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Report of the fifth meeting of the Children's Vaccine Initiative Consultative Group

São Paulo, Brazil
25-26 October 1995

CHILDREN'S VACCINE INITIATIVE

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Contents

Summary

Convened in the Americas for the first time, the Fifth Annual Consultative Group Meeting of the Children's Vaccine Initiative (CVI), took place on 25-26 October, 1995, in São Paulo, Brazil. Dr J.W. Lee, Executive Secretary of the CVI and Director, Global Programme for Vaccines and Immunization (GPV), WHO, welcomed the 175 participants from around the world who came from scientific institutions, industry, national health ministries, international organizations and the donor community. Reiterating the theme of the meeting, "Progress Since the World Summit for Children: 1990-1995," Dr Lee stated that it was an appropriate time to be analyzing the progress made, not only because it had been five years since the launch of CVI, but also because the CVI Secretariat had become more established in a single location, and the coalition of its members had become more cohesive. From this solid base, Dr Lee encouraged CVI to move forward and invited Sir Gustav Nossal, Director of the Walter and Eliza Hall Institute of Medical Research in Australia, to accept chairmanship of the meeting.

Sir Gustav Nossal introduced Dr Adib Jatene, the Minister of Health of Brazil, who officially welcomed participants to the meeting and to the city of São Paulo. In his presentation of the Brazilian experience with vaccines and immunization campaigns, Dr Jatene touched upon a number of themes which were later discussed, from a global perspective, throughout the meeting: disease control and the utilization of widespread immunization campaigns; improvements in vaccine supply and quality; and the need for continued vaccine research and development. Other important themes discussed at the meeting were public sector collaboration with industry and the need for increased advocacy to raise both political commitment and financial resources for vaccines. Described by Sir Gustav as a heartwarming way to begin the meeting, Dr Jatene concluded his morning presentation by awarding four Oswaldo Cruz Medals, approved by President Fernando Enrique Cardoso, to Dr Claudio do Amaral Jr. and Professor Walter Leser of Brazil, Dr Donald Henderson of the USA, and Dr Isao Arita of Japan. Concluding remarks to the opening session were made by Dr Hiroshi Nakajima, Director-General of the World Health Organization, who encouraged participants to take an active role in the meeting and to share their expertise in helping chart the future of CVI.

Following the opening, the first session on Wednesday, 25 October, was "Disease Control: 1990-1995." It included presentations on topics ranging from polio eradication to measles elimination and the control of neonatal tetanus. While achievements have been notable in the delivery of some of the traditional Expanded Programme on Immunization (EPI) vaccines, less progress has been made in the introduction of new vaccines. A presentation on the introduction of the hepatitis B vaccine in Zimbabwe highlighted some of the barriers which must be overcome in new vaccine introduction. Presentations in the second session of the meeting, "Vaccine Supply, Self-Sufficiency and Quality," included a review of efforts to reduce some of these barriers and increase access to high quality vaccines. After a review of the Brazilian experience with vaccine supply, self-sufficiency and

quality assurance, the second presentation addressed global progress in these areas. The third presentation detailed financing mechanisms such as the new UNICEF tender, and the targeting of assistance to countries with high disease burden and financial need. Finally, speakers in the last session of the day, "Vaccine Research and Development," reviewed progress in the past five years in the areas of new vaccines and vaccine technologies, infant immunization, and the potential for an HIV vaccine. Thanks to breakthroughs in biotechnology, predictions for the future include a greater choice of newer, safer, higher quality and, most likely, more expensive vaccines.

Thursday, 26 October, began with a session on "Contributions of Industry: 1990-1995." With regard to the future achievements predicted in vaccine research and development, as well as those already made, the role of industry is pivotal. The need for increased public-private cooperation was promoted during this session, and explored later in the day during the workshop on intellectual property rights. As a review of CVI progress, and as a framework from which to begin workshop discussions, the second session of the morning was "CVI's Role into the 21st Century." Presentations in this session addressed the steps involved from vaccine development to introduction, and the role which CVI can play to facilitate the progress of a vaccine along the way. Designed to complement the main plenary sessions, and to encourage the active involvement of the participants attending the CVI Consultative Group, four workshops were structured so as to be an integral component of the meeting. Convened during the middle of the day Thursday, the workshops addressed the topics of: 1) Advocacy for Vaccines and Immunization; 2) Choosing Desirable Vaccines and Vaccine Combinations for the 21st Century; 3) Intellectual Property Rights: Access to New Technologies and Products; and 4) Financing the Introduction of New Vaccines. Through active discussions, workshop participants expressed their ideas and helped chart the future of the Children's Vaccine Initiative. Reports of these workshops were to be prepared for the CVI Task Force on Strategic Planning. Presentations during the final session on Thursday, "Advocacy," stressed the extraordinary value of vaccines, methods for mobilizing communities for immunization programs, and the Rotary International approach to grass-roots fundraising.

Sir Gustav Nossal, Chair of the Fifth Annual Consultative Group, summarized the main plenary sessions of the meeting. He began by giving CVI high marks in vaccine research and development. He referred to the research explosion which has taken place since the 1990 World Summit for Children as an "embarrassment of riches." There is now a wide range of diseases being addressed; diverse ideas are being explored as to how best strengthen immune responses; aggressive research is being pursued on mucosal immunity and oral routes for vaccines; and there are numerous ideas on different vaccine combinations. In addition to new vaccine research and development, remarkable progress has been made in the application of existing vaccines. We have now reached a point where polio eradication seems to be an achievable goal in the near future, and some success has been achieved in measles control. The re-emergence of diphtheria in Europe is, however, a sobering reminder that we need constant vigilance in our disease control and eradication programmes. Regarding collaboration with industry, Sir Gustav gave CVI fair marks and noted that leaders from industry need to be involved in CVI as full partners. With its capabilities and resources, the involvement of industry is essential. Nonetheless, as progress continues in vaccine research, development and production, there will be a continuing struggle for resources. Perhaps what is needed is the demand for a reallocation of priorities. Such a demand relates to the need for advocacy. We must, stated Sir Gustav Nossal, be ambassadors for CVI and advocate at cocktail parties, as well as in the workplace, for "the greatest and most cost-effective health intervention of all time."

1.

Background

Launched in 1990 at the World Summit for Children, the Children's Vaccine Initiative (CVI), was created with the belief that the continued development of new and improved vaccines is the most effective way to reduce childhood morbidity and mortality on a global level. The long-term vision of CVI is the development of a "super-vaccine" which, with a single dose administered shortly after birth, could provide cost-effective prevention against a wide range of infectious diseases. While the long-term goal of creating a "super-vaccine" may seem daunting, progress towards this goal is being made through the achievement of a number of intermediate objectives ranging from research on new combination vaccines, to improvements in vaccine supply, quality and financing. The three main strategies which CVI is using to achieve both its long-term goal and short-term objectives include: 1) consensus building and information sharing among the diverse people and groups working in the vaccine field; 2) the coordination of priorities, particularly with regard to new advances in vaccine development and the identification of "gaps" in vaccine research and funding; and 3) the promotion of advocacy efforts needed to raise awareness and political commitment for the development and introduction of new and improved vaccines.

The long-term vision of the Children's Vaccine Initiative is shared by its five co-sponsoring agencies: the Rockefeller Foundation, the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). Membership in CVI is open and inclusive of a broad-based coalition of individuals, industry representatives, donors, government agencies, non-governmental organizations and United Nations organizations which are working towards the common goal of reducing childhood morbidity and mortality through the development and delivery of new and improved vaccines. This broad-based coalition is known as the CVI Consultative Group (CG). In order to help coordinate the diverse activities of the group, the CVI Secretariat was established in Geneva, Switzerland. The Executive Director is Dr J.W. Lee and, since May of 1995, the first full-time Coordinator of CVI is Dr Roy Widdus.

Once a year, since its launch in 1990, CVI has organized a Consultative Group Meeting. This meeting is the one time each year when the CVI Secretariat, its co-sponsors and its broad-based coalition of supporters all come together to share new information and ideas for future collaboration. Previous meetings have taken place in Switzerland, Japan and the Netherlands. This year's Fifth Annual Consultative Group Meeting, hosted by the Government of Brazil, took place in the city of São Paulo on 25-26 October, 1995. The meeting was particularly important for two reasons. First, through a series of plenary presentations, participants were able to review the progress made during the first five years of CVI. Second, the meeting was structured so that members of the Consultative Group could participate in workshops and help chart the directions CVI will take into the 21st Century.

2.

Opening of the fifth annual Consultative Group Meeting

Dr J.W. Lee, Executive Secretary of the Children's Vaccine Initiative and Director, Global Programme for Vaccines and Immunization (GPV), WHO, opened the Fifth Annual Consultative Group Meeting of CVI by welcoming its 175 participants who had travelled from different geographic regions, and who represented the diverse areas of vaccine research and development, public health, industry, donor agencies and co-sponsoring institutions. Reiterating the theme of the meeting "Progress Since the World Summit for Children: 1990-1995," Dr Lee stated that it was an appropriate time to be analyzing the progress made by CVI, not only because of the five-year mark, but also because the CVI Secretariat had become more grounded and its coalition of members had become more cohesive. From this solid base, Dr Lee encouraged CVI to move forward and invited **Sir Gustav Nossal,** Director of the Walter and Eliza Hall Institute of Medical Research in Australia, to begin that process through his chairmanship of the Fifth Annual Meeting.

In his keynote address at last year's Fourth Annual Meeting in Amsterdam, Sir Gustav likened CVI to a toddler who was "walking and talking, but still finding its feet." As Chair of the Fifth Annual Meeting, he invited CVI to take heart in the strides it has made and the great progress which has been achieved in the past five years, a relatively short period of time in human history. Sir Gustav then proceeded to identify three particularly noteworthy accomplishments in the overall field of vaccines and immunization.

First, giant strides have been made towards the global eradication of polio. Eradication has already been achieved in the Western Hemisphere, and the Western Pacific Region is now close to achieving polio eradication as well. Second, the first steps have been taken towards meeting the World Health Assembly's resolution to introduce the hepatitis B vaccine as the seventh vaccine included in WHO's Expanded Programme for Immunization (EPI) list of recommended childhood vaccines. Sir Gustav did note, however, that although many countries now have plans to introduce the hepatitis B vaccine, he wished actual implementation could be quicker. Finally, the third outstanding accomplishment of the past five years, as identified by Sir Gustav, is the scientific research which has led to the potential use of nucleic acids themselves as possible vaccines.

Introduced by Sir Gustav, **Dr Adib Jatene**, the Minister of Health of Brazil, officially welcomed participants, on behalf of the Government of Brazil and the Brazilian people, to the Fifth Annual Consultative Group Meeting and to the city of São Paulo. Acknowledging the importance of childhood vaccines in general, and to Brazil in particular, Dr Jatene discussed the Brazilian experience with vaccines and immunization. In his presentation of the Brazilian experience, he introduced a number of themes which were later discussed from a global perspective during the different sessions of the meeting. These themes included: disease control and the utilization of widespread immunization campaigns; vaccine production, quality and financing; and the need for further research to develop new vaccines for existing infectious diseases.

Widespread national immunization policies did not begin in Brazil until the first oral polio campaigns in the 1960s and 1970s. The National Programme of Immunization (PNI) was established in 1973. Immediately confronted with a meningitis epidemic, the PNI had to quickly develop a new strategy for vaccine delivery: massive immunization campaigns which involved all sectors of Brazilian society. The most outstanding example of the success of this type of campaign is the eradication of polio from Brazil which has been officially recognized by both the Pan American Health Organization (PAHO) and WHO. The most recent efforts in disease control, using this same type of campaign, have been directed towards the control of measles. After a measles epidemic occurred in 1990 with an outbreak of over 60,000 cases, the government responded by immunizing 48 million children within a two year period. Between 1992 and 1994, fewer than 100 cases were reported in the entire country.

In order to support its widespread immunization efforts, the Ministry of Health of Brazil launched a self-sufficiency programme in 1985 which will be coordinated by a National Immunobiological Products Authority, currently being established. Activities of the self-sufficiency programme include a system for quality assurance, licensing and testing, and the organization of a national distribution center which ensures that the cold chain is maintained during vaccine distribution. Brazil currently meets half of its own vaccine needs by production and is in the process of opening new plants for DTP and BCG production. Issues which still need to be addressed in terms of vaccine production include international intellectual property rights which may increase the development costs of newer products, technology transfer, and technical and managerial assistance programmes.

Although Brazil has achieved a great deal of success in terms of disease control utilizing established vaccines, Dr Jatene emphasized the urgent need for research efforts directed at improving existing vaccines such as BCG and meningitis B, and to further the development of vaccines which are currently in clinical trials for such parasitic diseases as leishmaniasis, schistosomiasis and malaria. Research in the area of new vaccines is particularly important for a country like Brazil given its biodiversity and the potential for the emergence, or re-emergence of a wide range of infectious diseases.

Later described by Sir Gustav as a positive, heartwarming way to begin the meeting, Dr Jatene concluded his morning presentation by awarding four Oswaldo Cruz Medals. The Oswaldo Cruz Medal honours both Brazilians and foreigners who have worked in the fields of science and education towards advances in medicine and public health. They are awarded to individuals who have made contributions to global, collective well-being. Officially approved by President Fernando Enrique Cardoso, the medals were awarded by Dr Jatene to: Dr Claudio do Amaral, Jr.; Dr Donald Henderson; Dr Isao Arita; and Professor Walter Leser.

Concluding remarks to the morning's opening session were made by **Dr Hiroshi Nakajima**, Director-General of the World Health Organization. On behalf of CVI and its co-sponsors, Dr Nakajima thanked the Government of Brazil for being such a gracious host for the Fifth Annual Consultative Group Meeting. He also showed his appreciation by stating that this meeting was special in that it was the first time the consultative group had assembled in the Americas; a region which has shown great progress in its commitment to vaccine self-sufficiency and immunization.

Dr Nakajima re-emphasized the theme of the meeting by stating that "five years down the road" from the World Summit for Children, the meeting was the perfect opportunity to review the remarkable progress which had been made in disease control, vaccine supply

and quality, and vaccine research and development. He encouraged participants to take an active role in the workshops scheduled to take place during the second day of the meeting, and to share their expertise in charting the future of CVI. This invitation to active participation, as Dr Nakajima pointed out, was also an opportunity for people to recommit themselves "to another five years of work in pursuit of the CVI goal of expanding protection against infectious diseases."

Before turning the microphone over to the chair of the first session and inviting participants to begin the review of progress made since 1990, Dr Nakajima provided a brief review of the changes in the vaccine world which have taken place among the CVI co-sponsors themselves. Since their initiation of CVI, the five original co-sponsors have both recommitted themselves to the collaborative effort, and have continued to pursue individual objectives which contribute to the overall CVI belief that the development of new and improved vaccines is the most effective way to reduce childhood morbidity and mortality on a global level.

For example, at last year's consultative group meeting in Amsterdam, Dr Nakajima announced the creation within WHO of the Global Programme for Vaccines and Immunization (GPV), directed by Dr J.W. Lee. The GPV now provides a base for CVI, and Dr Lee serves as the CVI Executive Secretary. The World Bank has initiated a three-year grant to the CVI Secretariat following its *1993 World Development Report—Investing in Health.* The Rockefeller Foundation, another co-sponsor, has continued its support to the CVI Secretariat, as well as having founded the International AIDS Vaccine Initiative (IAVI). UNDP has committed itself to the development of human and institutional resources through the creation of the International Vaccine Institute (IVI) in Seoul, Korea. Last but not least, UNICEF has continued to redefine its strategies for vaccine procurement and assistance to help countries achieve sustainable vaccine supply and financing.

3.

Review of progress since the World Summit for Children

A. Disease control: 1990-1995

Dr J.W. Lee, chair of the first session of the meeting, "Disease Control: 1990-1995," introduced **Dr Bjorn Melgaard**, Chief of the Expanded Programme on Immunization (EPI), WHO/GPV. Dr Melgaard, speaking on the topic, "Global Polio Eradication," began his presentation with a timely quote from a Danish philosopher, "It is difficult to prophesy, especially regarding the future. One might start, however, by studying the past. Where are we coming from, where are we now and so, where are we going?" In terms of the eradication of polio, we are coming from a situation where the global coverage of OPV3 for children under one year of age was 48% in 1985, up to 85% in 1990 and then down to an estimated 82% in 1995. Does this indicate that where we are going is a downward trend in the coverage level of OPV3?

Dr Melgaard does not think so. Although he stated that the 1990 effort could not be sustained, overall coverage does continue to increase again slowly. Of particular note is that over 80% coverage has been achieved and maintained in the 1990s, and the African region has now surpassed the 50% coverage mark for OPV3. High rates of coverage are being maintained through such activities as national immunization days (NIDs) which were held in 63 countries in 1995, and Operation MECACAR, a combined effort of NIDs between 16 bordering countries in Europe, the Mediterranean and Central Asian Regions. Operation MECACAR has achieved a coverage level of over 90%. The immunization days are being complemented by increasing viral surveillance of the disease, and an increasing laboratory network which will allow more countries and regions to increase surveillance of polio cases and cases of acute flaccid paralysis (AFP).

Of course the best evidence of the impact of a disease control programme is the incidence of new cases occurring. Great progress has been made in the control of polio. While 35,000 cases were reported in 1988, the number of new cases dropped to 10,000 in 1993 and 7,500 in 1994. Also encouraging are the results of a group known as the Taylor Commission which examined the impact of polio eradication campaigns on other health services. External positive benefits of polio eradication include improved planning and management capabilities in the health services sector, as well as increased social mobilization. Negative benefits include a "skewed allocation of resources." In the question and answer period following the session, Dr Mark Kane of WHO/GPV responded to a question posed by Sir Gustav and noted that although there have been a few instances where resources were diverted from polio campaigns to other on-going programmes, such as the introduction of hepatitis B, the number of these diversions has been few and far between.

Nonetheless, additional resources must still be mobilized if polio eradication is to be achieved. It is estimated that an additional US $500 million will be needed to purchase the vaccines necessary and provide for the human and logistical resources required to oversee

the global effort. In early 1995, Dr Nakajima of WHO established the "Commission for the Certification of the Eradication of Poliomyelitis." It is hoped that with additional political commitment and financial resources, this commission can be dissolved in the year 2004 and global polio eradication can be declared.

The second speaker in the session on disease control was **Dr Ciro de Quadros**, Director, Special Program for Vaccines and Immunization (SVI), Pan American Health Organization (PAHO). Dr de Quadros began by noting the appropriateness of his presenting on the topic of measles in the city of São Paulo. As stated by the Brazilian Minister of Health in his opening address, the city of São Paulo and the entire country of Brazil responded rapidly to an outbreak of measles in 1990. In fact, the epidemic was controlled within two years. After first presenting global background data, Dr de Quadros discussed the strategy for measles control promoted by PAHO over the past five years, the basic elements of which are modeled on the São Paulo experience.

The coverage level of immunization against measles has increased tremendously since 1978. Globally, the coverage level has now reached the important 80% marker, similar to the coverage level for polio. Nonetheless, there are still an estimated 40 million cases of measles per year and 1.5 million deaths. Measles accounts for approximately 11% of the deaths of children under the age of five. As Dr de Quadros noted, one of the great tragedies of this figure is the fact that measles is a vaccine preventable disease.

The current strategy for measles control promoted by PAHO in the Americas has three main components. First, the "catch-up" component includes the immunization of young people between the ages of 9 months and 14 years. Second, the "mop-up" component focuses efforts on districts with low overall coverage. Third, the final component increases the age of routine measles immunization from 9 months to 1 year, thus increasing vaccine efficacy. This basic strategy was applied in Cuba in 1988 and throughout the English-speaking Caribbean in 1991. In these two areas, there have been no laboratory confirmed measles cases in the last two and three years, respectively. As noted, the largest campaign in the hemisphere took place in Brazil in 1991-1992. Nearly 50 million people were immunized and measles transmission has now been interrupted in many states.

In Latin America today, over 90% of children between 9 months and 14 years have received one dose, if not two, of measles vaccine. Coverage rates in the region range from just under 80% to 100%. To date, there have been 4,200 cases of measles reported in the Americas for 1995. Approximately half of these cases occurred in Canada which is now considering implementing the same measles control strategy which has been so successful throughout Latin America.

As discussed by Dr de Quadros, the biggest bottleneck in measles control is the build-up of "susceptibles." This build-up is caused by the fact that some children are never immunized, and some that are immunized don't develop immunity. This accumulation of susceptibles is what accounted for the outbreak in the United States in 1990-1991. To address this problem, PAHO is suggesting further "catch-up" measles campaigns in which children under the age of five are vaccinated every four to five years, regardless of previous vaccination history. Given the high coverage rates throughout the region and the well-developed control strategies, PAHO is hopeful that measles will be eliminated from the Americas by the year 2000.

Following the presentations by Dr Melgaard and Dr de Quadros, **Dr François Gasse**, Medical Officer at WHO/GPV/EPI, was invited to speak on the topic of "Neonatal Tetanus". In his introduction of Dr Gasse's presentation, Dr Lee, referred to the control

of neonatal tetanus as a "sleeping success." He implied that although progress in the control of polio and measles may be more visible, there has also been a great deal of success in the control of neonatal tetanus. Dr Gasse then opened his presentation by first stressing the dangers of the disease, and then discussing control strategies and progress achieved. "Second only to measles as the leading killer of children," an estimated 800,000 to one million newborns died from tetanus in the early 1980s. Before routine immunization began, tetanus accounted for approximately 25% of infant mortality rates and between 8% to 69% of neonatal mortality rates.

