numerals refer to the dosage and sequence (second or third), when more than one dose is required to achieve effective immunisation.

Source: Adapted from World Health Organization, Expanded Programme on Immunization: Progress and Evaluation Report (Forty-Second World Health Assembly, Provisional Agenda Item 18.2, A42/10, 6 March 1989).

Table 3

Prevention of Death Through Immunization for Four Major Diseases in Developing Countries

(As of December 1988)

	(a) Newborns	(b) Surviving infants	(c) Prevented neonatal tetanus deaths	(d) Prevented pertussis cases	(e) Prevented pertussis deaths	(f) Prevented measles cases	(g) Prevented measles deaths	(h) Prevented poliomyelitis cases
	(in thousands)							
5 largest developing countries as listed in Table 1	77,176	70,633	274	28,357	325	30,803	918	195
Other developing countries (excluding China)	21,464	19,558	51	6,594	75	8,546	256	45
Total for developing countries	98,640	90,191	325	34,950	400	39,349	1,174	239

Notes:

a) Based on 1987 estimated population and crude birth rates.

b) Based on estimated number of newborns and infant mortality rate.

c) Based on mortality estimates from surveys or reports, a vaccine efficacy of 0.95 and immunication coverage reported as of December 1988. Countries without data were arbitrarily placed in one of three neonatal tetanus mortality classes: 5, 10, or 15 per thousand live births.

d) Based on an estimated incidence of 80% of newborns in the absence of an immunization programme, a vaccine efficacy of 0.8 for three doses, and immunization coverage reported as of December 1988.

e) Based on mortality estimates of one-third of measles deaths, a vaccine efficacy of 0.8 for three doses and immunization coverage reported as of December 1988.

f) Based on an incidence estimation of 100% surviving newborns in absence of an immunization programme, a vaccine efficacy of 0.95 and immunization coverage reported as of December 1988.

g) Based on arbitrary case fatality rates ranging from 2% to 4%, a vaccine efficacy of 0.95 and immunization coverage reported as of December 1988.

h) Based on an estimated incidence of 5 per 1,000 newborns in the absence of an immunization programme, a vaccine efficacy of 0.95 and immunization coverage reported as of December 1988.

Source: Adapted from World Health Organization, Expanded Programme on Immunization: Progress and Evaluation Report (Forty-Second World Health Assembly, Provisional Agenda Item 18.2, A42/10, 6 March 1989).

Table 4

Mortality and Morbidity From Four Major Diseases in Developing Countries

(As of December 1988)

	Deaths from neonatal tetanus(1)	Deaths from Measles(2)	Deaths from pertussis(3)	Total deaths	Cumulative percentage of total deaths	Polio-myelitis cases(4)	Cumulative percentage of cases
	(in thousands)				%	in thousands)	%
5 developing countries s listed in Table 1	590	1,263	402	2,256	79	159	75
ther developing countries excluding China)	164	330	121	615	21	53	25
otal for developing ountries	754	1,593	523	2,871	100	212	100

otes:

sing the immunization coverage data from Table 1, the following assumptions have been made:

1) Neonatal tetanus: Based on survey data or, in the absence of survey data, extrapolated from countries with similar socioeconomic conditions.

2) Measles: It is assumed that the vaccine efficacy is 95% and that all unimmunized children will contract measles. Coverage is assumed to be "zero" in countries for which data are not available.

3) Pertussis: It is assumed t.. the vaccine efficacy is 80% and that 80% of unimmunized children will contract ertussis. Coverage is assumed to be "zero" in countries for which data are not available.

4) Poliomyelitis: In view of the narrow limits of variation of results of poliomyelitis surveys, and in the absence of an immunization programme, a fixed incidence rate of 5 cases per thousand newborns is used. A vaccine efficacy of 95% is assumed. Coverage is assumed to be "zero" in countries for which data are not available.

ource: Adapted from World Health Organization, Expanded Programme on Immunization: Progress and Evaluation Report, (Forty-Second World Health Assembly, Provisional Agenda Item 18.2, A42/10, 6 March 1989).

Table 5

Diseases in Developing Countries Ranked by Total Disease Burden

Disease	Total Disease Burden Value (IME units)[a]
Streptococcus pneumoniae	6,612,261
Hepatitis B virus	2,394,256
Plasmodium spp.	2,111,795
Salmonella typhi	1,308,121
Escherichia coli	978,248
Rotavirus	925,042
Shigella spp.	828,068
Streptococcus Group A	811,477
Mycobacterium leprae	657,349
(*Escherichia coli*)	(550,248)[b]
(Rotavirus)	(488,542)[b]
Hemophilus influenzae type b	471,336
Vibrio cholera	229,217
Respiratory syncytial virus	183,326
Parainfluenza virus	145,954
Neisseria meningitidis	68,252
Rabies virus	67,821
Dengue virus	34,365
Yellow fever virus	32,887
Hepatitis A virus	30,229
Japanese encephalitis virus	18,075

[a]Infant mortality equivalence units.

[b]Values represent the anticipated disease burden from certain diarrheal pathogens if a plausible increase in oral rehydration therapy is assumed.

Source: National Academy of Sciences, *Diseases of Importance in Developing Countries* (Vol. II of *New Vaccine Development: Establishing Priorities*) Washington: National Academy Press, 1986.

11. Notwithstanding the large numbers of preventable deaths and cases of disease as reflected in Table 4, so much progress has been achieved thorugh this kind of coordinated global attack that new goals are being set. Perhaps the most significant recent develooment is the action taken by the Forty-First World Health Assembly in committing WHO to the global eradication of poliomyelitis by the year 2000.[5/]

12. And the EPI mission is likely to be enlarged by the inclusion of other widespread and preventable diseases such as Hepatitis B, a highly infectious disease which affects entire populations in many developing countries and is transmitted primarily in the first five years of life. The International Task Force on Hepatitis B Immunization seeks to integrate hepatitis B vaccine, the cost of which has been reduced substantially in recent years, into EPI in the next five to ten years.[6/]

13. Thus it is clear that there are compelling unmet needs in human health, especially in the Third World, and that at least some of these needs can be met in substantial measure through cooperation and coordinated effort within the international community. Once the systems for delivering the vaccines to entire populations and monitoring the effectiveness of immunization are in place--as they are in more and more Third World countries and as they have been for some years in most industrialised countries--the critical issues revolve around the availability, effectiveness, and cost of vaccines. Here major problems exist but there also appear to be ways of overcoming them.

14. From the point of view of meeting health needs in the Third World, probably the most significant category of problems relates to the so-called "orphan vaccines". That is, those vaccines that have no significant market in the industrialised countries. Most of the capacity for developing new vaccines,

improving them, and then producing them in large quantities is concentrated in the industrialised world and is, inevitably, concentrated on vaccines for diseases that are widespread in that world. Robbins and Freeman sum up the situation in these words:

> [A] waiting strategy will certainly not make available vaccines that have no market in the industrial world. As things stand now, several important vaccines that are scientifically feasible, according to the [U.S. National Academy of Sciences'] Institute of Medicine, are likely to be neglected by commercial firms for lack of a market in the industrialized nations. Such vaccines include ones against shigellosis, leprosy and infections caused by Streptococcus pneumaniae (in infants) and enterotoxigenic E coli (E. coli that produce intestinal toxins). The same may be true for improved versions of the vaccines for measles, polio, cholera, typhoid, Japanese encephalitis and yellow fever.
>
> Thus market forces militate against the production of critically needed vaccines for the Third World, and even the vaccines that have a chance of being produced are for the most part unlikely to be affordable any time soon, if ever. In some cases the EPI may have to consider buying potentially inferior products (such as the plasma-based vaccine for hepatitis B instead of a genetically engineered one) because they are the least costly. Even that option is not always open: manufacturers who have employed relatively low

cost technologies to make vaccines may remove their less expensive products from the market when they introduce versions made with a more advanced technology.7/

15. A similar conclusion is reached by the Dutch Biotechnology and Development Monitor:

> Commercial vaccine development is guided by the demand in industrialised countries, where priorities differ from those in developing countries...As a result a kind of vacuum does exist for those diseases that hardly occur in the North, but are very damaging for the South.
>
> To obtain the large volume of inexpensive vaccines needed for the Expanded Program on Immunization, the administrators had to apply a "waiting strategy". This means that they waited to buy vaccines until these had been sold in the developed world for many years. The manufacturers thus had long since recouped their research and development costs and could consider selling their product at close to the cost of production...Several commercial producers, however, are expected to leave this market and use their capacities for more profitable products.8/

16. While the situation is discouraging, it is certainly not without hope. And there are important possibilities for developing and producing the "orphan vaccines" that will not get developed through the market forces of the

industrialised countries. Robbins and Freeman outline four approaches, each of which has advantages and disadvantages.

