WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

REPORT

WORKSHOP ON LABORATORY SURVEILLANCE FOR MEASLES ELIMINATION IN THE WESTERN PACIFIC REGION

Manila, Philippines
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WORKSHOP ON LABORATORY SURVEILLANCE FOR MEASLES ELIMINATION IN THE WESTERN PACIFIC REGION

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NOTE

The views expressed in this report are those of the participants in the Workshop on Laboratory Surveillance for Measles Elimination in the Western Pacific Region and do not necessarily reflect the policies of the World Health Organization.

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Keywords:

Measles laboratory, IgM ELISA, rash disease surveillance, molecular epidemiology, internal quality control

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SUMMARY

The Workshop on Laboratory Surveillance for Measles Elimination in the Western Pacific Region was held in Manila, the Philippines, from 24 to 25 August 2004.

The WHO Regional Office for the Western Pacific has established a regional goal to eliminate measles, with laboratory support of surveillance as an indispensable element of the programme. This first workshop on the Regional Measles Laboratory Network was convened to establish a network in the Region to help ensure all the member countries and areas in the Region would be served by reliable measles laboratories, satisfying WHO criteria for accreditation in an optimal manner.

The main objectives of the workshop were to review the current status of measles laboratory surveillance in the Region and to proffer solutions to outstanding problems, as well as to finalize the proposed laboratory accreditation guidelines and clarify the role of each tier of the Regional Measles Laboratory Network.

Currently, eight countries are reporting case-based measles data to the Who Regional Office for the Western Pacific, with a further 15 having case-based surveillance. The quantity of samples is expected to increase as more countries introduce case-based surveillance; genotyping will become more important and guidelines will need to be developed.

Measles laboratories will have different expected roles at different levels of function and are categorized into three tiers: global specialized laboratories (GSL), regional reference laboratories (RRL) and national measles laboratories (NML). It was recommended that accredited NMLs should serve each country and area of the Region, while those that do not have the capacity to perform measles testing in the Pacific will be covered by certain NMLs identified as subregional reference laboratories (SRL). Two regional reference laboratories and 17 national laboratories have been designated in the Western Pacific Region with one GSL/RRL in process of appointment. Designation and expected roles of subnational measles laboratories in large countries, such as China and Viet Nam ,still need to be addressed, especially in the context of limited resources. As part of the establishment of the Regional Measles Laboratory Network, a process of accreditation was developed and agreed upon. Some key indicators identified include timeliness of reporting, minimum annual number of serological tests, accuracy of measles and rubella IgM detection confirmed by parallel testing at a RRL, implementation of internal quality control, and scores of WHO-approved proficiency tests and on-site review checklists. NMLs, which have achieved a minimum standard on all criteria, will be granted WHO accreditation by the Western Pacific Regional Office.

The workshop concluded that the goal of the Regional Measles Laboratory Network, which is being established using the principles of the Poliomyelitis Laboratory Network, is to provide integrated, effective support to the Region's efforts in measles elimination. The objectives of the Network should be to develop standards for the laboratory diagnosis of measles and provide the necessary support as the programme evolves, and to establish mechanisms for reference and support of national laboratories in the diagnosis of measles and other rash illness. In addition, the Network should serve as a bank of measles virus isolates for molecular epidemiology and reference sera for quality control. Characterization of the virus is necessary at early stages because accumulation of baseline data is indispensable for differentiation of indigenous and imported infections at later stages.

The recommended procedure for laboratory confirmation of acute measles cases is detection of measles specific IgM antibody in a serum sample obtained at first contact with the suspected case; preferably within an optimal timing of four to 28 days. Validation of measles and rubella kits utilized for testing in countries that are not using validated kits should be given high priority. There should be a focus on internal quality control, including the use of appropriate and approved standard operating procedures, as well as external quality control ensured by accreditation visits with proper documentation of routine records, proficiency testing and activities.

An initial hands-on training course should be held at the earliest opportunity with priority given to those laboratories in need of technical support. As the Regional Measles Laboratory Network expands, continued training of laboratory and field staff will be indispensable.

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1. INTRODUCTION

The WHO Regional Office for the Western Pacific has established a regional goal to eliminate measles. Laboratory support for surveillance, in confirming reported cases of clinically suspected measles and providing useful information to identify high-risk areas for further action, is an indispensable element of the measles elimination programme.

This first workshop of the regional measles laboratory network was intended to establish a network in the Region and to adopt laboratory accreditation guidelines. Discussions focused on what would be required of the measles laboratory network in pursuing the goal of measles elimination, such as timely reporting and transporting of specimens. Special attention was given to establishing a system for equipment maintenance, supply distribution and in-house laboratory quality assessment.

1.1 Objectives

The objectives of the workshop were:

(1) to assess the status of measles laboratory surveillance in the Region, discuss measures to strengthen it, and propose solutions to outstanding problems;

(2) to finalize the proposed laboratory accreditation guidelines; and

(3) to clarify the role of each tier of the measles laboratory network.

1.2 Opening remarks

In his opening remarks, delivered by the Director, Programme Management, the Regional Director noted the significance of the workshop, as the Regional Committee, in its fifty-fifth session in September 2003, had adopted a resolution that measles elimination should be one of two new pillars to strengthen the expanded programme on immunization (EPI) in the Region. The Regional Committee confirmed that measles elimination should be a regional goal and that a target date should be established at the earliest opportunity, based on an annual review of progress. Furthermore, in July 2004), the Measles Task Force has conducted its initial meeting in order to address a target date. Significant progress was made at that meeting and the final meeting report is awaited; however, 2012 has been suggested as a target date for measles elimination.

The Regional Director also stated the multiple benefits to be derived from the achievement of measles elimination. In the short term, a region that has eliminated measles will not only dramatically reduce suffering and deaths due to measles, but will also no longer need to invest in expensive outbreak responses, such as national or sub-national measles campaigns. In the long term, measles elimination strategies can be used to increase awareness and improve routine EPI services to so-called "unreached" or "difficult-to-reach" communities and children.

However, in order for the Region to reach its goal, it is critical to have excellent laboratory capacity in place. Although significant progress has already been made in this area, much remains to be done in the strengthening of existing laboratory capacity. Establishment of the Measles Regional Laboratory Network is a key component in this initiative. He stated that the workshop would serve as a vehicle to provide guidance to Member States and the Regional Office towards the development of an appropriate measles laboratory system, as measles elimination in the Region is a relatively new initiative.

The Regional Director concluded his address by asking the participants for their commitment and dedication towards attaining measles elimination through the provision of high quality laboratory services through the Western Pacific Regional Measles Laboratory Network, which was officially inaugurated at its first meeting.

1.3 Appointment of Chairperson, Vice-Chairperson and Rapporteur

Dr Michael Catton of the Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne, Australia, was appointed as Chairperson; Dr Masato Tashiro of National Institute of Infectious Diseases (NIID), Tokyo, Japan, as Vice-Chairperson; and Dr Paul Rota of Center for Disease Control and Prevention (CDC), Atlanta, United States of America, as Rapporteur for the workshop.

2. PROCEEDINGS

2.1 Overview of global/regional progress on measles elimination

Dr Ernest Smith, Medical Officer, WHO Western Pacific Regional Office, gave an overview of the global measles situation and the Region's progress on measles elimination.

2.1.1 Global goal: measles mortality reduction

The 2003 World Health Assembly adopted a resolution (WHA 56.20) to reduce measles mortality by 50% by 2005 compared with 1999 levels, in keeping with United Nations General Assembly special session on children (2002). WHO and United Nations Children's Fund (UNICEF) globally have defined 45 priority countries where 94% of all measles deaths occurred in 2001. Four of these countries are in the Western Pacific Region: Cambodia, the Lao People's Democratic Republic, Papua New Guinea, and Viet Nam.

Countries with strong immunization programmes have already eliminated measles. Over 98% of measles deaths occur in Global Alliance for Vaccines and Immunization (GAVI)-eligible countries. As a result GAVI will now fund measles control in African countries, and there may be funding in the future for GAVI-eligible countries in this Region.

As measles control improves, increasing rubella is seen because of increased laboratory testing of acute fever and rash cases. It is clear rubella control also needs to be considered as part of measles control. Good surveillance is the key to establishing rubella epidemiology and the potential use of measles-rubella (MR) vaccine.

2.1.2 Target setting experience in other regions

In the WHO Region for the Americas (Pan-American Health Organization) the target date for measles elimination was set in 1994 at the same time as poliomyelitis elimination was certified, because of motivation and political commitment. The target date set, 2000, was considered realistic but challenging, and elimination was achieved by November 2002.

