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8.1 Management of Cases

In the absence of specific therapy, the treatment of human cases of yellow fever must be chiefly supportive.

A serious drawback in the treatment of yellow fever is the lack of prompt recognition of the disease. A presumptive clinical diagnosis can be missed even in the presence of classical manifestations of the disease. This is particularly true when cases occur sporadically or at the beginning of outbreaks. Milder cases of yellow fever (especially when they occur in the absence of more severe cases) are almost never clinically diagnosed except where laboratory back-up is present and when an active yellow fever epidemiological team is in the region. Adequate medical care is often not readily available and patients are taken to a hospital in the late stages of disease, when treatment may not be helpful. Moreover, most local hospitals are not well equipped with the intensive care facilities that may be necessary for yellow fever patients. Since patients are rarely admitted to teaching hospitals, many medical students and physicians do not become acquainted with the disease. Consequently, clinical diagnosis is often delayed, even in the presence of typical illness. Confusion with viral hepatitis, malaria, leptospirosis, and noninfectious diseases that may lead to haemorrhagic manifestations is common, at least when the patients are initially examined. Often, a simple test for the detection of albuminuria is not performed; nor is an appropriate clinical history taken, and the epidemiological facts are not considered. During an epidemic, this situation may be quickly reversed, as awareness of the disease increases. Even in these circumstances, the disease may be misdiagnosed, as in the 1972–73 yellow fever outbreak in Brazil where it was found that 7 of 29 patients hospitalized for viral hepatitis were actually suffering from yellow fever (34).

Vigorous therapeutic measures are required for the treatment of yellow fever, particularly during the period of intoxication when obvious clinical manifestations appear. Although several organs can be compromised, it is usually the liver and kidneys that are most severely damaged.

As the disease may occur in remote areas, treatment has often to be provided under less than ideal conditions. In view of this, medical care has to be considered at two levels: peripheral and hospital health care.
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8.1.1 Peripheral health care

Suspected cases of yellow fever should be protected from the bites of mosquitoes under a bed net or in a securely screened room. Medical care at peripheral level can be provided only for the clinical manifestations of the first phase of the disease (fever, aches, nausea, vomiting, discomfort, restlessness, dehydration). Treatment of these manifestations as shown in Table 6 is recommended.

It is essential that bed rest should be strictly observed. This will lessen the patient’s metabolic requirements and reduce the strain on the liver, kidneys, and heart (35).

When a health worker suspects that a person is suffering from yellow fever, he should report the fact immediately to the nearest health centre or hospital. Should a decision be made to transport the patient to a hospital, where more specialized care can be provided, he or she should be removed with extreme care, to avoid aggravating the condition, and should remain protected from mosquito bites.

8.1.2 Hospital health care

Better medical care can be provided for yellow fever patients in hospital. The availability of specialized facilities, especially intensive care units, is particularly useful for the management of the severe manifestations present in the intoxication stage of the disease (see also Table 6).

It is possible that some patients may be hospitalized during the first stage of the illness. In this case, all the therapeutic measures indicated in the previous section apply to hospital medical care. More potent drugs, however, can be administered to control vomiting and agitation.

The classical manifestations present during the stage of intoxication are usually associated with hepatic and renal dysfunction, but other organs may also be involved. Bleeding, electrolyte disturbances, acidosis, oliguria, and shock are some of the severe manifestations present at this stage, usually developing during its terminal phase, around the fifth to seventh day of illness. Monitoring should therefore be intensified before this period or as soon as signs of clinical deterioration are detected, and appropriate therapy should be instituted without delay.

8.1.3 Patient monitoring

The temperature, blood pressure, arterial pulse, and the quantity of fluid lost in urine and vomitus should be carefully monitored. The erythrocyte volume fraction, blood urea, creatinine, sodium, and potassium serum levels should be determined daily or more frequently, as required, together with sodium, potassium, and
<table>
<thead>
<tr>
<th>Stage of illness</th>
<th>Manifestation</th>
<th>Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Fever, headache</td>
<td>Paracetamol; sponging with cool water (avoid aspirin because of the bleeding diathesis)</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Vomiting, abdominal pain, hiccups</td>
<td>Metoclopramide (by rectal suppository, if available); give chips of ice to suck</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>Oral fluids: salt solution for diarrhoeal diseases or sugared water or citrus fruit juice, 5-10% glucose in saline or Ringer's solution (given i.v.)</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>Diazepam</td>
<td>Same</td>
</tr>
<tr>
<td>Intoxication</td>
<td>Same manifestations as for infection stage</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>—</td>
<td>Blood transfusion (estimate blood loss, determine erythrocyte volume fraction, haemoglobin, and arterial pressure); plasma volume substitutes</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td>7.5% NaHCO₃ (determine arterial blood pH, total CO₂, and pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Maintain renal blood flow; peritoneal dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>Tranquilizers: diazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>i.v. fluids—blood or plasma; plasma volume substitutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td><strong>Associated infections:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial infections&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Broad-spectrum antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Synthetic antimalarials</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> During the stage of remission that appears between infection and intoxication, treatment should be in accordance with the above guidance, depending on the symptoms manifest.

<sup>b</sup> Complete bed rest must be strictly observed during all three stages of illness.

<sup>c</sup> The transfer of patients to a hospital should be effected with great care, preferably by ambulance or helicopter.

<sup>c</sup> If present, usually observed during the stage of intoxication.
creatinine concentrations in the urine. Liver function may be
monitored by determining the levels of serum aminotransferase. Red
and white blood cells and platelet counts, prothrombin time
determinations, tests for fibrin breakdown products, and urine
analyses should be performed. Arterial blood gas determinations
($pCO_2$, total $CO_2$ and $pH$) are helpful in monitoring acid–base status.
status.

(1) *Nausea, vomiting and abdominal pain*. Metoclopramide is the
antiemetic of choice; in patients with severe vomiting, the rectal route
of administration may be required. Phenothiazine compounds, which
have a hypotensive effect, should be avoided for the control of
hiccups, delirium, nausea, and severe vomiting in patients with signs
of haemodynamic instability.

(2) *Bleeding*. Protection of the gastric mucosa may help to prevent
haemorrhage; nasogastric suction or use of antacids and cimetidine to
reduce the gastric HCl secretion is recommended. Blood transfusions
may be required, especially when extensive bleeding occurs. An
estimation of the blood loss by vomiting and intestinal haemorrhage
must be made, together with determinations of the erythrocyte
volume fraction, haemoglobin, and blood pressure in order to assess
the amount of blood to be replaced. Preferably, fresh blood should be
administered. Plasma substitutes can be used when blood is not
readily available (36).

(a) *Vitamin K*. It has been claimed that the administration of
massive doses of vitamin K is of great benefit to patients with low
prothrombin levels (37). It is unlikely, however, that vitamin K
would be of value, because liver cells are extensively damaged in
severe yellow fever and would therefore be unable to metabolize the
vitamin.

(b) *Heparin*. The pathogenesis of bleeding manifestations is still
controversial. In the old literature, for instance, laboratory-based
observations were conflicting, some suggesting that the blood
coagulation was normal (38, 39), whereas others gave the
impression that blood coagulation was altered (40). The investiga-
tors who found normal blood coagulation believed that the
bleeding manifestations were associated with vasodilatation and
fatty degeneration of the capillary walls. Subsequently, thrombo-
cytopenia and prolonged prothrombin time were demonstrated in
yellow fever cases (37). Further studies have shown that multiple
abnormalities of the coagulation system are present in rhesus
monkeys (41) and also in patients (42, 43), and that such
abnormalities may be due to accelerated intravascular coagulation.
These findings suggested the possibility that heparin treatment
would be beneficial.

Heparinization seemed to decrease the severity of coagulation
abnormalities caused by yellow fever, but did not prolong the life-
span of infected persons or monkeys. Indeed, 5 out of 6 patients who were given 5000 units of heparin intravenously every 6 hours died (43). All 5 fatal cases, however, were heparinized when bleeding was already established, and they died within 2–3 days after the treatment was initiated or sooner. The single survivor received heparin on the fifth day of the illness, but the only evidence of haemorrhage present in this case was “dark” stools. If there is clear evidence on the basis of laboratory tests for disseminated intravascular coagulopathy, then cautious consideration should be given to the use of heparin treatment.

(3) Electrolyte disturbances and acidosis. Electrolyte disturbances and acidosis are usually present in severe cases and appropriate treatment should be given. Determinations in monkeys revealed acidaemia, an increase of potassium, and a decrease of sodium serum levels at the terminal stage of the disease (44). Data available for man are scanty. Studies carried out during the epidemic of yellow fever in Rio de Janeiro, Brazil, in the late 1920s showed that patients develop hyperkalaemia (38).

(4) Renal failure. Oliguria or anuria is an ominous manifestation of the disease. The cause of acute renal failure in yellow fever is not well understood. It has been demonstrated at autopsy that acute tubular necrosis is a major pathological feature in the kidneys of monkeys and man and is possibly therefore the cause of acute renal failure. However, recent studies in monkeys (44) suggest that acute renal failure is first associated with physiological changes resembling prerenal azotaemia and that this disease, which reduces effective renal blood flow, later progresses to acute tubular necrosis. This view is supported by the dramatic decrease in the excretion of urinary sodium and the absence of pathological changes in the kidney until hours before death.

As the following tabulation demonstrates, urine and plasma electrolyte and creatinine determination usually allows the differentiation of prerenal azotaemia from acute tubular necrosis.¹

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>U/P⁰ creatinine</th>
<th>UNaⁱ</th>
<th>FENa²</th>
<th>Osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>40</td>
<td>20</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Renal (acute tubular necrosis)</td>
<td>20</td>
<td>40</td>
<td>1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

⁰ U/P = urine to plasma ratio
¹ UNa = urine sodium concentration (mmol/litre)
² FENa = fractional excretion of sodium = (U/P Na – U/P Cr) × 100.

¹ A. Prata, University of Brasilia; J. C. Almeida Netto, University of Goias; personal communication, 1983.
The therapy of prerenal azotaemia involves the correction of fluid volume contraction. This must be done extremely carefully to avoid volume overload and preferably in an intensive care unit. Unpublished observations suggest that peritoneal dialysis may be of some benefit in acute renal failure associated with yellow fever. Therefore, it seems valid to explore the usefulness of this therapeutic procedure in the future, especially if clinical laboratory findings indicate acute tubular necrosis. Specific indications for dialysis include volume overload, hyperkalaemia, severe acidosis, neurological abnormalities, severe hyponatraemia, and hypercatabolism.

(5) Delirium. Delirium may appear in the final stages of the disease and require tranquillizing therapy: diazepam may be administered orally or parenterally for this purpose. In cases without pulmonary complications, paraldehyde may be used; it may be given by oil-retention enema at a dose of 0.2 mg of paraldehyde per kg of body weight.

