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GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION

SCIENTIFIC ADVISORY GROUP OF EXPERTS (SAGE)

Ad Hoc Meeting: 17 - 19 October, 1994

Geneva

WORLD HEALTH ORGANIZATION

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Cover picture: The last case of poliomyelitis in the Americas

OPENING

Welcome

Dr R.H. Henderson, Assistant Director General, welcomed participants to the meeting. He paid tribute to the late Dr Henrik Zoffmann, until recently Director of EPI, who had brought warmth and humour to the international immunization scene and who had concentrated in particular on developing surveillance in an integrated and dynamic manner.

Dr Henderson emphasized the importance of partnership, always a strong feature in the development of EPI, involving UNICEF and NGOs as well as many donor and developing country governments. More recently, the contribution of Rotary International, together with the technical inputs of the Centers for Disease Control and Prevention (CDC) and the support of various governments had enabled the prospect of polio eradication to become a reality. The Children's Vaccine Initiative (CVI) has now involved the World Bank, Rockefeller Foundation and UNDP in child immunization. The CVI also provided the impetus for restructuring WHO's vaccine related programmes.

Dr Henderson highlighted the levels of political and public health commitment that have made it possible for supplementary immunization, such as National Immunization Days (NIDs), to be widely conducted. Restricted vision of the potential scope of public health activity can be just as limiting as shortage of resources, he said.

Dr Henderson underlined the need for GPV to assure the quality of interventions, whether vaccine potency and quality, the cold chain, injection practices or laboratory procedures.

Future GPV Priorities

Dr J.W. Lee, Director of GPV, recalled WHO's greatest achievements in immunization: the global eradication of smallpox and the establishment of EPIs over two decades in every country in the world. The future of GPV rests on the strengths of efforts in surveillance and health infrastructure development. These tools will form a base for the expanded control of disease and the introduction of new vaccines.

Dr Lee outlined the priorities for GPV under his leadership, including:

* improving the performance of countries with low levels of immunization, with the emphasis on countries achieving less than 50% coverage;

* achieving the disease control targets set by the World Health Assembly and the World Summit for Children. Polio eradication is likely to be achieved on time, and while targets for neonatal tetanus elimination and for control of measles and hepatitis B may not be met on time, they will be met

eventually;

* creating better disease surveillance systems not just for the EPI diseases but for all diseases of importance for primary health care. This must be accompanied by an improved capacity to provide epidemiologic investigation and laboratory analysis;

* introducing new vaccines into EPI programmes in addition to the original six vaccines. GPV must provide advice to countries on the effective use of these vaccines;

* ensuring that adequate supplies of high quality vaccine are available wherever and whenever they are needed. Countries must be encouraged to move towards self- sufficiency in vaccine supply;

* developing new vaccines with an emphasis on the full continuum of vaccine development from research through licensing, production and distribution to use by national programmes.

Donor Partnerships in Immunization

In her Keynote Address, **Ms Ann Kern** highlighted the increasing competition for aid, emphasizing the need for scientists to view donors as equal partners. It was essential to forge a closer alliance with the broad donor community, comprising not only government aid representatives but also international agencies, bilateral donors, developing countries (the all-too-often forgotten contributors to immunization), NGOs and national committees. While it was important to contact the highest levels of government or agencies, she also underlined the importance of establishing good communication with desk officers within the agencies concerned, especially the aid agencies.

Ms Kern noted the particular concern of donors that three of their stated priorities had not been adequately reflected in EPI programmes and that this threatened the future of funding support. The three priorities were: ensuring sustainability of immunization programmes at country level; greater involvement of recipient countries in programme planning and management; and further integration of immunization within the broader health services.

In addition, the integration of CVI and GPV had been an issue of considerable concern at recent meetings of the donor community. However, consultations on the final structure and arrangements for the integration were continuing in an increasingly positive atmosphere. Since there appeared to be general agreement that SAGE should provide the scientific advice to both CVI and GPV, it might play a constructive role in helping to reassure donors about the value of the integrated approach. However, Ms Kern cautioned against assuming that the CVI/GPV integration had been effected until all the necessary details had been worked out and the promised consultations had taken place.

SESSION I: UPDATE ON IMMUNIZATION PROGRAMME IMPLEMENTATION

Disease Reduction Efforts

Progress towards global eradication of polio

The eradication of polio will be considered to have been achieved when wild poliovirus transmission has been interrupted and no wild poliovirus can be found, despite intensive efforts to do so. The strategies recommended by WHO for polio eradication are:

* routine immunization with high levels of coverage in all countries;
* national immunization days in all polio endemic countries for a period of several years;
* intensive surveillance for acute flaccid paralysis utilizing a global network of certified virology laboratories;
* outbreak response immunization;
* mopping-up immunization in the final, localized reservoirs of wild poliovirus transmission.

As a result of these strategies, the number of reported polio cases fell below 10,000 for the first time in 1993 and more than 143 countries are now reporting zero cases of polio. Six emerging polio-free zones have been identified: the Americas, where eradication was certified in September 1994; Western and Central Europe; North Africa; Southern and East Africa; The Middle East and the Arabian Peninsula; and the Western Pacific. Significant progress has been achieved in China where more than 80 million children were immunized in the first full NID in the winter of 1993-1994. As a result, only one case of wild poliovirus infection has been confirmed so far in 1994. Obstacles to polio eradication include: shortage of funds for vaccine purchase, laboratories, logistics, and personnel; insufficient political commitment; falling immunization coverage; and the damaging effect of political unrest in some countries.

The priorities for polio eradication in 1995 include: achieving eradication in the Western Pacific Region in 1995; activating polio eradication strategies in the countries of the Indian subcontinent, which account for two thirds of the world's polio cases; coordinated, multinational NIDs in contiguous countries of Central Asia, the Caucasus and the Middle East; and advocacy to boost political commitment and raise funds. The year 2000 target implies that all countries must be operational by 1997. Building the foundation for eradication in the African Region is crucial and is needed as soon as possible if the global target is to be met on time.

Measles

The effort to control and eventually eradicate measles is one of the most exciting but also one of the most challenging public health projects ever, with the potential to affect millions of young lives each year. Measles control will advance over the next few years by:

* ensuring that political support and financial resources are made available to achieve the mid-decade goals and beyond;

* pressing for high, uniform measles immunization coverage in every country, district and community;

* ensuring that the highest risk individuals are properly immunized;

* supplementing routine immunization by selective urban or national immunization campaigns;

* providing a technical basis for programme managers to respond to outbreaks in an appropriate manner (involving mainly situation analysis and communication efforts rather than supplementary immunization activities);

* progressing in a phased manner, as resources permit, to eliminate measles from countries, sub-Regions and eventually from Regions of the world;

* ensuring appropriate field and bench research is undertaken to provide the proper tools and strategies for measles control in the future.

SAGE concluded that many steps need to be taken before it would be in a position to recommend that the already adopted goals for the global eradication of measles should be adopted as internal planning goals. A question mark was raised over whether addressing the treatment of measles (through support to the "Sick Child" initiative) was a diversion of resources away from prevention.

Elimination of Neonatal Tetanus by 1995

The target set and endorsed by the previous Global Advisory Group for EPI in 1993 is less than one case of neonatal tetanus (NT) per 1,000 live births in every district of the world. Neonatal tetanus will then be considered to be eliminated as a major public health problem and less than 150,000 cases are expected to occur annually worldwide if the achievements are maintained.