In the WHO Region for Europe and the WHO Region for the Eastern Mediterranean, it was decided that about 10 years would be needed, based on the experience in the Americas Region. The other WHO regions, the Africa Region and the South-East Asia Region, have not yet set target dates.

2.1.3 Western Pacific Region's progress towards measles elimination

There has been an over 95% reduction in reported cases since 1974, and there is now an elimination goal in the Region, building upon existing achievements of EPI in preventing disease. Yet measles still causes suffering, hospitalization, and complications (blindness, and brain damage) as well as deaths – all preventable. There is a strong foundation for the Region's efforts in measles elimination:

The Regional Committee, in resolution RC54.R3:

- "URGES Member States to "develop or strengthen national plans for measles elimination....; to offer, in principle, all children two doses of measles vaccine....; to develop or strengthen measles surveillance systems and laboratory confirmation.....
- REQUESTS the Regional Director to report progress regularly to the Regional Committee and to propose a target date for regional elimination in due course."

Measles remains the leading cause of vaccine-preventable childhood mortality in the Region. However, the estimated deaths, with 35 000 in 1999, continue to decline steadily. According to data reported to the Regional Office, ten countries have announced a target date- four by 2005, and six by 2010; a further 13 have reported they have not yet set any target date, and 9 have provided no response. Eighteen countries have announced they have a measles elimination goal, and 9 have a national measles plan – nearly ALL have provisions for delivery of a second dose, although many are still not incorporated into the routines EPI schedule [done through supplementary immunization activities (SIAs)]

Currently, eight countries are reporting case-based measles data to the Regional Office; a further 15 report having case-based surveillance. The Regional Office needs to work with them closely to encourage reporting.

Case-based means that the surveillance system collects a minimum data set at national level on each case, including, but not limited to information on age, gender, vaccination status, place of residence, travel history, date of rash onset, disease outcome, etc. The data on each case are usually defined as the minimum data set. Case-based measles surveillance in elimination settings usually implies laboratory support for confirmation of the clinical diagnosis via identification of measles-specific IgM-antibodies and/or identification of measles virus in appropriate clinical specimens. Case-based surveillance allows for analysis of measles epidemiology to guide control efforts. As countries approach elimination status it becomes important for every suspect case of measles to be reported and included in the national database. When measles is still relatively common, case-based surveillance may need to be selective - only collecting the data on a sample of cases or a minimal data set.

The process to date for setting a target date has been based on three strategies: two doses of measles vaccine, case-based surveillance and laboratory support. Assessment of the readiness of each country was based on having planned or implemented those strategies. However, the process of conducting an annual review of progress (classifying countries as "in progress", "ready "or "not ready") has several limitations :

- The classification process is reactive and not pro-active.
- Some issues are complex to assess.
- Financial aspects are not included.
- It does not address political commitment.

Therefore, following the recommendation of the Technical Advisory Group, the Measles Task Force was convened to further assess the situation and make a recommendation on setting a target date. The Task Force recommended:

(1) Setting a target date for elimination will hasten political commitment and the mobilization of resources and should be done as soon as possible. The Measles Task Force recommends that the Western Pacific Region set 2012 as the target date for measles elimination.

(2) It is feasible but will be challenging to eliminate measles in every country in the Region by 2012, i.e. within seven years of setting the target. Overall 2012 is the year to which the Region should aspire, but China represents a particular challenge. Measles elimination by 2012 will be feasible for some provinces, however others may require more time.

(3) The Western Pacific Regional Office should work with countries to build political commitment and define the resource requirements by the time of the fifty-sixth session of the Regional Committee in September 2005, so that 2012 can be set as the target date. WHO should help countries to estimate the cost of achieving and maintaining elimination status.

(4) To monitor and report the evolving epidemiology of measles in the Region, an integrated epidemiological and laboratory surveillance system that includes an accredited laboratory network should be established. Particular attention should be paid to establishing a subregional surveillance and laboratory network for the Pacific.

Clearly progress is being made, and it is likely that the Region can look forward to agreement in the near future on a target date for the elimination of measles.

2.2 Structure of the Regional Measles Laboratory Network

Dr Kazunobu Kojima, Scientist (Laboratory Virologist), WHO Western Pacific Regional Office, and Coordinator of the Regional Measles Laboratory Network, gave an overview of the process for the establishment of the Network. The Regional Measles Laboratory Network is to be instituted on the existing and well functioning poliomyelitis laboratory network, with guidance by a WHO quality assurance system, that will be reviewed annually by WHO.

Every Member State in the Region should be served by an accredited national measles laboratory. This will allow strong diagnostic capacity in each country, with standardized methods for IgM enzyme-linked immunosorbent assay (ELISA), and access to regional reference laboratories (RRL) for support in training, viral isolation and molecular epidemiology to identify pathways of transmission. WHO support under the Regional Measles Laboratory Network will include provision of some essential supplies and consumables, and training as appropriate.

Measles laboratories will have expected different roles at different levels of function. The Global Specialized Laboratory (GSL) will provide technical support and evaluation and develop diagnostic methods. The RRL will provide support on virus isolation and characterization (genotyping) and referral of virus strains to the GSL (strain bank), in addition to confirmation and validation of selected specimens referred by national measles laboratories (NML). Subregional reference laboratories (SRL), which will be primarily established in the Pacific, with NML, will perform measles IgM testing of domestic samples, and possibly measles virus isolation, as appropriate. In certain large countries (like China and Viet Nam)

it will be necessary to establish subnational measles laboratories that will function under the supervision and support of the NML, with a commitment from WHO in terms of limited budgetary and technical support.

As part of the establishment of the Regional Measles Laboratory Network, a process of accreditation will be developed. Some key indicators identified include:

- timeliness in reporting: 80% measles IgM test result should be reported within seven days of receipt;
- annual number of tests: 50 measles IgM test;
- conformity to results of RRL: accuracy should be 90%;
- proficiency test (PT): 90%; and
- score for annual on-site review: 80%.

The expected key roles of measles laboratories will depend on the phase of measles elimination in each country or area in the Region. For countries in the initial phase of measles control, the laboratory role will be confirmation of outbreaks (with no need for laboratory confirmation of isolated cases). For countries in the mid-phase of measles control activities, and that have introduced case-based surveillance, all suspected cases should be confirmed by measles IgM testing. For countries in the final stages of measles elimination, in addition to ensuring measles IgM testing for all cases, isolation of measles virus for its further characterization becomes critical. However, even in the earlier phases of the initiative, it is important to gather sequence data from indigenous measles viruses as a genetic baseline for further analysis, including judgement of importation.

Discussion:

One participant requested information on choosing reliable equipment brands and models, but it was pointed out that it is not easy to generalize. Local availability of equipment service providers has to be considered.

There was a question about the GSL/RRL in the Western Pacific Region to which samples should be sent. The National Institute of Infectious Diseases (NIID), Tokyo, Japan, was in the process of official designation at the time of meeting. The Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne, Australia, as a RRL, and, in addition, the Centers for Disease Control (CDC), Atlanta, United States of America, as a GSL, can be considered until pathways are established. There is a need to keep Regional Laboratory Coordinator informed.

In the mid and elimination phases, every case needs to be tested. However, but in an outbreak, there is no need to test every case and countries will need to rely on the EPI link to laboratory-confirmed cases. It is also preferable to obtain genetic information on representatives from each chain of transmission to give an idea of transmission patterns.

Getting viral culture strains to laboratories will be challenging and may require other technologies. Measles virus is very susceptible to heat, and therefore urine samples may be preferable. IgM should be the priority for laboratory confirmation of reported cases, not viral isolation.

2.3 Plan of action of the Regional Measles Laboratory Network

Dr Kojima gave a presentation on the plan of action of the Regional Measles Laboratory Network. The Network is still in its formative stage and much remains to be done to achieve full operational capacity. Plans and priorities are for identification and designation of national, regional reference and global specialized laboratories. So far, two regional reference laboratories and 17 national laboratories have been designated. Designation of subnational measles laboratories in large countries like China and Viet Nam still needs to be addressed, especially in the context of limited resources and budgetary support

from WHO. Assessment of subregional reference laboratories in the Pacific island countries and areas is also an urgent task to ensure quality service of the laboratories to other countries, and support from the Pacific rim laboratories in Hawaii and the Centers for Disease Control, Atlanta, United States of America, especially for the territories associated with the United States of America.

The quality of laboratory outputs, both internal and external, needs to be addressed. Internally, this includes accreditation, definitions of adequate blood specimens, validation of equipment and implementation of standard operating procedures. Externally, there is a need to address specimen collection (e.g. timing) and shipment, especially in large countries.

