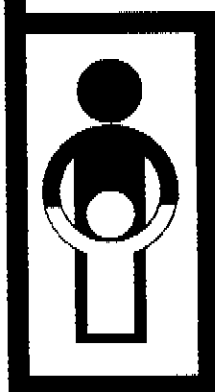


Yellow fever -- Technical Consensus Meeting

Geneva, 2-3 March 1998



**GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION**

**DIVISION OF EMERGING AND OTHER COMMUNICABLE
DISEASES SURVEILLANCE AND CONTROL**



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Executive summary

The Yellow Fever Technical Consensus Meeting, organized jointly by the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC) and the Global Programme on Vaccines and Immunization (GPV), was held in Geneva March 2-3, 1998 to examine the reasons for the dramatic re-surgence of outbreaks within the past 10-15 year period. Participants reviewed the strategies for the prevention and control of yellow fever in Africa and South America and identified the present barriers to implementation of effective programmes. The recommendations from this meeting will serve as the basis for action plans to reduce morbidity and mortality from yellow fever.

With the recent increase in epidemics, yellow fever is once again a major public health concern. One important reason for the re-emergence of the disease is low immunization coverage in countries where the disease is present. Some reasons for poor coverage are lack of adequate funds for vaccine and injection equipment, lack of interested partners, and lack of political will and commitment for inclusion of yellow fever vaccine in the routine Expanded Programme on Immunization (EPI) activities. Where yellow fever has been included in EPI programmes, the overall performance of these programmes in some countries has not been adequate. Factors contributing to the spread of yellow fever outbreaks include an increase in the distribution and density of the mosquito vectors, and economic development that has caused increased intrusion of man into forested areas, substandard water systems that provide breeding sites for the vector, and widespread international air travel.

Immunization coverage of less than 60% is not high enough to prevent epidemics. Depending on vegetation, vector efficiency, and vector density in the area, coverage of 80% or more may be needed to prevent disease outbreaks. Using these factors along with the interval since the last epidemic, urban to rural ratio, frequency of epidemics, and history of previous yellow fever immunization programmes, countries could be placed in order of priority for resources and financial assistance.

As outbreaks occur, countries rely upon emergency immunization programmes to control yellow fever. Prompt recognition of cases is a prerequisite and required for rapid implementation of immunization campaigns. Yet, surveillance programmes in many countries at risk are presently inadequate. Suspect cases are often not investigated because the clinical picture of yellow fever can be confused with other diseases or cases occur in remote regions and do not come to the attention of medical authorities. Laboratory confirmation of the diagnosis is required, but samples are collected infrequently, often because specialized laboratory facilities for yellow fever testing are not accessible. An estimated 200 000 yellow fever cases with 30 000 deaths occur each year, almost all in sub-Saharan Africa. The annual number of

cases occurring is grossly under-reported. Furthermore, some countries do not report yellow fever for fear of international stigma.

The following recommendations were proposed and endorsed by meeting participants:

1. Prevention through routine immunization and preventive mass immunization campaigns

- Countries with routine immunization schedules should increase and/or maintain high routine coverage, plan and implement preventive mass ("catch-up") campaigns, and after outbreaks, assess and target high risk groups for priority immunizations.
- Countries that have not yet included yellow fever immunizations in EPI should determine their immunization schedule, mobilize resources, and phase introduction of vaccine by areas of highest risk.

2. Detection, reporting and investigation of suspect cases

- Surveillance should be strengthened including laboratory capacity to confirm suspect cases from at-risk countries.
- A sensitive syndromic definition should be developed and validated.
- Yellow fever should be integrated into the surveillance programs with the 18 priority diseases targeted by the WHO Regional Office for Africa (AFRO), and with initiatives for surveillance of other haemorrhagic fevers.
- Surveillance should be part of national programmes, and if this is not possible, areas of highest risk should be given priority, especially during seasons in which outbreaks usually occur.

3. Laboratory support

- At-risk countries should have national laboratory capability for IgM testing, and access to sub-regional laboratories for confirmatory testing as needed.
- Yellow fever diagnostic tests should be established in laboratories as part of broader programme for diagnosis of viral infections.
- An electronic communications network for laboratories should be strengthened.
- Quality control and proficiency testing programmes should be established in national and sub-regional laboratories.

4. Outbreak response

- Inter-country planning and epidemic preparedness should be strengthened.
- A national multi-disciplinary epidemic committee must be established as a coordinating body for outbreak response.

5. Vaccine supply

- Basic information must be collected for accurately forecasting needs to ensure availability of vaccine.
- An emergency stock of 1 million doses should be held in both Africa and South America for outbreak response.
- National health authorities should be made aware of mechanisms by which yellow fever vaccine can be purchased at the lowest possible price.
- Vaccine and injection materials should be "bundled" for use in preventive campaigns or outbreak response campaigns.

6. Key operational research issues

- The disease burden during inter-epidemic periods should be determined to increase awareness and support for immunization programmes.
- Determine extent of adverse events related to immunization of six- to nine-month old infants during campaigns
- Determine the factors potentially affecting the immunogenicity of yellow fever vaccine, (such as HIV-infection, malnutrition, and anti-malarial drugs)

1. Introduction

1.1 Objectives

Dr J. M. Olivé, Acting Chief, EPI, outlined the objectives of the meeting. In view of the dramatic resurgence of yellow fever in the past 10 years, with an estimated 200 000 cases occurring each year mainly in sub-Saharan Africa, this meeting was called:

- 1) to determine, after the 1988 declaration of yellow fever immunization goals, why there has been so little progress in the control of yellow fever;
- 2) to conduct an in-depth review of the current recommended strategies and the successes and failures of countries in Africa and South America;
- 3) to determine the surveillance requirements and the current capacity of countries for surveillance;
- 4) to consider the expected vaccine demand arising from implementation of the various strategies, and the current and future supply of yellow fever vaccine;
- 5) to propose solutions for the financial support and human resources required for implementing routine immunization programmes and outbreak response.

1.2 Participants

Thirteen temporary advisors, two members of international organizations and secretariat members from WHO Headquarters (15), the African Region (3) and the Region of the Americas (2) participated in the meeting. The agenda and list of participants are attached as Annexes 1 and 2.

1.3 Opening ceremony

Dr R.H. Henderson, ADG, on behalf of the Director General of WHO, Dr H. Nakajima, opened the meeting. Dr T. P. Monath was elected Chairman and Dr Barbara Hull of Trinidad and Tobago, Rapporteur.

1.4 Global overview

The chairman, Dr Monath, provided an overview that set the stage for the discussions by outlining the secular trends in yellow fever incidence, geographic distribution, under-reporting, rates of infection, disease and mortality, age-specific incidence, the ability to predict outbreaks, immunization coverage and other immunization issues.

Although yellow fever outbreaks occur continuously in both Africa and South America, the number of cases reported in Africa exceeds that in South America. The chronic under-reporting is shown by the high ratios of actual reported cases (3:1 to 250:1) found in epidemics where thorough virological and epidemiological investigations have been completed.

Possible reasons for under reporting included:

- 1) occurrence in remote areas;
- 2) difficult clinical differentiation and poor access to serologic and virologic testing;
- 3) consultation of traditional healers for jaundice and removal of pre-terminal patients from hospital;
- 4) reluctance of countries to report, due to international stigma and the financial cost of intervention activities.

The factors that increase the risk of yellow fever epidemics and their international spread are those related to:

- 1) Vectors
 - a. Re-infestation by *Aedes aegypti* in rural endemic areas and in urban areas.
 - b. Changes in vector competence.
 - c. Spread of *Aedes albopictus* in South America and its identification in the African region, breeding in areas of active transmission of yellow fever virus (a possible bridging vector between sylvatic and urban yellow fever zones).
 - d. Multiple sylvatic vectors at high density areas in Africa, with high rate of epizootic transmission.
- 2) Development
 - a. Increasing settlement of forested areas.
 - b. Road construction, increased accessibility to and increased volume of air transportation.
 - c. Water supply deficiencies that favour *Aedes aegypti* breeding.
- 3) Programmatic issues
 - a. Unvaccinated coastal and urban populations.
 - b. Mass campaigns versus routine immunization in South America.
 - c. Preference to immunize for outbreak control and not routinely as part of EPI, resulting in low vaccine coverage in Africa.