17. The first involves raising money through the UN system to buy vaccines at prices close to their market price. In other words, these prices would include development costs and profits. The hope is that the promise of a new, lucrative market would encourage the pharmaceutical industry, which is primarily based in the industrialised countries, to make the needed investment in development.

18. For this approach to be successful, international collaborative initiatives like the Expanded Programme on Immunization would have to predict well into the future the number of doses that would be purchased. On the negative side, agencies that are already involved in large-scale vaccine procurement for use in developing countries like UNICEF and the Pan American Health Organization (which is the regional office for the Americas of WHO) would need to commit themselves to buying given quantities of vaccines at top prices for a long period of time. It is by no means clear that they would be able to make this commitment.

19. A second option outlined by Robbins and Freeman would be for the UN system to create an international institute of some kind to develop and manufacture its own vaccines. Such an institute would, in effect, bypass existing major commercial manufacturers of vaccines. Robbins and Freeman comment on both the potential and the problems associated with this aproach:

> If the institute were equipped with advanced technology and staffed by the finest epidemiologists, molecular biologists, fermentation engineers and other professionals from around the world, it might well produce rapid results.
>
> Such an institute could pursue new technologies that are par-

ticularly appropriate to Third World public health needs without having to earn rapid profits. For example, workers might be able to insert genes for antigens from different bacteria and viruses into a single carrier organism--such as the vaccinia virus that once constituted the smallpox vaccine, or the baccillus Clamette-Buerin (BCG), which is used as the vaccine against tuberculosis--to produce a single vaccine capable of eliciting immunity to a wide range of infections. The institute staff might also be able to advance the development of stable cocktails, or mixtures, of antigens that would immunize against several diseases at the same time, thereby improving the ability of the developing countries to provide complete coverage for their children.

As the UN's health programs expand, the possibility that the organization could operate such an institute increases, but the disadvantages of the solution are as tangible as its appeal. The creation of such a center would be both costly and time-consuming, and the politics of international cooperation are brutal. 9/

20. The importance of vaccine development and production, conclude Robbins and Freeman regarding this approach, "is too critical to the health of the world to rely at the start on an international center alone."

21. The third approach would involve establishing development and production units in Third World countries, especially those with large populations and sufficient scientific and industrial infrastrucutre to make this approach

possible. This approach is in fact being pursued by the Pan American Health Organization, with support from the Rockefeller Foundation, in Latin America, where two regional vaccine centres--in Mexico and Brazil--have been proposed.10/

22. Robbins and Freeman outline some of the problems with this alternative:

> A major roadblock...is the fact that the World Bank and other agencies that might provide loans to establish such units are increasingly concerned with meeting banker's standards (seeing a good return on an investment) when they finance new industrial enterprises. The development and production of vaccines to meet the health needs of the Third World is unlikely to turn a profit.
>
> Even if financing can be obtained, the full benefits of this approach will take years to realize. It will take time for any institute to produce a product, time for the institute to address the range of needs in its region and more time still until a network of such institutes can meet all the vaccination needs of every region in the developing world.11/

23. This, in fact, has been the experience with the PAHO initiative in Latin America. For two years since the completion of the initial feasibility study in October 1987, the effort to implement this scheme has been focused on building the appropriate coalitions of support and expertise in the two countries where

the vaccine production centres would be established and exploring sources of start-up financing. Nonetheless, Robbins and Freeman conclude that:

> The idea is nonetheless worth trying as as a long-term strategy... If the centers [in Latin America] are successful in demonstrating that otherwise competitive nations can cooperate to solve a regional health problem, international aid organizations may decide to help establish similar centers in Africa and Asia.

24. The fourth approach set forth by Robbins and Freeman is the one in which they are themselves most actively involved. The see it as "a rapid and short-term strategy for obtaining tangible results before the end of this century." It would involve the UN system, as in the first alternative, raising money to pay manufacturers. However, with this approach, the funds would be earmarked specifically for the development of "orphan vaccines" that were critically important in meeting Third World health needs. The public sector institutes and private companies that develop these vaccines would then seel them to EPI or other international and regional procurement programmes at or near the cost of production--i.e., with no development costs added on.

25. The advantage of this approach over the first alternative described above, according to Robbins and Freeman, is that identifiable (and by implication, manageable) amounts of money would have to be raised for each vaccine. The EPI and other international agencies would then receive a long-term commitment for supply of vaccine at a low price. Indeed, this objective is already being achieved, at least in some measure, by PAHO through its Regional Vaccine Procurement Programme for vaccines that have already been developed and widely

administered in industrialised countries. Thus, in 1985, PAHO was able to provide a vial of ten doses of polio vaccine for US $.25, which means a price per dose of $.025. Similarly, measles vaccine was $.16 per dose and DPT vaccine $.021 for a ten-dose vial. By 1989 the standard PAHO/EPI price for the DPT ten-dose vaccine was still only US $.0427. And the Procurement Programme had contracted with one of its suppliers for one-dosage measles vaccine at $.30 per dose. 12/

26. But there is also a substantial problem with this fourth alternative, as Robbins and Freman note. It would involve, certainly in the short term, spending most of the money raised for vaccine development outside the Third World in the industrialised countries "where most manufacturers with good track records in translating laboratory discoveries in a full-scale production capacity are currently located." 13/

27. Robbins and Freeman may well be right that this is "a necessary concession now, to ensure speedy, consistent and high-quality vaccine production." But it also entails a high price for the ability of the Third World to meet its own health care needs in the future. Indeed, judging from the experience with the PAHO/EPI Procurement Programme in Latin America, something more perverse may well happen.

28. While the PAHO programme has indeed made possible a very substantial expansion of immunization programmes in Latin American countries by providing vaccines at low cost, one consequence has been the atrophying of what limited facilities there were in several Latin American countries for producing their own vaccines. One after another, these facilities have stopped functioning, unable to compete in price and unable to maintain the critical standards of quality

control. This means that while more lives of mothers and children are being saved in Latin America, Latin American countries are becoming still more dependent on outside sources to meet their most essential health care needs.

29. Robbins and Freeman, it must be emphasised, recognise this hazard and urge that, over the long term, a concerted effort be made "to transfer much of the resulting technology to the developing countries so that they can build on any technology they have already acquired and make their own vaccines."[14/] And while there is certainly merit in their favored approach, as there are some advantages to the other three options they outline, there is also yet another possibility that seeks to draw upon critical elements in all of the different approaches outlined by Robbins and Freeman but in a different configuration that at least offers the possibility of avoiding or minimising some of the disadvantages in each of these options. That alternative is outlined in the remainder of this report.

B) A New Approach to Vaccine Production in the Third World

Need for a New Approach

30. The progress of the Expanded Programme on Immunization over the past decade and a half in working toward its goal of providing immunisation for all children of the world for the six infectious diseases noted above demonstrates what can be achieved through meaningful and effective international cooperation. That sense that some really significant human welfare goals can actually be accomplished within a given time frame, not simply promulgated as slogans, is crucial to launching a new phase of coordinated effort in trying to, literally, wipe off the face of the earth at least some of the age-old scourges of disease and hunger.

31. For all that has been accomplished, much more still needs to be done. The relatively easier (but still assuredly difficult) tasks have already been undertaken--i.e., immunization against diseases for which effective vaccines already existed. The particular focus of the new approach outlined here is on the so-called "orphan vaccines". For it is part of Third World reality that large populations in developing countries are still suffering from regionally significant diseases that should be amenable to prevention with new or more effective vaccines. Many of these diseases are uncommon in the industrialised countries where modern vaccine development is centered. Others are routinely treated medically in the North, an alternative which is often either impractical or not cost effective in the South.

