A century of progress in combating yellow fever*

P. L. J. BRÈS

Yellow fever was responsible for several epidemics among the settlers in tropical areas of the Americas and Africa during the 17th to the 19th centuries. Scientific research into its cause and epidemiology was started at the beginning of the present century and progressed well ahead of other viral disease research. However, epidemics still occur and the worst one ever recorded was in Ethiopia in 1960–62. Epidemiological research has recently provided new findings on the ecology of the virus and the risk of epidemics. Recent breakthroughs in the molecular study of the virus should provide new tools for further progress in treatment and control of the disease. Meanwhile, the risk of urbanization of the disease, deficiencies in treatment, limitations in vector control, and erratic policies in preventive immunization present real problems.

At the beginning of the present century, the mystery surrounding yellow fever was broken by a series of discoveries and progress in research that are still an object lesson in methodology. The successful utilization of yellow fever vaccine in the 1940s, however, led to a loss of interest among scientists and only within the last ten years has our knowledge begun to advance rapidly again. The present status of yellow fever (prevention strategies, clinical and pathological aspects, treatment, and future research) was reviewed recently at an international seminar sponsored by the Pan American Health Organization (1). This Update article describes some historic yellow fever epidemics, the present epidemiological situation, and recent research findings.

HISTORIC EPIDEMICS AND RESEARCH ON YELLOW FEVER

Until the epidemics which affected Barbados, Cuba, Guadeloupe, and Yucatán (Mexico) in 1647–49, yellow fever could not be distinguished from malaria, dengue and

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other plagues that confronted sailors, soldiers and colonists in tropical areas on both sides of the Atlantic. Whether yellow fever originated in Africa is controversial; it is probable that the virus existed in the forests of Central and South America and that the efficient domestic mosquito vector, *Aedes aegypti*, was transported in the water tanks of sailing vessels from Africa to the Americas.

In the Americas, yellow fever raged during the 18th and 19th centuries. Among the devastating epidemics, it is reported that the British lost 20,000 out of 27,000 men in the attack on Cartagena (Colombia) in 1741 and 8,000 out of 15,000 in Cuba in 1762, while the French army lost 25,000 men in Santo Domingo in 1803. Yellow fever periodically decimated the crews of sailing ships and civilian populations in various ports, and reached New York in 1668 where at least 20 epidemics occurred in the summer months. An epidemic in the Mississippi valley in 1878 caused 13,000 cases and 5,000 deaths and the last epidemic in the USA caused 1,000 deaths in New Orleans in 1905. The first attempt to dig the Panama canal in 1880–88 failed after 52,000 cases of yellow fever and malaria were registered among the 85,000 workers.

In Africa, the first epidemic which was certainly yellow fever decimated the English troops at Saint-Louis in Senegal in 1778. Further outbreaks occurred frequently in the ports of the west coast from Senegal in the north to Angola in the south.

In Europe, a few cases used to appear occasionally during the summer in French ports that traded with America. Yellow fever also reached Spain where it persisted until 1830 with a total of about 100,000 victims. An outbreak in Lisbon in 1857 caused 1,800 cases, a third of whom died.

**Research on yellow fever**

An accurate description of the classical forms of yellow fever, with the three clinical periods of infection, remission and intoxication, had already been made in the 19th century (1). Fulminant forms with death in 3 days, without the full-blown clinical picture, were also known. Fatal meningeal forms have been seen at the beginning of some outbreaks. The frequency of subclinical and mild (influenza- or dengue-like) forms became evident only when laboratory diagnosis was possible after 1930.

Landmarks in research to overcome yellow fever between 1900 and 1950 have been detailed in a book describing the work carried out mainly by the Rockefeller Foundation; this book is still a valuable source of information on the subject (2). Important steps in the conquest of yellow fever are summarized below.

In 1900, the United States Army Commission in Cuba headed by Walter Reed confirmed that the disease was transmitted by the mosquito *Aedes (Stegomyia) aegypti* (first reported in 1881 by a Cuban physician, Carlos Finlay) and established that the agent passed through bacteriological filters. This was the first demonstration of a human disease caused by a virus. The Commission's conclusions led to public health campaigns against this mosquito in Cuba and in Panama where digging of the Canal was resumed in 1904 and completed in 1914. Similar campaigns were extended to most Caribbean and South American cities from where yellow fever was thus progressively eliminated. In the "key centre" theory, large towns were considered as foci where the virus could be maintained for long periods by the influx of immigrants (2).