Given the importance of tetanus control, as well as the fact that it is among one of the traditional EPI vaccine preventable diseases, the participants at the 1990 World Summit for Children called for the global elimination of neonatal tetanus by the end of the decade. The main strategies employed in the fight against neonatal tetanus include: "1) delivery of tetanus toxoid vaccine to pregnant women and to all women of childbearing age in *high risk areas;* 2) ensuring clean delivery and cord care practices to all pregnant women; and 3) effective surveillance aimed at detecting and reacting to every NT case."

Data on neonatal tetanus incidence indicate that these immunization control strategies are working. An estimated 735,000 neonatal deaths are prevented each year. This figure is attributed to an increase in the coverage of pregnant women between 1988 and 1994. Data from every WHO region, except the Western Pacific, show a downward trend in the number of neonatal tetanus cases reported in the last five years. In Africa, the number of reported cases dropped from 6,918 in 1989 to 3,441 in 1994. In the Americas, reported cases decreased from 1,430 in 1989 to 587 in 1994 (21 of the 47 countries reported zero cases.) In the Eastern Mediterranean and in Southeast Asia, reported cases declined between 1989 and 1994 from 6,314 and 14,102, respectively, to 3,353 and 2,285. Of particular note is the marked effect in Southeast Asia of using the strategy which focuses on the immunization of women at high risk. After increasing vaccination coverage of pregnant women with TT2+, Bangladesh, India and Indonesia were able to prevent a total of more that 450,000 deaths in 1994. On a less positive note, annual incidence rates increased in the Western Pacific from 282 to 422 between 1989 and 1994.

Similar to the polio eradication and measles control campaigns, one of the main challenges faced in the control of neonatal tetanus is sustaining both political and financial resources. It is estimated that an additional US $30 million is needed to supplement current efforts if the 55 million women who live in high risk areas are to be immunized with the necessary three doses of TT. However, it is hoped that the development of a slow release tetanus toxoid vaccine, which ensures longer and more effective immunity with one injection, may help to reduce this cost while increasing coverage rates. Responding to a question by Dr William Hausdorff of Wyeth-Lederle Vaccines and Pediatrics in the US, Dr Gasse noted that another challenge in employing the current neonatal tetanus elimination strategy is that it focuses on immunizing women. The problem is actually two-fold and is caused by both discrimination against women and perceptions of female fertility/infertility. This challenge can be overcome, Dr Gasse stated, through good programme planning and the education of doctors. Overall, the elimination of neonatal tetanus means the prevention of one million newborn and 50,000 maternal deaths every year.

The final presentation in the session, "Disease Control: 1990-1995," was made by **Dr Thomas More Chaita**, Deputy Director of Maternal and Child Health at the Ministry of Health and Child Welfare in Zimbabwe. Dr Chaita, presenting on the topic of "The Introduction of New Vaccines," focused his remarks on field experience in Zimbabwe and the introduction of hepatitis B vaccine. With data based on surveys of endemicity carried

out by the University of Zimbabwe's Medical School, as well as information gathered from the National Blood Transfusion Service and the National Cancer Registry, the Ministry of Health began its quest for funding in 1992. Once financial collaboration was secured from the Fund for Private Assistance in International Development (PAID), Rotary International and Africare, the government began to prepare for the introduction of the new vaccine.

The overarching goal of the project was to have universal child immunization against hepatitis B. Some of the objectives towards the achievement of this goal included: 1) immunizing all children under 1 year of age; 2) training all health personnel in hepatitis B immunization; 3) raising community awareness; 4) strengthening the entire EPI; 5) strengthening diagnostic capability, as well as surveillance capability of hepatitis B infection; and 6) monitoring and evaluation of the project. An important part of the strategy was the combination of the hepatitis B immunization schedule with the existing EPI schedule, thus avoiding any disturbance in the system already established. After a consultative meeting in 1993 and a series of training workshops in May of 1994, the national launch of the hepatitis B vaccine in Zimbabwe was held at the end of September, 1994.

The Ministry of Health has encountered a number of problems with the introduction of the new vaccine. Before the vaccine was introduced, there seemed to be a lack of appreciation of the hepatitis B problem, as well as some "foot dragging" due to concerns about sustainability. Since the national launch in 1994, some new challenges have been posed including a change in the target population, a corresponding change in budget estimates, an erratic vaccine supply and complex funding procedures. To date, the introduction of the hepatitis B vaccine in Zimbabwe is still in progress, with only three provinces reporting active immunization programmes against the disease. In his comments at the end of Dr Chaita's presentation, Dr Mark Kane echoed Dr Chaita's comments regarding the importance of simple, sustainable financing mechanisms for hepatitis B immunization programmes.

Before the close of the session, Dr Lee invited **Dr Philip Stoeckel** of France to make some remarks on behalf of Dr Charles Mérieux who was unable to attend the meeting. Dr Stoeckel recalled the outbreak of meningococcal meningitis which occurred in 1975 in São Paulo. He said that it was an important event for Mérieux, as well as for Brazil. It was at this time that Mérieux saw a tremendous increase in the global demand for vaccines. Reaffirming the Mérieux Foundation's support for the vaccine community and CVI, Dr Stoeckel announced that the Foundation planned to hold trainings in the areas of epidemiology and health delivery systems, and would conduct field trials of rapid, simple diagnostics for measles, tetanus and hepatitis B.

B. Vaccine supply, self-sufficiency and quality: 1990-1995

The second session of the meeting, "Vaccine Supply, Self-Sufficiency and Quality: 1990-1995," was chaired by **Dr Isao Arita**, Chairman of the Agency for Cooperation in International Health (ACIH), Japan. For his introductory remarks, Dr Arita offered his assessment of the progress of CVI towards its original goal as defined in the New York Declaration of 1990, the development of new and better vaccine(s). Dr Arita's remarks bridged the first two sessions of the meeting. First, he reviewed progress made in vaccine development, particularly as it relates to some of the existing EPI vaccines. Second, he discussed the need to focus on the current topic of vaccine supply, financing and quality control.

Regarding the development of new and improved vaccines, Dr Arita stated that progress may be judged according to ten steps in the development of any vaccine: "1) strategy; 2) trial product; 3) clinical trial; 4) field trial; 5) production in small scale; 6) license; 7) price and marketing; 8) procurement; 9) large scale production; and 10) dispatch to the field and post licensing monitoring." Judging vaccine development against these steps, Dr Arita believes that progress has been slow in the past five years. The only studies to have reached step four are OPV formulation, improved measles vaccine and acellular pertussis vaccine. Perhaps, he suggested, the need exists to accelerate the ten step process and follow the wisdom of the New York Declaration which states that vaccine research should be accompanied by plans to guarantee the large-scale, quick and cost-effective production of new and improved vaccines. In other words, more attention needs to be paid to steps six through ten in vaccine development.

Placing particular emphasis on the production of vaccines in developing countries, Dr Arita noted that local vaccine production in many countries cannot meet the national demand, nor can it meet the quality standards set by WHO. To this end, CVI established Task Forces for Situation Analysis and Quality Control which, in the past three years, identified 14 developing nations as priority countries for development. After consultative visits, the Task Forces found that many of the producers in these countries lack good manufacturing practices (GMP). However, through commitment and better technology, improvements are being made. Notable production progress has been made in Egypt, Iran and Viet Nam, through such methods as joint ventures, production sharing, multi and bilateral cooperation. In his closing statement, Dr Arita emphasized the importance of the issues to be raised in the forthcoming session, "To me, vaccine self-sufficiency in developing countries would be the key to ease the current difficulty of meeting global vaccine demand, as well as rapid introduction of better or new vaccines when they become available."

Dr Jorge Kalil, Director of the Transplant Immunology Lab in São Paulo, was nominated to speak on the topic of "The Commitment of Brazil to Vaccine Self-Sufficiency." Dr Kalil spoke from experience. In January of 1995, after Dr Jatene was named the Minister of Health, Dr Kalil was asked to chair a committee to assess the production of vaccines in Brazil. The National Programme for Immunobiological Self-Sufficiency (PASNI) supplies 50% of vaccine doses used in the Brazilian National Immunization Programme (PNI). This is significant given that the childhood immunization programme in Brazil is one of the largest in the world, with a projected 270 million doses used in 1995.

Regarding self-sufficiency in vaccine quality and production, PASNI has been attempting to improve quality control and is extending GMP to all the vaccine production facilities in Brazil. Three new plants for DTP vaccine production will be operational within the next year, and one new plant for the production of BCG is near completion. When all the DTP plants are operational, and if they reach their maximum output, then national demand for this vaccine will be exceeded by supply. Improvements are also being made in rabies and measles vaccines through cell culture techniques. Other strategic objectives of PASNI include developing an efficient meningitis B vaccine and producing a recombinant hepatitis B vaccine.

Additional short-term objectives of the Ministry of Health and PASNI, which demonstrate the Brazilian national commitment to vaccine self-sufficiency, include: 1) to reduce the time requirements and improve the quality control procedures at production facilities; 2) to complete the review and approval of all the equipment and processes used in the production of immunobiologicals; 3) to strengthen the vaccine development network, including strengthening the ties between university laboratories and private companies;

4) to improve the pricing and financing policies of vaccine production so that scarce resources are used wisely; 5) to better monitor vaccine demand, utilization and coverage; and 6) to establish a National Immunobiological Authority which should coordinate all vaccine development and production efforts in Brazil.

While Dr Kalil discussed vaccine self-sufficiency from a national perspective, the second speaker of the session was invited to speak from a global perspective. This included progress since 1990 regarding the ability of countries to purchase, as well as produce vaccines. **Dr Terrel Hill**, Principal Advisor of the Child Survival Unit at UNICEF, spoke on the topic of, "Global Progress in Establishing Sustainable Financing of Existing and New Vaccines." Dr Hill opened his presentation by thanking his colleagues and reporting that the Task Force on Situation Analysis, created by CVI and chaired by Dr Arita, could report significant progress towards the establishment of sustainable vaccine supply and financing mechanisms for a number of countries around the world.

The Task Force and its collaborators began by assessing the vaccine supply needs of different countries, and then categorizing countries by their ability to become self-sufficient in meeting those vaccine needs. Based on the category, or "band" that a country is classified under, the Task Force can help set realistic targets for achieving sustainable, national strategies for vaccine supply and financing. In addition to being useful for national planning, this "vaccine support strategy" is used by UNICEF, WHO and a number of donors, to determine which countries are in the need of the most assistance, be it for the financing of routine need or the introduction of new vaccines. Countries are categorized as being in one of four bands, A through D, with A band countries being those who need the most financial assistance, and D band countries being those who are closest to self-sufficiency in vaccine supply.

Since the introduction of the vaccine support strategy in 1990, the percentage of countries meeting their sustainability targets has increased in each of the four bands. There has been significant increase in the percentage of countries in all the bands with regard to the financing of routine national vaccine need. Countries in bands B-D have also been asked to increase financing of new vaccines. Using their national budgetary funds, or loans from the World Bank, countries are now conttributing an aggregate total of millions of dollars towards vaccine financing. Responding to a question later posed by Mr Frank Hartvelt of UNDP, Dr Hill explained that funds saved from the success of the vaccine support strategy are currently reallocated to other programmes within a country, such as water and sanitation projects. There is, however, some discussion about creating a globally managed fund for vaccines, particularly for the introduction of new vaccines. Such a fund would allow for reallocating funds saved from one area of vaccine supply to another.

Dr Hill attributes the success of the vaccine support strategy to five main activities:1) increased government commitment to national immunization programmes; 2) advocacy on the part of donors towards the recognition that immunization programmes should be a national priority; 3) flexible payment and supply mechanisms, such as the Vaccine Independence Initiative (VII); 4) better management of local vaccine production; and 5) increased quality in local vaccine production.

Although there has been great success in the past five years towards the sustainable financing of routine vaccine supply, the next major challenge is achieving the same level of success in the financing of new vaccines. One strategy which is being implemented by UNICEF with regard to the bulk purchase of new vaccines is the UNICEF tender. Using the tender, or competitive bulk procurement process, an additional US $10-15 million

would be enough to move ahead with the procurement and introduction of hepatitis B and yellow fever vaccines for the countries identified as having the greatest need (based on financial need, disease burden, programme strength and national commitment). Also pending are offers for the introduction of Hib and DTP combination vaccines.

While some of the financing of new vaccine introduction will be provided through creative donor strategies, such as the UNICEF tender, increased financing must also come from national governments. Dr Hill summed up the important message of his presentation through the following saying, "For want of a nail, a shoe was lost. Because the shoe was lost, the messenger didn't arrive and the war was lost." Financing, Dr Hill said, is that nail. It is important to continue to develop affordable, sustainable mechanisms to access new vaccines. In the question and answer period following the presentation, Dr Peter Ndumbe of the University of Yaoundé in Cameroon, noted that many countries which are priority countries for new vaccines are African countries which fall within UNICEF's band A and band B. Given that the financing of new vaccines in these countries is likely to come from donor sources, as well as national governments, Dr Ndumbe stressed the importance of joint planning. This, he said, could help prevent countries from becoming discouraged as they try different mechanisms to finance new vaccines.

The complement to ensuring sustainable financing of existing and new vaccines is ensuring the quality of those vaccines. **Dr Julie Milstien**, a scientist working in Vaccine Supply and Quality (VSQ), WHO/GPV, spoke on the topic of "Progress in Commitment to Vaccine Quality." Increased attention has been paid to vaccine quality since the World Summit for Children. In 1992, the World Health Assembly passed a resolution stating that vaccines should meet WHO quality requirements if they are to be used in national immunization programmes. The resolution also asked the Director-General to develop a strategy by which WHO could gather information ensuring that countries were controlling the quality of vaccines produced. The VSQ unit at WHO now has two main objectives towards assuring vaccine quality: "1) to control the source of vaccines used; and 2) to strengthen national control authorities (NCAs) to ensure that vaccines produced and used in the country meet the relevant standards of safety, potency and efficacy."

With regard to the first strategy mentioned, controlling the source of vaccines used, one must look at the four major vaccine sources of any country. The first, local production, may be classified as a national supply source. The other three sources are international and include production sharing (where vaccine components are imported and finished locally), direct procurement from an external producer and the supply of vaccines from a donor such as UNICEF. With regards to ensuring the international supply of vaccines, a series of steps are performed by WHO. These steps include: reviewing the production process, assuring the competence of the NCAs in the producing country, regularly inspecting production facilities for compliance with good manufacturing practices (GMP), randomly selecting and testing lots of final vaccines and investigating any complaints from the field. Currently, of the 17 manufacturers which supply vaccines to UNICEF, a third are from developing countries. Five of the additional seven producers under review to become UNICEF suppliers are also from developing countries.

Guaranteeing the quality of local production, or of a national supply source, may be more difficult than reviewing the quality of vaccines produced by a finite number of international suppliers. To assess the quality of locally produced vaccines, reviews of 63 DTP and 21 tetanus toxoid producers were completed. These studies showed that improvements were needed in both vaccine purity and potency. About 50% of the producers were not even using standard WHO procedures for potency testing. According to Dr Milstien,

the problems in vaccine quality can be traced to a lack of government commitment to high quality vaccines, as exhibited by the lack of independent national control authorities. Governments must allow producers the independence necessary to plan, produce and oversee the production of vaccines in an economically feasible, realistic manner.

In order to help support national producers in achieving high quality production, Dr Milstien announced the creation of a consortium of vaccine producers with its first organizational meeting in São Paulo, immediately following the Fifth Annual Consultative Group Meeting. The objectives of the consortium include: "1) to provide good quality and sufficient quantity of vaccines for national use at an affordable price; 2) to share technology and management skills on a not-for-profit basis; and 3) to establish communication among vaccine producers." To become a member of the consortium, producers must have a functioning NCA. Membership itself will be considered equivalent to a WHO certification of the producer.

While the consortium of vaccine producers is another step towards improving vaccine quality, efforts must be continued in this area. As Dr Milstien concluded, the quality of vaccines used is the most important indicator of progress in this area. Between 1993 and 1995, the percentage of DTP being supplied which was of known good quality increased from an estimated 54% to 61%. The goal for the year 2000 is to ensure that *only* vaccines of known good quality are used in national immunization programmes. Concurring with Dr Milstien were Dr D.A. Henderson of the Johns Hopkins University in the USA and Dr Peter Ndumbe. After first referring to Dr Hill's presentation and praising the progress made in financing through the Vaccine Independence Initiative, Dr Henderson noted that he was more worried about quality control issues, particularly given that a number of production laboratories do not produce at a critical level to ensure quality. Quality, he said, should be the number one priority. Dr Ndumbe thanked the VSQ unit at WHO for their work in quality control throughout Africa, especially for their work in Nigeria.

C. Regional highlights

Mr Frank Hartvelt, Deputy Director of the Science, Technology and Private Sector Division at the United Nations Development Programme (UNDP), stressed the importance of the session on "Regional Highlights" by noting that CVI is global in scope and thus needs to be firmly anchored in both developed and developing countries. As chair of the session, Mr Hartvelt opened his remarks by stating that vaccine related activities in every country should be determined by the capabilities within that country. These capabilities may be related to production, research, economies of scale, or public health programmes. Of particular interest to UNDP are CVI activities related to capacity building and strengthening national vaccine production. UNDP focuses its capacity building activities on human resources development through staff training in a number of areas, and on institutional development through the improvement of organizational and management structures.

Since 1990, capacity building efforts at a regional level have emerged as a supplement to local efforts. Mr Hartvelt mentioned what he considers to be two particularly promising efforts, the Regional System for Vaccines (SIREVA), and the International Vaccine Institute (IVI). SIREVA is the regional network of quality control laboratories established in Latin America to foster efforts towards improving and ensuring vaccine quality. The recently established IVI, based in Seoul, Korea, will focus on human resources and institutional development for vaccine related activities throughout Asia. Mr Hartvelt sees these two efforts as having positive regional impacts which extend to programmes supported by

national governments, international organizations, private sector companies and institutes. In concluding his opening remarks as chair of the session, Mr Hartvelt stated that CVI is a visionary initiative which can have an enormous impact at the regional, as well as country level.

Speaking on behalf of the countries in Africa, **Mr Oni Olawale**, Vaccine Supply and Quality Professional for the Africa Regional Office, focused his regional highlights on plans which have been developed during the past five years, to achieve goals within the next five. The focus within the region needs to be on ensuring vaccine planning, production and quality control. Towards that end, all local EPI managers will be asked to develop national vaccine supply plans in 1996. Furthermore, the regional office will coordinate with donor agencies so that complete production, procurement and assessment plans are developed for three priority countries within Africa. A complete inventory will also be carried out of the critical control functions being implemented in the following producing, or procuring countries: Botswana, Burundi, Côte d'Ivoire, Cameroon, Kenya, Nigeria, Senegal, South Africa, Swaziland, Tanzania and Zimbabwe.

Intermediate range plans for Africa, with a target date of 1998, include the introduction of hepatitis B in all countries in the region with at least a 70% coverage level. In addition, a consistent supply of vaccines for routine immunizations and national immunization days (NIDs) must be guaranteed. For the year 2000, the Africa region will be aiming towards the following global targets: 1) to have all vaccines used be of known good quality; 2) to ensure that all countries have developed national vaccine plans; and 3) to help countries develop mechanisms for sustainable financing. Finally, Mr Oni stated that all new vaccines must be made available to countries which have an existing epidemiological need, and that donors should continue their support within the region so that the poorer African countries are included in the global progress towards disease control.

Dr Akira Homma, Regional Advisor on Biologicals for PAHO, opened his presentation by noting that one of the major regional highlights for the Americas was the creation, just last year, of the Special Program for Vaccines and Immunization (SVI) within PAHO. Directed by Dr Ciro de Quadros, SVI represents a merging of responsibilities for both EPI and SIREVA. Formally begun last year as well, the establishment of SIREVA is considered one of the major regional achievements since the World Summit for Children in 1990. A regional quality control network within SIREVA has established a Technical Advisory Group which met in Mexico City in 1995 to discuss national laboratory protocols and begin the development of regional reference materials, one of their defined priorities. Two additional countries in the region have established national control laboratories, thus leaving only one DTP producing country without a national control laboratory. Future plans of the regional quality control network include human and institutional development through training programmes on new methodologies of quality control, and the establishment of an e-mail and internet system to facilitate communication between laboratories.

Other regional highlights for the Americas, as mentioned by Dr Homma, include progress in research and development, as well as a new certification programme for DTP producers. Progress in the area of research and development includes: 1) participation by 6 countries in an on-going study of *S.pneumoniae* and *H.influenzae*, aimed at strengthening epidemiological surveillance; 2) a multi-country collaborative programme among Brazil, Chile and Mexico, to develop a conjugated typhoid fever vaccine; and 3) numerous comparison and efficacy studies regarding *N.meningitidis* serogroup B vaccines which were developed in Cuba and Norway. The certification programme for DTP producers is also a truly regional

highlight in that it involves participation and collaboration from a number of Latin American countries. Progress in this has involved: 1) a workshop on good manufacturing practices (GMP); 2) a workshop on DTP validation, held in Mexico and supported by the Food and Drug Administration (FDA) of the USA; and 3) the establishment of an Expert Group for the DTP Certification Programme. This group will visit the different DTP producing laboratories throughout the region.

