



Surveillance of Ebola Virus
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SURVEILLANCE OF EBOLA/MARBURG FEVERS

by

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Following the extensive outbreaks of Ebola fever in Sudan and Zaire in late 1976 an informal consultation was organized by WHO to review epidemiological investigations and control measures carried out during these outbreaks and to make recommendations on further studies which were as follows:

An essential factor in planning for future outbreaks of diseases of international significance (such as Marburg virus-like disease) is the development of mechanisms for identification of cases and/or outbreaks as early as possible and for prompt reporting to local and national health authorities and WHO. Specific mechanisms to assure prompt reporting of outbreaks must be developed at local and national levels. Delays in recognition and reporting of such outbreaks result in continued transmission of the disease and prolonging the initiation of the clinical, epidemiological, and laboratory investigations which are essential to provide the necessary data for formulation of appropriate methods of prevention and control. Since diseases such as Lassa, Marburg and the other viral haemorrhagic fevers are not currently required to be reported to WHO, it is urged that reporting of these diseases be made mandatory and that a specific category for reporting these diseases requiring special consideration to WHO be created. Health agencies of neighbouring countries should also exchange reports and keep lines of communication open.

WHO should serve as the focus for co-ordination of international activities related to the study and control of such outbreaks of disease. Because these outbreaks often require co-ordination of efforts being made by numerous countries and because the resources available in these countries must be utilized in the most efficient and logical fashion, WHO should create and maintain a means for achieving this international co-ordination.

A prime function of WHO in such emergencies would be to provide international co-ordination of requests for assistance from the country experiencing the outbreak as well as identifying the resources necessary to combat the epidemic and from which countries these would be derived. Resources generally fall within the categories of personnel, equipment and supplies, and funds. Planning on the international scale for such outbreaks would include the development of specific headings or classifications of items and check lists for each of these headings. WHO could then serve as the focus for forming an international team to respond to a request for assistance by an affected country, or could serve to facilitate and/or co-ordinate bilateral assistance arrangements which could take place directly between an affected country and a resource country. With respect to personnel, it was felt that maintaining check lists of institutions and their individual personal resources might be more advantageous than just preparing a list of individual persons since the identification of institutions would essentially

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serve to identify teams of experts who already know how to work well together. With respect to equipment and supplies, check listing is good, but stockpiling should be discouraged since outdating occurs at a rather rapid rate, making this an expensive procedure. Consideration could be given to contracting with companies to provide supplies and equipment when they are needed. WHO should investigate the possibility of maintaining a disaster or a contingency fund which might be tapped in the event of occurrences such as the outbreaks of haemorrhagic fever in the Sudan and Zaire. Possible co-ordination of contingency funding with the International Red Cross and the United Nations Disaster Relief Organization should also be investigated.

The necessity of having a system for widespread dissemination of information in the event of such outbreaks was underlined. Such a system should serve the purpose of informing the public through the news media and also providing appropriate clinical, epidemiological, and other information to medical and hospital personnel, so that a basic understanding of the nature of the disease in progress, the means of spread and appropriate measures for prevention and control are understood by all.

Three of the major problems to be faced when combating outbreaks of such disease are those of communication, transport and dissemination of information. Such complicated problems and arrangements are best handled by a skilled and experienced expert in logistics. WHO should, therefore, study the problem of identifying and training persons in co-ordination, administration and logistics who could be called upon to co-ordinate such activities at a local and/or national level in an emergency. Furthermore, such persons should be aware of the importance of working with persons in key positions inside the affected country because of their familiarity with the local and national scene.

The importance of early disclosure of disease activity, prompt reporting of such episodes to the national and international level as soon as possible was emphasized. In anticipation of the occurrence of future episodes, WHO should prepare specific and detailed operational plans for undertaking surveillance, epidemiological studies, laboratory support, logistics and communications, dissemination of the information and identification and efficient utilization of resources existing in member countries which might be called upon in the future.

i. Organization and management of surveillance

The surveillance team should be headed by an experienced epidemiologist and should include one or more medically trained staff who can advise on the clinical features of the disease. The remainder of the team may consist of locally-recruited personnel trained on the spot and supervised by one or more epidemiologists. They should have standardized forms for case evaluation and for village surveillance reports. Good and regular transportation systems for members of the surveillance team is essential.

ii. Clinical features

In the earliest stages of infection the symptomatology is non-specific and a clinical diagnosis is difficult until more characteristic features of the illness become apparent or when several similar cases occur during an epidemic.