(6) Shock. Treatment of shock should commence as soon as signs or symptoms of this condition (restlessness, lethargy, cold extremities, circumoral cyanosis, rapid and feeble pulse, narrowing of pulse pressure, hypotension) occur. Treatment involves the vigorous intravenous administration of fluids, which may include blood, plasma, or plasma substitutes. Close monitoring of blood pressure and erythrocyte volume fraction should be observed. Special attention should be given to avoiding the risk of over-hydration, which may lead to pulmonary oedema and heart failure.

(7) Bacterial infections. Secondary bacterial infections (including pneumonia) may occur in yellow fever. Appropriate cultures should be obtained, but since it is unlikely that the specific infectious organism will be identified in time, broad spectrum antibiotic therapy may be started as soon as an intercurrent bacterial infection is suspected. Careful physical examination, chest X-ray, and blood leukocyte counts are useful indicators of bacterial infection. Antibiotic dosage may need to be adjusted if renal failure is associated with the disease.

(8) Malaria infection. Malaria may also be associated with yellow fever, and indeed malaria can simulate some characteristics of the disease (35). If parasitaemia is present, appropriate antimalarial drugs should be administered (63).

8.1.4 Research needs

Unfortunately, knowledge of the pathophysiological processes involved in yellow fever is still scanty and incomplete. Undoubtedly, the lack of such knowledge has hindered improvements in therapy. Therefore, a high priority should be placed on studies to improve the
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definition of pathophysiological parameters of the disease and ultimately to develop guidelines for treatment. It is particularly important to have a better understanding of the events associated with extensive liver injury. The necrosis of cells of the reticuloendothelial system, particularly B-cell areas of spleen and lymph nodes, requires further study. Questions that need answering include: are these changes secondary to shock and corticosteroid excess, or are they more directly related to yellow fever pathogenesis; and does yellow fever infection interfere with the host's immune response? As there is no definitive evidence yet that disseminated intravascular coagulation occurs in yellow fever, this aspect deserves further examination. Although it has been claimed in the past that shock might be due to capillary vascular damage and subsequent plasma leakage, there is no firm evidence supporting this hypothesis, and investigations are needed to clarify this point. The possibility that renal failure may be due to prerenal azotaemia and to a functional decrease in glomerular filtration rate, which has been postulated as an explanation of the hepatorenal syndrome, needs to be examined. Furthermore, the electrolyte disturbances and the possible role of endotoxaemia must be explored. Obviously such studies should include attempts to develop appropriate therapeutic measures. Careful planning with such aims in view should be made in advance by a team of experts. It will also be necessary to assemble material that can be rapidly transferred to the field, including equipment to carry out the tests to monitor patients, such as blood gas determinations, electrolytes, determinations of urine and blood chemistry, specialized haematological tests, arterial and venous pressure, and other physiological parameters.

8.2 Vector Control

Vector control may be considered under two broad headings: preventive measures and emergency measures.

8.2.1 Preventive measures

Preventive measures are only practical in human habitats, i.e., in towns and villages, and are mainly directed against A. aegypti. The principal measures involved are:

1) Source reduction. Water-containers that are in daily use require frequent emptying and scouring to remove eggs; they should be kept covered or screened to prevent access by mosquitoes. In this connection, the provision of wells, or piped water where possible, would reduce the need for water storage. Containers, mainly tyres, tins, and jars, should be destroyed or buried. Source reduction should be promoted through community participation at all levels, including political and administrative support, teaching in schools, posters,
frequent use of the media. Public sanitation services also have a role to play in the removal of larger artificial breeding places such as derelict vehicles. If source reduction is carried out effectively, the density of *A. aegypti* may be kept to a level that precludes interhuman epidemics.

(2) Use of insecticides. When the cooperation of the community is difficult to obtain to achieve source reduction, it is frequently necessary to use insecticides for vector control. The use of temephos at a dilution of 1 mg per litre is safe for man when added to containers of drinking-water. Various insecticides may be used for breeding sites with *non-potable water* (see Table 7). Organochlorine compounds are not suitable for use because of widespread resistance of *A. aegypti* to these compounds (see Table 8). The use of adulticides is generally reserved for emergency situations. There is a WHO publication dealing with equipment for vector control (45).

Table 7. Insecticides suitable as larvicides in mosquito control 
(not for use in drinking-water)

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Chemical type*</th>
<th>Dosage of a.i. b (g/ha)</th>
<th>Formulationc</th>
<th>Duration of effective action (weeks)</th>
<th>Toxicityd (oral LD50 of a.i.e for rats; mg/kg of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpyrifos</td>
<td>OP</td>
<td>11-25</td>
<td>EC,GR,WP</td>
<td>3-17</td>
<td>135</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>PY</td>
<td>2.5-10f</td>
<td>EC</td>
<td>1-3</td>
<td>&gt;2,940f</td>
</tr>
<tr>
<td>Diflubenzuron</td>
<td>IGR</td>
<td>25-100</td>
<td>GR,WP</td>
<td>1-4</td>
<td>4,640</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>OP</td>
<td>100-1,000</td>
<td>EC,GR</td>
<td>1-3</td>
<td>503</td>
</tr>
<tr>
<td>Fenthion</td>
<td>OP</td>
<td>22-112</td>
<td>EC,GR</td>
<td>2-11</td>
<td>330f</td>
</tr>
<tr>
<td>Fuel oil</td>
<td>—</td>
<td>—</td>
<td>solution</td>
<td>1-2</td>
<td>negligible</td>
</tr>
<tr>
<td>Iloprofos</td>
<td>OP</td>
<td>1-100</td>
<td>EC,GR</td>
<td>7-16</td>
<td>2,100</td>
</tr>
<tr>
<td>Malathion</td>
<td>OP</td>
<td>224-1,000</td>
<td>EC,GR</td>
<td>1,2</td>
<td>2,100</td>
</tr>
<tr>
<td>Methoprene</td>
<td>IGR</td>
<td>100-1,000</td>
<td>SRS</td>
<td>4-8</td>
<td>34,600</td>
</tr>
<tr>
<td>Paris green</td>
<td>CA</td>
<td>840-1,000</td>
<td>dust,solution</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Permethrin</td>
<td>PY</td>
<td>5-10f</td>
<td>EC</td>
<td>5-10</td>
<td>&gt;4,000f</td>
</tr>
<tr>
<td>Phoxin</td>
<td>OP</td>
<td>100</td>
<td>EC</td>
<td>1-16</td>
<td>1,000</td>
</tr>
<tr>
<td>Pirimiphos-</td>
<td>methyl</td>
<td>OP</td>
<td>50-500</td>
<td>1-11</td>
<td>2,018</td>
</tr>
<tr>
<td>Temephos</td>
<td>OP</td>
<td>50-112</td>
<td>EC,GR</td>
<td>2-4</td>
<td>8,600</td>
</tr>
</tbody>
</table>

* OP = organophosphorus compound; PY = synthetic pyrethroid; IGR = insect growth regulator; and CA = copper-arsenic complex.

b a.i. = active ingredient.
c EC = emulsifiable concentrate; GR = granules; WP = Water-dispersible powder; SRS = slow-release suspension.

d Toxicity and hazard are not necessarily equivalent.
e Dermal toxicity.
f The lowest levels are recommended for fish-bearing waters.

Because of their low dermal toxicity, and on the basis of experience with their use, these products have been classified in the WHO Hazard Classification in Class III, Table 5 (products unlikely to present acute hazards in normal use).

h Apply at 142-190 l/ha, or 19-47 l/ha if a spreading agent is added.
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Table 8. WHO computer records of insecticide resistance in *Aedes aegypti* in Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>Area and locality</th>
<th>Year</th>
<th>Insecticide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Larvae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benin</td>
<td>Cotonou, Alepaka</td>
<td>1968</td>
<td>DDT</td>
</tr>
<tr>
<td>Benin</td>
<td>Cotonou, Alepaka</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Benin</td>
<td>Cotonou, Alepaka</td>
<td>1968</td>
<td>HCH</td>
</tr>
<tr>
<td>Benin</td>
<td>Godome</td>
<td>1968</td>
<td>DDT</td>
</tr>
<tr>
<td>Benin</td>
<td>Godome</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Benin</td>
<td>Godome</td>
<td>1968</td>
<td>HCH</td>
</tr>
<tr>
<td>Benin</td>
<td>Dahé-Bopa</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Benin</td>
<td>Dahé-Bopa</td>
<td>1968</td>
<td>HCH</td>
</tr>
<tr>
<td>Benin</td>
<td>Godomey</td>
<td>1968</td>
<td>DDT</td>
</tr>
<tr>
<td>Benin</td>
<td>Godomey</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Bobo-Dioulasso</td>
<td>1965</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Douala</td>
<td>1972</td>
<td>HCH</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Kumba</td>
<td>1965</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Kumba</td>
<td>1965</td>
<td>HCH</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Wouri-Douala</td>
<td>1965</td>
<td>HCH</td>
</tr>
<tr>
<td><strong>Central African Republic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo</td>
<td>Bangui</td>
<td>1971</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Congo</td>
<td>Brazzaville, Ouenze</td>
<td>1966</td>
<td>dizinon</td>
</tr>
<tr>
<td>Congo</td>
<td>Brazzaville, Ouenze</td>
<td>1966</td>
<td>HCH</td>
</tr>
<tr>
<td>Congo</td>
<td>Brazzaville,</td>
<td>1971</td>
<td>HCH</td>
</tr>
<tr>
<td>Congo</td>
<td>Ravin de la Glacière</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo</td>
<td>Pointe Noire</td>
<td>1971</td>
<td>HCH</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>Bouaké</td>
<td>1967</td>
<td>HCH</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>Bouna</td>
<td>1968</td>
<td>DDT</td>
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<td>HCH</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>Tiassalé</td>
<td>1965</td>
<td>dieldrin</td>
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<td>1965</td>
<td>HCH</td>
</tr>
<tr>
<td>Ghana</td>
<td>Navrongo, Kassena</td>
<td>1971</td>
<td>HCH</td>
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<td>Upper Region, Lawra</td>
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</tr>
<tr>
<td>Liberia</td>
<td>Monrovia</td>
<td>1968</td>
<td>DDT</td>
</tr>
<tr>
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<td>Salaya</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Liberia</td>
<td>Salayea</td>
<td>1968</td>
<td>HCH</td>
</tr>
<tr>
<td>Madagascar</td>
<td>Maevatanana</td>
<td>1974</td>
<td>HCH</td>
</tr>
<tr>
<td>Mali</td>
<td>Sibla</td>
<td>1967</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Mali</td>
<td>Sibla</td>
<td>1967</td>
<td>malathion</td>
</tr>
<tr>
<td>Senegal</td>
<td>Dakar</td>
<td>1966</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Senegal</td>
<td>Dakar</td>
<td>1966</td>
<td>HCH</td>
</tr>
<tr>
<td>Senegal</td>
<td>Diourbel, N’goye</td>
<td>1966</td>
<td>HCH</td>
</tr>
<tr>
<td>Senegal</td>
<td>Sombel, Gouille</td>
<td>1976</td>
<td>DDT</td>
</tr>
<tr>
<td>Senegal</td>
<td>Sombel, Gouille</td>
<td>1976</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Senegal</td>
<td>Kebermer, N’diompi</td>
<td>1973</td>
<td>dieldrin</td>
</tr>
<tr>
<td>Togo</td>
<td>Agouvé</td>
<td>1969</td>
<td>HCH</td>
</tr>
<tr>
<td>Togo</td>
<td>Gboto</td>
<td>1968</td>
<td>dieldrin</td>
</tr>
</tbody>
</table>
8.2.2 Emergency measures

By far the most important measure in the emergency control of vectors of epidemic yellow fever is to effect a rapid reduction in the man-biting section of the mosquito vector population so that transmission is brought to an end or drastically reduced as promptly as possible. This can be achieved by the use of appropriate chemical insecticides, i.e., those to which the vectors are susceptible; these are mainly applied as space-sprays against the adult vectors and are frequently supported by larvicides and sometimes also by residual treatments.