In 1927, inoculation of monkeys in Africa (at Accra and Dakar) with the serum of yellow fever patients produced a disease similar to that in man and the agent was found to be transmissible from monkey to monkey by injection of filtered serum and by *Aedes aegypti*.

In 1930, the virus was adapted to the Swiss white mouse by intracerebral passages. This virus could then be utilized in neutralization tests and a vast antibody survey was initiated.
on both continents to delimit the endemic zones (95,000 sera were examined from 1931 to 1949).

In 1933, the unexpected resurgence of yellow fever in Rio de Janeiro in 1928–29 led to the discovery of rural epidemics in Brazil without the involvement of *A. aegypti*. This transmission of the disease, which was called jungle yellow fever, was linked to a monkey-to-man cycle originating in the forest.

In 1938, serial passage of the virus in tissue culture and in chick embryo tissues produced the 17D strain which proved to be a safe and efficient vaccine without hepatotropism and with only minimal neurotropism.

Since the 1940s, until very recently, very little progress was made in the physiopathology of yellow fever and its bearing on treatment. This was due to the lack of adequate medical research equipment in remote areas where jungle yellow fever usually occurs, or lack of preparedness for dealing with epidemics. However, as mentioned above, an international seminar recently reviewed the current status of the disease, with emphasis on diagnosis, care and management of patients, and made recommendations for improvement and further research (1).

**PRESENT EPIDEMIOLOGICAL SITUATION**

In compliance with the International Health Regulations, yellow fever cases are reported to WHO and are made known through the Organization’s Automatic Telex Reply Service and publication in the *Weekly epidemiological record*, which also presents each year an analysis of the epidemiological situation. Cases are reported under code No. 060 of the International Classification of Diseases and qualified as “urban yellow fever” (060.1) when *A. aegypti* is the vector, even in rural areas, and as “jungle yellow fever” (060.0) when mosquitoes other than *A. aegypti* are involved, even if there is transmission from man to man. Synonyms less frequently utilized for jungle yellow fever are sylvan yellow fever and sylvatic yellow fever (2).

**The Americas**

Yellow fever is endemic in the area between latitudes 10°N and 40°S in the Americas. Urban transmission has not occurred since 1942, except for one possible case during an outbreak of jungle yellow fever in Trinidad in 1954.

Jungle yellow fever is endemic in Bolivia, Brazil, Colombia and Peru with a total yearly incidence of about 100 cases, but the notifications are probably an underestimate. Epidemics occur with some periodicity in these countries and at unpredictable intervals in other countries of the endemic zone. The virus reached the north of Argentina in 1966 and Paraguay in 1974. In 1948 the disease appeared south of the Panama canal, progressed northwards and reached Belize, south of Mexico, in 1958. In 1974, cases occurred again south of the Panama canal but rapid control measures stopped further progress. In 1979, an epidemic in Trinidad was reminiscent of the episode of 1954 but had no extension to urban centres in spite of heavy infestations by *A. aegypti*. In all outbreaks the victims were mostly males aged 15 to 45 years and less frequently females. Exceptionally, children below 6 years of age were involved, as in the outbreak in Bolivia in 1981.

**Africa**

The endemic zone in Africa lies between latitudes 16°N and 10°S. The annual incidence of cases is characterized by larger outbreaks than in the Americas with no predictable
periodicity or localization. Urban-type yellow fever outbreaks transmitted by *A. aegypti* have been notified in rural areas on several occasions but no large centre has been hit since 1946.

The pattern of jungle yellow fever outbreaks is different in East and West Africa. East Africa was included in the endemic zone after serological surveys in the 1930s, but is usually a "silent zone" owing to the absence of notified cases, except on two occasions when very severe epidemics occurred. The first one caused 40,000 infections, more than 15,000 clinical cases, and 1500 deaths in the Nuba mountains of Sudan in 1940; the second, in south-west Ethiopia in 1960–62, is the most severe outbreak ever known, with 30,000 deaths among 100,000 cases in a rural population of one million. Outbreaks of jungle yellow fever are more frequent in West Africa than in East Africa. Severe outbreaks occurred recently in Ghana and Burkina Faso in 1983. Two non-vaccinated French tourists, who visited together the endemic zone of Senegal in 1979, died in different intensive care units in Paris where the etiology was clinically unsuspected until the virus was isolated after the patients died. Sporadic cases of jungle yellow fever are usually missed as they are generally mild or because of inadequate surveillance.

