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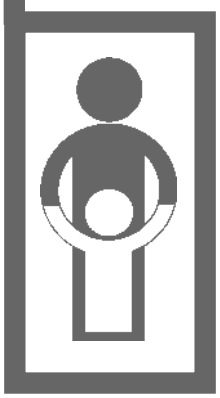
Consensus meeting on assessment and monitoring of vaccine-preventable diseases

Geneva, 27-29 October 2000



DEPARTMENT OF VACCINES AND BIOLOGICALS

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Glossary

AEFI	Adverse events following immunization
AFP	acute flaccid paralysis
CRS	congenital rubella syndrome
CVP	Bill and Melinda Gates Children's Vaccine Program
DHS	Demographic and health survey
EIP	Evidence and Information for Policy cluster of WHO
EMRO	Eastern Mediterranean Regional Office
GAVI	Global Alliance for Vaccine and Immunization
GTN	Global Training Network
Hib	*Haemophilus influenzae* type b
HIPC	the Heavily Indebted Poor Countries
IFA	Information for Action
MMR	measles, mumps, rubella
NT	neonatal tetanus
RSV	respiratory synctyial virus
SEARO	South East Asia Regional Office
SMO	Surveillance Medical Officer
TCG	Technical Consultative Group
UNICEF	United Nations Children's Fund
V&B	Vaccines and Biologicals
WER	Weekly Epidemiologic Report
WHA/WSC	World Health Assembly/World Summit for Children
WHO	World Health Organization
VPDs	Vaccine Preventable Diseases
WPRO	Western Pacific Regional Office

Executive summary

The general purpose of this meeting was to strengthen assessment and monitoring of vaccine preventable diseases. In particular, the aim was to build consensus and share information within the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) on issues related to monitoring and assessment, review progress since last years' meeting, increase efficiency of monitoring networks, and develop new strategies where needed. The meeting focused in three major areas: 1) strengthening monitoring of immunization safety; 2) assessment and monitoring related to new vaccine introduction (e.g. burden estimation, economic evaluation, surveillance related to new vaccines; strengthening the quality of immunization coverage estimates); and 3) ensuring effective surveillance/monitoring for accelerated disease control.

With regard to ensuring immunization safety, regional plans, progress and guidelines were reviewed, as were WHO/UNICEF initiatives and strategic plans. Several regions recounted immunization safety incidents in 1999 and their impact on national immunization systems. The need to link training in immunization safety monitoring to training in proper management of safety issues was emphasized. Proper monitoring/management includes rapid detection and investigation of immunization safety issues to identify any programmatic errors or vaccine problems, rapid corrective actions as needed, and effective communication with the public and media to maintain public confidence in immunizations. During 1999, training in immunization safety monitoring and management was initiated through the Global Training Network (GTN), regional workshops were held to develop country-specific action plans, and, in the Eastern Mediterranean Region, media training was initiated. Participants in such training included national immunization staff and national regulatory authorities. It is still too early to determine the impact of the training, although preliminary evidence from Egypt suggests more rapid detection and effective handling of safety issues subsequent to the training. Immunization campaigns represent an opportunity and urgency to initiate immunization safety monitoring. The number and rate of adverse events may increase due to the following factors: 1) a massive number of doses administered over a short time period; 2) health worker fatigue; 3) the fact that during a campaign many recently-trained volunteers may be giving injections. The latter two factors may increase the risk of programmatic error.

Assessment and monitoring related to new vaccine introduction includes the disease burden estimation, economic evaluation, surveillance and coverage monitoring. In all, 110 countries have introduced hepatitis B immunization into their routine system. However, there is still a great need to do so in African countries. Of the 110 countries, only 66 reported immunization coverage data to WHO in 1999.

Nearly half of all countries of the world have introduced rubella vaccine, and further guidance on rubella vaccine use is expected from a Vaccines and Biologicals (V&B) meeting scheduled for January 2000. Spectacular progress has been made in introducing *Haemophilus influenzae* type b (Hib) vaccine into the Americas, and pneumonia/meningitis surveillance has been initiated in many of these countries to assess impact. Several new assessment methods are available or in the pipeline including protocols to assess the disease burden due to congenital rubella syndrome (CRS), hepatitis B, Hib, pneumococcal disease, respiratory syncytial virus, and *Shigella*. WHO-sponsored burden studies are underway in several countries including six on Hib, five on respiratory syncytial virus, and one each on CRS and *Shigella*. Plans are to initiate additional burden studies on pneumococcal disease and congenital rubella syndrome during the next biennium. Economic evaluation of new vaccine introduction is a concurrent activity. WHO is developing practical tools to facilitate economic evaluations within countries, and technical support to promote the use of such tools.

Estimating the burden of disease related to new or classic vaccines is an ongoing process. The aim is to have estimates of morbidity, mortality and disability by country, age-group, and sex. The process involves developing estimation methods, documenting the assumptions of these methods (and the empirical basis for the assumptions), consulting with experts (on the disease, estimation methods, and country-specific issues), and subjecting the estimates to expert review. The process is on-going as new information will always be used to improve the estimates.

Immunization coverage is now the "centre-piece indicator" of the Global Alliance for Vaccine and Immunization (GAVI). However, the accuracy of immunization coverage figures in many countries is concerning. Moreover, immunization coverage is being used increasingly as a surrogate indicator of overall health sector performance, equity, access to primary health care, and health sector reform. A proposal has been written which outlines short-, medium- and long-term activities to improve the accuracy of coverage data. This includes the development of a time series of coverage "best estimates" using recognized elicitation methods, tools to document the monitoring system in terms of strengths and weaknesses, updated validation tools (e.g. cluster surveys, lot quality technique), and methods to improve estimates. The long-term approach includes country-specific problem-solving to deal with the underlying causes of poor data quality. GAVI has promised some seed money to begin addressing the short-term problems, and efforts are currently underway to identify funding for longer-term activities.

With regards to accelerated disease control, global and regional progress and plans related to measles monitoring were reviewed, including the development of the measles laboratory network. In addition, lessons were shared from the polio eradication initiative on how to effectively integrate laboratory activities and surveillance. An algorithm for monitoring neonatal tetanus elimination was proposed. Although complete consensus was not achieved, suggestions were made on how to improve the algorithm, and issues of validation of elimination status using a lot quality technique were discussed.

Finally, the process and content of the annual World Health Organization/United Nations Children's Fund (WHO/UNICEF) joint data collection activities were reviewed and consensus achieved on modifications, and the issue of quarterly reporting of supplemental immunization activities was discussed.

Recommendations on Part 1: Immunization safety monitoring/assessment

1a) More emphasis should be placed on safety issues in clinical trials. In the conduct of these trials, data monitoring boards should be staffed with persons with experience in the study of vaccine-related adverse events. There is recognition that rare events may not be detected during conventional clinical trials due to limitations of sample size and this underlines the need for enhanced post-marketing immunization safety monitoring.

1b) Better indicators on the monitoring and management of imunization safety concerns should be developed, and some of these should be integrated into joint WHO/UNICEF annual reporting process.

1c) Adverse events following immunization (AEFI) monitoring/surveillance should be renamed as "immunization safety" monitoring/surveillance, consistent with other more positively named activities (e.g. blood safety, food safety, drug safety, transport safety).

1d) Information on all vaccine ingredients should be included in the WHO publication: "International list on the availability of vaccines".

1e) Caution should be exercised when considering the recall of a vaccine due to an AEFI report. The implications of recall should be clearly communicated beforehand to international partners.

1f) The WHO/HQ document: "Supplementary information on adverse events following immunization" should be distributed to all national immunization staff and (national regulatory authorities) NRA directors.

1g) Mass campaigns should be used as an opportunity to implement immunization safety monitoring. Prior to mass campaigns, information on the expected rates of adverse events, and immunization safety monitoring should be part of planning and training at all levels.

1h) WHO/HQ should be informed in a timely manner by countries and Regional Offices on immunization safety concerns that might have international implications.

1i) WHO/HQ should issue timely official statements on emerging immunization safety issues to assist national immunization staff in pro-actively dealing with the issue.

1j) The media training material developed by HQ should be evaluated after its use in the Eastern Mediterranean Region and opportunities explored to offer the workshop to other Regions.

1k) Educational material on safe immunization, including safe injection practices and AEFIs should be prepared for and included in medical and paramedical undergraduate curricula and used for in-service training.

1l) Efforts should be made by WHO/national immunization staff to inform key media on general immunization safety issues.

1m) While prompt and thorough investigation of immunization safety concerns by national immunization staff is needed, an independent review by a national/international committee of experts should be conducted when:

- specific expertise is needed,
- increased credibility or neutrality are needed,
- the incident may have international implications, and
- there may be a potential "conflict of interest".

1n) Effective links should be established in all countries between national immunization staff, national vaccine regulatory authorities, as well as drug regulatory authorities.