The quantity of samples is expected to increase as more countries introduce case-based surveillance. Genotyping will become more important and guidelines will need to be developed. Use of dried blood samples for serology should be a priority issue, including guidelines for outbreak response and on the number of samples.

Technical issues need to be addressed. Ensuring budgetary support for the network and adequate shipping arrangements (both for IgM and viral isolates) are critical for the functional implementation of the Regional Measles Laboratory Network. In addition, data management and reporting channels need to be further developed, and workshops for information sharing and training need to be considered.

Given all the actions required above, priorities need to be identified, considering all the needs, in the most timely and efficient manner. Major events to be undertaken urgently include accreditation, technical support, referral of specimens from NMLs to RRLs and establishment of a subregional measles laboratory network in the Pacific.

Discussion:

It was suggested that a study of vaccine efficacy should be conducted to find out whether the current vaccine is efficacious. The currently circulating strain H1 is 2 to 4 lineages different from the vaccine strain, therefore, although there is little evidence to suggest suboptimal efficacy of the vaccine, it is reasonable to assume that efficacy will be lower against the newly found strains. The fact that measles immunity from immunization wanes without being boosted by a second dose or natural exposure also needs to be considered.

There is a need to consider budgetary support for each NML to enable the sending of samples to the RRL, given that parallel testing is a requirement for accreditation. The issue of resources is important in keeping the Network running. From experience, weak government support may be anticipated, even in a high-income countries.

2.4 Criteria for laboratory accreditation

Mr David Featherstone, Global Project Leader, Global Measles Laboratory Network, WHO Headquarters, gave an overview of the accreditation procedures for NMLs. The WHO global accreditation programme for the measles laboratory network is similar to that which was implemented for the poliomyelitis laboratory network. The global accreditation process has already been implemented in other WHO regions and will soon be implemented in the Western Pacific Region. Assessment is done to ensure all countries have access to laboratories that are operating at similar high standards of performance and timeliness for measles testing. Its aim is to build up laboratory capacity and ensure strong functionality. The assessment also provides quality assurance of surveillance data for measles control programmes.

The accreditation process includes an annual proficiency test, which takes place over one or two days each year. However, this provides no information on other laboratory functions, and may not be

representative of the laboratory's actual performance. Annual review will occur for all measles and rubella laboratories in the network. An onsite review may occur every one to three years, depending on the quality and capability of the laboratory, and as opportunity or need arises.

To perform assessment, all data for the previous 12 months are reviewed during the visit. Laboratories are expected to achieve a minimum standard on all criteria. The six criteria to be met for accreditation of a national measles laboratory are:

(1) Test results are reported by the laboratory on at least 80% of serum samples within 7 days of receipt.

(2) Serological tests are performed on at least 50 serum specimens annually.

(3) The accuracy of measles and rubella IgM detection is at least 90%.

(4) Internal quality control (QC) procedures for IgM assays are implemented.

(5) The score on the most recent WHO approved proficiency test is at least 90%.

(6) The score for laboratory operating procedures and practices reviewed with the checklist is at least 80% (Onsite assessment).

The three assessment levels are: pass, provisional or fail. If the laboratory fails assessment because of laboratory data results, there is a second chance. If the laboratory fails on the second assessment, there is a need for duplication of tests in another appropriately qualified laboratory with spare capacity.

To fulfil the criterion for the number of tests performed a year, the tests need not be measles IgM assays, but can be another form of ELISA assay, which will demonstrate capability and experience.

Referral of specimens is essential for validation of laboratory results and requires that a proportion of samples be sent to the RRL. The quantity to be sent depends on the type of assay used. If using a validated assay, then 10% of both positive and negative samples with every outbreak must be represented. A minimum of 10 samples should be sent if annual samples number is less than 100. Should non-a validated assay be employed, then 20% of samples from every outbreak should be validated at the RRL.

Referral of samples should be done four times a year, or immediately if problems arise within a laboratory.

Discussion:

One participant questioned the necessity of rubella testing as he believed it easy to differentiate rubella from measles owing to the clinical manifestations. However, it is widely believed that the programme requires generic assessment to cover both measles and rubella as other regions conduct this. Many countries in Western Pacific Region are notifying rubella outbreaks as measles and this varies according to the country situation. According to experiences in the Americas, some IgM-positive serum samples from dengue cases give false-positive results in the measles IgM assays used in the Americas.

Although Dade Behring ELISA kits are widely employed as they are easy to use, reliable and have very good sensitivity and specificity, and rubella assays are made in the same format, countries may choose another assay. One country uses immunfluorescence , as they do not have many cases, but is considering using ELISA kits from Denka Seiken, found to be comparable to Dade Behring kits in terms of performance, but much cheaper. WHO has an agreement with Dade Behring and can assist countries

in buying at a WHO discounted price. PanBIO (an Australian company) kits are used in another country but may not be ideal.

There is a need for WHO to validate different test kits. The results of an assessment of different test kits has been published in the *Journal of Clinical Microbiology* (Vol. 38: 99-104; Vol. 41: 4790-4792), but it could not test all available assays. Six were assessed, and the Dade Behring kit was fully validated from WHO.

Every suspected cases should get an EPID number, unique to that case. WHO-approved cell lines can be provided by the designated network laboratory if requested through WHO.

2.5 Proficiency testing and quality assurance

Dr Michael Catton, Medical Director, Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne, Australia, gave a presentation on proficiency testing in the global network. The objectives of proficiency testing are (1) to ensure quality (sensitivity of testing: discrimination of true measles IgM-positive sera), and (2) to ensure specificity of testing (discrimination of true negative sera) using a meaningful but manageable panel size to give a good measure of the quality of laboratory services.

Since 2001, VIDRL has sent out a number of panels to WHO regional offices in Africa, the Eastern Mediterranean and South-East Asia to be forwarded to over one hundred participating laboratories. The distribution is opportunistic. Panel composition is 20 specimens, which is considered enough to give a meaningful reflection of performance while remaining a manageable number to test. They comprise measles IgM positives and negatives, parvovirus, rubella and dengue samples. Pre-issue sample validation is through two methods.

A high standard of testing was achieved for the first panel, with 91% of laboratories scoring 19 out of 20 or better. Timely and complete reporting of results could be improved, with only about 60% of participants returning results.

Key issues for the implementation of proficiency testing in the Western Pacific Region include the assembly of a database of participating laboratories, with contact details, and a plan for the logistics of panel delivery, distribution of panels, analysis of results and reporting. Remaining issues for continued functioning of proficiency testing are replenishment of specimen stocks, sourcing of rubella IgM-positive specimens and development of rubella proficiency-testing panels.

Discussion:

There was a request from VIDRL for assistance in obtaining serum for the proficiency testing. About 8 ml is needed for each panel, especially for rubella and dengue.

Experiences in the Americas show some IgM-positive serum samples from dengue cases give false-positive results in the measles IgM assays.

It has been confirmed that proficiency testing is done confidentially, but not reported. Although duplicate testing would be advantageous, at present VIDRL does not have the volume of samples for this.

It is advised that, when a proficiency-testing panel is received, the samples should be centrifuged first. While there may be worries about shipment, the antibody has been found to be very stable, and delays in transit do not appear to affect results. Also it is also recommend not to freeze proficiency-testing panels, but to keep them at 4° C at all times. Several freeze-thaw cycles might reduce the IgM to below the detection level in some samples.

2.6 Assignment of national measles laboratories to each regional reference laboratory for virological analysis and assistance

Dr Kojima gave a presentation on the rationale for assigning national measles laboratories to regional reference laboratories.

Regional reference laboratories will undertake measles virus isolation, which is not necessarily conducted at national measles laboratories but is indispensable for characterization of the virus, such as by genotyping, molecular epidemiology, and establishment and maintenance of a strains bank. Prompt feedback of the test results and technical support to national measles laboratories will be expected. Parallel testing of selected serum specimens at regional reference laboratories is also important, as the concordance of the results of both ends is a criterion for accreditation of national measles laboratories.

The proposed assignment of national measles laboratories to regional reference laboratories is based on the geography of the Western Pacific Region. Those in the north of the Region (Cambodia, Hong Kong (China),the Lao People's Democratic Republic, Macao (China), Mongolia, the Philippines, the Republic of Korea and Viet Nam) will use the NIID in Japan, while those in the south (Brunei Darussalam, Fiji, French Polynesia, Guam, Malaysia, New Caledonia, New Zealand, Papua New Guinea and Singapore) will use VIDRL in Australia. Provincial/prefecture laboratories in China will use the national measles laboratory in China. This is a proposed structure and is open for further review.