The incubation period for Marburg ranges from 3 to 9 days whereas in the far larger epidemics of Ebola the incubation period ranges from 4 to 16 days with an average of 7 days.

The onset is abrupt with severe frontal and temporal headache and severe malaise. Generalized aching pains, particularly in the lumbar region, are common and the eyes are extremely sensitive and painful on pressure. A high fever is apparent by the second day of illness and the patient becomes increasingly debilitated. A severe watery diarrhoea, abdominal pain and cramping, nausea and vomiting are early symptoms. Knife-like chest or

pleuritic pains, sore throat and cough are common, the throat discomfort being sufficiently severe to prevent eating or drinking. A characteristic maculo-papular rash appears between days 5 and 7 involving the whole body. It lasts 4-5 days, is not itchy and is followed by a fine desquamation. On black skin the rash is "measles-like" and may not be so obvious, and is often only recognized later with the appearance of desquamation. A pronounced conjunctivitis may occur and there is often an enanthem of the palate accompanied by tapioca-like lesions on the tonsils. A pharyngitis may be present and the throat is often extremely dry and there may be fissuring and open sores in the tongue and lips. Many patients on admission to hospital may have "ghost-like" drawn features, deep-set eyes, expressionless faces and extreme lethargy. The patient is anxious and often sullen. Rapid cachexia and dehydration follow and there may be a relative bradycardia and lymphadenopathy.

A high proportion of cases develop severe haemorrhagic manifestations between days 5 and 7. Fatal cases always have some form of bleeding often from multiple sites. The gastrointestinal tract and the lungs are more frequently affected. Haematemesis and melaena and sometimes the passage of fresh blood in the stools are often accompanied by bleeding from the nose, gums and vagina and sub-conjunctival haemorrhages are common. Petechiae, haematuria and bleeding from needle puncture sites are frequently seen. Death, when it occurs, is usually between 7 and 16 days and is preceded by severe blood loss and shock.

Involvement of the central nervous system may be apparent with paraesthesia, lethargy, confusion, irritability, aggression and signs of meningeal irritation. Other features may be present which include oliguria, oedema, pancreatitis, myocarditis and orchitis.

Clinical and differential diagnosis. Because Marburg and Ebola viruses are readily transmitted from person to person particularly to medical and nursing staff and those caring for patients, early diagnosis and isolation of the patient are essential. The diagnosis must be considered in all febrile patients in or travelling from known or suspected endemic areas of Africa.

The sudden onset of fever, headache and malaise soon followed by chest pain, diarrhoea and vomiting and rapid cachexia should alert physicians to the possibility of Marburg and Ebola fevers. The history, physical examination and epidemiological background should then be carefully assessed.

The appearance of a characteristic maculo-papular rash and the rapid onset of cachexia may confirm the suspicion of Marburg/Ebola fever and the onset of haemorrhagic manifestations may confirm this. The differential diagnosis may be difficult. Lassa fever must be considered but the onset is generally more insidious and a sore throat, pharyngitis and, in the later stages, facial oedema are more characteristic of Lassa.

Malaria generally presents with fever and headache. Blood smears should be examined for malaria parasites but the presence of parasites does not exclude concurrent viral infection. Anti-malarials should be administered routinely as a therapeutic trial.

Typhoid fever may present with fever, headache, rash, gastrointestinal symptoms and often lymphadenopathy, relative bradycardia, cough, leukopenia and sometimes a sore throat. It is perhaps the most difficult infection to distinguish from either Lassa or Marburg/Ebola infections. A therapeutic trial with chloramphenicol or tetracycline may serve to differentiate the disease. Blood culture if it can be performed during the first few days of illness is often successful in culturing the organisms.

Haemorrhagic complications can result from both yellow fever and Congo/Crimean haemorrhagic fever group viruses. Careful epidemiological investigation may indicate the pattern of disease as being transmitted by mosquitoes or ticks. Virus isolation and serological investigation will distinguish these viruses. A history of previous yellow fever vaccination may also serve to eliminate a diagnosis of yellow fever.