1o) WHO, with its partners, should develop a bulletin on immunization safety.

Recommendations on Part 2: Assessment/monitoring related to new and under-utilised vaccines

2a) In the introduction of new and under-utilized vaccines, comprehensive plans should be developed considering the "whole" process, including vaccine costs, assessment of disease burden, development of surveillance, cold chain, logistics, and safety issues.

2b) WHO should prepare best practices guidelines on monitoring the impact of hepatitis B immunization, including the collection and analysis of serologic data.

2c) The approach to disease burden estimation proposed by the Department of Vaccines and Biologicals (WHO/HQ), that includes a consultative process with countries/regions, is endorsed and should be rapidly pursued.

2d) Disease burden and economic models, particularly those incorporating country data, should be used for prioritising the introduction of new and under-utilised vaccines.

2e) WHO/HQ should finalize protocols for economic evaluation of hepatitis B, Hib, and rubella vaccine introduction. All regions should prepare a prioritised list of diseases/countries for economic evaluation studies. Based on the prioritised list, country specific studies should be initiated during the year 2000.

2f) The HQ "Draft Proposal for a Two-Year Start-Up Project on Improving Immunization Coverage Data Quality" is endorsed, however, it should be expanded to also include disease burden estimation, economic evaluation and surveillance related to new vaccines. Staff should be allocated to regional offices to work in these areas. These staff should visit countries and find, research and analyse the currently available data.

2g) An extra "working" day should be added to regional or sub-regional immunization meetings to address issues related to improving estimates/data quality, including disease burden estimates, economic evaluation and immunization coverage data.

Recommendations on Part 3: Monitoring/surveillance for accelerated disease control

3a) A global minimum set of core variables for measles control should be developed through a consultative process with the Regions.

3b) Following the recommendation of last year's meeting, the global database on supplementary immunization including measles / vitamin A and polio, should be strengthened through the provision of country data (both retrospective and prospective) from Regions to HQ on at least a quarterly basis. A staff member from HQ should work on a periodic basis with regional office staff to maintain and update the database.

3c) The susceptibility modelling methodologies for measles used in EURO should be made available to other Regions, especially countries in the outbreak-prevention/elimination stage.

3d) In the analysis of coverage data, routine immunization coverage should not be confused with supplementary immunization coverage data.

3e) The time schedule presented for the annual joint reporting process should be followed (Annex 4). All Regional Offices should participate in the finalization of the joint form and efforts should be made to send the finalized joint form to countries in mid-February 2000 in synchrony with UNICEF. HQ should develop efficient methods for data entry/transfer at Regional and national levels.

3f) The proposed algorithm for neonatal tetanus elimination (Annex 5) may be applied to the 57 countries that have not eliminated or documented elimination; however, the existence of community-based surveillance should be included when assessing the reliability of surveillance in rural areas. Additional validation procedures should be considered to document whether the neonatal tetanus elimination goal has been achieved in these countries.

Opening, objectives, election of chairman and rapporteur

Mr Michel Zaffran opened the meeting on behalf of Dr. Bjorn Melgaard, director of the department of Vaccines & Biologicals (V&B). He described the three major objectives of V&B (promoting new innovations; strengthening routine immunization systems and accelerating disease control) and some recent developments in international immunization, such as formation of a Global Alliance on Vaccines and Immunization (GAVI). The overall global environment is currently favourable to meet the challenges related to the safety of immunization and measurement of immunization system impact. The general aim of this meeting was to strengthen assessment and monitoring of immunization systems. In particular, the aim was to build consensus and share information within WHO and UNICEF on issues related to monitoring and assessment, review progress based on recommendations made since the last meeting, increase efficiency of monitoring networks, and develop new strategies where needed. The meeting focused in three major areas: 1) Establishing the evidence-base needed to support new vaccine introduction; (e.g. burden estimation, economic evaluation, surveillance related to new vaccines); 2) Strengthening monitoring of immunization systems (e.g. improving estimates of coverage data; establishing immunization safety monitoring; strengthening district-level monitoring systems); and 3) Ensuring effective monitoring surveillance/ monitoring for accelerated disease control. Dr T. Gaafar was elected as chairman and Dr M. Hodge as rapporteur.

Part 1:
Monitoring/management of immunization safety

1.1 Review of regional progress, plans, and guidelines related to monitoring and management of immunization safety issues

Objective: to discuss how monitoring/management of immunization safety issues will be strengthened in regions, and review changes/progress since last year's meeting.

1.1.1 South-East Asia Region – Dr A Thapa

A cluster of three deaths associated with routine measles vaccine in an eastern district of Nepal was described. An investigation by UNICEF, local staff and a central team identified a programme error related to poor sterilization technique. In this episode the programme manager was made aware of the situation through the media and police as there were no official reports. This episode also highlighted the need for a coordinated investigation. The incident resulted in loss of immunization programme credibility and risks to local health workers.

In the absence of a regional/country plan, the issue of injection safety is inadequately addressed in South East Asia Regional Office (SEARO) countries. Strategies for SEARO include an inter-country workshop on injection safety planned for 2000 for which the assistance of HQ is requested. Inadequate staffing, focus on polio eradication and a lack of regional/country plans are major constraints. There are strategies to address these issues, including an inter-country workshop planned for 2000 for which the assistance of HQ is solicited.

Discussion on SEARO presentation

- The general problem of shortage of personnel for monitoring was noted and it was indicated that substantial progress had been made since last year's meeting in November 1998 by placing additional staff (or resources for additional staff) in the Eastern Mediterranean Regional Office (EMRO), European Regional Office (EURO), South-East Asia Regional Office (SEARO), Western Pacific Regional Office (WPRO), and in some country offices.

- It was reported that the programme in Nepal had recovered and that analysis of unopened vials had shown no problem with the vaccine. One of the primary aims of immunization safety monitoring is to prevent or rapidly address programmatic errors. When an adverse event following immunization occurs, attention is often focussed more on investigating the vaccine than programmatic practices. Nevertheless, there is a need to strengthen procurement systems and national regulatory authorities, and to ensure coordinated action between National Regulatory Authorities (NRAs) and immunization staff.
- The Chairman asked about WHO/HQ policy on vaccine quality and the prequalification procedure for vaccine producers. All this information is available on the WHO website.

1.1.2 Eastern Mediterranean Region – Dr F. Kamel

Several major recent episodes of AEFIs occurring in EMR were described. It was reported that 21 infants died in Yemen when insulin was given instead of DPT during routine immunization. An incident occurred in Egypt with 5 deaths unduly reported to be associated with DTP vaccination. In Jordan, an episode of mass hysteria related to school immunization with Td vaccine resulted in temporary cessation of the routine immunization programme.

As a response to these events, three planning workshops were held in coordination with WHO/HQ. All countries were represented at the workshops with the exception of Pakistan, Iraq, Somalia and Afghanistan. National immunization staff and NRA representatives participated in the workshops as well as the director of surveillance. UNICEF staff were also invited. Countries were committed to developing monitoring systems for immunization safety that are integrated with existing surveillance activities and strengthening NRAs. The outcomes of the workshops included the development of national plans with the specific objectives of early detection and timely action to rectify any programmatic errors, as well as to address media and public concerns. Forms, data management protocols, feedback procedures and training components were formulated. It was decided to establish expert committees for causality assessments. Indicators were set for monitoring and evaluation. Routine reporting, on a quarterly basis, by Member States to EMRO was also initiated. There are plans to follow-up countries with technical and financial support to ensure implementation of their plans. Two media training workshops were also held; experience from these workshops will be presented later.

Discussion on EMRO presentation

EMRO was congratulated on the progress made and the co-ordination with UNICEF. The need for countries to develop their own vaccine pre-qualification process was emphasized, so that local communities have confidence in the vaccines used in their areas. There was also discussion on the need to involve drug control authorities in the process of strengthening immunization safety monitoring.

1.1.3 Western Pacific Region – Dr Y. Sato

Regional immunization safety guidelines have been and prepared and distributed. Staff have been trained through the Global Training Network (GTN). Technical and financial assistance have been provided to countries from the regional level. The guidelines define regional objectives, provide case definitions for AEFIs, and describe the process on how to report/investigate and respond to AEFIs. Immunization safety guidelines also have been prepared in relation to pilot measles campaigns that will be conducted in Cambodia, Laos and Viet Nam. A pilot Immunization Safety Surveillance System is under development in the Philippines. An interesting initiative is the development by the government of the Philippines of a video on immunization safety monitoring.

A regional workshop is planned for the second quarter of 2000, in order to prepare National Immunization Safety Monitoring Plans, involving NRA staff and immunization staff, in co-ordination with WPRO and WHO/HQ.