Speaking on behalf of the 50 countries which comprise the European region, ranging from Iceland to Israel, was **Dr David Salisbury**, Principal Medical Officer of the Department of Health, UK. Dr Salisbury divided his review of European progress into four main areas: 1) re-emerging infectious diseases; 2) the success of operation MECACAR; 3) new vaccine development; and 4) vaccine manufacturing problems. Numbers one and four represent, unfortunately, setbacks to progress in the European region. The re-emergence of infectious diseases is a serious, widespread problem which has far-reaching ramifications. The diphtheria epidemic in the former USSR, which started in Moscow and St. Petersburg, continues to spread throughout the Newly Independent States (NIS). With a higher monthly incidence in 1994 than 1995, the total number of cases in the NIS for 1995 is expected to exceed 150,000. The number of cases of tuberculosis in Europe is also on the rise. The increase in the number of cases in the UK is approximately 5-10%, and the increase in Eastern Europe is estimated to be even higher. Finally, the incidence of cholera has also been increasing in the region. The re-emergence of these infectious diseases in Europe is problematic for two reasons. First, these diseases should, by now, be relegated to history books. Second, their re-emergence has caused a huge diversion of resources away from the establishment of sustainable vaccine supply and manufacturing in Eastern Europe.

On a more positive note, the European region has seen progress in the past five years with the success of the collaborative immunization programme, Operation MECACAR, as well as in new vaccine development and introduction. As described by Dr Melgaard during his discussion of global polio eradication, Operation MECACAR involves the cooperation of 16 border countries in Europe, Central Asia and the Mediterranean. Statistics are showing that the incidence of polio has dropped considerably in the region. In June through August 1995, only four cases of polio were reported, while 84 cases were reported during the same period in 1994. In addition to the success of Operation MECACAR, the European region has seen some success in the introduction of hepatitis B vaccine into routine use in the following countries: Albania, Bulgaria, France, Germany, Italy, Poland, Portugal, Romania and most of Spain. Introduction of the vaccine is still urgently needed, however, in much of Eastern Europe. Northwestern European nations have yet to decide whether or not they will introduce the vaccine given the low prevalence of hepatitis B. However, they have followed through with the widespread introduction of the *Haemophilus influenzae* B vaccine (Hib).

Regional highlights for Southeast Asia were presented by **Dr S.P. Tripathy**, Director of Health Research for the Southeast Asia Regional Office. Dr Tripathy began by commenting on the fact that although the region is comprised of only ten member countries, it contains more than a third of the world's population. All of the ten countries are developing countries, with five being in the category of least developed countries. Given the large population and relatively poor economic status, vaccine supply and financing are particularly important issues for the region. There are 32 vaccine producers in the region: 26 in India, 2 in the Democratic People's Republic of Korea, and 1 each in Bangladesh, Indonesia, Myanmar and Thailand. Most of these are public sector producers and face a number

of problems including: 1) outdated production technology; 2) old infrastructure; 3) the breakdown of equipment; 4) inadequate management; 5) the need to strengthen quality control; 6) inadequate staff training; and 7) virtually non-existent research and development.

To achieve progress in the future, vaccine producers will need to introduce new technologies, new vaccines and new methods for quality assurance, including GMP. In addition, the roles of public vs. private vaccine producers must be further examined, especially with regard to the possibility of joint ventures. Two recent advances have been made in the region through the mixing of public and private companies to improve vaccine production. Perum Bio Farma of Indonesia, a public sector initiative, has updated its manufacturing by undertaking the following measures: hiring a new president and new director from the private sector; acquiring a substantial amount of capital for production renovation through foreign aid; improving both technical and managerial training; and securing technical cooperation from external sources, such as CVI and the governments of Japan and the Netherlands. The Government of Thailand was also successful in incorporating private sector support. Through an agreement with Pasteur Mérieux, it was able to improve vaccine production and quality through the transfer of technology and the modernization of the production of EPI vaccines. Dr Tripathy believes that these efforts to improve local production will ultimately benefit the region in the production and introduction of new vaccines, such as hepatitis B or a much needed dengue fever vaccine.

Dr R. Tangermann, EPI Medical Officer for the Western Pacific Regional Office (WPRO), also focused his remarks on self-sufficiency in vaccine production and supply. Before he began discussing production, however, he highlighted the great progress which the countries of the Western Pacific Region have made towards the eradication of polio. In 1994, five cases of wild polio virus were reported from different areas around China, and in the first half of 1995 only two and six cases were reported, respectively, in the Mekong Delta Region of Southern Viet Nam and in Cambodia. If progress continues, the Western Pacific will follow the Americas as the second region to eradicate polio.

Regarding vaccine self-sufficiency and supply, progress has been made through the development of a regional plan of action to improve vaccine production, and the compilation of a list of experts and regional producers who may be called upon for assistance. Of particular importance is the regional expertise developed in Australia, Japan and Korea, which can be shared with other countries. This should help overcome some of the current constraints to vaccine self-sufficiency which include outdated plants and equipment, weak NCAs and inadequate staffing and management. In addition to self-sufficiency through local production, some countries in the region are achieving self-sufficiency through sustainable procurement plans. Under the Vaccine Independence Initiative (VII), UNICEF has helped the Government of the Philippines establish a revolving fund through which the government can efficiently purchase vaccines. Most of the EPI vaccines used in the Philippines are now procured through government funds. A similar VII mechanism, a revolving fund for vaccine purchase, is now being jointly established by the ten Pacific Island Countries. To defray some of the financial burden, the Government of Australia has offered to provide hepatitis B vaccine for the ten countries for a period of three years.

A common theme throughout the presentations on regional highlights was the need for a continued focus on vaccine financing, supply and quality. As a response to this need in Asia, the International Vaccine Institute (IVI), introduced by Mr Hartvelt in his opening remarks, is being established jointly by the Republic of Korea and UNDP. **Mr Jaechol Hahn**, Deputy Director-General of the UN Systems Bureau from the Minis-

try of Foreign Affairs in Seoul, Korea, spoke briefly at the end of the regional highlights session to voice his government's support of the IVI. Summarizing the details of the support, Mr Hahn stated that the proposed site for the IVI is within the Research Park of Seoul National University. Housed amidst other science and technology facilities, the IVI will occupy about 15,000 square meters at a building cost in excess of US $25 million. The Government of the Republic of Korea will provide US $6 million for laboratory equipment and supporting facilities, and will then pledge approximately 30% of the annual operating budget, estimated to be US $12 million to $15 million. The remainder will be raised by UNDP. Mr Hahn concluded his remarks by stating that the Republic of Korea is "fully committed to the goals of IVI and hopes that other states and international organizations will render their valuable support and join in this endeavour."

Following the remarks by Mr Hahn, **Dr Richard Mahoney**, Director of Institutional Development for the International Vaccine Institute, spoke at greater length on the mission of the IVI. Beginning with the need for the IVI, Dr Mahoney noted that only a portion of diseases are vaccine preventable and that human and institutional resources are lacking in new vaccine development, particularly within developing countries. Given that need, the IVI is being established in Seoul, Korea, as a capacity building resource organization for Asia. It will be a legal, international organization with an independent Board of Trustees, international recruitment, and both financial and administrative flexibility. It will not serve as a regulatory agency, nor will it be a vaccine producer. Its main objectives will be to disseminate information and provide training and technical services to people, institutions and governments throughout the region. In summing up his presentation, and to highlight the importance of the investment by UNDP and the Republic of Korea in the IVI, Dr Mahoney quoted Professor Lester Thurow from the Massachusetts Institute of Technology, USA:

> *Suppose you are reading a history book a thousand years from now, in the year 3000. What do you think it is going to say about us, when all the little things have been forgotten? I think historians will say that we were the people who invented biotechnology. Biotechnology will revolutionize the world. It will change the very nature of disease.*

The discussion period following the session on regional highlights was opened by Mr Sakamoto of the Ministry of Health and Welfare, Japan. Mr Sakamoto directed his question to Dr Mahoney and asked how cooperation will be established between the IVI and WHO, particularly with regard to WHO regional activities. Dr Mahoney answered that he hopes interaction will be on a technical level. Speaking on behalf of WHO, Dr Lee further responded to Mr Sakamoto by stating that IVI activities should not conflict with WHO regional plans, and that they should be fully compatible with the *CVI Strategic Plan*. He also said that he considers the IVI to be an exciting development and a "youngest brother in the vaccine community." Furthermore, Dr Lee stated that he looks forward to seeing the specific terms by which the IVI proposes to work with CVI. Not entirely appeased by the promise that there would be no duplication of activities between newer organizations such as IVI and SIREVA, and existing organizations, Dr Jorgen Weber of Canada posed the question, "How will action be fostered, rather than stymied by additional bureaucracies?" The chair of the session, Mr Frank Hartvelt, stated that part of the job of CVI is to coordinate the activities of different organizations and make sure that such a duplication of activities does not occur.

D. Vaccine research and development

The chair and first speaker of the session on "Vaccine Research and Development," was **Dr John La Montagne**, Director of the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA. Dr La Montagne, speaking on the topic of "Progress in Development of New Vaccines: Vaccine Technologies for the Future of CVI," began his presentation by reflecting back to the New York Declaration and the World Summit for Children in 1990, when the original mission of CVI was defined. The New York Declaration was a call to action of sorts, for the development of vaccines which could prevent more diseases, be combined, be administered easily, and perhaps even be given at birth to protect individuals against a wide range of infectious diseases for their lifetime. While such a "super-vaccine" has yet to be developed, a number of important developments have occurred in the past five years, fueled by new technology. Stating that intellectual discoveries often lead to new innovations in vaccine development, Dr La Montagne predicted that many new advances in vaccine development will occur through biotechnology and the use of recombinant DNA techniques.

What does the future hold for vaccines? According to Dr La Montagne, one can expect advances on a number of different fronts in the near future. First, newer, safer vaccines will be developed and introduced, such as acellular pertussis vaccine. Second, the choice of vaccines will be greater. In the USA for example, there will be a number of different haemophilus B vaccines that a consumer can choose from. Third, the increasing globalization of the vaccine field will favour more efficient producers. This is likely to mean that there will be consolidation and partnerships formed within the vaccine industry which will lead to larger producers. Fourth, there will be improved strategies for quality control. Fifth and finally, vaccines may be developed for more infectious diseases, such as sexually transmitted diseases, parasitic diseases and fungal diseases.

Regarding progress in new vaccines in particular, there is an incredible number of vaccines which are currently in the development pipeline. The actual number in development has increased by 20% to 30% between 1993 and 1995. While 1995 will most likely be thought of as the year of acellular pertussis (aP) vaccine, a number of other vaccines are also in phase III clinical trials. Among the promising new vaccines are: DTaP for infants, a conjugate of the *s.typhi* Vi polysaccharide to a protein carrier, rotavirus vaccines, pneumococcal conjugate vaccines, a vaccine for Lyme disease, a malaria vaccine and a new cholera vaccine.

These new developments are being made possible by promising new technologies in the vaccine field. Recombinant DNA based vaccines are already being developed against such diseases as hepatitis B. The new pertussis vaccine is an example of one of the new purified subunit vaccines. Vectors, such as vaccinia, BCG and salmonella are being developed, as are novel combination approaches such as multiple antigenic peptides (MAPS). There is in vitro production of some viral antigens, and the use of new models has led to such breakthroughs as the expression of an antigen against chlamydia through a polio vaccine.

Although progress has been notable in the development of new vaccines over the past five years, certain obstacles still exist as we approach the 21st century. Some infectious diseases, such as certain rotaviruses and HIV, have a number of different serotypes which make developing one vaccine difficult. There is also an inability to culture some pathogens, such as treponema and those for certain sexually transmitted diseases (STDs). Still other STDs, as well as many gastro-intestinal illnesses, appear to require mucosal immunity for protection. Another factor which may complicate new vaccine development is

the complex pathogenesis of certain viruses, particularly those with a long latent stage, and the complex lifecycles of certain parasitic infections. In general, there is a lack of animal models for the testing of all vaccines, and progress in immunogenicity is weak due to a lack of adjuvants.

Dr La Montagne noted that the means to overcome the obstacles to new vaccine development may be found in some of the more established approaches, or in one of the new, exciting approaches being developed. Some of the more established approaches include the attenuation of live viruses, either in animals or through cell culture passage, or the use of inactivated strategies such as virus subunits, inactivated organisms, inactivated toxins, capsular polysaccharides, protein polysaccharide conjugates, or synthetic peptides. Exciting, new approaches in vaccine development include the use of nucleic acids (naked DNA) and the use of recombinant DNA where there is a deletion, or an addition of genetic materials. Research is also being carried out regarding the use of pseudoparticles, or pseudovirions (where a deletion is made in the genome), and in the use of anti-idotype antibodies. Finally, progress is being made in the area of adjuvants. While aluminum remains the only licensed adjuvant in the US, a number of others are being evaluated. It is likely that these will be needed for the further development of subunit and recombinant vaccines.

In his concluding remarks, Dr La Montagne made a number of predictions for the future of vaccines. First, there will continue to be a great increase in new vaccine development. Changes will occur and the option will exist to replace established vaccines with better vaccines, as well as to add new vaccines to established combinations. This increased choice may be manifested in different combinations of vaccines, vaccines made with nucleic acids (naked DNA), or new vectors for vaccines. There may also be new, therapeutic vaccines developed for such infections as HSV or HIV, or non-traditional targets for vaccines, such as auto-immune diseases and cancers. As Dr La Montagne so aptly noted, it will be important that CVI help manage this transition from the "bench to the bush," so that everyone works together to "reap the fruits of this powerful new technology to the benefit of children and adults everywhere."

Following Dr La Montagne's global overview on progress made and future prospects in vaccine development, **Dr Paul-Henri Lambert**, Chief of Vaccine Research and Development (VRD), WHO/GPV, spoke specifically about "Limitations to Infant Immunization and Approaches to Overcome Age-Related Immunodeficiency." While there have been significant advances in the last five years with regard to vaccine development, "the child," Dr Lambert noted, "has not changed." One of the main issues which needs to be considered when contemplating the possibility of achieving the long-term CVI vision—developing a super-vaccine which can be delivered at birth, or shortly thereafter—is whether or not such a vaccine is truly desirable.

As Dr Lambert stated, there are a number of advantages to immunizing children under 6 months of age. First, early immunization can provide protection to an infant against a wide range of diseases within its first few month of life. Early immunization may protect an infant against such infectious diseases as pneumococcal pneumonia, *haemophilus influenzae* type b, rotavirus, measles and pertussis. Second, early immunization makes it easier to achieve high levels of vaccine coverage due to the fact that newborns are generally more integrated into some sort of health care system. It has been shown, for example, that it is easier to achieve a high level of coverage of BCG when it is administered at birth than when it is delayed.

While there are definite advantages to early immunization, it also poses some difficulties. Dr Lambert stated that infants may be characterized as having a certain degree of "immunological immaturity" as demonstrated by their susceptibility to both intracellular micro-organisms and bacterial diseases. This immaturity affects the ability of their immune system to respond to several different vaccines when given early in life. Among difficulties posed by immunizing infants who have immature immune systems is that they have yet to fully develop antibody producing B lymphocytes and T cells, responsible for the elimination of extracellular encapsulated bacteria and the elimination of intracellular micro-organisms, respectively. The slow development of antibody producing B lymphocytes during the first two years means that infants have difficulty responding to vaccines designed to build a response against polysaccharide encapsulated bacteria. The lack of maturity of T cells during the first two months makes it difficult to immunize infants with protein-based vaccines, as well as some live vaccines.

Another difficulty posed by early immunization, is that an infant will already have some antibodies transferred from its mother, either through the placenta or through intestinal absorption from breast feeding. While these antibodies are selective, those that are transferred may persist for up to 15 months. Although they do protect young infants against some infectious diseases, they will interfere with a newborn's immune response to a number of vaccines including "tetanus toxoid or corresponding Hib conjugates (1st dose), pertussis vaccine (PT), polio (OPV type 3) and measles." Different approaches are now being tried in the development of vaccines to circumvent maternal antibodies. However, the transformation from an immature to a mature immune system in an infant may still be thought of as a progressive, step-by-step training process. Given that an infant must still develop its own mature immune system, independent of that transferred from its mother, Dr Lambert thinks it unlikely that immunizations given at birth, or within the first month of life, will become the recommended norm for all future vaccines. Nonetheless, as more is learned about the development of the newborn immune system, it will become possible to develop new methods of immunization for infants.

Responding to Dr Lambert's presentation on infant immunization, and acknowledging that some neonate infections such as toxoplasmosis can be very harmful, Sir Gustav posed a question regarding the "flip-side of immunity from maternal antibodies." What, he asked, are natural pathways which make early infection desirable? Dr Lambert answered by noting that although some early infections may seem desirable given that they are milder in infants, these infections may be harmful to the person at a later date. An early infection from hepatitis B, for example, may be more harmful to a person 30 years later. Dr Seth Berkley agreed and noted that the later, oncogenic potential of many early infections is still unknown.

The third presentation within the session, "Vaccine Research and Development," was given by **Dr Seth Berkley**, Associate Director of the Health Sciences Division at the Rockefeller Foundation. Speaking on the topic of "HIV/AIDS Vaccines," Dr Berkley discussed both the pressing need for an HIV vaccine, as well as the current International AIDS Vaccine Initiative (IAVI) spear-headed by the Rockefeller Foundation. Opening his presentation with some compelling statistics, Dr Berkley stated that 16 million people are currently infected with HIV. Of the 5,000 to 10,000 new cases which occur daily, 90% are in developing countries. Furthermore, Dr Berkley estimated that even if the amount of funding currently directed at HIV prevention was to increase ten to fifteen-fold, the spread of the epidemic would not be halted. What is needed, he believes, are better prevention technologies such as female controlled microbicides, better barrier methods, better diagnostics to identify and treat STDs and most importantly, an HIV vaccine.

A number of advances have been made in the last decade with regard to the study of HIV. In fact, more may be known about HIV now that any other organism in history. Nonetheless, a number of scientific questions remain unanswered. Topping the list of questions are, "What is the nature of the immune response for the prevention of infection?" and, "What is the nature of the immune response for the prevention of disease?" We still don't know the immunological importance of the different subtypes of HIV, nor do we know the surrogate markers of protection. There is also a lack of appropriate animal models for the study of an HIV vaccine. Compounding and, perhaps, causing some of these unresolved scientific obstacles, is the fact that there is a limited number of potential HIV vaccines moving through the development pipeline. Furthermore, those which are in the pipeline are limited in scope by the fact that the majority are being developed for HIV B, the sub-type which is prevalent in the USA and Europe, not in the developing world where most new infections are occurring.

Given the number of unresolved questions and obstacles, one wonders if the development of an HIV vaccine is impossible. Dr Berkley does not think so. Supporting his belief that an HIV vaccine is possible, he cites the fact that there are 35 current studies showing the efficacy of retroviral vaccines in different animal models. The problem, he believes, is that there is a "market failure" with regard to the development of an HIV vaccine, particularly one designed for use in Asia and Africa. This market failure stems from the fact that although society would benefit from such a vaccine, there are a number of obstacles which keep industry from pursuing further research and development. These obstacles include: the probability of success in the near future, opportunity costs, the costs of clinical trials and potential profitability. Nonetheless, industry involvement is needed in that the private sector can contribute financing, research and development expertise, experience with regulatory approvals, efficient manufacturing practices and good distribution systems. The goal of the IAVI is the coordination of a targeted research effort for an HIV vaccine which can be used globally. This effort should include industry, as well as governmental and non-governmental organizations.

Through a coordinated effort, research towards an HIV vaccine should bear in mind the following ideal characteristics: 1) thorough protection—the vaccine must be durable and protect the individual against all routes of infection; 2) safety; 3) easy delivery—a minimal number of doses, long shelf-life and heat stability; 4) an unambiguous marker of seroconversion; and 5) low cost. In his description of an ideal HIV vaccine, Dr Berkley voiced an optimism for future vaccine progress. He also acknowledged the toll that HIV has taken to date through his concluding quote from the World Bank's *World Development Report of 1993*, "Historians will look back on the latter half of this century as having one great medical triumph, the eradication of smallpox, and one great medical tragedy, AIDS".

In the discussion session following the presentations on vaccine research and development, Dr Ndumbe spoke about the problem of cost associated with new vaccine development. He highlighted the need for vaccines which are cheap and affordable, and noted that many developing countries are still having trouble with the supply and delivery of existing vaccines. Of the new vaccines which are chosen for research and development, they should be of interest to developing countries. Many countries in Africa, for example, are particularly interested in the development of a malaria vaccine and a vaccine which would prevent ebola fever. Dr D.A. Henderson noted that the cost of a new vaccine is largely dependent upon the manufacturing site and standards set, and stated that perhaps we should not insist on the uniform application of standards set by US and European

industries. Rather than stop development of certain vaccines due to prohibitive costs, perhaps those countries with the disease burden and limited resources should assume a risk/benefit analysis. A malaria vaccine which causes one death in 10,000 would not be licensable in the US, Dr Henderson stated, but it might be highly licensable, as well as desirable in other countries.

E. Contributions of industry: 1990-1995 and beyond

Dr Tom Vernon, Executive Director of Medical, Scientific and Public Health Affairs at Merck & Company, Inc., was the chair of "Contributions of Industry: 1990-1995 and Beyond," the first session on Thursday morning, 26 October. Speaking from a perspective which includes both public and private sector experience, Dr Vernon said that he was, "hopeful, yet realistic about bringing industry's undeniable potential to CVI." Dr Vernon's hopefulness stems from the repeated references in CVI materials to the importance of the private sector and the acknowledgment that industry has a great deal to offer given its wealth of resources, both in terms of human and financial capital, as well as its practical knowledge, innovation and established facilities. Agreeing with a recent letter written by Dr Roy Widdus to industry leaders, Dr Vernon reiterated the message that industry has a great deal to offer in the field of vaccine research and development.