It is estimated that in 1993 over 700,000 deaths from neonatal tetanus were prevented as a result of maternal immunization and other interventions. However, about 480,000 (70%) of these deaths were prevented in only 3 countries: India, Bangladesh and Indonesia. Meanwhile, 91 developing countries already have an estimated rate of

neonatal tetanus of below 1 per 1000 live births nationwide. Of these, 50 countries may have already achieved the target by district.

The recommended strategies to eliminate neonatal tetanus are:

* routine immunization of pregnant women with at least two doses of tetanus toxoid;

* identification of high risk areas and immunization of women of child-bearing age;

* promotion and use of clean delivery practices through provision of health education and trained birth attendants;

* effective surveillance to detect, investigate and reach every suspected case of neonatal tetanus reported.

Thailand and Egypt, among others, have been successful in demonstrating the effectiveness of these recommended strategies.

According to 1993 estimates, half a million deaths due to neonatal tetanus are still occurring worldwide, with 80% of these deaths in 12 countries. Out of 14 other countries where NT remains a major public health problem, 12 are in the African Region. Together these 26 countries contribute 90% of the global incidence of NT.

The main obstacles to achievement of the elimination target are:

* some priority countries remain uncommitted to the elimination of NT. However, China is to start immunizing women in high risk counties in the highest risk provinces;

* 20% of NT cases are occurring in countries with civil unrest. However, Afghanistan and Angola are to organize "Days of Tranquillity" to immunize women and children in 1994/95 and 1994 respectively;

* less than 10% of NT cases are reported. Community level surveillance is difficult. However, exceptional progress in being made in Indonesia;

* additional resources are needed to cover the cost of vaccines and logistic costs required to reach the high risk areas and provide intensive immunization. US$ 30 million would be enough to cover these needs and ensure the elimination of neonatal tetanus.

By 1995, major strides towards the elimination of NT can be made through immunizing in high-risk areas (including organizing Days of Tranquillity where necessary), provided there is sufficient political commitment and that US$ 30 million can be made available for use in the 26 priority countries.

Progress in the control of hepatitis B

Significant progress has been made over the past year in the control of hepatitis B. There has been renewed commitment from the GPV towards control of hepatitis B and the disease has been further integrated into the EPI with the assignment of a technical staff member.

* Approximately 73 countries (up from 50 countries a year ago and from 22 countries in 1991) now have a national policy of routine childhood immunization with hepatitis B vaccine. Together these countries account for approximately 40% of the world's children and almost 60% of the world's HBV carriers. The majority of countries in the Western Pacific and Eastern Mediterranean Regions of WHO have HB vaccine integrated into their National Immunization Programmes.

* UNICF is moving towards the provsion of HB vaccine to targeted countries with the following characteristics: a low GNP per capita, dependence on donors for vaccine, a high prevalence of HBV carriers in the general population (more than 5%), strong immunization programmes (more than 70% coverage with DTP 3), and hepatitis B control as a high priority in the Ministry of Health. This policy will assist a number of countries in the African Region to obtain HB vaccine.

* The World Health Assembly has set a disease control target aimed at reducing the number of children becoming HB carriers by 80% by the year 2000. This would have profound implications for control of chronic liver disease and liver cancer for the next century.

* The 1993 World Development Report issued by the World Bank states that: "In most developing countries, such an EPI plus cluster (the six traditional antigens plus hepatitis B, yellow fever and certain nutritional supplements) in the first year of life would have the highest cost effectiveness of any health measure in the world today".

The potential of the EPI for better child health

It was noted that major progress had been made in reaching high global levels of immunization coverage, although achievements vary widely between Regions and countries as well as between areas within countries. The impact of this success on disease incidence has been marked. The burden of ill health, both for the EPI target diseases and for other causes of morbidity and mortality is, almost certainly, higher in children not being immunized than among those who are.

The major contribution EPI can make to the development of better child health is to extend effective immunization services to those children not yet fully immunized and to

communities that are either under-served by health services or are under-using existing facilities.

There is no apparent justification, at this time, for extending EPI policies outside immunization and surveillance. The prime objective of EPI policy should be to more completely accomplish and extend existing objectives.

With this principle in mind, the EPI priority strategies should be:

* to analyse and correct those factors resulting in persistent low performance, or slippage once high achievements have been made;

* development of effective disease surveillance, including creation of a supporting laboratory network and surveillance for adverse events following immunization;

* achievement of the defined disease reduction targets;

* development of information allowing the appropriate introduction of new vaccines and the provision of expert information on their use;

* assuring the quality of immunization by the development and use of safe immunization practices, especially those related to injection techniques.

SESSION 2: UPDATE ON GLOBAL VACCINE PRODUCTION, QUALITY CONTROL AND SUPPLY

The Vaccine Development and Introduction Continuum

Moving a vaccine candidate from a theoretical concept to a viable product follows certain key steps which can be described as a "vaccine continuum", comprising research, development, production and production quality assurance, marketing, use and evaluation. Although each stage of this process involves different participants - including industry, regulatory agencies, research institutions, and national agencies - the key decision of each is whether or not the vaccine candidate merits the next level of investment.

The new GPV structure, incorporating VRD, VSQ and EPI activities under one umbrella, has strengthened WHO's ability to support and accelerate the availability of new vaccines for use in developing countries. Joining research and development to supply mechanisms and use in immunization programmes bridges the gaps in development and marketing as well as creating the framework for a strong programme capable of coordinating and leading a vaccine through the entire continuum.

A key objective for GPV should be the identification of field needs and the promotion of vaccines to meet these needs. GPV should actively promote the development, production and rapid introduction of vaccines needed in the field rather than passively waiting to evaluate new vaccines as they become available on the basis of vaccine company response to industrialized country markets. The impact of GPV can be maximized by taking advantage of the complementary expertise in each unit and integrating activities along the vaccine development and introduction continuum.

These activities include:

* promoting research and providing forums for information exchange;
* supporting development and testing of vaccine candidates for licensure;
* finding mechanisms to address Intellectual Property Rights;
* providing market estimates;
* helping governments to assure funding for affordably priced vaccines;
* supporting programmes through identifying effective immunization strategies;
* developing training and addressing logistics systems;
* building capacity to define the epidemiology of each disease;

The GPV can and should provide concrete operational support throughout the vaccine development and introduction continuum. By coordinating and targeting the activities of VRD, VSQ and EPI, GPV can leverage its influence with vaccine companies and have a significant impact on their vaccine investment decisions. GPV can help realize the CVI and WHO goals of rapid availability and use of new and improved vaccines for the children who need them most, working towards the overall goal of expanding the prevention of infectious diseases.

Assuring Adequate Supplies of Quality Vaccines.

With the reorganization of WHO, a new unit for Vaccine Supply and Quality (VSQ) was created with a remit to:

* assure adequate qualities of high quality vaccine for national programmes

* increase national independence in the provision of vaccine through strategies directed towards more sustainable financing and procurement or production practices which suit each country's particular needs and ensure the best use of funds.

Studies by the CVI Task Force on Situation Analysis revealed that countries often fail to predict their vaccine needs and use vaccine inefficiently. The major obstacle to improved production is not poor equipment or facilities but lack of management skills. The key to improved quality is stronger national control authorities.

The VSQ is working to provide a series of tools that will allow regional and country offices to address the problems of supply and poor quality. These tools include

forecasting software, vaccine vial monitors, guidelines on National Plans and financing mechanisms such as the Vaccine Independence Initiative. Work in progress includes a focus on a targeting strategy directing donations of vaccine to those most in need, while supporting self-sufficiency efforts in those countries able to become independent; establishment of networks to share technical data; and a standardized approach for all producing countries to ensure that they receive appropriate and consistent advice such as the distribution of WHO GMP standards and the selection and briefing of production and QC consultants.