32. As the feasibility study on vaccine production and development for the Pan American Health Organization notes, this next phase in controlling widespread

infectious diseases in the Third World builds on two "revolutions". The first is in the delivery of vaccines to those who need them through the Expanded Programme on Immunization globally and regionally and through the work of international agencies like UNICEF. The other "revolution" concerns vaccine design, development, and production based on advances in genetic engineering and biotechnology. The PAHO feasibility study sums up the impact of these two "revolutions" in the following words:

> In recent years the new technologies have made it possible to produce unprecedented numbers of new and improved vaccines. By selecting vaccine candidates for development and production which can fit into the existing immunization programmes, additional diseases can be controlled at minimal increases in cost of delivery.[15/]

33. The new approach outlined here strives to capture and build upon these two revolutions in the next phase of disease eradication in the Third World. It combines elements of the four options outlined in the preceding section of this report, drawing on their strengths while minimising their limitations.

Objectives

34. One major objective of this approach seeks to control and eradicate disease in the Third World through the development, production, and distribution of new and improved vaccines, particularly for diseases that are widespread in developing countries and with which there is little or no concern in the industrialised world--i.e., the so-called "orphan vaccines." The types of

diseases for which new or greatly improved vaccines are needed in the Third World are listed in Table 6, which is based on the 1986 study of the Institute of Medicine of the U.S. National Academy of Sciences. For most, although not all, of these diseases there is very limited demand in industrialised countries, and much of that demand is generated by persons from the industrialised countries traveling in the Third World.

35. The U.S. National Academy of Sciences has developed a listing of some 20 candidates for accelerated vaccine development, which would provide protection against the diseases identified in the preceding table. Kenneth Warren has identified some of the scientific problems involved, as well as the outlook for progress in developing and deploying candidate vaccines in Appendix 2. This listing is given in Table 7.

36. This new approach should also encompass vaccines which are not now "orphan" but may become so in time. In other words, the diseases which these vaccines seek to prevent are now of concern in the industrialised countries, but as efforts at eradication grow in effectiveness, may become of much less concern to the industrialised countries even while they continue to pose substantial risks to human health in developing countries. Of course, in the best of all possible worlds, total global eradication, as in the case of smallpox, eliminates the need for any further vaccination in North or South. But there still may be some "second" or "third generation" orphan vaccines that will cease to be of major interest to the industrialised countries but still command attention in the Third World. The initiatives described here should not preclude taking up the further development and production of such vaccines.

37. The second major objective of this approach is to enhance Third World capacity for developing and producing new vaccines. While several of the

Table 6

Diseases for Which New or Improved Vaccines are Needed in the Third World

PATHOGEN	POTENTIAL EFFECTS	CASES PER YEAR (AND DEATHS)	INDUSTRIAL DEMAND
Dengue virus	Fever, shock, internal bleeding	35,000,000 (15,000*)	Small (travelers to endemic areas)
Intestinal-toxin-producing *Escherichia coli* bacteria	Watery diarrhea, dehydration	630,000,000 (775,000*)	Small
Hemophilus influenzae type b bacterium	Meningitis, epiglottal swelling, pneumonia	800,000 (145,000*)	Great
Hepatitis A virus	Malaise, anorexia, vomiting, jaundice	5,000,000 (14,000)	Small
Hepatitis B virus	Same as hepatitis A; Chronic cirrhosis or cancer of liver	5,000,000 (822,000)	Moderate
Japanese encephalitis virus	Encephalitis, meningitis	47,000 (7,000*)	Small (travelers)
Mycobacterium leprae	Leprosy	1,000,000 (1,000)	None
Neisseria meningitidis bacterium	Meningitis	310,000 (35,000*)	Some (during epidemics)
Parainfluenza viruses	Bronchitis, pneumonia	75,000,000 (125,000*)	Great
Plasmodium protozoa	Malaria (with anemia, systemic inflammation)	150,000,000 (1,500,000*)	Moderate (travelers)
Rabies virus	Always-fatal meningitis and encephalitis	35,000 (35,000*)	Small
Respiratory syncytial virus	Repeated respiratory infections, pneumonia	65,000,000 (160,000*)	Great
Rotavirus	Diarrhea, dehydration	140,000,000 (873,000*)	Great
Salmonella typhi bacterium	Typhoid fever (with platelet and intestinal damage possible)	30,000,000 (681,000*)	Small (travelers)
Shigella bacteria	Diarrhea, dysentery, chronic infections	250,000,000 (854,000*)	None
Streptococcus Group A bacterium	Throat infection, then rheumatic fever, kidney disease	3,000,000 (52,000*)	Small
Streptococcus pneumoniae bacterium	Pneumonia, meningitis, serious inflammation of middle ear	100,000,000 (10,000,000*)	Small to moderate
Vibrio cholerae bacterium	Cholera (with diarrhea, dehydration)	7,000,000 (127,000*)	Small (travelers)
Yellow fever	Fever, jaundice, kidney damage, bleeding	85,000 (8,000*)	Small (travelers)

Notes:
*) Diseases for which children account for roughly half of the deaths or more. The number of cases and deaths are estimated.

Source: National Academy of Sciences, Institute of Medicine, New Vaccine Development: Establishing Priorities, Washington: National Academy Press, 1986, as presented by Anthony Robbins and Phyllis Freeman, "Obstacles to Developing Vaccines in the Third World," Scientific American, November 1988

Table 7

Candidates for Accelerated Vaccine Development: Diseases of Importance in Developing Countries

Pathogen	Vaccine Envisaged	Target Population[a]
Dengue virus	Attenuated live vector virus containing gene for broadly cross-reacting protective antigen	Infants and children in endemic areas; travelers to endemic areas
Escherichia coli (enterotoxigenic)	A combination of purified colonization factor antigens and possibly other antigens	Infants < 6 months
	Genetically engineered attenuated strains	Infants < 6 months
Hemophilus influenzae type b	Conjugated polysaccharide	Infants
Hepatitis A virus	Attenuated live virus	Susceptibles of all ages; routine for preschool children
	Polypeptide recombinant vaccine produced in yeast	Susceptibles of all ages; routine for preschool children
Hepatitis B virus	Polypeptide produced by recombinant DNA technology	Areas with high perinatal infection: all infants at birth (if possible). Other areas: all infants, simultaneous with other vaccinations, at earliest possible age
Japanese encephalitis virus	Inactivated virus produced in cell culture	Children in epidemic and endemic areas; foreign visitors to epidemic regions
Mycobacterium leprae	Armadillo-derived *M. leprae*	Immuno-prophylactic: all children in endemic areas. Immuno-therapeutic: all recently infected persons
Neisseria meningitidis	Conjugated capsular polysaccharides, Groups A,C,Y, and W135	Infants, 3 to 6 months
Parainfluenza viruses	Trivalent, subunit vaccine (which must contain fusion proteins)	Infants
Plasmodium spp.	*Plasmodium falciparum*, synthetic or recombinant sporozoite antigen preparation	All infants at risk, military personnel, travelers
	Multivalent synthetic or recombinant sporozoite antigen preparation (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*)	All infants at risk, military personnel, travelers
Rabies virus	Vero cell derived vaccine	Persons at high risk, plus post-exposure prophylaxis
	Glycoprotein produced by rDNA technology in mammalian cells	Persons at high risk, plus post-exposure prophylaxis
	Attenuated live vector virus containing gene for protective glycoprotein antigen	Birth cohort in areas of high risk

Table 7 (continued)

Pathogen	Vaccine Envisaged	Target Population[a]
Respiratory syncytial virus	Polypeptides produced by recombinant DNA technology	Infants at earliest possible age
	Attenuated live virus	Infants at earliest possible age
Rotavirus	Attenuated high passage bovine RV	Infants at earliest possible age (preferably with oral polio vaccine)
	Attenuated low passage bovine RV	Infants at earliest possible age (preferably with oral polio vaccine)
	Rhesus monkey RV	Infants at earliest possible age (preferably with oral polio vaccine)
Salmonella typhi	Attenuated galE mutant *S. typhi* strain TY21a	Children; young adults at risk; travelers from developed countries to endemic areas
	Aromatic amino acid dependent strains of *S. typhi*	Children; young adults at risk; travelers from developed countries to endemic areas
Shigella spp.	Probably plasmid mediated outer membrane protein invasion determinant (there are a small number of promising options needing investigation to determine best approach)	Infants at birth or earliest possible age; elderly for epidemic strains
Streptococcus A	Synthetic M protein segment (excluding portions cross-reacting with human tissue)	Children, < 3-4 yrs
Streptococcus pneumoniae	Conjugated polysaccharides, polyvalent	Infants
Vibrio cholera	Genetically defined live mutant *V. cholerae* (A-B+ or A-B-) with respect to toxin subunit synthesis	Children, esp. < 2 yrs
	Inactivated antigens	Children, esp. < 2 yrs
Yellow fever virus	Attenuated live virus produced in cell culture	Young children

[a] Calculations of benefits are conducted assuming delivery at ages consistent with schedules of vaccinations recommended by the World Health Organization Expanded Program on Immunization (see Chapters 6 and 7).

