REPORT
FIFTH MEETING ON LABORATORY SURVEILLANCE FOR POLIOMYELITIS ERADICATION IN THE WESTERN PACIFIC REGION

Manila, Philippines
16-17 August 2001
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POLIOMYELITIS ERADICATION IN THE WESTERN PACIFIC REGION

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The views expressed in this report are those of the participants in the fifth meeting on Laboratory Surveillance for Poliomyelitis Eradication in the Western Pacific Region and do not necessarily reflect the policies of the World Health Organization.
SUMMARY

Representatives of the Regional Poliomyelitis Laboratory Network met in Manila on 16 and 17 August 2001. The meeting was attended by representatives of the regional reference and national poliomyelitis laboratories; temporary advisors from the Centers for Disease Control and Prevention (CDC), United States of America; Dr Walter Dowdle of the Taskforce for Child Survival and Development; and representatives from the WHO South-East Asia Regional Office and the WHO Regional Office for the Eastern Mediterranean.

Key issues that were addressed now that the Western Pacific Region has been certified as poliomyelitis-free included maintaining the high-quality performance of the Regional Poliomyelitis Laboratory Network, with special focus on biosafety and internal quality control, as well as minimizing the risk of the emergence of virulent Sabin-vaccine-derived poliovirus strains.

Network laboratories have maintained high levels of performance for several years and have continued to do so even after certification of poliomyelitis-free status. Members of the Regional Laboratory Network, however, expressed concern about maintaining certification standards for reporting and investigating acute flaccid paralysis (AFP) cases and collecting adequate stool specimens, as after certification, priorities may be moved to other public health activities and a certain complacency may develop, under the assumption that poliovirus transmission has stopped in the Region.

The Poliomyelitis Laboratory Network, however, continues to be well established in the Western Pacific Region, and is being used to provide essential information for action in responding to importation of wild poliovirus and detection of vaccine-derived poliovirus (VDPV). Performance levels have been maintained at those required for certification of poliomyelitis-free status. The formal system for annual accreditation of laboratories in the Network is well established, and all are performing at WHO accreditation standard. For those laboratories that are provisionally accredited, appropriate steps have been undertaken to improve their laboratory performance.

The majority of outstanding laboratory equipment needs have now been met, mainly through the generosity of partner agencies and governments, but support is still required for maintenance of that equipment, specifically under biosafety concerns. The workload of the Laboratory Network is expected to further increase, mainly due to the new requirements for intratypic differentiation of all poliovirus isolates. Thus, even more funding support is required to ensure that the Laboratory Network is maintained at least until global certification.

Special attention needs to be given to further standardizing the laboratory data management system, establishing a support system for equipment maintenance, distribution of selected supplies and developing standardized approaches on in-house quality control. Additional support is also required to meet the continuing demand for training in basic laboratory techniques. Long-term commitment to supporting the Laboratory Network would allow better long-term planning and coordination and subsequently more efficient use of resources. The Regional Poliomyelitis Laboratory Network is a tremendous resource for the Region, which can be built upon for the control of other diseases, including measles, and eventually allow countries to develop responsive communicable disease surveillance systems closely linked to public health laboratories.
A quality laboratory network also plays a crucial role in accelerated measles control and a measles laboratory network is currently being established in the Region. The primary functions of the measles laboratory are to:

(1) monitor and verify virus transmission by confirmation of suspect cases using anti-measles IgM assays and identification of measles virus strains and genetic characterization of viral isolates; and

(2) monitor the susceptibility profile of the population to determine target ages for campaigns and to measure the impact of immunization programmes and campaigns.

A regional network of measles laboratories is essential to ensure that all the functions of the measles laboratories can be carried out successfully. Cooperation, coordination and communication must be regular, open and complete between laboratories at all levels and between national laboratories and their counterparts in immunization services, disease surveillance and data management and analysis.
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1. INTRODUCTION

On 29 October 2000, the Regional Certification Commission on Poliomyelitis Eradication declared the Western Pacific Region poliomyelitis-free as no indigenous wild poliovirus had been detected since 19 March 1997 under conditions of high quality surveillance in all countries and areas.

The Regional Poliomyelitis Laboratory Network, established in 1992, made a significant contribution to that effort and continues to provide accurate and timely information to the poliomyelitis eradication programme as the Western Pacific Region works towards global poliomyelitis eradication and certification. Since the onset of the last poliomyelitis case due to indigenous wild poliovirus in the Region on 19 March 1997, over 27 000 acute flaccid paralysis (AFP) cases have been reported in the Region, and around 90% of all AFP cases have had two stool specimens taken within 14 days of onset of paralysis for laboratory analysis.

In spite of a high workload, laboratory performance standards have been consistently improving, as documented through the process of annual laboratory accreditation. All network laboratories continue to provide regular reports to the WHO Western Pacific Regional Office, which allow continuous monitoring of standard performance indicators, published on a weekly basis.

In 2000, cases of poliomyelitis caused by a vaccine-derived poliovirus (VDPV), which appears to have reverted to both a neurovirulent and transmissible strain, occurred in the Dominican Republic and Haiti. Although no final decisions have yet been made, implications of the outbreak in countries free of poliomyelitis for many years may include retrospective sequencing of Sabin-like poliovirus isolates in high-risk areas, as well as prospective sequencing, resulting in an increasing laboratory workload.

Laboratory containment of wild poliovirus infectious/potentially infectious materials remains a key priority following certification of the Region’s poliomyelitis-free status in October 2000. Major progress has been made to date. National laboratory inventories on wild polioviruses and potentially infectious materials have been completed in 10 countries and for 17 of the Pacific island countries and areas. All other countries in the Region are expected to conclude the process before the end of 2001. Although laboratory containment of wild poliovirus infectious/potentially infectious materials involves institutions and laboratories outside the Regional Poliovirus Laboratory Network, the network laboratories continue to play a crucial role in awareness-building and enhancing the containment process through technical and information support.

As progress is made on implementation of the accelerated measles control programme, the need for laboratory investigation will increase. Surveillance measures will be built on the success of the Poliomyelitis Laboratory Network.

1.1 Objectives

The objectives of the meeting are:

1. to review the current status of the Regional Poliomyelitis Laboratory Network with regard to levels of performance, and to identify and document outstanding problems related to routine laboratory responsibilities and propose solutions;
(2) to recommend specific strategies and guidelines to strengthen and expand
laboratory containment of wild poliovirus infectious/potentially infectious materials;

(3) to make recommendations for a Regional Measles Laboratory Network, in
accordance with the recommendations of the preceding 12th Meeting of the Technical
Advisory Group (TAG) on the Expanded Programme on Immunization and Poliomyelitis
Eradication in the Western Pacific Region; and

(4) to identify available resources to address specific operational issues, e.g., the
management of Sabin-derived-reverted polioviruses and non-polio enterovirus isolates.

1.2 Organization

The meeting was attended by representatives of the regional reference and national
poliomyelitis laboratories; temporary advisors from the Centers for Disease Control and
Prevention (CDC), United States of America; Dr Walter Dowdle of the Taskforce for Child
Survival and Development; and a secretariat.

Annex 1 shows the timetable of the meeting, and Annex 2 contains the list of participants.

1.3 Opening ceremony

Dr Richard Nesbit, Director of Programme Management, in behalf of Dr Shigeru Omi,
Regional Director of the WHO Western Pacific Region, welcomed all participants by
congratulating them on their remarkable contribution towards freeing the Region of poliomyelitis
and official certification by the Regional Certification Commission. He acknowledged that
certification as a historic public achievement, which would not have been possible without the
support of the Poliomyelitis Laboratory Network.

Dr Nesbit stated that the documentation of high standards of laboratory surveillance in the
Region had played an essential part in convincing the Regional Certification Commission, not
only that transmission of wild poliovirus in all countries and areas of the Region had been
interrupted, but also that virological surveillance capacity was in place to quickly and reliably
detect any importation of wild poliovirus.

Dr Nesbit noted that, over the past four years, over 27 000 AFP cases had been reported in
the Region. About 90% of them had had two stool specimens taken within 14 days of onset of
paralysis for laboratory analysis. In spite of that high workload, laboratory performance
standards had been consistently improving, as documented through the process of annual
laboratory accreditation. All national and regional reference laboratories had been accredited in
2000.

Dr Nesbit acknowledged the Regional Poliomyelitis Laboratory Network's technical
support for establishing national inventories of wild poliovirus infectious and potentially
infectious materials and thus making substantial progress towards achieving Phase 1 of
laboratory containment as an essential part of ensuring that the Region remained poliomyelitis-
free. He noted that the network laboratories served as models of excellent and reliable
containment procedures.