The major objectives of the Regional Plan of Action for achieving self-sufficiency in vaccine production and supply in the Western Pacific Region are:

* to strengthen local production and promote self-sufficiency in vaccine production in selected countries; and

* to strengthen national capabilities in vaccine quality control with the aim of achieving WHO recommended standards.

The major strategies are:

* to utilize existing expertise and centres of excellence within the Region;

* to make frequent visits by WHO staff, other experts and representatives from the donor community; and

* to organize inter-country training courses for national staff.

SAGE urged the countries that could afford to provide support for the Western Pacific efforts, notably Australia and Japan, to support this initiative.

In the South East Asia Region, vaccines are produced in Bangladesh, DPR Korea, India, Indonesia, Mongolia, Myanmar, and Thailand. At present, only measles vaccine (from one manufacturer in India) is being exported on a large scale. To date none of these vaccine producing countries, nor any of the other countries in the South East Asia Region (SEAR), have national control systems in place which can perform all the necessary functions for national control of quality for all vaccines being produced. The Regional Office thus proposes to focus initially on the strengthening of national control systems in all countries, relying for laboratory support on a group of centres of excellence, and collaborating in activities along the same lines as in the Western Pacific region. The strategic plan includes designation of a focal point, and assurance of adequate vaccines supplies, particularly for national immunization days. Indicators for meeting vaccine demand, quality, and self-financing by countries will be maintained and monitored to assess progress in implementation of the plan.

SAGE concluded that all regional initiatives for vaccine self-sufficiency should be given full support. The resources needed to implement the initiative should be sought from national, bilateral and multilateral agencies.

New Approaches to Quality Control

While high quality vaccines are desirable, the activities needed to ensure them are complex, requiring independent production, quality control, and quality assurance units at the manufacturing facility as well as an independent and competent National Control Authority (NCA). The NCA must perform six critical functions in countries producing vaccines: make decisions on the selection, source, and licensing of vaccines through a properly constituted system; review clinical data for assurance of vaccine efficacy; conduct lot-by-lot vaccine release based at minimum on protocol review; perform final product laboratory testing on vaccine lots; ensure through inspections that good manufacturing practice is being followed at the manufacturing facility; and administer a system of post-marketing surveillance for adverse events following immunization. Even countries receiving vaccines through UNICEF need to perform some of these critical functions. Inventories of the performance of these functions by selected vaccine producing countries indicates gaps in performance which need to be addressed.

GPV activities to promote availability of high quality vaccines are focused on three areas:

* strengthening local production by assessing capacity, quality and costs involved, and developing strategies which, on implementation, will improve the situation, particularly for countries producing DTP vaccines and eventually for new vaccines;

* assuring the quality of UNICEF vaccine supply, by assessing the manufacturers and the NCAs, testing samples, and responding to problems in the field;

* strengthening NCAs through conducting inventories of functions performed, developing training material and guidelines, and providing technical support to regional initiatives.

Funding exists for the first two of these activities, but not for the third. Additional funds will be necessary for implementation of strategies to improve production. Because of the number and scope of the activities involved, implementation of measures to strengthen production and quality control in individual countries is best done through regional initiatives such as SIREVA as described below.

Regional Network for Quality Control for Vaccines

The Network of Quality Control Laboratories in the Region of Latin American countries and the Caribbean Region is coordinated by SIREVA/PAHO. Initially, the Regional Network will comprise the National Control Authorities and National Quality Control Laboratories of DTP-producing countries (Argentina, Brazil, Chile, Colombia, Cuba, Ecuador, Mexico, Venezuela). At a later stage, other interested countries will be invited to take part.

The Network is expected to address the following key areas: harmonization of protocols and methodologies, registries and licenses; development and production of standard reagents and reference vaccines; organization of collaborative studies on new quality control techniques; validation of laboratory methodologies; development of programmes for scientific and technical exchange and training; implementation of a regional post-marketing surveillance system; control of all vaccines (traditional, new or improved) used in clinical research carried out in the Region; and maintenance of active ties with USFDA, NIBSC/UK and the Bureau of Biologics/Canada, as well as other international bodies that regulate biologicals.

SESSION 3: UPDATE ON RESEARCH AND DEVELOPMENT

SAGE was briefed on the criteria used to set up the strategic planning of the CVI and its "end to end" mission (from research to development, manufacturing, supply, distribution, immunization and evaluation). The medium-term objectives of the CVI are: ensuring a sustained supply of quality vaccines; product development and introduction in vaccination programmes; capacity building programmes; and global and regional supportive services to ensure the achievement of the CVI goals. The approaches of the CVI strategic plan include: regionalization; a focus on the needs of Africa; the need for improved economic analysis; multi-agency participation; and collaboration with industry.

Priorities for vaccine research and development, as defined at the last SAGE meeting (June 1994), involve three goals for GPV: the simplification of vaccination procedures, promotion and coordination in the development of new vaccines (which should broaden the potential impact of EPI), and the introduction of new vaccines into the Programme. There is a need for support for the development of new vaccines to help prevent some of the major infectious diseases, as well as to coordinate research and development activities within WHO and with national and international agencies, industry and the CVI. Over the past decade, more than ten new vaccines of interest to GPV have moved from the research stage to advanced development and four of them are now licensed.

Vaccine research and development priorities in developing countries include a particular emphasis on acute respiratory infections (such as pneumococcal pneumonia), measles, tuberculosis, malaria, dengue, typhoid, meningococcal meningitis, Japanese encephalitis and diarrhoeal diseases. The main problems in establishing vaccine production in developing countries include: infrastructure problems, lack of technical expertise, poor quality control and financial constraints. WHO approved protocols are important for setting up clinical trials for new vaccines.

SAGE concluded that:

* in spite of the modest budget available, VRD (and previously PVD) has been able to provide seed money for many important projects and to exert effective leverage;

* the CVI can play an important role in generating money for some of the GPV projects;

* there is a need to ensure private sector participation in GPV projects;

* there is a need for assistance from donors in defining strategies to increase the availability of funds for research.

SAGE discussed the advantages of using DTP as a basic vaccine combination for adding antigens such as Hib, IPV, HB and in the future, pneumococcus, typhoid, meningococcus, as well as others. As many as 75% of the world's children live in countries with local production of DTP and it may provide a good opportunity to involve these countries in the development of future vaccine combinations. Major benefits include: fewer visits for the child as well as savings in operational support and vaccination equipment. However, costs may be higher at the beginning of production, problems may arise over intellectual property rights and dual standards may be generated if some countries' local producers are unable to participate in making new combinations. As a first step in the strategy, the DTP production in developing countries should be improved. In addition, a series of workshops and meetings should be held to discuss issues such as: partnerships between developing countries and the major industrial producers; bulk procurement of some antigens; updated requirements for combinations; quality control and licensing; the definition of critical research issues, and the feasibility of using purer toxoids and acellular pertussis vaccine components.

The short term goals for improving DTP production include: the improvement of basic GMP and QA/QC; the improvement of purity; the harmonization of production and control; the use of consistent, good quality adjuvants; and the establishment of regional networks. Intermediate goals include the extensive use of acellular pertussis and highly purified mutant toxins and the preparation of new combination vaccines. The longer term goals should focus on the use of the newest technology applied to DTP: new delivery systems, alternative routes of delivery (such as oral vaccines) and completely purified components. It was pointed out that there were differences between private and public sector motivations for these efforts.