1.1.4 Region of the Americas – Dr C. Castillo

An outline of policies used in AMRO for investigating and responding to AEFI was given. The importance of informing concerned parties about the results of AEFI investigations was highlighted. The process of responding to programmatic and vaccine related events was described. Steps for reporting of AEFI from the country level to AMRO were discussed and the need for good communication and training in this area was shown; the most important overall goal of these steps is to maintain public trust in the immunization programme.

1.1.5 European Region – Dr C. Roure

Injection safety has been identified as a priority in EURO but a major constraint is inadequate supplies of injection and sterilization equipment in some areas. The first Technical Consultation on hepatitis B virus (HBV) was organized by the Viral Hepatitis Prevention Board in September 1998 where the safety of hepatitis B vaccine was discussed, resulting in a press release, a Weekly Epidemiologic Report (WER) article and website information. This exercise was associated with good collaboration with WHO/HQ.

At the Programme Managers' Meeting in November 1998 the issue of the alleged relationship between measles, mumps, rubella (MMR) vaccine and autism was discussed. It is planned to undertake further regional discussion on monitoring methods for immunization safety. Vaccine safety issues are included in the regional plan; regional guidelines for the safe disposal of injection equipment will be developed. Most countries in the region have a National Regulatory Authority. It is aimed to ensure that all countries use vaccines that meet WHO-standards. Immunization safety monitoring should be integrated with existing surveillance activities. There is a need for workshops similar to the ones implemented in EMR.

Discussion on preceding presentations

- The Chairman acknowledged the good relationship between HQ and regional offices. He stated that there is a need to co-ordinate data collection.
- The need to evaluate training on AEFI and the overall cost of adverse outcomes to immunization were discussed.
- Vaccine-related incidents might be associated with the inherent characteristics of the vaccine/response of recipient or related to the specific characteristics of the vaccine-lot. The first response is usually immediate cessation of use of the vaccine.
- The Chairman reported that in EMR the planning workshops had greatly facilitated Immunization Safety Monitoring. Separate media workshops were held. It is still too early to evaluate the impact of the workshops.
- Most AEFIs are related to programme error, yet there is often political pressure to recall the incriminated vaccine. Therefore, one of the most important factors is rapid investigation and appropriate corrective actions before the credibility of immunizations is damaged.
- The Chairman noted that immunization safety monitoring was included in the planning and implementation of mass campaigns in EMR but that it was difficult to maintain interest in immunization safety monitoring for routine immunization.
- The institutional regulatory framework for vaccine quality and the need for credible, independent national authorities monitoring vaccine safety were discussed. It is difficult to interpret immunization safety data without knowing the characteristics and quality of the surveillance system. The incidence of febrile convulsions may be used to calibrate AEFI data from mass measles campaigns.
- It was stated that it is important to maintain good communication at all levels in AEFI investigation. It cannot be assumed that all countries have access to the internet for distribution of WHO policy and consideration should be given to this issue.
- Problems have been related to Vitamin A use in mass campaigns. Rumours of adverse events have prevented the inclusion of Vitamin A in mass campaigns in some areas. A proactive safety assessment protocol has been developed and used successfully in a mass campaign in India.

1.1.6 African Region

Very few countries in AFR are monitoring AEFI. One concern is that by highlighting the issue of AEFI there may be detrimental effects on the overall immunization programme. Mass campaigns are being conducted in many areas and there is a policy to include immunization safety monitoring and rapid response in these campaigns. Immunization safety monitoring for routine immunization activities is less well developed. A draft regional plan has been prepared and distributed for comments. There is a plan to strengthen the system for monitoring immunization safety at the regional level and there is strong support for this approach. There is a need for training at the regional managers meetings.

Additional discussion on regional progress

- It was recommended that questions related to injection site abscesses be included in cluster surveys, particularly in AFR.
- A monitoring system, in existence in Slovenia since the early 1960s with records by name and lot number was described. Feedback on analyses of the data to reporting units has been very helpful in strengthening the system. Official statements from WHO on adverse events and side effects are often very useful for national managers.
- It was recommended that the term "Immunization Safety Monitoring" (as opposed to adverse events monitoring), incorporating the role of injection safety and other areas of surveillance, is the best terminology. It is a positive term, without negative connotations when translated into other languages.
- In AFRO, training material is often only available in English, whereas there are also large training needs in many francophone countries.
- The issue of the "no-swab" policy for mass measles campaigns was discussed. The AFRO delegate considered that this policy might contribute to a significant proportion of adverse events.
- It was noted that there are four main causes of AEFIs: 1) cases where the vaccine is the true cause; 2) problems with storage or administration; 3) reactions due to patient characteristics; or 4) temporal associations of adverse events unrelated to the vaccine. Most AEFI are related to programmatic error. There is a need to concommitently strengthen immunization safety monitoring systems and skills to properly handle safety issues when they are detected.

1.2 Update and discussion on WHO/UNICEF initiatives and strategic plans related to immunization safety

Objective: Review progress since last year's meeting, new WHO/UNICEF initiatives, and strategic planning for immunization safety particularly as it relates to monitoring/management of AEFIs

1.2.1 WHO initiatives – Dr P. Duclos

There has been much activity in the area of assessment and monitoring for vaccine-preventable diseases. The aim is to develop a mechanism for the rapid detection of AEFI and a prompt and effective response to AEFI. A Global Advisory Committee on Vaccine Safety has been developed with provisions for the establishment of necessary specific ad hoc task forces, as recommended by the committee. The WHO Global Safety Advisory Committee includes members with expertise in paediatrics, immunology and molecular biology, epidemiology and pharmaco-epidemiology and adverse events. Technical assistance has been given to regions and countries, covering the implementation of reaction mechanisms, the development of training materials for national immunization staff and NRA staff. Major objectives are: 1) establishment of effective reaction mechanisms to AEFIs; 2) development of a comprehensive set of resource materials by the end of the year 2000; 3) Training of immunization and NRA staff from all countries on monitoring/management of AEFIs by the end of 2001. All NRAs should have access to an AEFI monitoring system by the end of 2002.

Tools are being developed to ensure vaccine safety from the time of clinical trials, to vaccine distribution, and to the point of use. It is aimed to ensure that the potential risks of new technologies, and up-to-date requirements on vaccine safety are readily available. Establishment of reporting tools, the monitoring of response to complaints from the field and the establishment of mechanisms to minimize programme errors, have also been given high priority.

Milestones will include establishment of a Task Force on Safety assessment of cell substrates by the end of 2000. Country level studies will be undertaken. Guidelines to assess the safe administration of vaccines and adequate destruction of injection equipment are under preparation.

Technical assistance has been given to regional offices and countries, including assistance with reviews and the development of guidelines. Revision, preparation and the publication of technical documents have been undertaken. Information has been placed on the web and background documents have been prepared. Review articles have been commissioned on AEFI, including reviews for hepatitis B and tetanus-diphtheria, and a special issue of the *WHO Bulletin* has been prepared. A Global Training Network curriculum on AEFI has been developed, together with media training. Collaboration with the drug monitoring program has been emphasised. Several conferences, including the World Vaccine Conference, have been used to raise awareness on vaccine monitoring. WHO/HQ intends to serve as the "global watchdog" for concerns with immunization safety with the establishment of email discussion groups.

For the future, there is a need for immunization safety assessments and development of better indicators to monitor progress.

1.2.2 UNICEF initiatives – Dr U. Kartoglu

There are many factors that influence the quality of immunization practices. After vaccine enters a country there are many human-operated systems that control the handling and use of vaccines. The following joint publications have been prepared: WHO/UNICEF Joint Policy on mass immunizations/selective campaigns – bundling, WHO/UNICEF Joint Policy on Immunization Injection Safety. This joint policy states that by the end of 2000, all countries using standard disposables should switch to auto-disable (AD) syringes. By the end of 2003 it is aimed that all countries use AD syringes. The successful implementation of this policy will depend on the effectiveness of technology transfer. It is also UNICEF policy that all supplementary immunization should use AD syringes, and all disposable syringe orders should be bundled with safety boxes. In addition, UNICEF funds will no longer be used to purchase standard disposable syringes.

In relation to human factors, in-service training workshops will be supported and "safe immunization practices principles" will be incorporated into the undergraduate curriculum. It is important to document immunization safety experiences in different parts of the world. A CARK Maternal and Child Health forum has appointed a working group on safe immunization practices with the cooperation of several partners.

Discussion

- The need for establishing priorities for African countries was raised. Despite the constraints and challenges in AFR, there is a need to develop immunization safety surveillance in Africa at this time.
- Concern was expressed that boards examining vaccine efficacy rarely include personnel with expertise on vaccine safety.
- The draft document: "Supplementary information on adverse events following information" was introduced and it was requested that comments on the document be returned within two weeks.
- It was noted that the introduction of new antigens into the routine immunization schedule of countries, including hepatitis B and Hemophilus influenza type B (Hib) vaccines, compounds difficulties related to immunization safety assessments.
- There has been little activity regarding the issue of compensation. Several studies have given insight into this issue as well as the perception of risk related to immunization.