Dr Vernon's hopefulness is tempered by his realism about the degree to which industry and CVI can work together, at least in the short-term. Industry he stated, is not currently involved to a satisfactory extent in CVI. This, he believes, is largely due to ideological differences between the public and private sectors, and the continued misunderstanding that industry, driven by a profit motive, cannot at the same time utilize its resources for a positive societal benefit. Nonetheless, Dr Vernon noted that Dr Widdus is dedicated to including industry in the planning and on-going work of CVI, and acknowledged his efforts to reach out to industry leaders to ask their views on how the CVI Secretariat might facilitate industry's participation in CVI objectives. If such a partnership can be achieved, the potential for private sector contribution to the work of CVI is tremendous.

Dr Vernon then proceeded to introduce the featured speaker of the session, **Mr Jacques Martin**, Chair, Biologicals Committee, International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Mr Martin began by relating how he started his career in industry 20 years ago, at roughly the same time that the Expanded Programme on Immunization (EPI) began. Industry, he said, is proud to have played a part in the great success which immunization programmes have achieved. In the last decade alone, the number of doses of vaccines used has increased ten-fold. Given its continued progress, the vaccine industry has, he believes, reached a point of transformation. Due to a great effort in research and development over the past five years, the economics of vaccine manufacturing are changing. The changing economics will affect who produces vaccines, where they produce them, and how much they will cost. This economic transformation will, in turn, necessitate a reassessment of how vaccines and immunization programmes are valued.

Mr Martin remarked that a great effort in research and development has been taking place, spurred on by such modern technologies as recombinant DNA, DNA immunization, new adjuvants and new delivery systems. With 100 vaccines in clinical trials and 150 more in pre-clinical development, scientists have never been so active. However, the cost of developing just one new vaccine is high, at a price of US $200 million to $400 million. This is due not only to difficulties encountered in initial scientific research, but also in the costs associated with assessing vaccine safety and efficacy. Industry is, according to Mr Martin, covering a large portion of the costs of vaccine research and development

through an estimated annual expenditure of approximately US $500 million (not taking into account the contributions of biotech companies.) Of industry expenditures, 25% to 30% is devoted to new innovations, while 70% is directed towards funding the extensive studies required in the development and production scale-up of new vaccines. These high costs have led to a concentration in the international vaccine industry. There are now fewer than ten active companies, only five of which have a large impact internationally. Additionally, the high costs increase the motivation of the large companies to patent their developments and ensure their intellectual property rights so they have a proportionate return on their investments.

Mr Martin believes that in addition to the high costs of developing new vaccines, the overall volume of vaccines produced will increase as new vaccines are made available and immunization programmes are implemented to their fullest extent. While transfers of technology are often considered to be an appropriate way in which to increase vaccine availability, they are not necessarily the most economically feasible way. With current large scale production, vaccines are offered on a two-tiered system with lower prices afforded to developing countries. Prices for certain existing vaccines may be reduced even further if trade barriers are dismantled and markets become more competitive. While a country may wish to acquire technology for reasons of national independence and hard currency savings, local production may not be economically justifiable and industry will not, according to Mr Martin, support economically unjustifiable projects. It will, however, contribute to the establishment of appropriate quality control processes for existing production facilities.

Due to the elevated costs of research and development, the price of new vaccines will be higher than the price of existing vaccines, even if the two-tiered pricing system is retained. In answer to the question, "Will these new vaccines be affordable?," Mr Martin responds that there must be a reassessment of the value of vaccines and immunization programmes. In addition to higher research, development and production costs, Mr Martin believes that the value of preventive vaccines alone justifies a higher price. Currently, vaccines are much less expensive than therapeutic drugs, yet they can protect an individual for life against a deadly disease. In order for the CVI vision to be achieved, the international community must, stated Mr Martin, rethink its priorities and allocation of resources. It must rethink the value of vaccines and not expect unrealistic pricing by the private sector. This will necessitate new political mobilization and advocacy efforts on the part of CVI.

Sir Gustav opened the discussion session following Mr Martin's presentation by stating his agreement with the point that there are many reasons why a country would want to be the recipient of a technology transfer and develop its own vaccine production. Additionally, he stated, biotechnology is a relatively inexpensive way for a country to begin to modernize and enter the world of high technology. Taking into consideration the reasons for technology transfer, Sir Gustav was interested in Mr Martin's thoughts on a rapidly developing country, such as Thailand, seeking to build its vaccine production capabilities. Mr Martin responded by stating that his comments regarding vaccine production and economies of scale were primarily related to the production of EPI vaccines, and that each country should analyze its individual market for other vaccines, as well as the potential value added through local production.

Expounding on the issue of local production, as introduced by Sir Gustav, Dr R.B.J.C. van Noort of the National Institute of Public Health and the Environment from the Netherlands, stated that 50% of EPI vaccines are produced locally and that one can't simply tell countries to forget about local production. Furthermore, while he real-

izes the importance of the private sector, he thinks that the very important contributions of public institutes and universities should be fully noted, and that they should be given credit for subsidizing vaccine development costs through the organization and management of field trials. Mr Martin responded by clarifying that he did not say that only large companies should produce vaccines. However, he did emphasize his belief that there are undeniable economic realities which favor large producers. Regarding the important role played by public institutions, Mr Martin noted his agreement.

Also related to the issue of large scale production and the high cost of vaccine development, Dr Henderson questioned the base figure quoted by Mr Martin of US $200 million. Relating that it seemed to be very high and that he had heard it is only a crude figure (50% comprised of forgone opportunity costs), Dr Henderson wondered where the figure comes from and if it is an appropriate figure to be using. The figure is important in that it can hinder the initiation of research and development of new vaccines. Mr Martin stated that the figure originally came from SmithKline Beecham and is based on the development costs for the hepatitis B vaccine. Although the amount is significant, Mr Martin believes that it is a realistic figure for a vaccine which will be used internationally and must pass through all the development and regulatory tests. On a closing note, Professor Moises Spitz of the National Microbiology Institute in Argentina, challenged industry with the rhetorical question, "How would the history of science and mankind be different if Pasteur had patented all of his achievements?"

4.

CVI's role into the 21st century

Dr Jaime Sepulveda, Director of the National Institute of Public Health in Mexico, acted as chair of the session entitled "CVI's Role into the 21st Century." The previous sessions in the CVI Fifth Annual Consultative Group Meeting focused on progress made in specific issue areas since the World Summit for Children in 1990. The purpose of this session, however, was to look at progress made in the coordination of the activities of different issue areas, and to look at how CVI might best fulfill its role in the 21st century as a coalition devoted to building consensus, coordinating activities and promoting advocacy for vaccine research and development.

Rather than begin the session by attempting a global overview of worldwide coordination activities in vaccine research and development, **Dr David Salisbury**, Principal Medical Officer of the Department of Health in the United Kingdom, was invited to speak specifically about his country's progress in coordinating vaccine research and development. Referring to the UK as the "golden standard" which all countries may look to as an example of how to integrate different activities, Dr Sepulveda introduced Dr Salisbury and his presentation entitled "The Spectrum of Vaccine Research and Development: From the Molecule to the Ampoule." Dr Salisbury began by stating that it is very difficult to establish an "end to end mission" by which one can manage the different stages of the vaccine continuum including basic science research, establishing and securing regulatory approvals, manufacturing, supply and the actual operation of immunization programmes. All of these stages are funded differently and managed differently. Nonetheless, Dr Salisbury reviewed some of the recent highlights achieved through government funding of vaccine research and development in the UK which, he stated, contribute to the future establishment of a CVI continuum.

The UK continuum begins with the Edward Jenner Vaccine Research Institute, a new research center started through the combined efforts of the private and public sectors. Glaxo Wellcome contributed £10 million in start-up costs and has pledged to meet half of the running, operational costs. The other half of the operational costs will be met, over the next decade, by a number of different government agencies including the Medical Research Center (MRC), the Biological Sciences Research Council (BSRC) and the Department of Health (DH). The research center priorities include the study of immune system mechanisms, formulation studies and the establishment of animal models for vaccine evaluation. Funded and managed by the Department of Health, the next stop on the continuum is the Centre for Applied Microbiology and Research (CAMR). With research priorities set by the DH, and funded annually at approximately £2 million, CAMR is involved in basic research, surveillance and manufacturing. Current CAMR priorities include research on meningococcal and measles recombinant antigens, the surveillance of immune system responses to certain vaccines and the manufacture of antigens.

Managed by the Department of Health, the National Institute for Biological Standards and Control (NIBSC) receives its funding from the DH, various research councils and private industry. The NIBSC channels its extensive research background on a number of different vaccines into its primary responsibilities which are the batch testing of vaccines and immunologicals, and the setting of world-wide biological standards. Next, the Medical Research Council (MRC) is a government agency which collaborates with the DH. In addition to its support for vaccine related research, the MRC is initiating, in November of 1995, a Strategic Planning Group which will make recommendations and set priorities for future research according to the public health needs of the UK, as well as other countries worldwide. Responsible for vaccine related research further down the continuum is the Public Health Laboratory Service (PHLS) and its Communicable Disease Surveillance Centre (CDSC). This organization, funded by and accountable to the DH, is largely involved in "phase II reactogenicity and immunogenicity studies." For example, one study has focused on the evaluation of acellular pertussis vaccines, while another has focused on meningitis vaccines.

Near the end of the vaccine research and development continuum is the Department of Health. The DH is responsible for the overall management of the national immunization programme of the UK. In accordance with its responsibility, the DH creates immunization strategies by using mathematical modeling which involves a number of different vaccines. It also conducts different evaluations of candidate vaccines and is currently coordinating an evaluation of combination vaccines which have, as one of their components, the new, acellular pertussis vaccine. This evaluation is being carried out by other organizations in the continuum, the CDSC, the NIBSC and CAMR. Additionally and perhaps most importantly, the DH purchases all vaccines for the national immunization programme through open, international tenders. Finally, the Office of Science and Technology coordinates 15 panels in its Technology Foresight Programme. The programme is designed to disseminate information and facilitate informed spending decisions by industry and government. Particularly relevant to CVI is the Health and Life Sciences Panel which makes recommendations applicable to the UK continuum and its coordinated efforts in vaccine research, formulating, testing, manufacturing and purchase. In concluding his presentation, Dr Salisbury reminded the audience that the Government of the UK is the final customer at the end of the vaccine continuum and is, as it should be, integrally involved throughout the development process.

Dr Roy Widdus, Scientific Coordinator of the Children's Vaccine Initiative, presented "CVI's Mission, Activities and Strategic Plan." Thanking Dr Salisbury for his presentation, Dr Widdus stated that the challenge for CVI is to see that the success of the UK is replicated on a global scale. Before beginning his review of CVI activities and discussion of how such a success might be replicated, Dr Widdus took a moment to answer the often asked question, "What is CVI?" He described it as "an informal coalition dedicated to expanding protection against infectious diseases through the development and introduction of new and improved vaccines." Membership, he said, is inclusive. He views all collaborators within the vaccine field as members of CVI. The CVI Secretariat, in contrast, is a small group of people responsible for the coordination of CVI activities. Dr Widdus likened the relationship between the CVI Secretariat and its broader-based coalition to that between a conductor and an orchestra; helping the various members to act more cohesively.

Commenting on the fact that infectious diseases are still the leading cause of worldwide mortality and morbidity, causing 16 to 20 million deaths annually, Dr Widdus reminded the audience that the final goal of CVI and its collaborators is the reduction of disease. While immunization coverage levels may serve as adequate process measures, the real outcome which must be measured is the reduction in the incidence of disease. The most notable successes to date have been the eradication of smallpox and progress made towards the eradication of polio. In addition to polio eradication efforts, there has been substantial progress since 1990 in the reduction of the disease burden of a number of EPI diseases. According to statistics gathered by WHO/GPV/EPI, immunizations prevent 90% of potential deaths from diphtheria, over 60% of deaths from pertussis, 60% from measles, 60% from neonatal tetanus, 30% of deaths from hepatitis B, and approximately 5% of potential deaths from tuberculosis and yellow fever. The progress made in the reduction of deaths caused by these diseases can be attributed to increased coverage and improved technology. However, little progress has been made in the last five years towards reducing mortality and morbidity caused by typhoid, cholera and rotavirus, or from acute respiratory infections such as haemophilus B. No impact at all is being made with regard to a number of parasitic diseases like malaria, which is responsible for over two million deaths annually.

What we still need are better vaccines. These vaccines should be protective against a wide range of infectious diseases, and should be of consistently high quality. They should be easy to deliver, requiring only the minimal number of heat-stable doses. Finally, they should be effective early in life and freer from adverse side effects. While the list of characteristics for an ideal vaccine(s) seems well established, the process for developing that vaccine is somewhat less so. Referring to the process by which vaccines are researched and developed, Dr Widdus stated that rather than being a linear process, or pipeline, it often resembles a large number of disconnected pipes. Increased coordination by CVI should, however, help to facilitate the process so that it is easier to produce better vaccines that prevent disease.

Dr Widdus stated that CVI can promote the development of better vaccines through the achievement of its intermediate objectives. First, CVI seeks to build consensus among those in the vaccine field. Its strategies for consensus building include the annual Consultative Group Meetings where ideas and information are exchanged between all coalition members, and the creation of Task Forces on Strategic Planning, New Vaccines, and Supply and Situation Analysis. Task force members are being drawn from both the public and private sector, and from a wide geographic range. Second, CVI seeks to coordinate priorities and direct resources to funding gaps. Future activities towards the achievement of this objective may take the form of cost-effective analyses on the research and development of certain vaccines. Other activities may include studies on vaccine introduction. Currently, there is no vaccine in wide use in developing countries which was licensed less than 25 years ago. We need to find out what we are doing wrong that the benefits of vaccine research and development are not reaching everyone. Third, CVI promotes advocacy measures for vaccines and immunization. Because vaccines are a form of preventive medicine, they often don't receive the notice or acclaim that they should receive. Increased advocacy efforts on the part of CVI should help raise both awareness and financial resources for the development of better vaccines.

In the discussion following the session on "CVI's Role into the 21st Century," Dr Vernon of the USA posed a question to Dr Salisbury regarding the orderly research continuum he introduced. Noting that research is not always linear, Dr Vernon wondered if there was

"opportunity for genius" left at the Jenner Institute. Dr Salisbury responded that yes, opportunity for creative scientific investigation existed, particularly because the Jenner Institute is at the beginning of the research continuum and looks at immune processes, not candidate vaccines. Furthermore, the spectrum which he introduced shows a coordinated government effort and does not include all efforts made by academic institutions and private groups. Then, in response to a compliment by Dr Scott Halstead on the organization of the continuum, Dr Salisbury went on to say that he didn't create the different institutions in the continuum. The institutions were there and the challenge for the Department of Health was to see what each could best contribute, and then link them together. The vaccine continuum was not necessarily a straight line he said, but really "an amazing tour of alpine scenery." Finding the comparative advantage of different organizations and then linking them together is, according to Dr Salisbury, the same challenge that CVI will face internationally.

Comments were also raised in the discussion session about the advocacy role of CVI. At the end of his presentation Dr Widdus had posed a question with regard to whether or not CVI needed a special group, or task force on advocacy. Dr John La Montagne responded that yes, an advocacy group is needed. Paradoxically, as immunization programmes are more effective in their prevention of disease, people tend to notice them even less. Dr Mahoney agreed. However, he suggested that the group devoted to advocacy be more of an on-going, continuous group, rather than another task force.

5.

Workshops for the revision of CVI strategic plan

Designed to complement the main plenary sessions of the meeting, and to encourage the active involvement of the participants attending the CVI consultative group, the workshops were structured so as to be an integral component of the meeting. Held on the second day, the four workshops addressed the topics of: 1) Advocacy for Vaccines and Immunization; 2) Choosing Desirable Vaccines and Vaccine Combinations for the 21st Century; 3) Intellectual Property Rights: Access to New Technologies and Products; and 4) Financing the Introduction of New Vaccines. Through active discussions, the moderators of these workshops were able to draw on the expertise of the various participants. The final product of each workshop was a paper, the essence of which will be forwarded to the Task Force responsible for updating the new *CVI Strategic Plan*. Summaries of each paper are included as annexes to this report.

The first workshop, "Advocacy for Vaccines and Immunization," was co-moderated by **Dr Isao Arita**, Chairman of the Agency for International Health (ACIH) in Japan, and **Mr Andrew Burness**, President of Burness Communications, USA. **Ms Ellen Wilson** of Burness Communications and **Mr John Maurice** of the CVI Secretariat were the workshop rapporteurs. The purpose of the workshop on advocacy was to highlight the crucial role of advocacy for the future of vaccine development and public health, and to do so from two perspectives: that of the "advocate" who informs national politicians for the purpose of raising money, either directly or bi-laterally for specific projects, or for the CVI Secretariat; and that of the "decision maker" who is on the receiving end of the request from the advocate. Questions raised in the workshop included: What information is pertinent to the decision-maker who is being approached to support CVI? Do published articles in professional journals help? Does cost-effectiveness information actually influence decisions regarding vaccines and immunization? How valuable is media coverage? And which strategies should be used by CVI to educate and inform national politicians? (Please see Annex 5 for workshop summary.)

Co-moderating the second workshop, "Choosing Desirable Vaccines and Vaccine Combinations for the 21st Century," were **Dr S. Ramachandran**, a Fogarty Scholar from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), USA, and **Dr John La Montagne**, Director of the Division of Microbiology and Infectious Diseases, NIAID/NIH. **Dr Bruce Gellin**, also of NIAID/NIH, acted as rapporteur for the session. The stated objective of this workshop was to examine the transformation of vaccines from "commodities" that have been available to national immunization programmes, to an expanding menu of desirable technologies that will require new strategies for evaluation and selection by programme managers, national control authorities, vaccine purchasers and local and multinational vaccine producers. In turn, these may have profound impacts on existing programmes and budgets. The workshop also examined a variety of perspectives on the process for selection of new vaccines

for development and incorporation into immunization programmes (health, economic, manufacturing and logistic.) The overall goal of the workshop was to prepare a framework by which national and regional decisions on choosing vaccines and vaccine combinations for the 21st century can be made. (Please see Annex 6 for workshop summary.)

The third workshop, "Intellectual Property Rights: access to new technologies and products," was co-moderated by **Mr Charles Caruso**, International Patent Counsel of Merck & Co., USA, and **Dr Isaias Raw**, Director of the Butantan Institute in Brazil. **Elizabeth Fuller, Esq.,** of the CVI Secretariat, acted as rapporteur for the workshop. This workshop was designed to address the fact that many new and exciting products and technologies, governed by patents and international licensing agreements, will enter the vaccine market in the coming years. This licensing raises a number of questions. How can innovations be made accessible to the developing world in a way which ensures that their developers are appropriately recompensed? Can this be done in a way that uses vaccine production facilities already in place in the developing world that meet acceptable standards? And, for those countries which cannot reasonably be expected to produce locally, such as the UNICEF "Band A" countries, are there other ways of dealing with IPRs? For example, would a separate agreement be possible by which royalties are forgone for vaccines purchased by UNICEF for use in the poorest countries? (Please see Annex 7 for workshop summary.)

Co-moderating the workshop on "Financing the Introduction of New Vaccines," were **Dr Terrel Hill**, Principal Advisor of the Child Survival Unit at UNICEF, and **Dr Bjorn Melgaard**, Chief of WHO/GPV/EPI. The rapporteur for this workshop was **Ms Amie Batson** of Vaccine Supply and Quality (VSQ), WHO/GPV. As the workshop organizers stated, the financing to introduce new vaccines into immunization programmes must come primarily from national budgets. However, while some countries are able to finance their existing and new vaccine needs, the neediest countries will not, and perhaps cannot introduce new vaccines if they do not receive some form of support. This workshop explored whether or not the introduction of new vaccines is a financial priority and how it should be decided which vaccines should be financed and for which countries. The workshop also addressed how the financing might be structured to achieve the objectives of sustainable supply of existing vaccines and timely introduction of new ones. The targeting strategy adopted by WHO and UNICEF and the results of the recent UNICEF tender were used as starting points for the discussion. (Please see Annex 8 for workshop summary.)

6.

Expanding advocacy for immunization and vaccines: strategies to implement locally

The chair of the session on "Expanding Advocacy for Immunization and Vaccines: Strategies to Implement Locally," was **Dr Scott Halstead**, Director of Infectious Disease Research for the Naval Medical Research and Development Command. Dr Halstead opened the session by providing a consolidated version of CVI objectives. The two most fundamental CVI objectives, as described by Dr Halstead are: 1) to help those working in the vaccine field make the appropriate choices so that the best vaccines possible are developed and delivered; and 2) to motivate policy makers and world leaders to find the necessary resources to make this vaccine research, development and delivery possible. The central element to the achievement of both these objectives, said Dr Halstead, is advocacy.

The first objective—helping those in the vaccine field make appropriate choices so that the best vaccines are developed and delivered—incorporates a number of technical elements. The desired elements of a new vaccine include heat stability, affordability, prevention against a wide range of infectious diseases, and simple delivery (either a single injectable dose or an orally delivered vaccine). In order to achieve the technical advances necessary to create such a vaccine(s), both policy makers and scientists alike must be committed to disease prevention. This commitment will come when people demand it. In Dr Halstead's words, "there must be a pull from the prospective consumer of children's vaccines." This pull will come from advocacy efforts which raise people's awareness about the public and personal health benefits of better vaccines. The second objective—motivating policy makers to find the resources for vaccine research, development and delivery—is also directly related to advocacy. There must be a "push" from national budgets, as well as both public and private capital sources, for the development of better children's vaccines.