Dr Nesbit emphasized the importance of discussing in the meeting how to supplement and
extend AFP surveillance, particularly important in light of the poliomyelitis outbreak in the
Dominican Republic and Haiti caused by VDPV. Although vaccine-derived poliomyelitis was
still a rare event and extended and prolonged circulation of VDPV had been in areas with very
low immunization coverage and poor surveillance, the outbreak also had implications for
countries that had been free of poliomyelitis for many years. Increased requirements for
intratypic differentiation methods and sequencing of non-conclusive results would result in an increasing laboratory workload.

Dr Nesbit noted that the meeting would also cover such important issues as in-house quality control, biosafety issues, correct shipment of specimens and isolates and laboratory data management.

Dr Nesbit concluded by saying that, as progress was made on implementation of the accelerated measles control programme, the need for laboratory investigation would increase and surveillance measures would be built on the success of the Poliomyelitis Laboratory Network.

Dr Wilina Lim was requested to serve as chairperson, Dr Hiroyuki Shimizu as vice-chairperson and Dr Nguyen Thi Hien Thanh as rapporteur.

2. PROCEEDINGS

2.1 Overview of the Poliomyelitis Laboratory Network

2.1.1 Global update

Since the last regional laboratory meeting in 1999, the Global Poliomyelitis Laboratory Network has seen considerable expansion, development and refinement. It has also seen a massive increase in workload and impressive improvements in proficiency and timeliness of laboratory performance. There are now 147 laboratories in the Global Network; 124 at subnational and national level, 16 at regional reference level and 7 at global specialized level. Apart from sharing the common goal of poliomyelitis eradication, these laboratories also share common methods, standard reagents, uniform data collection and reporting methods, and standards of performance. The Global Network now functions as a truly supportive network, sharing information and advice, technical information, training facilities, consultative staff and mutual respect.

Together, these laboratories process more than 50 000 stool specimens a year, isolate more than 2000 polioviruses and 10 000 non-polio enteroviruses, carry out intratypic differentiation (ITD) of all the poliovirus isolates, and provide genomic sequencing information on almost all wild poliovirus isolates obtained. This is all carried out in an accurate and timely way that ensures information for action in the final stages of the poliomyelitis eradication initiative. In the remaining foci of wild poliovirus transmission, laboratory information, particularly genomic sequence information, is ensuring that attention and resources are focused on the areas and activities most needed.

The poliomyelitis laboratory accreditation scheme has been in place since 1997. Of the 147 laboratories in the Global Network, 135 are currently fully accredited, 6 are provisionally accredited, 2 have been reviewed and could not be accredited, and 4 are pending. For the laboratories that are provisionally accredited or have failed to be accredited, detailed plans of action have been developed to address identified problems and ensure that the laboratories meet full accreditation requirements.

Recognizing the increased level of proficiency of many of the national laboratories, and the mounting workload for regional reference laboratories to carry out ITD, the accreditation scheme has been expanded to include accreditation of national laboratories carrying out ITD.
During the course of 2000/2001 selected national laboratories received appropriate equipment, supplies and training to enable them to undertake ITD.

Implications of increased surveillance and response activities for the Network include: a large increase in sample numbers, with increased requirements for supplies and equipment; workload and staffing issues; expectations of improved turnaround time; and demands for timely sequencing to determine whether a wild poliovirus is endemic or imported and to confirm that it is genuine.

Immediate implications from the Hispanola outbreak include: all polioviruses (from AFP and non-AFP cases) need ITD, using both antigenic and molecular based assays or molecular ITD and sequencing, resulting in some national laboratories requiring assistance with ITD; use of ITD reagents and controls has increased; non-viable wild controls are required for each of the ITD methods; and regional sequencing capacity needs to be expanded.

Implications also result for the Network from ongoing laboratory containment activities, with Network laboratories expected to generate inventories of their wild poliovirus and potentially infectious materials, with constant updates and regular biosafety cabinet assessments.

2.1.2 Western Pacific Region

Laboratory results

More than 13,500 stool specimens from over 6800 AFP cases were processed by national and subnational poliomyelitis laboratories in the Region in 2000. From 1 January to 31 July 2001 (data as of 10 August 2001) a total of 6297 stool samples from 3213 AFP cases were processed.

Routine proficiency monitoring

Monitoring of routine laboratory proficiency, timeliness and non-poliomyelitis enterovirus (NPEV) isolation rate, has continued through the monthly laboratory results reporting system. For the Region as a whole, in 2000, 87% of laboratory results were available within 28 days of specimen receipt in the laboratory, and 91% of results were available within 42 days. In 2001 up to 10 August, 92% of laboratory results were available within 28 days of specimen receipt in the laboratory, and 100% of results were available within 42 days.

Since 1996, the surveillance timeliness criterion that has been used is that 80% of all poliomyelitis isolates should have intratypic differentiation results available within 90 days of onset of paralysis. Eighty-five percent of all cases with poliovirus isolates had final results available within 90 days in 2000. As of 10 August, in 2001, 90% of all poliomyelitis isolates from AFP cases in 2001 have had intratypic differentiation results available within 90 days of onset of paralysis. During its last meeting in May 2001, the Technical Consultative Group on the Global Eradication of Poliomyelitis (TCG) recommended reducing the interval between onset of paralysis and receipt of ITD results to > 60 days (target >80%).

Although no longer a criterion for laboratory accreditation, the NPEV isolation rate is still used as an indirect measure of laboratory sensitivity. For the Region as a whole, the NPEV isolation rate in 2000 was 12%. Rates vary from laboratory to laboratory (4-50%), but all national laboratories in the Regional Network continue to report NPEV isolation rates compatible with the geography, climate and social factors present in the areas they serve. The regional NPEV isolation rate in 2001, up to 10 August, was 9%.
Status of WHO laboratory accreditation

The WHO poliomyelitis laboratory accreditation scheme continues to provide documentation that a laboratory has the capability and the capacity to detect, identify and promptly report wild polioviruses that may be present in clinical and environmental specimens. The accreditation process further provides a mechanism for identifying resource and training needs, a measure of progress, and a link to the WHO Global Poliomyelitis Laboratory Network. Accreditation is reviewed annually by WHO and is based on laboratory performance during the immediately preceding 12 months with complete data.

A laboratory proficiency test was carried out in the second quarter of 2000. All of the 10 national laboratories tested achieved a score of 100% during the first distribution. The 2001 proficiency test is currently (August to September) being carried out. All national laboratories have been visited and reviewed using the standard accreditation checklist. All laboratories were accredited, with one national laboratory (Papua New Guinea) provisionally accredited, for 2000. A detailed plan of action was developed for the laboratory in Papua New Guinea. Provisional accreditation was mainly based on the low number of stool samples processed. An aseptic meningitis study has commenced again to provide additional stool specimens for poliovirus testing (number of expected AFP cases is only 20) and timeliness of test results, which was below the required 80% for the period reviewed during the accreditation visit, has improved to 100%.

The poliomyelitis laboratory network in China has been conducting annual proficiency tests since 1992. Proficiency standards have consistently improved since that time, with all 31 passing the test in 2000 and 2001. Furthermore, since 1999 all except one of the 31 provincial poliomyelitis laboratories in China have demonstrated that they are operating at WHO accreditation standard and have been accredited.

Coordination of the laboratory surveillance system

Coordination of laboratory activities is founded on the monthly laboratory reporting system, established in 1994. The system continues to work well, with network laboratories reporting results and performance indicators on a regular basis. Results and performance feedback continue to be provided to all laboratories in the network on a monthly basis, and laboratory results are regularly reported in the Poliomyelitis surveillance weekly report, issued by the Regional Office.

One of the performance criteria for the laboratory network in the Western Pacific is that all poliovirus isolates, regardless of their source, are being referred to a regional reference laboratory (RRL) for ITD. In order to decrease the workload of the RRLs, staff of selected national laboratories have been trained to use PCR technology for enterovirus and other virus testing. Proficiency tests are currently being conducted.

Since the beginning of 2001, and stimulated by recent poliomyelitis outbreaks in Haiti and the Dominican Republic, caused by VDPV, all poliovirus isolates have had to undergo two ITD methods recommended by the Global Poliomyelitis Laboratory Network (one method should be antigenic and the other one molecular). All isolates with non-conclusive ITD results should be immediately referred to a global specialized laboratory for sequence analysis. Regional guidelines are currently been developed to specify surveillance (including virological) requirements to allow timely and reliable detection of VDP viruses and determine the extent of circulation.

One VDPV was isolated from an AFP case in the Philippines, with 96-98% homology to Sabin 1 in 5-NTR, capsid and 2A regions. The 3' end sequence revealed an unknown unique enterovirus sequence. The main conclusion was that the isolate was a clear recombinant between...
the vaccine strain and some non-polio enterovirus. Further analysis showed that the virus was not derived from previous VDP viruses, including isolates from Haiti and the Dominican Republic. The 3D sequence was not related to any sequences of known polio and enteroviruses. An important reversion for neurovirulence was found, but intensified epidemiological investigations revealed no indication of extended circulation of the virus.