Consideration of these factors might lead to better outbreak prediction and control. Prediction of disease outbreaks can also be based on entomological surveillance as was shown in Senegal, where increased isolation of yellow fever virus from forest mosquitoes preceded cases of yellow fever in several West African countries.

Despite the recommendation in 1988, which was re-emphasized in 1990, that yellow fever 17D vaccine be incorporated into the EPI in Africa, only 17 African countries had attempted to do so. Since 1990, only five countries have officially reported >40% coverage. Since 1995, only three countries have attained this level of coverage. Some suggested reasons for poor coverage were:

- 1) the long intervals between outbreaks;
- 2) their low-profile occurrence in rural areas;
- 3) lack of data on endemic disease burden;
- 4) high cost of vaccine and delivery;
- 5) competing health priorities.

2. Proceedings

2.1 Outline of daily sessions

Four sessions were conducted during the meeting. Each began with an overview of the topic followed by reports of country experiences or presentations by WHO programmes. At the end of the session, the moderator opened the session for discussion. On the first day, two sessions were held. The first was prevention of yellow fever through routine immunization and mass campaigns and the second was yellow fever surveillance and laboratory support. On the second day the topics were yellow fever outbreak response and vaccine supply. Also on the second day, the meeting participants divided into four working groups, each focused on one of the session topics. The meeting concluded with the four moderators summarizing the recommendations made by their respective working group.

2.2 Session 1 - Prevention of yellow fever through routine infant immunization and mass campaigns

2.2.1 Overview - WHO African Region

Yellow fever in Africa is characterized by periodic epidemics with intense rates of virus transmission, attack rates as high as 30/1000 population and case fatality rates of 20-50%. Both sylvatic and *Ae. Aegypti*-borne epidemics occur in the region. Of the 34 (including Eritrea) countries in Africa at risk for yellow fever, outbreaks of yellow fever occurred between 1992 and 1996, in Benin, Burkina Faso, Gabon, Ghana, Kenya, Liberia, Nigeria, and Sierra Leone. There was a sharp decline in the number of reported cases compared with the preceding five years, that may be due to cyclical changes in virus activity and/or to emergency mass immunization conducted in response to previous outbreaks. There are two strategies for yellow fever prevention and control. For outbreak prevention, immunizations are given routinely as part of EPI or in mass immunization campaigns to quickly compensate for low coverage due to an ineffective or absent routine immunization programme. For controlling outbreaks, countries rely on surveillance to detect yellow fever cases and then perform mass immunizations in response to the outbreak. The WHO African Region advocates the four activities in these two strategies: routine immunization, mass immunizations for outbreak prevention, surveillance and outbreak response immunizations. The first two activities were the subject of this session.

- 1) **Routine EPI:** Following the introduction of yellow fever immunization into the EPI programme in 1991, the African Region has set a target for the year 2000 of attaining a minimum of 80% yellow fever vaccine coverage of children under 5 years in all 34 countries where the disease is endemic. Several reasons were advanced to explain the non-incorporation of yellow fever vaccine into the routine EPI following the 1988 and 1990 resolutions of the UNICEF/WHO Technical Group. Methods to overcome the following impediments are needed if the year 2000 goal is to be achieved:
 - a. lack of political will and commitment of many African governments;
 - b. lack of funds for yellow fever vaccine;
 - c. lack of interested partners;
 - d. poor programme performance in several countries;
 - e. the non-inclusion of yellow fever vaccine in the routine EPI at the start of the programme.

- 2) **Mass immunization campaigns:** Experience in West Africa between 1940 and 1953 had demonstrated the effectiveness of mass immunization in preventing yellow fever. Since 1984, one country, Burkina Faso, had achieved 91% coverage with yellow fever vaccine in children 1-14 years old by administering the vaccine during mass immunization campaigns for either measles or bacterial meningitis. Mass immunization campaigns planned for other antigens are therefore an opportunity to add yellow fever vaccine, either countrywide or in high-risk areas. However, there is a continuing need to raise funds for both routine and mass immunization.

2.2.2 *Burkina Faso*

The endemic areas for yellow fever in Burkina Faso are in the southern region of the country, bordering Benin, Togo, Ghana and Cote d' Ivoire. Cases had been identified between 1983 and 1996, occurring during the rainy season and usually in the under 15-year age group. As noted in the previous presentation, vaccine is administered as part of routine immunization or in mass immunization campaigns, the latter of which has resulted in greater coverage. In routine immunization, yellow fever and measles are mixed in the same syringe and administered. The immunization is recorded on EPI cards. This vaccine mixing procedure is not recommended by WHO and the vaccine manufacturers because of the possibility of incompatibility of vaccines resulting in inactivation of one or both viruses, instructions state only to use the diluent that is specifically shipped with the vaccine and uncertainty about resulting efficacy.

Coverage rates for both measles and yellow fever are similar. The following constraints in the EPI presently prevent achieving high coverage with yellow fever vaccine:

- 1) poor public awareness of yellow fever and its prevention;
- 2) general lack of motivation of health care workers;
- 3) difficulties in sustaining the cold chain due to lack of a continuous butane gas supply;

-
- 4) mobility of the agricultural population;
 - 5) concerns about safe injection materials.

The mass immunization campaign approach had been used since 1985. A combination of fixed decentralized immunization sites and mobile teams are used in the programme. There have been four yellow fever immunization campaigns:

- in 1985 for individuals <15 years (with meningitis immunization);
- in 1995 for children <5 years (with measles immunization);
- in 1996, a single antigen campaign for those of ages <15 years living in two endemic regions; and
- In 1998, a catch-up campaign in one district, in conjunction with measles immunization.

As a result of these campaigns, 97.4% in children under five years of age received yellow fever vaccine.

Burkina Faso is presently 100% self-sufficient in supplying its yellow fever vaccine needs. Vaccine was purchased from the Institute Pasteur in Dakar, Senegal for \$0.25 per dose. Burkina Faso plans to transfer yellow fever vaccine to the Vaccine Independence Initiative (VII) in 1998 and shift the procurement of yellow fever vaccine to direct purchase from vaccine producers. The country is seeking ways to purchase vaccine at a lower cost and will continue, resources permitting, to implement mass immunization campaigns in high-risk areas of the country.

2.2.3 *Ghana*

Ghana has experienced both urban and jungle yellow fever since the beginning of the century. Many cases and deaths among children were reported in the late 1970s and early 1980s and outbreaks have occurred as recently as 1997.

Through routine EPI immunization, coverage in children under one year of age showed great fluctuations during the early 1990s, but has shown a steady increase to a level of 40% in 1997.

The low EPI coverage was attributed to these factors:

- 1) low priority accorded to yellow fever by the government;
- 2) poor appreciation of the impact of yellow fever;
- 3) lack of political support for routine yellow fever immunization;
- 4) inadequate supplies of vaccine;
- 5) poor performance of state routine immunization centres.

Until recently, immunizations of all age groups usually were conducted in areas affected by yellow fever outbreaks. However, political concern during outbreaks was not translated into financial commitment for improved prevention activities. It was recommended that data from an improved surveillance system be used for ad-

vocacy to ensure the Government's commitment of funds for yellow fever control. The true public health impact of yellow fever during interepidemic periods in Ghana, as well as in other yellow fever endemic countries, is unknown. Assistance from WHO/AFRO will be required to address the issues stated above that are hampering routine immunization programs.

2.2.4 Overview - WHO Region of the Americas

Yellow fever in the Americas is distinguished from that in Africa, by causing sporadic cases or outbreaks with lower attack rates (1-2/1000 population) than are observed in Africa. Yellow fever presently is exclusively sylvatic in the endemic countries of South America. Of the eight enzootic countries, five (Bolivia, Brazil, Colombia, Peru, Ecuador) reported cases in the 1990s; 82% of the cases were from Bolivia and Peru. The highest prevalence of infection was in males older than 15 years and was associated with occupations that bring the worker in contact with virus-infected mosquitoes. Although the last case of urban yellow fever was reported in 1942, *Aedes aegypti* is abundant in many of these countries and the proximity of enzootic areas to *Aedes*-infested urban areas poses a constant threat of urban epidemics.