(1) Adult vector control. Suitable insecticides for use in space-sprays are listed in Table 9. Use of organochlorine insecticides is inappropriate in many areas owing to the widespread resistance of *A. aegypti* to these compounds. The insecticides commonly used are malathion and fenitrothion.

Three types of equipment—thermal foggers, mist blowers, and aerosol applicators—are used for the application of space-sprays.\(^1\) Brief descriptions of these three types are given below.

(a) Thermal foggers (portable or vehicle-mounted). These deliver a powerful blast of visible fog.

---
\(^1\) Names of suppliers of the various types of equipment are available on request, from the Division of Vector Biology and Control, World Health Organization, 1211 Geneva 27, Switzerland.
Table 9. Insecticides suitable as cold aerosol sprays and for thermal fogs for mosquito control

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Chemical type</th>
<th>Dosage of a.i. (g/ha)</th>
<th>Toxicity(^c) (oral LD(_{50}) of a.i.(^b) for rats; mg/kg of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cold sprays</td>
<td>Thermal fogs(^d)</td>
</tr>
<tr>
<td>Bioremethrin</td>
<td>PY</td>
<td>5–10</td>
<td>20–30</td>
</tr>
<tr>
<td>Chlordane</td>
<td>OP</td>
<td>10–40</td>
<td>150–200</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>PY</td>
<td>0.5–1.0</td>
<td>—</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>OP</td>
<td>56–280</td>
<td>200–300</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>OP</td>
<td>250–300</td>
<td>270–300</td>
</tr>
<tr>
<td>Fenthion</td>
<td>OP</td>
<td>112</td>
<td>—</td>
</tr>
<tr>
<td>Ildofenphos</td>
<td>OP</td>
<td>100–200</td>
<td>—</td>
</tr>
<tr>
<td>Malathion</td>
<td>OP</td>
<td>112–683</td>
<td>500–600</td>
</tr>
<tr>
<td>Naled</td>
<td>OP</td>
<td>56–280</td>
<td>—</td>
</tr>
<tr>
<td>Permethrin(^g)</td>
<td>PY</td>
<td>5–10</td>
<td>—</td>
</tr>
<tr>
<td>Propoxur</td>
<td>C</td>
<td>53–76</td>
<td>—</td>
</tr>
<tr>
<td>Resmethrin</td>
<td>PY</td>
<td>7–16</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^{a}\) PY = Synthetic pyrethroid; OP = organophosphorus compound; and C = carbamate.

\(^{b}\) a.i. = active ingredient.

\(^{c}\) Toxicity and hazard are not necessarily equivalent.

\(^{d}\) The strength of the finished formulation applied depends on the performance of the spraying equipment used.

\(^{f}\) Because of their low dermal toxicity, and on the basis of experience with their use, these products have been classified in the WHO Hazard Classification in Class III, Table 5 (products unlikely to present acute hazards in normal use).

\(^{k}\) Dermal toxicity.

\(^{g}\) Also used in mixtures with knock-down agents or synergists.

(b) Mist blowers (portable or vehicle-mounted). These deliver relatively large droplets in the form of a cold mist and are suitable for treating houses and large areas; they can be used for adult vector control and for larvicidal applications.

(c) Aerosol (ultra-low-volume; ULV) applicators (portable or vehicle- or aircraft-mounted). These deliver very fine droplets of the ULV-insecticide formulation, which remain suspended in the air to kill flying insects. They are suitable for treating around and inside houses. As low volumes of insecticide are used, they are relatively cost-effective for treating large areas from the air. Equipment must be carefully calibrated, so that droplet size is controlled; droplet size should be monitored by the exposure of Teflon-coated or silicone-coated slides and examination under the microscope.

Aerial application is often the method of choice in emergencies where an extensive area needs to be treated in a short time. The aircraft should be fitted with rotary atomizers or other suitable spray nozzles previously calibrated to give the correct dosage. Although the aircraft spraying system may involve a high initial cost, aerial
spraying may be economic overall because of the very large areas that can be treated quickly. In addition, since emergencies tend to occur during the rainy season when secondary roads and tracks may be impassable, aerial spraying is often the only practicable control measure in rural areas. Small fixed-wing aircraft are generally used and are flown at 160 km/h, at a height of 30 m above the ground and swath spacing of 50–100 m. In emergencies any agricultural spraying aircraft, including helicopters, can be used. If vector control is integrated with an immunization programme, a single application may be sufficient. However, continuous entomological and epidemiological monitoring is needed to determine the application schedule. ULV applications should be carried out by highly skilled pilots trained to undertake this type of spraying at the correct speeds and heights.

Aerial spraying can be carried out in urban and rural areas against domestic vectors and may also be used against wild vectors in uninhabited areas. Care should be taken to minimize any adverse ecological effects of spraying.

Vehicle-mounted fogging or cold aerosol apparatus is very practical for urban or suburban areas with a good road system, because of its sturdiness, reliability, and ability to cover large areas; one machine can cover up to 1500–2000 houses per day. It is necessary to calibrate the equipment, vehicle speed, and the swath to determine the coverage obtained by a single pass. A good map of the area showing all the roads and houses is of great help in carrying out operations. Considerable health education work may be required to persuade the inhabitants to cooperate by having their windows and doors open and not obstructing the vehicles carrying out the treatments.

For vehicle-mounted equipment, the spray vehicle is driven across wind so that the fog or mist moves at right angles to the line of travel and the speed of the vehicle is normally 5–15 km/h. The spray machine normally gives a swath width of 60–90 m. For A. aegypti control, fog and ULV applications should be conducted in the daytime and when air velocities are below 10 km/h.

When the area to be treated is not very large, or in areas where vehicle-mounted equipment cannot operate, portable back-pack equipment can be used to apply insecticidal mists. One operator can treat up to 100–150 premises per day. The weight of the machine and the vibration caused by the engine make it necessary to allow the operators to rest and therefore 2–3 operators are needed per machine. For speedy and extensive coverage, an area treatment (rather than a house or room treatment) is essential. This method is particularly useful for interior treatments of houses when A. aegypti is highly endophilic. Treatment of vehicles may also be important; small aerosol spray cans are most useful for this purpose.

The following estimates have been made of the minimum coverage per day with certain aerosol and thermal fog equipment.
8. CONTROL AND PREVENTION

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Possible daily coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin-engined aircraft, e.g., C-47 or large helicopter, ULV spraying</td>
<td>6000 ha</td>
</tr>
<tr>
<td>Light fixed-wing aircraft or small helicopter, ULV spraying</td>
<td>2000 ha</td>
</tr>
<tr>
<td>Vehicle-mounted cold fogger, e.g., LECO</td>
<td>225 ha</td>
</tr>
<tr>
<td>Vehicle-mounted thermal fogger, e.g., Dyna-Fog</td>
<td>150 ha</td>
</tr>
<tr>
<td>Back-pack ULV mist blower, e.g., Fontan</td>
<td>30 ha</td>
</tr>
<tr>
<td>Hand-carried thermal fogger, e.g., Swing Fog</td>
<td>5 ha</td>
</tr>
<tr>
<td>Hand-carried indoor ULV aerosol generator, e.g., Mity Moc</td>
<td>5 ha or 250 houses</td>
</tr>
</tbody>
</table>

Residual spraying may also be of value in emergency yellow fever control operations in the African Region where there is a high level of domestic breeding of *A. aegypti*. Selective spraying, in which the residual spray is applied by hand compression sprayer, is applied to the inside and outside walls of containers and to any wall close to the container; up to 60 cm each side and above it may be appropriate. Potable water should be protected from contamination by the residual spray. Insecticides used in residual spraying are listed in Table 10.

(2) Larval control. Although the use of larvicides will not rapidly reduce transmission, since the adult vector population is not immediately affected, they can assist in maintaining the vector population at a level below which an epidemic will not occur or recur. Suitable larvicides and application techniques are the same as for preventive measures of vector control (section 8.2.1).

8.2.3 Vector control in international health

Preventive and emergency vector control measures should be carried out in international ports of entry such as seaports, airports, train stations, and bus and haulage terminals. Space-spraying and larviciding are appropriate methods of insect control, with space-spraying being extended to include the disinsection of international aircraft and shipping, including small craft.