**Regional laboratory data management system**

A review of the current mechanisms employed in the polio laboratories of the Regional Network to record, maintain and report laboratory data, together with the mechanism used in the Regional Office to receive, consolidate, analyse and report those data, was performed by an external consultant after a briefing at WHO Headquarters on current laboratory data management systems and plans for establishing an integrated data management system. Based on findings and recommendations from that review, a plan of action will be developed and implemented to make the laboratory data management system more functional and appropriate.

**Conclusions**

The Regional Poliomyelitis Laboratory Network continues to be well established in the Western Pacific Region, and is being used to provide essential information for action in responding to importation of wild poliovirus and detection of VDPV. Performance levels have been maintained at those required for certification of poliomyelitis eradication since the Region was declared poliomyelitis-free. The formal system for annual accreditation of network laboratories is well established and all laboratories in the Regional Poliomyelitis Laboratory Network are performing at WHO accreditation standard. For those laboratories that are provisionally accredited, appropriate steps have been undertaken to improve their laboratory performance.

The majority of outstanding laboratory equipment needs have now been met, mainly through the generosity of partner agencies and governments, but support is still required for maintenance of such equipment, specifically considering biosafety concerns. The workload of the Regional Poliomyelitis Laboratory Network is expected to increase further, mainly due to the new requirements for intratypic differentiation of all poliovirus isolates. Thus, even more funding support is required to ensure that the Network is maintained at least until global certification.

Special attention needs to be given to further standardizing the laboratory data management system, establishing a support system for equipment maintenance, distribution of selected supplies and developing standardized approaches on in-house quality control. Additional support is also required to meet the continuing demand for training in basic laboratory techniques. Long-term commitment to supporting the Regional Poliomyelitis Laboratory Network would allow better long-term planning and coordination, and subsequently more efficient use of resources. The Regional Poliomyelitis Laboratory Network is a tremendous resource for the Region, which can be built upon for the control of other diseases, including measles, and eventually allow countries to develop responsive communicable disease surveillance systems closely linked to public health laboratories.

2.1.3 South-East Asia Region

Tremendous progress has been made in poliomyelitis eradication in the WHO South-East Asia Region, with the number of wild poliovirus laboratory-confirmed poliomyelitis cases going down from 2016 in 1998 to 38 in 2001 (as of 13 August). AFP surveillance quality reached certification standards in 2000, with a non-polio AFP rate of 1.78 per 100 000 under age 15 and 80% of cases having two adequate stool specimens taken. The poliomyelitis laboratories in the South-East Asia Region tested over 20 000 stool samples in 2000, with 93% of all laboratory
reports available within 28 days of receipt in the laboratory. Only one laboratory, in the Democratic People's Republic of Korea, is not yet accredited.

All polioviruses are dispatched to a regional reference laboratory or a global specialized laboratory for ITD within two weeks of confirmation of virus-typing results, and ITD results are reported at least within 28 days of receipt of sample (but often in less than two weeks). Sequencing results for all programmatically important cases are available within 0-14 days of identifying wild polioviruses.

To enhance the existing data management system within the national laboratories, “polio laboratory information for action” (PLIFA) was developed as a joint effort of WHO and national virologists. The system allows easy tracking of specimens from arrival to final reporting of results, and can include AFP case, contact, healthy child survey and environmental specimens. Furthermore, the system allows monitoring of timeliness of sample flow and accuracy of reporting. It can be customized to meet the specific needs of individual laboratories for data entry, reporting and analysis. It is compatible with the existing IFA programmes used by poliomyelitis surveillance and epidemiology units and can decrease the workload when laboratory data is transferred electronically.

2.1.4 Eastern Mediterranean Region

The number of reported poliomyelitis cases in the WHO Eastern Mediterranean Region decreased from 2342 in 1988 to 505 in 2000. There were 42 wild polioviruses reported (from five countries) in 2001 (as of 27 July) compared to 479 in 1999. The non-polio AFP rate has improved from 0.7 in 1995 to 1.7 per 100,000 under age 15 in 2001 (annualized). All countries, except Bahrain, Cyprus and Djibouti, report rates of above one. Fourteen countries have over 80% of AFP cases with adequate stool specimens, four countries achieve rates between 60% and 79%, and rates in five countries remain under 60%.

The Regional Poliomyelitis Laboratory Network is composed of 12 laboratories, of which all except Jordan are fully accredited. The Network processed over 7000 stool samples in 2000, and 81% of the results were available within 28 days of receipt. The average time between paralysis onset and confirmed results is 68 days.

Wild poliovirus was isolated in 2001 in Afghanistan, Egypt, Pakistan, Somalia and Sudan. Comparing the situation with 2000, there is substantially reduced transmission of indigenous wild poliovirus in Afghanistan and Pakistan. Exportation of viruses to Iran from Pakistan and Afghanistan occurred in 1999 and 2000, while indigenous transmission of such an imported virus was established in Iran in 2000.

Much progress has also been made with laboratory containment of wild poliovirus infectious/potentially infectious materials, and 17 national plans of action have been developed (except Afghanistan, Iraq, Palastine, Somalia, United Arab Emirates and Yemen). Laboratory surveys have been implemented in five countries so far, and Omar and Qatar have completed their national inventories.

2.2 Supplementing and extending AFP surveillance

2.2.1 Laboratory surveillance for VDPV

Following recommendations of the Global Poliomyelitis Laboratory Network, all poliovirus isolates, regardless of origin, should be forwarded to a WHO-accredited laboratory for ITD by at least two approved methods, one of which must be antigenic (ELISA preferred) and one molecular (probe hybridization or diagnostic PCR preferred). Isolates should be forwarded for ITD within 14 days after isolation, at least for AFP cases.
All poliovirus isolates showing discrepant ITD results should be sent immediately to a global specialized laboratory (or a laboratory recognized by WHO as having the capacity to carry out poliovirus sequence analysis) for ITD confirmation and analysis of genomic sequence.

**AFP surveillance for VDPV**

The national/sub-national AFP surveillance systems should analyse AFP data on at least a monthly basis, looking for evidence of clustering of cases. All poliovirus isolates from identified clusters should be sent to a global specialized laboratory (or a laboratory recognized by WHO as having the capacity to carry out poliovirus sequence analysis) for ITD confirmation and screening for sequence analysis.

It might be necessary to conduct retrospective analysis of VDPV from areas identified as being at potential risk of establishing circulation of VDPV.

**Response to circulation of VDPV**

If there is evidence of circulation of VDPV, immediate consultation between Ministries of Health and WHO country, regional and global poliomyelitis eradication teams and laboratories involved should commence to conclude on implications and necessary actions to be taken.

The Global Certification Commission (GCC) has concluded that the investigation and response to a circulating VDPV must be similar to that of an imported wild poliovirus. Contained transmission of a VDPV (i.e., cases for <1 year and limited geographic spread) has no impact on regional certification. Evidence of prolonged (>1 year) or geographically extensive VDPV circulation may postpone regional certification (regions not yet certified) or require re-evaluation of regional certification status (certified regions). The GCC will re-evaluate the implications of VDPV circulation based on the recommendations the TCG made during its last meeting in May 2001.

2.3 **Current relationship between the laboratories and the programme – stopping the oral poliovirus vaccine (OPV) debate**

Genomic sequencing of polioviruses from Egypt and Haiti/Dominican Republic has confirmed that sustained circulation of VDPVs can occur and cause outbreaks of paralytic poliomyelitis. Although VDPV circulation has only been identified on two occasions, and in areas where immunity was low, for strategic purposes it is essential to plan as if VDPVs will circulate after OPV stops. Experience and opinion in both industrialized and developing countries clearly demonstrates that the eventual cessation of OPV immunization, as soon as possible after global certification, will be imperative.

Optimizing population immunity while stopping OPV will probably require a flexible approach, depending on the country or setting. The principle strategic options for optimizing population immunity are either shifting to routine immunization with IPV or stopping OPV through pulse immunization. The appropriate option for a particular country or setting will depend on a number of factors including the local demography, the routine immunization schedule and coverage, efficacy of IPV in that setting, and the potential for generating VDPV circulation.

To define the best strategic option for each potential setting, WHO/CDC have developed a programme of work that focuses on the following issues:
VDPV surveillance: to determine the frequency of VDPV circulation, risk factors for generating circulation of VDPVs, and optimal VDPV surveillance strategies.

IPV: to determine global production capacity, cost for developing country use, efficacy in developing country setting and potential for Sabin-IPV production.

OPV: to determine the impact of pulse OPV on VDPV circulation.