In June 1997, the Executive Committee of the Directing Council of PAHO adopted a resolution urging member states to include yellow fever vaccine in their national immunization programmes working in all areas at risk of transmission of the virus. This is recognized as an important step in preventing both sylvatic and urban yellow fever cases. Most countries in the Americas where yellow fever is endemic have already included this vaccine in the EPI, but others have not and efforts must be made to insure that these countries comply with the resolution. In the American Region, the role of the national immunization programmes includes epidemiological surveillance, as well as vaccine related responsibilities. In addition to childhood immunization, vaccine is offered, if needed, to other groups such as adults entering an enzootic area.

Mass immunization has been used in response to outbreaks and to increase yellow fever immunity around areas with transmission of jungle (sylvatic) yellow fever. Immunizations have also been recommended to increase herd immunity in *Aedes aegypti*-infested areas inside the enzootic area. Vaccine is purchased from Brazil at a cost of \$0.15 per dose and the time lapse between requesting and receiving vaccine is one week. Therefore, emergency immunization activities should they be needed, could be enacted quickly. There are programmes in the country or at the regional level to assure vaccine quality.

2.2.5 Peru

The objectives of yellow fever outbreak control in Peru are to reduce the morbidity and mortality in risk areas and to prevent urban epidemics. Peru has experienced outbreaks of yellow fever at intervals of approximately every 3 years over the past 50 years. The disease is endemic in river basins where the sylvatic vectors are found. In the 1995 epidemic, of 449 reported cases, 85% were male, >90% were older than 15 years, and 74% were agricultural workers. These findings confirm the sylvatic origin of this recent yellow fever outbreak. Yellow fever activity is presently occur-

ring in Peru. Thirty cases of sylvatic yellow fever were reported during the first two months of 1998. *Aedes aegypti* indices are monitored, but there has been no proven *Aedes* involvement in transmission. To identify potential vectors capable of transmitting yellow fever, mosquitoes collected in endemic areas are being tested for yellow fever virus.

Mass immunizations are conducted in response to outbreaks and for the protection of migrants entering high-risk jungle areas from the highlands. The coverage achieved over the three-year period 1995-1997 was 71.4% of the population at risk (1.1 million persons in the risk areas and 600 000 migrants).

2.2.6 *Trinidad*

Trinidad has experienced four outbreaks of sylvatic yellow fever this century, the last of which occurred in 1978 - 1980. Virus activity was first detected, in an area known to be enzootic, by observing dead Red Howler monkeys (*Alouatta sp.*) and by the isolation of virus from *Haemagogus* mosquitoes. During the 1978 - 1980 outbreak, there were 19 cases and 8 deaths. All were young men, and all but one had proven forest exposure in the area affected by the epizootic. Outbreak response immunization was started in the immediate area following the first human case and was extended to the general population after the second case. The epizootic eventually spread to a peri-urban area close to the capital, but urban transmission did not occur.

Vaccine was offered in a mass campaign, to the population over one year of age, with the exception of those holding valid yellow fever immunization certificates. This resulted in coverage of over 90% of the population. This outbreak response immunization was hampered by the disadvantages associated with placing emergency orders for vaccine, caused disruption of health services and had a negative overall economic impact on the country.

Following the epidemic, the decision was taken in 1980 to intensify infant immunization. Yellow fever vaccine was administered to all children presenting for the measles immunization. The resulting coverage was higher than 85% each year. The combination of high population coverage providing immediate protection, and incorporation of yellow fever immunization in the EPI providing protection for each birth cohort, has prevented human disease in spite of epizootics in 1988 and in 1996. Aggressive vector control programs were implemented and this undoubtedly contributed to the lack of urban transmission by *Aedes* mosquitoes.

2.2.7 *Summary - Yellow fever immunization programmes*

Regional resolutions have been passed in Africa and the Americas supporting the incorporation of yellow fever vaccine into the routine infant immunization programme. However, many countries have not yet made the commitment to routine immunization and few countries have achieved coverage of 80%. The reasons put forward for the lack of action are **attitudinal** (lack of motivation, commitment, political will, lack of public awareness), **financial** (vaccine cost, competing priorities of other vaccines), and **programmatic** (poor health centre administration, weak surveillance). These vary by country. The regional offices' recommendations were re-emphasised, especially the need to improve monitoring of routine vaccine coverage

and the quality of reporting. It will be necessary to devise methods, possibly serosurveys, for estimating the effectiveness of immunization. The efficacy of the vaccine under conditions encountered in many areas, e.g., concurrent HIV infection, malaria treatment, is unknown.

In weighing the merits of mass immunization campaigns for disease prevention, the factors to be considered include:

- 1) geographical prioritisation;
- 2) optimal season for campaign;
- 3) scope of the campaign (national or sub-national);
- 4) age groups to be vaccinated;
- 5) concurrent administration with other vaccines, e.g., measles;
- 6) adverse events monitoring;
- 7) evaluation of effectiveness;
- 8) degree of risk for an urban outbreak.

A system of prioritizing countries was proposed in the working document titled "Yellow Fever" prepared by Drs. J. Vainio and F. Cutts. It was based on interval since the last epidemic, urban to rural ratio, frequency of epidemics in one area, vegetation zones and history of previous yellow fever immunization programmes. The document contains a thorough summary of the epidemiology of yellow fever in Africa. Data indicate that coverage of less than 60% is certainly not high enough to prevent outbreaks. Depending on vegetation, vector efficiency, and vector density in the area, coverage of 80% or more may be needed to prevent outbreaks.

A goal of measles eradication may be set in the next few years, especially if the polio eradication goal is achieved. In preparation for this, it is important to obtain as much information as possible on the epidemiology of yellow fever and to monitor and evaluate different strategies for yellow fever control through immunization as these programmes may be conducted concurrently. Some countries have already saved costs by using yellow fever vaccine as an add-on to other national campaigns. Since yellow fever immunization is recommended at the time the child is to receive measles vaccine, the coverage rates of both may be compared to monitor and identify additional vaccine delivery problems, e.g., reluctance to give or receive two injections during the same visit.

Mass immunization programmes have been used principally for outbreak control. When indicated by epidemiological data, some countries have targeted specific groups as being at high risk, e.g., migrants from non-endemic regions to an enzootic area (as in Burkina Faso and Peru), forest workers (as in Trinidad), international refugees, or military personnel or specific high-risk areas of the country.

2.3 Session 2 - Yellow fever surveillance and laboratory support

2.3.1 Overview

Sensitive surveillance systems are necessary to rapidly detect outbreaks for timely implementation of intervention measures, and to measure progress towards outbreak prevention. Yellow fever surveillance is also conducted to understand the natural history and epidemiology, especially in regions where the risk of transmission is highest.

Recognition of yellow fever cases in the early stages of an outbreak is difficult because of the wide range of clinically similar conditions, many of them highly prevalent in yellow fever endemic zones of Africa and South America. The differential diagnosis may include malaria, viral hepatitis, dengue, leptospirosis or other haemorrhagic fevers. The interval between onset of an outbreak and first report to health authorities has often exceeded two months in the past, but there are some indications that this period is becoming shorter. Prompt reporting depends upon the recognition of suspect cases based on clinical symptoms and requires the wide dissemination and use of a standard clinical case definition. The recommended case definition for suspect yellow fever is:

An illness characterized by acute onset of fever followed by jaundice within 2 weeks of onset of first symptoms AND one of the following
1) bleeding from nose, gums, skin or GI tract or 2) death within 3 weeks of onset of illness.