Advocacy efforts for better children's vaccines face a formidable challenge. Policy makers, scientists and consumers must reassess the value of vaccines. According to Dr Halstead, there is currently a distorted value system with regard to vaccines, particularly as compared to therapeutic drugs. Even though people recognize that vaccines are an extremely effective method of preventing disease, they are often considered to be of low cost, and thus low value. This, Dr Halstead believes, is due to the fact that vaccines were originally developed in heavily subsidized public laboratories and then purchased and provided by governments either free of charge, or at a very low cost. Therapeutic drugs, on the other hand, are generally developed and marketed by the private sector at a much higher cost and are often seen as more valuable. For example, people may be willing to pay more for a drug to treat an infection than they would have paid for a vaccine to prevent the infection in the first place.

Given the need for renewed advocacy efforts, the next issue is how that need can be fulfilled. Dr Halstead noted four important steps necessary in advocacy for children's vaccines. First, there is the need for renewed enthusiasm about the potential health benefits for children's vaccines. Second, those working in the vaccine field must be bold enough to advocate for high quality vaccines and let others know their real value is not pennies, but dollars per dose. Third, campaigns must be designed so that policy makers and governments are made aware of the true economic benefits of vaccines. The value of a vaccine is even more striking if it is costed out over the lifetime of a consumer. Finally, a worldwide CVI movement needs to be started. In order to achieve this, Dr Halstead called for CVI committees in every country of the world, dedicated to advocacy for children's vaccines.

Following Dr Halstead's remarks on the global need for renewed and expanded advocacy efforts, **Dr Jaime Sepulveda Amor**, Director of the National Institute of Public Health, Mexico, spoke on the topic of advocacy for children's vaccines from the perspective of both a public health professional and a national policy maker. Specifically, Dr Sepulveda described the recent Mexican experience with regard to advocacy. He began by describing the background of the national vaccination programme and then described how local strategies involving advocacy helped to strengthen and ensure the overall success of the programme.

The year 1986 marked the beginning of national immunization days in Mexico. After the outbreak of the measles epidemic in 1990, these national immunization days were incorporated into a larger, more universal vaccination programme which was necessary to combat the epidemic. In order to achieve success, the national vaccination programme incorporated a number of advocacy related strategies. First, local vaccination committees were established to help coordinate activities and spread awareness. Second, the government mobilized all levels of society by coordinating local groups to help with the vaccinations activities, and by obtaining support from various civic groups. Finally, vaccines and vaccination efforts were integrated into all levels of the health system. The operational mechanisms of the vaccination programme also incorporated advocacy efforts by concurrently increasing both awareness and availability. These operational mechanisms included: 1) establishing a permanent supply of vaccines at health posts; 2) organizing vaccine brigades; 3) ensuring a constant vaccine supply in hospitals; 4) coordinating school based vaccination and health campaigns; and 5) organizing awareness campaigns using the indigenous languages found in different parts of Mexico. Advocacy through community education also supplemented the programme operation.

The impact of the national vaccination campaign seems to have been very positive, at least in terms of coverage levels. A 1990 survey of 250,000 households, both urban and rural, showed that the coverage level of the complete EPI vaccination schedule for children aged 1 to 4 years was 46%. In 1994, the coverage level for the same group was 92%. Due to the positive outcome, the national vaccination programme has been continued and now includes national health weeks during which vaccines are given in conjunction with doses of vitamin A, drugs which fight intestinal parasites and packets of oral rehydration therapy. The lessons learned from the success of the programme in Mexico are, according to Dr Sepulveda, two-fold. First, vaccine programmes should be integrated into primary health care systems, but they require the technological and logistical support of vertical programmes. Second, there needs to be political appeal, through advocacy efforts, to ensure the success of a broad-based national campaign.

Speaking on advocacy efforts from the perspective of a civic group was **Dr Archimedes Theodoro**, Chairman of the National PolioPlus Committee of Brazil for the Rotary Foundation. As acknowledged by the "Health for All" gold medal awarded by the World Health Organization, the Rotary Foundation has, on a global level, played a very important part in current polio eradication efforts through their advocacy and fundraising efforts. There are currently five regional PolioPlus committees which are designed to work within the geographical regions, as defined by WHO, where polio is endemic. The only area which is not covered by these committees is the Western Hemisphere where polio was declared eliminated in September of 1994. The Rotary Foundation was instrumental in this elimination of polio from the Americas. In his presentation, Dr Theodoro explained how the Brazilian Rotarians, in particular, contributed to this effort.

To begin their advocacy efforts in Brazil, the local Rotarians organized a PolioPlus Committee as part of a larger PolioPlus Programme in 1986. The Committee began its work by pledging to the Brazilian Government that they would help buy vaccines for 20 million children, to be used in biannual national immunization days, for a period of five years. To comply with their promise, the Brazilian Rotarians then began a widespread advocacy and fundraising campaign. The PolioPlus Committee worked in conjunction with the Ministry of Health and the Pan American Health Organization (PAHO) to mobilize the private sector in Brazil and secure funds to supplement the National Immunization Programme. In addition to advocating for funds from local businesses, the PolioPlus Committee directed its advocacy efforts towards the mobilization of human resources. They helped organize the training and supervision of volunteer vaccinators; set up refrigerators and ice boxes to help ensure the cold chain; provided vehicles and fuel; and conducted census activities to determine which children still needed to be immunized. Finally, the Brazilian Rotarians helped initiate, and are still promoting, widespread surveillance in an effort to prevent the reintroduction of the wild poliovirus in Brazil.

As Dr Theodoro stated, Brazil's experience, "clearly demonstrates that the most effective advocates are those who are actively involved in the problem." On a worldwide level, Rotary International is continuing its support for polio elimination. It has created an Ad Hoc Task Force on International Advocacy with a dual objective. First, to encourage donors, businesses and foundations to commit both financial and human resources to help achieve the goal of polio eradication by the year 2000. Second, to continue to encourage the governments of polio endemic countries to comply with the WHO polio eradication strategy. According to Dr Theodoro, the key to the success of the Rotary Foundation's efforts is its ability to build coalitions and partnerships with other groups. Through enlisting additional partners, each with defined roles and responsibilities, the Rotary Foundation is able to multiply its advocacy efforts.

Summary and closing remarks

Sir Gustav, Chair of the CVI Fifth Annual Consultative Group, began his summary of the meeting by stating that it was not yet appropriate to provide a "state of the union" address on CVI, as if talking to a room full of US senators and congressmen. CVI, he said, was still too new. He likened the members of CVI to primary school children and said that rather than provide a formal report card, it would be more appropriate to just make a few notes for the guidance of the parents.

Sir Gustav began by giving high marks to CVI in vaccine research and development. He referred to the research explosion which has taken place since the 1990 World Summit for Children as an "embarrassment of riches." There is now a wide range of diseases being addressed; diverse ideas are being explored as to how best strengthen immune responses; aggressive research is being pursued on mucosal immunity and oral routes for vaccines; and there are numerous ideas on different vaccine combinations. Although research on the whole has been going well, there are still two bottlenecks which have been noted, the more expensive development and clinical trial phases. In defense of recent efforts, Sir Gustav noted that these two areas have always been bottlenecks due to the higher costs involved. Furthermore, acellular pertussis has been developed and tried, and three other relatively new vaccines have been introduced, hepatitis A, hepatitis B, and *haemophilus influenzae* B. The area which has proven more problematic, due to lack of organization and resources, is the introduction of new vaccines in developing countries. Sir Gustav stated that he was glad to hear that this is an area which CVI would like to address in the future.

In addition to new vaccine research and development, remarkable progress has been made in the application of existing vaccines. We have now reached a point where polio eradication seems to be an achievable goal in the near future, and some success has been achieved in measles control. Nonetheless, 1.5 million deaths per year due to measles are still too many. The current polio eradication and measles control efforts bring up an interesting question with regard to the application of existing vaccines. "What, if anything," asked Sir Gustav, "should be done with new vaccines developed for the same diseases?" More specifically, should one try to develop and introduce the new, more thermostable vaccine for polio and the new vaccine against measles which can be given to infants under 9 months? Sir Gustav believes we should continue to press forward, as hard and fast as we can, with the delivery of existing vaccines. However, we should also continue to research new, improved vaccines as insurance against future disease burden. The re-emergence of diphtheria is, he said, a sobering reminder that we need constant vigilance in our disease control and eradication programmes.

For the next subject on the report card, collaboration with industry, Sir Gustav gave CVI fair marks. Leaders from industry need to be integrally involved in CVI as full partners. Furthermore, we need to encourage the continuation of a pluralistic system in vaccine manufacturing. As was stated by Mr Jacques Martin, there are now only five large interna-

tional vaccine producers. According to Sir Gustav, there should always be at least four or five multinationals which are mass producing vaccines so there will be adequate competition and fair pricing. This does not, however, preclude the importance of some transfer of technology to developing countries who wish to increase their self-sufficiency and level of technology. There will always be room for "niche players," or specialized producers. What Sir Gustav cautioned against was encouraging small, inefficient producers which may produce inferior products at a higher cost.

As progress continues in the areas of vaccine research, development and manufacturing, there will be a concurrent struggle for resources. One solution, according to Sir Gustav, is to work towards the reallocation of global resources spent on health. The current health budget of the world is US $2 trillion. Of that, US $190 billion, or 10%, is spent in developing countries. Only $4 to $4 1/2 billion, or 5%, of that amount represents international aid flows from developed to developing countries. What those figures mean, is that there is very little support given to developing countries for health. Furthermore, a very small percentage of all health spending is spent on vaccines. Of the $2 trillion global total for health, $6 billion, only 0.3%, is spent on vaccines. This figure looks even smaller when compared to the $200 billion, or 10% of the total, which is spent on drugs. Given these statistics, one would think that there should be plenty of room for an increased allocation of funds to vaccines, particularly vaccines in developing countries. Perhaps what is needed is the demand for a reallocation of priorities.

The demand for a reallocation of priorities and the increased allocation of funds for vaccine research and development, directly relates to the last subject on Sir Gustav's CVI report card, advocacy. While he didn't give CVI a mark on its advocacy efforts, Sir Gustav did caution that advocacy needs to be constant. Referring to the Consultative Group Meeting as a gathering of the faithful, he said that we shouldn't just preach to the converted. Rather, as Dr Theodoro from the Rotary Foundation stated, we should all act as ambassadors for CVI. Not one to encourage reticence, Sir Gustav said that we should all advocate at cocktail parties and in the workplace for "the greatest and most cost-effective health intervention of all time." To the question, "Do we need a CVI task force on advocacy?," Sir Gustav answered yes. However, he said that everyone should continue to make a personal effort towards advocacy, using the successes of CVI to breed more success.

Following Sir Gustav's summary, the Executive Secretary of the Children's Vaccine Initiative, **Dr Lee**, presented the concluding remarks of the Fifth Annual Consultative Group Meeting. After thanking all the participants for finding the time in their busy schedules to attend the meeting, Dr Lee said that there was one particularly important message from the meeting which he wished to highlight. That message, he said, is that CVI is still evolving. It is still searching for what needs to be done and exploring how best to do it. After a period of consolidation, CVI is now on a much firmer base from which to move forward. This consultative group meeting was particularly important in helping CVI to chart the new directions it will take into the 21st century.

Of the many issues raised at the meeting, one issue which was brought up repeatedly is the need for increased advocacy efforts. It is clear that the CVI Secretariat must enlist the help of all parties and avoid preaching to the converted. Furthermore, these advocacy efforts must be targeted so that a renewed commitment is secured from the same level of policy makers that originally launched CVI at the World Summit for Children. On the technical side, there has been much progress in the delivery of vaccines to children in the developing world and there is a call for CVI to continue to strive for better, higher quality

vaccines. There is also a call, said Dr Lee, for CVI to broaden its scope of work on new vaccines to include vaccines against diarrheal diseases and acute respiratory infections. Finally, with regards to vaccine supply and financing, Dr Lee noted two main changes. The new vaccine procurement strategy developed by UNICEF, and the increased commitment from developing countries towards vaccine self-sufficiency, have freed up a great deal of funds in the area of vaccine financing. In all these areas, and in many others, CVI has received valuable feedback which can be incorporated in the new *CVI Strategic Plan*. Dr Lee noted that the participation at this CVI meeting, particularly through the workshops, was both refreshing and revitalizing. Once again, Dr Lee thanked the participants and invited them to attend the Sixth Annual Meeting.

Annex 1:

Agenda

Wednesday, 25 October, 8.30 a.m. - 6.00 p.m.

Welcome

8.30-10.00 **Opening of the Meeting**
Dr J.W. Lee, Executive Secretary of the Children's Vaccine Initiative

Welcome
Dr Adib Jatene, Minister of Health, Brazil

Remarks
Dr H. Nakajima, Director-General, World Health Organization (WHO)

10.00-10.30 *Coffee Break*

Progress since the World Summit for Children

10.30-12.30 **Disease Control: 1990-1995**
Session Chair: Dr J.W. Lee, Executive Secretary, CVI and Director, Global Programme for Vaccines and Immunization (GPV)

i. Global Polio Eradication
Dr Bjorn Melgaard, Chief, Expanded Programme on Immunization (EPI), WHO/GPV

ii. Measles
Dr Ciro de Quadros, Director, Special Programme for Vaccines and Immunization (SVI), Pan American Health Organization (PAHO)

iii. Neonatal Tetanus
Dr François Gasse, Medical Officer, WHO/GPV/EPI

iv. Introduction of New Vaccines
Dr Thomas More Chaita, Deputy Director of Maternal and Child Health and Family Planning Division, Ministry of Health and Child Welfare, Zimbabwe

v. Discussion

Vaccine Supply, Self-Sufficiency and Quality: 1990-1995
Session Chair: Dr I. Arita, Chairman, Agency for Cooperation in International Health (ACIH), Japan

i. The Commitment of Brazil to Vaccine Self-Sufficiency
Professor Jorge Kalil, Director of Transplant Immunology Lab, São Paulo, Brazil

ii. Global Progress in Establishing Sustainable Financing of Existing and New Vaccines
Dr Terrel Hill, Principal Advisor, Child Survival Unit, UNICEF

iii. Progress in Commitment to Vaccine Quality
Dr Julie Milstien, Scientist, Vaccine Supply and Quality (VSQ), WHO/GPV

iv. Discussion

12.30-2.00 *Lunch*

2.00-3.00 **Regional Highlights**
Session Chair: Mr Frank Hartvelt, Deputy Director, Science, Technology and Private Sector Division, United Nations Development Programme

i. Africa
Dr Oni Olawale, Advisor, Africa Regional Office

ii. Americas
Dr Akira Homma, Regional Advisor on Biologics, PAHO

iii. Europe
Dr David Salisbury, Principal Medical Officer, Department of Health, UK

iv. Southeast Asia
Dr Tripathy, Director, Health Research, Southeast Asia Regional Office

v. Western Pacific
Dr R. Tangermann, EPI Medical Officer, Western Pacific Regional Office

vi. Mr Jaechol Hahn, Deputy Director-General, UN Systems Bureau, Ministry of Foreign Affairs, Seoul, Korea

vii. The International Vaccine Institute
Dr Richard Mahoney, Director, Institutional Development, The International Vaccine Institute, Seoul, Korea

viii. Discussion

3.00-3.15 *Coffee Break*

3.15-6.00 **Vaccine Research and Development**

Session Chair: Dr John La Montagne, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA

i. Progress in Development of New Vaccines: Vaccine Technologies for the Future of CVI
Dr John La Montagne, National Institutes of Health, USA

ii. Limitations to Infant Immunization and Approaches to Overcome the Age-Related Immunodeficiency
Dr Paul-Henri Lambert, Chief, Vaccine Research and Development (VRD), WHO/GPV

iii. HIV/AIDS Vaccines
Dr Seth Berkley, Associate Director, Health Sciences Division, Rockefeller Foundation

iv. Discussion

Children's Vaccine Initiative Reception

6.00-7.00 Hosted by Dr J.W. Lee, Executive Secretary, CVI, at the Dante Pazzanese Institute of Cardiology Conference Center, immediately following the meeting.

Thursday, 26 October, 8.30 a.m. - 5.15 p.m.

8.30-9.30 Contributions of Industry: 1990-1995 and Beyond

Session Chair: Dr Tom Vernon, Executive Director, Medical, Scientific and Public Health Affairs, Merck & Company, Inc.

i. Mr Jacques Martin, Chair, Task Force on Biologicals, International Federation of Pharmaceutical Manufacturers Associations (IFPMA)

ii. Discussion

CVI'S role into the 21st century

9.30-10.30 Session Chair: Dr J. Sepulveda Amor, Director, National Institute of Public Health, Mexico

i. The Spectrum of Vaccine Research and Development: From the Molecule to the Ampoule
Dr David Salisbury, Principal Medical Officer, Department of Health, UK

ii. CVI's Mission, Activities and Strategic Plan
Dr Roy Widdus, Coordinator, CVI

iii. Introduction to Workshops

10.30-10.45 *Coffee Break*

Workshops to aid in the revision of CVI strategic plan

10.45-12.30 **Workshops**

i. Advocacy for Immunization and Vaccine Development
Moderator(s): Dr I. Arita, Chairman, Agency for Cooperation in International Health (ACIH) and Mr Andrew Burness, President, Burness Communications, Washington, D.C., USA
Rapporteurs: Ms Ellen Wilson, Burness Communications and Mr John Maurice, CVI Secretariat

ii. Intellectual Property Rights
Moderator(s): Mr Charles Caruso, Merck & Co., USA, and Professor Isaias Raw, Director, Butantan Institute, São Paulo, Brazil
Rapporteur: Elizabeth Fuller, Esq., CVI Secretariat

iii. Choosing Desirable Vaccines and Vaccine Combinations for the 21st Century
Moderator(s): Dr S. Ramachandran, Fogarty Scholar, NIH/NIAID, USA and Dr John La Montagne, NIH/NIAID, USA
Rapporteur: Dr Bruce Gellin, NIH/NIAID, USA

iv. Financing New Vaccine Introduction
Moderator(s): Dr Bjorn Melgaard, Chief, WHO/GPV/EPI and Dr Terrel Hill, Principal Advisor, Child Survival Unit, UNICEF
Rapporteur: Ms Amie Batson, WHO/GPV/VSQ

12.30-2.00 *Lunch*

2.00-3.30 **Workshops Continued**

3.30-3.45 *Break*

Expanding advocacy for immunization and vaccines: Strategies to implement locally

3.45-4.45 **Session Chair: Dr Scott Halstead, Director, Infectious Disease Research, Naval Medical Research & Development Command**

i. Dr Jaime Sepulveda Amor, Director, National Institute of Public Health, Mexico

ii. Dr Archimedes Theodoro, Chairman of the National PolioPlus Committee of Brazil, Rotary Foundation

iii. Discussion

Summary and closing remarks

4.45-5.15 Sir Gustav Nossal, Director, The Walter and Eliza Hall Institute of Medical Research, The Royal Melbourne Hospital, Australia

Dr J.W. Lee, Executive Secretary, CVI

Annex 2:

List of participants

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Annex 3:

Address by Dr Adib Jatene, Minister of Health, Brazil

Dr. Hiroshi Nakajima, Director-General of the World Health Organization, Distinguished members of the Children's Vaccine Initiative Consultative Group, my Colleagues, Ladies and Gentlemen.

It is a great pleasure for me to welcome you to São Paulo, on behalf of the Brazilian government and the Brazilian people, for this Fifth Annual Meeting of the Consultative Group of the Children's Vaccine Initiative, sponsored by The World Bank, the Rockefeller Foundation, the World Health Organization, the United Nations Children's Fund (UNICEF) and the United Nations Development Programme (UNDP).

The expertise and professional experience of this audience confirm the importance of the issues we are about to discuss. I do not need to stress the relevance of childhood vaccination in general, and in Brazil in particular, but I would like to make a few comments in this regard.

Vaccination activities have been carried out in Brazil since the nineteenth century, starting with smallpox. The major impulse in Brazilian immunization policies, however, took place in the 60's and 70's with the first campaigns of oral polio vaccination in 1961, the introduction of laboratory methods for the diagnosis of this disease a few years later, and the production of lyophilized smallpox vaccine and BCG vaccine.

In 1973, the same year that smallpox was eradicated, the Ministry of Health started the National Programme of Immunization (PNI), which immediately faced the challenge of the 1973-74 meningitis A-C epidemic.

This acute situation led the programme to adopt a more aggressive approach, with the involvement of the whole Brazilian society, and the launching of massive immunization campaigns. One successful example of this new strategy was the campaign against polio, which started in 1980, and led to a very sharp decrease in the number of cases. You all know that Brazil has eradicated polio from its territory, which is an achievement officially recognized and certified by the Pan American Health Organization and the World Health Organization.

Due to a technical cooperation project with Japan in 1980, Brazil obtained the capacity to produce measles vaccine. This project has deserved praise from the Japanese International Cooperation Agency (JICA).

In 1985, the Ministry of Health launched a programme for self-sufficiency in immunobiological products aiming to: scale up production and improve quality control procedures for anti-venom sera (a product that could not be imported due to particular Brazilian poisonous species); organize a national centre for the distribution of

immunobiological products, ensuring the cold chain required for vaccine distribution; set up a system for quality assurance, licensing and batch-by-batch testing; and update traditional technologies of vaccine production, moving towards good manufacturing practices.