1.3 Discussion on immunization safety monitoring targets (PAHO, WPRO)

Objective: Share regional experiences on what immunization safety monitoring/ management targets were set and how they will be achieved

1.3.1 PAHO – Dr H. Izurieta

The XIII (Technical Advisory Group) TAG meeting of PAHO addressed the issue of immunization safety and there has been an ongoing decentralization of management and expertise on immunization safety. Educational materials have been prepared for health workers and the public with the target of ensuring a quick and effective response to AEFIs. Advocacy for safe injections and dissemination of information have been given priority. Supervisory visits, surveys and program evaluations have also been undertaken.

1.3.2 Western Pacific Region – Dr M. Hodge

Regional guidelines on immunization safety have been developed and new personnel have been appointed in WPRO. Passive surveillance systems exist in many countries, including Australia and New Zealand. An immunization safety monitoring system is under development in the Philippines as an outcome of the mass campaign that was implemented in 1998. Immunization safety monitoring will be included in pilot measles mass campaigns in Cambodia, Laos and Viet Nam in 1999/2000. A regional meeting will be held in the first half of 2000, involving national immunization and NRA staff to plan for immunization safety monitoring in all countries of the region.

1.4 Training on post-marketing monitoring and management of immunization safety

Objective: Provide an update on the Global Training Network in terms of who is being trained, training materials/methods, and expected results

1.4.1 Global Training Network – J. Milstein

The Global Training Network was established in 1996 to provide a curriculum specifically for countries procuring vaccines directly. Countries procuring imported vaccines require sophisticated regulatory authorities. The University of Capetown conducts a course on immunization safety monitoring. The University also participates in the WHO international program for drug monitoring. Meetings have been held with Regional Office, the sub-Regional Office and the national immunization staff to develop a curriculum; this was also sent to expert review panels and regions for comments. NRA and immunization staff are trained together.

1.5 Media training – *J. Clements, T. Gaafar*

Objective: Provide an update on progress and discuss experiences about training in media management

The media-training workshop conducted in EMR focussed on pre-emptive action. The skills needed to properly deal with the media when dealing with immunization safety issues were transferred through two 3-day workshops called "partnership building with the media". Several skills were taught in the workshop including active listening, awareness of body language, presentation on camera, and giving a presentation on camera. The workshops were taught through a modular approach. Representatives were invited from the media for their comments. The second half of the workshop was region-specific. It is planned to follow-up the outcomes of the workshop with the participants, translate the workshop to other languages and conduct training in other regions, involving partners, such as UNICEF and the United States Agency for International Development (USAID).

Part 2:
Assessment/monitoring related to new and under-utilized vaccines

2.1 Assessment/monitoring related to new vaccines – *J. Wenger*

Objective: Provide a brief overview of future directions for monitoring and assessment particularly with regard to introduction of new vaccines and in particular review surveillance/monitoring for Hib

Vaccines for pneumococcal disease, respiratory syncytial virus, rotavirus, and shigella are currently under development. Development of HIV, TB and malaria vaccines are ongoing projects, but vaccines are not expected in the near future. The World Bank is considering new vaccine introduction in many country loans. The Bill and Melinda Gates Children's Vaccine Program (CVP), the Heavily Indebted Poor Countries (HIPC) Debt Relief Initiative and the Global Alliance for Vaccines and Immunization (GAVI) are other recent developments that may facilitate introduction of these more expensive vaccines. Evaluation of the efficacy of new candidate vaccines (e.g. pneumococcal vaccine, types A, B, C meningococcal vaccine, Japanese encephalitis vaccine) is ongoing in many developing countries. Other activities include: disease burden studies and development of burden estimation methods, economic evaluation of new vaccine introduction, evaluation of new supply and financing mechanisms and technical support for new vaccine introduction.

In assessing the burden of hepatitis B, projections are often made from available seroprevalence data. Despite several ongoing country-specific burden studies on Hib, burden data are still lacking from several regions of the world. Regions and countries need to make decisions based on the best available estimates of disease burden and cost effectiveness of vaccine introduction. HQ collaboration with regions and countries includes providing technical assistance for burden studies, burden estimation, economic evaluation, and surveillance/monitoring for diseases related to new vaccines. Surveillance for hepatitis B and Hib will require different approaches compared to what is currently done for diseases prevented by the classic vaccines; guidelines to assess the impact of Hib/HepB vaccines are under development. There is a need for feedback on the usefulness of WHO recommendations related to new vaccine introduction.

2.1.1 Experience from the Pan American Health Organization (PAHO) – assessment/monitoring for Hib disease

The impact of Hib vaccination in Uruguay and Chile was described. Uruguay vaccinated children <4 years, whereas Chile vaccinated children at 2, 4 and 6 months of age. In Chile the impact in terms of a reduction in morbidity took a longer time to be apparent than in Uruguay. By December 1999, 81% of countries in the Americas will have included Hib vaccine in their routine immunization system. Most countries are purchasing vaccine directly from manufacturers. A dramatic decline in the cost of Hib vaccine has been noted in recent years. In most national budgets in the Americas, there is a specific budget line for Hib vaccine. In Colombia and Mexico resources have been pooled from a number of different sources to pay for Hib vaccine.

The introduction of Hib vaccine has been very successful for several reasons: a strong regional immunization program, a high awareness of immunization in the region, the ready availability of safe and effective vaccines, and a very high awareness of meningitis amongst health professionals.

Uruguay and Chile introduced Hib vaccine as a model for the rest of the Region. With the introduction of Hib vaccine, surveillance must also be strengthened. Surveillance objectives include the need to determine the incidence of meningitis and pneumonia by specific pathogens. The model includes a network of sentinel hospitals.

Algorithms for case classification have been prepared, together with a process for evaluation of surveillance indicators. Training programmes have been developed, especially for "training of trainers". A computerised database has been established.

Countries introducing Hib vaccine are monitoring and reporting vaccine coverage and have noted substantial declines in the incidence of reported Hib invasive disease.

Discussion

- A concern was raised about the sustainability of new vaccine introduction. It is important to develop multi-year plans that implicate government resources to sustain the use of new vaccines which are generally more expensive.
- Surveillance for Hib in PAHO is being undertaken in sophisticated hospitals with good diagnostic resources. Nevertheless, there are challenges in standardizing interpretation of x-rays for diagnosis of Hib pneumonia.
- The use of combined vaccines is strongly recommended in PAHO.
- There is need to consider new vaccine introduction as a "package" which includes disease burden assessment, surveillance, training and supervision. Purchase of new vaccine is only one part of the introduction process.
- There are challenges in monitoring the impact of hepatitis B introduction, i.e. measurement of a reduction in the Hep B carrier rate. There is a need for baseline data on the carrier rate prior to vaccine introduction, so that impact can be assessed. A surrogate indicator of impact involves monitoring hepatitis B vaccine coverage which allows for an estimation of impact. An in-depth literature review is underway by WHO/HQ to document current seroprevalence data by country, and a simple tool to estimate impact is under development.

2.2 New monitoring/assessment methods in the pipeline: Report from the Steering Committee on Epidemiology and Field Research – *S. Robertson*

Objective: Discuss new monitoring/assessment methods, studies, and modelling that are pertinent to immunization strategies and activities being implemented in countries

2.2.1 V&B Steering Committee on Field Epidemiology and Field Research

The Steering Committee on Epidemiology and Field Research was established in 1995, and its members include epidemiologists specialized in different vaccine-preventable diseases, as well as epidemiologists/programme managers from each WHO Region who have demonstrated skills in conducting field research studies. They meet annually. Activities of this Steering Committee include:

- Development and production of population-based disease burden assessment protocols. To date, these have been completed (documents available on request) for congenital rubella syndrome (CRS), *Haemophilus influenzae* type B, respiratory synctyial virus (RSV), and *shigella*.
- Sponsorship and subsequent monitoring (including site visits) for country-specific disease burden studies, with particular emphasis on developing countries.
- Developing practical models of the epidemiology of certain vaccine-preventable diseases using demographic and serologic data.
- Conducting and/or sponsoring global reviews of the epidemiology of specific vaccine-preventable diseases. To date, these have been completed for CRS and rubella, diphtheria, mumps, pertussis, and yellow fever.