Source: National Academy of Sciences, Diseases of Importance in Developing Countries (Vol. II of New Vaccine Development: Establishing Priorities), Washington: National Academy Press, 1986.

approaches discussed in the preceding section of the report recognise the ultimate importance of this objective, the new aproach outlined here makes it one of the primary objectives from the beginning.

38. While international cooperation through the sharing of knowledge and experience is absolutely essential to maintaining, and indeed accelerating, progress in the eradication of widespread and debilitating diseases, and self-sufficiency in vaccine development and production is an impractical goal, even for the largest countries, virtually total dependence on outside sources for virtually all major vaccines is an unhealthy condition. It is all the more unhealthy when the capacity for developing and producing new vaccines is heavily concentrated in countries that have little or no direct interest in some of the most widespread diseases in those countries which are so dependent on outside help. Some significantly greater measure of collective self-reliance in vaccine development and production is thus a critical component of any comprehensive strategy for control and eradication of endemic diseases in the Third World and should not be confused with self-sufficiency, which is an unfeasible goal.

Organisational Structure

39. In pursuit of these two objectives, it is proposed that two closely linked entities be created:

a) The Consultative Group for International Vaccine Research (CGIVR), which would seek to stimulate and coordinate research and development on new and improved vaccines for diseases of major importance in the Third World.

b) A truly transnational enterprise for vaccine production and distribution known as the International Vaccine Corporation (IVC).

39. These two entities would need to be closely linked since CGIVR would, in effect, be the R&D arm for IVC. More concretely, CGIVR would coordinate the commissioning of R&D work on specific vaccines, with the research institute actually doing the work directly connected with IVC. This connection is vital as the development process moves out of the laboratory into pilot plant production, testing and clinical trials, and ultimately, scaling up for full commercial production. The structure and functions of each of these two entities is described in the paragraphs following.

Consultative Group on International Vaccine Research (CGIVR)

40. The CGIVR would seek to draw on skills, knowledge, and experience worldwide in research and development of vaccines for diseases that are widespread, if not endemic, in the Third World. The basic model would be the Consultative Group on International Agricultural Research, which has done so much to stimulate and coordinate research on agricultural problems of priority concern to developing countries.

41. The Consultative Group on International Agricultural Research should be regarded as only the most general kind of model for CGIVR. There are substantial differences in the problems being addressed by CGIAR and those that would be the concern of CGIVR. In fashioning CGIVR, due regard should be given to responsible criticisms of CGIAR, and an effort made to learn from the CGIAR experience.

42. CGIVR would in effect function as the R&D arm of the International Vaccine Corporation. It would seek to mobilise funds from the international development community, coordinate R&D assignments on specific vaccines, and monitor the results. It would maintain close links with IVC, helping to arrange for testing and clinical trials of new or improved vaccines which would be produced through

pilot plant facilities maintained by IVC.

43. In order to assure close coordination between CGIAR and IVC, the Managing Director of IVC would be a member of CGIVR. CGIVR, or institutions associated with it, would license the technology they had developed for new or improved vaccines to IVC for production. However, neither would be a captive of the other. In other words, CGIVR would also have the option of licensing its technology to other producers, and IVC would not be limited to CGIVR-developed vaccines as the only source of its technology. Nonetheless, the assumption is that, all other things being equal, new or improved vaccines developed through CGIVR would be licensed to IVC and most of IVC's production would be based upon technology license from CGIVR.

44. Like the Consultative Group for International Agricultural Research, CGIVR would consist of two components--the Consultative Group as such and the Technical Advisory Committee (TAC). As in the case of CGIAR, the Consultative Group for International Vaccine Research would include UN and other international organisations and donor government agencies, as well as representatives of developing country institutions concerned with the development and production of vaccines within the broader field of public health. The Consultative Group would meet at least once a year to consider proposals for funding R&D work on vaccines which had been screened by the TAC.[16/]

45. TAC itself would be composed of leading scientists and public health officials from both South and North. Because of the wide range of diseases that would be addressed through the CGIVR structure, TAC would have a number of sub-committees, each focused on a specific vaccine. In reviewing proposals for R&D work on vaccines, TAC and its subcommittees would also address the question of which institution or institutions would be most appropriately situated to

undertake the research being proposed.

46. One of CGIVR's major responsibilities would be arranging for testing and clinical trials of vaccines being developed under its auspices. As is now the case, public health institutions in developing countries would actually conduct the trials. A current example is a vaccine to prevent diarrhea which is being developed through WHO and four varieties of which are being tested by Peruvian health workers through the Lima-based Institute of Nutritional Investigation. 17/

47. In objections and functions, CGIVR would be not dissimilar to the Task Force on Child Survival. The Task Force is sponsored by five international agencies and foundations (WHO, UNICEF, the World Bank, UNDP, and the Rockefeller Foundation), with the Carter Center at Emory University in Atlanta, Georgia, a public policy research and action group established by former U.S. President Jimmy Carter, serving as the secretariat. (See Appendix 3 for a description of the Task Force.) 18/

48. CGIVR's concerns would also overlap with the Special Programme for Research and Training in Tropical Diseases (TDR), a joint undertaking of UNDP, the World Bank, and WHO. According to Kenneth Warren (see Appendix 2), TDR has recently established a new programme for vaccine development, which is supporting work on tuberculosis, dengue and Japanese encephalitis, hepatitis A and polio, meningococcal meningitis and pulmonary viruses such as parainfluenza and respiratory syncytial virus. Also related is the R&D group of the WHO/UNICEF Expanded Programme of Immunization (of which the Director of the Carter Center which provides the secretariat for the Task Force on Child Survival is currently the Chairman). Special efforts would need to be made to see that CGIVR was

effectively and constructively related to these initiatives. Indeed, it may be that one of these existing initiatives could be adapted to perform the functions of CGIVR without creating a new structure.[19/]

49. While CGIVR would, as indicated, draw upon skills, knowledge, and experience in both North and South and both the private and the public sectors, the overriding thrust of its activities would be on implanting or strengthening capabilities for vaccine development and production in the South. There are useful precedents in vaccine R&D for pursuing such an objective--for example, the work of Dr. William Thilly of MIT and Dr. Robert Dugre of the University of Quebec in Montreal which has resulted in establishing rabies vaccine production in Colombia and similar efforts, also being supported by the Rockefeller Foundation, to develop a vaccine for dengue in Thailand.[20/]

50. The work of Thilly and his colleagues at MIT is indicitive of trends in research that, as they come to fruition, could have significant impact on both the production and delivery of vaccines in developing countries. There are four MIT professors working on stabilisation and delivery of inexpensive multivalent vaccines in a form suitable for innoculation of newborn infants without need for subsequent innoculation. There are five basic components:

1. Making cheap antigens.
2. Combining antigens to make a multivalent vaccine.
3. Stabilising the antigens so that they will remain stable under ambient conditions (e.g., body temperature).
4. Encapsulating the antigens so that they will be released slowly over time, eliminating the need for subsequent innoculations.
5. Creating simplified delivery mechanisms (e.g., a small plastic packet filled with vaccine and penetrated with several short

needles).[21]

CGIVR would seek to stimulate work along these and related lines at research facilities in both developed and developing countries but always with an eye to strengthening capabilities for further research in the latter countries.

51. The various CGIVR functions and relationships to other entities, including IVC, are shown in diagramed form in the flow chart in Figure 4.