**ECOLOGICAL STUDIES**

The aim of ecological studies of yellow fever is to understand how the virus can be maintained in nature, and how it spreads and causes sporadic, endemic or epidemic cases. The ecological patterns of the virus are somewhat different in the Americas from those in Africa, but in both continents the virus is maintained among monkeys by mosquitoes in tropical forests (forest enzootic cycle) and is transmitted from monkey to man (jungle yellow fever) and from man to man (urban yellow fever if *A. aegypti* is involved, or jungle yellow fever if other mosquitoes are the vectors), as indicated in Table 1. Regional differences concerning the species of monkeys and mosquitoes are shown in Table 2.

**The enzootic forest cycle**

In South America, the virus is maintained in an enzootic cycle in the equatorial rain forests of the Amazon, Orinoco and Magdalena river basins by continuous wandering epizootics progressing to areas where non-immune monkeys can be infected (Fig. 1). Monkeys napping in the forest canopy during the midday hours are bitten by *Haemagogus* mosquitoes which breed in tree holes. As the mosquito is infected for life, it has been considered to be a better virus reservoir than monkeys whose short-lived viraemia plays only a transient amplification role in letting many mosquitoes become infected (2). Sporadic human cases or epidemics, which are reported as jungle yellow fever, result from direct

<table>
<thead>
<tr>
<th>Table 1. Transmission modes in ecological cycles of yellow fever virus</th>
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<tr>
<td>Cycles</td>
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<tr>
<td>Enzootic forest cycle</td>
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<tr>
<td>Jungle yellow fever</td>
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<tr>
<td>Urban yellow fever</td>
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### Table 2. Monkeys and mosquitoes involved in regional transmission cycles

<table>
<thead>
<tr>
<th>Region and cycle</th>
<th>Monkeys</th>
<th>Mosquitoes</th>
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<tbody>
<tr>
<td><strong>America</strong></td>
<td></td>
<td></td>
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<tr>
<td>Enzootic forest cycle</td>
<td>A. auvatta</td>
<td>Heemogogus fanninomys</td>
</tr>
<tr>
<td></td>
<td>Cebus</td>
<td></td>
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<td></td>
<td>Ateles</td>
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<tr>
<td></td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Jungle yellow fever</td>
<td>As above</td>
<td>H. fanninomys</td>
</tr>
<tr>
<td>Urban yellow fever (before 1942)</td>
<td>Nil</td>
<td>A. aegypti</td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzootic forest cycle</td>
<td>Cercopithecus</td>
<td>A. africanus</td>
</tr>
<tr>
<td></td>
<td>Colobus (East Afr.)</td>
<td></td>
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<tr>
<td>Jungle yellow fever in forest-savanna</td>
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<td></td>
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<tr>
<td>mosaic and humid savanna</td>
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<tr>
<td>Jungle yellow fever in semi-humid</td>
<td></td>
<td></td>
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<tr>
<td>and dry savanna</td>
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<td></td>
</tr>
<tr>
<td>Urban yellow fever</td>
<td>Nil</td>
<td>A. aegypti</td>
</tr>
</tbody>
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![Fig. 1. Epidemiological patterns of yellow fever in ecological zones of the Americas](image1)

![Fig. 2. Epidemiological patterns of yellow fever in ecological zones of Africa](image2)
contact with this cycle when man enters the forest. Our knowledge about this pattern of infection has remained unchanged since the 1930s, except that transovarial transmission of the virus by *Haemagogus* has recently been shown in the laboratory and its importance in the field has to be assessed. The role of marsupials as vertebrate hosts in areas where monkeys are absent is still unclear.

In equatorial Africa, *Cercopithecus* monkeys, together with *Colobus* in East Africa, are bitten in the canopy of the Lower Guinea forest block by *A. africanus* mosquitos which breed in tree holes (Fig. 2). This mosquito bites mainly at night and as man rarely enters the forest after dusk, human infections from this cycle are rare. *A. aegypti* is present in the forest but plays no role in this cycle of transmission of the virus. The role of Lemuroids as vertebrate hosts is still uncertain.