Priorities regarding the assignment of laboratories are (1) designation of a northern regional reference laboratory in Japan, (2) establishment of mechanisms and routes for the shipping of specimens and (3) development of guidelines for specimen numbers and frequency of shipments, and assurance of feedback from regional reference laboratories to national measles laboratories.

Discussion:

Although a draft structural relationship between national measles laboratories and regional reference laboratories has been proposed, mainly based on the geographical location of the countries, it is suggested to take airline routes into consideration as well.

Because of the capacity and limited budgetary resources of regional reference laboratories, it is important to get a idea of the number of samples that will be sent.

2.7 Measles testing for Pacific island countries and areas – report from the satellite meeting.

The Pacific islands comprise 20 countries and areas, with a population range of from around 1000 (Niue) to over 800 000 (Fiji). Distances both within and between countries are often extreme, and many people live in relative isolation with limited access to health services.

The geography of the Pacific islands creates many challenges for the establishment of the Measles Laboratory Network in the Pacific, particularly, the transport of samples to laboratories for testing. In addition, the laboratory capacity for measles serology in the Pacific is limited, with only four of the 20 countries and areas having the ability to perform measles serology. These are Fiji, French Polynesia, Guam and New Caledonia. No facilities can perform viral isolation, and this will require support from outside the Pacific region.

The most practical option for the establishment of the Measles Laboratory Network in the Pacific is through alignment with the current WHO/Pacific Public Health Surveillance Network (PPHSN) LabNET. Measles (and rubella) are core target disease of LabNET, and LabNET has strong ownership from Pacific island health professionals. Furthermore, the LabNET structure of L1, L2 and L3 laboratories is

consistent with the proposed structure of the Measles Laboratory Network, with the L2 laboratories serving as 'subregional laboratories'. WHO support could be directed in the following areas: funding and coordination, especially for reagents and transport containers, accreditation of L2 laboratories, expansion of laboratory capacity for rubella testing, and introduction of new techniques for sample collection (e.g. dried venous blood spot technique).

The satellite meeting concluded that the establishment of the Measles Laboratory Network in the Pacific would face challenges primarily due to limited national capacity for measles serology. Cooperation from countries both within and outside the Pacific will be essential to develop diagnostic capability for measles testing. LabNET provides a good framework for the establishment of the Measles Laboratory Network in the Pacific islands, and WHO support could be directed through this initiative.

2.8 Updates on international shipping of specimens

Mr Richard Duncan, Technical Officer, EPI, Office of the WHO Representative in the South Pacific, gave a presentation on the update to the *United Nations Recommendations on the Transport of Dangerous Goods. Model Regulations*, which are designed to harmonize regulations to facilitate safe transport of hazardous materials internationally. They were first published in 1957 and established minimum requirements for all modes and aspects of transportation. The regulations address criteria of materials, standards of packaging and system of communicating hazards. The *Model Regulations* are in their 13th revised edition (2003).

The *Model Regulations* have nine hazard classes, with Class 6 comprising "Toxic and Infectious Substances". Division 6.2 – Infectious Substances includes micro-organisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, biological products (derived from living organisms), cultures (prepared for intentional generation of pathogens), genetically modified micro-organisms and organisms, and medical or clinical wastes.

There has been a major modification in the way substances are classified in the 13th revised edition of the *Model Regulations*. Previously, classification was based on risk groups (1, 2, 3, 4), according to laboratory risk and not according transport exposure. The *Model Regulations* did not specify pathogen risk groups. The result was inconsistencies in the classification among countries, and overregulation, which led to noncompliance. In the current 13th revised edition, a new category system has been introduced based on detailed, case-by-case, risk assessment of micro-organisms known to be pathogens. The assessment considers the scientific data on risks of transmission and infection posed during transport for each species of micro-organism. It is not a relaxation of standards, but a readjustment according to appropriate risk assessment. The new *Model Regulations* are to be implemented from 1 January 2005.

2.9 Alternative methods for measles laboratory assay and sample collection

Dr Masato Tashiro, Director, Department of Virology, National Institute of Infectious Diseases (NIID), Tokyo, gave two presentations, first, on a new cell line that is useful for measles virus isolation and diagnosis testing, and second, on a particle agglutination antibody method, developed at the request of WHO, that is easy and inexpensive to conduct.

In the past, Vero cells were used, but these are relatively insensitive to wild measles virus. Fifteen years ago, the B95a cell line, which is highly sensitive to wild measles virus, was established. This cell line expresses EB virus, and therefore needs to be handled as an infectious substance at all times. (All virus isolation work is done at BSL-2).

For measles virus, two receptors have been identified: CD46 (used by laboratory strains) and SLAM (wild measles viruses). Vero/SLAM cell lines that express both CD46 and SLAM cell receptors

and are highly sensitive to both vaccine and wild measles virus have now been developed. These cell lines are also susceptible to rubella virus and can be used for isolation of both measles and rubella. The Vero/SLAM does not express EB virus and therefore these cells do not have to be treated as infectious substances at all times. This provides a significant safety advantage for laboratories performing virus isolation and facilitates shipment of the cell line to laboratories within the Network. Although Vero/SLAM cell lines require an expensive antibiotic (G418) to maintain the transfection necessary for expression of the SLAM receptor, it was reported that cell passage could be made up to 50 times in the absence of G418 in the cell culture medium, without it significantly losing its unique sensitivity to wild measles viruses.

Measles capture IgM PA assay has been developed in NIID and provides a simple method for measles IgM detection. The specificity compared with Behring was lower, but still acceptable for countries in the control phase. The WHO network has been evaluating the PA method since 2001. It has been found to have 81% overall sensitivity compared with the 91% sensitivity of the Behring EIA recommended by WHO. The advantage is that it allows confirmation at first contact with the health facility. The kit has a long shelf-life, is stable for a long period at room temperature and is readily available. The cost per test is about US$1.00.

There are many systems available for IgM serology; however, there is considerable variation in quality and cost. Measles and rubella are assessed independently. Many laboratories currently use Behring kits, some of which are supplied by WHO. There is a need to assess other assays if they are to be used in the measles control programme.

At the 2002 WHO Steering Committee Meeting, the PA assay was found to be promising, but unlikely to replace ELISA due to lower specificity and sensitivity. However, it still has a potential role in the front line of health services where ELISA machines are not practical. After 2002, interest was shown in the commercialization of the assay. The cost of the assay depends on the volume of production/demand – greater volume gives a cheaper price.

Discussion:

Despite there being reports that cell passage could be made up to 50 times for the Vero/SLAM cell line without jeopardizing its sensitivity to wild measles virus, this should be carefully assessed in an extensive manner.

With SLAM cell line, CPE will appear three to five days after inoculation and is very clear. Especially from a safety point of view, use of this new cell line is highly recommended. NIID can provide the cells to countries upon request.

Mr Featherstone, Global Project Leader, Global Measles Laboratory Network, Department of Immunization, WHO Headquarters, gave a presentation on alternative sampling methods to serum for measles diagnosis. Some countries have had difficulty in collecting and shipping serum, and dried blood samples and oral fluids have been used as alternatives. VIDRL has done a lot of work on dried blood samples for the Behring assay, while oral fluid has been tested extensively in the United Kingdom. However, these have not yet been used or compared in Network laboratories.

WHO recently compared serum, dried blood samples and oral fluids in Uganda (tested at CDC, Atlanta), Cote d'Ivoire and Turkey (national laboratories). All measles cases in the study had three samples collected, to ensure a robust assessment of the three types of samples before introduction into countries.

The dried blood sampling method uses filter paper marked with disks for collection of blood that contain about 5 microlitres of serum. The filter paper template is easy to produce using a laser printer.

Blood is collected from the finger or heel of the patient using a sterile lancet and dropped on the filter paper. Once a sufficient sample is obtained, it goes through an extraction process and is analysed using the standard Behring assay. The overall effectiveness of this technique in the three study areas showed comparable results to the standard serum method. The dried blood sampling method could also be used for virus detection and genotyping, using a nested polymerase chain reaction (PCR) technique.

The oral fluid technique relies on the exudates of fluid coming from between the gum and tooth that contain immunoglobulin in same composition as blood, at a much lower concentration (3.2 times less), but is much easier to collect. Due to the lower concentration, there is a need to increase the sensitivity of the assay method. The Behring assay is not sensitive enough, but the commercially available Microimmune assay is suitable. The oral fluid method was found to be comparable to standard serum assays in terms of sensitivity and specificity. In oral fluid samples, measles and rubella RNA could be amplified by PCR. Oral fluid is the standard sampling method used in the United Kingdom, and PCR/sequencing is used to genotype measles and rubella positive cases.