In a review of the role of GPV in upstream research, it was noted that the strength of GPV Steering Committees lies in: being able to identify and help to fill the gaps; coordinating vaccine research; using small amounts of funding as leverage for a number of important projects; and stimulating international scientific collaboration.

In the area of new adjuvants, GPV is commissioning research on the potential of polyphosphasene use for reducing the dose and cost of conjugate vaccines. Research will also be commissioned on the use of mucosal adjuvants and on nucleic acid vaccines as an example of the Programme's ability to incorporate and assess new approaches to vaccination using the latest technologies.

The microencapsulation of antigens to develop single-dose vaccines was reviewed. The problems encountered when developing this technology for single dose tetanus toxoid vaccines have been addressed and are now largely being solved. Meanwhile considerable progress has been made in efforts to develop diarrhoeal disease vaccines and excellent results are being obtained with new cholera and shigella vaccines. GPV is playing an essential role in setting up trials, with the participation of the international scientific community.

The role of GPV in field research was discussed, using the example of meningococcal A/C conjugate vaccines. The aim is to incorporate these vaccines into routine childhood immunization programmes in those areas at risk of epidemics. Key activities underway include the design of a strategic plan, organization of workshops as needed, utilization of Steering Committee expertise to conduct research and evaluation of the vaccine candidates, standardization of assays, and phase 1 and 2 trials and efficacy studies. Although field research is expensive, it is essential to evaluate the efficacy of the vaccine through randomized controlled trials. In order to incorporate vaccines into EPI, studies on vaccine effectiveness and marketing should be carried out in addition to epidemiological studies. Also highlighted was the importance of: ensuring input from EPI users on selection of disease priorities; epidemiological input in Steering Committees; and close cooperation with vaccine producers as well as with the quality control and supply unit of GPV.

REVIEW OF POLICIES, PRIORITIES AND STRATEGIES

A sub-group of SAGE reviewed the overall programme policies, priorities and strategies with special emphasis on issues relating to EPI; the conclusions and recommendations of that group, as modified and endorsed in plenary session are presented below.

Disease Reduction Targets

SAGE was in overall agreement with the objectives and policies being pursued to achieve the disease reduction targets for polio, neonatal tetanus, measles and hepatitis B. These diseases are sufficiently important to warrant their identification for targeted reduction separate from the rest of EPI. The activities required for the achievement of the established targets have the capacity both to increase immunization coverage levels and to extend the geographic range of immunization services. These targets help Governments to focus their aims and objectives for immunization on specific goals such as those involved in the disease reduction initiatives. However, there is a danger that, in focusing on a limited number of EPI diseases, those **not** targeted risk being forgotten. The as-yet uncontrolled occurrence of diphtheria in several countries highlights this particular problem. Moreover, there is little monitoring or surveillance and few control measures in place for pertussis and non-neonatal tetanus. SAGE was concerned that the lack of a target should not infer a lack of interest in diseases for which targets had not been set.

Disease Surveillance

There was unanimous agreement that effective disease surveillance was the crucial strategy in mounting a disease control programme such as the EPI. It is seen as critically important as a means of measuring what has been achieved and of identifying where problems persist and which groups should be targeted by future activities.

Surveillance should be a process that strengthens the whole of public health, providing information on a range of diseases, as well as other aspects of PHC. Once established, it should collect data that serves as the basis for modifying programmes in order to make them more effective. SAGE stressed that surveillance is an essential programme component, equally important as vaccination for polio eradication, neonatal tetanus elimination and measles control. Any system developed, while possibly based initially on a single disease, must have the capacity to be extended to cover other diseases and should move towards being an essential element of primary health care. Although creating effective surveillance does not necessarily entail a major investment of human and other resources at the outset, it is not easy to establish effective surveillance. One of the most effective ways of doing so is to designate officials or advisers to be responsible for its introduction and continued operation. The cost of implementing surveillance will increase significantly as it becomes progressively more active, directing activities to persisting disease foci.

Disease Control Strategies

SAGE accepted that polio can be globally eradicated by the year 2000. Its strategies are well established and remain relevant in their present definition. Failure to achieve the target will reflect a lack of political commitment and resources rather than inappropriate technical policies.

SAGE also accepted that the elimination of neonatal tetanus as a public health problem, defined as less than one case per 1,000 live births in each district, is also attainable. However, given the present level of resources and commitment, elimination is extremely unlikely to be achieved by the end of 1995. The Director General and the World Health Assembly should be made aware of this fact before the present target date is reached.

Measles remains a major threat to public health and there is no doubt of the immense benefits that will accrue once it is controlled. However, in view of measles epidemiology and the sub-optimal efficacy of existing vaccines in infants, the current morbidity reduction target is flawed. Experience has already shown that measles is extremely difficult to control, due to the infectiousness of the virus, and a sustained reduction in incidence to very low levels is unlikely in most countries, using current strategies.

Within the past year, strategic approaches to measles control have changed. New strategies involve the introduction, where appropriate, of programmes involving the mass

administration of vaccine to a wide age range of children over a short period of time. In the development of these policies, which appear appropriate for intensifying activities aimed at measles control, it is important that Governments are fully aware that the objective of mass campaigns in addition to routine services is to stop virus transmission and achieve virus eradication. SAGE urged that the GPV should closely follow the experience being gained in countries that have adopted the new measles control policies.

SAGE discussed the objectives and timing of the recommendations for universal immunization with HB vaccine. No concern was voiced over the policy for areas of intermediate and high endemicity of HBV infection. However, there was concern about the objective of the targets for areas of low endemicity, given the cost of hepatitis B vaccine and the advent of vaccines against other pathogens of importance in those areas. SAGE noted that more data are needed on implementation of HB immunization in countries which have added this vaccine to their national immunization programme.

Immunization Days

SAGE examined the role of immunization days and concluded that, whether offering single or multiple antigens, they can serve a valuable purpose in amplifying the services being offered through routine techniques.

When conducting immunization days, it is important to be clear about the objective, whether this is to raise immunization coverage or to interrupt virus transmission. It is also important to be aware of the need to develop "next-step" policies. Following mass immunization days, administering polio and measles vaccines, susceptibles will accumulate and, except in the case of single importations, the occurrence of cases will indicate virus transmission and potentially extensive epidemics. By the time the first cases are detected, it will almost certainly be too late to carry out effective containment. The strategy of intensive "mopping-up" immunization in high risk areas will minimize the risk of extensive disease transmission when diseases are reduced to focal areas or when transmission has apparently stopped.

Use of Human Resources

SAGE discussed whether it was a priority strategy to focus resources, including time and personnel, on improving immunization and targeting disease control in localities with low immunization coverage and high disease incidence. There was general agreement that this was a priority use of resources. The highest risk areas are those countries and areas with low coverage coupled with a high population density, followed by those with low coverage and a low population density. Many of these countries are in Africa and there is every justification in specifically targeting additional resources and effort to assisting countries in that Region/continent to overcome the various problems. However, four key considerations should be highlighted:

* Africa is not homogeneous and there are areas in the south, east and north with high achievements in both immunization and surveillance.

* Within those areas, polio is either occurring at low levels or appears to have already been eliminated. There is now full justification for establishing activities to extend these emerging polio-free zones into surrounding areas and countries.