In 1990, an epidemic of measles occurred with more than 60 thousand cases. In a major effort, almost 48 million children under 15 years of age were vaccinated against measles in 1992. In the two years after this campaign, the total number of cases in the entire country was <100.

Since 1985, the investments in this programme have amounted to US$90 million. Today, the country is able to meet approximately half of its vaccine needs with its own production; the polio vaccine demand represents half of our imports.

At the present time, new plants for DTP and BCG vaccine production are being opened. A recombinant Hepatitis B vaccine is currently undergoing clinical trials and pilot production will be scaled up soon. A new meningitis B vaccine is being developed in collaboration with other Latin American countries.

The Brazilian Ministry of Health is striving to acquire new technologies of vaccine production using continuous cell culture and recombinant DNA techniques. New approaches such as naked DNA vaccines are being carefully monitored by our technical staff.

To coordinate all these efforts, a National Immunobiological Products Authority is being set up.

In addition to the progress achieved in the production of established vaccines, there is an urgent need for the development of new types of products, falling into two categories:

1. Against conditions for which at the present time there is no available vaccine. Leishmaniasis, schistosomiasis and malaria candidate vaccines, developed by Latin America scientists, are currently in different stages of clinical trials. It is also relevant to mention the links between the vaccine research and development programme and the newly emerging infectious diseases, particularly important in Brazil because of the large biodiversity.
2. Existing vaccines which need improvement, such as BCG and Meningitis B.

We must not forget the economic aspects of these issues.

Although vaccines which have been produced for over two decades have a relatively low price in the international market, newly developed products still protected by intellectual property rights are very costly. As an example, while the cost of a single dose of DTP or measles vaccine is only a few cents, that of a Haemophilus B vaccine is over 20 dollars.

This illustrates that public health and private enterprise do not always share the same interests.

We are fully aware that the production of vaccines by public institutions is not cost-effective. Management problems, particularly those concerning high qualified personnel in the public sector, must be addressed. Human resources policies based on technical competence should be discussed, as well as technology transfer and technical assistance programmes.

I know that most of these concerns are shared by many of you and are not restricted to Brazil. In this context, we are proud of hosting this Fifth Meeting of the Children's Vaccine Initiative, a programme that has contributed to the understanding and solving of several of these issues. I hope you will have a very productive meeting during these two days, and I wish you a pleasant stay among us.

Thank you very much for your attention.

Annex 4:

Address by Dr H. Nakajima, Director-General, WHO

We are now five years "down the road" from the World Summit for Children, held in New York in 1990. This meeting in Brazil—the Fifth CVI Consultative Group Meeting—provides us historic opportunities.

It gives a chance to review progress. And there has been remarkable progress in disease control, in assuring vaccine supply and quality, and in vaccine development.

The meeting enables you to help CVI and its collaborating organizations, by charting the best strategies for difficult issues in the workshops tomorrow. Introduction of these workshops into the format of the Consultative Group Meeting is evidence of our desire to use this meeting—and your expertise and time—as effectively as possible.

Finally, the meeting provides the opportunity to recommit ourselves to another five years of work in pursuit of the CVI goal of expanding protection against infectious diseases. The challenge of providing better vaccines and better vaccination methods is demanding and especially important in today's economic climate where health interventions must be the most cost-effective possible.

This meeting in Brazil is special in more than just the chronological sense of marking five years since the New York World Summit for Children. It is special because it is the first time the CVI Consultative Group has assembled in the Americas—a region that has shown the way in their countries' commitment to vaccine self-sufficiency and immunization. It is also special because, I believe, it marks the emergence of a better recognition of what CVI is **collectively**, and what functions the CVI Secretariat and the many CVI collaborators should undertake. The special issue of CVI *Forum* prepared for this Conference describes recent progress in immunization, vaccines and the emerging role the CVI Secretariat envisages to help its collaborators achieve success. The simple existence of CVI has stimulated significant changes in the last five years in the way the "vaccine community" does business. Just among CVI cosponsors, there have been major changes. UNICEF, recognizing the importance of future vaccines, has changed this year its vaccine procurement methods and strategies for targeting assistance. My creation in WHO of the Global Programme for Vaccines and Immunization has revitalized and better integrated our activities under the leadership of Dr J.W. Lee.

Following its *1993 World Development Report—Investing in Health*—the World Bank will this year start a three-year grant to CVI Secretariat to help rationalize and improve the quality of the world's vaccine supply.

UNDP has invested in capacity building through fostering the International Vaccine Institute in Seoul, Korea.

The Rockefeller Foundation has expanded its support to the CVI Secretariat and is exploring ways to promote AIDS vaccine development.

Illustrating this expansion of commitment by mentioning CVI cosponsors does not mean that I think they are the most important partners in the CVI coalition. Every organization working to expand control of infectious diseases through providing "better" vaccines is a partner in achieving CVI goals. Whether they publicly embrace the ultimate vision of a single dose vaccine against many diseases, or nearer term goals in vaccine development, supply, quality or delivery, they are part of the global "vaccine community". This **obviously** includes industry with their vaccine production and development expertise.

I know that the CVI Secretariat and WHO's GPV are working to find appropriate ways to collaborate more effectively with industry.

Together, I am sure we can build a workable consensus on what goals are in the interests of global public health, and better coordinate our individual organization's efforts to accomplish what needs to be done. This is the challenge and the promise of the Children's Vaccine Initiative.

Your participation in this meeting gives me the satisfaction of knowing that the vision we articulated in CVI's Charter—the 1990 Declaration of New York—is reshaping global efforts towards better vaccines to control infectious disease. I am sure it would also give great satisfaction to the late Director of UNICEF, James Grant, with whom I worked to establish CVI.

Finally, I should like to express my appreciation, and that of the other CVI cosponsors and collaborators, to the Government of Brazil for being such a warm host for this meeting.

I wish you all a successful outcome.

Annex 5:

Summary Report of the Workshop on Advocacy for Vaccines and Immunization

Co-Moderators:

Dr Isao Arita, Chairman of the Agency for International Health in Japan (ACIH)
Mr Andrew Burness, President of Burness Communications, USA

Rapporteurs:

Ms Ellen Wilson of Burness Communications
Mr John Maurice of the CVI Secretariat

Purpose of workshop

Highlight the crucial role of advocacy for the future of vaccine development and public health from the perspective of the "advocate" who informs national politicians for the purpose of raising money, and from the perspective of the "decision maker" who is on the receiving end of the request from the advocate.

Overall recommendations and conclusions

1. Advocacy should support fundraising initiatives.
2. CVI needs to better reach the developing world, many parts of which do not know about or, in some cases, do not support CVI. Many of these efforts could be done through CVI presentations at existing fora around the world, including ICC and EPI meetings.
3. CVI should hire a professional communications/marketing senior staff person, or office, to manage public relations, advertising and fundraising efforts for CVI.

Reaching developing countries

The workshop made clear that CVI advocacy efforts need to better reach developing countries in a systematized way. Several participants from India remarked that some of their colleagues do not know what CVI is, what its goals are and what it offers the developing world. One participant said, "It has taken three years for most of my colleagues to understand CVI. With the public, it will take even longer." Another participant from India commented that many people in her country believed that CVI is seeking to create a super vaccine for developed-world children, not for developing-world children. A participant from Africa noted that people in the WHO regional office and in the UNDP field office in Africa did not know about CVI. He stated that "There are many decisions and much information that is only shared among the higher levels of the founding fathers of the CVI. Those at the central or peripheral levels do not know what CVI is all about. It is crucial that we get everyone who is supposed to be involved in CVI up to speed on it."

However, participants suggested that advocacy for CVI in developing countries could be done through "selling" CVI at meetings that are held regularly around the world such as ICC, EPI and WHO regional meetings, as well as Rotary and other private sector meetings. Participants also noted that if efforts are made to promote CVI in developing countries, then local professionals must be involved as presenters of the Initiative.

Hiring a professional communications/marketing senior staff person, or office

Several people suggested hiring a professional information officer to manage an advertising, public relations and fundraising campaign on behalf of CVI. This idea was first highlighted by Dr Arita, who said that in the smallpox campaign a professional communications person had been extremely helpful in disseminating materials to the media to further the campaign. Dr Scott Halstead also raised the need for a professional public relations/marketing person for CVI. He said, "In addition to Dr Roy Widdus, we need a second person at his level whose only job is to organize an advertising, public relations and fundraising campaign. He or she may need to be backed up by a committee on advocacy." This suggestion was reflected and re-enforced by other participants throughout the workshop.

Results from the advocacy questionnaire

Mr John Maurice presented the results of the advocacy questionnaire which had been mailed to 500 persons with invitations to the CVI Consultative Group Meeting. Only 31 responses were received. While the results are from self-selected respondents and are not indicative of all views, they do provide an interesting perspective on advocacy.

The first question was, "Where do you think lack of information or commitment is a barrier to achieving CVI goals?" Of the areas offered for the respondents' selection, there were 26 marks for research and development (particularly with regard to exchange between the public and private sectors), 22 marks for new vaccines (regarding both priorities for new vaccines and strategies for introducing them), 14 marks for supply and quality, and 14 marks for immunization programs.

To the question, "Who lacks information?," respondents answered that just about everybody lacks information—from parents to international organizations to industry to politicians. Respondents particularly singled out governments, specifically health ministry officials, as having insufficient information.

To the question, "What information could bring about most change for the better?," research, technology and good manufacturing practices got the most responses, with epidemiology and cost-effective analyses next. Respondents felt that information should be presented through articles, particularly in the lay press for the general public, face-to-face briefings, and radio and television broadcasts.

Finally, in response to the question about the top three advocacy goals, respondents seemed to be split along regional lines. The Africans called for greater government spending on immunization. The Asians called for better quality vaccines and stronger production of vaccines, particularly combination products. The Americans called for more emphasis on the introduction of new vaccines, and the Europeans asked for stronger economic analysis, identification of targets, drafting of strategic plans, and transfer of technology to developing world producers.

Ideas to promote advocacy and fundraising

1. CVI should seek to create different messages for different donor and other key audiences.
2. CVI should put its advocacy efforts behind polio eradication as a concrete first step in reaching the final goal of the dream vaccine because polio eradication is easier to understand than CVI. Polio also offers a success. In support of this idea, Mr Ted Trainer stated that "a message will be most successful if it sells something concrete over the short term with a high payoff and a high likelihood of success. It's important to have salient, short-term activities that work toward delivering a long-term objective."
3. Dr Halstead suggested that money should be raised to conduct CVI-type activities, not just for polio, because these activities are greatly needed to prepare for vaccine needs beyond the year 2000.
4. CVI should assign individual responsibility for advocacy and fundraising for CVI to each participant in the CVI Consultative Group Meeting.
5. In developing countries, advocacy efforts should be tailored to each country, or region to be targeted. One strategy will not work the world over. For example, advocacy efforts in Africa should be directed at all levels of society, starting with the general population and then moving to government leaders. In India, however, policy makers have no understanding of CVI. Therefore, advocacy efforts should be directed first at the policy makers.
6. Money for CVI should be raised for specific goals and CVI should be accountable for achieving those goals.
7. Mothers, children, pediatricians, nurses and health care workers should be tapped as natural advocates of CVI.
8. CVI should make use of the skills of private sector partners in terms of marketing and advocacy. A larger effort needs to be made toward ensuring that CVI is truly a public-private venture. The private sector is often left out, but its skills are very much needed.
9. CVI should organize ambassadors around the world to promote the Initiative.
10. CVI should position itself as combating the most important diseases in each country to be targeted around the world.
11. CVI, as an advocate for the use of vaccines, should address the issue of the value of vaccines. A conscious, careful campaign should be conducted to describe the value of vaccines as the most effective, life-saving, preventative measure available to health workers. The value of preventing disease needs to be compared favourably with that of saving lives.

Problems that CVI still needs to confront

One of the major problems that still seems to plague CVI is its identity. One participant noted that CVI needs to create a "brand name" recognition for itself. However, CVI's goal of a single-dose dream vaccine is fairly clear and offers a good brand-name identity. In fact, it is the short-term activities that CVI is embarking on to reach the long-term goal of a single-dose vaccine that are unclear

In speaking of CVI's identity, one participant—film maker George Allez—set forth an excellent and uplifting description. He stated that "there are moments in history that are fraught with opportunity. When I try to explain CVI, I say that we are on the threshold of a golden age in immunology and CVI is here to manage this golden age of immunology."

Participants in Advocacy Workshop

Mr George Allez, Producer, Ash Film Productions, USA.

Dr Isao Arita, Chairman, Agency for Cooperation in International Health (ACIH), Japan.

Dr Igor Barinsky, Head, Comparative Virology Laboratory, The D.J. Ivanovsky Institute of Virology, Russia.

Dr Elizabeth Benites de Escala, Sub-Director, National Institute of Hygiene and Tropical Medicine, Ecuador.

Dr J.V. Bennett, Director for Scientific Affairs, Task Force for Child Survival, Carter Center, USA.

Mr Andrew Burness, Burness Communications, 7910 Woodmont Avenue, Suite 1401, USA

Mr Arthur D. Case, Managing Director, South African Vaccine Producers (SAVP), South Africa.

Dr Stephen L. Cochi, Chief, Polio Eradication Activity, Centers for Disease Control and Prevention (CDC), USA.

Dr Scott Halstead, Director, Infectious Disease Research, Naval Medical Research and Development Command, USA.

Mr Jee-hoon Han, Director of Overseas Department, Korea Green Gross Corporation, Korea.

Mr Frank Hartvelt, Deputy Director, Science, Technology and Private Sector Division, United Nations Development Programme (UNDP), USA.

Dr N. Kandun, EPI Manager, Ministry of Health, Indonesia.

Dr C.J. Lucas, TNO Prevention and Health, The Netherlands.

Dr M. Mahfoudi, Chief, National Immunization Programme, Morocco.

Mr Jacques-Francois Martin, Chief Executive Officer, BIOCINE, France.

Mr John Maurice, CVI Secretariat

Dr Bjorn Melgaard, Chief, Expanded Programme for Immunization (EPI), WHO/GPV, Switzerland.

Dr Iman Mochny, EPI/CVI Focal Point, Southeast Asia Regional Office, WHO, India.

Dr William Muraskin, Professor, Queens College, City University of New York, USA.

Dr Peter Ndumbe, Director, Centre for the Study and Control of Communicable Diseases, University of Yaoundé, Cameroon.

Dr Nguyen-Thi-Kê, Institute of Vaccine, Vietnam.

Dr G.L.N. Prasada Rao, Director, Pasteur Institute of India, India.

Dr Ira Ray, Director, National Institute of Biologicals, India.

Dr Jaime Sepulveda Amor, Director, National Institute of Public Health, Mexico.

Dr Gurinder S. Shahi, Coordinator, Operations Development, International Vaccine Institute, Korea.

Ms Adelaide Eleanor Shearley, EPI Manager, Ministry of Health and Child Welfare, Zimbabwe.

Dr Gustavo Sierra, President, National Vaccine Research Development Programme, Cuba.

Dr Jaspal Sokhey, Director, Central Research Institute, India.

Dr D.W. Stainer, President, Stainer Associates, Canada.

Dr Archimedes Theodoro, Chairman, PolioPlus Committee, Rotary Foundation of Brazil, Brazil.

Dr Edward Trainer, Programme Manager, PolioPlus, Rotary International, USA.

Dr Jan van den Ende, Board of Directors, South African Vaccine Producers (SAVP), South Africa.

Ms Ellen Wilson, Burness Communications, Bethesda, USA.

Annex 6:

Summary Report of the Workshop on Choosing Desirable Vaccines and Vaccine Combinations for the 21st Century

Co-moderators:

Dr John La Montagne, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health
Dr S. Ramachandran, Fellow, Fogarty International Center, National Institutes of Health

Rapporteur:

Dr Bruce Gellin, Medical Officer, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Purpose of workshop

To examine the on-going transformation of vaccines from "commodities" available to national immunization programmes, to an expanding choice of technologies requiring new strategies for their evaluation and selection.

Outcomes of the workshop

The workshop acknowledged that the following assumptions would underlie any decisions leading to new vaccine development:

1. **Variety and choice.** There are, and will continue to be, a growing number of antigens and approaches for improving existing vaccines and creating new vaccines.
2. **A dynamic menu.** The rapid pace of technology will continue to add new choices. What is desirable today may not be desirable tomorrow, and the desirable technology of tomorrow may be unforeseen and unpredictable today.
3. **Thinking ahead: transition from near-term to long-term.** Along the road to future vaccines and approaching the goal of the ideal vaccine, there will be a number of intermediate products.
   - What would be the most useful for vaccines for the next 10 to 15 years?
   - What are the best intermediate products?
4. **The development of combination vaccines is not linear.** The next generation(s) of the CVI Strategic Plan should take into consideration that the process of vaccine development is not linear and that what may be the most efficient or expedient step for the interim may not be the same for a longer range product.
5. **DTP-based combinations as one option.** The CVI strategic plan should readdress whether the DTP-based combination vaccine strategy is the right one and the only one. Not all desired combination vaccines will necessarily be combinable with

DTP or DTaP. Therefore, reliance only on a DTP-based combination strategy may be a limitation in the future. Experience to date with DTP-combination vaccines has shown that major vaccine companies have experienced more difficulties than had been anticipated, in particular with the immunogenicity of combinations that contain acellular pertussis and Hib conjugate vaccines. In many settings, DTaP-Hib combinations have resulted in diminished antibodies to Hib when compared to those elicited when Hib is administered separately from DTP. The clinical significance of these findings is uncertain. Despite this interaction, a DTaP-Hib combination vaccine has been widely used in Canada and has led to the near eradication of Hib there. Such immunologic interactions have not been seen with a five-component DTP-Hib-IPV product, emphasizing the need to demonstrate effectiveness in the field.

6. **Change is threatening to stable systems.** Replacing existing vaccines with new vaccines may be disruptive to on going programmes, yet premature elimination of some technologies may preclude unanticipated technological leaps from occurring. The development and use of new vaccines should not be limited by existing infrastructure and programmes, although the flexibility of these systems may be a barrier in the near term.

7. **The better the data, the better the decision: regional considerations.** Choices will be made on the basis of regional considerations such as the burden of diseases (e.g. whether or not to include Hib), cost benefit analyses and social acceptability (e.g. whether to replace DTP with DTaP or OPV with IPV). Therefore, the identification and development of appropriate data by which options can be compared is a necessary early step.

8. **Vaccine must be of acceptable quality.** Substandard vaccines must be eliminated from immunization programmes. Lack of efficacy and questionable safety will jeopardize immunization programmes and public health interventions.

9. **Changes in the marketplace.** Local private markets will continue to grow and their potential market will be increasingly recognized by vaccine manufacturers.

10. **Setting priorities in a setting of limited resources.** Even if health budgets were to expand, the growing number of options will demand objective priority setting to optimize programme resources. Given limited resources it is unlikely that there will be more money available to purchase all new vaccines that come along, regardless of their anticipated impact on public health. Therefore, decisions about vaccine purchases, and thus on vaccine development, will need to acknowledge that additional money is likely to come from other programmes and may negatively impact on them.

11. **Management of change.** A strategic plan for vaccine development must be revisited on a regular basis.

12. **Harmonization of regulatory requirements.** This could greatly reduce the costs of vaccine development. Therefore, CVI might help focus discussion in the international community to accomplish this and increase interaction with the biological standards component of WHO to facilitate this progress. It was recognized that many obstacles exist. However, they should not cloud the vision of CVI and the promise of new vaccines. The gains of EPI came from inexpensive and available "commodity" vaccines. Future vaccines should not be tested by this standard since new biotechnology will initially be more costly and complicated.

Background

Since its birth, the overriding goal of the Children's Vaccine Initiative has been the hope of taking full advantage of current and emerging vaccine technology to improve the health of infants and children around the world. The Initiative not only hopes to accelerate the development and use of vaccines against diseases that are not currently "vaccine preventable" but also to simplify the complex logistics of vaccine delivery through the creation of vaccines that, among other characteristics, require fewer injections and fewer contacts.

The past decade has ushered in a new generation of vaccines. Several have worked their way through the development and evaluation process, have become licensed products, and have been inserted into immunization schedules in many parts of the world. These include hepatitis A and B, Haemophilus influenzae B conjugate vaccines, acellular pertussis vaccines, and varicella vaccines. Several others, including vaccines for rotavirus and conjugated pneumococcal and meningococcal vaccines look to be promising vaccine candidates that may soon be approved for use in some populations. An even longer list of new vaccine antigens and new approaches to vaccines are in earlier stages of development. While the present and future availability of improved and new vaccines offers the promise of even more efficient and powerful preventive tools against infectious diseases, each new product brings an increased delivery challenge. Not withstanding the good that these products may bring, additional injections and immunization visits may increasingly provide real disincentives to full compliance and completion of the immunization schedule.

Technologies that simplify delivery may be more expensive to produce. However, they may provide substantial savings. Therefore, there may be a number of ways to greatly expand the effectiveness of new vaccines without a parallel increase in cost. Further, competition in the marketplace and economies of scale in manufacturing should reduce both costs and price over time. Therefore, "affordability" must not only be seen in terms of current vaccine prices for the newer vaccines. The availability of a rapidly growing number of candidate antigens, each manufactured by different processes, adds to the potential for physicochemical and immunologic interactions between components (antigens, adjuvants, and technologies). This highlights the need for formal product development and evaluation for any proposed candidate vaccine product.