To implement the programme of work and translate the results into policy, WHO has proposed expanding the TCG’s scope to include defining the strategic options for stopping OPV. The TCG would recommend the best strategic options to the WHO Director-General, through the Strategic Advisory Group of Experts (SAGE), for discussion at the 2003 World Health Assembly. Furthermore, WHO has started to convene a steering committee to ensure that the best scientific evidence is available to facilitate the TCG decisions. The committee's responsibilities include advising on, monitoring and evaluating the results of the required research, taking direction from and reporting to the TCG.

2.4 Accreditation and proficiency issues

In 2001, accreditation review visits have so far been conducted by WHO to the national laboratories in Malaysia, New Zealand, the Philippines and the Republic of Korea, as well as to the regional reference laboratories in Australia and China. All remaining accreditation visits are scheduled for during the second half of the year. The 2001 faecal proficiency test (PT) was recently shipped to all national laboratories, except Papua New Guinea, where shipment is planned in early September. Results are still due within 42 days of receipt of shipment.

Descriptions of the methods for performing ITD by ELISA, probe hybridization and diagnostic PCR methods have been included in the new Poliomyelitis laboratory manual. The diagnostic PCR method for ITD has been successfully introduced into several laboratories and accreditation for ITD functions will be carried out in the near future. The PCR-RFLP method still has no standard method described, other than experimental methods described in the literature. Although the number of laboratories using the method is small, it is considered important that a standard method is described that can be referred to in laboratory accreditation reviews.

Monoclonal antibody neutralization is a method for ITD used in some network laboratories, but again no validated methodology or reagents are currently available and there is a significant problem with provision of non-infectious wild poliovirus controls and PT components.

Proficiency tests for ITD functions are currently available for ELISA from RIVM and for PCR and probe from CDC. Distribution still occurs on an ad hoc basis, and reporting mechanisms have not yet been standardized. It is, however, planned to establish a regional distribution system and forecast reagent requirements on a regular basis.

After having been trained in the PCR method in November 2000, selected national laboratories have performed ITD PTs (Hong Kong - PCR and probe, New Zealand and Singapore - PCR).

2.5 In-house quality control

Laboratory quality assurance (LQA) is concerned with the organizational processes and the conditions under which laboratory activities are planned, performed, monitored, recorded and reported. Adherence by laboratories to the principles of LQA ensures the proper planning of activities and the provision of adequate means to carry them out. It promotes full and accurate reporting, and provides a means whereby the integrity of the activities can be verified.
Setting up an LQA system in a laboratory means defining the organizational structure, responsibilities, procedures, processes and resources necessary to:

- prevent risks;
- detect deviations;
- correct errors;
- improve efficiency; and
- ensure data quality and integrity

It is the responsibility of the Director or Chief of the laboratory to establish, implement and ensure compliance with LQA. However, LQA is the responsibility of all laboratory personnel. A number of elements make up the LQA process, and are detailed below.

2.5.1 Staff

The poliomyelitis laboratory should have the necessary staff with suitable qualifications and experience to carry out all the functions and responsibilities required of the poliomyelitis laboratory safely and accurately. The laboratory should prepare an organogram of the poliomyelitis laboratory, reflecting the hierarchy and lines of authority and including the functions and responsibilities of each person. Each post should have a job description including post, functions and responsibilities, academic training required and experience necessary.

2.5.2 Staffing levels

Staffing levels should be adequate to enable all the functions expected of the poliomyelitis laboratory to be carried out without compromising safety or the integrity of the processes being performed in the laboratory. There are specialized activities within the laboratory that require staff with considerable experience, such as cell culture production, reading of cytopathic effect in virus cultures, performing ITD and sequencing. At least one person with at least 12 months relevant experience should carry out these activities. It is advisable for at least one other person to work in parallel with the experienced person to gain understanding of the activity and thus to build capacity within the laboratory and allow for backup in the event of staff absence.

The fundamental objective of the human resources policy is to have reliable staff, with the scientific and/or technological training to enable them to apply appropriate laboratory procedures correctly, and remunerated according to the labour market. The laboratory must regularly arrange and coordinate training courses to extend and update the skills of both technical and scientific staff, according to needs identified and as proposed by the heads of department. Such training should be offered as a means of contributing to the success of the LQA process. A continuing education programme must be developed which includes training on site as well as external training.

The human resources programme should include the technical evaluation of staff and follow the performance of each staff member, based on job description. This system should allow the correction of errors or weak points, and can also be used as a tool for promotion, where merited.

2.5.3 Space

The poliomyelitis laboratory should have adequate space to safely perform all activities, store all necessary equipment and allow for easy cleaning and maintenance. There should be an adequate number of rooms to enable separation of infectious from non-infectious activities. Cell-culture and media-making facilities should be separated as much as possible from all other activities, preferably in a room(s) completely separated from the laboratory where viral or other microbiological activities are being carried out. There should be a clear delineation of different
working areas in order to minimize the chances of contamination of clean areas. If possible there should be a logical arrangement of activities in a laboratory or laboratories to minimize the distance infectious materials must be carried and to ensure that infectious materials are not being transported through clean areas.

2.5.4 Standard operating procedures (SOPs)

SOPs describe in a detailed way the activities performed in the laboratory so as to provide uniformity, consistency and reliability in each activity; reduce systematic errors; and provide training and guidance for new staff.

SOPs should be drawn up by specialized technical staff in the laboratory, revised by their immediate supervisor and approved by the director of the laboratory

Changes in SOPs should be implemented by specialized technical staff in the laboratory, revised by their immediate supervisor and approved by the director of the laboratory. Any method that undergoes changes from the standard and official method should be validated before being put into practice, comparing with the previous method the following characteristics:

- **Accuracy:** the degree of correlation with the value achieved by the previous method.
- **Precision:** the variation of the results as represented by the standard deviation or the coefficient of variation.
- **Sensitivity:** capacity of the test procedure to record small variations between concentrations.
- **Reproducibility:** the precision of the procedure when it is performed under different conditions.
- **Specificity:** the degree of uniformity of the response to the substance in question.
- **Robustness:** the ability to provide accurate and precise results under a variety of conditions.

2.5.5 Documentation

Documentation is the set of quality manuals, standard operating procedures, instructions, forms, reports, analytical protocols and data records which serve as evidence of the LQA and permit the tracing of data. Responsibility for the preparation and revision of documents should rest with the LQA, or with the person appointed, depending on the complexity of the laboratory.

2.5.6 Laboratory safety

Each laboratory should have available the WHO *Biosafety manual* (second edition, World Health Organization, 1993), which describes the essential biosafety, chemical, fire and electrical safety requirements to protect staff, the community and the environment. All staff should be aware of the manual and should proceed according to its contents. All new staff should be made aware of the risks involved in working in a poliomyelitis laboratory before starting work in the laboratory, and should be required to verify that they have read the *Biosafety manual*. The director is responsible for implementation of and compliance with the provisions of the manual.

When poliomyelitis eradication is achieved, the laboratories will be the only remaining source of the virus. Safe handling and, ultimately, maximum containment of poliovirus and potentially infectious materials in the laboratory is crucial. Wild poliovirus in the laboratory constitutes a special risk category, that is, with little or no risk to the immunized worker, but a potential threat to successful eradication if transmission occurs in the community.
To ensure safe handling of wild polioviruses and potentially infectious materials as eradication nears, poliomyelitis laboratories should follow the recommendations of the Global Action Plan for Laboratory Containment of Wild Polioviruses and institute BSL-2/polio biosafety levels.

2.5.7 Audits

The objective of an audit is to carry out a systematic and independent examination to determine whether the quality of activities and their results comply with the established documentation, and to confirm whether those activities are appropriate for achieving the objectives proposed and whether they have been implemented effectively.

Audits may be internal, performed by staff who do not have direct responsibility for the areas audited, or by the LQA department. External audits are performed by the WHO annual accreditation of poliomyelitis laboratories or by international bodies.

2.5.8 In-house quality control/standard preparations for titration and test controls

Although NPEV isolation rates are good indicators for cell sensitivity, they are not foolproof, and regular sensitivity assays are essential to assess the ability of cell cultures to isolate polioviruses. Thus, there is a need to establish standard procedures and regular testing protocols. Standard preparations of authenticated Sabin strains should be prepared for each of the poliovirus serotypes. All poliovirus controls should be Sabin polioviruses of known origin and passage history. Once prototype Sabin poliovirus controls are established and documented, other poliovirus controls should be destroyed.

In the near future, known tittered prototype Sabin viruses will be distributed to all laboratories but, in the meantime, laboratories can separate Sabin serotypes from OPV vaccine vials. All vaccine manufacturers’ Sabin strains are currently undergoing VP1 sequencing for a reference database.