**Jungle yellow fever**

In South America, frequent epizootic thrusts, which have been compared to the pseudopods of an amoeba, occur on the fringe of the rain forest along riverine gallery forests, and outbreaks in humans appear annually or periodically in southern Brazil, eastern parts of Bolivia and Peru, Colombia, Venezuela and the Guianas. At longer intervals, the virus can also penetrate further into the so-called "epidemic zone" (Fig. 1). In addition to cases occurring when man enters the gallery forests where the virus is present, jungle yellow fever can result when infected *Haemagogus* mosquitos invade plantations or villages close to the forest. Investigations have been planned for a further study of the bionomics of *Haemagogus* which may be found at floor level in the gallery forests and can bite inside and outside houses up to 300 m from the forest. The possible role of other mosquitos and that of *Sabethes chloropterus*, which is drought-resistant, has also to be studied.

In East and Central Africa east of Cameroon, the jungle yellow fever transmission cycle was first described in the 1940s. The semi-domestic *A. simpsoni* mosquito, which breeds in plant axils, is infected after biting monkeys in the fringe of the forest or when raiding village plantations and transmits the virus to man, or they can be infected by biting man. In the epidemic in Ethiopia in 1960, the infection rate was lower in the Didessa valley where the virus was transmitted from monkey to man by *A. africanus* than in the Omo valley where *A. simpsoni* transmitted the virus from monkey to man and from man to man. In the epidemic in 1940 in the Nuba mountains (Sudan), a drier zone than Ethiopia, the incriminated mosquitos were *A. aegypti* in most villages and probably "wild" mosquitos, such as *A. vittatus*, *A. furcifer*, *A. taylori*, *A. luteocephalus* and *A. metallicus*, in the villages where *A. aegypti* was absent.

In West and Central Africa west of Cameroon, *A. simpsoni* does not bite man. The transmission cycles of jungle yellow fever have recently been studied (3). The wild mosquitos invade villages at some distance from the gallery forests where they live. Sporadic cases are most often detected only by serological tests as the forest cycle virus is less virulent and infections are frequently subclinical or confused with other diseases such as malaria. In other circumstances and perhaps if the virus has been passed several times in vertebrates, outbreaks involving all age groups may appear simultaneously in certain villages and not others in the same area. *A. furcifer* is the main vector, and the above-mentioned "wild" mosquitos in the Sudan are also implicated according to their breeding sites (Table 2). In villages where *A. aegypti* is present it can also sustain the man-to-man transmission cycle (mixed outbreaks), and where water is stored inside houses (as in the dry savannas) it alone can continue the transmission during the dry season. The endemic/epidemic potential of the virus in the different types of savannas which radially surround the Guinean rain forest is sketched in Table 3.

There is indirect proof of transovarial transmission of the virus in *A. furcifer*, which
Table 3. Epidemiological dynamics of yellow fever virus in different ecological zones of West Africa

<table>
<thead>
<tr>
<th>Enzootic zone</th>
<th>Rain forest of Lower Guinea block</th>
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<tbody>
<tr>
<td>Endemic/epidemic emergence zone</td>
<td>Forest-savanna mosaic</td>
</tr>
<tr>
<td>Endemic zone</td>
<td>Riverine gallery forests of humid savanna</td>
</tr>
<tr>
<td>Unstable endemic/epidemic front</td>
<td>Riverine gallery forests of semi-dry savanna</td>
</tr>
<tr>
<td>Potential epidemic zone</td>
<td>Riverine gallery forests of dry savanna Urban centres</td>
</tr>
</tbody>
</table>

explains resurgences of the virus at the same place for several consecutive years at the beginning of the rainy season when the infected eggs hatch, if the new generation of infected mosquitoes are numerous enough to start an amplification cycle in monkeys. The virus has recently been isolated from eggs and larvae of one cattle tick and was infective for monkeys. As already suspected, ticks could exceptionally act as long-term reservoirs and long-distance carriers.