Disease burden data are essential to guide vaccine design, development, and introduction. Some existing vaccines are under-utilised in many countries due to insufficient burden data. A standard protocol on assessing Hib burden in children under 5 years of age (WHO/VRD/GEN/95.05) is available in English, French, and Russian, on request. Six population-based disease burden studies on Hib are underway using this protocol (in Bulgaria, Dominican Republic, Guatemala, India, Poland, and the Russian Federation. In addition, the Steering Committee has commissioned a global review of population-based data on the burden of Hib meningitis in children under 5 years of age. A generic protocol for assessing RSV disease burden (WHO/V&B/in press) is available; burden studies based on this protocol are underway in five countries (Guinea Bissau, Indonesia, Mozambique, Nigeria, South Africa). A generic protocol for assessing Shigella disease burden (WHO/V&B/99.26) is available; a field test of this protocol will be carried out in Viet Nam in 2000-2001.

New work is being undertaken in the area of rubella and congenital rubella syndrome (CRS). In 1996 about 30% of countries were using rubella vaccine. By 1999, almost 50% of countries were using rubella vaccine in their routine schedules, many without any appropriate monitoring of CRS risk/burden. Guidelines for the surveillance of congenital rubella syndrome and rubella (WHO/V&B/99.22) will

soon be available in English and French. One study on the CRS disease burden is underway in India; a request for proposals to conduct other studies on CRS disease burden has been announced, and the deadline for receipt of proposals in Geneva is February 2000. The final decision on which studies will receive funding will be taken at the meeting of the Steering Committee on Epidemiology and Field Research in May 2000. A modelling project is being conducted to examine the impact of private sector rubella vaccination on the incidence of CRS; this model will be linked with serological and demographic data from Brazil, Ethiopia, and India. A global meeting on preventing CRS will be held in WHO/HQ, 12-14 January 2000.

In addition, the Steering Committee on Epidemiology and Field Research maintains the V&B Vaccine Trial Registry, which tracks the studies supported by WHO. Several publications are available on the Vaccine Trial Registry, and an update is expected in 2000.

Discussion

- 80% of WHO-funded vaccine trials are being carried out in developing countries, particularly AFR.
- Regional resources should be linked, where possible, to the activities of the V&B Steering Committee on Epidemiology and Field Research.

2.3 Cost-effectiveness analysis for prioritizing new vaccine introduction – plans for working with the Regions/countries – *U. Kou*

Objective: Share the status of economic evaluation of hepatitis B, Hib and pneumococcal vaccines. Clarify the role/importance of economic evaluation of new vaccines. Outline HQ experiences and strategies for the future, including proposal for involvement of Regional Offices in economic evaluation.

The economic evaluation for new vaccine introduction involves comparative analyses of alternative courses of action, in terms of cost and consequences, in order to determine the most cost-effective way of delivering vaccines. This process facilitates optimization of limited resources and ensures that decision-making is based on knowledge of costs and benefits. It also strengthens the negotiation process related to resource allocation. CVI has developed a computerized model for rapid economic evaluation of new vaccines. WHO guidelines are also under preparation to conduct an economic evaluation of some new vaccines. The time required for such an evaluation in a country is ± 2 months.

There is recent experience with economic evaluation for hep B vaccine in the Gambia, Tanzania and Bolivia. Analyses have also been undertaken for Hib and pneumococcal vaccines. There are many constraints to conducting economic evaluation. These constraints are related to lack of skilled person-time and financial resources to support such evaluations New positions are being established in regional offices as focal points for new vaccine introduction.

Discussion

- In countries with resource constraints, it is important for the health priorities to be identified.
- The CVI model can be applied to any country of the world as an initial step. Working through the process is often helpful for country-level staff.
- Cost-effectiveness analyses are useful to feed (but not replace) the decision making process related to new vaccine introduction.
- Regional priorities related to "new" or "under-utilized" vaccines:
  - AFRO: hepatitis B, Hib, yellow fever, meningococcal meningitis, pneumococcal disease
  - PAHO: pneumococcal disease, respiratory syncytial virus
  - SEARO: hepatitis B, Hib, rubella, Japanese encephalitis
  - EURO: hepatitis B, Hib, rubella, mumps
  - EMRO: Hib, rubella, mumps
  - WPRO: hepatitis B, Hib, rubella, Japanese encephalitis

2.4 Strategic planning related to monitoring/assessment of vaccine-preventable diseases (VPDs) – presented by a representative from each WHO Region, WHO/HQ, UNICEF/HQ

Objective: to review plans, priorities, concerns related to surveillance/monitoring for VPDs particularly in the context of the Strategic Plans of each Region

2.4.1 South-East Asia Region

All 10 countries of the region are undertaking acute flaccid paralysis (AFP) surveillance. Bangladesh is the first country to implement integrated surveillance of AFP, measles and neonatal tetanus (NT). A system of surveillance medical officers has been introduced in Bangladesh. Only a single unit is responsible for surveillance at the Regional level. Data collection tools include Technical Consultative Group (TCG) tables and country reports, the Joint WHO/UNICEF monitoring form, donor reporting templates, etc. In Vaccines and Biologicals (VAB)/SEARO, databases are being developed, which include immunization coverage, survey coverage, and monitoring of VPDs. Linking of the Information for Action (IFA) software tool to Geographic Information System (GIS) tools and through GIS training, has strengthened data management. A weekly polio bulletin has been produced and a quarterly VAB/SEARO newsletter has been prepared. Constraints include a turnover of staff in VAB/SEARO and pressure on Surveillance Medical Officer (SMO) - based surveillance systems".

2.4.2 Region of the Americas

Routine measles vaccination coverage has been found to be lower than coverage achieved during campaigns. Priorities include assessing measles coverage by municipality, with at least 95% of municipalities reporting. For measles surveillance it is aimed to collect samples from every chain of transmission. Other goals include the development of a unified regional measles surveillance system and to integrate measles with rubella surveillance. A standardised reporting system (using the PAHO software called "MESS") will be used in most countries of the region by the year 2000.

The strategy for NT elimination is based on the identification of high-risk districts (in the attack phase or districts currently reporting cases and in the maintenance phase or districts recently reporting cases). Most countries are now administering Td. In 1998, 16 countries in the region were reporting NT cases. An important strategy is to identify silent areas.

With polio eradication the goal has been to achieve at least 1 AFP case report per 100,000 children under the age of fifteen years. The rate of two adequate stool sample collection is almost 80% on a regional level but this rate has declined slightly in recent years.

2.4.3 Eastern Mediterranean Region

All countries are collecting case-based data for AFP and some have started collecting case-based data for measles. Some countries have no routine surveillance system. Sometimes the data are not analysed or used for public health action. Another problem is a shortage of trained staff and communication constraints in some areas. The private sector is active in Member States and these providers are not always included in the surveillance system. Most countries are using the IFA software tool. There is a network of 12 polio labs. There is weekly reporting of AFP/polio case-based data, measles line lists, and aggregate counts of cases, and quarterly reporting of adverse events (as well as immediate reporting if a crisis situation). Nine countries report the line list as a hard copy. Twelve countries send data by email, two countries send by diskette and the remainder of countries send the data by fax.

The main problem related to AFP reporting is insufficient completeness and timeliness. This problem has improved considerably after introduction of email transmission of data. Another problem relates to unclean data. Data are presented on the EMRO website, including AFP/polio surveillance and laboratory data.

AFP, NT and measles surveillance was established in Afghanistan in 1997 through sentinel sites. In the future it is planned to ensure that regional computer systems are Year 2000 (Y2K) compliant. Assessment and strengthening of measles surveillance will continue, including measles case-based data. A campaign database will also be established.

2.4.4 European Region

Current priorities for the European Region include the re-emergence of epidemic-prone diseases and a limited capacity for surveillance at the national level in some countries. A new surveillance unit has been established in the Regional Office with the aim of providing information for advocacy and fund-raising. Specific targets have been set to meet EURO objectives. A WHO EURO website has been established. For vaccine-preventable disease monitoring the key product is to achieve high coverage with WHO-recommended antigens in all administrative areas. The key activity is to improve accuracy and timeliness of coverage data. It is also aimed to prepare guidelines for the use of coverage as a managerial tool for national program managers. Links are being fostered with the EU communicable diseases network.

The 51 countries of the European Region are reporting in different formats and these data are collated at the regional level. A regional computer-based information system has been developed for infectious disease surveillance, with the following objectives – automation of data entry and revision, ensuring the highest possible quality of data received, and presenting data in a meaningful way. The system allows for internet – based input. The AFP component of this system is well developed. Eight countries e.g. Spain, Italy, France, and Poland enter directly through the internet. Structures have been developed for measles, malaria and AIDS. A prototype system for measles should be operational by the end of the year.

2.4.5 African Region

Surveillance for vaccine-preventable diseases is carried out through an integrated surveillance unit in AFRO. AFP surveillance has been used to strengthen surveillance for other diseases. In most countries there are 5-10 surveillance officers active at the provincial level. Both disease surveillance and coverage data are being given priority. It is planned that resources be based at the regional level and uploaded to the HQ level. All immunization and lab managers are sending monthly AFP reports to the regional level via “sub-regional block” epidemiologists.