IgM has been shown to be relatively stable using the alternative sampling methods. Oral fluids samples in the United Kingdom are sent in the post at ambient temperature, and IgM detection does not appear to be affected. There are minimal data on IgM stability at higher temperatures. For dried blood samples, there have been several experiments which have shown IgM to be stable in samples at room temperature for various lengths of time. RNA stability for both oral and dried blood samples has not been evaluated at elevated temperatures, but in spiked dried blood samples, measles RNA can be detected for >150 days at 37°C.

The safety of these techniques (both for patient and transmission of infection) is good, although the dried blood technique involves invasive sampling. Transporting procedures for dried blood samples requires packaging as diagnostic specimens, but a reverse cold chain is not required for short periods. Oral fluids survived the United Kingdom postal service at ambient temperature.

The cost for dried blood samples is similar to serum, but is higher for oral fluids due to higher assay costs. This might decrease with economies of scale. Collection devices and processing are similar for all three methods and the transport costs for dried blood samples are much reduced.

Constraints include limited data on dried blood sampling for rubella, and the sample volume being limited by the number of spots obtained. This is an issue for confirmatory testing by the regional reference laboratories. Additional training is needed for collection of samples and for the assay method. Also at present there is no rubella IgM assay that is commercially available for oral fluids. Serum is still considered the gold standard; however, countries in the mortality reduction phase with hard to reach populations or infrastructure difficulties may benefit from using the new methods.

In summary, oral fluid and dried blood samples have a good correlation with serum for measles IgM detection. For measles, both oral fluid and dried blood are suitable for IgM and RNA detection. In the case of rubella, oral fluid has been found suitable for IgM and RNA detection in the United Kingdom, but only limited data are available for dried blood. Limitations exist in all three sampling methods. Where serum sampling methods are working, there is probably no need to change. Further investigations are needed on the stability of oral fluid IgM, the rubella IgM assay for oral fluids, and the cost of measles oral fluid assay.

Discussion:

VIDRL has done some work on PCR and oral fluids dried on filter paper and found that, in 39 patients with paired nose/throat swabs and oral fluids, the results were the same in 67% of cases. Thus oral fluids might be an option for further evaluation.

Dried blood sampling appears to be useful for sero surveillance in those countries that choose to use it. It was suggested to focus on IgM, but a lot of work has also been done in VIDRL on IgG. Although stability was not assessed, given the general understanding that IgM should be less stable than IgG, similar results could also be expected for dried blood samples.

2.10 Genotyping (or other advanced techniques)

Dr Paul Rota, Supervisory Microbiologist, Measles Virus Section, Centers for Disease Control (CDC), Atlanta, United States of America gave a presentation on genotyping for measles virus. Molecular techniques must be used in conjunction with standard case reporting and tracing work. Molecular data provides added value in monitoring transmission pathways and identifying sources of virus. Also it is the only way for a laboratory to confirm a suspected vaccine reaction. CDC has been working with WHO to standardize nomenclatures for measles since 1998. There is a standardized methodology for variable regions on the measles genome: the N and H genes. Sequences obtained by PCR from the N gene are compared against a list of WHO reference strains, then assigned to known or new genotypes.

A series of standard strain names, similar to those used for influenza, provides information as to when and where viruses were isolated (molecular and epidemiological information). All vaccines are in genotype A. Genotypes that have not been detected in the last 15 years are considered inactive.

Ongoing efforts for standardization and improvement include use of new cell lines that are easier to work with and ship, providing guidance on designation of new genotypes, and publication of reference material describing the genotypes.

A summary of global distribution of wild measles virus was provided. The most commonly detected genotypes in Europe are D7 and D6. H1 is predominant in Asia (China, Japan, Mongolia.) and D3 in the Philippines. There is an extraordinary amount of work done in China and excellent virological surveillance. In the United States of America, the pattern of virus genotypes detected reflects the various sources of importation of virus. Genotype information has also helped to identify the sources of importation.

The detection of genotype D9 in Indonesia is interesting. D9 was first detected and isolated in Venezuela during 2001-2002, and the source of this virus was uncertain at the time. Since South and Central America did not have good baseline virological surveillance before accelerated control measures were initiated in the early 1990s, the pattern of endemic genotypes is not known. However, the simultaneous detection of genotype D9 viruses in Indonesia, a country with endemic measles, suggested that genotype D9 had been recently introduced into Venezuela, and did not represent long-term circulation of a previously undetected endemic genotype in the Americas.

Molecular data have limitations. Genetic analysis can confirm that outbreaks are not linked if different genotypes or different lineages within a genotype are detected in separate outbreaks. However, if genetically homogeneous strains are detected from multiple sites or on a continuing basis, it will be difficult to differentiate between ongoing transmission of a single, endemic genotype and multiple importations of virus from the same source.

Genotype B2 was isolated in South Africa from a case imported from Angola. Genotype B3 is the most prevalent genotype in western Africa. B2 was last detected in 1984 and was not detected again until recently. This shows that South Africa has done a good job in reducing endemic measles transmission and detecting imported viruses. It also indicates that virological surveillance is incomplete in many areas, since the circulation of the genotype B2 viruses in western Africa was not detected over a 20-year period.

Genetic analysis of measles viruses obtained in Burkina Faso before the measles SIA showed evidence of multiple chains of transmission within the endemic genotype, B3. After the measles SIA, measles viruses isolated from outbreaks were genetically homogenous, suggesting that most of the transmission chains had been interrupted and the outbreaks were the result of a single introduction of virus. This type of pattern has been seen before in areas that have relatively good measles control, but are still experiencing sporadic outbreaks.

What can molecular data tell us? If transmission has been eliminated, there should be no consistent identification of a single endemic genotype. Therefore, molecular epidemiological data can provide an additional means to measure the effectiveness of measles control programmes.

In conclusion, genetic characterization of wild measles viruses provides a means to facilitate the study of transmission pathways of the virus and is an essential component of laboratory-based measles surveillance activities. Virological surveillance needs to be expanded in all areas of the world and conducted during all phases of measles control. Samples should be obtained from each chain of transmission. Timely reporting and dissemination of genotype data are needed. Also, it is necessary to address logistical problems. As the WHO laboratory network expands, continued training of laboratory and field staff will be indispensable.

Attempts should be made to obtain measles isolates or genetic material from all countries with endemic transmission to identify indigenous genotypes prior to implementing control efforts. At least 5 to 10 samples should be obtained from each chain of transmission.

To identify transmission patterns in areas where measles elimination has been achieved, laboratories should continue to obtain viral isolates from each chain of transmission.

For measles virological surveillance, the preferred specimens are either a urine sample or a throat/nasal swab (or both) taken at first contact with the suspected case. It is very important to take the specimen for virus isolation at first contact with the suspected case. Greatest success for virus isolation or RT-PCR can be expected if the specimen is taken within 0 to 5 days of rash onset. Virus isolation rates are 40% of IgM positive cases if specimens are taken 0 to 5 days after rash onset, whereas no viruses can be isolated after six days.

Discussion:

After doing real time PCR for other viruses, one laboratory found that high levels of Ct value did not mean specific amplification, and wanted to know the experience of others in real time PCR and the cut off level/threshold cycle of other laboratories. CDC uses a default cut off.

If a country in the elimination phase finds a new genotype, there is a need to look at more than just genotype information. This could be missing cases and, if there is no good surveillance system, genotyping information will be of limited value.

2.11 Status of Regional Measles Laboratory Network activities in the South-East Asia Region

Dr Nalini Withana, Measles Laboratory Network Coordinator, WHO South-East Asia Regional Office, gave a presentation on the measles and rubella laboratory network in the South-East Asia Region. The Region has eleven countries, most being poliomyelitis-free. Only India still is endemic for poliomyelitis.

Poliomyelitis eradication still remains the highest priority for the Region. All countries except India have been free of wild poliovirus for over three years and poliovirus circulation is at its lowest ever this year, with only 33 cases reported by mid-August. Interruption of wild poliovirus circulation is within sight.

There is no goal yet for measles elimination, but a clear desire for mortality reduction. Building on the AFP surveillance infrastructure, the South-East Asia Regional Office has commenced measles activities in its Member States. The South-East Asia Measles Laboratory Network was established in 2002. It has a hierarchical structure with at least one national measles laboratory in each Member State, one Regional Reference Laboratory at the National Institute of Health (NIH), Thailand, and CDC, Atlanta, as the designated Global Specialized Laboratory for the Region. In most countries, poliomyelitis and measles laboratories are located in the same institute, and this has facilitated laboratory reviews.