**Urban yellow fever**

The following characteristics of *A. aegypti*-transmitted epidemics were well known in the past and are probably still applicable: occurrence in all age groups, intrinsic incubation period in man of 3–6 days, period of viraemia of 4–5 days, extrinsic incubation period of 8–12 days in the mosquito to become infective at 18°C (shorter period at higher temperatures and interruption of transmission at lower temperatures), and longevity of the infected mosquito of about 6–8 weeks. Epidemics were burnt out after 18 days without any new case when at least half of the surviving population was immune, or more than half if mosquitoes were particularly abundant. The risk of urban epidemics was linked to an *A. aegypti* density estimated at a threshold of 5 houses containing foci of larvae per 100 houses visited. In 1978, it was found that *A. aegypti* females could transmit the virus transovarially to a small proportion of their offspring and these eggs can thus maintain the virus in nature during dry seasons.

**A NEW LOOK AT THE VIRUS**

The yellow fever virus is a small enveloped round virus of 50 nm containing ribonucleic acid (RNA), and is now classified as the prototype of *Flavivirus* genus in the *Flaviviridae* family. It was one of the best studied viruses at the beginning of this century and its host range and organ tropisms were well determined. Later on, it was neglected in virological studies until very recently.

In addition to its adaptation to mice, the virus can now be cultivated in chick embryo cells, several mammalian continuous cell lines (particularly those derived from monkeys), and in even more sensitive mosquito cell lines such as *A. pseudoscutellaris* (MOS 61) and *A. albopictus* (C6-36). The morphogenesis of the virus during its multiplication in cells has recently been studied. Like the other flaviviruses, yellow fever virus particles bulge within the endoplasmic reticulum of infected cells and are liberated by reverse pinocytosis when cell lysis occurs.

It has been known since 1930 that the yellow fever virus is identical in the Americas and in Africa, as indicated by neutralization tests. However, modern techniques have recently
shown clear differences at the molecular level, e.g., by T1-oligonucleotide fingerprinting. It is now possible with this technique to identify viral topotypes characteristic of different geographical regions and to follow the pathways of a given topotype during extensive or repeated outbreaks and see its slow genetic alterations in the same place after some time. Oligonucleotide fingerprinting has also shown a difference between the 17D vaccine strain and the original virus isolated at Accra, and between the two substrains 17D-204 and 17DD utilized for vaccine production.

Further antigenic differences are evidenced by monoclonal antibodies which recognize epitopes common to all flaviviruses, or only to yellow fever viruses, or are specific to certain of their strains (4). A difference was also demonstrated between the vaccine substrains.

In the infected cell, the virus genome serves as template for the RNA of new virus particles and codes for two categories of viral proteins: structural proteins (capsid, envelope and membrane) and up to 12 non-structural proteins according to the virus strains. Polyacrylamide-gel electrophoresis analysis of these proteins is also a technique which permits differentiation of viral strains. The sequence of the 10 862 nucleotides which constitute the genome of the 17D virus has recently been established, showing those which are responsible for coding each of the above listed proteins (5). This achievement opens several important perspectives: to follow strain variations with genetic probes for nucleic acid hybridization, to link differences in strain virulence with certain nucleotide sequences, and to select immunogenic sequences without any undesirable effects which could be inserted by genetic recombination into the genome of a vector such as vaccinia virus or could be modified to get a new live vaccine in which other antigens might be inserted. A non-structural glycoprotein (NS-1, previously known as gp48) is expressed at the surface of cells infected with yellow fever virus or other flaviviruses including dengue virus and has been shown to induce protection in animals. Passive transfer of monoclonal antibodies against this protein could be utilized to stop the infection, or the protein itself could be used as an immunizing agent to prevent it (6).

Rapid laboratory techniques

The histopathological lesions of the liver lobules in yellow fever resemble those caused by other haemorrhagic fever viruses and are no longer considered as pathognomonic. Classical virus isolation methods are based on inoculation of newborn mice, intracerebral passages, and identification by neutralization with a confirmed specific reference serum, which can be carried out only in specialized laboratories and require 10–21 days to provide an answer. Serological diagnosis is based on the haemagglutination inhibition and complement fixation tests, which provide an answer in 24 hours but often lack specificity in persons who had previous contact with another flavivirus, and on the neutralization test, which is more specific (although not in every case) but time-consuming. These techniques require paired sera collected at 8-day intervals to show a rise of immunoglobulins G (IgG).