8.3 Immunization

Two vaccines have been used in Africa for the control of yellow fever epidemics or for their prevention. One was developed in 1940 at the Pasteur Institute, Dakar, Senegal, and consisted of desiccated brain of mice inoculated with the French neurotropic strain of yellow fever virus. More than 80 million immunizations were successfully
Table 10. Insecticides suitable as residual spray applications against mosquito vectors

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Chemical type</th>
<th>Dosage of a.i. (g/m²)</th>
<th>Duration of effective action (months)</th>
<th>Insecticidal action</th>
<th>Toxicity² (oral LD₅₀ of a.i. for rats; mg/kg of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendiocarb</td>
<td>C</td>
<td>0.4</td>
<td>2-3</td>
<td>contact and airborne</td>
<td>55</td>
</tr>
<tr>
<td>Chlorphoxin</td>
<td>OP</td>
<td>2</td>
<td>1-3</td>
<td>contact</td>
<td>500⁶</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>PY</td>
<td>0.5</td>
<td>4 or more</td>
<td>contact</td>
<td>&gt;4000⁶</td>
</tr>
<tr>
<td>DDT</td>
<td>OC</td>
<td>1-2</td>
<td>6 or more</td>
<td>contact</td>
<td>113</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>PY</td>
<td>0.05</td>
<td>2-3</td>
<td>contact and airborne</td>
<td>&gt;2840⁶</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>OP</td>
<td>1-2</td>
<td>3 or more</td>
<td>contact and airborne</td>
<td>503</td>
</tr>
<tr>
<td>Lindane (gamma-HCH)</td>
<td>OC</td>
<td>0.2-0.5</td>
<td>3 or more</td>
<td>contact and airborne</td>
<td>100</td>
</tr>
<tr>
<td>Malathion</td>
<td>OP</td>
<td>1-2</td>
<td>2-3</td>
<td>contact and airborne</td>
<td>2100</td>
</tr>
<tr>
<td>Permethrin</td>
<td>PY</td>
<td>0.5</td>
<td>2-3</td>
<td>contact</td>
<td>&gt;4000⁶</td>
</tr>
<tr>
<td>Pirimiphos-methyl</td>
<td>OP</td>
<td>1-2</td>
<td>2-3 or more</td>
<td>contact and airborne</td>
<td>2018</td>
</tr>
<tr>
<td>Propoxur</td>
<td>C</td>
<td>1-2</td>
<td>2-3</td>
<td>contact and airborne</td>
<td>95</td>
</tr>
</tbody>
</table>

⁴ C = carbamate; OP = organophosphorus compound; PY = synthetic pyrethroid; and OC = organochlorine compound.
⁵ a.i. = active ingredient.
⁶ Toxicity and hazard are not necessarily equivalent.
⁷ Dermal toxicity.
⁸ Because of their low dermal toxicity, and on the basis of experience with their use, these products have been classified in the WHO Hazard Classification in Class III, Table 8 (products unlikely to present acute hazards in normal use).

performed by scarification and, during the period of its widespread use, yellow fever virtually disappeared from the French-speaking countries of Africa. However, the vaccine was found to cause encephalitis in a small but significant proportion of children below 12 years of age. The second vaccine, the 17D (Rockefeller) vaccine, is produced in chicken embryos. The risks of encephalitis associated with its use are minimal and it is now the only vaccine produced.

8.3.1 Production of the vaccine

The World Health Organization has published requirements for the production of yellow fever 17D vaccine that must be met if an international vaccination certificate is to be issued (46, 47). The main provisions are:
— the vaccine strain used and the production procedure must be approved by WHO;
records of production of each batch must be sent to WHO and be shown to comply with requirements for efficacy and safety.

The WHO requirements may be used by national control authorities before licensing the vaccine. Countries that do not have control authorities may request from WHO the records submitted by the manufacturers and they may need the assistance of WHO for the quality control of vaccine supplies.

High-quality 9-day-old chicken embryos are inoculated with the approved WHO seed lot and infected viable embryos are harvested not later than the twelfth day of age. After grinding, the embryo suspension is centrifuged and the supernatant is diluted as required to obtain the desired titre for immunization. The diluted suspension is lyophilized, sealed in ampoules, and stored at \(-20^\circ\mathrm{C}\).

According to the WHO requirements, the vaccine must be tested to ensure that there is no bacterial, viral, or mycotic contamination in the eggs or in the vaccine seed that could be pathogenic to man. However, the elimination of avian leukosis virus has not yet been made mandatory by WHO because it is difficult to obtain eggs free of this virus. Moreover, epidemiological studies of persons immunized in 1944 with contaminated vaccine have not shown any increased risk of malignancies (48).

The containers must be sealed under vacuum or filled with dry, high-grade nitrogen. The manufacturers must check that the sealing of containers is satisfactory and the national control authorities may require an assay for residual moisture. It is easy to see when these two conditions are deficient, since the lyophilized vaccine shell in the container becomes pink-red instead of grey-pink, is sticky instead of being porous and breakable, and is difficult to dissolve when the solvent is added.

A list of institutes manufacturing yellow fever vaccines approved by WHO is given in Annex 5.

At present the quantity of yellow fever vaccine available in the world is limited. The relatively short shelf-life of the vaccine does not permit the accumulation of large stocks. The demand for vaccine is somewhat irregular, being suddenly high during epidemics and low during inter-epidemic periods. The WHO Regional Office for Africa has a reserve of vaccine that is available without delay when a country faces an epidemic. A reserve of primary and secondary seed lots for the preparation of vaccine is also available should yellow fever outbreaks become generalized or massive, as has happened in the past, or should the disease threaten other tropical areas to which \textit{A. aegypti} could transmit the virus, such as South-East Asia.

\subsection{Cold-chain}

Since it contains a live, attenuated virus, the 17D vaccine may deteriorate during storage under certain conditions.
The WHO requirements provide that the stability of the vaccine must be tested by the manufacturer by storage at 37°C for 2 weeks. Before being issued from a depot for the maintenance of reserves of vaccines, all vaccines should be kept at a temperature below −20°C. The vaccine distributed to peripheral immunization posts must be stored at a temperature lower than +4°C until the expiry date (1 year after delivery by the manufacturer).

Some manufacturers now add non-allergenic, stabilizing substances to the vaccine to improve its thermostability. However, particularly in warm climates, it is safer to maintain the stabilized vaccine in a reliable cold-chain from the depot to the immunization location, as follows:

- Central store: 8 months at −20°C
- Transport to region: −20°C to +8°C
- Regional store: 3 months at −20°C
- Transport to district: −20°C to +8°C
- Static immunization unit: 1 month at +4°C to +8°C
- Mobile immunization team: 1 week at +4°C to +8°C

The WHO Expanded Programme on Immunization provides advice for the establishment of a cold-chain and suggests devices to monitor the temperature during storage and shipment (49).

The ultimate assessment of proper storage conditions is to send to a control laboratory, which may be designated by WHO, three containers sampled at different points along the cold-chain and at the end of the immunization session.

8.3.3 Immunization practice

The lyophilized vaccine is supplied in flame-sealed ampoules or in flasks tightly sealed with a rubber stopper and a metal ring. The label must indicate the expiry date and the number of doses (1, 5, 10, 20, 50, 100, or 200).

1. Rehydration of vaccine. The lyophilized vaccine is reconstituted by adding the quantity of diluent that is indicated by the manufacturer. This procedure must be carried out aseptically; special care must be taken when this operation is effected under field conditions to avoid any contamination with dust. The vaccine suspension is carefully homogenized by several aspirations and expulsions with a sterile syringe. Aseptic precautions in diluting the vaccine should also be taken when the contents of several ampoules are pooled to prepare 50- or 100-dose vials that are fitted on to jet injectors. The container is kept in an ice-bath and protected from light under a piece of dark cloth. The reconstituted vaccine must be used within 1 hour and then discarded.

2. Injection. A dose of 0.5 ml of the vaccine is inoculated subcutaneously in adults and children. Whenever only a few
individuals are to be immunized, containers with a small number of doses are used and syringes are convenient for inoculation. If a disposable sterile syringe is not available for each vaccinee, single-dose glass syringes are used for each vaccinee and must be sterilized by boiling. Whenever the number of vaccinees is high and they can be assembled in a continuous line, it is advantageous to use jet injectors with 50-dose or 100-dose containers. All parts of the apparatus in contact with the vaccine must have been previously disinfected, and no disinfectant should be left in the needle and the nozzle; injectors should be checked to deliver an exact volume of 0.5 ml.

(3) **Indications and contraindications.**

(a) *Infants.* As a precaution against possible encephalitic complications (see page 62), infants under 9 months old are not generally immunized. It may none the less be considered advisable to immunize children at 6 months if they live in rural areas that have a history of yellow fever epidemics and even at 4 months in an active epidemic focus, as any maternally acquired antibody may have waned and the risk of their contracting the disease is likely to be greater than that of complications from the vaccine.

The minimum ages for yellow fever immunization in Africa according to the prevailing circumstances may be tabulated as follows:

<table>
<thead>
<tr>
<th>Circumstances governing immunization</th>
<th>Minimum age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine prevention</td>
<td>9 months*</td>
</tr>
<tr>
<td>Prevention in rural areas with high infection risk (emergence zone) or where epidemics have occurred</td>
<td>6 months</td>
</tr>
<tr>
<td>Prevention in an active epidemic focus</td>
<td>4 months</td>
</tr>
</tbody>
</table>

**NO CHILD LESS THAN 4 MONTHS OLD SHOULD RECEIVE YELLOW FEVER VACCINE.**

* Children visiting or residing in urban areas who do not go to rural areas may be immunized at 12 months.

(b) **General contraindications** are those for other live vaccines: immunization should be avoided in the case of persons suffering from acute febrile illness; shingles (herpes zoster); chronic respiratory, cardiac, and renal diseases; diabetes; immunodeficiencies; or undergoing chemotherapy for cancer.

(c) **Allergy.** The vaccine is made from diluted chicken embryo extract. Although its protein content must be no more than 0.25 mg per 0.5-ml dose, the immunization of persons known to be suffering from an allergy (e.g., asthma, urticaria) must be preceded by an intradermal test with 0.1 ml of the vaccine, or as specified by the manufacturer. If rapid swelling of the skin is observed around the
injection site, extending irregularly in different directions, immunization should be interrupted. If there is no or only a minimal reaction, the remaining 0.4 ml of vaccine may be injected. The 0.1-ml inoculation may suffice for immunization, but tests for neutralizing antibody are required to determine whether immunity has been established. Tests for sensitivity should be performed by a physician who has access to therapeutic materials (e.g., epinephrine) in case anaphylactic reactions occur.

(d) Pregnancy. As a general rule, no live vaccine should be injected into women during the first trimester of pregnancy. However, inquiries by WHO did not reveal evidence of any damage to the fetus when pregnant women received the 17D vaccine. If the risk of natural yellow fever is considered higher than the theoretical risk in pregnancy, immunization should be performed.

Although no adverse effects of 17D vaccine on the fetus have been reported, it should be emphasized that careful large-scale, follow-up studies have not been done. Studies could be accomplished during future mass immunization campaigns, but these would require a special investigation.

8.3.4 Postimmunization immunity

Used correctly, a single dose of 17D vaccine confers long-lasting immunity in almost 99% of immunized persons.

(1) Postimmunization antibodies in primary immunization. Antibodies able to neutralize the yellow fever virus appear on the seventh day after immunization, whereas antibodies detected by the haemagglutination-inhibition test appear after the tenth day (Fig. 6) and are present at low titre. Complement-fixing antibodies do not appear after 17D immunization unless the person has been previously exposed to a flavivirus (14).

A single 17D immunization probably results in neutralizing antibody that persists for life without the need for booster injections. A study of sera from persons immunized 30–35 years previously showed persisting neutralizing antibodies in 97% of them (50). During a serious outbreak in Senegal in 1965, it was demonstrated that mass immunization can halt an epidemic and protect a population for a long time since only the non-immunized portion of the population—namely, children up to the age of 8 years—was severely affected (25).

In spite of the apparently long duration of immunity in most persons, the validity of the international certificate of vaccination is limited to 10 years.