The national measles laboratories are fully equipped and have communication facilities. A virologist and one technician from each of the laboratories have been trained at regional workshops. All laboratories are using the Dade Behring kits and are following the recommended procedures for measles and rubella testing. Proficiency testing panels have been distributed annually and all laboratories have passed.

Samples are collected either by the surveillance staff or by the laboratory staff visiting the outbreak sites, and the laboratories have assisted in the confirmation of measles and rubella outbreaks. All viruses isolated in the Region are sent to CDC for sequencing. Confirmatory tests on 10% of positives and negatives are being done; >90% results are reported to the programme within seven days and laboratory data are forwarded to the South-East Asia Regional Office monthly.

Measles laboratory information system software has been developed based on the system developed by the South-East Asia Regional Office and WHO Headquarters for the poliomyelitis laboratories. The system is user-friendly, enables virologists to analyse data, generates graphics and reports, tracks specimens and monitor timeliness. It has been pilot-tested and is undergoing final evaluation before being distributed to all the laboratories in the network.

Laboratory development is in parallel with measles surveillance activities. Staff are trained and undergo proficiency testing in a workshop; once they pass and are doing continual work, the laboratories are nominated by the countries. Participants in the workshop were given reagent kits. The current measles network has 15 laboratories, which are all doing well. Proficiency tests have been distributed three times, and all passed. The WHO South-East Asia Region has a three-tier structure (CDC as the global reference laboratory, a regional reference laboratory in Thailand and national laboratories). There are four laboratories in Indonesia, and one of these was chosen to do the confirmatory tests for the other laboratories in the country.

All laboratories have ELISA readers, washers and incubators, some supplied by the South-East Asia Regional Office. They also all have communications equipment (e-mail and fax). Initially all laboratories used different test kits but this has been standardized according to WHO recommendations. The South-East Asia Regional Office procures reagents twice a year and sends them to countries. The accreditation process has not been implemented yet, but will commence shortly.

After the Measles Laboratory Network was started, rubella testing increased and circulation was identified in Bhutan.

Collection and transportation of samples is costly and new sample collection methods should be implemented [e.g. dried blood spot (DBS)]. It is hoped to start a pilot project in Indonesia to test new collection methods.

The current focus is on the confirmation of outbreaks due to the measles control phase in the South-East Asia Region. Generally laboratory test samples are tested once a week to reduce kit/strip wastage. Confirmation for individual cases is not recommended. Samples are tested for measles, and if negative, for rubella dengue and chikungunya. Containers for collection have been provided by the South-East Asia Regional Office. Most countries use an AFP stool transport system for measles shipment.

National measles laboratories report within seven days to EPI Officers. The reporting system to the South-East Asia Regional Office is being developed. Results are currently reported once a month for inclusion in the bulletin. Problems exist in data recording and data transmission and due to the mismatch between surveillance and laboratory data.

2.12 Experience of measles control in China

Dr Xu Wenbo, Head, National Measles Laboratory, Chinese Center for Disease Control and Prevention, gave a presentation on experiences in China. Measles vaccine was approved in China in 1968, and EPI started in 1978. In 1985, a two-dose schedule was introduced, with a 90% decrease in measles mortality and morbidity compared with the pre-vaccine era. China has made great progress in measles control, but there are still measles outbreaks, 50% in 5 to 10 counties, where the most vulnerable populations live. Most cases are less than 8 months old or in adults. The highest incidence is in Western China

The National Measles Laboratory was established in 2001. The support role played by the laboratory depends on the stage of measles elimination in the province being served (e.g. control vs. elimination). Counties still experiencing outbreaks have only 10 confirmed cases. Measles classification is done according to WHO recommendations. The Measles Laboratory Network, which is established in 31 provinces and 331 prefectures for the rapid identification of measles cases, plays a key role in measles surveillance. Objectives of the Network are to provide guidelines for laboratory diagnosis of measles in China, to provide technical assistance to provincial and prefectural laboratories on measles surveillance, and to conduct molecular characterization of measles virus including confirmation and identification of source of virus and pathways of transmission.

Some of the responsibilities include:

- supporting the usage of IgM-ELISA as the standard assay for the diagnosis of acute measles infection;
- training of staff of provincial and prefecture laboratories;
- confirmatory testing on specimens submitted from the provincial and prefectures laboratories;
- proficiency testing in the provincial and some prefecture laboratories; and
- carrying out serological surveys to measure the level of population immunity in China.

Discussion:

There was a discussion regarding meeting the timeliness indicators for reporting.

A concern was raised about the differentiation of IgM as to whether this is induced by wild virus or vaccine, especially when doing mass campaigns. IgM usually lasts for about 28 days after vaccination and it should disappear after 2 months.

2.13 Country presentations

2.13.1 Cambodia

Measles/rubella testing started in October 2000 in collaboration with the National Immunization Programme, which is responsible for sample collection. Central to the improvement of the laboratory system, laboratory training has been conducted in the areas of standard operating procedures, test performance and reporting.

Specimen management consists of collection, transport, referral and storage. Serum specimens are collected, which are then appropriately labelled and shipped within the cold chain, according to fixed procedures, either by taxi or air. Transport is an issue, especially the length of time often required for specimens to be sent from cases to the national level, and ensuring funding for this.

Since the start of the Network in 2000, many cases of measles have been detected, with minimal rubella. The majority of the samples tested are positive for measles IgM.

Discussion:

The responsibility for measles surveillance was discussed. The referral pathway is not very clear, with the laboratory just receiving samples from the National Immunization Programme. However, this is beyond the responsibility of the laboratory.

2.13.2 The Philippines

There is already a target date for measles elimination by 2008, starting from the 1998 campaign for children under the age of 15 years. In February 2004, the first follow-up campaign was undertaken for all children born after the initial campaign, rounded up to eight years because of low coverage among the youngest children in the 1998 campaign. So far 92% coverage has been achieved, and ongoing mop-up is likely to increase the final coverage. This campaign was the first to carry out validation of coverage (using a rapid coverage assessment) and mop-up of areas with low coverage. The rapid coverage assessment was based on the selection of sites using spot maps to cover both easy and hard-to-reach areas. For each *barangay*, four sites were selected and the status of five eligible children was assessed based on the mark from vaccination or the history, as the mark did not always stay on. The validation showed that fixed sites had resulted in poorer coverage than door-to-door immunization. It also showed that, in areas with good local government unit support, coverage was higher. Lessons learnt to date include: microplanning should be used to address staffing problems; the door-to-door strategy is critical for achieving high coverage; and rapid assessment is an essential tool for ensuring coverage is achieved with unreliable target population estimates.

Measles surveillance and laboratory confirmation are key pillars of the measles supplementary immunization activities (SIA). This has been implemented since 1998, with the initial SIA used primarily

to detect areas where measles transmission is still occurring and to differentiate between indigenous and imported cases.

Measles surveillance is built on AFP surveillance and has three components: case detection in the hospital setting and outbreak investigation; IgM testing (for at least 50% of cases); and data analysis and reporting. The cost of transportation is a limitation.

A pilot study conducted to establish the surveillance system with laboratory support showed that surveillance was possible, and it was started officially in 1999 and fully implemented in 2000. Reports are collated at the national level. Measles-negative samples are tested for rubella.

2.13.3 Republic of Korea

Measles cases have been reduced markedly through a two-dose schedule for measles and rubella. Despite this, an outbreak of measles occurred in 2000 and required a catch-up campaign to be implemented to control the number of cases.

There is a measles elimination plan and there has been a change in policy from control to elimination. Key to the strategy is post-vaccination surveillance and the laboratory-based surveillance network in the 16 provincial laboratories, with its strengthening of proficiency testing in the provincial laboratories.

2.13.4 Fiji

Fiji has the support of the Ministry of Health for its role as a subregional reference laboratory for other Pacific island countries and areas. The health system in Fiji covers about 300 islands, of which about half are inhabited. The island group is divided into four. Many of the islands need to be accessed by boat, and the journey can take up to two days and nights. The main public health laboratory is at Mataika House in Suva.

Measles coverage is high. There is a two-dose measles schedule and conducted SIAs in 1998 and 2001. Fiji has set a target date of 2008 for measles elimination. The public health laboratory does surveillance for dengue, filiarisis, measles and leptospirosis, in addition to functioning as an L2 Laboratory for other Pacific islands. Since 2000, Fiji has been testing measles samples from Kiribati, Nauru, Samoa and Tuvalu.

Samples for testing can take about 10 to 15 days to reach the laboratory from the service level, and are usually tested within seven days. Centres are informed by telephone of results. The issues facing the laboratory network in Fiji are a lack of capacity for measles testing at the subregional level, transportation, storage of samples (continuous freezing and thawing), funding for reagents, batching of samples for transport, and delays in getting results from regional laboratories.