As a concept, multiantigen or combination vaccines are one approach to the goal of simplifying the process of vaccine delivery. The existence and utilization of DTP, MMR and trivalent OPV clearly demonstrate that combined vaccines are not a new concept. While it would be ideal to be able to blend together the desired antigens for particular individuals, groups or regions, the rigors, resources and time that must be invested to demonstrate safety and efficacy for each such product preclude such a solution. With this need comes the cost of development, estimated to be as much as $300 million per licensed product. Given limited resources and an expanding menu of options the goal of the workshop is to begin to develop an approach to decision making in this arena.

Perspective of vaccine developers, manufacturers and users

Dr George Siber (Massachusetts State Biological Laboratories, USA), provided a glimpse into the future and highlighted three promising technologies that could accomplish many of the CVI goals for desirable vaccines.

- Controlled release vaccines
- Vectored vaccines
- DNA vaccines

1. Controlled release vaccines

A desired antigen can be encapsulated inside synthetic polymers and subsequent release can be continuous, or in pulses designed to mimic booster schedules. Controlled release vaccines can be administered by injection, or via oral or nasal administration and should stimulate a strong, high affinity immune response. One design that has undergone extensive evaluation is composed of polylactic acid-poly glycolic acid, similar to absorbable suture material. Such materials have been in use for decades. Their safety profile is well known and they are approved by the USFDA. This approach is also an attractive approach from a manufacturing standpoint since it can be done on a large scale and is relatively uncomplicated.

Initial animal studies of microspheres incorporating tetanus were disappointing and compared unfavorably with aluminum phosphate absorbed tetanus toxoid since the bulk of the antigen was released early with minimal antigenic effect. These studies demonstrated that a number of physical and chemical interactions limited immunogenicity. More recent studies that use Hib-T vaccine (where tetanus is coated with Hib polysaccharide) may overcome this limitation and may also provide sufficient immune response to Hib. Such an approach would mesh well with CVI's DTP-combination strategy as it might also be possible to microencapsulate a number of other desired antigens including hepatitis B and pneumococcus.

Does the development of this technology beg the question of an idealized schedule? Clearly, as we learn more about the immune system we will need to gain a better understanding of the optimal immunization schedule to induce a desirable and life long immune response.

Microspheres present a number of safety concerns that will need to be addressed if this technology is to move forward. Among the questions to be answered:

- If given orally, will persistence be long lasting?
- How difficult will data on reactogenicity and adverse reactions be to obtain?
- How safe is a controlled release product in an individual that is allergic to that product?

Therefore, while encapsulation is promising, it should not deter current momentum to develop DTP-based combination vaccines. In the long-term, these technologies may merge.

2. Vectored vaccines

DNA codes a desired antigen and is introduced into an attenuated virus or bacterial vector. There is a growing list of potential vectors. BCG may be an attractive candidate for developing country use since the safety of BCG is well established; it can be administered at birth,

and it is heat stable. From a manufacturing standpoint, it is easy to grow on a large scale and many manufacturers already have the know how to manufacture BCG. BCG has a large capacity for DNA, and a single dose may give long-lasting protection.

Recent progress in a BCG-vectored Lyme vaccine has demonstrated that a protective IgG (Th1) response can be generated from a single nasal dose and persists for at least two years.

While bacterial vectors are an attractive approach since prokaryotes do not manufacture glycoproteins, viral glycoproteins are not made by bacteria. Further, the immune response to the vector itself may be a limiting factor by impeding immune responses on subsequent doses. In addition, if already immune to TB, such an approach is unlikely to be immunogenic. Finally, the use of BCG or another attenuated live vector may be limited since these vectors may disseminate in immunocompromised hosts.

3. DNA vaccines ("naked" DNA)

Purified plasma DNA encoding an antigen can be incorporated into nuclei following delivery by intramuscular injection, the mucosal route, or intradermally. DNA directs the assembly of protein antigens for which it codes. These are transported to the cell surface and presented to the host's immune system where they trigger all arms of the immune response.

Experimental studies with an influenza preparation have demonstrated several attractive features of this approach:

- Higher antibody titers are obtained following vaccination than following infection with wild virus.
- Broad protective cytotoxic immunity is produced. In the influenza model, antigenic drifts and shifts of wild virus do not affect the overall effectiveness of this approach.

This approach also:

- Avoids the need and expense of antigen purification.
- Allows multiple genes to be introduced and expressed.
- Induces B cells and CD8 cytotoxic T cells.
- Avoids inhibition by preexisting (e.g. maternal) antibodies.
- Avoids safety concern of live vectors.

However, since neither vectored vaccines nor DNA vaccines can produce polysaccharides, protein polysaccharide conjugate vaccines are likely to be in the mix for the foreseeable future.

Dr William Hausdorff, Wyeth-Lederle Vaccines and Pediatrics, emphasized that priorities, once set, are not fixed but must respond to changing technologies, successes and failures of product development efforts, and changes in demand. Therefore, a range of possible products must be considered and reconsidered. For example, in the USA, the proposed shift from OPV to IPV may reset priorities for DTaP-combination vaccines. In this setting one could envisage the development of intermediate combinations that were not on the drawing board a few years ago, such as a DTaP-IPV vaccine and a separate Pneumo conj-Mening conj-Hib combo that could mesh with the immunization programme. Different combinations are possible, and not all need to be based on DTP.

Alternatively, a maternal immunization strategy may not only lead to the development of vaccines designed for women of childbearing age that would protect neonates from infectious diseases but may also impact on vaccines that will be administered to those neonates. For example, in theory, one could envisage two candidate RSV vaccines, a subunit vaccine that would be given to women of childbearing age and a live attenuated vaccine for neonates.

Changes in the immunization schedule itself could also affect the desirability of vaccine combinations. For example, vaccines that protect against STDs may be best administered to school age children or young adolescents rather than in childhood. If this is the case, it may be desirable to consider an adolescent combination vaccine that also includes hepatitis B vaccine or, one day, an AIDS vaccine. Finally, market size and pricing structure is the key to making choices among vaccine candidates to develop. The more undefined, the more difficult to entice industrial partners.

Dr Octavio Oliva (Oswaldo Cruz Foundation, Rio de Janeiro) pointed out that, similar to the large, multinational vaccine companies, smaller vaccine manufacturers must make choices from among the many approaches to vaccine development. In addition, it is also essential that these manufacturers:

1. Develop optimal management systems that will ensure future corporate viability.
2. Ensure that they will have access to new technologies. This will necessitate collaborative technical assistance for the development of specific products important in a country or region (e.g. vaccines that protect against *N. meningitidis* [serogroup B], typhoid fever, hepatitis A, yellow fever and dengue).
3. Develop partnerships with large and small vaccine companies and/or biotechnology companies that will facilitate the best utilization of new technologies. This will be part of a larger national picture of technology development manufacturing capability.
4. Identify and secure appropriate consultants to provide insight into the many new, and sometimes competing, technologies that are important for future vaccine development and production (e.g. freeze drying process for measles vaccine production). Sharing available information among manufacturers in an objective way will greatly assist in the selection of appropriate technology. This is one area where informal cooperation between SIREVA and CVI has already begun to assist in decision making.

The decision making process: decision analysis, cost-effectiveness studies and economic modeling

Dr Mark Miller (CDC) gave a presentation on this subject. Any priority setting exercise should start by identifying the ultimate goals from the perspectives of each of the participants and recognize that there are likely to be competing interests. This can help to identify areas in which consensus can begin to be developed and partnerships crafted.

Decision analysis may help to provide an objective comparison among the various options and should be incorporated into the dynamic strategic planning process. In addition, models should be developed that can facilitate these decisions.

Because resources (money, effort and time) are limited, priorities will force choices to be made. Informed decisions rely on the best available data. Identifying and developing data (epidemiological, economic) is a likely initial step. While neither intuitive nor ideal, cost-effectiveness analyses have utilized the concept of DALY (disability adjusted life year) as a standardized denominator and allows for direct comparison of different options (e.g. bed nets vs. vaccine programme for malaria control). More importantly, DALY provides a means to incorporate more than only mortality as key data and factors in "quality of life" indices such as morbidity and disability. However, it is important that the assumptions built into the model remain clear.

However, what is "desirable" may be different from what is currently technologically and programmatically feasible. Technological feasibility must take into account that unanticipated leaps of technology (or unanticipated setbacks in product development) may greatly affect projected lead times. Similarly, access to new technologies may also affect the rate at which new technologies can move forward. In contrast, the likelihood that a new technology is utilized, if available, may depend on available resources (costs and cost-effectiveness) as well as willingness to adopt a new approach over a more traditional one.

Economic modeling attempts to integrate epidemiologic and economic data to compare various scenarios. Economic models not only assess whether a particular intervention is cost effective but the impact of the incremental benefit from the incremental cost (What do you get for a dollar spent and how much more do you get if you spend more?). Components of economic models for vaccine development include an assessment of the benefits (new and/or incremental) of the vaccine, including reductions in morbidity, mortality and disability as well as indirect costs such as impact on the economy (savings gained by a reduction of lost time and wages) and benefits gained from reductions in inconvenience. Cost-benefit analyses regarding the development of new vaccines also need to include an assessment of the impact that an improved or new vaccine will have on the both the costs and the effectiveness of the immunization programmes.

Determining the "cost" component of new vaccine development for cost-benefit analyses must include: actual costs of development and costs that may result from anticipated and unanticipated adverse events; and indirect costs such as the relative inconvenience of a vaccine and its impact on lost time and wages. These factors should be balanced against the calculated cost per disease averted.

Economic analyses can be used to define research and development priorities and influence pricing policies. For example, a cost-effectiveness analysis of the use of IPV vs. OPV in the United States demonstrated that a high price had a negative impact on the market share and that a lower price led to not only a larger market share but also an increase in the company's total profits.

Cost-effectiveness studies on new vaccine development can also influence the decision among a variety of options, such as the use of a vaccine vs. other public health measures (e.g. development and use of vaccines that protect against a range of infectious diarrheas (cholera, shigella, rotavirus) vs. cost of ensuring a clean water supply which would provide still additional benefits. Yet it is important to realize that cost effectiveness analyses studies are limited by the assumptions that are incorporated into the model.

Unfortunately, decisions are often made for political reasons rather than being based on scientific or economic grounds. The recent decision by the USA to move toward IPV rather than OPV, was based on an economic analysis which estimated that the cost of preventing

one case of Vaccine Associated Paralytic Polio (VAPP) was approximately $3-4 million, illustrating that economic considerations are not the only factor that go into such decisions. Thus while economic models need to incorporate the realities of the country which will use them, they can still be powerful tools in the decision making process since many decisions are made primarily for political and socioeconomic considerations. In developing countries, the lack of resources ultimately has the most powerful impact on the choice made since desirable products often cannot be paid for, even if they are the right choices.

New generations of vaccines must not only be safe and effective, but they will increasingly need to have additional benefits. To be used, they must be demonstrated to be cost-effective, if not cost-saving, by improving the overall process of immunization; a realization that needs to be incorporated into the CVI strategic plan. For example, the likelihood of disease eradication should also be included in cost-benefit analyses, since eradication will ultimately lead to discontinuation of vaccines, and the subsequent cost savings in perpetuity. Also, reducing the number of doses and/or immunization contacts should also be factored into analyses since this will impact on savings in vaccine delivery and allow health workers to perform other public health functions.

A central role for CVI

Since there are a variety of participants in the process, manufacturers, governments (ministries of health and finance), NGOs and PVOs, consumers, and society at large, CVI can facilitate the necessary interactions and begin to develop an adjustable cost-effectiveness model that can be useful for all.

CVI could be an effective forum to gain consensus on the combinations that could be used for the next decade. An important goal is to minimize further complexity in an already complex system. For example, CVI should play a leading role in organizing head to head trials of competing technologies, particularly to help sort out the potential adjuvant candidates. Because no other institution has taken it up, CVI should fund research aimed at defining the epidemiology of diseases for which new vaccines are, or soon will be, available (e.g. Hib, RSV).

Concluding comments

Dr S. Ramachandran, Fogarty International Center, NIH presented the following thoughts on the management of change. Vaccines will continue to be highly cost-effective and new vaccines will further prevent the massive burden caused by infectious diseases, especially in developing countries. However, at present there is not a ready mechanism to incorporate new vaccines into immunization programmes, as has been unfortunately seen with the slow progress in adding hepatitis B vaccine to the EPI schedule worldwide.

Despite the fact that it has been repeatedly proven that vaccines are one of the most cost-effective and safest approaches to the control of infectious diseases, countries, particularly developing countries, give very low budgetary priority to immunization programmes for both adults and children. Experts and programme managers in immunization must be more demanding and outspoken with respect to resource allocation for vaccine development and deployment.

The selection of desirable combination vaccines will necessitate attention to the management of change. This will include:

1. Recognizing that socioeconomic feasibility is an important element in the decision making process and must be factored into the strategic planning process.
2. Taking leads from other technologies (e.g. cellular telephone technologies and computers) and applying lessons to bring about the next generation of vaccines.
3. Maintaining strong support for basic research, as it is a likely source of innovative technological leaps that would be unlikely to come about with incremental improvements.
4. Recognizing that change will not occur all at once, and that change will not necessarily replace existing technologies.
5. Developing a regional approach to new vaccine development because of the epidemiological patterns of diseases and local ecologies, rather than a unified global approach.

Participants in Workshop on Choosing Desirable Vaccines

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Dr Luis Barreto, Assistant Vice President, Clinical and Medical Affairs, Connaught Laboratories, Canada.

Dr Kenneth Bart, Associate Director for Medical and Scientific Affairs, Office of International Health, Department of Health and Human Services, USA.

Mrs Conception Camp Huergo, President, Finlay Institute, Cuba.

Ms Carmen Chirino Inara, Venezuela.

Mr Alain Cognard, Director for Latin America, Pasteur Mérieux, Argentina.

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Dr Lisette Gonzalez, Coordinator, Clinical Trials, United Biomedical, Inc., USA.

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Dr Maurice Hilleman, Director, Merck Institute for Therapeutic Research, Merck Research Laboratories, USA.

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Dr J.M. Mehta, Vice-President, Serum Institute of India Research Foundation, India.

Dr Mark Miller, Medical Epidemiologist, Centers for Disease Control and Prevention (CDC), USA.

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Dr Peter F. Wright, Chairman of Product Development Group, Pediatric Infectious Diseases, Vanderbilt University Medical Center, USA.

Annex 7:

Summary Report of the Workshop on Intellectual Property Rights: Access to New Technologies and Products

Co-Moderators:

Dr Isaias Raw, Director, Butantan Institute, São Paulo, Brazil,

Mr Charles Caruso, Patent Counsel for Merck & Co., New Jersey, USA

Rapporteur:

Elizabeth Fuller, Esq., Consultant to CVI

Purpose of workshop

To initiate a process within CVI for exploring how intellectual property rights affect the availability and cost of future vaccines

Discussion of background paper

Several weeks prior to the meeting in São Paulo, a paper written by Mr. William Packer of the Virus Research Institute of Cambridge, Massachusetts, was distributed to likely participants in the workshop. This paper had been requested to elicit discussion about the impact of Intellectual Property Rights (IPRs) on the introduction of new vaccines and to consider many options for overcoming the impediments presented by IPRs. The most controversial option presented was that governments of developed countries exert "...pressure on their manufacturers under 'Government Use' provisions in patent law to ensure access for developing countries." He also presented several less controversial ideas for getting vaccines into developing countries, including bilateral negotiations between manufacturers and developing countries; CVI acquisition of technology; linking UNICEF purchases to the transfer of technology and/or IPR licensing to developing world producers.

Mr Charles Caruso, in referring to Mr. Packer's report, stated that he was opposed to any form of "government coercion."He provided some basic information about the patent system, and the various types of IPRs: patents, "know how", and trade secrets. He advocated face to face negotiations between the parties as the most desirable method of transferring technology or procuring vaccines.

Dr Isaias Raw, was concerned that, in his experience, the only offer made by large manufacturers to developing countries is bulk purchasing arrangements. He presented the view that the developing world is fully capable of manufacturing vaccine for its own local markets, and that many developing countries would utilize the five year grace period of the TRIPS Agreement (the Uruguay Round Treaty that addresses IPR issues) to gear up their manufacturing capabilities. He voiced his support for the formation of a vaccine manufacturers' consortium to provide increased leverage in future negotiations and to utilize the strength of numbers.

Elizabeth Fuller presented Mr William Packer's paper in his absence, along with a brief paper outlining the importance of IPRs and their impact on new vaccines. This paper included a cursory patent search on acellular pertussis (acP) and Haemophilus influenzae B (Hib) conjugate vaccines. The purpose of this search was to show the complexity of IPRs in vaccine production as well as to demonstrate how much information about IPRs is publicly available. She proposed the idea of extending the existing tiered pricing structure to royalties for UNICEF purchases for the world's poorest countries.

In response to Mr William Packer's paper, Dr William Hausdorff, Associate Director for Scientific Affairs at Wyeth-Lederle, prepared written comments reflecting the belief that one must make a distinction between intellectual property rights, technology transfer, and appropriate economic benefits. Furthermore, any discussion on these topics should focus on "specific vaccines and specific scenarios." While stating that, "The new UNICEF tender announcement starts to move in that direction," he also noted that, "It may be valuable for WHO and the CVI to examine how similar issues have been addressed in other parts of the pharmaceutical industry (i.e., antibiotic production)."

Dr Celeste Emerick, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, expressed views that were similar to Dr Raw's position on bulk filling arrangements, referring to IPRs as being concentrated in the hands of a small number of large multinational corporations. Her experience with large manufacturers was that their offers were limited to final processing of the product. She proposed a specific role for CVI in aiding developing countries either by negotiating directly with IPR holders on their behalf, or by actually acquiring IPRs directly and passing them to manufacturers in the developing world. While indicating the potential intermediary role for CVI, Dr Emerick was also supportive of direct negotiations between Brazil and international manufacturers. Furthermore, Dr Emerick felt that Brazil should comply with the IPR protection of GATT aimed at "harmonizing international legislation on intellectual property through the adoption of basic criteria for protection."

Mr John Gilmartin, UNICEF Supply Division, Copenhagen, offered the view that conflict over IPRs is not related to the novelty of the technology, but to the market value of the resultant vaccine and to the liquidity of the related technology market. He proposed that the issue of IPRs required further understanding, suggesting that CVI could most effectively shed light on this subject by undertaking a structured study of IPRs in vaccines. As the Mercer study was pivotal in focusing the vaccine supply strategy, a similar detailed, professional exploration of IPRs and their strategic role in new vaccines is a high priority.

Dr George Siber, Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts, USA, expressed dismay that in the case of hepatitis B, Hib and acP, global introduction of the vaccines has been hampered by IPRs. The main obstacle has been the granting of exclusive licenses, for example, the pertactin (69k) component of acP. He presented, as an alternative, a structure under which exclusive licenses are granted only for private sector markets. Simultaneously, a separate license would be negotiated for manufacturers for public sector use. In this way, he argued, the innovation fostered by the patent system would not be hampered as the profitable markets would remain so. The definition of the "public sector" may prove a barrier to implementation of this idea.

During the discussion which followed, it was noted that IPRs and increased royalties were the natural outgrowth of increased innovation. There was a call to "mobilize resources in a new way," to cover incremental royalty costs. With regard to transfer of technology,

negotiation on a case-by-case basis with the vaccine manufacturers is crucial. It was strongly stated that IPRs should never lead to absolute monopolies, because this would impinge on public health issues.

General areas of consensus

The workshop agreed on the following statements:

Research and Development and innovation to develop and bring to the field new vaccines should be supported by protecting IPRs and promoting mechanisms for the utilization of IPRs (including competitive licensing) which would optimize their access by the public sector.

There is a need for those in the field of vaccine production to be more sophisticated about IPRs. This includes, the need for more information gained through patent searches.

Access to technologies and products is generally obtained by good faith negotiation between the parties. Technology licensing is customarily a complex process, requiring competent legal, financial and marketing advice. CVI should (with appropriate caveats) provide a list of competent advisors in the technology licensing field for the benefit of those in the public sector who are interested in pursuing technology licensing.

Specific approaches for ensuring access to new vaccines

The workshop discussed such access for countries in the developing world, dividing them into two categories, IPRs as they affect countries which procure vaccines, and IPRs as they affect those countries able to produce locally.

With regard to **countries which procure vaccine**, the topics discussed were:

1. **Tiered royalty system.** This is a potential way of reducing the final price of vaccines for use in very poor countries. Holders of IPRs normally charge vaccine manufacturers a royalty which is a fixed percentage of the sales price, regardless of the identity of the buyer. With newer vaccines, the royalty price is likely to become a larger percentage of the cost of a vaccine. The idea is that a lower royalty rate could be negotiated for sales to UNICEF for use in the world's poorest countries, while royalties for sales to the more profitable markets would be increased to make up for the lost profit. This would create a tiered royalty pricing system analogous to the general tiered pricing system for vaccines already in place. This approach could be of genuine benefit to UNICEF and was felt to have, with further clarification and study, some promise.

   Implementation would be through alteration of the standard, or "boilerplate" language in the licensing agreements between the vaccine manufacturers and the IPR holders (generally universities or biotech companies) to include a separate royalty rate for all purchases by UNICEF of vaccine for final use in a discrete group of countries. The difficulties presented by this approach were the obstacles to altering a well established way of doing business; and monitoring difficulties.