In each laboratory, SOPs should be developed and followed exactly for every sensitivity assay. Viruses used for sensitivity should be grown to high titre in as few passages as possible from seed prototype viruses, and stocks should be validated with known titres.

2.6 Biosafety issues

Principles of biosafety and containment usually describe safe methods for managing infectious materials in the laboratory environment where they are being handled and maintained. The main purpose of such methods is to reduce or eliminate exposure of laboratory workers, other persons and the outside environment to potentially hazardous agents. Containment is usually divided into primary, protection of personnel and the immediate laboratory environment from exposure to infectious agents (provided by both good microbiological techniques and the use of appropriate safety equipment); and secondary, protection of the environment external to the laboratory from exposure to infectious materials (provided by a combination of facility design and operational practices).

Each laboratory should develop or adopt a biosafety or operations manual, and appropriate training of personnel should be conducted, including refresher courses. Regular maintenance and certification needs to be organized for various pieces of equipment in the laboratory, but is particularly important for biosafety cabinets, centrifuges, autoclaves, clean benches and CO2 incubators. Some countries may still lack local expertise for these functions and building local capacity through training and regular supply of replaceable items may improve the current approach of contracting certification out to external experts on an ad hoc basis.
2.7 Shipping specimens and isolates

Postal, airline and other transport industry personnel have concerns about the possibility of their staff becoming infected as the result of exposure to infectious microorganisms that may escape from broken, leaking or improperly packaged material. The packaging of infectious materials for transport must, therefore, address these concerns and be designed to minimize the potential for damage during transport. In addition, the packaging will serve to ensure the integrity of the materials and timely processing of specimens.

There are no recorded cases of illness attributable to the release of specimens during transport, although there are reported incidents of damage to the outer packaging of properly packaged materials. The shipment of unmarked and unidentified infectious materials, improperly packaged, obviously increases the overall potential for exposure for all persons.

The international regulations for the transport of infectious materials by any mode of transport are based upon the Recommendations of the United Nations Committee of Experts on the Transport of Dangerous Goods (UN). The Universal Postal Union (UPU) reflects these recommendations in its regulations, particularly for packaging. The International Civil Aviation Organization (ICAO) and the International Air Transport Association (IATA) have also incorporated the UN Recommendations in their respective regulations, as have other international transport organizations. WHO serves in an advisory capacity to these bodies.

An infectious substance is defined as a substance containing a viable microorganism, such as a bacterium, virus, rickettsia, parasite or fungus, that is known or reasonably believed to cause disease in humans or animals. This definition is taken from the current UN Recommendations on the Transport of Dangerous Goods. Prions are not included in this definition, although they are considered to be infectious agents.

With respect to packaging and transport situations, infectious substances include:

(1) all cultures containing or suspected of containing an agent which may cause infection;

(2) human or animal samples that contain such an agent in quantities sufficient to cause infection should an exposure to them occur due to a transport mishap;

(3) sample(s) from a patient with a serious disease of unknown cause; and

(4) other specimens not included above and designated as infectious by a qualified person, e.g. a physician, scientist, nurse, etc.

A diagnostic specimen is defined as any human or animal material including, but not limited to, excreta, blood and its components, tissue and tissue fluids collected for the purposes of diagnosis, but excluding live infected animals. Diagnostic specimens resulting from medical practice and research are considered a negligible threat to public health.

Diagnostic specimens obtained from patients with suspected infectious diseases may contain limited quantities of an infectious agent. Very few agents might be the source of an infection as a result of a transport mishap. If exposure to the specimen due to transport mishap could result in an infection, the diagnostic specimen must be packaged, labelled and transported as an infectious substance. Diagnostic specimens collected during an investigation of an outbreak of a serious disease of unknown cause must be handled as infectious substances.

Because of the distinction between risks associated with infectious substances and diagnostic specimens, there are variations to the packaging, labelling and documentation requirements. The packaging requirements are determined by the UN and are contained in ICAO
and IATA regulations in the form of packaging instructions (PI) 602 and 650. The requirements are subject to change and upgrade by those organizations.

2.8 Laboratory data management

External review of the data management system revealed that the AFP case data is held in an application that can best be described as patched and decaying and will become increasing difficult to support, because of the inconsistent way it has been maintained, the lack of documentation and the difficulty in finding staff with knowledge of the Foxpro software currently in use. The problem will worsen as an attempt is made to support both the inherited system and the newer systems being developed.

The fragmentation of the data holdings increases the possibility of error, makes it impossible to do any automatic checking between laboratory data and cases data, and makes it effectively impossible to supply the indicators in the format WHO Headquarters has asked for.

There is no effective documentation of the system or the processes, making the whole system very ‘key-person-dependent’. The system is also very labour-intensive. It uses an unreasonable amount of senior staff members' time, and the detection of anomalies and errors is ad hoc and depends on the skills and knowledge of those senior staff members.

Given the current way laboratory data are stored, it would be extremely difficult, time-consuming and labour-intensive to produce the requested laboratory data transfer files for WHO Headquarters. Thus, recommendations include as a key element the development of a new MS-Access software application to manage routine AFP case and laboratory data and the results of related ad hoc investigations. The development of the AFP and measles information management systems should be planned simultaneously so that it can proceed synergistically to maximize the re-use of standardized components and minimize the need to maintain disparate software.

The software development team would develop, document and then adhere to standards for applications, documentation of applications and for testing and release of applications. Establishment and documentation of data management procedures would ensure that:

- routine reports are complete, accurate and timely, produced with a minimum of effort and are not key-personnel-dependent;
- Western Pacific Regional Office scientific and professional staff receive only value-added reports and are able to 'manage by exception'.

Except for China, laboratory data is currently supplied directly by laboratories in a variety of formats. Loading and management of these data is cumbersome and time-consuming, and there is no automatic linking of laboratory and case data. Hence there are no routine reports derived from consideration of combined data.

To enable electronic handling of the laboratory data, the supply of data needs to be standardized, both in terms of form and content. Thus, it is essential within the Regional Poliomyelitis Laboratory Network to:

- agree on the standard data items to be supplied by laboratories (including coding where appropriate);
- agree on the file transfer formats; and
- agree on the routine reports and feedback that the Western Pacific Regional Office will provide to supplying laboratories.
Benefits for the Western Pacific Regional Office would include: an integrated approach, making it much easier to maintain the system and manage AFP case data, both from the laboratory and the epidemiological investigation; much less labour input to load and manage data and increased capacity to use the data for decisions (both because a wider range of reports could be produced and because their production would be faster – due to easier ability to link laboratory and case data and more staff time being available for value-adding analysis and reporting activities, rather than being spent on routine data handling).

This would also improve the ability to meet global reporting requirements and provide a much wider range of routine feedback to network laboratories.

2.9 Laboratory containment of wild poliovirus infectious/potentially infectious materials

It has been emphasized that, as circulation of indigenous wild poliovirus in the Region has been interrupted, the only known sources of wild poliovirus remaining are the Region’s laboratories. Substantial progress has been made with laboratory containment of wild polioviruses and potentially infectious materials, as acknowledged by the Regional Certification Commission. However, in order to complete Phase 1 of the containment process, the Regional Certification Commission has urged all countries, which have not yet done so, to make every effort to complete national inventories before the next meeting of the Commission.

This was supported by the TAG, which additionally recommended that every country should start meeting the requirements for global certification by arranging for the storage of retained wild poliovirus infectious or potentially infectious materials under BSL-3/polio conditions, arranging for the transfer of retained wild poliovirus infectious or potentially infectious materials to a WHO-designated interim repository, or destroying wild poliovirus infectious or potentially infectious materials or rendering them non-infectious. The TAG also requested that the Western Pacific Regional Office should start the process to designate an interim repository.

All countries have a national plan of action in place and have identified a responsible body for the containment process. Twenty-seven countries have completed their national inventories, and five (French Polynesia, Guam, Malaysia, New Caledonia and the Republic of Korea) are close to completing theirs. Four countries (Australia, China, Japan and the Philippines) still require more time due to the large number of laboratories to be searched, and are expected to complete their national inventories in 2002.

So far, over 17 000 institutions and laboratories have been identified for inclusion in the search. However, response rates are not yet always complete. Wild poliovirus infectious and/or potentially infectious materials have been identified in about 50 institutions/laboratories. Approximately 20% of the identified institutes/laboratories have already destroyed the materials.

Guidelines on the establishment of regional interim wild poliovirus repositories are currently under development by WHO Headquarters. It was noted that the issue of legal ownership of stored isolates must be resolved, and advice will be sought from the WHO legal department. Current assessment of requirements for a regional interim repository indicates that the Region might not need one, but further discussions will be held.