(2) Reimmunization. The persistence of specific neutralizing antibodies after primary immunization does not affect the efficacy of
Fig. 6. Immunoglobulin response to 17D yellow fever vaccine.<sup>a,b</sup>

* Neutralization of yellow fever 17D virus by whole serum drawn sequentially from four individuals following primary immunization. 0.1 ml of heat-inactivated serum, diluted 1:2, was incubated at 37 °C for 60 minutes with an equal volume of virus suspension containing 233 PFU. 0.2 ml was inoculated on to BHL-21 cell monolayers. N antibody was measured as percentage reduction in PFU over controls. A source of labile serum factor was used. HI titres are expressed as the geometric mean for four individuals.


reimmunization. However, there is no accelerated type of neutralizing antibody response (secondary type response) such as may be observed with other viruses, and the rise in antibody may be lower than after primary immunization.

(3) *Immunization of persons immune to other flaviviruses.* Pre-existing immunity to other flaviviruses does not impair the response to 17D immunization.

(4) *Combined immunization.* There have been several studies on the combined use of yellow fever vaccine and other vaccines. The combined injection of smallpox (now no longer in use), measles, and 17D vaccines *at the same site* resulted in a decrease in the rate of seroconversions to yellow fever from 97% to 85% of recipients, but it should be noted that the injection was made intradermally (51). The simultaneous injection of yellow fever, smallpox, and measles vaccine *at different sites* gave a seroconversion rate of 96.6% for yellow fever and 94.8% when DPT (diphtheria, pertussis, tetanus) was added, thus showing no interference. Cholera immunization should not be given
together with yellow fever vaccine, or in the preceding 3 weeks, since it reduces the yellow fever neutralizing antibody response, at least temporarily (52, 53). Pooled human immunoglobulin given before, at the same time as, or after yellow fever 17D vaccine does not impair the rate of serological conversion, even when the globulin contains a high titre of yellow fever neutralizing antibodies. However, the duration of immunity has not been evaluated.

8.3.5 Postimmunization complications

The 17D vaccine is normally well tolerated. No abnormalities in liver function tests are associated with 17D immunization (54). However, minor reactions may be observed a few days after immunization. More severe reactions include encephalitis and allergic reactions.

(1) Minor postimmunization reactions. On about the sixth day after immunization, fewer than 5% of vaccinees may present a low-grade fever and slight headache and backache, which usually disappears in 1–2 days. There is no inflammation at the injection site or in the regional lymph nodes.

(2) Neurological complications. WHO requirements for vaccine production provide that the neurotropism of the vaccine seed virus should be checked in monkeys. In order to avoid any increase in the neurotropic properties of the vaccine, serial passages of the seed virus are not permitted. Because of these precautions no more than 17 cases of encephalitis have been recorded over a period of 40 years. They all occurred in children: 12 in infants less than 4 months old, 2 at 4 months, 1 at 6 months, 1 at 7 months, and 1 at 3 years of age. The last-mentioned case was the only fatal one (55); all the others made a full recovery. Although it is possible that some cases may have gone unrecorded, their number would be very small in proportion to the tens of millions of immunizations that have been performed without known encephalitic complications. The risk is minimal if due consideration is given to the circumstances in which children less than 9 months old may be immunized and the contraindications to immunization are respected (see page 59). Immunization with 17D vaccine was reported in one study (56) in 1967 to provoke the onset of multiple sclerosis or to exacerbate the disease, but this report has not been confirmed and no further cases of multiple sclerosis have been recorded in persons immunized against yellow fever.

(3) Allergic reactions. Skin rash, erythema multiforme, urticaria, angioneurotic oedema, and asthma have been described, but occur very infrequently (approximately 1 per 1000 000) and predominantly in persons with a history of allergy, especially to eggs (57–60).
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Very rarely, severe reactions may occur suddenly shortly after immunization. These are of the immediate hypersensitivity type (type I), sometimes accompanied by anaphylactic shock and circulatory collapse. Those responsible for the immunization session should have the necessary drugs (i.e., epinephrine) for resuscitation immediately available.

Allergic reactions of the Arthus phenomenon type, characterized by local swelling and necrosis following less than 24 hours after immunization, have occurred in rare instances. Some of these cases have been fatal. Two separate but apparently similar episodes have been reported but not previously published.

(a) Côte d'Ivoire (Ivory Coast), 1974. Thirty-nine cases of severe reactions with 8 deaths were reported during a mass campaign, in which 730,000 immunizations were performed by jet injection using 17D vaccine produced in Dakar, Senegal. On this basis, the incidence of severe reaction was 5.3 per 100,000 immunizations. The case-fatality rate was 20.5%. The cases occurred at 9 different immunization centres. All those affected were adults, except for a single child in whom the clinical picture (suggesting bacterial infection at the inoculation site) was distinct from that in the adults. Previous histories were obtained from 16 cases; 9 had received yellow fever 17D vaccine prior to the immunization resulting in the reaction.

The clinical features were quite uniform; after immunization in the morning, patients presented in the afternoon or evening with fever and signs of local (inoculation site) inflammation (oedema, heat, pain, pruritus). No lymphadenopathy was observed. In severe cases, oedema and inflammation extended distally and proximally and were followed by cardiovascular collapse that did not respond to corticosteroids. Only one autopsy was performed. Tissues at the site of inflammation showed congestion, haemorrhage, and ischaemic necrosis of the dermis with infiltration of neutrophils and eosinophils; death was due to congestive heart failure and pulmonary oedema. No mention was made of the presence or absence of vasculitis.

Three patients were diabetic, of whom 2 died. Haematological examinations revealed a mild eosinophilia in 4 patients. Sera from 6 patients were studied further: 2 contained precipitating substances in the presence of 17D vaccine; 3 had an abnormal serum electrophoresis; and 4 contained complement-fixing antibodies to normal chicken embryo extract at low titres (1:8–1:16).

Two lots of vaccine used in the campaign were found to contain acceptable levels of protein (0.2 mg/0.5 ml) according to WHO requirements; however, the vaccine lots actually given to the patients with reactions were not tested.

During the campaign, 5-dose vaccine ampoules were pooled to prepare 50 and 100 doses for use in the jet injectors. As it is difficult to implicate bacterial contamination or a toxin on the basis of the
clinical picture, several reviewers concluded that the illness most closely resembled an allergic reaction initiated by antigen-antibody complexes—i.e., a Type III hypersensitivity reaction. Hypersensitivity reactions to egg protein may have been responsible; an error of dilution might have occurred when the vaccine was pooled.

(b) Ghana, 1982. On 26 October 1982, an undetermined number of staff at an agricultural research institute at New Tafo were immunized with 17D vaccine (Dakar, lot 785). Six individuals developed fulminating reactions between 2 and 6 hours after immunization; there were 2 deaths (33.3%). All those affected were adult males aged 29–51 years. Vaccine was given from a 50-dose vial; according to the information received it was delivered "intra-muscularly", presumably with syringe and needle. Reactions were uniform: swelling, tenderness, and blisters at the inoculation site, fever and headache. Death (2 cases) followed several hours after onset of the local reaction. The same lot of vaccine was used elsewhere without adverse reactions; the protein content of 50-dose vials is one-fifth that of 10-dose vials.

Histopathological examination of tissues from the 2 fatal cases was not particularly revealing. There was mild to moderate inflammation (mixed polymuclear and mononuclear cells) of the subcutaneous tissue taken from the site of inoculation in one case. There was also a quantity of unidentified crystalline material that polarized light and was in the deep tissues of the inoculation site.

Sera from 4 patients were tested for antibodies; 2 of the 4 had antibody patterns suggesting that they might have received yellow fever immunization at some time before the injection producing the reaction.

The clinical features in these cases resemble those in the 1974 Côte d'Ivoire episode. However, the occurrence of a large number of adverse reactions in a single group of individuals at one location is evidence against egg hypersensitivity as the cause.

Because mass immunization campaigns in Africa are often conducted by mobile teams in remote areas, it should be recognized that other, similar episodes may have gone unreported in the past. In future campaigns, immunization teams should be made aware of possible adverse reactions of this type and should be prepared to provide vaccinees with access to medical facilities. If such reactions are observed, every effort should be made to preserve for analysis the actual vaccine material given to the patients. Blood specimens should be taken from individuals with reactions, medical histories should be obtained, and clinical laboratory tests should be performed in order to establish the etiology; severe reactions should be reported to the responsible health authorities and to WHO, and advice should be sought regarding special tests on specimens from patients.
8. CONTROL AND PREVENTION

8.3.6 Strategies applicable for public health programmes of immunization

Two different strategies have been followed for yellow fever immunization during the past 40 years in Africa, one being the “emergency” immunization programme and the other the routine mass immunization programme. Emergency immunization takes place once an outbreak has begun, in an attempt to limit the spread of infection by immunizing all persons in the focus, regardless of their former immune status. A routine mass immunization programme for yellow fever is aimed at immunizing in advance all populations considered to be at risk.

(1) Emergency immunization. To ensure the success of emergency immunization, careful preparations must be made and a sensitive surveillance system is needed to recognize any spread of the virus, not only in human populations but also in mosquitos and monkeys. In 1978, the detection of an epizootic in monkeys across the south of Senegal initiated a pre-epidemic “fire-fighting” operation that protected the population. However, the epidemic broke out on the other side of the border in the Gambia, where there had been no intervention.

Possible schemes of intervention should be planned, based on historical data or epidemiological investigations. Contingency plans should include an inventory of existing resources in terms of personnel and material. Advance arrangements should be made for bilateral aid or through WHO cooperation. A directory of the required personnel should be kept up to date. Special training of personnel may also be beneficial.

The extent of the focus and the population to be immunized can be estimated by prompt epidemiological investigation. A coordinator of all operations should be designated.

Public concern during outbreaks may help considerably in rapidly gathering populations at immunization points. A mobile team with two jet injectors (one as a spare) can perform 1000–1500 immunizations per hour with 50- to 100-dose vaccine vials. Several mobile teams are necessary.

One problem may be to obtain at short notice the large supply of vaccine needed, as well as the necessary injectors. WHO stocks for emergencies may be of assistance in this situation.

One advantage of the “fire-fighting” strategy is that personnel for immunization may be lent temporarily by other services, and the vaccine is used only for persons at risk. One disadvantage is that immunity does not appear until 7 days after immunization and deaths may be expected to occur in the interim period. Good cooperation is needed with both the epidemiologists and the entomologists responsible for the emergency control of mosquito vectors.
(2) Routine mass immunization. Routine mass immunization programmes were conducted in French-speaking countries in West and Central Africa from 1940 to 1960; they led to the disappearance of yellow fever from these areas so long as the policy was maintained and periodic campaigns were carried out to immunize young children born since the previous immunization session. These programmes ceased in 1960, however, and epidemics began to recur in 1965.

A country in the endemic zone that wishes to undertake a preventive programme of mass immunization may decide either to immunize all age groups at once, with further periodic sessions for immigrants and children older than 9 months born since the last session, or progressively to build up protection by immunizing each new generation of children. If yellow fever vaccine is considered for inclusion in a national Expanded Programme on Immunization, there are obvious logistic advantages in administering it at the age of 9 months at the same time as measles vaccine. In rural areas of the endemic zone that are considered at high risk, the minimum age for routine immunization may be lowered to 6 months.