Other bacterial infections may have to be considered in a differential diagnosis and a search should be made for possible sites of bacterial infection. Smears and cultures should be examined and the blood picture examined. The presence of a leucocytosis will often serve to distinguish bacterial infections from those of Lassa or Marburg/Ebola where a leucopenia is a constant finding.

Viral hepatitis, leptospirosis, rheumatic fever, typhus and mononucleosis are other diseases which produce signs and symptoms which may be confused with Marburg/Ebola fever in the early stages of the illness.

iii. Epidemiological features

The following definition should be adopted for epidemiological investigations:

- (a) confirmed case: a person with acute clinical symptoms with isolation of the virus and/or presence of specific antibodies;
- (b) probable case: a person having for three days headache, lumbar pain, high fever, abdominal pain, nausea, vomiting and haemorrhage without any other specific diagnosis and no sedation after anti-malaria and antibiotic treatment; knowledge of a contact with a confirmed case or another probable case is essential;
- (c) possible case: a person with only three days of fever and headache without any other diagnosis and not responding to treatment as above and with a contact with a confirmed or probable case three weeks previously;
- (d) contact: a person having had direct contact with (a), (b) or (c), i.e. sharing the same room or meals, having given care or participated in burial; either two days before onset, during the disease or immediately after death.

The prevalence of the disease in all age groups with a predominance in adults and in both sexes with a predominance in males has been noted. The attack rate in infected communities varied from 3.5 per 1 000 to 15.3 per 1 000 in the Sudan and from 8 per 1 000 in the infected community of Yandongi in Zaire to less than 1 per 1 000 in neighbouring communities. This indicated that the virus was not as highly transmissible as previously thought.

Transmission of the disease from person to person is not common and requires extremely close contact. Infection results from contact with blood or body fluids with high virus concentration especially those containing blood. Entry might be through skin abrasions or mucous membranes. Transmission through droplets seems unlikely - some persons having shared the same room as patients without being infected, but this cannot be ruled out. Nursing, either at home or in hospital, is by far the most common means of contact. Syringes insufficiently sterilized may have played a role. No biting insect could be incriminated.

The secondary attack rate was about 15 per cent. in Zaire. In the Sudan active cases documented showed a secondary spread of 13 per cent., a tertiary spread of 14 per cent. and a quaternary spread of 9 per cent. Transmission seemed to stop spontaneously after four generations, but in exceptional circumstances at least eight generations could be documented.

There is a strong suspicion that the disease is a zoonosis. Monkeys did not seem to play a role in these epidemics and rodents, or bats, may perhaps be the animal reservoir. It may be assumed that "jungle" cases of Marburg virus-like disease occur from time to time and die off spontaneously. Exceptionally as in the previous outbreaks in the Sudan and Zaire, unusual nosocomial transmission creates an amplifying cycle and brings the virus to the fore. This resembles the episode in the Federal Republic of Germany in 1967, whereas South African cases in 1975 are more illustrative of the "jungle" type of transmission.

iv. Laboratory features

Clinical laboratory studies have necessarily been limited because of the risk to laboratory personnel. A leucopenia early in the course of illness has been a constant feature together with a low erythrocyte sedimentation rate. An alteration in the granulocyte series has been noted with the appearance of atypical plasmacytoid lymphocytes while the Pelger-Huët anomaly of neutrophils was recorded. South African patients had severe disseminated intravascular coagulation probably resulting from the failure by the liver to synthesise coagulation factors and from depression of bone marrow. These features were not evident in German patients although there was a fall in thrombocytes while prothrombin and thrombin times, partial thromboplastin times and fibrinogen levels were not obviously affected.

A constant finding was a noticeable elevation of serum glutamine oxaloacetic and pyruvic transaminase levels, the former being consistently high and serving as a diagnostic aid. Serum amylase was also raised in some cases and especially in one patient in South Africa with acute pancreatitis. Several patients had hypoproteinaemia which resulted in varying degrees of oedema.

Pathology. Marburg and Ebola viruses are pantropic and produce lesions in almost every organ, but the liver and spleen were most conspicuously affected. Severe degeneration of lymphoid tissue, spleen and liver resulted in large accumulations of cellular and nuclear debris.

The pattern of disease was that of stimulation of the reticulo-endothelial system, inhibition of the lymphatic system and vascular changes leading to vascular occlusion and the formation of thrombi and haemorrhages.