A key need is accreditation of the laboratory, and WHO support would be welcomed.

The volume of testing is low compared with the number of suspected measles cases reported.

Discussion:

Regarding transport, cold chain and funding are the main issues and DBS might be a better option. In Fiji, during outbreak there a team goes out and investigates and can send samples back. If the outbreak is in the islands, the Navy transports the samples.

2.13.5 Viet Nam (Ho Chi Minh City)

Viet Nam follows the WHO-recommended plan of action, with a focus on SIA. There is a large population of 81 million people. Measles incidence from 1995+ shows frequent outbreaks, with significant underreporting. There are two national measles laboratories, one in the north and one in the south.

In 2004, two IgM positive cases were reported in the north, and only one case in the south, which shows the significant impact of the SIA. The number of cases tested is not evenly divided between facilities. Both laboratories use specimens (whole blood) collected from patients that meet the WHO case definition and the samples are tested by ELISA, using reagents supplied by WHO. Specimens that are negative for measles are tested for rubella.

Since 2002, measles incidence has been decreasing, while rubella incidence is increasing. This is considered a result of the measles SIA, but why rubella is going up is uncertain.

Discussion:

It is a good idea to use alternative methods of transport, not just relying on equipment for measles, but borrowing from other programmes.

2.14 Rubella and its role in measles surveillance

Surveillance is carried out for congenital rubella syndrome (CRS), which is the main burden from rubella. Rubella in children is usually a mild, with less than 50% of children developing rash. The burden of CRS not well characterized, but it is estimated that there are more than 100 000 CRS cases globally each year in countries with no rubella vaccine. Most of the time, rubella vaccine is given as measles rubella (MR) or mumps measles rubella (MMR); therefore, there is a link with the measles control programme.

Studies in 50 developing countries in 1996 showed a CRS burden of 0.4 to 4.3/1000 live births. The measles case definition often catches rubella cases and measles is often the first differential diagnosis; thus the programmes often are linked and the IgM assay is very similar. Therefore, reasonable rubella surveillance can be achieved with minimal additional cost. Many countries have integrated measles/rubella surveillance. For countries with a low incidence of measles, it might be better to test for rubella first. For rubella, age and gender-specific information is important.

Discussion:

The current protocol will not detect dual infection of measles and rubella, however measles should be first priority, especially in control-phase countries.

2.15 Required reporting format and data management

Dr J. Devasundaram and Mr B. Bersonda, EPI, WHO Western Pacific Regional Office, gave presentations. The process of designing data systems starts out by identifying all potential stakeholders and their functional groups. The ultimate performance of the system will depend on an interactive process, which includes all the potential stakeholders or their representatives jointly contributing towards the design of the system based on their needs and job functions.

This requirements-gathering phase then progresses towards a conceptual system design phase, resulting in the data system being built according to a prioritized list of functions. This list of functions is

determined by the availability of resources - time, human and financial. For a data system to be successful, it is imperative that such an approach be undertaken from the outset, involving as many of the stakeholders as can possibly be accommodated at various stages of the requirements-gathering process and during the testing phase of the application. Each of the participating stakeholders then has a valid, direct, experiential reason to make their data system a continued success.

Data management is critical to the success of any system and it is important to give it sufficient attention from the onset of the measles laboratory network. A system to efficiently collect, validate, analyse and transfer data needs to be developed, which is driven by the three principles of good data management which are completeness, accuracy and timeliness. In this regard, WHO Regional Office for the Western Pacific is proposing to develop a standard measles laboratory database to support laboratories in data management and, at the same time, maintain a regional standard dataset. The Regional Office should also identify any other data management issues in the laboratories. It should provide support, where possible, for the purpose of enhancing data management within the laboratories and to initiate regular monthly reporting of measles laboratory data to the Regional Office.

2.16 Assessment of needs for technical support

Dr Kojima and Mr Featherstone gave presentations on assessment of needs. The basis of the accreditation system is the assessment questionnaire, which records information on personnel, such as contact details, number, qualifications, experience, current serological capacity; strategies, including kit types, kit usage, sample throughput, current isolation capacity (equipment; type, condition); and data management, such as type, experience, personnel, resources and reporting structure. This may precede or follow a visit from a WHO virologist.

From the questionnaire, an assessment of the training needs can be developed. This can be implemented either through individual on-the-job training or through a workshop. Some of the strengths of training in developing the network include standardization of testing, reporting and quality assurance (QA), technical skills, network building, communication, and resolution of problems. For training to be effective, the appropriate person must attend, and follow up is critical to success.

It is often helpful to have a workshop at the start of network establishment. Usually one workshop suffices, but additional workshops may be necessary to address staff turnover, introduction of new methods or specific problems. Workshops are often expensive, but are good investments if appropriate persons are trained.

Regarding equipment and supplies, the Measles Laboratory Network has a standard equipment list. Laboratories may be able to borrow other laboratories' equipment (ELISA reader and washer, autoclaves, incubators, refrigerator/freezer). Laboratories should try to incorporate laboratory costs into surveillance activities, and WHO may be able to assist in meeting some laboratory needs. Not all assay kits are equal in sensitivity and specificity, and it is important that laboratories are aware of the characteristics of their equipment.

Discussion:

There is a need for the Regional Laboratory Coordinator to be aware of the real needs of each laboratory, in addition to the questionnaires that have been sent, which laboratories must remember to submit.

Macao (China) has no financial problem but would appreciate help from WHO concerning cell cultures, among others.

The national measles laboratory in Malaysia is still a young laboratory and requires implementation of quality assurance programme and assistance in training.

The Lao People's Democratic Republic requests reagents, test kits and a laboratory database, as well as assistance with quality assurance and control for measles and rubella testing.

The Republic of Korea needs to negotiate for ELISA kits at WHO discounted prices.

In Hong Kong (China), surveillance and case finding are complete, with laboratory results. There is a concern over the results from private laboratories, which have a limited connection to the public sector laboratories with regards to laboratory control and reporting to the Ministry of Health. In the United States of America, 95 % of testing takes place in private sector, but this is reported by clinicians.

Cambodia is keen to have a study tour, acquire new laboratory techniques and establish the ability to perform PCR for measles in the future. Funds for transportation, laboratory testing and incentives are also requested.

In Brunei Darussalam, there is no measles testing. However, refresher training by WHO would be welcomed, in case the need arises, and the country would like to be included in the proficiency training and data management system.

Mongolia requests support for transportation costs, equipment, the accreditation process, serology test kits and introduction of data management.

New Zealand is still in the process of selecting its national reference laboratory for measles. A workshop would be very useful, especially for trouble-shooting and developing different scenarios.

Papua New Guinea needs training and kits. The liaison between surveillance and laboratory groups needs to be strengthened.

The Philippines there is a demand for EPI coordination and a national EPI centre. Collection of specimens for virus isolation is a problem. There is an intention to receive proficiency training and to upgrade quality control, and the database needs to be reviewed.

Fiji is in need of training on data management and quality control..

French Polynesia needs some support for quality control, control and positive specimens, and guidance on which tests kits to use with a minimum number of specimens.

New Caledonia has a clear position/plan as it is likely that, although measles-free for years, the Pacific islands may be sensitive to re-introduction. The problem is that there have been no samples for a long time. A broader case definition, clear advice and assessment by WHO may be useful. Kits should be provided free of charge for the laboratories, and support for shipping costs (not from L2) but from peripheral locations to L2 laboratories would help in networking.

Guam requests bench training.

The National Measles Laboratory in Singapore is a hospital-based laboratory. The staff are very stretched when a large number of cases require analysis.

North Viet Nam has a problem in that staff are limited, most of them are retired and young staff do not have experience and need training by WHO. Transport from other provinces is also a problem. Many measles patients present to hospital late, and therefore there is no chance to isolate the virus.

The problems in South Viet Nam are in: (1) funding, (2) reporting, (3) training in new techniques, and (4) supplies of reagents and cell lines. Funding for both domestic and international transport of specimens would be appreciated. The database for management and reporting requires support.

There is a huge number of measles laboratories in China, with many still needing to establish a way to maintain subnational laboratory functions, especially in the Western Provinces which are much poorer. Workshop and training course will be very important to keep the subnational laboratories working and functional.

3. CONCLUSIONS

The main conclusions of the workshop were:

(1) The foundations for measles elimination are strong routine immunization achieving high coverage with proper surveillance and laboratory support. The goal of the Regional Measles Laboratory Network is to provide integrated, effective support to the Region's efforts in measles elimination.