In reviewing the situation in the Western Pacific Region, the GCC recognized the need for consistent certification requirements across regions, noted the experience gained in the Western Pacific Region in implementing the Phase 1 containment guidelines, and discussed the fact that full cooperation in implementing containment guidelines is dependent on further progress towards global eradication. Subsequently, the GCC advised the Regional Commissions that, while it may not be possible for Member States to fully implement Phase 1 containment guidelines prior to regional certification, countries must have achieved substantial progress,
including, at a minimum, a national plan, establishment of a national coordinating mechanism and initiation of the inventory process, before regional polio-free certification can be considered.

The GCC, during its last meeting, restated its previous decision that, prior to global certification, all regions will need to provide data demonstrating full implementation of Phase 2 activities of the Global plan of action for the containment of wild polioviruses.

Progress is being made worldwide in implementing the first phase of laboratory containment. So far, 112 countries have appointed a responsible national task force and created a national plan of action, and 10 have submitted national inventories. Over 300 laboratories with wild poliovirus materials have been identified. In the other WHO region that has already been certified poliomyelitis-free (Region of the Americas), laboratory containment activities are well under way. Canada is in the final stages of preparing their national inventory, and the United States of America has started an extensive pilot-testing phase.

Laboratory containment activities have greatly increased in the European Region as it prepares for certification as poliomyelitis-free; 48 of 51 Member States have appointed a task force, and 27 of those have started contacting laboratories. The South-East Asian, Eastern Mediterranean, and African regions are still endemic, but many poliomyelitis-free countries in those regions have begun preparations for laboratory containment.

As the eradication of wild poliovirus approaches, minimizing the risk of reintroducing the virus into a population becomes an increasing priority. Progress achieved so far in the implementation of the Global plan of action is encouraging. A systematic and well-documented approach has been established for identifying laboratories with wild poliovirus infectious or potentially infectious materials, and there has been cooperation from laboratories and governments worldwide. Nevertheless, the complexities and challenges to implementing the laboratory containment procedures worldwide must not be underestimated, particularly in industrialized countries.

The Global plan of action for the containment of wild polioviruses seeks to directly address and minimize the risk for three of the four conditions that could lead to an accidental reintroduction of wild poliovirus to a community from a laboratory: (1) the presence of wild poliovirus infectious materials in a laboratory; (2) an event (e.g., break in standard procedure) that exposes a worker to infectious materials containing poliovirus; (3) a susceptible worker who replicates and sheds the virus in his/her stool; and (4) susceptible persons in the community who are directly or indirectly exposed to that worker. Although absolute containment cannot be assured, implementation of the activities outlined in the Global plan of action effectively minimize the risk of a situation that allows all the first three conditions to occur. The fourth condition is linked to eventual decisions on post-eradication immunization policies.

Experience with laboratory containment activities suggests that countries where biomedical research programmes and laboratory infrastructure are in the early stages of development generally do not store materials of concern. Such countries can more rapidly compile a list of laboratories and identify those containing wild poliovirus infectious or potentially infectious materials. However, far more time and effort is required to implement the survey and inventory activities in countries with a well-developed research programme and laboratory infrastructure, particularly in industrialized countries.

WHO Member States will assume full responsibility for laboratory containment within their respective countries. This process will be monitored by national authorities, the national certification committees, and the Regional and Global Certification Commissions. Although much progress has been reported to date, all countries of the world will need to demonstrate that the risk of reintroducing wild poliovirus to a poliomyelitis-free world from their laboratories has been effectively minimized in order for global certification to occur as anticipated in 2005.
2.10 Development of a measles laboratory network

2.10.1 Background on measles control

In 1989, the World Health Assembly resolved to reduce measles morbidity by 90% and measles mortality by 95% by 1995, compared with measles in the prevaccine era. In 1990, the World Summit for Children established the goal of 90% vaccine coverage for measles in 12-month-old children by 2000. In the Western Pacific Region, reported measles vaccine coverage achieved 95% by 1996 and the 1995 morbidity and mortality reduction goals were reached. This was achieved by routine immunization with one dose of measles vaccine. Despite these successes, progress was not uniform throughout the Region, and measles remained a significant problem. It is estimated that between 26 000 and 39 000 young children died of measles and its complications in 1995 in the Region. In addition, surveillance was inadequate, with surveys and sentinel surveillance indicating that a maximum of one-third of measles cases were being reported.

In response, a Regional plan of action for accelerated measles control was prepared in 1996. The objectives were:

1. to reduce the burden of measles in every country of the Region, starting in 1999; and
2. to develop measles surveillance to the extent that outbreaks of measles could be rapidly investigated and controlled, and epidemics predicted and prevented.

The strategies to achieve these objectives were:

1. to evaluate the burden of measles disease through measles surveillance; and
2. to reduce measles morbidity and mortality and prevent measles outbreaks.

Those strategies were to be carried out by implementing an active surveillance system, integrated into AFP surveillance systems; laboratory confirmation of suspect measles cases; and delivery of two doses of measles vaccine through extremely high routine first dose coverage and a second dose by campaigns or routine activities, as indicated.


1. to halve the annual number of measles deaths by 2005, compared with 1999 estimates;
2. to achieve and maintain interruption of indigenous measles transmission in large geographical areas with established elimination goals; and
3. to convene a global consultation in 2005, in collaboration with other major partners, to review the progress and assess the feasibility of global measles eradication.

The strategies recommended for reducing measles mortality include:

1. providing a first dose of measles vaccine to successive cohorts of infants;
2. ensuring that all children have a second opportunity for measles vaccination;
3. enhancing measles surveillance and integrating epidemiological and laboratory information; and
(4) improving the management of every measles case.

This Global plan recommends that countries and regions that have already adopted a measles elimination goal should pursue it, but that countries that have not done so should only adopt the goal of measles elimination once the country or region is poliomyelitis-free. Currently there is no Regional Committee resolution on measles elimination in Western Pacific Region. The proposed revised Regional plan of action for accelerated measles control, presented at the twelfth meeting of the TAG, 13-15 August 2001, has similar objectives to the global plan.

2.10.2 Global Measles Laboratory Network

In 1996, a Plan of action for a global laboratory network for the diagnosis of measles was drafted by WHO. Much progress has been made in establishing the Network. In addition to global strain banks and specialized laboratories, there is a well-developed regional measles laboratory network in the Region of the Americas, and comprehensive regional networks in the European, Eastern Mediterranean and Western Pacific regions are being established. Subregional networks are currently being developed in the African and South-East Asia regions.

In the Western Pacific Region, the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne, Australia, has already been designated as a regional reference laboratory (RRL). It is anticipated that two more RRL will be designated, one each in China and Japan. The Pacific island countries and areas have set up the Pacific Public Health Surveillance Network (PPHSN), part of which is the Public Health Laboratory Network (four laboratories in Fiji, French Polynesia, Guam and New Caledonia) that function as the national laboratories for all the Pacific island countries and areas. All other countries and Hong Kong (China) and Macao (China) are expected to have national laboratories in the Network. Many countries will also have subnational laboratories. It is expected that China will have a measles laboratory in every province and many at lower levels. All laboratories must have the capability to conduct a rubella IgM assay on suspected cases that test negative for measles IgM.

Accelerated control and elimination of measles requires the coordinated efforts of immunization services, disease surveillance and laboratory services. All are integral to accelerated measles control and elimination, and the effort will fail if any one of them fails. The immunization services deliver vaccines as part of routine services and carry out supplementary immunization campaigns and outbreak response immunization. Disease surveillance collects and analyses data on measles incidence and epidemiological data on suspected cases, including date of onset, age, vaccination status and location.

A measles laboratory has two main functions:

1. to monitor and verify measles virus transmission:
   - serological confirmation of outbreaks;
   - serological confirmation of sporadic cases;
   - identification of measles virus strains; and

2. to monitor the susceptibility profile of the population:
   - age-group susceptibility to measles;
   - evaluation of the impact of campaigns.

Those activities are carried out at the national level. However, the measles virus is easily carried across national borders, so a regional and global effort is required to achieve and maintain excellent measles control. The First Global Measles Laboratory Network Meeting was held at WHO Headquarters, Geneva, on 11 May 2001, to advance the coordination of the laboratory work of measles control.
In December 1999, WHO published a *Manual for the laboratory diagnosis of measles virus infection*, (WHO/V&B/00.16); (available from: http://www.who.int/vaccines-documents/DocsPDF00/www509.pdf). This document presents the organization and roles of the Global Measles Laboratory Network and the technical aspects of collecting, handling, shipping and testing specimens for anti-measles IgM and isolating measles virus from clinical specimens. It also outlines the management of laboratory data as part of the surveillance system and measles control effort.