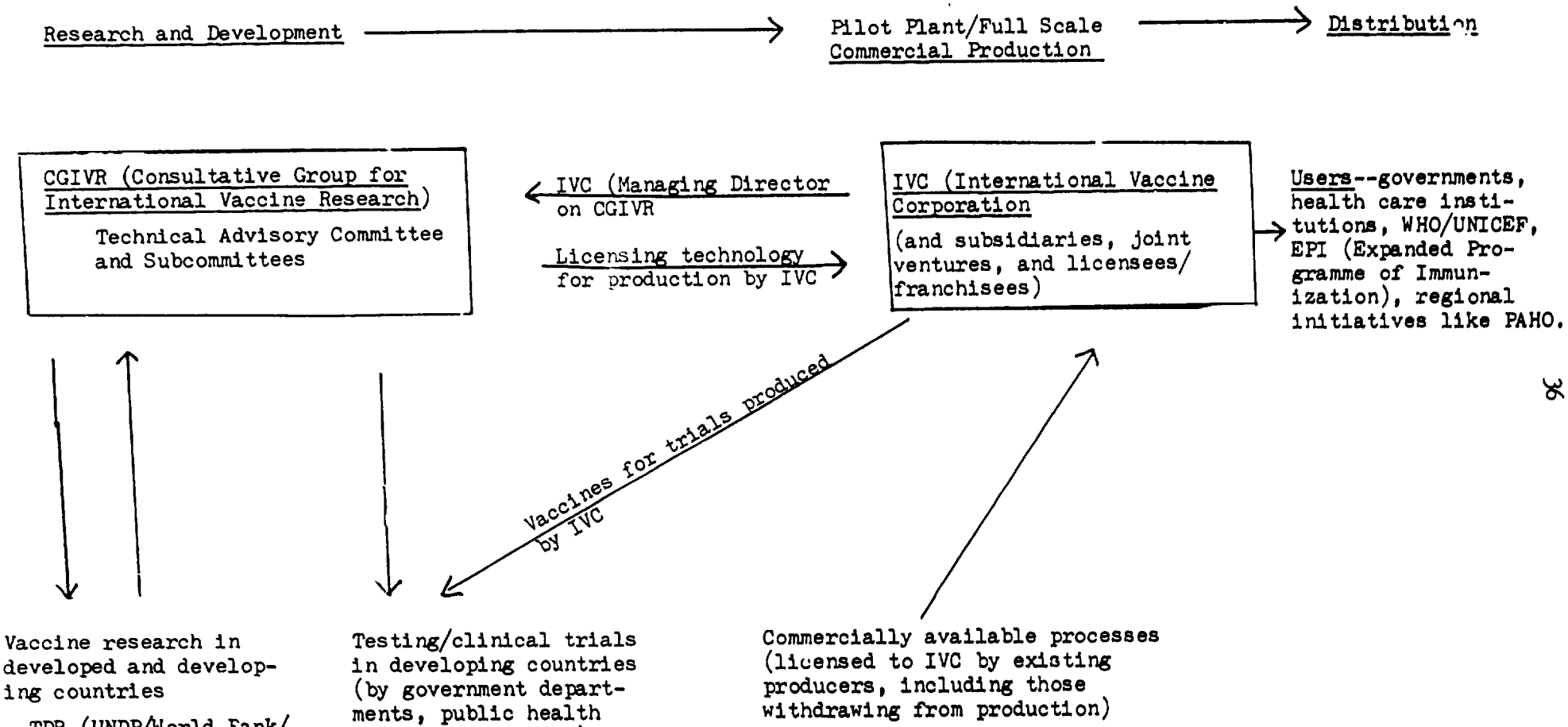
International Vaccine Corporation (IVC)

52. The International Vaccine Corporation would undertake the production and marketing of "orphan vaccines" in developing countries. IVC would work in close collaboration with CGIVR, in effect its R&D wing, on pilot plant production and scaling up to high-volume commercial production new and improved vaccines developed through CGIVR. IVC would be responsible for producing vaccines used in clinical trials arranged through CGIVR.

53. In addition, IVC would seek licenses from existing industrialised country producers of vaccines widely used in developing countries. It is generally anticipated that someof these producers will begin to withdraw from the production of such vaccines as they seek to redeploy their production toward products with higher profit margins for them. Assuming that IVC can develop production facilities that can achieve similar economies of scale and quality control as existing producers of these vaccines, these lines of production should provide a steady income stream during the early stages of the evolution of this approach to vaccine development and production in developing countries, which will necessarily take some years before it is fully operational with newly developed or improved vaccines coming out of the CGIVR pipeline, going through clinical testing, and having been scaled up for commercial production.

Figure 4

Flow Chart for New Approach to Vaccine Development and Production in Developing Countries



54. IVC would work through regional and national subsidiaries which would undertake actual vaccine production. In some instances, these subsidiaries might be based upon existing facilities upgraded to produce vaccines of the highest quality with the latest techniques. Examples include the Instituto de Salud Publica de Chile, the recently established India Vaccine Corporation, and proposed production facilities in Mexico and Brazil being developed under the auspices of the Pan American Health Organization (PAHO). In other instances, new production facilities would have to be created. IVC might also use independent production facilities under contract, provided it was able to exercise truly effective quality control. By concentrating the production of a particular vaccine in one or a limited number of its production facilities, IVC would seek to take advantage of the economies of scale that are often possible with vaccine production.

55. Quality control is the sine qua non of vaccine production. For vaccines produced by IVC to gain acceptance, the highest standards would need to be maintained. There are some public health professionals working with and in developing countries in the battle against infectious diseases who are skeptical about the capacity of developing countries to meet these standards while using the latest techniques based upon biotechnology and genetic engineering without a much more substantial infrastructure in biotechnology and genetic engineering than now exists in all but a handful of the largest and most advanced developing countries. On the other hand, there are promising lines of research, which CGIVR should give priority to fostering, that involve new techniques of vaccine production that are "self-correcting" and which would greatly facilitate the production of vaccines based on these techniques in the developing world, such as the work at MIT described above.[22/]

56. In addition to undertaking the production of new and improved "orphan vaccines," IVC might also explore the possibility of entering into technical collaboration agreements with some of the present producers of vaccines that are being used on a large scale through the WHO Expanded Programme on Immunization and acquired for EPI through bulk purchasing arrangements such as the Pan American Health Organization's Revolving Fund. Because these bulk purchasing arrangements have made it possible to achieve sharply reduced prices (ranging from U.S. $.01 to $.21), it seems unlikely that the production of these vaccines represent highly profitable product lines to their present producers, which are virtually all public or private-sector enterprises in industrialised countries.[23/]

57. As long as enterprises in the industrialised countries with the relevant technology and experience can be given assurances that products based on their technology and experience manufactured in developing countries will not find their way back into the primary markets of these enterprises in the industrialised countries in direct competition with their own products, it is at least possible that these enterprises would be willing to play a constructive role in helping to transfer their technology and experience in the production of vaccines now being used by EPI to IVC's manufacturing facilities in the Third World.[24/]

58. Staffing of IVC with competent and experienced managerial and technical personnel would be crucial to its performance. There are at least three sources for such personnel, all of which would need to be pursued. There are, first of all, persons with both management and technical skills already working in closely related areas such as the pharmaceutical industry in a number of larger and more advanced developing countries. A second source is managers and technical

personnel from developing countries now working in manufacturing and research facilities in the industrialised countries. And a third possible source would be industrialised country personnel, especially those in public sector institutions, who would undertake assignments of varying length with IVC in helping to establish new and upgrade existing lines of vaccine production in developing countries.

59. Marketing of IVC's production would be done primarily through the Expanded Programme on Immunization and the public Health programmes of developing country governments. The availability of low-cost, high-quality vaccines through IVC would be a key source of leverage in expanding still further and enhancing the impact of the work of EPI and other efforts to control, and ultimately eradicate, infectious diseases from the face of the Earth.

60. In legal form, the International Vaccine Corporation should be chartered as a multinational enterprise in a smaller, neutral country. Its various operating subsidiaries would presumably be incorporated under the laws of the countries in which they were situated. Another possibility to be explored would be the chartering of the parent coporation through the UN or some other supra-national body.