Isolation of the virus by intrathoracic inoculation of male A. aegypti or Toxorhynchites mosquitos is more sensitive than inoculation of newborn mice but it still requires about two weeks and a specialized laboratory. More rapid isolation methods have recently been utilized in the field by inoculation of the blood (or serum) kept at low temperature in continuous mosquito cell lines (MOS 61, C6-36) and these gave a result in 3–4 days. The virus has been identified using monoclonal antibodies by immunofluorescence or enzyme-linked immunosorbent assay (ELISA). Furthermore, instead of cultivating the virus, its circulating antigens may be detected directly in the blood by capture with an ELISA method during the first days after onset of the disease. The sensitivity of this very rapid method, taking only 3 to 4 hours, has to be improved (7).
Serological diagnosis of yellow fever can now be made in a few hours in the field by the immunoglobulin M (IgM) antibody capture immunoassay, which detects specific IgMs which appear 3-4 days after onset of the disease and persist for only 2 to 3 months (8). Cross-reactions are possible if the patient had previously been infected by another flavivirus but the non-specific titres are much lower than with the yellow fever virus antigen. Treatment of sera with dithiothreitol breaks the IgM-virus immunocomplexes and enables isolation of the virus at the same time as the IgMs are detected.

PERSPECTIVES FOR CONTROL AND PREVENTION

The conquest of urban yellow fever in the Americas and Africa was achieved during the first half of this century only by public health measures for eradication of A. aegypti. Since 1938, the vaccine has been a further potent weapon to control the disease. Although the virulence of the virus seems to be less now than in the past, yellow fever is still a severe health problem in countries of the endemic zones and presents a threat because of the increasing possibility of invasion or reinvasion of many places by A. aegypti.

The risk of urbanization

As in the past, yellow fever could take root at any moment in large towns of the endemic zone. However, there have recently been several examples of jungle yellow fever outbreaks very close to urban centres in the Americas and Africa and viraemic patients have been hospitalized without antimosquito precautions in cities where A. aegypti indices of infested houses were as high as 50%, without initiating the urban transmission cycle. The reason for failure in transmission might be because the virus has lost its virulence and/or A. aegypti its vectorial competence. Genetic analysis of wild strains of the virus might provide an explanation concerning their virulence.

Vector competence of local strains of A. aegypti and the risk of urbanization in Asia have been studied by and puzzled entomologists since the opening of the Panama canal. Experimentally, A. aegypti mosquitoes collected in different places of Asia are able to transmit the virus to monkeys or newborn mice with variable success, depending on their origin and the strain of virus utilized. This conclusion has been extended to some other Asian mosquitoes such as A. pseudoscutellaris, A. polynesiensis and might be applicable to A. albopictus. An interference with dengue or other flaviviruses by virus competition in the mosquito or presence of cross-protective antibodies in the population has been suggested as an explanation although dengue is not widespread everywhere on the risk front in Asia, and dengue and yellow fever have coexisted in American cities in past centuries. However, the available data on mosquitoes and viruses are still incomplete and one cannot pronounce firmly on this matter. Theoretically, the risk of yellow fever in Asia is greater now than in the past because of rapid modern transport which can introduce viraemic persons or infected mosquitoes in any of the receptive areas. This justifies strict application of the International Health Regulations concerning yellow fever.

Limitations of vector control

In the Americas, soon after confirmation of the role of A. aegypti at the beginning of this century, eradication of yellow fever was believed possible if patients were placed under mosquito nets and if mosquito breeding sites were reduced below the critical threshold of 5% of infested houses. Owing to relaxation in vector control, the jungle yellow fever virus offered A. aegypti an opportunity to break this hope and there was an epidemic in Rio de
Janeiro in 1928–29. The Pan American Health Organization in 1947 promoted a vast regional A. aegypti eradication campaign based on the efficacy of DDT. After great initial success and despite considerable expenditure, reinvasions started to appear in 1956 and spread to several countries because of frequent national administrative failures and the ban on DDT. As a result, all four dengue virus serotypes have caused epidemics in several countries during the past two decades and A. aegypti has even been found in rural settings and, recently, up to altitudes of 2200 m in Colombia. A technical group convened by PAHO/WHO in 1982 insisted on the necessity of A. aegypti control/eradication in the face of yellow fever and dengue haemorrhagic fever threats. 