The precise details of how the various laboratories in the Network will be monitored and accredited are still to be worked out. It is anticipated that the global level will assess and accredit the regional reference laboratories and they in turn will assess and accredit the national laboratories. It is anticipated that the accreditation will be annual and include a proficiency panel, laboratory surveillance indicators, database management assessment and an annual site visit. National laboratories will have primary responsibility for assessing and accrediting subnational laboratories.

A regional measles surveillance database is currently being developed. Versions are currently in use in Cambodia, the Lao People’s Democratic Republic, the Philippines, Viet Nam and parts of China. The database includes a laboratory component. It is hoped that the database will promote the close cooperation and coordination of national-level laboratory, EPI and surveillance staff, and facilitate data management and analysis. It is planned that routine reports will be forwarded from the national level to the EPI unit at the WHO Regional Office for the Western Pacific.

The laboratory confirmation of suspect cases of measles is necessary in order to conduct accelerated measles control. Testing for rubella IgM on measles IgM-negative cases, isolating measles virus and characterizing the molecular structure of the isolates all improve measles control and monitoring. All of these data must be shared with EPI and surveillance staff routinely and in a timely manner in order to be useful in the fight to control and eliminate measles. The technical expertise to conduct and interpret the tests and the proper data management and sharing of data are equally important. Cooperation and coordination among the laboratory, EPI and surveillance staff at the same level, as well as cooperation and coordination of all laboratories in the Network, are necessary to ensure the lowest incidence of measles and measles-related deaths.
3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Regional Poliomyelitis Laboratory Network

3.1.1 Conclusions

Network laboratories have maintained high levels of performance for several years now and continue to do so even after certification of poliomyelitis-free status. For the Region as a whole in 2000, 87% of laboratory results were available within 28 days of specimen receipt at the laboratory. In 2001 (as of 10 August), 92% of results have been available within 28 days of receipt at the national laboratory, and 100% within 42 days. Results of ITD of poliovirus isolates from AFP cases were available within 90 days of onset of paralysis for 85% of isolates submitted in 2000 and 90% of isolates submitted in 2001 (as of 10 August).

Members of the Regional Poliomyelitis Laboratory Network, however, expressed concern about maintaining certification standards for reporting and investigating AFP cases and collecting adequate stool specimens as, after certification, priorities may be moved to other public health activities and a certain complacency may develop, under the assumption that poliovirus transmission has stopped in the Region.

There were reported episodes of wild poliovirus importation in 2000 in Cape Verde and in 2001 in Bulgaria, resulting in paralysis cases. A poliomyelitis outbreak caused by VDPV type 1 in Hispaniola in 2000/2001 and circulation of type 2 VDPV in Egypt from 1988 to 1993, resulting in 32 cases of poliomyelitis, highlight the need to institute AFP and virological systems that can, not only reliably identify poliomyelitis cases caused by imported wild poliovirus in a timely manner, but also identify cases due to VDPV and areas of VDPV circulation.

In 2001, an AFP case with a VDPV and possible circulation was identified in the Philippines. In that instance, the national, regional and global laboratories collaborated closely and were able to provide important sequence data to permit timely programmatic action.

All national laboratories in the Regional Poliomyelitis Laboratory Network, including the three RRLs, are performing at WHO accreditation standard. All laboratories were visited and fully accredited for 2000, except for one laboratory that was provisionally accredited. All but one of the 31 subnational laboratories in China were shown to be operating at WHO accreditation standard in 2000.

Proficiency tests for 2001 have been successfully distributed to all but one national laboratory, with shipment scheduled for the one laboratory that has not yet received the PT. Currently, laboratories are still required to report PT results within 42 days of receipt, but according to the revised laboratory manual, this interval has to be reduced to 28 days in the future.

The TAG has recommended that countries should aim to reduce the time period between onset of paralysis and availability of ITD results from 90 to 60 days. While the meeting agreed in principle with the TAG recommendation, there are concerns that the laboratories can only contribute to a certain extent, as delays often occur during investigation steps prior to receipt of specimens or isolates at the laboratories.

One of the performance criteria for the Regional Poliomyelitis Laboratory Network in the Western Pacific Region is that all poliovirus isolates, regardless of their source, are being
referred to an RRL for ITD. In order to decrease the workload of the RRLs, staff of selected national laboratories have been trained to use PCR technology for poliovirus testing. PT panels for PCR and NAPH (already routinely used in several laboratories) have been sent to these laboratories. PT panels for ELISA are expected to be sent before the end of the year.

Currently the Regional Office is only storing and distributing typing reagents. Cell lines and proficiency test panels for national laboratories are reliably distributed by the RRL. The distribution system for ITD reagents and ITD proficiency test panels, however, functions on an ad hoc basis, managed by the global specialized laboratories, and requires strengthening, especially under the new requirements of two recommended ITD methods for all poliovirus isolates, regardless of source.

A review of the current mechanisms employed in poliomyelitis laboratories of the Regional Poliomyelitis Laboratory Network to record, maintain and report laboratory data, together with the mechanism used in the Regional Office to receive, consolidate, analyse and report those data, was performed by an external consultant after a briefing at WHO Headquarters on current laboratory data management systems and plans for establishing an integrated data management system.

3.1.2 Recommendations

(1) All poliovirus isolates, regardless of origin (i.e., AFP cases, enterovirus or environmental surveillance), should be forwarded to a WHO-accredited laboratory for ITD by at least two approved methods, one of which must be antigenic (ELISA preferred) and one molecular (probe hybridization or diagnostic PCR preferred).

(2) In order to establish ELISA tests at laboratories carrying out ITD functions but not yet having introduced the method, WHO Headquarters should send reagents and PT panels as a priority matter.

(3) All poliovirus isolates should be forwarded for ITD in a timely manner (for AFP cases within 14 days after isolation; for isolates from other sources as an interim on a quarterly basis).

(4) All poliovirus isolates showing discrepant ITD results should be immediately (within 7 days) sent to a global specialized laboratory (or a laboratory recognized by WHO as having the capacity to carry out poliovirus sequence analysis) for ITD confirmation and analysis of genomic sequence.

(5) The meeting strongly recommends analysing reasons for delays on an ongoing basis to identify and correct problems and also provide feedback to the surveillance units on delays in receipt at the laboratory.

(6) Regular close collaboration between surveillance units and network laboratories must be maintained for early detection of potential poliovirus circulation and priorities set for virological investigation of samples taken from AFP cases with high index of suspicion or clusters of AFP cases.

(7) Based on an assessment made in the laboratories concerned, a storage and distribution system for ITD reagents, and eventually ITD proficiency test panels, should be established by the Regional Office.

(8) The meeting welcomed the new Poliomyelitis laboratory manual, which should be adopted for use by all network laboratories. Individual laboratories should develop their own SOP based on the Manual. Any method that presents changes from the standard and official method should be validated and well documented before it is put into practice.
(9) Following the recommendation of the Third Laboratory Meeting to report all non-poliovirus isolates found to grow in L20B cells to the RRL for confirmation, identification and possible inclusion in the global databank, the Western Pacific Regional Office should collect and compile such data from selected national laboratories.

(10) The Western Pacific Regional Office should define, document and communicate a standard minimum data set, edit checks and transfer format for laboratory data from both national and regional reference laboratories.

3.2 Regional Measles Laboratory Network

3.2.1 Conclusions

The measles laboratory plays a crucial role in accelerated measles control. The primary functions of the measles laboratory are to (1) monitor and verify virus transmission by confirmation of suspect cases using anti-measles IgM assays, identification of measles virus strains and genetic characterization of viral isolates and (2) monitor the susceptibility profile of the population to determine target ages for campaigns and to measure the impact of immunization programmes and campaigns.

A regional network of measles laboratories is essential to ensure that all the functions of the measles laboratories can be carried out successfully. Cooperation, coordination and communication must be regular, open and complete between laboratories at all levels and between national laboratories and their counterparts in immunization services, disease surveillance and data management and analysis.

The national measles laboratories must also assay for anti-rubella IgM because, as measles control becomes better, a greater proportion of suspect cases of measles will be rubella infection. It will be important to document these rubella infections as rubella vaccine is already used in many countries of the Region, and it is anticipated that many of the remaining countries will introduce rubella vaccine. The laboratories can provide data to assess how and when to introduce rubella vaccine, as well as to confirm cases.

3.2.2 Recommendations

(1) The participants should endorse the establishment of the Regional Measles Laboratory Network.

(2) The WHO Western Pacific Regional Office should work with national governments and the Global Measles Laboratory Network staff at WHO Headquarters to identify and enrol regional reference laboratories and national laboratories.

(3) The Regional Measles Laboratory Network needs to develop and finalize regional accreditation standards.

(4) The Regional Measles Laboratory Network needs to develop a system to assess and certify anti-measles IgM assay kits.

(5) All national laboratories should also test for anti-rubella IgM.