61. Vaccines licensed for production by IVC would presumably be patented under the patent laws of various countries where they were being produced and in accordance with the provisions of those patent laws as they related to products used in human health care. However, the guiding principle in dealing with property rights for vaccines would be the provision of "public access" under appropriate circumstances (e.g., non-exclusive licensing). The UN system in general and WHO in particular have an active interest in maintaining this principle in work that they support or with which they are otherwise associated.

and one of these agencies might well be the vehicle for holding the rights and licensing them. Thus, a Mexican doctor developing a synthetic malaria vaccine has indicated that he would like to offer that vaccine on behalf of the people of his country to the rest of the world by assigning patent rights to WHO.[25] Once IVC is operational, WHO might then license the technology to IVC for production.

62. IVC would be governed by its Board of Directors. The Directors would be elected by IVC's shareholders, which would be the major investors in the enterprise.

63. Investment capital for IVC should be sought from several sources. Among these are developing country governments and financial institutions, donor agencies, both national and multilateral, in the international development community, and an emerging new phenomenon in the USA and several other industrialised countries--the social investment community. Social investors, which are sometimes individuals but more often religious or educational institutions and public sector and trade union pension funds, seek investment opportunities that offer the promise of significant social impact. The worldwide battle against infectious diseases, especially in developing countries where so many such diseases are concentrated and have such a debilitating effect on the people of these countries, should be an attractive cause around which to mobilise interest and resources from this growing segment of investors in industrialised countries.[26]

64. For IVC to play a significant role in global vaccine production, substantial start-up capital would be needed, probably on the order of $100 million. While this is a sizable sum, substantial amounts of money are already being expended in the development and manufacture of vaccines, at least some of

which might be redirected to IVC if it offered the possibility of producing high-quality vaccines at prices that would be competitive with, if not lower than, existing producers.

65. The possibility of organising IVC as an enterprise for limited profit should be considered. Social investors will consider taking a less than market rate of return on their investment, especially if the element of risk is diminished. The risk issue might be addressed through investment guarantees provided through the UN system and/or industrialised country governments, some of which have developing country investment guarantee programmes already in place. Any profits beyond those provided to shareholders as a return on their investment should be plowed back into expansion of production facilities and R&D on new and improved "orphan vaccines."

Some Next Steps

66. The first step would seem to be informal consultation with representatives of some of the key entities already addressing the larger problematique of developing and producing vaccines for use in developing countries. These entities include the Task Force for Child Survival, the Expanded Programme on Immunization, and the Special Programme for Research and Training in Tropical Diseases (TDR), along with the various agencies sponsoring these initiatives or related undertakings which include WHO, UNICEF, the World Bank, UNDP, UNIDO, and the Rockefeller Foundation. Another key group of institutions are public sector entities engaged in research, development, and in some cases, production of vaccines in industrialised countries such as the Netherlands, Denmark, Finland, Norway, and Sweden. Also essential to the early stages of exploration of the possibilities discussed in this report would be leading public health officials

from developing countries at both the national and regional level, especially those directly involved in efforts to strengthen the development and production of vaccines in developing countries such as the Pan American Health Organization's scheme to establish regional vaccinology centres in Latin America.

67. The emphasis in these informal consultations should be on finding ways of adapting existing arrangements, creating new structures only where there are no alternatives presently available. In many ways, the central components of the proposed Consultative Group on International Vaccine Research already exist so that CGIVR could be "created" through a slightly different orchestration of these existing undertakings. While something like the International Vaccine Corporation does not seem to exist at the international level, some of its operating components are already in place in developing countries, even though in some instances it would be necessary to upgrade substantially these facilities.

68. Depending on the outcome of these informal consultations, the next step would appear to be the creation of an Enterprise Planning Group to undertake the task of developing a prospectus and business plan for IVC. The process of developing the prospectus and business plan should involve consultation with potential investors. It is possible also that the services of one or more investment bankers should be engaged to facilitate the task of mobilising start-up capital.

69. Assuming that these steps could be largely accomplished in 1990, the basic organisational structure for IVC might be in place by 1991, thus positioning it to play a key role in the battle against infectious diseases in developing countries during the last decade of this century. Indeed, a crucial factor in mobilising participation in and support for the new approach to the development and production of vaccines in the Third World outlined here is the articulation

of ten-year and longer range goals that are both achievable and will capture the imagination and interest of those concerned with concrete, practical ways to improve human welfare. This is potentially the greatest asset of the initiatives outlined here--a belief among concerned and committed persons that, because of past successes, the international community can contain, and ultimately overcome, the age-old scourge of disease that has plagued humankind since the beginning of time.

Notes

1. Anthony Robbins and Phyllis Freeman, "Obstacles to Developing Vaccines for the Third World," Scientific American, p. 90 (emphasis added).
2. "New and Improved Vaccines," Biotechnology and Development Monitor, September 1989 (No. 1), p. 17 (emphasis supplied).
3. Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University, p. viii.
4. World Health Organization, Expanded Programme on Immunization, Report of the EPI Global Advisory Group meeting (Abidjan, Ivory Coast, October 1988), p. 5. [citation to be verified]
5. World Health Assembly Resolution 41/28 as cited in the EPI Progress and Evaluation Report submitted to the May 1989 World Health Assembly (A42/10). [citation to be verified]
6. International Task Force on Hepatitis B Immunization, Information Sheet.

Seattle, Washington: PATH (Program for Appropropriate Technology and Health).

7. Robbins and Freeman, op. cit., p. 94.

8. "New and Improved Vaccines," Biotechnology and Development Monitor, September 1989 (No. 1), p. 18.

9. Ibid., pp. 94-95.

10. Pan American Health Organization, Enhanced Disease Prevention in the Americas: Regional Vaccinology Centers (feasibility study), Washington: PAHO, October 1987.

11. Robbins and Freeman, op. cit., p. 95.

12. Pan American Health Organization, EPI Newsletter/Expanded Programme on Immunization in the Americas, December 1984, p. 8: PAHO Revolving Fund for Vaccines, price data sheets for 1987-89.

13. Robbins and Freeman, op. cit., p. 95.

14. Ibid.

15. PAHO, Feasibility Study, p. 3.

16. CGIAR Consultative Group on International Agricultural Research, New York: CGIAR, 1976.

17. "A Vaccine to Prevent Diarrhea?: Peruvian Health Workers Test Four Varieties," UNDP Source, September 1989, pp. 16-18.

18. Task Force for Child Survival, "Initiative to Accelerate Development of New and Improved Vaccines for Use in Developing Countries," Atlanta, Georgia: Carter Center, April 1989.

19. UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Diseases (TDR), New Approaches to Research Capability Strengthening, n.d. (?--1988); ibid., Tropical Diseases: Progress in

International Research, 1987-1988 (Ninth Programme Report), 1989.

20. Letter from Scott B. Halstead, Acting Director, Health Sciences Division, Rockefeller Foundation, July 25, 1989; S.B. Halstead, "Aedes Aegypti: Why Can't We Control It?" Bulletin of the Society of Vector Ecologist, December 1988, pp. 304-311.

21. Letter from William G. Thilly, Professor of Applied Biology and Director, Center for Environmental Health Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts, October 2, 1989.

22. Letter from Richard T. Mahoney, Vice-President and Director, Technology Promotion, PATH (Program for Appropriate Technology and Health), July 25, 1989; letter from Scott Halstead, op. cit.

23. PAHO, EPI Newsletter, op. cit., December 1984.

24. Interview with a Technical Advisor at the World Bank, June 1989.

25. "New and Improved Vaccines," Biotechnology and Development Monitor, September 1989 (No. 1), p. 17.

26. The leading organisation of social investors in the USA, the Social Investment Forum headquartered in Boston, reports a tripling of its membership in the last four years. SIF also reports the emergence of social investment movements in the United Kingdom, the Netherlands, Federal Republic of Germany, and other European Countries. (Interview with SIF Executive Director, September 1989.)

Appendix 1

DECLARATION OF TALLOIRES
12 March, 1988

Remarkable progress in health has been achieved during the past decade. Global recognition that healthy children and healthy families are essential for human and national development is steadily increasing. Consensus has been reached on the strategy for providing primary health care programmes. The international community has become engaged in partnership with national governments in the creation of successful global programmes, ensuring the availability of financial support and appropriate technologies. These include:

1. *immunization programmes* which now protect over 50% of infants in developing countries with polio or DPT vaccines, preventing some 200,000 children from becoming paralyzed with poliomyelitis and over a million children each year from dying of measles, whooping cough, or neonatal tetanus;
2. *diarrhoeal diseases control programmes* which now make available for 60% of the developing world population life-saving fluids (particularly oral rehydration salts), the use of which may be preventing as many as a million deaths annually from diarrhoea;
3. *initiatives to control respiratory infections* which hold promise in the years ahead of averting many of the 3 million childhood deaths from acute respiratory infections occurring each year in developing countries and that are not prevented currently by immunization;
4. *safe motherhood and family planning programmes* which are so important in protecting the well-being of families.