The ultimate aim of a mass immunization programme is to protect the entire susceptible population well in advance of a possible exposure to yellow fever virus so that the time lag between giving the vaccine and the appearance of protective antibody is of no consequence. Although immunization of 80% of the population has frequently been said to provide sufficient herd immunity to prevent or halt an epidemic, the coverage necessary may in fact be higher or lower, depending on several conditions; with yellow fever the number of virus-infected vector mosquitoes in an area is critical. Moreover, in practice it is seldom possible to reach all susceptible persons; to set 80% as the goal is therefore almost certain to result in a lower level of coverage. Reaching a high level of coverage assumes the existence of a well-supervised and continuing programme that reaches all children as they attain a suitable age and that does not overlook immigrants into the programme area.

When yellow fever breaks out in a partially immunized population, it may be necessary to undertake a "fire-fighting" operation, as discussed above, that involves all the population at risk. In such conditions there is no time to verify the immune status of each person—an undertaking that is at best uncertain as well as costly. As a single immunization probably protects for life, a preventive programme of routine mass immunization seems more rational than the introduction of "fire-fighting" campaigns, but cost-benefit studies should be made before the decision is taken on which policy to adopt.
9. National and Regional Strategies

Countries of the endemic zone (see Fig. 1) may expect to have to deal with problems caused by sylvatic, intermediate, or epidemic yellow fever, according to local epidemiological conditions as defined above. Thus, yellow fever virus may cause either sporadic cases only or rapidly extending outbreaks.

In the African Region, the problem of yellow fever has been most often dealt with by Member States on an ad hoc basis. The result has been delays in intervention, increased economic losses, and enhanced human suffering. In only some instances were preventive or control measures based on a methodical investigation of the epidemiological situation.

A lack of resources remains the main obstacle to the prevention and control of yellow fever. This is aggravated by insufficient coordination of existing national and regional facilities and inadequate programming of necessary activities. Furthermore, communities have not been involved in the control of the disease at the primary health care level and so do not bear their share of responsibility.

Each country in the endemic zone is encouraged to define a national strategy against yellow fever taking into consideration their epidemiological and socioeconomic conditions, as recommended below. Furthermore, WHO has encouraged the development of a regional strategy that would increase national means for prevention and control.

9.1 Formulation of National Strategy

Prevention and control of yellow fever require well-defined objectives and targets. These objectives include the delineation of endemic and epidemic zones in the country, the establishment of an epidemiological surveillance system, the preparation of contingency plans for emergencies, the implementation of preventive mass immunization for groups at risk, and the control of mosquito vectors wherever feasible. The means of evaluating progress towards the attainment of these goals should be clearly defined. It is part of the strategy to make use of all favourable conditions in a pragmatic manner and to identify existing or potential constraints to be overcome.
9.1.1 National political commitment

The success of this strategy presupposes a national political commitment to provide long-term support for the necessary activities. The national commitment may take the form of a committee comprising officials from political and administrative bodies and from departments, units, and organizations involved in yellow fever control activities. Their task will be to decide on policy matters and coordinate control activities as well as to mobilize national and external resources. It is essential to calculate the cost of the programme, and the funds needed should be provided for in the national budget. In some countries, it may be necessary to introduce legislation to facilitate the organization of activities required to control the disease.

Once the policy has been specified and the objectives defined, the yellow fever control strategy should fit into the overall national health development strategy. The programme should describe the major line of action to be taken in all the sectors involved.

9.1.2 Delineation of yellow fever endemic and epidemic zones

A first indication is given by the climatic conditions and the vegetation distribution in different parts of the country. Sporadic cases may be expected in the forest area (sylvatic yellow fever), sporadic or self-limited outbreaks in the intermediate forest–savanna mosaic zone, and extensive epidemics in the Guinea and Sudan savanna area. Sporadic cases depend on the closeness of contact between man and the forest, and outbreaks may be caused and amplified by A. aegypti breeding in domestic water-collection systems. Unless great ecological changes have occurred in a region, past history provides valuable information on the epidemiological patterns of yellow fever.

In areas at risk, seroepidemiological surveys should be carried out to ascertain the exact situation. The presence of yellow fever antibodies in young children (1–3 years) who have not received vaccine indicates recent circulation of the virus. The presence of specific IgM antibodies in older age groups could be interpreted in the same way. Further investigations may include the inventory of mosquito vector species and their testing for the presence of virus. In areas where monkeys are abundant, they should also be tested for yellow fever antibodies.

9.1.3 Establishment of an effective epidemiological surveillance system

Epidemiological surveillance is a critical component of the strategy for the prevention and control of yellow fever.
As explained previously, an efficient routine surveillance system may be based on a careful scrutiny of icteric diseases in hospitals and dispensaries and a rapid reporting of information. Should a particular area require closer surveillance, periodic seroepidemiological surveys as mentioned above are recommended.

National laboratories should be equipped to perform various tests to confirm the diagnosis of yellow fever. The minimum provision would consist of histopathological examination of liver specimens and detection of complement-fixing antibodies in paired sera. Rapid techniques (ELISA) are now available for detecting IgM-specific antibodies and viral antigen; they offer significant advantages over conventional tests. Further laboratory examinations should be available in countries where yellow fever is a constant threat. In the absence of such capabilities, practical systems for obtaining and transporting specimens to a WHO reference laboratory should be developed.

The staff of the health services at all levels should be trained in the recognition of the disease and the techniques necessary for taking laboratory samples. Community participation in surveillance may also play an important role.

9.1.4 Contingency planning for emergencies

Countries should have a standing committee for all disasters, including yellow fever outbreaks. This committee will plan, organize, coordinate, and evaluate measures to deal with outbreaks. The following points are of particular importance in this planning:

— formulation of principles for determining whether an emergency exists;
— formulation of principles for determining the area and population at risk;
— identification of trained persons and institutions that can be mobilized at short notice to participate in emergency operations, including the ways of obtaining community participation;
— identification of specialist clinicians and materials needed for care;
— instructions for assessing needs that require financial and technical cooperation from international and bilateral agencies;
— compliance with international health regulations.

9.1.5 Immunization policy

In recent years mass immunization against yellow fever has been conducted only as an emergency measure when an outbreak has been detected (see section 8.3.6, page 65). The situation is now changing and several countries have started routine immunization programmes with the expectation that a single immunization may give long-lasting protection. Ideally, the entire population should be immunized and
this immune status should be maintained by immunizing newcomers to the population (children, immigrants). If the resources and logistic facilities are inadequate for this purpose, priority should be given to immunizing the population at greatest risk, from an appropriate minimum age (as discussed on page 59) to 15 years of age or more according to the local epidemiological circumstances. The first to be immunized should be those in rural areas with a high risk of infection (emergence zone; see page 19) or where epidemics have previously occurred. Immunization against measles at 9 months in a national Expanded Programme on Immunization offers an opportunity to immunize against yellow fever at the same time.

9.1.6 Vector control

During epidemics, vector control is one of the emergency measures and is directed mainly against domestic *A. aegypti*, both to reduce the adult (infected) mosquito density and to reduce the number of larvae. As discussed previously, where sylvatic vectors are involved, aerial spraying may be considered.

9.1.7 Integration of anti-yellow-fever measures into other health programmes

The central epidemiology and disease control unit will plan, manage, implement, and evaluate yellow fever prevention and control activities. Yellow fever control activities should be an integral part of primary health care. This will make it possible to apply basic sanitary measures, such as prevention of mosquito breeding, destruction of larval breeding places, measures of individual protection, and community participation. Since many disciplines are involved, yellow fever prevention and control should be supported by other health programmes, such as those for maternal and child health, basic sanitary measures, health manpower development, health education, biomedical research, water supply and environmental sanitation, urban sanitation, and waste disposal systems.

9.1.8 Community participation

Community participation in yellow fever control activities is an essential prerequisite for the success of the programme. Efforts should be made to improve public awareness of the disease, its effects, the mode of transmission, and methods of prevention. Each country will take into consideration its own particular cultural, social, and political characteristics. Health education programmes should be strengthened to encourage the population to participate in basic sanitary measures, to prevent breeding of mosquitoes, and to cooperate with immunization campaigns.
9.2 Regional Strategy

The prevention and control of yellow fever will reduce endemic morbidity and mortality, as well as the risk of epidemics, which can adversely affect the socioeconomic conditions of the countries involved. Hence, yellow fever control should be viewed in the context of "Health for all by the year 2000". The yellow fever control strategy in the African Region must therefore be oriented to overcome the obstacles and constraints that confront the countries of the Region. Disease control programmes are needed to investigate and control an outbreak or to assist in the etiological diagnosis of suspected cases. If necessary, the WHO Regional Office for Africa may call upon resources from other WHO regions as well as from other international organizations.

Yellow fever vaccine is produced in the African Region and is available at production cost because of the support given by WHO. An emergency stock of vaccine is kept in reserve for sudden demand by countries facing outbreaks. However, yellow fever vaccine production in the African Region should be further developed in order to raise the level of production to meet the total needs.

Exchange of information is another function that the WHO Regional Office for Africa can perform for the benefit of Member States. This exchange may cover a wide variety of information, including the most recent epidemiological data, which are crucial for the taking of timely measures for prevention and control.

9.2.1 Research

A considerable amount of knowledge on the epidemiology of yellow fever in the African Region has been accumulated over the past decade. However, there is still much that is not known and further research on yellow fever is to be encouraged. The following points are of special interest:

— the economic cost of epidemics and the cost-effectiveness of routine yellow fever immunization compared with that of emergency control measures;
— the development of surveillance techniques that permit the detection of yellow fever virus infection in vectors and hosts prior to the development of outbreaks among the human population;
— the determination of ecological factors that increase vector populations and virus activity in endemic areas, and research into the factors responsible for the absence of yellow fever in other areas of the region;
— the taxonomy, biology, genetics, distribution, and role in yellow fever virus transmission of principal and secondary vectors, including research on sibling species, vector competence, and transovarian transmission;
— the molecular structure of the virus, mechanisms and markers of virulence and its attenuation, and application of these data to the epidemiology of yellow fever;
— the pathogenesis of yellow fever with special emphasis on pathophysiological mechanisms in order to develop improved methods of treatment;
— the efficacy of interferon, antiviral drugs, and symptomatic therapy, including traditional local treatment;
— the role of humoral and cell-mediated immunological responses in recovery and protection, and the significance of possible cross-protection by other flaviviruses;
— the improvement and modernization of current vaccine production, including the development and use of stabilizers, improved lyophilization and containers, improved quality of eggs, and standardization of methods of titration;
— the development of 17D vaccine produced in cell culture, which may improve the availability of vaccine, reduce its cost, and eliminate possible side-effects;
— monitoring of potential adverse reactions during future mass yellow fever immunization programmes, including allergy (e.g., Arthus reactions) and the effect of immunization on pregnant women and on immunosuppressed individuals.
10. **International Health Regulations**

The purpose of the International Health Regulations (1969) is to ensure that maximum security is provided against the international spread of diseases with only minimum interference to world traffic.