Macroscopically both the liver and spleen were enlarged and dark in colour. On section the spleen revealed no follicles and the pulp was soft and mushy. The liver was extremely friable and blood poured out freely on section leaving the organ a light yellow colour. Histologically severe congestion and stasis was obvious in the spleen. There was proliferation of reticulo-endothelial elements in the red pulp and the formation of large numbers of macrophages. Necrosis of the red pulp was accompanied by destruction of lymphoid elements. In the Malpighian bodies lymphocytes were markedly depleted. There was widespread degeneration and necrosis of liver cells and hyaline changes were frequently seen. Hyaline-necrotic-eosinophilic bodies similar to the councilman bodies of yellow fever were seen on several occasions. Kupffer cells were swollen and bulging and full of cellular debris and red blood cells. Sinusoids were also full of debris while mononuclear accumulations were seen in the periportal spaces. Even at the height of the necrotic process in the liver there was evidence of regeneration of liver cells.

Mononuclear transformation of lymphoid tissue as well as necrotic lesions were found not only in the liver and spleen but also in the pancreas, gonads, adrenals, hypophysis, thyroid, kidneys and skin.

The lungs showed few lesions except for circumscribed haemorrhages and evidence of endoarteritis especially in the small arterioles.

Neuropathological changes were confined mainly to glial elements scattered throughout the brain. No lymphocytic reaction was observed but multiple haemorrhages into the brain substance were seen. Glial lesions were either proliferative in the form of glial knots, nodules and rosettes or degenerative in the form of nuclear pyknosis or karyorrhepias. All glial elements were affected including astrocytes, microglia and oligodendroglia. Cerebral oedema was found in all the human brain material examined.

Virological and serological diagnosis. Specific diagnosis requires isolation and identification of the virus or evidence of antibody development between paired serum samples.

Attempts to isolate the virus must be carried out only in high security laboratories (i.e. those with a Class III biocontainment facility).

- v. Routine and active methods for detecting cases, including establishment and improvement of reporting systems

and

- vi. Conduct of case and outbreak investigations including collection of specimens, use of forms, etc.

Search for cases. When a workable case definition is established, it is the epidemiologist's job to learn as quickly and thoroughly as possible the extent of the outbreak. If the epidemic is on-going, or if it is uncertain that cases have ceased to occur, prospective case-finding methods must be employed. This implies an active search on the part of the epidemiologist and support personnel, utilizing a variety of measures, and must be clearly distinguished from passive surveillance, such as the existing system of routine reporting of communicable diseases. It will also be necessary to define the occurrence of cases which have recovered or died prior to initiation of the epidemiological investigations. Retrospective case-find methods must be employed, and, again, this implies an active effort rather than reliance on passive or routine reporting systems.

Prospective methods of surveillance. During an outbreak active cases must be found without delay and hospitalized or isolated depending on the severity of the infection and its mode of transmission. Cases can be found by visits to hospitals, clinics, general practitioners, dispensaries, etc. In each, a single responsible individual must be identified who will be able to examine records of attendance, admission, etc. and with whom frequent contact is made by the epidemiologist. This individual may be a hospital infectious diseases control officer, hospital administrator, nurse, physician, dispenser etc.; clinical laboratories too can often provide useful information. Another useful method of case finding is to examine absentee records at schools, factories and large offices. In remote areas, in the absence of established medical services, the only method is by house-to-house visits. Establishing "fever clinics" may be a useful method of detecting on-going cases.

The case definition in several instances may be too specific and it may be necessary to "broaden" the case definition. Yellow fever, for example, may present simply as a non-specific febrile illness and one must then examine the records of all cases of fever, as well as anyone presenting with jaundice, haemorrhages and so forth.

In outbreaks of diseases transmissible from person to person, once a case is identified, it is essential to determine with whom he/she has been in contact during and immediately prior to the onset of illness. This is most important in severe infections such as Ebola in order to predict further cases and take appropriate action. As much information as possible needs to be collected about the mode of contact, length of time of exposure, etc. At the same time retrospective contacts must be sought: how did the patient acquire his infection, when, and where; who were his/her contacts? This will allow an accurate estimate of the incubation period to be established which is extremely useful for predicting future cases. It may also provide an indication of the mode of transmission.