2.4.6 Western Pacific Region

AFP surveillance is being used in the Region as a platform to strengthen the surveillance of other vaccine-preventable diseases, particularly measles. In particular, active surveillance for AFP is now being extended to other vaccine-preventable diseases, and effective laboratory systems are also being developed for measles. By the end of 2000, integrated systems should be in place in all countries. Five-year plans to control vaccine-preventable diseases have been developed in many countries and a regional plan for accelerated measles control is being implemented, including the development of a national case-based surveillance system.

2.4.7 UNICEF

The World Summit of Children in 1990 set a number of goals to be met by the end of the decade. A major end-decade assessment will review the status of these goals through the use of "multi-indicator cluster surveys (MICS2)". Such surveys were also conducted at the mid-decade (called "MICS1"). MICS2 will assess a total of ± 75 indicators related to end-decade goals and should be completed by September 2000, with data processed and analysed (by DHS) by the beginning of the year 2001. MACRO (which conducts Demographic and Health Surveys) will be contracted for data processing. In all, 99 countries will undertake survey activity and 63 will assess immunization achievements. The overall cost of the end-decade surveys is estimated to be ±USD30 million, of which ±5 million is from UNICEF – mainly national UNICEF budgets.

2.5 Making/improving estimates of morbidity and mortality – a proposal – *C. Nelson, T. Burton*

Objective: As per recommendations from last year's meeting, propose and discuss the process of making morbidity/mortality estimates

2.5.1 Assessment and monitoring of VPDs – C. Nelson

New partners, including the GAVI, the World Bank and the Bill and Melinda Gates Children's Vaccine Program are asking for burden estimates and economic evaluation to prioritize among various immunization strategies and other public health interventions. Currently there is inadequate transparency and documentation of available burden estimates and economic analysis and many estimates are not directly comparable.

V&B in collaboration with the Evidence and Information for Policy (EIP) cluster of WHO will develop methods of estimation and develop draft burden estimates by country, age and sex. The process will include consultation of experts in the natural history of the disease, methods for estimation, and local knowledge. The methods, assumptions and empirical basis for the assumptions will be subject to expert review and involve a consultative process with the Regions and countries. Tools for burden estimation and economic evaluation will be made available for use in the field.

There are two general frameworks for developing burden estimates: 1) aggregation (e.g. incidence-based or natural history models) and 2) disaggregation (e.g. proportional morbidity/mortality models). Burden estimates will be made based on the best available information and then adjusted/improved with time as more/better information is available.

Discussion

If countries have good estimates, these should be used. Current disease burden estimates should be documented in such a way that they are transparent. WHO is under much pressure to rapidly produce disease burden estimates based on the best available information. Person-time is required in regional offices to collaborate with this work in order to ensure the best-available estimates. Much of the available data are available in the "grey" literature and regional level staff could play a critical role in collecting/analysing available such data during or following country visits.

Three major steps are involved in application of the process within Regions and countries:

- Applying standard methods in making preliminary estimates
- Distribution of these estimates to the country
- Movement of the methodology to the country level

This process has been started with neonatal tetanus. New vaccine target diseases will be addressed initially, including hep B and Hib. Measles will be analysed in the future.

2.6 Improving estimates of immunization coverage – *M. Birmingham*

Objective: Propose specific actions, both long and short term to improve immunization coverage estimates

The importance of immunization coverage data quality and proposed plans to improve these data were presented. Coverage will become the centrepiece indicator, particularly for GAVI. An analysis of reliability and consistency of coverage data showed a high proportion of missing data and outliers. There is evidence that both under-estimation and over-estimation of coverage is occurring. Partner agency funds are increasingly being tied to coverage data, as these data are being used to assess programme performance. The incomplete response to the indicator "proportion of districts achieving $\geq$ 80% coverage" on the 1999 joint UNICEF/WHO reporting form was alarming and suggested that many countries at the national level are not collecting/analysing district-level coverage data. Even if discrepancies of data (administrative versus survey) could be explained, this would be a positive step.

There is a plan to increasingly monitor data quality/accuracy, improve transparency in data reporting, and develop a "best estimate" time-series of immunization coverage. Tools and methods will be developed or updated. These include a tool for documenting the system (data collection/calculation procedures as well as the strengths/weaknesses of the system), methods for validation of coverage estimates (e.g. cluster survey methodology/lot quality technique), methods to improve the accuracy of estimates (e.g. imputation/elicitation methods), as well as supervisory "spot check tools". A proposal has been prepared to provide person-time in regional offices to work in this area.

Part 3:

Vaccine assessment and monitoring for accelerated disease control: focus on measles control/elimination

3.1 Global perspective on measles monitoring – *A.M. Henao*

Objective: Provide a global perspective on plans, priorities, progress in measles monitoring in relation to accelerated measles control/elimination efforts

Measles policy needs to be developed on the basis of epidemiological data. There is a move to use two phases for measles control/elimination: 1) measles control, and 2) outbreak prevention/measles elimination. Increasingly countries are implementing mass measles campaigns as part of a comprehensive strategy involving surveillance and routine immunization. It is aimed for countries to develop 3 – 5 year country plans. For evaluation of campaigns the following issues should be addressed: proportion of target population immunized, impact on measles morbidity, quality of service, strategy costs and major lessons learned.

Evaluation of the campaigns has shown that there is a need to work more in micro-planning. Development of a global database on supplementary immunization is necessary for forecasting of vaccine needs. A global measles laboratory network is under development and a WHO Measles Bulletin is published.

3.2 Regional perspectives on measles monitoring issues – Presented by a representative from each region

Objective: Provide a regional perspective on plans, priorities, progress in measles monitoring in relation to accelerated measles control/elimination efforts

3.2.1 African Region

Aggressive measles activity will not be carried out in Nigeria, Angola and the Democratic Republic of the Congo (DRC), so as not to compromize the global polio eradication effort. Model-based estimates indicate that there are about 9.3 million cases of measles/annum (375,341 cases reported i.e. about 4% reporting efficiency) in AFR. The World Health Assembly/World Summit for Children (WHA/WSC) goal is to achieve a 90% mortality decline and a 95% mortality decline to 2.1 million cases and 96,555 deaths. The model-based estimates used in the calculation are problematic for several reasons. They depend mostly on coverage and assumptions about case fatality rates, and do not account for supplemental immunization activities. With the current trend in coverage the WHA/WSC goals will not be achieved until 2012. There are several countries in the southern block of AFR that have measles elimination goals. Goals for measles surveillance include:

- Integrating active surveillance.
- Integrating district level outbreak investigation.
- Integrating measles surveillance sites.
- Developing a measles/YF lab network.

There is a need to improve the denominator data in assessment of routine immunization coverage. There is a need to consider the implications of using "compatible" and "probable" terminologies in the measles case classification system, particularly in the elimination setting.

3.2.2 Region of the Americas

More than 51% of measles cases reported in the region were from Bolivia. House-to-house campaigns were implemented in the main cities and active searches were conducted. Most cases in Brazil are being reported in the northeast. Surveillance in the Dominican Republic requires strengthening. Most outbreaks in the Region are among unvaccinated children under five years of age. In all, 27,122 suspected measles cases have been reported in the region this year. The genotype of current outbreaks is G6. Alternative denominators (BCG or DTP coverage) will be applied to routine coverage data. It is aimed to integrate measles and rubella surveillance. It is also aimed that priority countries will develop action plans, including Argentina (1999-2000), Bolivia (1999-2000) and Brazil (1999-2000), the Dominican Republic (1999-2000), Haiti (1999-2000). A national measles immunization campaign will be held in Nov.-Dec. 1999 in Bolivia.

3.2.3 Eastern Mediterranean Region

Major problems for measles relate to under-reporting and continuing outbreaks. The regional target is to eliminate measles by 2010. Planning workshops were conducted in September 1998. Measles "catch-up" campaigns have been conducted in several countries and further campaigns will be conducted through the year 2000. Case-based surveillance with laboratory investigation is active in several countries. There is very low routine coverage in Somalia and Afghanistan. Countries have been asked to identify high-risk areas and to implement supplemental immunization activities in these areas. Reviews of measles surveillance have been conducted in six countries. Follow-up meetings and surveillance workshops are planned.

3.2.4 European Region

It is aimed to eliminate indigenous measles from EUR by 2007. The aim is to reduce measles susceptible to low levels by 2005. In the strategic plan it is aimed to achieve high coverage with the first dose of measles vaccine, to introduce a second dose, either through routine or through supplementary immunization. It is aimed to achieve political commitment and to develop national plans based on local epidemiology. The regional level has also assisted countries in identifying the susceptibility status of their populations, which will help guide strategies.