In Africa, a reduction in A. aegypti breeding sites was promoted early in this century and reinforced after the epidemic in the Nuba mountains in 1940. These measures were successful even though A. aegypti living in the forests continued to threaten to invade villages and towns. As in the Americas, reinvasion occurred in the cities after the 1960s as a result of relaxation of administrative measures. Furthermore, wild mosquitos such as A. furcifer can invade villages and are out of reach in the forest.

Emergency antimosquito measures—by aerial spraying of the infected area, domiciliary spraying, and mandatory reduction of breeding sites—remain a necessity for control or immediate prevention of yellow fever outbreaks. A drastic interruption of transmission cycles by domestic and wild mosquitos is the objective during the seven days necessary for the vaccine to provide its full protective effect.

Lack of an efficient immunization policy

The 17D Rockefeller yellow fever vaccine prepared in accordance with the WHO requirements for biological standardization is the only vaccine in use at present; because of its neurotropism it is contraindicated only in children below 6 months of age. As with other live vaccines, it is not recommended during the first trimester of pregnancy but reports from vaccination centres have not revealed any untoward effect. The remote risk of adverse effects after immunization has to be balanced with the risk of infection which is ever present in endemic zones. Because of limited thermostability, the vaccines have to be transported and stored in a cold chain all the way from the manufacturer until their use in the field. Vaccine preparation, even today, accords closely with the original 1938 technique in chick embryonated eggs which has some drawbacks: allergic reactions may occur in persons sensitized to egg proteins and the production capacity is limited. In order to meet large demands during epidemics, WHO has to maintain a reserve of vaccine ready for use and of seed-lot virus to prepare more vaccine.

In both Africa and the Americas, immunization is often restricted to the population at risk where an outbreak occurs and generally 1 to 3 million doses of vaccine are required. This “fire-fighting” strategy is usually started when the number of victims is already considerable and another 7 days are necessary, after immunization, for the vaccine to begin to protect. Preventive immunization is therefore desirable but will have to be based on a sound definition of the target population. In the Americas, adult workers in forests where the virus might circulate and inhabitants on the fringe of the forest are the high-risk groups. This strategy of preventive immunization was successful during construction of the Trans-Amazonian Highway. However, the size of the target group might increase in future because of the risk of urbanization of the disease. In Africa, the entire population of French-speaking countries in the endemic zone was immunized every 4 years from 1940 to 1960 and the incidence of yellow fever fell to zero (3). All the rural and urban populations in the endemic zones are at risk and should be immunized preventively after the age of

6 months. The advantage of the 17D vaccine in a large programme is that one injection will provide good immunity for more than 35 years, and probably for a lifetime in many cases. The 17D vaccine may be given simultaneously with measles vaccine to children at 9 months of age and if cost-effectiveness analyses are favourable, it could be included in the expanded programmes for immunization of less-than-one-year-old children, thus providing a progressive build-up of durable immunity in successive generations.

Future prospects

Much knowledge is already available on the ecology of yellow fever. However, the virulence of strains and the competence of vectors still remain largely unknown with regard to understanding the occurrence of epidemics and predicting them.

Deficiencies in our knowledge of the physiopathology of the disease and its treatment should not be allowed to continue. The creation of mobile or fixed units with capabilities for conducting clinical research and to treat patients rapidly during outbreaks has been advocated by the technical group which met in Brazil in 1984 and this deserves urgent practical consideration (1).

Because of the limitations and high costs of spraying programmes, a good deal of vector control could be achieved by health education to reduce the A. aegypti breeding sites; this method proved to be efficient at the beginning of this century against the urbanization of the disease.

Improvement of the vaccine is much to be desired. A more thermostable vaccine in chick-embryo cultivated cells without egg allergens and with no limitation in production should be available soon. Genetic engineering of a killed vaccine seems now feasible but considering the conditions of use in developing countries, a live vaccine requiring only a single injection would be preferable. Even if a specific drug should become available one day, preventive immunization will remain a necessity against yellow fever, in the same way as a vaccine is desirable against malaria.

In conclusion, many factors influence the future of yellow fever and their counterbalancing effects are unpredictable. If urbanization of the disease is a great risk at present, deforestation (where it takes place) pushes back the emergence zone. The activity and maintenance of the virus in the forest cycle depends on the amplification process in susceptible monkey populations which are disappearing from certain areas and little is known about the role of alternative vertebrate hosts. The as yet unanswerable question is: how fragile is the virus reservoir and what will be the natural evolution of the disease by the end of this century?

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