Retrospective methods. The search for cases which occurred prior to initiation of the epidemiological investigation can be accomplished by:

1. Review of records at hospitals, clinics, physicians' offices, etc. Often, it will be possible only to screen such records by admission or discharge diagnosis or chief complaint, and the epidemiologist must be prepared to put aside records with many different diagnoses or chief complaints that might prove to fit the case definition upon closer inspection.
2. Direct surveys, which may be performed by house-to-house visits (possibly using a randomized sampling technique) to determine by interview with the residents the past occurrence of illness or death compatible with the clinical case definition. Often this will be combined with the collection of a specimen for retrospective laboratory diagnosis, possibly from the surviving case(s), contacts, and matched controls (see also below).

3. Serologic surveys. A useful method for determining the prevalence of infection and estimating the incidence of infection during a past outbreak is the serologic survey. This is also the only available means of defining inapparent infections in a population. Ideally, serologic surveys should be conducted using a randomized sampling technique, which will allow adequate samples in each age and sex group considered, as well as geographical stratification if indicated by the distribution of cases or other factors. However, these refinements are often not possible and a sampling technique which is practical under the given field conditions may be selected.

Specimens required

- Acute phase whole blood obtained from patients who have been sick for less than 7 days. Blood should be collected in sterile receptacles and despatched in liquid nitrogen (this requires special plastic screw tubes), dry ice or kept chilled with refrigerant packs (cold dogs). The separation of sera from blood clots is not recommended unless facilities are available to protect laboratory workers from infectious aerosols.
- Convalescent sera from patients at least 14 days after disease onset. Whereas paired samples from the same patient are desirable, single convalescent sera are valuable and should be looked for. Sera should be separated from blood clots and sent frozen as above.
- Liver specimens taken by post-mortem with a biopsy needle (biopsy from sick patients is contra-indicated as it may cause bleeding of the liver) should be divided in two: one being placed in 10% buffered formalin and the other handled as an acute blood specimen.

Relevant information must be included with specimens: locality, name of patient, age, sex, date of sampling, date of onset of the disease, summary of clinical findings and pertinent epidemiological information such as number and history of similar cases, history of contact and occurrence of disease in hospital staff. Specimens for shipment to laboratories abroad must be packed in compliance with the international regulations. They must be sent to high security laboratories who should be informed by cable of the airwaybill number, flight number (connecting flights if necessary) and the estimated time of arrival. A copy of the cable should be sent to WHO, attention Chief, Virus Diseases unit.

At this stage, the differential diagnosis has to be made rapidly with salmonellosis which is the major cause of an acute disease simulating a viral haemorrhagic fever. Treatment with chloroquine, tetracycline or chloromycetine will allow a differential diagnosis by eliminating the possibility of malaria and bacterial infections. Supplies of aspirin, multivitamins and iron tablets may prove useful to obtain cooperation from the population.

Generally it is not feasible to establish viral diagnostic facilities in the field at the site of an outbreak. However, if electricity is available certain advanced techniques can be utilized as has been demonstrated in Zaire. Antibodies can be tested by the immunofluorescence (IF) technique. It should also be possible, at least theoretically, to detect viral antigens by IF tests in cells taken from acutely ill patients such as: leucocytes, bone marrow, throat and conjunctival swabs and urinary sediments.

Clinical and laboratory investigations. When appropriate, the epidemiological team should include one or more medically trained professionals who will provide consultation and advise those providing clinical services in the affected area on the following subjects: (1) the clinical features, possible complications, sequelae, intensive care, and management and treatment of patients; (2) isolation of patients and quarantine procedures; (3) disinfection of articles contaminated by secretions and excretions, disposal of urine and faeces; (4) ambulance services or other means of transport of patients to minimize travel stress to patients and contact with others; (5) the kind of laboratory specimens required for specific diagnosis and clinical management, their method of collection, handling, storage and transport; (6) precautions to be taken regarding autopsies and handling of corpses. The specific needs in each of these areas must be defined in the context of the

outbreak and the local resources available, and a systematic approach with assignment and, if necessary, training of local personnel, nurses, health inspectors, sanitarians, etc.