Yellow fever is one of the diseases subject to the Regulations. Because of the extreme danger of the disease spreading to regions where *A. aegypti* is present in the cities, it is emphasized that the health authorities in countries where cases of yellow fever occur should fulfil their obligations with respect to the various international provisions for the control of yellow fever. Extracts from the International Health Regulations are given in Annex 4.

Information that has to be reported in compliance with the Regulations should be cabled or telexed to WHO, Geneva (27821-OMS-CH-EPIDNATIONS).

The map in Fig. 1 (page 2) shows the countries that are included in the endemic zone.

Information that is reported to WHO concerning yellow fever appears in the *Weekly epidemiological record* and also in the Automatic Telex Service (Telex number: 28150 CH) whenever there is some urgency for its dissemination. Each year the *Weekly epidemiological record* reviews the situation regarding yellow fever in the world.

The World Health Organization also publishes annually a booklet containing a list of the immunization requirements of individual countries (61). Updating during the current year appears in the *Weekly epidemiological record* whenever changes are communicated to WHO. A further booklet is available that lists all the authorized yellow fever vaccinating centres (62).
References

REFERENCES


REFERENCES


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Annex 1

Meeting on Prevention and Control of Yellow Fever in Africa

Dakar, Senegal, 30 May to 3 June 1983

Participants

Dr P. A. K. Addy, Ministry of Health, Accra, Ghana
Dr P. Brès, Pasteur Institute, Paris, France (Chairman)
Dr M. Cornet, ORSTOM, Pasteur Institute, Dakar, Senegal
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Annex 2

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Annex 3

Immunological Diagnosis of Yellow Fever

Immunological techniques for the diagnosis of yellow fever are of two main types: (1) techniques for the direct detection of yellow fever antigen in sera or liver tissue; (2) techniques for indirect diagnosis by detecting IgG or IgM antibodies in sera.

1. Direct tests for yellow fever antigen

(a) Immunofluorescence staining of sections of liver tissue. The sections must be fixed with formalin, embedded in paraffin, and then treated with trypsin or protease to expose the antigen sites before immunofluorescence staining.\(^1\) Immunoperoxidase staining and other staining techniques also appear promising. All these methods need further study, however.

(b) Enzyme-linked immunoassays of sera or liver tissue suspensions. A test based on the ELISA technique has been shown to be very sensitive for the detection of yellow fever virus in the blood of experimentally infected monkeys and it has also been tried successfully on human sera. It uses human IgM antibodies or type-specific monoclonal antibodies immobilized on polystyrene plates for the capture of yellow fever antigen.\(^2\) Suspensions of liver tissue can be used in place of sera. Recent data indicate that the ELISA technique can also be adapted for the detection of circulating IgM virus complexes and that this constitutes a highly sensitive method for rapid, early diagnosis (Lhuillier, M., unpublished data, 1984).

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2. Indirect tests for yellow fever antibodies

(a) Immunoﬂuorescence test. This offers a very simple technique for the serological diagnosis of yellow fever. Spot slides of Vero cells infected with yellow fever virus and several heterologous flaviviruses are prepared, as described by Johnson et al. Sera to be tested are serially diluted and incubated with infected cells on spot slides. They are then washed and stained with antihuman IgM or IgG conjugated to fluorescein isothiocyanate.

The speciﬁcity of the immunoﬂuorescence reaction with cells infected with yellow fever virus is determined by the presence or absence of a reaction with cells infected with the other flaviviruses. In primary yellow fever infection, IgG antibodies are quite speciﬁc: there is either no reaction or a very weak reaction with cells infected with other flaviviruses. In the case of yellow fever after other arbovirus infection, IgG antibodies react with cells infected with other flaviviruses but IgM antibodies are most often speciﬁc. However, IgM antibodies are not always present and IgG antibodies can compete with IgM for attachment to the antigen, thus limiting the usefulness of the test. This interference can be avoided by using the ELISA technique for the detection of IgM antibodies described below.

(b) Enzyme-linked immunoassays. Several modiﬁcations of the ELISA technique have recently been demonstrated to be useful in the serological diagnosis of yellow fever. In one such modiﬁcation for detecting IgG antibodies, a puriﬁed, type-speciﬁc antigen isolated from the membranes of yellow-fever-virus-infected cells is used to coat polystyrene plates. The sera to be tested for IgG antibodies are added and, after appropriate incubation and washing, the plates are treated with enzyme-conjugated antihuman IgG followed by substrate. This technique is highly sensitive and has similar speciﬁcity to the serum-neutralization test.

Other methods are applicable to the detection of IgM antibodies. Polystyrene plates are coated with μ-chain-speciﬁc, antihuman IgM followed by the test serum. After appropriate washing, yellow fever antigen is added. The antigen used may be in the form of sucrose-acetone-extracted mouse-brain antigen, identical to that used for conventional serological tests. With appropriate intermediate wash-

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ings, the plates are treated successively with either an enzyme-conjugated broad flavivirus group-reactive monoclonal antibody or hyperimmune mouse ascitic fluid, followed by enzyme-conjugated antimouse IgG.\(^1\)\(^2\)\(^3\) This technique has the advantage of measuring IgM antibodies of high specificity without interference by IgG antibodies. In primary yellow fever infections, a rapid diagnosis is possible since IgM antibodies are highly specific and reflect recent infection. During superinfection in patients with previous exposure to heterologous flavivirus, cross-reactions occur but IgM antibody titres are generally higher to yellow fever than to other antigens.

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Annex 4

Extracts from the International Health Regulations (1969)

Third Annotated Edition, Geneva (1983)\(^1\)

Article 3

1. Each health administration shall notify the Organization by telegram or telex within twenty-four hours of its being informed that the first case of a disease subject to the Regulations, that is neither an imported case nor a transferred case, has occurred in its territory, and, within the subsequent twenty-four hours, notify the infected area.

2. In addition each health administration will notify the Organization by telegram or telex within twenty-four hours of its being informed:

   (a) that one or more cases of a disease subject to the Regulations has been imported or transferred into a non-infected area—the notification to include all information available on the origin of infection;

   (b) that a ship or aircraft has arrived with one or more cases of a disease subject to the Regulations on board—the notification to include the name of the ship or the flight number of the aircraft, its previous and subsequent ports of call, and the health measures, if any, taken with respect to the ship or aircraft.

3. The existence of the disease so notified on the establishment of a reasonably certain clinical diagnosis shall be confirmed as soon as possible by laboratory methods, as far as resources permit, and the result shall be sent immediately to the Organization by telegram or telex.

Article 4

1. Each health administration shall notify the Organization immediately of evidence of the presence of the virus of yellow fever,

\(^1\) For administrative use, the complete edition of the Regulations must be consulted.
including the virus found in mosquitoes or in vertebrates other than
man, or the plague bacillus, in any part of its territory, and shall
report the extent of the area involved.

2. Health administrations, when making a notification of rodent
plague, shall distinguish wild rodent plague from domestic rodent
plague and, in the case of the former, describe the epidemiological
circumstances and the area involved.

**Article 5**

Any notification required under paragraph 1 of Article 3 shall be
promptly supplemented by information as to the source and type of
the disease, the number of cases and deaths, the conditions affecting
the spread of the disease, and the prophylactic measures taken.

**Article 6**

1. During an epidemic the notifications and information required
under Article 3 and Article 5 shall be followed by subsequent
communications sent at regular intervals to the Organization.

2. These communications shall be as frequent and as detailed as
possible. The number of cases and deaths shall be communicated at
least once a week. The precautions taken to prevent the spread of the
disease, in particular the measures which are being applied to prevent
the spread of the disease to other territories by ships, aircraft, trains,
road vehicles, other means of transport, and containers leaving the
infected area, shall be stated. In the case of plague, the measures
taken against rodents shall be specified. In the case of the diseases
subject to the Regulations which are transmitted by insect vectors, the
measures taken against such vectors shall also be specified.

**Article 7**

1. The health administration for a territory in which an infected area
has been defined and notified shall notify the Organization when that
area is free from infection.

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*1 (1) The period stipulated in paragraph 2 should begin when the last case is
identified as a case, irrespective of the time at which the person may have been isolated.

(2) The time-limits in paragraph 2(a), equal to twice the incubation period of
the disease, are minimum limits and health administrations may extend them before
declaring an infected area in their territory free from infection and continue for a
longer period their measures of prophylaxis to prevent the recurrence of the disease or
its spread to other areas. (WHO Official Records, No. 72, 1956, p. 38, and No. 79,
1957, p. 499)
2. An infected area may be considered as free from infection when all measures of prophylaxis have been taken and maintained to prevent the recurrence of the disease or its spread to other areas, and when:

(a) in the case of plague or cholera, a period of time equal to at least twice the incubation period of the disease, as hereinafter provided, has elapsed since the last case identified has died, recovered or been isolated, and there is no epidemiological evidence of spread of that disease to any contiguous area;

(b) (i) in the case of yellow fever not transmitted by *Aedes aegypti*, three months have elapsed without evidence of activity of the yellow-fever virus;
(ii) in the case of yellow fever transmitted by *Aedes aegypti*, three months have elapsed since the occurrence of the last human case, or one month since that occurrence if the *Aedes aegypti* index has been continuously maintained below one per cent;

(c) (i) in the case of plague in domestic rodents, one month has elapsed since the last infected animal was found or trapped;
(ii) in the case of plague in wild rodents, three months have elapsed without evidence of the disease in sufficient proximity to ports and airports to be a threat to international traffic.

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*Article 13*

1. Each State shall forward annually to the Organization, in accordance with Article 62 of the Constitution of the Organization, information concerning the occurrence of any case of a disease subject to the Regulations due to or carried by international traffic, as well as on the action taken under these Regulations or bearing upon their application.

2. The Organization shall, on the basis of the information required by paragraph 1 of this Article, of the notifications and reports required by these Regulations, and of any other official information, prepare an annual report on the functioning of these Regulations and on their effect on international traffic.

3. The Organization shall review the epidemiological trends of the diseases subject to the Regulations, and shall publish such data, not less than once a year, illustrated with maps showing infected and free areas of the world, and any other relevant information obtained from the surveillance programme of the Organization.

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*Article 18*

1. Depending upon the volume of its international traffic, each health administration shall designate as sanitary airports a number of the
airports in its territory, provided they meet the conditions laid down in paragraph 2 of this Article, and the provisions of Article 14.