* Many countries in the African Region started their EPI from a very low baseline, often with a poor infrastructure on which to build. Their achievements have been all the more praiseworthy in view of the obstacles already overcome.

* The major problems in provision of immunization services are concentrated in a small number of countries, including the three most populous and several affected by continuing civil unrest and war. In these countries, intensified and innovative strategies will be needed to produce satisfactory immunization coverage and disease reduction.

SAGE considered that priority should be given to extending the excellent programmes that already exist. Initially there should be a focus on low coverage/high population density countries, progressing to low coverage/low population density countries, where the problems of dealing with persistent disease transmission should be simpler.

Emphasis on Research and Vaccine Introduction

There was agreement on the need to look periodically at changes in the relative burden of different diseases. As vaccines become available against common diseases, such as those causing life-threatening diarrhoea, there will be a need to respond quickly and incorporate them into immunization schedules. The fact that such diseases contribute to a large percentage of disease burden is a justification for their priority introduction into immunization schedules in certain countries. However, the introduction of new vaccines should not threaten the sustainable funding for vaccines already in use.

Financial Resources

SAGE reviewed the persistent problem of inadequate resources to support all planned and desired activities. In future, there will be a need for planners to match the targets being set with both the strategies required and the resources likely to be available to implement them.

Experience has shown that countries themselves are the major source of funds and the one most likely to be sustained indefinitely. Once senior health planners and budget controllers have experienced the benefit and cost effectiveness of immunization, they are usually keen to invest national funds in sustaining EPI. Efforts should be made to ensure

that budget lines for vaccine purchase are included in national budgets.

It should be recognized that traditional development assistance donors can not be expected to meet increasing needs or even, in some cases, to maintain current levels of support to immunization programmes, due to financial constraints. With the forecast that development assistance is to be reduced for the first time, more imagination will be needed in seeking support and in identifying new sources of funding. Professional guidance on fundraising would be desirable. It is possible that the newly emerging industrialized countries may prove to be interested in supporting immunization in less developed countries.

Recommendations

1. GPV should give top priority to achievement of the disease reduction targets for polio, neonatal tetanus, measles and hepatitis B.

2. The policies being followed for polio eradication and neonatal tetanus elimination are confirmed as appropriate and should be pursued with every effort to implement the strategies required and to secure the resources needed to achieve success.

3. The success of polio eradication in the Western hemisphere, recently confirmed by an independent team of distinguished scientists, should act and be used as a stimulus for accelerated polio eradication in all other WHO Regions. As more Regions and countries become polio-free, the risk of importations into non-endemic countries will be progressively reduced.

4. The new strategic approach for the control and eventual elimination of measles should be introduced, as appropriate, in all Regions. GPV should ensure that the achievements of those countries conducting elimination activities are fully assessed and the lessons incorporated into global policies and strategies, so that the benefits can be shared.

5. The target dates presently established for reducing neonatal tetanus, measles and hepatitis B are unlikely to be achieved. The strategies established to reach these targets should be reviewed and, where necessary, adjusted to accommodate scientific needs and managerial realities.

6. The GPV should aim, as a key strategy, to encourage and support the development of immunization systems based on a sound health infrastructure. Developing systems to achieve high coverage and control target diseases should also strengthen that infrastructure.

7. The GPV should further seek to establish active disease surveillance as the key strategy for achieving the disease reduction targets. As surveillance is established it should be developed in a way that creates a sustainable system able to detect and monitor other communicable diseases and to function as an integral part of all public health systems.

8. The GPV should focus additional immunization and disease reduction activities in low performance countries. Countries with low coverage coupled with high population densities should receive priority support, followed by countries with low coverage and low population densities.

9. GPV should actively raise consciousness among policy makers, health care workers and the general community as to the risks associated with unsafe injection practices and the measures that can be taken to reduce these risks.

10. By 1995, a Plan of Action for Safe Injection Practices should be developed at the WHO Headquarters and Regional levels. Countries should develop a Safe Injection Plan of Action by 1997.

11. GPV should give priority to developing and extending its role of providing technical information and expertise on all matters relating to immunization and vaccines. This should include acting as a source of information and update on new vaccines and those being developed.

REVIEW OF THE SUBGROUP ON VACCINE SUPPLY AND QUALITY ISSUES

A sub-group of SAGE reviewed issues relating to vaccine supply and quality; the conclusions and recommendations of that group, as modified and endorsed in plenary session are presented below.

SAGE noted that the success of the GPV in preventing infectious diseases is dependent upon assuring an adequate supply of high quality vaccines. Systems must be in place to support not only today's vaccines but tomorrow's as well. A number of topics related to this goal were addressed.

The Role of GPV in Accelerating the Introduction of New Vaccines: Identifying Priorities and Mobilizing Resources.

Up till now, new vaccines have usually been introduced into worldwide programmes on an individual, piecemeal basis. Advocates of a specific vaccine have collected the data needed to support its introduction without any mechanism for deciding what priority that vaccine should have in relation to other new vaccines. SAGE concluded that GPV needs to play a critical role in a standardized, systematic evaluation of vaccines and vaccine candidates that could play a role in global immunization programmes. This evaluation should take into account: assessments of the health burden to be prevented; data needs that must be addressed, such as requirements for epidemiological studies; and feasibility

of development and implementation, as well as other considerations. The GPV, and its partners, need to be involved at an early stage in all aspects of the vaccine continuum in order to generate the support needed for funding of research, development, and eventual introduction of the new high-priority vaccines.

Standardized approaches have already been used to assess priorities for vaccine research and development. These include a methodology for setting vaccine development priorities developed by the U.S. Institute of Medicine (for the National Institutes of Health) and methodologies used by the CVI. The GPV must establish a mechanism to assess priorities and could review the above methodologies to determine if they are applicable and, if not, modify them or develop new ones. Multiple partners need to be brought into the evaluation process, including country representatives, manufacturers, (both public and private), donors and UN agencies, including WHO and UNICEF.

SAGE addressed resources needed by GPV *inter alia* for supply and quality assurance. It concluded that the donor "pool" supporting immunization activities needs to be expanded. At each SAGE meeting, GPV should report not only on funds raised but on the number of new donors added. In addition, countries must be encouraged to take financial responsibility for their immunization programmes instead of relying on an ever-shrinking pool of funds from international donor agencies. In the developed world, governments must be convinced that support of international vaccine programmes not only makes good sense from a humanitarian perspective, it also makes financial sense when diseases such as polio can be eradicated and vaccination stopped, or when the risk of importation is dramatically reduced.

In the developing world, many countries have the capacity to become vaccine self-sufficient. SAGE endorses the Global Plan for Vaccine Self-Sufficiency, which is designed to target external efforts to countries most in need and help others to cover their own vaccine needs either through procurement and/or production. "Donor dependence" syndrome must be stopped and every country should develop a long term national supply plan which includes the possibility of introducing new vaccines where appropriate.

Focusing of GPV Vaccine Supply Assistance and Activities

SAGE concluded that the Vaccine Self-Sufficiency Plan and the UNICEF Targeting Strategy adequately lay out the basis for providing vaccine supply assistance to countries. It also concluded that the highest priority for VSQ must be to assure adequate quantities of high quality, affordable vaccine. Supply is especially important to meet the disease eradication, elimination and reduction targets. VSQ should focus on mechanisms of supply to meet today's and tomorrow's vaccine needs. However, SAGE concluded that it is not the role of VSQ to manage day-to-day vaccine distribution or crises. That role should be played by UNICEF, the Regions, individual countries and the producers.