2. **Payment of royalties by International organizations.** This was seen as an area which had promise as a new way of mobilizing resources. However, as a practical matter such an expensive endeavour was considered highly unlikely given the fact that the international organizations are generally in an era of retrenchment.

3. **Manufacturer donating royalties.** This approach was not considered feasible.

With regard to the **countries able to produce locally**, the topics discussed were:

1. **Bulk filling approach.** This is an arrangement by which vaccine is produced by large vaccine manufacturers and sold to the finisher in bulk form to be packaged and labeled locally. The cost of the bulk is significantly lower to the purchaser than the finished product. Consequently, the royalty costs would probably be lower as well (this may vary with the licensing agreement). This option was seen by some local manufacturers as a substitute for genuine technology licensing agreements. Many developing countries believe that this is a way of fostering dependence in countries fully capable of local production.
2. **Joint venture arrangements.** All parties agreed that this is generally a good idea. Commercial industry representatives emphasized the importance of negotiation on a case-by-case basis.
3. **Government coercion.** This was discarded as a nonstarter.
4. **Public sector license.** There was a further discussion of this idea with some focus on the definition of the public sector. The belief was expressed that when the public sector funds the research which leads to the patentable process or product, then there should be some provision to allow the public sector to benefit. There is, however, the problem of dividing up the market years in advance of having a final marketable product. There was also some concern expressed about the long-term financial viability of public sector producers.

Participants in Workshop on Intellectual Property Rights

Dr Seth F. Berkley, Associate Director, The Rockefeller Foundation, USA.

Mr Charles M. Caruso, International Patent Counsel, Merck & Co., Inc., USA.

Mr Arthur D. Case, Managing Director, South African Vaccine Producers (Pty) Ltd., South Africa.

Dr Maria Celeste Emerick, Coordinator of Technological Development, Oswaldo Cruz Foundation, Brazil.

Dr Louis Champion, Pasteur Mérieux Soros E Vaccinas, Brazil.

Dr Patricia Costa Giomi, Manager, International Regulatory Affairs, Lederle-Praxis Vaccines and Pediatrics, USA.

Dr Jose Luis Di Fabio, Advisor on Vaccine Research, Production and Quality Control, Pan American Health Organization, USA.

Dr Djoharsjah, Director, Finance and General Affairs, Perum Bio Farma, Indonesia.

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Dr William Hausdorff, Associate Director for Scientific Affairs, Wyeth-Lederle Vaccines and Pediatrics, USA.

Professor Donald A. Henderson, Johns Hopkins University, School of Public Health and Hygiene, USA.

Dr R.H. Henderson, Assistant Director-General, The World Health Organization, USA.

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Dr Manuel Limonta, General Director, Center for Genetic Engineering and Biotechnology, Cuba.

Dr Cristiane Machado Quental, Advisor for Technological Cooperation, Oswaldo Cruz Foundation, Brazil.

Dr Joao Quental, Director, Bio-Manguinhos/Oswaldo Cruz Foundation, Brazil.

Dr Richard Mahoney, Director, Institutional Development, The International Vaccine Institute, Korea.

Mr Jacques-Francois Martin, Chief Executive Officer, Biocine, France.

Dr Julie Milstien, Scientist, GPV/VSQ, The World Health Organization, Switzerland.

Dr G.L.N. Prasada Rao, Director, Pasteur Institute of India, India.

Professor Isaias Raw, Director, Butantan Institute, Brazil.

Dr Ira Ray, Director, National Institute of Biologicals, Add. Director General of Health Services, Government of India.

Dr George Siber, Director, Massachusetts Public Health Biologic Laboratories, USA.

Dr Moises Spitz, National Institute of Microbiology, Argentina.

Dr D.W. Stainer, President, Stainer Associates, USA.

Mr Yoshikazu Tada, Manager, Planning and Management Division, BIKEN, Kanonji Institute, Japan.

Dr Thomas M. Vernon, Executive Director, Medical, Scientific and Public Health Affairs, Merck Vaccine Division, USA.

Dr Jorgen C.W. Weber, Consultant, J.C.W. Weber, Canada.

Annex 8:

Summary Report of the Workshop on Financing the Introduction of New Vaccines

Co-Moderators:

Dr Terrel Hill, Principal Advisor of the Child Survival Unit at UNICEF
Dr Bjorn Melgaard, Chief of WHO/GPV/EPI

Rapporteur:

Ms Amie Batson, Vaccine Supply and Quality (VSQ), WHO/GPV

Purpose of workshop

To answer the following questions:

- Is the introduction of new vaccines a priority given limited funds?
- If so, which vaccines and which countries should be supported?
- How should the financing be structured to achieve the objectives of rapid introduction and sustainable supply of existing and new vaccines?

Background

The immunization community is building on past investment in infrastructure by moving forward in two ways: going "deeper" to prevent diseases with the existing vaccines, and going "broader" to introduce new vaccines to prevent other diseases. The disease control initiatives are strategies to go deeper; using existing vaccines to eradicate polio, eliminate neonatal tetanus and control measles. Equally important, adding "new" vaccines like hepatitis B vaccine, yellow fever vaccine and other potentially useful vaccines like Hib and DTP combos will enable governments to control disease and prevent deaths in an extremely cost-effective way, by building on existing infrastructure.

Over the last fifteen years, the immunization community has focused most of its attention on building systems: building a delivery infrastructure, building demand, building a trained health staff, and building a global procurement system. These systems were developed by focusing on the traditional EPI vaccines which cost only pennies per dose. The low cost was due to a variety of economic factors including that these vaccines were "old", no longer impacted by IPRs, and being produced in facilities with excess capacity. These low prices created the expectation that vaccines should cost only pennies per dose and the perception that vaccines were not valuable—they were not worth more than pennies per dose.

The perceptions and systems in place were first challenged by the recommendation to include hepatitis B vaccine. This vaccine was protected by IPRs and was not pennies, but dollars a dose. The public sector financial structure was simply unable to handle this level

of financing, and to this day we are left with a vaccine which is used only in industrialized countries and developing countries which are relatively wealthy. Disease magnitude and programme capacity to introduce a new vaccine are not determining which countries include the vaccine—national wealth is.

A second challenge to the system was the recommendation to include yellow fever vaccine. This vaccine cost roughly $0.20 per dose, but was only recommended for a small group of countries. The 33 high risk countries who need the vaccine are largely in sub-Saharan Africa and again finance, not health needs, has dictated the decision about who has access to the vaccine.

Even for those less interested in Hepatitis B or Yellow Fever vaccine, these two cases illustrate the weaknesses in the vaccine supply and financing structures. It is clear that none of the new antigens which are becoming available—Hib, pneumococcal conjugate or rotavirus—are going to be affordable for children in the poorest countries unless fundamental changes are made.

Historical problems

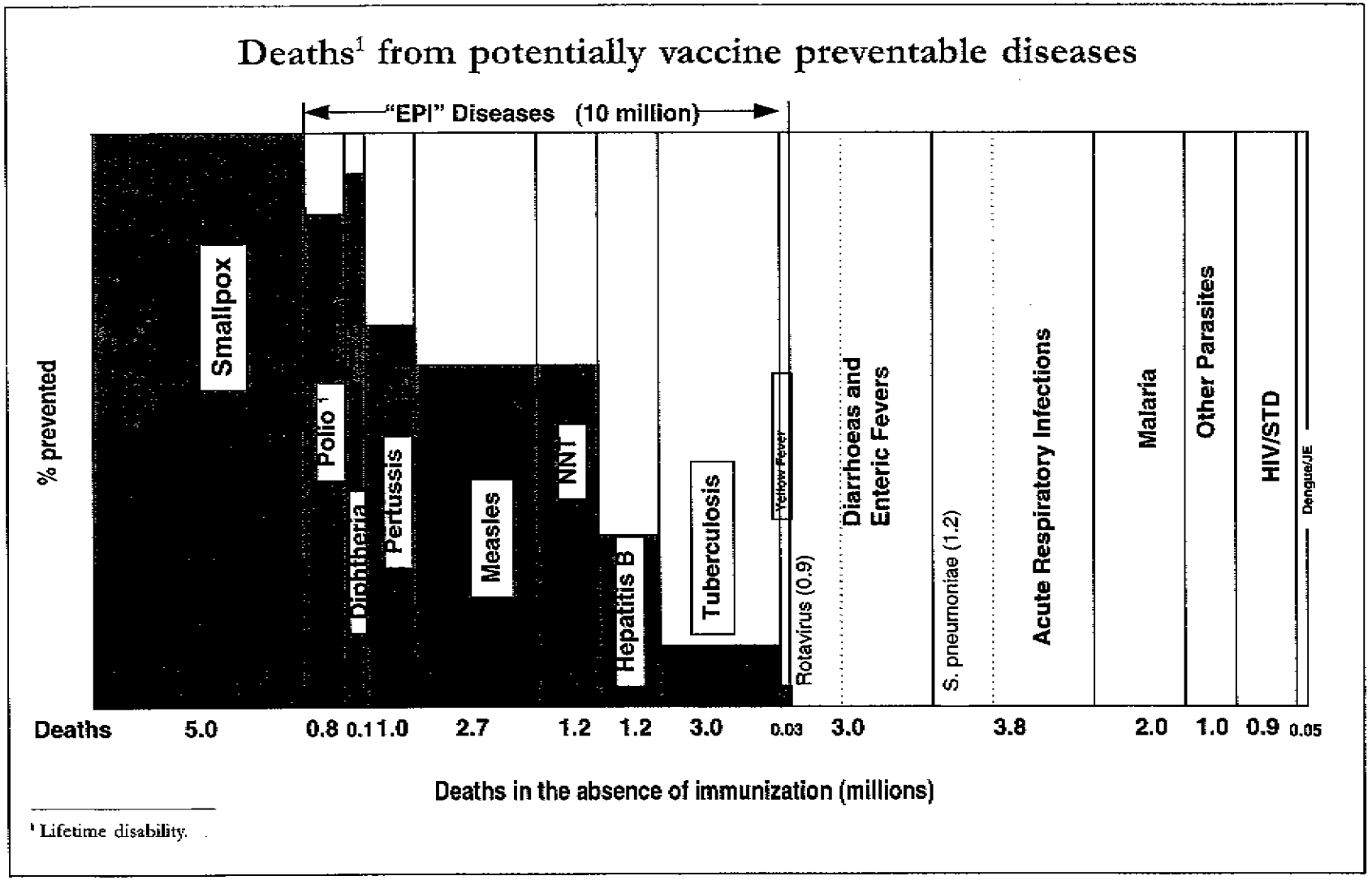
- new vaccines whose costs include royalties, licensing fees and investment in production capacity will be significantly more expensive than the "old" vaccines;
- even when new vaccines are available, they are not accessible to the neediest countries who can not afford them at any price;
- donor support for new vaccines is uncoordinated and uncertain. There is no process to define priority vaccines or to define where support should be targeted;
- it is unclear what is the priority of funding new vaccines versus the priority of funding OPV for polio eradication, or diphtheria for the diphtheria epidemic;
- countries with local vaccine industries may not wish to procure vaccine from commercial manufacturers, however, technology transfer will be limited and difficult.

Is the introduction of new vaccines a priority?

1. The current disease objectives to eradicate polio, control measles and eliminate neonatal tetanus are underfunded. In today's funding environment and with these competing goals should national immunization programmes be burdened with adding new vaccines as well?
2. New vaccines are very expensive compared to the "old" EPI vaccines. Is it "worth" the money?

Workshop discussion

New vaccines are a priority: *The World Development Report* clearly states that immunization is one of the most cost-effective health interventions available. Every country should have a basic package of immunization for infants. The *WDR* showed the high cost-effectiveness was not only for the existing vaccines, but also for adding a new vaccine against the disease of hepatitis B, and for increasing overall delivery level to reach 90% of the population.


Deaths[1] from potentially vaccine preventable diseases
"EPI" Diseases (10 million)
% prevented
Smallpox
Polio [1]
Diphtheria
Pertussis
Measles
NNT
Hepatitis B
Tuberculosis
Yellow Fever
Rotavirus (0.9)
Diarrhoeas and Enteric Fevers
S. pneumoniae (1.2)
Acute Respiratory Infections
Malaria
Other Parasites
HIV/STD
Dengue/JE
Deaths 5.0 0.8 0.1 1.0 2.7 1.2 1.2 3.0 0.03 3.0 3.8 2.0 1.0 0.9 0.05
Deaths in the absence of immunization (millions)
[1] Lifetime disability.

It was pointed out that WHO/GPV had just developed its strategic plan and the objective to introduce new priority vaccines more rapidly was one of its top goals.

The group all agreed that the most important activity to promote the introduction of new vaccines was increased ADVOCACY. Governments, donors and technical agencies needed more information presented in a more compelling way to raise the priority of these vaccines. The workshop recommended that more attention be given to advocacy and to cost-effectiveness analysis .

If introducing new vaccines is a priority, which countries should be supported?

1. Defining the neediest countries

UNICEF, WHO and an increasing number of governments and donors have adopted a Vaccine Support Strategy (see annex 1) which separates countries that require continued financial support from those who are or could be self-reliant. Dividing countries based on their ability to be self-sufficient allowed these agencies to set sustainability targets in accord with government financial strength, develop a menu of support mechanisms targeted at the needs of the country, and coordinate limited donor support to "fill gaps" rather than substitute for government ownership.

2. Defining target levels of government financing

Countries comprising band A are assured of continued support for existing and new vaccines but must finance from 10-25% of their routine need. Countries in band B would be responsible for the cost of routine vaccines (80-100%) and would be provided some level of time limited support for new vaccines. For countries in bands C and D, aid for routine existing and new vaccines would be phased out quickly.

3. Increasing government financing of routine vaccines—achieving sustainable financing and supply

Using these levels of routine financing as a measure of country sustainability, roughly 25% of countries in band A are now fully or partly meeting their targets, compared to only 2% of countries in 1990. Roughly 70% of band B countries are currently in the process of meeting their targets, compared to 40% in 1990. Roughly 90% of countries in band C are financing their own vaccine supply versus 80% in 1990.

4. Defining priorities for donor support

Most of the financial burden of new vaccines will be the responsibility of the governments who wish to introduce the vaccines into their programmes. However, while countries in band C and D can access and afford the new vaccines, history has shown that the poorest countries, countries in band A and to some degree band B, will not be able to finance the new vaccines. History also shows that donors can not, will not and should not finance all new vaccines for all countries. Clearly, donor support should be targeted at the highest priorities—the introduction of priority vaccines for countries with the highest disease burden, strong immunization programmes, a commitment to their immunization programme and clear financial need. The following criteria have been set to identify the countries at highest priority for financial support of a new, priority vaccine:

- financial need (band A and for limited period band B);
- disease burden (e.g. for HepB vaccine countries where HBsAG> 5%);
- programme strength (e.g. countries where DTP3 coverage >70%);
- political will and programme sustainability (countries meeting or in first step of meeting sustainability financing targets for routine vaccines)
- Ministry of Health decision to include the vaccine.

Countries meeting these criteria are the highest priority for support. They have made the financial commitment to routine vaccines, they have the highest disease burden and strong programmes capable of supporting an additional vaccine.

Workshop discussion

The group felt the grid which separates countries into bands based on their ability to be self sufficient in vaccine financing is extremely useful. Donors in the workshop felt the grid would help their organization as well as other donors to identify and focus on the priority countries. They felt that the grid would increase coordination between donors and put spotlights on certain countries. It was felt that the grid should be updated every two years and regularly distributed to donors and agencies.

Although there was some discussion about the exact placing of the lines between bands, it was decided that the current definition of the graph was adequate. The grid did not need to be justified any longer and should be considered accepted. It was recommended that this grid and targeting strategy be an integral part of vaccine financing work.

The group agreed that the criteria outlined to identify priority countries were appropriate. They agreed that each criteria would need to be defined for each new vaccine. For example, the criteria of programme strength as defined by DTP3 coverage levels would be defined differently for different vaccines. Vaccines which would increase demand for immunization and thereby strengthen the programme should be introduced with low threshold levels of coverage. Vaccines which would burden the delivery structure, but not necessarily increase demand, should be introduced only in countries with high coverage levels.

Which vaccines should be supported?

Assuring the availability and use of new and improved vaccines capable of preventing millions of deaths is the ultimate objective. Two vaccines have already been recommended for inclusion in national immunization programmes by the World Health Assembly: hepatitis B and yellow fever vaccine. If these two vaccines—"old" products but the newest vaccines for national immunization programmes—cannot be introduced, what hope is there that the world will be able to introduce the next generation of vaccines? These vaccines are not only important for their ability to prevent millions of deaths, but they are the first in line to test the new supply and financing systems being established. If they cannot be introduced, the CVI call for new vaccines will be perceived as an empty objective which does not result in any real health impact. This will damage the credibility of the immunization community with governments and vaccine manufacturers and hurt our ability to access and introduce other vaccines down the line. As such, the procurement, financing and introduction of hepatitis B and yellow fever vaccines are the immediate priorities facing the immunization community.

The UNICEF 1996/97 tender has resulted in offers for hepatitis B and yellow fever vaccine for bands A and B countries at the best prices to date.

Workshop discussion

A group is needed to determine vaccine priorities looking at the full range of existing and potential vaccines. The immediate priorities, however, are hepatitis B and **yellow fever vaccine.**

How should the financing be structured to achieve the objectives of rapid introduction and sustainable supply of existing and new vaccines?

The group identified the following objectives for any vaccine financial structure:

- **Sustainable:** The financing must be for long term commitment;
- **Consistent with 5 year national plans:** The financing should be able to fill the gaps in the national plan for vaccine supply as the government gradually increases its national financing;
- **Promote upfront planning:** The financing should be dependent on upfront planning in which the internal and external financing is agreed to by the government . This plan should identify phase-in of government and phase-out of donors;
- **Assure timely release of funds:** The financing structure should release funds at agreed times so the vaccine supply is not interrupted. The financing structure may need to be independent of donor funding cycles;
- **Accountability!!!:** The financing structure needs to be transparent, with clear, agreed criteria for the release of funds;
- **Transparency:** The financing structure should be easily monitored;
- **Flexibility:** The financing structure should allow both tied and unspecified funds as there is a trade-off between donors providing funds because they feel confident the funds would only be used for a certain purpose, and the need for programming flexibility. The structure should also be able to respond to the different donor structures, requirements and funding cycles;
- **New funds:** The financing for new vaccines should be new funds rather than funds "stolen" or re-allocated from existing immunization or health programmes;
- **Minimize overhead charges:** The financing structure should minimize any overhead or management charges which would drain money from the purchase of new vaccines.

Ways to Raise Funds

The following ideas were proposed as ways to raise additional funds to support new vaccines

- UNICEF, CVI, WHO and manufacturers should approach donor governments to:
  - subsidize prices of vaccine provided to the neediest countries (i.e. tax break);
  - provide tax breaks on donations of vaccines by manufacturers.
- Issuance of CVI bonds underwritten by the World Bank.
- CVI sweepstakes to raise funds.

- Advocacy: success stories; illustrations of cost-effectiveness of immunization and cost-benefit arguments should be marshaled to raise the awareness of governments, donors, health professionals and the population at large.
- UNICEF should raise funds through its existing Supplementary Fund structure.

A study of how funds have been professionally raised by other groups should be made.

Financial Structure	Advantages	Disadvantages
Endowments	Self sustaining	Requires large sums of capital to remain untouched
Bilateral funds	Fits donor structures	Harder to coordinate
Vaccine Fund	Easy to target and coordinateCan be matched to national plans	Donor fears about accountability
Mixture of bilateral and Vaccine Fund	Flexibility for country and donor structures and needs	Need good coordination
Tiered pricing	Makes vaccine "affordable"	Requires trust between manufacturers and public sector
Cost Recovery/Cross subsidization in country (fee for adult, free to child...)	Allows governments to raise funds for infant immunization	Must be careful doesn't reduce demand for infant immunization.Must be careful it doesn't harm tiered pricing agreements
Sale of "Full" Product support	Way to provide additional support in epidemiology or cold chain management	Unclear if manufacturers have expertise or comparative advantage at providing these services

Summary of recommendations and conclusions

1. The targeting strategy (grid) grouping countries by ability to finance and ensure their vaccine supply is accepted and should GUIDE donor support for new vaccines.
2. Financing support for countries for specific new vaccines should be priorities based on the following criteria:
   - Priority vaccine/disease
   - Financial need (band A and B)
   - Programme impact (DTP3 coverage dependent on burden or demand builder)
   - Government commitment (national financing to sustainability target level)
3. Advocacy is critical for raising the priority of introducing new vaccines. Advocacy activities should be a top priority.

4. The procurement, financing and introduction of hepatitis B and yellow fever vaccines are the most immediate priorities facing the immunization community. The workshop recommended the establishment of a group to look at the full range of existing and potential vaccines in order to determine priorities amongst them, taking into account regional and national epidemiological differences.

5. Services and different forms of support should be provided to enable governments to take greater responsibility for vaccine financing.

   - Vaccine Independence Initiative
   - UNICEF procurement services for new vaccines for band A and B countries
   - Prioritized support to assure quality and reliability of locally produced vaccine

6. Support should be considered to help developing countries who must directly purchase new vaccines (band C and D countries) to achieve an affordable price

7. Every country should develop a national strategic plan outlining their vaccine demand, supply and financing.

8. The epidemiological capacity of countries should be strengthened so that countries know their disease burden and can determine the cost-effectiveness of introducing new vaccines.

9. UNICEF should utilize its relation with vaccine manufacturers and its procurement strategies to access new vaccines more quickly and at any affordable price for priority countries in bands A and B.

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