The gap between reporting of a suspect case and case confirmation is a function of the case investigation system and the availability of and access to a viral diagnostic laboratory. There is a network of WHO collaborating centres for arboviruses and haemorrhagic fevers that is supplemented by national laboratories, many of which have been involved in polio and measles eradication and elimination programmes. Case confirmation requires that one of the following laboratory criteria be fulfilled:

- 1) propagation of yellow fever virus in cell culture or laboratory animals;
- 2) presence of yellow fever virus-specific IgM antibody;
- 3) four-fold or greater rise in serum IgG antibody levels in paired acute and convalescent sera;
- 4) positive post-mortem liver histopathology;
- 5) detection of yellow fever virus antigen in tissues by immunohistochemistry;
- 6) detection of yellow fever genetic sequences in blood or organs by molecular diagnostic techniques, e.g., polymerase chain reaction (PCR).

Accurate laboratory analysis depends upon trained laboratory staff, appropriate equipment and supplies, the provision of reagents, and proficiency testing. Training courses have been conducted in Kenya, Ghana and Senegal. WHO provides diagnostic reagents to laboratories in Africa whom cannot produce reagents in their laboratory. Guidelines for specimen transport are included in the WHO publication *Guidelines for yellow fever surveillance at the district level*.

2.3.2 *Surveillance systems in the WHO African Region*

The African Region faces many challenges to improve surveillance. These include the following:

- 1) late and incomplete reporting;
- 2) lack of district level analysis and follow-up of reports of suspected cases;
- 3) multiple health care and reporting systems within the same country;
- 4) training of the same people by different programmes, each with their own focus;
- 5) inadequate laboratory facilities and/or untrained personnel;
- 6) inadequate logistics to investigate cases, collect and dispatch specimens to the laboratory.

An integrated approach is being used to overcome some of these problems. In this integrated approach, the health personnel at the health facility and district medical offices are pivotal as they represent the point where all the programmes, whether national or initiated by WHO/AFRO, are integrated in diagnosis, treatment and disease prevention.

2.3.3 *Laboratory support for yellow fever control in Africa*

Despite a 1993 WHO Regional Committee for Africa's resolution urging countries to develop well-staffed and properly equipped laboratory services for rapid confirmation of suspected cases of diseases, countries in Africa continued to experience undue delays in confirming the aetiology of diseases including yellow fever. This resulted in more comprehensive plan to strengthen laboratory diagnostic capacity in member states. Included in the plan are training of district health staff on proper sample handling and management, and the provision of relevant facilities and materials for reliable laboratory performance.

At present there are 15 laboratories on the African continent that have the facilities and expertise required for yellow fever virus isolation and serology. They include laboratories in Burkina Faso, Cameroon, Central African Republic, Cote d'Ivoire, Democratic Republic of the Congo, Egypt, Gabon, Ghana, Kenya, Madagascar, Nigeria, Senegal, South Africa, Uganda, Zambia. The capacity for yellow fever diagnosis by IgM antibody capture ELISA (MACELISA) exists in Benin, Congo, Guinea, Mali and Togo.

Much of this expertise is the result of a WHO-sponsored training programme of workshops that have been conducted in Central African Republic in 1993 (with the support of Institut Pasteur, Bangui), Kenya in 1995, Dakar in 1997 and annually in Ghana since 1991. The workshops were supported in part by the US Centers for Disease Control and Prevention (CDC) and the Japanese International Cooperation Agency. Over 50 laboratory staff have been trained and each provided with a 200-assay test kit.

To date, this capacity has been utilized between 1995 and 1997 to confirm outbreaks in Liberia, Sierra Leone, Nigeria, Benin, Ghana, Burkina Faso and Senegal, but has not been maximized. There are plans for expansion and better utilization of laboratory capacity in the context of Integrated Disease Surveillance. This will require provision of additional equipment, diagnostic reagents, training and proficiency testing. An accreditation scheme based on that used for the polio network needs to be established. Proficiency testing should be included as well as assessment of laboratory facilities, equipment and supplies; ability to report results in a timely manner; requirement to test a specified number of specimens; quality of operating procedures; and degree of concordant results with a reference. The development of a two-tiered system is envisioned. Yellow fever IgM ELISA will be available in all laboratories that can do HIV ELISA. If specimens from cases meeting the definition are negative, the samples will then be referred to a laboratory with broader expertise, i.e., virus detection.

2.3.4 Country experience, Kenya

A sentinel surveillance system with laboratory confirmation was established in Kenya by the Virus Research Center (VRC) in the Kenyan Medical Research Institute (KEMRI) following the 1992 outbreak. Continued low-level transmission has been detected between 1993 and 1996. The system is based on a number of sentinel health centres, mission hospitals and Government hospitals, both in and extending outside the area of the original outbreak. These institutions are supplied with 'yellow box' containing guidelines, forms and specimen collection equipment; materials are replenished on monthly visits. The case definition being used in Kenya includes fever plus CNS symptoms, or jaundice or haemorrhage. Staff of the institutions in the sentinel network collect blood samples. The serum is stored in freezers until retrieved by KEMRI staff. In addition to specimens from suspect yellow fever cases, hospitals in the surveillance network collect 20 blood samples per month from fever cases and these samples are being tested for evidence of recent yellow fever infection. Yellow fever diagnosis is based on MACELISA and IgG ELISA, but the laboratory at KEMRI also has the capability to perform immunofluorescence assays, haemagglutination inhibition, complement fixation tests, plaque reduction neutralization tests, and virus isolation in tissue culture and mice.

Yellow fever is not included in the government surveillance system, nor is there any intention at this time to include yellow fever vaccine in the routine EPI. KEMRI therefore performs an important surveillance function for Kenya and their staff meets regularly with the Director of Medical Services in the Ministry of Health. Financial support, equipment and supplies are provided to the VRC by the US Centers for Disease Control and Prevention (CDC) and by the US Army Medical Research Unit in Nairobi. CDC is presently supplying equipment and a technical consultant to improve biosafety in the laboratory. KEMRI presently receives external resources and funds to operate, but it will be mandatory to have greater government support to develop a sustainable surveillance and laboratory system.

2.3.5 *Country experience, Senegal*

Senegal has experienced outbreaks of yellow fever in 1965, 1981, 1995 and 1996. Yellow fever immunization was introduced into EPI in 1987. The 1996 outbreak that occurred 9 years after the introduction of yellow fever vaccine into the EPI, was diagnosed at the Institute Pasteur in Dakar by yellow fever MACELISA, isolation of virus in AP61 insect cells and by inoculation of mice. Vaccine coverage rates in 1994 were reported to be 46%. An immunization campaign was started in the affected and adjacent areas. On the day before immunization in each village, epidemiological and entomological investigations were completed. The immune status of the population measured by these studies before the outbreak was approximately 60%.

A project in Kedougou in eastern Senegal to monitor yellow fever enzootic activity began in 1976. A five-year periodicity of virus amplification in sylvatic mosquitoes has been observed in 1977-78, 1983, 1987, and 1993. These time periods coincided with increased risk of human infection in other parts of Senegal and neighboring countries. Data from the Kedougou project therefore may have utility in predicting future yellow fever outbreaks in the region.

A new sentinel surveillance system was established during the past year in partnership with the Ministry of Health and the Institute Pasteur in Dakar. Seventy sentinel sites in the main towns in Senegal are participating. The case definition is fever, with onset of jaundice within 15 days, or haemorrhagic signs, or unexplained death. Confirmation is based on the MACELISA on blood eluted from filter paper discs that have been pre-calibrated and sent to the field. Blood-saturated filter paper samples offer many advantages. Blood is collected by finger sticks, a method that is highly acceptable to the patient. The discs are inexpensive and are shipped to Dakar in envelopes at ambient temperature, thereby eliminating the need for a cold chain or logistics for rapid transport of samples. The sensitivity of the system to detect cases depends on strict adherence to the case definition and complete saturation of the paper discs. Results from experiments indicate that the use of filter paper discs for collecting and transporting blood samples has acceptable sensitivity for the detection of IgM resulting from wild virus infection, but might not detect vaccine-induced IgM antibody.

2.3.6 *Summary - Yellow fever surveillance and laboratory support*

Current capacity for the early detection of outbreaks of yellow fever in at-risk countries is inadequate and leads to delays in response to yellow fever outbreaks. There is a need to become more effective in each of the areas critical to effective surveillance including case detection, investigation and reporting, laboratory confirmation.