The Role of the CVI

SAGE holds the view that GPV and UNICEF should be in a position to take a lead role in the operational functions formerly performed by the CVI through its Task Forces and Product Development Groups. The operational gaps that the CVI identified should be increasingly filled by the reorganised GPV, which should then be the major technical body for vaccine development and introduction.

CVI would continue to play an important role in bringing together key partners to coordinate vaccine development and introduction, particularly working with the private sector, a role that UN agencies may not be able to fulfil so easily. The CVI approach of using the skills of many CVI supporters would continue to be an important way of working together to promote specific projects. In addition, CVI should highlight the advantages of new vaccines and take on a fundraising role.

The Role of GPV in the Quality Assurance of Vaccines used in the EPI

SAGE was particularly concerned that many of the vaccines in use today do not meet WHO standards. Sheer good luck and a lack of monitoring have probably prevented the reporting of more tragedies, such as those resulting from insufficiently potent tetanus toxoid which is used in several countries. Yet the need for quality control has not been understood beyond a small group of technical experts who are aware that the credibility of the entire programme is at stake. GPV has a responsibility to ensure that all countries, rich or poor, aim to use only vaccines of assured quality in their EPI.

SAGE concluded that GPV has a critical role to play in assuring worldwide vaccine quality and in promoting understanding of the importance of quality control among national governments, manufacturers and donors. It strongly endorsed the strategic plan for assuring vaccine quality with its 3 main components: strengthening local production; quality assurance for internationally supplied vaccines; and strengthening national control authorities.

The GPV needs to provide technical assistance to the Regions to support their plans for regional and country self sufficiency. These plans must include strengthening national capabilities for quality control and aiming for all vaccines to meet WHO standards as soon as practicable. Improvements in vaccine quality will probably require substantial increases in resources needed for local production. Strategies for obtaining these resources should be a key component of self-sufficiency plans.

SAGE concluded that quality control must be afforded a very high priority. The secretariat should determine the best means to develop political commitment and understanding of the importance of quality control.

Private Sector Collaboration in Reaching GPV/CVI Goals

The involvement of representatives from the private manufacturing sector in discussions on vaccine supply and quality is crucial since public health goals may differ from commercially directed goals. While too big a group to sit on the SAGE, they can be involved in subgroup discussions. Private sector representatives should also be brought into the process at regional and country levels as well.

Recommendations

1. In order to ensure that all countries have adequate quantities of the high quality vaccines needed to meet disease reduction targets as well as routine immunization needs the GPV should promote good planning at the country level and co-ordination at the regional and global level to ensure that a sufficient supply of vaccines is available and that funding exists for its purchase.

2. GPV should develop and implement a process to prioritize the development and introduction of new vaccines. This should be done according to a systematic method based on data which enable planners to assess the health benefits of a new vaccine, the cost of achieving them, as well as the availability of other interventions. Countries, donors, manufacturers, UNICEF, WHO and other CVI partners should be involved in this process. The prioritization process should be formalized and documented. GPV's role in pursuing identified priorities along the continuum should include:

* developing appropriate epidemiological data on disease burden
* providing advocacy for selected vaccines
* promoting partnerships between commercial and developing country manufacturers for shared production of new vaccines
* communication among all involved groups
* "marketing" the selected vaccines
* reaching consensus on equivalence of alternative vaccines so that a double standard does not exist for available vaccines.

3. The concept of targeting countries for donor assistance should be pursued. Since each country will have different needs, and thus will choose different ways to meet its objectives, the provision of external assistance should be based on a national vaccine supply plan which should detail long term strategies.

4. The regional plans for vaccine self-sufficiency and quality assurance should be pursued. An appropriate strategy is to make the best use of existing centres of excellence, building on these to strengthen infrastructure for vaccine research, production, and quality control, with the aim of meeting WHO standards. These regional plans will need financing from donor groups involved in the region, especially from bilateral donors, who can contribute both technical and financial resources.

5. New sources of funding are urgently needed to help finance the three major activities for improving quality control of vaccines: upgrading local production, assuring the quality of the international vaccine supply, and strengthening national control authorities.

6. While it is recognized that WHO cannot certify that vaccines meet WHO requirements (because this is the role of independent and competent national control authorities), WHO should play a role in facilitating inter-country networks which can strengthen the ability of individual national control authorities to assure the quality of vaccines produced within their borders.

7. An international roster of vaccine production and quality control consultants should be developed and coordinated by GPV to provide consistent advice to countries striving to strengthen local production and assure vaccine quality. GPV should ensure that these consultants are providing consistent and useful information to countries, through a briefing and debriefing system implemented at the global level.

8. Vaccine manufacturers should be involved throughout the process of vaccine research and development to meet developing country needs. They can be particularly helpful in providing a register of consultants with expertise in vaccine production technology available to help in production strengthening.

REPORT OF THE SUBGROUP ON VACCINE RESEARCH AND DEVELOPMENT

A sub-group of SAGE reviewed issues relating to vaccine research and development; the conclusions and recommendations of that group, as modified and endorsed in plenary session are presented below.

Review of GPV Steering Committee Activities

The work of three Steering Committees (SCs) was reviewed: the SC for Diarrhoeal Diseases, the SC for Encapsulated Bacteria and the SC for Acute Respiratory Viruses, including Measles. In aiming at the development of vaccines against specific diseases, each of these SCs has had to follow a similar process of defining research priorities in a work plan and identifying gaps in basic research. Important gaps for each SC were those areas which did not appear sufficiently attractive for development within the private sector. The SCs have bridged some of these critical gaps by providing seed funds for research projects (which often help attract substantial supplementary funding), by supporting development of a vaccine testing centre in Russia, and by direct investment in clinical trials in developing countries. Many high quality trials have already been

conducted in developing countries. WHO-facilitated vaccine trials are estimated to cost only a tenth as much as private sector trials.

It was noted that the vaccine development expertise and guidance provided through the GPV SCs is highly undervalued since it is mainly provided by volunteers. Moreover, WHO, the World Bank, UNICEF, and other United Nations agencies are collating substantial data from countries on the burden of vaccine-preventable disease and making this information freely available. These international public sector services provide the basis for defining future vaccine markets as well as facilitating the development of vaccines aimed at alleviating some of the major disease burdens in the developing countries. Further economic analysis of the cost-effectiveness of vaccines may prove helpful in "marketing" them to the public health sector

Over the past two years there have been several major breakthroughs in the development of vaccines being pursued by SCs, especially in vaccines against cholera, pneumococcal pneumonia, and meningococcal meningitis.

The SC working to develop a measles vaccine designed to protect children below the age of nine months is focusing on the immunological aspects of infection. A newly identified monkey model has enabled examination of important immunological determinants of measles infection. In addition, this SC has helped WHO to establish a bank of wild measles viruses and standardized reagents, essential tools for development of candidate measles vaccines over the next 3-4 years. SAGE is also cooperating with industry in the development of new simple diagnostic tests for measles, as requested by EPI for the improvement of disease surveillance.

Review of CVI Product Development Group (PDG) Activities

The PDGs have gained substantial experience in solving specific problems related to the involvement of industry in essential research. However, it was emphasized that each problem must be solved on a case-by-case basis. For example, the PDG working on a more heat-stable oral poliovirus vaccine (OPV) has collaborated with several private sector groups and institutions to test new stabilizers and to further develop the most promising one. In anticipation of the eventual introduction of a more heat stable OPV (once field trials have been successfully carried out), discussions have also been initiated between WHO, UNICEF and vaccine manufacturers.