Progress, to date, demonstrates that resources can be mobilized and that rapid and effective action can be taken to combat dangerous threats to the health of children and mothers, particularly in developing countries.

This progress is the result of:

- enthusiastic world-wide agreement on the development of health strategies based on primary health care;
- the commitment of national governments, multi- and bilateral development agencies, non-governmental organizations, private and voluntary groups, and people in all walks of life to give priority to these programmes;
- coordinated action by the sponsors of The Task Force for Child Survival: UNICEF, The World Bank, UNDP, WHO, and The Rockefeller Foundation.

We, The Task Force for Child Survival, conveners of the meeting "Protecting the World's Children — An Agenda for the 1990's" in Talloires, France, 10-12 March, 1988:

1. EXPRESS appreciation and admiration for the efforts made by the developing countries to reduce infant and child deaths through primary health care and child survival actions.
2. COMMIT OURSELVES to pursue and expand these initiatives in the 1990's.
3. URGE national governments, multi- and bilateral development agencies, United Nations agencies, non-governmental organizations, and private and voluntary groups to commit themselves to:
   - increase national resources from both developing and industrialized countries devoted to health in the context of overall development and self-reliance;
   - improve women's health and education, recognizing the importance for women themselves, recognizing women's contributions to national development, and recognizing that mothers are by far the

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most important primary health care workers;

- accelerate progress to achieve universal childhood immunization by 1990 and to sustain it thereafter;
- accelerate progress to eliminate or markedly reduce as public health problems the other main preventable causes of child and maternal mortality and morbidity, striving to reach sustained universal coverage of children and mothers by the year 2000;
- assure the development of new vaccines and technologies and their application, particularly in developing countries, as they become appropriate for public health use;
- promote expanded coverage of water supply and sanitation;
- pursue research and development, including technology transfer, in support of the above actions.

4. SUGGEST that the following be considered by national and international bodies as targets to be achieved by the year 2000:
   - the global eradication of poliomyelitis;
   - the virtual elimination of neonatal tetanus deaths;
   - a 90% reduction in measles cases and a 95% reduction in measles deaths compared with pre-immunization levels;
   - a 70% reduction in the 7.4 million annual deaths due to diarrhoea in children under the age of 5 years that would occur in the year 2000 in the absence of oral rehydration therapy, and a 25% reduction in the diarrhoea incidence rate;
   - a 25% reduction in case/fatality rates associated with acute respiratory infection in children under 5 years;
   - reduction of infant and under-5 child mortality rates in all countries by at least half (1980-2000), or to 50 and 70 per 1,000 live births respectively, whichever achieves the greater reduction;
   - reduction of current maternal mortality rates in all countries by at least half.

Achievement of these strategies would result in the avoidance of tens of millions of child deaths and disabilities by the year 2000, as well as a balanced population growth as parents become more confident their children will survive and develop. The eradication of poliomyelitis would, with the eradication of smallpox, represent a fitting gift from the 20th to the 21st century.

5. DRAW world attention to the potential *for enlarging* upon the successes outlined above to encompass low-cost, effective initiatives to:
   - improve the quality and coverage of educational services so as to obtain universal primary education and 80% female literacy, and
   - reduce to less than 1% severe malnutrition in children under 5 while also significantly reducing moderate and mild malnutrition in each country.
6. WELCOME the progress being made in drafting the Convention on the Rights of the Child and join the United Nations General Assembly in urging completion of the Convention in 1989, the 10th anniversary of the International Year of the Child.

We are convinced that vigorous pursuit of these initiatives aimed at protecting the world's children will ensure that children and mothers — indeed whole families — will benefit from the best of available health technologies, making an essential contribution to human and national development and to the attainment of Health For All By The Year 2000.

—Talloires, France

Source: Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University.

Appendix 2

Biotechnology and Vaccinology

by Kenneth S. Warren

Lewis Thomas has described immunization as one of the genuinely decisive technologies of modern medicine--it is effective, relatively inexpensive, relatively simple, and relatively easy to deliver. It is heartening, therefore, that we are now in the midst of two complementary revolutions, the biotechnology revolution, which is providing unprecedented opportunity to produce new and better vaccines, and the children's revolution of UNICEF, which, since the fall of 1984, has focused on immunizing all of the world's children. With respect to biotechnology John Maddox, in a recent editorial in Nature, observed that there is some disappointment concerning "artificially engineered versions of naturally occurring materials," and "genetic manipulation of plants." He was optimistic, however, about vaccines, citing the newly described vaccinia vector and vaccines in progress for malaria and schistosomiasis.[1] This optimism was obviously related to the promise of new vaccines, as to date only one genetically engineered vaccine, hepatitis B prepared in yeast, has been approved by the Food and Drug Administration (FDA). Nevertheless, a discussion of the status of vaccines presented at Bellagio III in Cartagena was entitled "Under the volcano: the inevitable new age of vaccines," a metaphor which suggests a pressure inexorably building which will result in a veritable explosion of new and better vaccines.[2] In spite of some setbacks to early enthusiasm such as the discovery of the extreme complexity of antigenic variation in trypanosomas, which cause African sleeping sickness, and the failure of some of the new malaria vaccines to elicit T cell memory, optimism continues relatively undiminished in many quarters. This is related not to the output of final tested products, but to the constantly accelerating capacity of genetic engineering to provide new and potentially potent vectors, of chemistry to develop synthetic vaccines, and of the ingenuity of scientists to overcome the myriad of obstacles which nature throws in their path.

The major problems with single protein, and particularly single epitope, polypeptide vaccines is their relative lack of antigenicity and the failure of host response due to genetic restriction. Examples of ways of dealing with these problems were presented at the Cold Spring Harbor vaccine meetings in September 1987. Satterthwait et al reported building synthetic dodecapeptides involving the repeating tetrapeptide found on the surface of P. falciparum sporozoite shaped in three dimensions by covalent replacements for hydrogen bonds.[3] One of these shaped peptides induced particularly high titers of antisera which reacted with the sporozoites. Other studies are underway involving the addition of T cell epitopes to the malaria polypeptides to induce immunological memory, and Francis et al have shown that T cell epitopes from ovalbumin or sperm whale myoglobin added to a foot and mouth disease protective polypeptide can overcome genetic restriction of the immune response.[4] A variety of means of immunostimulation are being developed and Clarke et al have shown that chimaeric proteins involving the foot and mouth disease polypeptide fused to the end-terminus of hepatitis B core antigen formed particularly immunogenic particles.[5]

Another major approach to vaccine development in the past has been through viral attenuation by multiple passages in laboratory animals or mammalian cell cultures leading to living avirulent, but still highly antigenic organisms. A particular problem is their occasional reversion to virulence. An example is the Sabin living (oral) polio vaccine. Now, using the techniques of genetic engineering, precise areas determining virulence can be deleted. These may control activities such as binding to target cells, toxin production and replication. Furthermore, genes for protective antigens can be inserted into a variety of living vector organisms which themselves constitute vaccines, thereby, enabling immunization against multiple infections simultaneously. One example of the latter is the vaccinia (the old smallpox vaccine) vector which has a genome large enough to incorporate the DNA for the protective antigens of at least 20 different infectious agents. In one study a vaccinia virus recombinant was prepared containing the coding sequence for hepatitis B virus surface antigen, herpes simplex virus glycoprotein D and influenza virus hemagglutinin.[6]