Detection of suspected cases of yellow fever is based on having a clear clinical case definition of suspected yellow fever and personnel in health facilities who are aware of the definition and have the training and motivation to report cases meeting the definition. Presently there is no internationally agreed definition of suspected yellow fever for reporting and investigation purposes. Furthermore, staff in peripheral health facilities in at-risk countries is not easily able to recognize cases because of difficulty distinguishing from other diseases with similar symptoms.

Investigation and reporting of each case of suspected yellow fever is essential if outbreaks are to be confirmed in a timely manner. Investigation of a suspect case involves filling in a simple case report/alert form, taking a blood sample, and transporting it to a laboratory where it is tested for yellow fever. The case report form should be simple, including only key information about the patient and his/her symptoms, e.g., type, date of onset, outcome. A blood sample must be taken by the health worker who sees the patient initially or by a district-based worker after receiving a report and should be sent/taken with the report form to the district level and from there the sample should go to a designated laboratory for testing. It is important that whoever collects the blood sample is adequately trained and has the necessary equipment and materials, e.g., blood collection devices, tubes, and labels. It is essential that a simple system be established for the transport of the blood sample to the laboratory. The following problems are impediments to rapid detection and reporting of suspected yellow fever cases:

- 1) few countries have formal guidelines on yellow fever surveillance at the peripheral and district levels;
- 2) peripheral and district health workers have poor training in surveillance (detection, investigation and reporting);
- 3) peripheral and district workers are often unaware of where to send blood specimens and reports;
- 4) specimen transport to laboratories is inefficient.

Laboratory confirmation of yellow fever is a key step before embarking on an outbreak response. Laboratory facilities for the confirmation of yellow fever should be placed at the level in the surveillance system where they will be utilized and where the quality of work can be sustained with staff, training and reagents. At a minimum, each country in endemic areas should have the capacity to confirm yellow fever with an IgM test such as MACELISA. In addition each country should have access to a laboratory that can carry out more sophisticated laboratory tests, e.g., virus isolation.

2.4 Session 3 - Outbreak response

2.4.1 Overview

While yellow fever is a vaccine preventable disease, the low vaccine coverage in many countries ensures that disease outbreaks will continue to occur. For many countries, yellow fever immunization programmes are put into place only after cases have been diagnosed. A timely response, in the face of an ongoing outbreak, requires preparedness on the part of public health officials. Awareness and understanding of the following components of outbreak response are required.

- 1) situation assessment, including the local response capability, the epidemiology of yellow fever in the country and the vectors present;
- 2) clinical management of cases, including actions to be taken on presumption of yellow fever, and supportive therapy;

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- 3) the role of the Epidemic Control Committee that should be immediately convened;
 - 4) collection and analysis of data on cases, deaths and control activities.

One confirmed case constitutes a public health emergency and requires prompt and appropriate intervention. While this threshold has been questioned by some as being too low, especially in areas where only sporadic sylvatic cases occur, the current sensitivity of yellow fever surveillance in most countries is not adequate. By the time the first case is identified, often many others have been infected and prompt epidemiologic assessment must be initiated.

The Epidemic Control Committee is essential to ensuring that the appropriate actions are taken and in coordinating the activities of all participants involved in response activities (*Prevention and control of yellow fever in Africa*, WHO, 1986). The committee has the following responsibilities:

- 1) define the population at risk of yellow fever;
- 2) plan control strategies;
- 3) assign responsibilities;
- 4) estimate resource needs;
- 5) identify resources;
- 6) identify laboratory support;
- 7) prepare for mass immunization campaign;
- 8) coordinate education and public awareness;
- 9) provide information to the news media;
- 10) monitor impact of control measures;
- 11) after the epidemic, evaluate impact, review performance and adjust strategy.

Ideally this committee of knowledgeable nationals should remain in place after the outbreak to help coordinate and monitor vector control programmes, support implementation of routine immunization programmes, and generally improve preparedness for outbreaks of all diseases with epidemic potential.

2.4.2 Country experience, Liberia

Liberia experienced an outbreak of yellow fever in 1995 in which there were 263 suspected cases in three districts; 60 cases were confirmed and there were 46 deaths among the suspected cases. Just over 1 million people were vaccinated in seven districts in response to the disease outbreak. This was followed in 1997 by the identification of a single fatal case in Lofa County. A localized immunization campaign involving 53 210 immunizations was undertaken in Lofa County.

There are a number of points of interest in the response to these outbreaks. The 1995 epidemic was first recognized in late October of that year. Although the response from the Health Authorities and the WHO regional office was rapid once the outbreak was recognized, the investigations revealed that the first cases had

occurred in August; over two months before the outbreak came to the attention of the Authorities. Mostly men aged 20 to 49 years were affected. This contrasts with the younger age group affected in most recent African outbreaks, but is similar to what is observed in South America where most infections are sylvatic. The initial immunization campaigns in November 1995 were undertaken with vaccine provided by a neighboring country pending the delivery of vaccine shipped from Institute Pasteur in Dakar, Senegal. The population that was immunized following the 1995 outbreak was determined more by the security situation than on a public health basis.

The rapid recognition of the case in Lofa County in 1997 was attributed to training in epidemiological surveillance that was conducted for health care workers just prior to the occurrence of the case. Immunization coverage of 53% in Lofa County appears to have been sufficient to limit the outbreak. However, since no additional cases were detected, this may have been an isolated sylvatic case.

2.4.3 *Country experience, Nigeria*

Nigeria, with a total population of 112 million, is the one country that has had the most yellow fever activity in recent years. There were epidemics nearly every year between 1986 and 1994. Although different areas of the country have been more severely affected in different years, the problem is countrywide. Since 1986, over 52 million doses of vaccine have been imported into the country and 33 million people vaccinated. In 1998, the Government embarked on a programme to vaccinate all Nigerians under the aged between 9 months and 30 years.

The Nigerian response to yellow fever highlighted a number of issues. Outbreaks continued throughout the late 1980s and early 1990s, despite the large number of doses of vaccine administered. Jet injectors continue to be used for mass immunization campaigns due to the cost or unavailability of auto-destruct injection equipment. This practice should be reviewed in view of the recent WHO recommendation to not use them. Between 1986 and 1996, vector densities of *Aedes albopictus* increased and may facilitate transmission of yellow fever virus. Following the recent outbreaks and associated immunization campaigns, serological surveillance may be useful in identifying non-immune populations at risk for infection. Increase in the population of yellow fever vectors detected through entomological surveillance was used to determine areas for mass immunization in the last five years. Nigeria has not experienced any major yellow fever outbreak since 1993.

2.4.4 *Summary - Outbreak response*

To assure timely and effective intervention after an outbreak is identified, the following aspects are critical. As stated in the overview, epidemic committees are a key means of co-ordinating the implementation of the response to an epidemic. These committees will usually be organized at a national level and will be generic in nature: dealing with epidemics of any etiology. In many African countries affected by yellow fever these committees will have a fairly regular cycle of outbreaks to deal with (meningitis, cholera, measles) in addition to the more sporadic outbreaks of diseases like yellow fever. WHO recommends training in the area of epidemic preparedness

using case-based training materials that will help maximise readiness for appropriate outbreak response. There also exists a need for co-ordination at the local level for implementing the plans devised by the national epidemic committee; local committees should be formed on an ad hoc basis where and when outbreaks occur.

International reporting to WHO (simultaneously to AFRO, AMRO and EMC/HQ) of yellow fever cases is required by the current International Health Regulations. The development of Sub-Regional Epidemiological blocks within AFRO would facilitate the alerting of any At risk neighbours of a country experiencing an outbreak of yellow fever. Informal e-mail networks often provide outbreak information more rapidly than formal notification mechanism; in South America such information is used to initiate action; however, in Africa any official action is commenced after formal notification to WHO.