2. Every sanitary airport shall have at its disposal:
   (a) an organized medical service and adequate staff, equipment and premises;
   (b) facilities for the transport, isolation, and care of infected persons or suspects;
   (c) facilities for efficient disinfection and disinfesting, for the control of vectors and rodents, and for any other appropriate measure provided for by these Regulations;
   (d) a bacteriological laboratory, or facilities for dispatching suspected material to such a laboratory;
   (e) facilities within the airport or available to it for vaccination against yellow fever.

Article 19

1. Every port and the area within the perimeter of every airport shall be kept free from Aedes aegypti in its immature and adult stages and the mosquito vectors of malaria and other diseases of epidemiological significance in international traffic. For this purpose active anti-mosquito measures shall be maintained within a protective area extending for a distance of at least 400 metres around the perimeter.

2. Within a direct transit area provided at any airport situated in or adjacent to an area where the vectors referred to in paragraph 1 of this Article exist, any building used as accommodation for persons or animals shall be kept mosquito-proof.

3. For the purposes of this Article, the perimeter of an airport means a line enclosing the area containing the airport buildings and any land or water used or intended to be used for the parking of aircraft.

4. Each health administration shall furnish data to the Organization once a year on the extent to which its ports and airports are kept free from vectors of epidemiological significance in international traffic.

Article 21

1. The Organization shall, at the request of the health administration concerned, arrange to certify, after any appropriate investigation, that a sanitary airport in its territory fulfils the conditions required by the Regulations.

2. The Organization shall, at the request of the health administration concerned, and after appropriate investigation, certify that a direct transit area at an airport in a yellow-fever infected area in its territory fulfils the conditions required by the Regulations.
3. These certifications shall be subject to periodic review by the Organization, in co-operation with the health administration concerned, to ensure that the required conditions are fulfilled.

Article 44

1. Except as provided in paragraph 2 of this Article, any ship or aircraft, which is unwilling to submit to the measures required by the health authority for the port or airport in accordance with these Regulations, shall be allowed to depart forthwith, but it shall not during its voyage call at any other port or airport in the same territory. Such a ship or an aircraft shall nevertheless be permitted, while in quarantine, to take on fuel, water and stores. If, on medical examination, such a ship is found to be healthy, it shall not lose the benefit of Article 33.

2. A ship or an aircraft arriving at a port or an airport situated in an area where the vector of yellow fever is present shall not, in the following circumstances, be allowed to depart and shall be subject to the measures required by the health authority in accordance with these Regulations:

(a) if the aircraft is infected with yellow fever;
(b) if the ship is infected with yellow fever, and *Aedes aegypti* have been found on board, and the medical examination shows that any infected person has not been isolated in good time.

Chapter III—Yellow Fever

Article 65

For the purposes of these Regulations the incubation period of yellow fever is six days.

Article 66

1. Vaccination against yellow fever may be required of any person leaving an infected area on an international voyage.

2. If such a person is in possession of a certificate of vaccination against yellow fever which is not yet valid, he may nevertheless be permitted to depart, but the provisions of Article 68 may be applied to him on arrival.¹

¹ For a model of a correctly completed certificate of vaccination, see Appendix, pp. 92–93.
ANNEX 4

3. A person in possession of a valid certificate of vaccination against yellow fever shall not be treated as a suspect, even if he has come from an infected area.

4. The yellow-fever vaccine used must be approved by the Organization, and the vaccinating centre must have been designated by the health administration for the territory in which it is situated. The Organization shall be assured that the vaccines used for this purpose continue to be of suitable quality.

Article 67

1. Every person employed at a port or an airport situated in an infected area, and every member of the crew of a ship or an aircraft using any such port or airport, shall be in possession of a valid certificate of vaccination against yellow fever.

2. Every aircraft leaving an airport situated in an infected area shall be disinfected in accordance with Article 25, using methods recommended by the Organization, and details of the disinfecting shall be included in the Health Part of the Aircraft General Declaration, unless this part of the Aircraft General Declaration is waived by the health authority of the airport of arrival. States concerned shall accept disinfecting of aircraft by the approved vapour disinfecting system carried out in flight.

3. Every ship leaving a port in an area where *Aedes aegypti* still exists and bound for an area where *Aedes aegypti* has been eradicated shall be kept free of *Aedes aegypti* in its immature and adult stages.

4. An aircraft leaving an airport where *Aedes aegypti* exists and bound for an area where *Aedes aegypti* has been eradicated shall be disinfected in accordance with Article 25, using methods recommended by the Organization.

Article 68

A health authority in an area where the vector of yellow fever is present may require a person on an international voyage, who has come from an infected area and is unable to produce a valid certificate of vaccination against yellow fever, to be isolated until his certificate becomes valid, or until a period of not more than six days reckoned from the date of last possible exposure to infection has elapsed, whichever occurs first.

Article 69

1. A person coming from an infected area who is unable to produce a valid certificate of vaccination against yellow fever and who is due to
proceed on an international voyage to an airport in an area where the vector of yellow fever is present and at which the means for securing segregation provided for in Article 34 do not yet exist, may, by arrangement between the health administrations for the territories in which the airports concerned are situated, be prevented from proceeding from an airport at which such means are available, during the period provided for in Article 68.

2. The health administrations concerned shall inform the Organization of any such arrangement, and of its termination. The Organization shall immediately send this information to all health administrations.

Article 70

1. On arrival, a ship shall be regarded as infected if it has a case of yellow fever on board, or if a case has occurred on board during the voyage. It shall be regarded as suspected if it has left an infected area less than six days before arrival, or, if arriving within thirty days of leaving such an area, the health authority finds Aedes aegypti or other vectors of yellow fever on board. Any other ship shall be regarded as healthy.

2. On arrival, an aircraft shall be regarded as infected if it has a case of yellow fever on board. It shall be regarded as suspected if the health authority is not satisfied with a disinsecting carried out in accordance with paragraph 2 of Article 67 and it finds live mosquitoes on board the aircraft. Any other aircraft shall be regarded as healthy.

Article 71

1. On arrival of an infected or suspected ship or aircraft, the following measures may be applied by the health authority:

(a) in an area where the vector of yellow fever is present, the measures provided for in Article 68 to any passenger or member of the crew who disembarks and is not in possession of a valid certificate of vaccination against yellow fever;

(b) inspection of the ship or aircraft and destruction of any Aedes aegypti or other vectors of yellow fever on board; in an area where the vector of yellow fever is present, the ship may, until such measures have been carried out, be required to keep at least 400 metres from land.

2. The ship or aircraft shall cease to be regarded as infected or suspected when the measures required by the health authority in accordance with Article 38 and with paragraph 1 of this Article have been effectively carried out, and it shall thereupon be given free pratique.
ANNEX 4

Article 72

On arrival of a healthy ship or aircraft coming from an infected area, the measures provided for in subparagraph (b) of paragraph 1 of Article 71 may be applied. The ship or aircraft shall thereupon be given free pratique.

Article 73

A State shall not prohibit the landing of an aircraft at any sanitary airport in its territory if the measures provided for in paragraph 2 of Article 67 are applied, but, in an area where the vector of yellow fever is present, aircraft coming from an infected area may land only at airports specified by the State for that purpose.

Article 74

On arrival of a train, a road vehicle, or other means of transport in an area where the vector of yellow fever is present, the following measures may be applied by the health authority:

(a) isolation, as provided for in Article 68, of any person coming from an infected area, who is unable to produce a valid certificate of vaccination against yellow fever;

(b) disinsecting of the train, road vehicle or other means of transport if it has come from an infected area.

Article 75

In an area where the vector of yellow fever is present the isolation provided for in Article 38 and in this Chapter shall be in mosquito-proof accommodation.
Appendix

MODEL OF A CORRECTLY COMPLETED INTERNATIONAL CERTIFICATE OF VACCINATION

To be valid in international traffic, vaccination certificates must be printed in English and French; a third language may be added. The certificate must be fully and correctly completed in English or French; completion in another language in addition is not excluded. — Pour être valables dans les voyages internationaux, les certificats de vaccination doivent être imprimés en français et en anglais; une troisième langue peut être ajoutée. Le certificat doit être complètement et correctement rempli en français ou en anglais, avec addition facultative d’une autre langue.

Signature of person vaccinated
Signature de la personne vaccinée

e.g.: 8 January 1981
ex.: 8 janvier 1981

Signature required
(rubber stamp not accepted)
Signature exigée (le cachet n’est pas suffisant)

Official stamp
Cachet officiel
ANNEX 4

INTERNATIONAL CERTIFICATE OF VACCINATION OR REVACCINATION AGAINT YELLOW FEVER
CERTIFICAT INTERNATIONAL DE VACCINATION OU DE REVACCINATION CONTRE LA FIÈVRE JAUNE

This is to certify that Ole OLSEN whose signature follows has on the date indicated been vaccinated or revaccinated against yellow fever.

<table>
<thead>
<tr>
<th>Date</th>
<th>Signature and professional status of vaccinator</th>
<th>Manufacturer and batch no. of vaccine</th>
<th>Official stamp of vaccinating centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 January 1981</td>
<td>Dr. John Doe M.D.</td>
<td>R.I.V. 63007</td>
<td></td>
</tr>
</tbody>
</table>

This certificate is valid only if the vaccine used has been approved by the World Health Organization and if the vaccinating centre has been designated by the health administration for the territory in which that centre is situated.

Ce certificat est valable que si le vaccin employé a été approuvé par l'Organisation mondiale de la Santé et si le centre de vaccination a été habilité par l'administration sanitaire du territoire dans lequel ce centre est situé.
Annex 5

Institutes Manufacturing Yellow Fever Vaccine Approved by WHO

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Commonwealth Serum Laboratories, Parkville, Victoria</td>
</tr>
<tr>
<td>Berlin (West)</td>
<td>Robert-Koch-Institut, Berlin (West)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Instituto de Produção de Medicamentos, Instituto Oswaldo Cruz, Rio de Janeiro</td>
</tr>
<tr>
<td>Colombia</td>
<td>Instituto Nacional de Salud, Bogotá</td>
</tr>
<tr>
<td>France</td>
<td>Institut Pasteur, Paris</td>
</tr>
<tr>
<td>India</td>
<td>Central Research Institute, Kasauli</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Yellow-Fever Vaccine Production Laboratory, Federal Laboratory Service, Yaba, Lagos</td>
</tr>
<tr>
<td>Senegal</td>
<td>Institut Pasteur, Dakar</td>
</tr>
<tr>
<td>South Africa</td>
<td>Department of Health, National Institute for Virology, Sandringham</td>
</tr>
<tr>
<td>Union of Soviet Socialist Republics</td>
<td>Institut poliomielita u virusnyh encefalitov (Institute of Poliomyelitis and Viral Encephalitides), Moscow</td>
</tr>
<tr>
<td>United Kingdom of Great Britain and Northern Ireland</td>
<td>Wellcome Research Laboratories, Beckenham, Kent</td>
</tr>
<tr>
<td>United States of America</td>
<td>Connaught Laboratories Inc., Swiftwater, Pennsylvania</td>
</tr>
</tbody>
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