(2) The Regional Committee has resolved to have two pillars to revitalize EPI: measles elimination and hepatitis B control through immunization. Thus, there is a need to build a strong network of high quality laboratories to assist in achieving and maintaining measles elimination.

(3) Adequate planning and integration of measles elimination activities, with appropriate accredited laboratories, is critical for achieving and maintaining measles elimination.

(4) The Measles Laboratory Network is being established using the principles of the Poliomyelitis Laboratory Network. In line with global objectives, the objectives of the network in the Region should be:

- to develop standards for the laboratory diagnosis of measles and provide the necessary support as the programme evolves;
- to establish mechanisms for reference and support of national laboratories in the diagnosis of measles and other rash illness;
- to provide training resources and facilities for staff of national laboratories;
- to provide a source of reference materials and expertise for the development and quality control of improved diagnostic tests;
- to serve as a bank of measles virus isolates for molecular epidemiology and reference sera for quality control (regional reference and global specialized laboratories) (Viral isolation and characterization are necessary at early stages to develop this bank and at later stages to distinguish between indigenous vs imported infections.); and
- to assure mechanisms allowing sustainable development of the Network.

(5) Nearly all countries in the Region are ready to pursue measles elimination. However, some are facing considerable challenges to establish adequate laboratory facilities for their populations.

(6) Experience shows that, if a measles elimination strategy includes a high quality initial campaign targeted to an appropriate age range, elimination can be achieved within one to three

years. Prompt action must be taken to establish adequate laboratory facilities so that laboratory support is in place at the appropriate time.

(7) There are promising new technologies that might have specific applications to meet the logistic challenges within the Region and merit further exploration.

(8) The TAG 14 suggested between 2010 and 2015 as the likely range of target dates for consideration. The Task Force on Measles Elimination has made significant progress in this regard. Its final report is awaited, but 2012 has been suggested.

(9) An accredited national measles laboratory should serve each country and area of the Region. The number of national laboratories will depend on the epidemiological priorities and resources available. National laboratories should work closely with the EPI programme manager and surveillance units.

(10) To appropriately monitor and report disease in the Pacific countries and areas (excluding Papua New Guinea), a subregional laboratory network for the Pacific should be established, consisting of an integrated epidemiological and laboratory surveillance system. This would be based on the existing Pacific LabNet in principle. Laboratory confirmation of reported cases and other virological assistance for those countries that do not have their own national measles laboratory should be served by a nearby country of the subregional laboratory network that has a well functioning measles laboratory with a good performance record. The four proposed subregional reference laboratories would perform the functions of a WHO national measles laboratory. Strengthening the technical and financial capabilities of these laboratories is a priority.

(11) The recommended procedure for laboratory confirmation of acute measles cases is detection of measles specific IgM antibody in a serum sample obtained at first contact with the suspected case, preferably within an optimal timing of four to 28 days. The laboratories should test specimens from suspected cases by IgM ELISA according to recommendations of the *Manual for the Laboratory Diagnosis of Measles Viral Infection* (WHO, 2000). The procedures should be updated in line with revision of the manual.

(12) Validation of measles and rubella kits utilized for testing in countries that are not using validated kits should be given high priority. The performance of these ELISA kits should be evaluated employing well-defined panels of sera from measles, rubella and other rash-illness cases in comparison with well recognized kits.

(13) Isolation and characterization of virus should be performed to facilitate molecular epidemiological studies, but not for diagnosis of acute disease. Virological surveillance is necessary in the early stages to create a genetic baseline, and in later stages to distinguish importations from endemic circulation. Virus isolation should be performed according to currently accepted standards at laboratories with sufficient capacity, recognizing the necessity for further characterization of the isolates at RRLs or GSLs.

(14) Following the model of the Poliomyelitis Laboratory Network, external proficiency testing should be employed to assure accurate and consistent performance.

(15) There should be a focus on internal quality control, including use of appropriate and approved standard operating procedures, such as specimen logging and handling records, equipment maintenance and calibration records, and freezer/incubator temperature recording, as well as quality assurance.

(16) External quality control should be ensured by accreditation visits, with proper documentation of routine records, proficiency testing and activities.

(17) Laboratories using validated test kits should send 10% of their samples to the NML or RRL for confirmation and validation. Laboratories using non-validated kits should submit 20% of their samples for testing. Since this is one criterion for accreditation, it should be supported and coordinated by the Western Pacific Regional Measles Laboratory Network, making use of existing specimen transportation methods. Shipping of above-mentioned specimens to RRLs should be at quarterly intervals, or more frequently if there are any uncertainties about the test results.

(18) Accreditation of NMLs, according to the established criteria will be conducted annually by the WHO Western Pacific Regional Office, beginning with countries given high priority based upon a combination of factors including, incidence approaching elimination, existence of case-based surveillance, and difficulty in meeting WHO performance indicators. On-site reviews may occur from every one to three years, depending on the capability of laboratories and/or as opportunities or needs arise.

(19) Following the satisfactory validation of dried blood and oral fluid sampling methods, consideration should be given to employing them on a case-by-case basis, especially in areas with transportation difficulties such as the Pacific island countries and areas.

(20) To meet the various training needs of national measles laboratories, an initial hands-on training course should be conducted at the earliest opportunity, with priority given to those laboratories in high demand. As the Regional Measles Laboratory Network expands, continued training of laboratory and field staff will be indispensable.

(21) Handling and transportation of any sort of specimen or virus isolate should be in line with the recently revised *United Nations Recommendations on the Transport of Dangerous Goods. Model Regulations Model Regulations*. 13th edition, and other relevant requirements as appropriate.

(22) A draft structural relationship of national laboratories to regional reference laboratories has been proposed and will be confirmed after all RRLs are officially designated. Consideration for the establishment of a fourth RRL will be determined in 12 months time.

(23) In countries where samples are tested in facilities that are not part of an accredited network, it is recommended that all positive samples and a representative proportion of negative samples are confirmed by the recognized national laboratory.

WORKSHOP ON LABORATORY SURVEILLANCE FOR MEASLES ELIMINATION IN THE WESTERN PACIFIC REGION

16 August 2004

Room 3201/WPRO
Manila, Philippines
24-25 August 2004

ENGLISH ONLY

TENTATIVE TIMETABLE

Time	Tuesday, 24 August	Time	Wednesday, 25 August
0800-0815	REGISTRATION	0800-0830	Review of Day 1
0815-0845	1. Opening ceremony • Opening remarks • Self-introduction • Election of Chairman, Vice Chairman and Rapporteur • Group photo	0830-0900 0900-0930 0930-0945 0945-1000	12. Status of measles regional laboratory network activities in South-East Asia Region (SEAR) countries 13. Experience of measles control in China (regional reference laboratory) 14. National measles laboratory presentations: a. Cambodia b. Fiji
0845-0915	*COFFEE BREAK*	1000-1030	*COFFEE BREAK*
0915-1000	2 Overview of global/regional progress on measles elimination	1030-1045	c. Philippines
1000-1030	3. Structure of the regional measles laboratory network	1045-1100	c. Republic of Korea
1030-1050	4. Regional plan of action (PoA) on measles laboratory network	1100-1125	e. Viet Nam (Ha Noi and Ho Chi Minh City)
1050-1120	5. Criteria for laboratory accreditation	1125-1145	15. Evaluation of rubella testing in the context of measles elimination
1120-1200	6. Proficiency Test and quality assurance		
1200-1300	*LUNCH BREAK*	1145-1300	*LUNCH*
1300-1320	7. Assignments of national measles laboratories (NMLs) to regional reference laboratories (RRLs) for further analysis and assistance.	1300-1330 1330-1350	16. Required reporting format and data management 17. Assessment of needs (resources and technical assistance), workshops in particular
1330-1400	8. Measles test for Pacific Island Countries (PICs) – report from the pre-meeting.		
1400-1430	9. Updates on international shipping of specimens		
1430-1500	*COFFEE BREAK*	1350-1420	*COFFEE BREAK*
1500-1620	10. Alternative methods for measles laboratory assay and sample collection	1420-1440	18. Conclusions and recommendations
1620-1710	11 Genotyping (or other advance techniques)	1440-1500	19. Closing ceremony
1800	*COCKTAILS/BUFFET*		

ANNEX 1

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

REGIONAL OFFICE FOR THE WESTERN PACIFIC
BUREAU REGIONAL DU PACIFIQUE OCCIDENTAL

WORKSHOP ON LABORATORY SURVEILLANCE FOR MEASLES ELIMINATION IN THE WESTERN PACIFIC REGION

Manila, Philippines
24-25 August 2004

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