For vaccine supply, a stock for epidemic response should be reserved at the regional or sub-regional level. In view of the information that in 15 epidemic situations more than 1 million doses of vaccine have been deployed, and that the highest recorded emergency response had involved 1.8 million doses, a minimum stock of 1 million doses should be held with the manufacturer (in both Africa and Europe). Allowances should be made for the rotation of the vaccine stock. An appropriate stock of auto-destruct injection materials must be available for use with this vaccine. The value of national level emergency stocks is dependent on the immunization practices in the country. In those countries in which yellow fever immunization forms part of the routine EPI programme, there are already supplies of vaccine immediately available with which to commence emergency activities. In other countries the shelf life of any reserved stocks of vaccine may expire before any outbreak occurs, resulting in wastage of vaccine or unsystematic preventive immunization.

Health education is an important component of the response process. Potentially viraemic individuals cannot be prevented from travelling from an outbreak area to other areas within a country (with the possible risk of initiating an urban cycle of transmission). However, public health programmes and the use of media can encourage individuals with fever and jaundice to seek care from local formal health services. Personal protection measures against mosquito bites and reduction of mosquito sources, while potentially providing health benefits in the broader and longer terms, would not have much impact on an established outbreak.

Vector control, in those countries where there is an established infrastructure for rapid vector control, e.g., South American cities where control of *Ae. aegypti* is an established part of the response to dengue, should form an early part of the response to a yellow fever outbreak. In

outbreaks of yellow fever in rural Africa, this is not likely to be a feasible or effective measure and should not distract resources away from the need to provide rapid mass immunization.

Political commitment of the government is essential for epidemic preparedness. An outbreak event provides an opportunity for sensitizing government officials to the importance of yellow fever control.

2.5 Session 4 - Vaccine supply

Several participants identified inadequate vaccine supply and high cost of yellow fever vaccine as constraints to successful implementation of control and prevention measures. The paucity of data on past yellow fever vaccine use and the lack of precise action plans make prediction of vaccine needs difficult

2.5.1 *Status of demand and availability of yellow fever vaccine*

The likelihood that a country would incorporate yellow fever was based on the following considerations:

- 1) the strength of the programme, measured by the coverage rate of measles vaccine;
- 2) the percentage of EPI vaccines financed by the government;
- 3) a suggested prioritisation process, using an estimated disease burden and other criteria, categorised each country's estimated risk as high, intermediate, or low. This was presented in the meeting background document entitled "Yellow fever" by Drs. J. Vainio and F. Cutts.

Prediction of yellow fever vaccine needs for routine immunization programmes was based on the assumptions that:

- 1) all countries who have already incorporated yellow fever into the EPI will continue to immunize children;
- 2) coverage rate for yellow fever will increase by 10% every year;
- 3) coverage rate for the first year of incorporation is half the measles coverage rate;
- 4) wastage rate is estimated at 40-70% (sometimes 6-7 doses from a 20 dose vial are actually administered).

For countries already using yellow fever vaccine in the EPI, their last reported vaccine coverage rate was used as the starting point. For others, half the measles coverage rate was the starting point for estimating yellow fever vaccine coverage

The estimated requirement for 34 African countries immunizing in all districts with a coverage rate of 80% is 46 million doses. For implementation using this strategy, production capacity may have to be increased. For those in high and intermediate risk countries the need will be 24 million doses, which is within the present production capacity.

Prediction of yellow fever vaccine needs for preventative mass immunization campaigns was based on the assumption that coverage would be 100% and the wastage rate 1.25. If all the population in high or intermediate risk areas of Africa in a single year were to be immunized, 240 million doses are needed, exceeding the present estimated production capacity, although mass campaigns are phased.

The Americas produce 40-50 million doses each year which is sufficient for the EPI campaigns. It is the supply for Africa that poses the problem.

Making accurate estimates of the doses need for outbreak response requires historical data and information which might be useful to predict the site, and time of future epidemics. These data are limited. For example, if Nigeria, in response to an outbreak, decided to vaccinate the entire population, 112 million doses of vaccine would be needed. Routine vaccine stocks within the country, if any, are used first for outbreak response. This supply would only partly solve the problem of having an emergency supply of vaccine but would be reinforced with one million doses stockpiled at the manufacturer ready for disbursement once an outbreak was confirmed.

Eighty-three percent of the population at high or intermediate risk for yellow fever in Africa live in five countries (Cameroon, Cote d'Ivoire, Ghana, Nigeria, and Senegal). Implementation of routine immunization and preventive mass campaigns in these countries would have significant major public health benefits. To ensure the adequate supply of quality vaccine, the co-ordination among countries (especially the five countries named above), suppliers and manufacturers should be well organized.

2.5.2 Supply and quality of vaccine

UN agencies that purchase vaccine for developing countries rely on WHO's advice on the acceptability and quality of vaccines. The National Control Authority of a vaccine producing country is assessed to assure the quality of locally produced vaccines. The NCA is critical to whether the vaccine manufacturer is accepted as qualified supplier. Currently only two manufacturers are listed as yellow fever vaccine suppliers for UN agencies.

With respect to vaccine supply, some manufacturers have given assurances that production can be increased by two- or three-fold. Given an established strategy and financial commitment, annual production capacity could be increased up to 140 million doses globally using the current technology. However, a note of caution was sounded that this may refer to vaccine stored in bulk form. Vaccine in the desired dose vials may not be readily available. The two possible approaches for increasing vaccine availability are increased production or the pre-qualification of more potential manufacturers.

3. Recommendations

3.1 General recommendations

- 1) International and national partners in the health sector (including ministries of health, NGOs, UNICEF, WHO, bilateral donors) should co-operate in the development of advocacy groups at the national level. A group such as this can support the ministry of health in its efforts to maintain governmental commitment to yellow fever prevention, surveillance and control, particularly after the stimulus provided by any outbreak is over.
- 2) At the ministerial level, formal inter-country dialogues should be established in which countries commit themselves to epidemic control activities, including programmes for yellow fever.

3.2 Prevention of yellow fever through routine infant immunization and mass campaigns

3.2.1 *Countries with yellow fever immunization in EPI*

- 1) Countries that have already introduced yellow fever vaccine in the EPI should receive support to strengthen their programmes to attain at least 80% coverage in order to prevent outbreaks. Reasons for the current low coverage should be investigated and a remedial action plan, with a reasonable time frame for implementation, should be prepared by the country and put into place with the help of WHO.
- 2) Coverage at all levels (district, national, regional) should be monitored and compared with measles coverage.
- 3) The factors outlined in Section 2.2.7 (2nd paragraph) should be considered in the planning of preventive catch-up campaigns. Adequate lead-time should be allotted for obtaining vaccine and injection materials including auto-destruct syringes.
- 4) If recent outbreaks have occurred, the country should institute outbreak investigation to understand the epidemiology (age group, geographic area involved) and consider additional activities beyond routine immunization of infants, e.g., immunization of migrant workers.

3.2.2 *Countries that have not included yellow fever immunization in EPI*

- 1) Countries with a policy for routine yellow fever immunization integrated into the routine EPI but not yet carrying out immunization activities should receive assistance in mobilizing the resources required for the introduction of yellow fever immunization and sustaining the programme.
- 2) Countries with no policy on yellow fever immunization should receive support to determine the priority for the introduction of yellow fever vaccine. If an outbreak has occurred in the last 20 years or endemic cases have been detected, the country should be urged to introduce yellow fever vaccine as soon as possible. If there is doubt of whether yellow fever is endemic, serological surveys of children under 10 years may be considered in areas of the country most likely to sustain transmission.
- 3) Countries should make plans for the introduction of routine immunization for yellow fever in a phased manner, beginning in the areas of highest risk.

3.2.3 *Operational research*

Assuming resources are available, operational research should be conducted in the following areas:

- 1) factors potentially affecting the immunogenicity of yellow fever vaccine such as HIV infection, malnutrition, and anti-malarial drugs;
- 2) factors potentially affecting adverse events after yellow vaccine;
- 3) active monitoring of adverse events in trials of yellow fever vaccine in HIV-infected infants.