Collection of laboratory specimens for specific etiological diagnosis. The epidemiologist or his designee should take responsibility for the proper collection and handling of specimens to assure that they reach the microbiological laboratory in good condition, with proper documentation, and with the minimal risk of accidental exposure of persons to the contaminated materials. All specimens should be collected in sterile containers and must be carefully labelled with appropriate identifying data. If only a few samples are obtained, each specimen may be labelled with the patient's name, age, sex and date of collection; if many samples are obtained, a numbering system is employed. A separate document is prepared (in duplicate, using carbon paper) with the assigned number and the following minimal information: name, age, sex, address, name of hospital, date of collection, date of onset of illness and history of vaccination (if appropriate). Labels should be waterproof and an indelible pen or soft pencil employed.

Blood should be collected with or without anticoagulant under aseptic conditions, preferably with the use of a vacuum tube (vacutainer) or disposable syringe and needle. For viral isolation, 10 ml of blood is obtained and the serum is separated promptly and under aseptic conditions. The clot may also be retained for isolation attempts or culture. For bacterial cultures, 5-10 ml whole blood is placed in appropriate culture medium.

Necropsy samples. Tissues are preserved both for isolation or culture and in fixative (formalin, gluteraldehyde) for histopathologic study.

All specimens for isolation attempts or culture must be processed immediately or maintained at low temperature until returned to the laboratory. Storage or transport at 4°C (wet ice, cold dogs, mechanical refrigerator) is acceptable for only a few (2-3) hours, after which freezing at ultralow temperatures (dry ice, liquid nitrogen) is required. A few viruses (e.g. cytomegalovirus) do not withstand freezing and specimens suspected to contain these agents should be held at 4°C.

Serological specimens. Confirmatory serological diagnosis depends upon the collection of appropriately-timed serum samples. Serum should be obtained as early during the acute phase of illness as possible and then at least 10-14 days later. In the case of the non-vector-borne haemorrhagic fevers, in which antibody titres may rise late, a third sample is collected 3-4 weeks after onset. Similarly, in many infections a late convalescent sample (4-8 weeks or longer after onset) may be useful in demonstrating a fall in titre when the first sample was obtained in the early convalescent rather than the acute phase.

Ten ml of blood is collected aseptically without anticoagulant. The clot is allowed to retract at ambient temperature and the serum separated, stored in a sterile screw-cap container, and labelled as previously described. Sterile sera may be stored or transported at ambient temperature for several days if necessary, but it is always preferable to maintain them at 4°C or frozen (in a mechanical freezer, on dry ice, or in liquid nitrogen).

Safety. All specimens must be considered potentially infective and dangerous. Persons given the task of collecting specimens or processing them in the field laboratory or in clinical laboratories should be instructed and supervised in good technique to minimize the risk of exposure. Depending on the situation, protective clothing (gloves, gowns, masks, etc.) may be required at each step at which specimens are handled. Measures to minimize aerosols, proper disposal or disinfection of contaminated materials or equipment, and careful technique (avoidance of spills or sharp instruments wherever possible, no smoking or eating in areas where specimens are handled, no mouth pipetting, etc.) are essential. When particularly dangerous agents are involved (e.g. Marburg, Ebola, Lassa), the persons handling specimens in the field and laboratory should be volunteers and should be carefully trained.

Contaminated needles, syringes, instruments, etc. should be disposed of properly.

In the case of highly dangerous viruses, needles, syringes, etc. should be placed in a leakproof container with 0.5% Na hypochlorite (1.5 dilution of household bleach). The

outside surfaces of tubes containing specimens are rinsed with disinfectant and placed in double plastic bags for transport to the laboratory for processing and storage.

Centrifugation and separation of blood samples present special hazards. Centrifuges with tightly closed heads and lids, should be used if available. After centrifugation, tubes should be opened carefully and the serum removed with a pipette fitted with a rubber bulb. In the case of highly dangerous viruses, samples are centrifuged in the double plastic bag. Separation of sera and other manipulations involving open vessels should be done in a plastic isolator or by personnel wearing protective clothing and masks. Plastic tubes and vials are preferred to glass in order to minimize the risk of breakage.

Safety precautions in the clinical laboratory present special problems. Again, training and supervision of staff is important. Protective clothing, use of isolator or safety cabinet if available, may be required in special circumstances. Disinfection of instruments (flow-through analysers, etc.) can be accomplished with 0.5% Na hypochlorite. Proper disposal or autoclaving of contaminated glassware and other materials is required.