3.2.5 South-East Asia Region

Countries in the region have been divided into two groups: those with highly endemic transmission and those with better immunization coverage and less-endemic transmission. The regional office has a draft strategic plan for measles. A new project entitled "Beyond Polio", involving: measles/vitamin A/injection safety has received funding from the regional level. Indonesia, Myanmar and Sri Lanka have linked measles surveillance to AFP surveillance. It is aimed that by 2000 all countries will have a long-term measles plan.

3.2.6 Western Pacific Region

A regional plan for accelerated measles control (1999-2003) has been developed. The overall aim is to introduce a second dose of measles vaccine, either through routine or supplementary immunization. Country surveillance systems are being developed for collection of case-based data for guidance of immunization policies. A regional laboratory network is under development, as well as a computerised regional database with core variables. Many countries in the region have implemented supplementary immunization campaigns including the Philippines, the Pacific Island countries, New Zealand, Australia and the Philippines. Pilot campaigns will be implemented in Cambodia, Laos and Viet Nam during 1999/2000. These campaigns will be monitored and evaluated and the lessons learnt will be used to guide strategies when campaigns are implemented at the national level in these countries.

Discussion on what needs to be standardized globally

Discussion focussed on the need for a standard set of core variables for use as a global measles initiative develops. Regions/countries may need to add to this core to meet Regional/national specificities.

3.3 Update on the global measles laboratory network – *D. Featherstone*

Objective: Share and discuss the global plan, priorities, and progress in establishing a measles laboratory network

In the control phase the major need is to determine the identity of circulating viruses. In the outbreak prevention/elimination phase, every outbreak should be laboratory confirmed. The laboratory's role is to monitor and verify virus transmission and monitor the susceptibility profile of the population. The measles lab network under development is being based on the polio lab network. There will be three tiers of labs: specialised labs, regional reference labs and national labs. National labs are selected along the same criteria as used for the polio lab network.

Standardised equipment and kits will be provided to some national labs from WHO resources. Training workshops are being implemented, including issues related to quality assurance and reporting/communication. Proficiency testing and an accreditation program will be developed. A draft global lab manual has been prepared. Transportation of specimens is an important issue, which is addressed in this manual.

A minimum sample of 100 micro-litres of serum is recommended for surveillance specimens. Urine samples for virus isolation need to be collected within 6 days of rash onset. Approximately 10 samples are required from each chain of transmission for virus isolation. An agreement for nomenclature has been prepared, similar to the nomenclature used for influenza. Two international strain banks have been developed.

3.4 Integrating laboratory activities with surveillance – lessons learned from the polio eradication initiative – *R. Sanders*

Objective: Provide insights on how to ensure good integration of laboratory activities with surveillance

A smaller network is easier to coordinate for quality control, information flow and support. Lab manuals help standardize procedures, use of reagents and also help to support an accreditation scheme. Surveillance should be integrated with the laboratory activities. Laboratory staff should be included in planning with regular meetings between lab and epidemiology staff. Group training is helpful. Establishment of a laboratory data system should be a priority (key variables/database structure/ data flow). Responsibilities should be assigned at every level. Clear channels of communication should be established.

The molecular epidemiology of wild poliovirus was discussed. Training materials for programme managers are being developed to help with the interpretation of dendrograms. There are increasing requests for case-based and summary information. Wild virus data are being used to identify geographic blocks. A data-exchange format has been developed.

3.5 Determining neonatal tetanus elimination – proposal for a standard algorithm – *M. Birmingham, M.A. Neill*

Objective: Develop consensus on a standard, yet operationally feasible and efficient algorithm to document neonatal tetanus elimination so that data are comparable by country and gathered in a standard way by both WHO and UNICEF

The World Health resolution for eliminating NT was set in 1988. NT elimination is an end-decade goal of the World Summit for Children and part of WHO 9th Programme of Work. There is a need to achieve consensus on how to document NT elimination.

An algorithm to determine NT elimination by district was presented and discussed. There may need to be an element of community-surveillance in the proposed algorithm; in Africa, cultural circumstances mean that many NT cases are not reported to health facilities. In most countries where this algorithm will be applied, the rate of clean deliveries will be <70%, and it may be applicable to delete the criterion related to clean deliveries. The algorithm proposed will not necessarily guarantee that NT incidence is truly less than 1/1000 in the community, but is a useful and standard way to document "programmatic" elimination and serves to focus additional efforts towards high-risk districts. Additional methods may be applied for validation of NT elimination, such as the lot quality technique and/or serologic surveys.

A finger stick method has been developed for NT serosurveys that has been applied in Burundi, the Central African Republic, and Haiti. Lot quality technique methods have been developed and applied in India and Indonesia.

The alternative is no standard way of documenting NT elimination. Recent experience has suggested that the "status quo" (i.e. no standard method for measuring NT elimination) is resulting in many countries underestimating their achievements with NT elimination.

3.6 Improving the process/content of data collected by WHO: Discussion about the past year's data collection experience and proposed modifications for next year

3.6.1 Annual data collection

It is proposed that next year's joint WHO/UNICEF reporting form follows the same schedule as 1999 (Annex 4). WPR was the timeliest region in submitting data received from the joint reporting exercise, whereas PAHO was the least timely and complete. Some inconsistencies were noted between the WHO and UNICEF forms at the country level. Data on indicators related to the immunization system were far more complete than those on new vaccine introduction.

3.6.2 Quarterly data collection on supplemental activities (particularly for polio, measles and vitamin A):

During the November 1998 meeting on immunization data issues, there was an agreement and recommendations to report supplemental immunization activities (both prospective and retrospective) on a quarterly basis. Since then, some progress has been made, but no regions have set up a mechanism to systematically obtain this information from countries on a quarterly basis. With the serious gaps in data at WHO/HQ on supplemental immunization activities, it is difficult to assess the quality of such activities, forecast needed vaccine for manufacturers, or report to partner agencies. The incomplete data has been one factor leading to the global shortage of (oral polio vaccines) OPV. Staff from HQ are available to help Regions set up a routine reporting mechanism with countries and a regional database. However, this would only be worthwhile if someone was designated within the Regional Office to develop and maintain the database.

An official letter accompanies the joint reporting forms from Ministry of Health (MOH). Discussion followed on the data exchange format, including the potential for web-based data entry. Reconciliation of regional level data with country level data is one of the reasons for the time delay in reporting. It was discussed that if HQ proposes an electronic data structure for the form, this would facilitate data entry at the Regional level. Proposed changes to form are shown in Annex 3.

Recommendations

Part 1: Immunization safety monitoring/assessment

1a) More emphasis should be placed on safety issues in clinical trials. In the conduct of these trials, data monitoring boards should be staffed with persons with experience in the study of vaccine adverse events. There is recognition that rare events may not be detected during conventional clinical trials and this underlines the need for post-marketing immunization safety monitoring.

1b) Better indicators on the monitoring and management of imunization safety concerns should be developed, and some of these should be integrated into joint WHO/UNICEF annual reporting process.

1c) AEFI monitoring/surveillance should be renamed as "immunization safety" monitoring/surveillance, consistent with other more positively named activities (e.g. blood safety, food safety, drug safety, transport safety).

1d) Information on all vaccine ingredients should be included in the WHO publication: "International List on the Availability of Vaccines".

1e) Caution should be exercised when considering the recall of a vaccine due to an AEFI report. The implications of recall should be clearly communicated beforehand to international partners.

1f) The WHO/HQ document: "Supplementary information on adverse events following immunization" should be distributed to all national immunization staff and NRA directors.

1g) Mass campaigns should be used as an opportunity to implement immunization safety monitoring. Prior to mass campaigns, information on the expected rates of adverse events, and immunization safety monitoring should be part of planning and training at all levels.

1h) WHO/HQ should be informed in a timely manner by countries and Regional Offices on immunization safety concerns that might have international implications.

1i) WHO/HQ should issue timely official statements on emerging immunization safety issues to assist national immunization staff in pro-actively dealing with the issue.

1j) The media training material developed by HQ should be evaluated after its use in the Eastern Mediterranean Region and opportunities explored to offer the workshop to other Regions.

1k) Educational material on safe immunization, including safe injection practices and AEFIs should be prepared for and included in medical and paramedical undergraduate curricula and used for in-service training.

1l) Efforts should be made by WHO/national immunization staff to inform key media on general immunization safety issues.

1m) While prompt and thorough investigation of immunization safety concerns by national immunization staff is needed, an independent review by a national/ international committee of experts should be conducted when:

- specific expertize is needed,
- increased credibility or neutrality are needed,
- the incident may have international implications, and
- there may be a potential "conflict of interest".

1n) Effective links should be established in all countries between national immunization staff, national vaccine regulatory authorities, as well as drug regulatory authorities.

1o) A joint WHO/UNICEF Bulletin on Immunization Safety should be developed.