3.3 **Yellow fever surveillance and laboratory support**

Surveillance for yellow fever is and will remain a critical public health activity in at-risk countries for the early detection of epidemics. This will allow an effective response. The following are recommended:

3.3.1 *Detection, reporting and investigation of suspected cases*

- 1) Each country at risk should include yellow fever surveillance in its national priorities for disease surveillance. The country should assess its current capacity for yellow fever surveillance and implement a plan of action to establish or strengthen such surveillance. The minimum requirements for a yellow fever surveillance system are detection, investigation, specimen collection and reporting system for suspected cases, linked to confirmatory testing of samples.
- 2) Surveillance should be carried out using a sensitive syndromic definition of suspected yellow fever in all at-risk countries.
- 3) The new WHO guidelines for yellow fever surveillance at district level should be widely disseminated and implemented to improve early detection of suspected cases. These guidelines should outline the sequence of events from the taking of a blood sample from a suspect case to confirming the cases in a qualified laboratory.

- 4) Strategies to strengthen yellow fever surveillance in AFRO should be synergistic with the WHO/AFRO strategy for integrated disease surveillance, which includes yellow fever as one of its 18 priority disease for surveillance in the African Region. This would include the potential to include yellow fever surveillance in the active surveillance protocol being developed by EPI in Africa. In addition, surveillance of yellow fever could be integrated with surveillance initiatives for haemorrhagic fevers as many countries are at risk from both yellow fever and the viral haemorrhagic fevers. Yellow fever surveillance could also be integrated with the intensive program of surveillance for acute flaccid paralysis (AFP).
- 5) Surveillance for yellow fever should be continuous and carried out on a national basis in at-risk countries. However, if resource restraints curtail surveillance activities then they should be based on a risk assessment and priority given to forest and intermediate zones where the disease is most likely to emerge. In addition, vigilance may need to be emphasized at certain times of the year when yellow fever is more likely to occur.

3.3.2 *Laboratory support*

Confirmation of recent yellow fever cases in Africa has been the direct result of WHO programmes for capacity building through laboratory training programs and the provision of diagnostic reagents. The following are recommended to further strengthen laboratory diagnosis.

- 1) All at-risk countries should have access to a qualified laboratory capable of confirming yellow fever by an IgM test. Furthermore, all countries should be aware of the sub-regional laboratories that can aid them in confirmatory testing. Procedures for specimen transport between laboratories and testing should be formally put in place.
- 2) The current efforts to assist laboratories in developing the ability to be multi-purpose should be further supported, e.g., use of polio network laboratories for yellow fever diagnosis. This approach allows laboratories to benefit from training and financial support from many sources and maximises the use of available equipment and supplies. Furthermore, the higher volume of testing from use of similar assay formats for different pathogens helps ensure that skills are maintained.
- 3) The laboratories capable of performing more sophisticated confirmatory tests should be incorporated into a cohesive network with electronic communication facilities and programs for the exchange of reagents, standards and proficiency panels.
- 4) Formal quality control and proficiency testing programs should be established. The WHO regional offices should administer these programs. WHO collaborating centres, acting as reference centres, should be an integral part of the programs.

3.3.3 Vector surveillance

Surveillance of vectors, i.e., *Aedes aegypti*, should be carried out in urban areas in order to assess the potential for urban spread of disease. This is particularly important in countries in South America where *Ae. Aegypti* has been re-introduced into yellow fever enzootic areas. Appropriate resources should be provided to support entomology training and logistics for conducting vector surveillance activities.

3.3.4 Operational research

Operational research is needed in the following areas:

- 1) field testing case definitions for suspected yellow fever so that an adequately sensitive and specific definition is promoted in at-risk countries;
- 2) integration of yellow fever surveillance with AFP surveillance and/or surveillance of other viral haemorrhagic fever;
- 3) accurate, efficient, simpler and more acceptable blood specimen sampling methods, e.g., filter paper IgM, for improving specimen referral to laboratories;
- 4) development of methods, such as rapid diagnostic tests or surveillance techniques, to demonstrate the disease burden of yellow fever during inter-epidemic periods
- 5) entomological surveillance in forest areas to predict human outbreaks of yellow fever.

3.4 Outbreak response

- 1) Ministries of Health must give priority to the setting up and regular meeting of national multi-disciplinary Epidemic Committees which will co-ordinate actions to increase national preparedness for epidemics and also meet on an ad hoc basis to define action plans to control outbreaks when they occur. These committees should oversee the documentation of the nature, quantity and physical whereabouts of resources potentially required for epidemic response. As a tool to aid the committees in responding to outbreaks, an up-to-date national inventory detailing the amount and geographic situation of strategically important resources for epidemic control including personnel (number and expertise), refrigerators, injection equipment, transport, etc. should be conducted.
- 2) The existing arrangements by which Ministers of Health in neighbouring countries meet, formulate joint plans, and make commitments for the control of epidemics, should continue to be supported. Countries not yet involved in such arrangements should be encouraged and supported to join existing groups or to come together to form new groupings as appropriate.

3.5 Vaccine supply

To ensure the adequate and timely supply of high quality vaccine, co-ordination of vaccine needs and supply is critical. For this purpose, demand-forecasting should be reliable and made well in advance of anticipated changes in demand, thereby giving manufacturers adequate time to respond.

3.5.1 Demand-forecasting issues

For improving the reliability of demand-forecasting and to co-ordinate with suppliers, the following data and information should be collected:

- 1) From each country in which yellow fever is endemic:
 - a. country plans for routine EPI, preventive mass immunization campaigns and history of response to outbreaks;
 - b. coverage rate (national, and sub-national, if immunization is to be held at the sub-national level),
 - c. wastage rate (national, and sub-national, if immunization is to be held at the sub-national level);
 - d. number of persons in the target population;
 - e. number of doses bought and sent out from the central storage site;
 - f. maximum and minimum levels of national stock.
- 2) From the manufacturers:
 - a. production capacity (maximum, minimum and time frame);
 - b. current and potential stock available (bulk, final product);
 - c. location where stocks are stored.

3.5.2 Vaccine supply

- 1) Countries, regional offices and headquarters of WHO should ensure long term commitment to the strategy, which will enable manufacturers to make management decisions. Financial resources with long term sustain ability should be ensured to enforce the strategy.
- 2) WHO and its international partners should ensure that an emergency, pre-paid stock of 1 million doses of yellow fever vaccine (preferably in 20 dose vials to limit wastage) is reserved in both Africa and South America with the vaccine manufacturers, so as to be available for immediate shipment in the event of an outbreak. The necessary amount of auto-destruct syringes and safety boxes should accompany this reserve stock. This will be especially important for countries where yellow fever vaccine is not incorporated into routine EPI programme, and therefore the vaccine delivery system would not contain adequate supplies of yellow fever vaccine.
- 3) Given that the price of yellow fever vaccine vary considerably depending whether it is purchased through a programme or directly from the manufacturer, countries should be provided information about sources which sell

vaccine at the lowest possible price, thereby encouraging countries to utilize yellow fever vaccine in resource-limited environments. Purchase of vaccine through the Vaccine Independence Initiative is suggested as one such mechanism.

- 4) To ensure availability of vaccines, other potential manufacturers for supply through UN agencies should be encouraged to undergo the pre-qualification process. Priorities should be established regionally on the basis of availability of vaccine.
- 5) The best number of doses per vial should be considered carefully to reduce wastage, and enable the programme to be sustainable. For routine immunization, 10-dose vials are strongly recommended.
- 6) National governments, bilateral donors and NGOs are strongly encouraged to ensure that the procurement of any vaccine for a mass campaign or routine immunization is always accompanied by the procurement of the appropriate amount of auto-destruct injection material to optimize the safety of injection procedures. Countries that already hold stocks of vaccine without the availability of auto-destruct should make it a priority to obtain such materials.