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In a recent report by Langford et al a hybrid gene encoding five different repeating epitopes from four different malarial antigens from both the sporozoite and blood stages of malaria were added to vaccinia; on injection into animals antibodies were elicited to all of the component epitopes.[7] Salmonella typhi vectors with metabolic defects resulting in the production of toxic intermediates or requiring nutrients not available in tissues replicate poorly in the human host. While these immunize against typhoid fever other protective antigens can be added (e.g. Shigella), and these will provide the unique forms of protection necessary to prevent mucosally related diseases of the gastrointestinal and respiratory tracts.[8] Recently the development of mycobacterial vectors has been made possible by the use of a shuttle phasmid combining both a phage and plasmid that can be passed back and forth between E. coli and mycobacteria.[9] The major adjuvant activity of mycobacteria might then be available for other antigens that could be administered by merely pricking the skin. In addition, antigenic activity can be manipulated within these systems by adding the genes for immunostimulating substances or by incorporating antigens into cell membranes by the addition of anchoring sequences such as that from the IgC immunoglobulin gene.[10]

In spite of all this scientific activity only one genetically engineered vaccine has been approved for human use by the FDA, as noted above. Nevertheless, there are an enormous number of vaccines in the pipeline being produced by a great variety of techniques, both old, new and amalgams of the two. At a workshop entitled Vaccine Innovation and Supply convened by the Institute of Medicine in 1986 it was reported that many agencies are working on the development of new and better vaccines.[11] The U.S. Army, which has a broad interest in producing vaccines for the infections of both the developed and the developing worlds, is studying 42 vaccines. The National Institutes of Health, through its prescient Program for Accelerated Development of New Vaccines, begun in the fall of 1980, noted work on 28 vaccines with a principal focus on the U.S.A. The Rockefeller Foundation, which is concerned particularly with the health of the developing world, reported six vaccines under investigation in the groups which it has been supporting with its relatively meager resources in conjunction with other funding agencies. The World Health Organization Tropical Diseases Research Programme has been focusing on vaccines for malaria and leprosy and its new Programme for Vaccine Development is supporting work on tuberculosis, dengue and Japanese encephalitis, hepatitis A and polio, meningococcal meningitis and pulmonary viruses such as parainfluenza and respiratory syncytial virus.

There are so many vaccines under development that the National Institutes of Health supported a major study by the Institute of Medicine to establish priorities for vaccines for both the developed and developing worlds.[12,13] The top five priorities for the latter, as determined not only by need but by the probability of the development of new vaccines in the near future, were pneumococcal pneumonia, malaria, rotavirus, typhoid, and bacillary dysentery. Nevertheless, with some diseases so many new vaccines are being developed that it is difficult to take them beyond the laboratory into scaled-up production and to test them in laboratory animals, primates and eventually in man. There are numerous vaccines for hepatitis B produced by different techniques from infected serum and by genetic engineering in a variety of cells. Several different rotavirus vaccines are now being tested in humans as described by Kapikian et al at the 1987 Cold Spring Harbor meetings.[14] Vaccines now in phase three testing in populations may soon become obsolete because of newer and better approaches. Examples are the Hemophilus influenzae B polysaccharide vaccines that are being linked to protein carriers to induce immunity in infants, and a cholera vaccine made up of killed organisms plus purified B (binding) subunit which may be superceded by living organisms in which the A (toxin) subunit genes have been deleted. Potential vaccines for malaria and schistosomiasis number as many as ten each and primate facilities are not available to test all of them.

It is sad to say that all of this activity remains inadequately funded. In spite of the approval of the NIH Program for Accelerated Development of New Vaccines in 1981 special funds for it were not appropriated. Many investigators are "bootlegging" vaccine research on their funding for more basic aspects of infectious diseases and molecular biology. On the international level, support by multilateral and bilateral agencies for the WHO Tropical Diseases Research Programme and the Programme for Vaccine Development initiatives is meager. In spite of this problem, a high level of research activity continues, and vaccinologists

Appendix 2 (continued)

remain deeply concerned with the health problems of the developing world, which contains 75% of the world's population, more than 50% of which are children. The percentage of infant and childhood deaths occurring in the developing world is respectively 97 and 98 percent of total such mortality.[15] They were particularly pleased, therefore, when UNICEF declared its revolution for children in 1983 in which immunization was one of four cost-effective measures selected to reduce infant and child mortality. Bellagio I in March 1984 was even more heartening because this seminal program took immunization as its primary focus.[16] The results of this effort are on display here at Bellagio III in Talloires. I can assure you that the vaccinologists of the world, enormously encouraged by this great initiative, are working all the harder to provide The Task Force for Child Survival and its component agencies with new and more powerful vaccines undoubtedly a major world population crisis it should be realized that there are better ways of controlling population than through the deaths of infants and children caused by infectious diseases. It must be remembered that many children are not killed, but blinded, rendered mentally deficient and crippled. These constitute a considerable financial burden on society. Thus, control of population by infectious diseases is simply not cost-effective.

As the successful campaign to eradicate smallpox was drawing to its conclusion over a decade ago, the World Health Organization started the Expanded Programme on Immunization (EPI). At that time, less than five percent of children in developing countries were receiving a third dose of DPT or polio vaccine. Ten years later, approximately 25% of the world's children were properly immunized. In 1983 UNICEF declared "a children's revolution" emphasizing four cost-effective means to rapidly decrease childhood mortality and morbidity in the developing world, one of which was immunization. At the urging of Jonas Salk and Robert McNamara UNICEF and WHO then decided to accelerate the global immunization campaign. This campaign was initiated at a conference in Bellagio, Italy in March 1984 sponsored by the World Health Organization, UNICEF, the United Nations Development Program (UNDP), the World Bank and the Rockefeller Foundation. The meeting was entitled "Protecting the World's Children: Vaccines and Immunization Within Primary Health Care." A Task Force for Child Survival was organized by the five sponsoring agencies led by William Foege, previously Director of the Centers for Disease Control. Since than a global campaign has been carried on largely by WHO and UNICEF with the assistance of the World Bank, UNDP and the Rockefeller Foundation.

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Source: Task Force for Child Survival, Protecting the World's Children: An Agenda for the 1990s (Report of the March 10-12, 1988, Talloires Conference), Atlanta: Carter Center, Emory University.

Appendix 3

The Task Force for Child Survival

The Task Force was formed in 1984 and is sponsored and funded by the World Health Organization, UNICEF, The World Bank, the United Nations Development Programme, and the Rockefeller Foundation. The overall mission is to assist its sponsors and others in accelerating global immunization and other child survival efforts. Its specific mission is to assist in developing country programs and accelerate research related to immunization activities.

The Task Force is incorporated in Georgia as a public non-profit corporation. The staff includes public health specialists, epidemiologists, support staff, and consultants who work with specific aspects of the child survival effort. This small staff serves as a working group for international health agencies to harness efforts in solving problems that either crosscut many agencies or are not addressed by any agency.

Activities

Programs: The current activities of the Task Force include a vaccine evaluation effort in Senegal, a surveilance enhancement project in Uganda, and consultation with individual countries to assist in implementing aggressive child survival programs.

Research: The Task Force is focusing on applied research needs--the obstacles to vaccination in developing countries. High-priority needs in the engineering, biochemical, and field research have been identified. Some field studies have been stimulated; sources of funding for other projects are being sought.

The Task Force consultants have undertaken collaborative field research in developing countries to assess intervention strategies related to poliomyelitis, measles, and neonatal tetanus.

Coordination of research needed to forward child survival objectives of The Task Force sponsors is also facilitated by the appointment of the Executive Director of the Task Force as Chair, Research and Development Group, Expanded Programme on Immunization, WHO.

Communication: Perhaps the most important role played by The Task Force is that it serves as an information exchange on the world immunization effort. Regular meetings with its sponsors provide a forum for information sharing and problem solving.

The Task Force sponsored and organized a meeting of 90 public health experts and other distinguished leaders in October 1985 in Cartagena, Colombia, to examine the movement. Another similar meeting in March of 1988 in Talloires, France, resulted in establishment of child survival objectives that were formalized in the "Declaration of Talloires."

Among those objectives are:

--the global eradication of poliomyelitis

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--virtual elimination of neonatal tetanus deaths
--a 90% reduction in measles cases and 95% reduction in measles deaths
--a 70% reduction in annual deaths due to diarrhea
--a 25% reduction in case fatality rates associated with acute respiratory infections in children under age 5

The Task Force publishes a newsletter, World Immunization News (WIN), in English, French, and Spanish, to keep the many people engaged in immunization efforts around the world abreast of the latest developments. Persons on the mailing lists of the five sponsoring agencies automatically receive WIN. Others may receive it by contacting The Task Force.

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