Transport. A difficult logistical problem is the expeditious and safe transport of specimens from the field to the diagnostic laboratory, especially when the outbreak occurs in a remote area, and the establishment of a reliable method will be an early task of the epidemiological team. It is generally preferable to hand carry and deliver specimens which are critical to the investigation or which contain especially dangerous agents, rather than to rely on an intermediate, uncontrolled carrier (e.g. the mails, public transport services, etc.).

The proper packaging and refrigeration of specimens for transport is extremely important to avoid loss and potential exposure of persons en route. Specific guidance may be found in the booklet "Collection and Transport of Virological Specimens", WHO, Geneva, 1977.

If this epidemic was found to be preceded or accompanied with sickness or death of wild or domestic animals, rodents or birds, a veterinary doctor is asked to collect samples of blood, throat swabs and stools from the sick animals, and autopsy material from freshly dead animals including blood, hair, spleen, brain, heart and lungs and bones. The precautions in the collection, labelling, handling and sending of these materials to the laboratory are exactly as before.

vii. Control methods

A distinction must be established between primary and secondary contacts. A primary contact is a person who has nursed or buried a confirmed or probable case, has spent a night under the same roof, had a meal at the same table or had face-to-face contact some time during a period beginning two days before the onset of the disease with a proven or probable case. A secondary contact is a person who, some time during the same period, spent one night under the same roof, shared a meal or had face-to-face contact with a primary contact.

Strict barrier nursing should be used for the treatment of confirmed and probable cases. Primary contacts should be isolated and their temperature taken twice daily. Secondary contacts are not confined. They are either informed to contact certain medical centres in case fever develops, or alternatively medical centres are given the identity of the secondary contacts. A contact becomes a probable case when fever lasts for 48 hours and no malaria parasites are found in the peripheral blood or if there is no response to antimalarial therapy.

Active surveillance is a prerequisite for rational measures to be taken at four levels:

- Area quarantine should be enforced for a duration of two estimated incubation periods (twice 14 days) after the last case. In view of the economic consequences, this measure should be regularly adapted to the situation. This measure is never absolutely effective but cuts down significantly long distance travel.
- Village quarantine should be combined with health education aiming at limitation of contact with patients. Bringing patients to the hospital is not necessarily the best

measure and depending on local circumstances household confinement may be preferable. If hospital isolation is decided it should be very strict because it attracts inevitably a great number of visitors.

- Household confinement consists of isolation of a patient in one house or room and only one person cares for the patient. Protective clothing are offered to the person looking after the patient.
- In all eventualities precise instructions for burial have to be given.
- International quarantine is only applied if cases occur in cities with international transport facilities and if primary contacts are not identified and quarantined.
- Individual quarantine should last for a period of 14 days, to take into account the fact that the incubation period may in certain cases exceed the average length of 7 days.

Members of medical teams will be considered according to their functions as possible primary or secondary contacts and should be quarantined accordingly. A decision on whether to treat a patient in a local centre and to send a specialized team there, or to evacuate the patient to a specially equipped centre, should be taken according to local circumstances.

Safety measures. It is important to limit as far as possible the number of persons at risk during an outbreak. These persons should be vaccinated against yellow fever, given malaria prophylactic treatment and should receive gamma globulin to prevent viral hepatitis. Personnel should be protected from infection through skin abrasions, conjunctivae or mouth and should wear: gloves, gowns, caps, boots or overshoes and masks. Goggles and respirators to cover eyes and mouth are necessary to examine patients. Full face respirators are necessary only for laboratory work and autopsies. Disinfectants, such as sodium hypochlorite or formalin, must be used for decontamination. A pressure cooker can be used as a portable autoclave for sterilization.

viii. Motivation to stimulate surveillance, including feedback bulletins, publicity rewards, etc.

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ix. Conduct of special surveys

The investigations carried out in Sudan and Zaire during the Ebola virus outbreak and the investigations carried out in Kenya following the Marburg incident in Nairobi will be discussed at the meeting.

x. Latest research developments

The latest research developments with Marburg and Ebola viruses will also be described at the meeting, particularly in methods of isolation and rapid diagnosis.