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Annex 2: Agenda

Monday, 2 March 1998

08:30 – 09:00	Registration	
09:00 – 09:10	Opening	Dr R.H.Henderson, ADG
09:10 – 09:20	Objectives of the meeting	Dr Olivé
	Adoption of the agenda	
09:20 – 09:45	Global overview:	Dr Monath
	<ul style="list-style-type: none">• The situation of yellow fever control programmes ten years later	
Session I:	Prevention of yellow fever through routine infant immunization and mass campaigns	
	<i>Moderator: Dr F. Cutts</i>	
09:45 – 10:00	AFRO overview	Dr Tapsoba
10:00 – 10:15	<i>Coffee break</i>	
10:15 – 10:30	Country experience; Burkina Faso – Questions	Dr Millogo
10:30 – 10:45	Country experience; Ghana – Questions	Dr Tomori
10:45 – 11:00	PAHO overview – Questions	Dr Oliva
11:00 – 11:15	Country experience; Peru – Questions	Dr Carrillo
11:15 – 11:30	Country experience; Trinidad – Questions	Dr B. Hull
11:30 – 12:30	Discussion: <ul style="list-style-type: none">• Proposed options for moving forwards	
12:30 – 14:00	<i>Lunch</i>	

Monday, 2 March 1998 (*continued*)

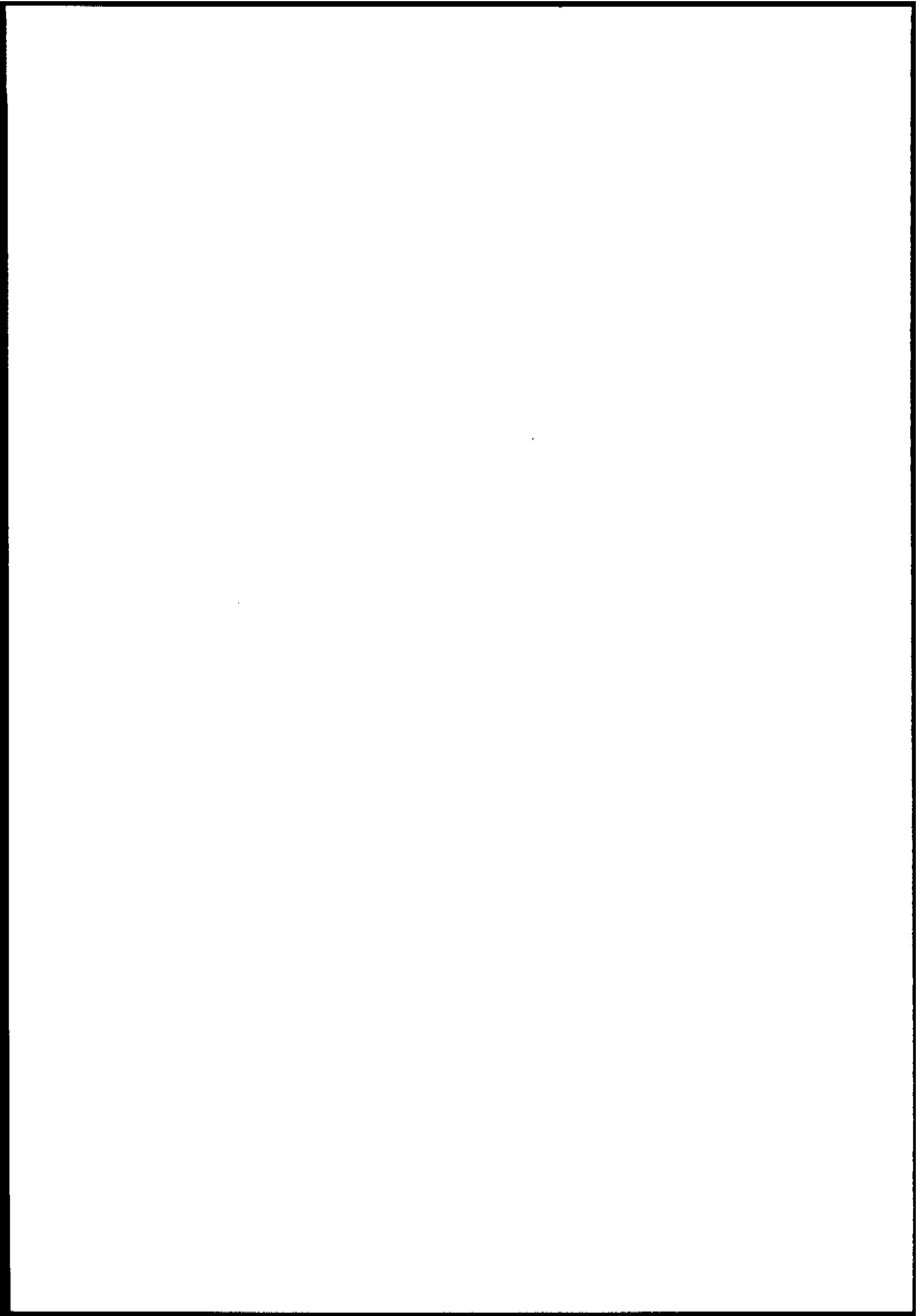
Session II	Yellow fever surveillance and laboratory support <i>Moderator: Dr M. Ryan</i>	
14:00 – 14:15	Overview	Dr R. Arthur
14:15 – 14:30	Surveillance systems in AFRO – Questions	Dr Yada, AFRO
14:30 – 14:45	Laboratory support for yellow fever control – Questions	Dr O. Tomori
14:45 – 15:00	Country experience for laboratory support, Kenya – Questions	Dr L. Dunster
15:00 – 15:15	Country experience, Senegal – Questions	Dr J. Thonnen
15:15 – 15:45	<i>Coffee break</i>	
15:45 – 17:00	Discussion: <ul style="list-style-type: none">• Do we have the required elements for surveillance given our objectives to control yellow fever?	
18:00	<i>Reception</i>	

Tuesday, 3 March 1998

Session III:	Outbreak response <i>Moderator: Dr M. Hardiman</i>	
09:00 – 09:10	Brief overview	Dr R. Arthur
09:10 – 09:30	Country experience, Liberia – Questions	Dr T. Freeman
09:30 – 09:45	Country experience, Nigeria – Questions	Dr A. Nasidi
09:45 – 10:30	Discussion: <ul style="list-style-type: none">• What is the optimal (technical and operational) response to outbreaks?	
10:30 – 10:45	<i>Coffee break</i>	

Tuesday, 3 March 1998 (*continued*)

Session IV	Vaccine supply <i>Moderator: Dr N. Dellipiane</i>	
10:45 – 11:00	Status of demand and availability of yellow fever vaccine – Questions	Dr M. Kawano, VSQ
11:00 – 11:15	Supply and quality of vaccine – Questions	Dr N. Dellipiane, VSQ
11:15 – 12:30	Discussion: <ul style="list-style-type: none">• How do we best make use of current available supply of vaccine?• How do we move forward and increase supply?	
12:30 – 14:00	<i>Lunch</i>	
14:00 – 16:00	(Working Groups for each of the four sessions to draft recommendations approximately two hours before the last session.)	
16:00 – 17:00	Recommendations for the future	Dr Monath, Dr Arthur-EMC, Dr Tomori, and Dr Olivé, EPI
	Closure of the meeting	Dr Monath



The Global Programme for Vaccines and Immunization, established by the World Health Organization in 1994, defines its goal as "a world in which all people at risk are protected against vaccine-preventable diseases". The Programme comprises three units:

**Expanded Programme on Immunization
Vaccine Research and Development
Vaccine Supply and Quality**

The Expanded Programme on Immunization focuses on the prevention of selected childhood diseases and, through support to national immunization programmes, aims to achieve 90% immunization coverage of children born each year. Its goals are to eradicate poliomyelitis from the world by the year 2000, reduce measles deaths and incidence, eliminate neonatal tetanus as a public health problem and introduce hepatitis B vaccine in all countries.

Vaccine Research and Development supports and promotes research and development associated with the introduction of new vaccines into the Expanded Programme on Immunization. This includes research and development of new vaccines, improvement of immunization procedures and support to epidemiological studies.

Vaccine Supply and Quality ensures adequate quantities of high quality, affordable vaccines for all the world's children, supports the efforts of governments to become self-reliant as regards their vaccine needs, and assists in the rapid introduction of new vaccines.

The Global Programme for Vaccines and Immunization produces a range of documents, audiovisual materials and software packages to disseminate information on its activities, programme policies, guidelines and recommendations. It also provides materials for group and/or individual training on topics ranging from repair of health centre equipment to curricula guidelines for medical schools, nursing colleges and training of vaccine quality control personnel.

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