(6) The Regional Measles Laboratory Network needs to develop and install a regional laboratory database as part of the regional measles surveillance database. The database should be offered to all laboratories in the Regional Network.
LIST OF PARTICIPANTS

1. REGIONAL REFERENCE LABORATORY STAFF

Dr Hiroyuki Shimizu, Department of Virology II, National Institute of Infectious Diseases
Gakuen 4-7-1, Musashimurayama-shi, Tokyo 208-0011, Japan
Tel: +81-42-561-0771, Fax: +81-42-561-4729, E-mail: hshimizu@nih.go.jp

Dr Bruce Thorley, Regional Poliovirus Reference Laboratory,
Epidemiology & Public Health Division, Victorian Infectious Diseases Reference Laboratory
10 Wreckyn Street, North Melbourne 3051, Victoria, Australia
Tel: 61-3 9342-2607/2600, Fax: 61-3 9342-2665, E-mail: bruce.thorley@mh.org.au

Dr Zhang Libi, Director, National Reference Laboratory for Poliomyelitis
Chinese Academy of Preventive Medicine, 27 Nanwei Lu, Beijing 100050, China
Tel: (8610) 6317-1710, Fax: (8610) 6317-1724, E-mail: npl@ccs.capm.ac.cn

2. NATIONAL POLIOMYELITIS LABORATORY STAFF

HONG KONG, CHINA

Dr Wilina Lim, Consultant - Medical Microbiologist, Government Virus Unit
Clinical Pathology Building, Queen Mary Hospital
Tel: (852) 2855-4112, Fax: (852) 2819-0704, E-mail: wllim@pacific.net.hk

MALAYSIA

Dr Mangalam Sinniah, Head, Division of Virology, Institute for Medical Research
Jalan Pahang, 50588 Kuala Lumpur
Tel: (603) 440-2345, Fax: (603) 2693-6323, E-mail: mangalam@imr.gov.my

MONGOLIA

Dr J. Mendsaikhan, Head - Department of Virology, Public Health Institute
General Director, Infectious Disease Clinical Hospital, , P.O. Box 199, Ulaanbaatar 13
Tel: (976) 1-458699, Fax (976) 1-458699, E-mail: jmend@magicnet.mn; gugus@magicnet.mn

NEW ZEALAND

Dr Qiu Sue Huang, Science Leader-Virology, Communicable Disease Group
Institute of Environmental Science and Research, Kenepuru Drive, Porirua
Tel: 64-4-914-0700, Fax: 64-4-914-0770, E-mail: sue.huang@esr.cri.nz

PAPUA NEW GUINEA

Dr Peter Siba, Head, Virology Unit
Papua New Guinea Institute of Medical Research
P.O. Box 60, Goroka, EHP,
Tel: (675) 732-2800, Fax: (675) 732-1998, E-mail: imrgka@datec.com.pg

PHILIPPINES

Dr Fem Julia E. Paladin, Head, Virology Department, Research Institute for Tropical Medicine
Department of Health, Filinvest Corporate City Compound, Alabang, Muntinlupa City
Tel: (632) 809-7599; 807-2628 (Loc. 605), Fax: (632) 842-2245/2828,
E-mail: fpaladin@ritm.gov.ph; fepent@info.com.ph
Annex 2

REPUBLIC OF KOREA

Dr Youngmee Jee, Senior Researcher, Laboratory of Enteroviruses, Department of Viral Diseases, National Institute of Health
5 Nokbun-dong, Eunpyung-gu, Seoul 122-701
Tel: 822-380-1493, Fax: 822-382-6542, E-mail: ymeejee@nih.go.kr

SINGAPORE

Dr Ling Ai Ee, Senior Consultant Virologist and Head of Virology Section, Department of Pathology, Singapore General Hospital
Outram Road, Singapore 169608
Tel: 65-326-5435, Fax: 65-323-4921, E-mail: gptlae@sgh.gov.sg

VIET NAM

Dr Nguyen Thi Hien Thanh, Laboratory of Enteroviruses, Ministry of Health
1 Yersin Street, Ha Noi 10000
Tel: (844) 826-6352, Fax: (844) 821-0853, E-mail: nihe@netnam.org.vn

Dr Phan Van Tu, Director, Laboratory of Enteroviruses, Pasteur Institute, Ministry of Health
167, duong Pasteur, Q3, Ho Chi Minh City
Tel: 84-88 202878, Fax: 84-88 231419, E-mail: phantu@hcmc.netnam.vn

3. TEMPORARY ADVISER

Dr Walter Dowdle, Director of Programmes, The Task Force for Child Survival and Development
750 Commerce Drive, Suite-400, Decatur, Georgia, Gainesville 30030, United States of America
Tel: 1 404 371 0466, Fax: 1 404 371 1087, E-mail: wdowdle@taskforce.org

4. OBSERVERS

Dr Mark Pallansch, Chief, Enterovirus Section, Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road MS-E05, Atlanta, Georgia 30333, United States of America
Tel: 404-639-2749, Fax: 404-639-4011, E-mail: map1@cdc.gov

Dr Peter Strebel, Chief, Global Measles Branch, Centers for Disease Control and Prevention, 1600 Clifton Road MS-E05, Atlanta, Georgia 30333, United States of America
Tel: 404-639-8764, Fax: 404-639-8573, E-mail: pms4@cdc.gov

Dr Roland Sutter, Chief – Polio Eradication Branch, Centers for Disease Control and Prevention, 1600 Clifton Road MS-E05, Atlanta, Georgia 30333, United States of America
Tel.: 404-639-8762, Fax: 404-639-8573, E-mail: rws4@cdc.gov

Dr Xu Wenbo, Institute of Virology, Chinese Academy of Preventive Medicine, 27 Nanwei Lu, Beijing 100050, China
Tel: (8610) 6317-1710, Fax: (8610) 6317-1724, E-mail: wenchun@public.bta.net.cn
5. SECRETARIAT

WHO WESTERN PACIFIC REGIONAL OFFICE (WPRO)

Dr Kevin Palmer, Acting Director, Combating Communicable Diseases
Regional Office for the Western Pacific, World Health Organization
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: palmerk@wpro.who.int

Dr Yang Baoping, Regional Adviser, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: yangb@wpro.who.int

Dr Sigrun Roesel, Medical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: roesels@wpro.who.int

Dr Yoshikuni Sato, Medical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: satoy@wpro.who.int

Dr Jeffrey McFarland, Medical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: mcfarlandj@wpro.who.int

Dr Osman Mansoor, Medical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: mansooro@wpro.who.int

Mr Wayne Antkowiak, Technical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: antkowiak@wpro.who.int

Dr Hiroko Tanaka, Technical Officer, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: tanakah@wpro.who.int

Dr Paulo Froes, Expanded Programme on Immunization
World Health Organization, Regional Office for the Western Pacific
United Nations Avenue, 1000 Manila, Philippines
Tel: (632) 528-8001, Fax: (632) 521-1036, E-mail: froesp@wpro.who.int
Annex 2

WHO CHINA

Mr Alan Schnur, Team Leader, Combating Communicable Diseases
WHO Representative's Office – China, 401, Dongwai, Diplomatic Office Building
Chaoyang District, Beijing 100600, China
Tel: (8610) 6532 7189 to 92, Fax: (8610) 6532-2359, E-mail: schnura@chn.wpro.who.int

Dr Lisa Lee, Medical Officer, Expanded Programme on Immunization
WHO Representative's Office – China,
401, Dongwai, Diplomatic Office Building, Chaoyang District
Beijing 100600, China
Tel: (8610) 6532 7189 to 92, Fax: (8610) 6532-2359, E-mail: leel@chn.wpro.who.int

WHO HEADQUARTERS, GENEVA

Mr David Featherstone, Scientist, Vaccine Assessment and Monitoring Unit,
Vaccines and Other Biologicals, World Health Organization
CH-1211 Geneva 27, Switzerland, Geneva
Tel: 4122-791-3799, Fax: 4122-791-4193, E-mail: featherstoned@who.ch

WHO REGIONAL OFFICE FOR SOUTH-EAST ASIA (SEARO)

Dr Nalini Withana, Virologist/Consultant, Regional Office for South-East Asia
World Health House, Indraprastha Estate, Mahatma Gandhi Road, New Delhi 110002, India
Tel: (91-11) 331 7804, Fax: (91-11) 331 8607, E-mail: withanan@whosea.org

WHO REGIONAL OFFICE FOR THE EASTERN MEDITERRANEAN (EMRO)

Dr Esther de Gourville, Regional Polio Laboratory Coordinator
World Health Organization, Regional Office for the Eastern Mediterranean
P.O. Box 1517, Alexandria, Egypt
Tel: 203 48 202 23/202 24, Fax: 203 48 389 16/332 85, E-mail: degourvilllee@who.sci.eg