Part 2: Assessment/monitoring related to new and under-utilised vaccines

2a) In the introduction of new and under-utilised vaccines, comprehensive plans should be developed considering the "whole" process, including vaccine costs, assessment of disease burden, development of surveillance, cold chain, logistics, and safety issues.

2b) WHO should prepare best practices guidelines on monitoring the impact of hepatitis B immunization, including the collection and analysis of serologic data.

2c) The approach to disease burden estimation proposed by the Department of Vaccines and Biologicals (WHO/HQ), that includes a consultative process with countries/regions, is endorsed and should be rapidly pursued.

2d) Disease burden and economic models, particularly those incorporating country data, should be used for prioritising the introduction of new and under-utilised vaccines.

2e) WHO/HQ should finalize protocols for economic evaluation of hepatitis B, Hib, and rubella vaccine introduction. All regions should prepare a prioritised list of diseases/countries for economic evaluation studies. Based on the prioritised list, country specific studies should be initiated during the year 2000.

2f) The HQ "Draft Proposal for a Two-Year Start-Up Project on Improving Immunization Coverage Data Quality" is endorsed, however, it should be expanded to also include disease burden estimation, economic evaluation and surveillance related to new vaccines. Staff should be allocated to regional offices to work in these areas. These staff should visit countries and find, research and analyse the currently available data.

2g) An extra "working" day should be added to regional or sub-regional immunization meetings to address issues related to improving estimates/data quality, including disease burden estimates, economic evaluation and immunization coverage data.

Part 3: Monitoring/surveillance for accelerated disease control

3a) A global minimum set of core variables for measles control should be developed through a consultative process with the Regions.

3b) Following the recommendation of last year's meeting, the global database on supplementary immunization including measles / vitamin A and polio, should be strengthened through the provision of country data (both retrospective and prospective) from Regions to HQ on at least a quarterly basis. A staff member from HQ should work on a periodic basis with regional office staff to maintain and update the database.

3c) The susceptibility modelling methodologies for measles used in EURO should be made available to other Regions, especially countries in the outbreak-prevention/elimination stage.

3d) In the analysis of coverage data, routine immunization coverage should not be confused with supplementary immunization coverage data.

3e) The time schedule presented for the annual joint reporting process should be followed (Annex 4). All Regional Offices should participate in the finalization of the joint form and efforts should be made to send the finalized joint form to countries in mid-February 2000 in synchrony with UNICEF. HQ should develop efficient methods for data entry/transfer at Regional and national levels.

3f) The proposed algorithm (Annex 5) for neonatal tetanus elimination may be applied to the 57 countries that have not eliminated or documented elimination; however, the existence of community-based surveillance should be included when assessing the reliability of surveillance in rural areas. Additional validation procedures should be considered to document whether the neonatal tetanus elimination goal has been achieved in these countries.

Annex 1:

Provisional agenda of the meeting on assessment and monitoring for vaccine preventable diseases, 27-29 October 1999

27 October 1999

Monitoring/management for immunization safety

08:30 - 09:00 Opening, objectives, election of chairman & rapporteur

09:00 - 10:30 Review of regional progress, plans, and guidelines related to monitoring, management of adverse events following immunization *(AEFIs) - (Representative from each Region)*

Objective: Discuss how monitoring/management of AEFIs will be strengthened in regions, and changes/progress since last year's meeting.

10:30 - 11:00 Break

11:00 - 12:30 Update and discussion on WHO/UNICEF initiatives and strategic plans related to immunization safety

(P. Duclos, J. Clements, N. Dellepiane, R. Edwards, UNICEF)

Objective: Review progress since last year's meeting, new WHO/UNICEF initiatives, and strategic planning for immunization safety particularly as it relates to monitoring/ management of AEFIs

12:30 – 14:00 Lunch

14:00 – 14:30 Discussion on AEFI monitoring targets

(PAHO, WPRO)

Objective: Share regional experiences on what AEFI monitoring/ management targets were set and how they will be achieved

14:30-15:00 Training on post-marketing monitoring and management of AEFI

(J. Clements, J. Milstien, P Duclos, P. Folb)

Objective: Provide an update on the Global Training Network in terms of who is being trained, training materials/methods, and expected results

15:00 – 15:30 Break

27 October 1999 (*continued*)

15:30 – 16:30 Media training
(J. Clements, T. Gaafar)

Objective: Provide an update on progress and discuss experiences about training in media management

16:30 - 17:00 Review of recommendations

28 October 1999

Assessment/monitoring of new vaccines

08:30 - 08:45 Assessment/monitoring of new vaccines
(J. Wenger)

Objective: Provide a brief overview of future directions for monitoring and assessment particularly with regard to introduction of new vaccines and in particular review surveillance/ monitoring for Hib

08:45 – 09:00 Experience from PAHO – assessment/monitoring for Hib disease
(H. Izurieta)

09:00 – 09:45 Discussion

09:45 - 10:00 New monitoring/assessment methods in the pipeline
Report from the Steering Committee on Epidemiology and Field Research
(S. Robertson)

Objective: Discuss new monitoring/assessment methods, studies, and modelling that are pertinent to immunization strategies and activities being implemented in countries

10:00 – 10:30 Discussion

10:30 – 11:00 Break

11:00 - 11:15 Cost-effectiveness analysis for prioritizing new vaccine introduction - plans for working with the Regions/countries
(U. Kou)

Objective: Share the status of economic evaluation of hepatitis B, Hib and pneumococcal vaccines. Clarify the role/importance of economic evaluation of new vaccines. Outline HQ experiences and strategies for the future, including proposal for involvement of Regional Offices in economic evaluation

11:15 – 11:45 Discussion - Strategic planning related to monitoring/ assessment of VPDs

28 October 1999 (*continued*)

11:45 – 12:45 Review strategic plans in relation to assessment/monitoring for VPDs

(representative from each WHO Region, WHO/HQ, UNICEF/HQ)

Objective: Review plans, priorities, concerns related to surveillance/monitoring for VPDs particularly in the context of the Strategic Plans of each Region

12:45 – 14:00 Lunch

14:00 – 14:45 Strategic Planning (continued)

Improving estimates

14:45 – 15:00 Making/improving estimates of morbidity and mortality – a proposal

(C. Nelson, T. Burton)

Objective: As per recommendations from last year's meeting, propose and discuss the process of making morbidity/mortality estimates

15:00 – 15:30 Break

15:30 – 16:00 Discussion

16:00 – 16:15 Improving estimates of immunization coverage

(M. Birmingham)

Objective: Propose specific actions, both long and short term to improve immunization coverage estimates

16:15 – 17:00 Discussion

29 October 1999

Vaccine assessment and monitoring for accelerated disease control: focus on measles control/elimination

08:30 - 09:00 Review of recommendations from previous day

09:00 – 09:10 Global perspective on measles monitoring
(AM Henao)

Objective: Provide a global perspective on plans, priorities, progress in measles monitoring in relation to accelerated measles control/ elimination efforts

09:10 - 10:10 Regional perspectives on measles monitoring issues
(representative from each Region)

Objective: Provide a regional perspective on plans, priorities, progress in measles monitoring in relation to accelerated measles control/elimination efforts

10:10 – 10:30 Discussion on what needs to be standardized globally

10:30 – 11:00 Break

11:0 - 11:15 Update on the global measles laboratory network
(D. Featherstone)

Objective: Share and discuss the global plan, priorities, and progress in establishing a measles laboratory network

11:15 – 11:30 Integrating laboratory activities with surveillance –
lessons learned from the polio eradication initiative
(R. Sanders)

Objective: Provide insights on how to ensure good integration of laboratory activities with surveillance.

11:30 – 12:00 Discussion

12:00 – 12:15 Determining neonatal tetanus elimination – proposal for a standard algorithm
(M. Birmingham, MA Neill)

Objective: Develop consensus on a standard, yet operationally feasible and efficient algorithm to document neonatal tetanus elimination so that data are comparable by country and gathered in a standard way by both WHO and UNICEF

12:15 – 12:45 Discussion

12:45 – 13:00 Review of wild poliovirus epidemiology and discussion

Objective: Review the epidemiology of wild polioviruses, particularly with regards to the remaining endemic foci

29 October 1999 (*continued*)

13:00 – 14:00 Lunch

Improving the process/content of data collected by WHO

14:00 – 15:00 Discussion about the past year's data collection experience and proposed modifications for next year

- annual data collection
- quarterly data collection on supplemental activities (particularly for polio, measles and vitamin A)
- weekly/monthly data for polio eradication

15:00 – 15:30 Break

15:30 – 16:30 Finalizing the process/content of data collection in 2000

16:30 – 17:00 Review of recommendations

17:00 – 17:15 Evaluation and closure

Annex 2:

List of participants at the meeting on assessment and monitoring for vaccine preventable diseases, 27-29 October 1999

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