Coordination of SC and PDG Activities

A matrix organization for coordinating the activities of the VRD SCs, former PDGs and other units (VSQ and EPI) within GPV was discussed. The new concept calls for the establishment of horizontally organized groups, tentatively identified as "Working Groups for Vaccine Research, Product Development, and Vaccine Introduction". These groups

would address strategy related to high priority vaccine candidates and would serve both CVI and GPV. It is envisaged that the Working Groups would incorporate the functions and terms of reference of the PDGs, allowing for input as needed from the SCs, other units and outside collaborators. The membership composition would be adapted to the specific needs of SAGE in the areas of research, vaccine scaling up and quality control, trials and eventual introduction into global immunization programmes.

Major Obstacles to Development and Delivery of Vaccines

A number of key issues were identified for successful vaccine development, including:

* the importance of liaison with research institutes and industry

* the need to identify resources for clinical and preclinical testing, as well as ensuring continued financial support for these activities

* the need for WHO to identify mechanisms for giving recognition to the work of others in the field of vaccine research

* the need to orchestrate the pace or timing of research efforts in order to ensure an orderly progression from basic research to clinical studies.

The review session succeeded in highlighting the major progress achieved in the development of many important vaccines, as well as orienting the follow-up discussions on collaboration with national research organizations and the private sector, intellectual property rights, quality control/standardization and priorities for research.

It was noted that the establishment and provision of standardized reagents and the development of standardized methods for measuring correlates of protection ensures internationally comparable research results and is an important contribution of WHO to vaccine development. Further work in this area is foreseen in GPV, especially with the establishment of a Vaccine Supply and Quality Control Unit. SAGE emphasized that the establishment of National Quality Assurance authorities can be expected to do much to open up further research opportunities.

Legal advice was sought on the issue of the lack of interest of the commercial sector when profits are not envisaged. The representative of the WHO Legal Counsel pointed out that the overriding priority of WHO is to assure that, once developed, a new vaccine is made available to the public sector in developing countries at the lowest possible price. For certain vaccines (especially vaccines for diseases where the burden falls almost exclusively on developing countries), WHO will need to invest sufficient funds to encourage industry to become interested in further product development. In some instances, intellectual property rights are retained by WHO, especially where multiple institutions have participated jointly in development of a product. These intellectual property rights may be licensed by WHO in order to assure preferential pricing for the

public sector in developing countries. While WHO and UNICEF are not able to guarantee any specific market, they are able to provide disease forecasts that may be of enormous value to industry in deciding whether to pursue particular avenues of research. It was clarified that, while WHO can accept donations from the private sector for research, it is WHO policy to avoid any conflict of interest.

Collaboration with the Private Sector

The representative of the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) outlined the private sector perspective on the development of vaccines. After 30-40 years during which there was little change in the constellation of vaccines available, there is now a general expectation that the situation will soon change. The next five years are expected to see changes resulting from investments in basic research, particularly in immunology and microbiology. There have been significant advances in the areas of oral immunization, mucosal immunity, adjuvants, as well as other technological innovations. However, this progress is being achieved at significant cost and in a commercial environment that is changing rapidly. The manufacture, quality control, and regulation of these new products represent an important challenge to the private sector and also to groups which regulate and use vaccines. Because costs for vaccine development have increased substantially, manufacturers are emphasizing the importance of setting priorities for future research investment. Efforts by the Children's Vaccine Initiative (CVI) to establish key priorities for research were acknowledged as very useful. The IFPMA representative identified four distinct categories of vaccine:

* existing vaccines which are in general use and for which intellectual property rights are no longer a factor. Availability of these vaccines depends on the accuracy of forecasted needs and on the level of funds provided for their purchase.

* existing, improved vaccines, not yet in use but which may eventually replace vaccines currently in use. The most promising improved vaccine candidate is acellular pertussis vaccine.

* new vaccine combinations for which a potential private market exists. These new combinations include hepatitis B-DTP vaccine and haemophilus influenza type B-DTP vaccine.

* vaccines with low market potential in the private sector, but high potential use in the public sector. These would include vaccines against diseases, such as malaria, which are mainly a problem in developing countries.

The IFPMA identified four areas of collaboration and interaction that would be beneficial. The first was the need for accurate epidemiological information to assist the private sector in identifying appropriate opportunities for future investment in research and development. Second, the increasing costs associated with development of new vaccines

was cited as a particular problem for the industry. Assistance in conducting clinical trials would be helpful. Third, intellectual property rights should be protected in a way that allows for efficient introduction of new vaccines. Finally, although two-tiered pricing was identified as an essential element in the development of new vaccines, it was agreed that this does not address the pressing need for vaccines in the fourth category. The IFPMA representative warned that the increasing costs of vaccine development would result in higher prices in the future. An example of this is the likely pricing of acellular pertussis vaccine.

The Role of Developing Countries in Research and Development

In keeping with the WHO mandate to serve the interests of all member states, it is important that developing countries be represented on all SCs. This will help facilitate the movement of vaccines from the laboratory to the field. Substantial experience already gained in conducting field trials in developing countries should be tapped. The developing countries emphasized the coordinating role of GPV in this area, as WHO is seen as a trusted partner in enabling such trials to be carried out.

The EPI has helped countries develop epidemiological skills that are helping to define the burden of vaccine preventable diseases, but further efforts should be encouraged in assessing the impact of diseases for which new vaccines are imminent. Mechanisms should be developed for the GPV Regional Advisers to convey the research needs and priorities of the countries in their regions. Their collective experience is a valuable resource in the development of future GPV research priorities. Priority setting exercises were encouraged to be certain that the research needs of basic science, quality control, and the developing countries were being appropriately addressed within the new GPV.

Increasing developing country expertise in basic research is a predictable future outcome which should not be underestimated. An excellent example of this is the development of tetravalent dengue vaccine in Thailand, in part through WHO support. The strengthening of the national control authority in Thailand, as well as the establishment of a vaccine trial centre in Bangkok were noted as important outcomes of the drive to succeed in development of this vaccine. Likewise, vaccine improvements have occurred in the laboratories of developing countries. The more heat stable yellow fever vaccine developed in Brazil is one good example.

Some governments - in particular the United States - have invested substantially in vaccine research. Some countries are funding domestic projects, while others are sponsoring research in developing countries, including field trials. Representatives of these governments cited the valuable role the GPV steering committees had played in helping them to participate in international networks of collaborative vaccine research. Some agencies - including USAID, the Ministère de la Coopération (France), the Japanese Agency for International Cooperation and the European Community - are already funding vaccine-related research in developing countries and would welcome the global priority setting guidance which WHO can provide as well as joint activities with

GPV.

In some cases vaccine manufacturing technology has been transferred from one developing country to another. The SIREVA network being developed in the Region of the Americas provides remarkable encouragement in this area.

Review of Existing GPV/CVI Priorities

While the priorities of GPV Steering Committees were considered reasonable, there was a need to integrate epidemiology and field research activities into the new GPV. For the Epidemiological experts should be included in the membership of Steering Committees and Product Development Groups involved in the development and introduction of new vaccines. Many aspects of vaccine research, development, and assessment require epidemiological expertise including : assessment of the disease burden, identification of risk factors for diseases, testing the efficacy and the effectiveness of vaccines in the field, post-marketing surveillance and special studies to provide early indicators of vaccine quality problems. Epidemiology will not only help guide vaccine development by identifying those infections of high priority, it will also inform the manufacturers of the likely size of potential markets, improve surveillance for adverse events and continue to document the important impact that vaccines have in preventing disease. Surveillance either through routine systems or through special studies will be necessary to provide the data to define the epidemiological burden. For some diseases, these data are not yet available and innovative methods may be needed to identify the true needs.

Improving quality control and vaccine standardization was also considered to be a high priority.This will hasten the development of expertise as well as leading to harmonization of standards and products.

Operational research remains a long term need for EPI programme managers and the EPI regional advisers have a key role to play in voicing this concern. In addition to providing information on current issues and concerns, field experience can provide guidance for future vaccine introduction. There is also a need for the active participation of GPV service delivery staff and for the involvement of vaccine quality control staff.

Coordination of Research with Other Funding Agencies

Interactions and collaborations with national agencies involved in vaccine development were identified as essential for future progress. Many of the organizations support a broad array of research and development activities, often using bilateral funding arrangements. The information and expertise within these agencies can be effectively tapped to help guide the development of vaccines according to international priorities, to assess progress and also identify options for the co-funding of initiatives.

The European Community representatives explained in detail the structure of their programme dealing with Biotechnology, which included vaccines for human use, veterinary use and specific vaccine for developing countries.

Recommendations

1. Existing VRD priorities for upstream research should be maintained, with the highest priority given to research into: diarrhoeal diseases, tuberculosis, meningococcal meningitis
and pneumococcal pneumonia, and new vaccination approaches (transdisease vaccinology).

2. The presentation of priorities for vaccine development and research, particularly to the donors, should be improved. A long-term strategic view, such as that articulated by the CVI, should be incorporated.

3. Support for field research, particularly epidemiological research, should become a priority. Since epidemiology can play a crucial role in vaccine research and development, epidemiological expertise should be fully represented within the proposed Working Groups.

4. Scientists from the developing world should be represented on the GPV advisory bodies and Working Groups in order to help define strategies for the introduction and use of new vaccines. Substantial experience already gained in conducting field trials in developing countries should be tapped.

5. A group should be established to consider vaccine standardization and quality control.

6. GPV should review international data on the problem of antigenic variation among hepatitis B viruses and on hepatitis B non-responders, with a view to informing future policy on the use of these vaccines.

7. A special focus should be placed on combination vaccines, particularly those vaccines that will involve the use of acellular pertussis antigens. Since other innovations, such as nucleic acid vaccines, are now actively being investigated, there is a need to address the special problems that may arise, not only in the research stage but also with the potential introduction into use of such vaccines.

CLOSING PLENARY SESSION

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Remarks of the Director General

The Director-General welcomed the members of SAGE and expressed his gratitude at their willingness to devote time to advising the Organization. The host of questions that had been posed to SAGE indicated that the reorganized GPV stood at a cross-roads. The advice of SAGE was crucial and would be thoroughly taken into account by the Secretariat and by WHO's policy making bodies.

The Director-General highlighted four areas which underlined the importance and immediacy of issues brought before SAGE. Firstly, advice was being sought on ways of improving disease surveillance. Surveillance was of key importance because of the need to track re-emerging diseases, such as cholera, diphtheria, tuberculosis and plague and because good surveillance systems strengthen primary health care in general. However, strengthening surveillance was difficult to achieve, especially in countries where conflicts have resulted in disruptive migrations, such as those between Rwanda and Zaire. SAGE's advice would therefore be particularly useful.

Secondly, the need to ensure the quality of vaccines was also an important but complex issue. The Director-General re-emphasized his personal commitment to finding ways of ensuring that the world's children received vaccines of assured quality - both today's vaccines and those of the future.

Thirdly, there was also a need to find ways of building partnerships with vaccine producers. Finally, the Director-General emphasized that priorities for disease prevention needed to be established and that over the course of time SAGE would be helpful in advising on the distribution of resources.

Remarks of the Meeting Rapporteur

Dr D.A. Henderson noted the remarkable willingness of SAGE members with different perspectives to strive for consensus, as illustrated by the near unanimity on the recommendations. This consensus allowed him to avoid restating these and reflect historically on progress over the last 15-20 years that was evident in the reports made to SAGE. From the initial thinking about expanding immunization efforts in 1968 through the 1970s when coverage was below 20%, to the increased commitments in the early 1980s following Bellaggio, such as those of Rotary International, resources, efforts and coverage had increased dramatically to levels that were undreamed of 15-20 years ago. In parallel with this progress had come the recognition that targeted vaccine research and development would yield benefits, illustrated by the creation of the previous Programme on Vaccine Development and the Children's Summit launch of the Children's Vaccine Initiative. Developing new strategies brought further gains, including elimination of polio

in the Americas and its pending elimination in the Western Pacific, aided by remarkable efforts in China.

With all this in place - especially the routine delivery system - immunization was poised to make new gains. Collaboration and optimal use of resources were critical to achieving more. Collaboration must include the private sector, because of their unique skills and because not all vaccines are attractive commercial products that will automatically become available.

As overall rapporteur Dr D.A. Henderson wished to emphasize three important areas, where further consideration might be warranted:

* Polio eradication was important in itself and because, as had been shown in the Americas, it could serve to strengthen other immunization and health efforts,

* Surveillance was critical for setting priorities and assessing progress. However, it was often embarked on later than was desirable. It too served the broader purpose of increasing general health system capability.

* Vaccine quality control was important because it was ineffective to use non-potent vaccines and ethically wrong to use vaccines unless their safety could be assured. Immunization programme and health system credibility would ultimately suffer if vaccine quality was not addressed.

Dr D.A. Henderson pointed to a complex but amazingly exciting decade ahead, with most new gains being achieved through collaborations, guided and supported by the mandated international organizations, such as WHO and UNICEF.

Remarks of the Director GPV

Dr Lee acknowledged the useful advice that SAGE has provided in a variety of areas including polio, surveillance and quality control strengthening. He also outlined the structure of GPV and its working relationship with CVI, which was still evolving. The overriding concern should be what arrangements best served the common goals of future progress in immunization and vaccine development. GPV's role, as a WHO programme, was clear. The CVI role was evolving but there seemed to be agreement that it would serve to promote consensus, advocacy, information exchange and dissemination. Each entity has an important role but some issues were still to be resolved, including the governance of CVI, the nature of its secretariat vis-a-vis GPV staff roles, and the need for coordination of product development and introduction across GPV units and with CVI partners.

Future Meetings

SAGE members made a number of suggestions to the Secretariat on ways of making future meetings more useful. These included: allocation of more time for sub-group meetings; pre-SAGE sub-group meetings; smaller working groups; fewer topics; preliminary work on draft position documents by the Secretariat, possibly with consultants, SAGE members, or working group assistance; and involvement of SAGE members in preparation of the agenda and discussion formats.

There was a general consensus that SAGE should concentrate on cross-cutting and strategic issues -- such as reviewing and, where necessary, updating the CVI strategic plan -- rather than tactical or technical details. It could also serve a role in monitoring the progress of the vaccine development/introduction working groups. It was also noted that it would be helpful if participants in the Meeting of Interested Parties could be briefed on or listen to some of the technical presentations and discussions.

It was also suggested that ways needed to be found to increase the involvement of vaccine companies and public sector vaccine manufacturers in the activities of SAGE and the GPV/CVI in general.

The weeks starting Monday 12 June and Monday 19 June 1995 were identified as possible dates for the next SAGE meeting. The final determination of the dates were left to the Secretariat, on the basis of participant availability.