Yellow fever as an endemic/epidemic disease and priorities for vaccination.

T. P. Monath
Acambis, 38 Sidney Street, Cambridge MA 01451 USA. E-mail : tom.monath@acambis.com

Introduction

Yellow fever is a viral hemorrhagic fever, characterized by hepatic and renal dysfunction, hemorrhage, cardiovascular shock and a case-fatality rate of 20% or higher. The disease occurs in tropical regions of South America and sub-Saharan Africa. Transmission is by the agency of *Stegomyia* spp. mosquitoes. Yellow fever is a zoonosis maintained in nature by mosquitoes transmitting virus between nonhuman primate species, most of which develop clinically inapparent infection. Humans are infected tangentially by mosquitoes that have acquired infection from nonhuman primates (jungle yellow fever). However humans are also effective viremic hosts, and interhuman transmission by *Stegomyia aegypti* (formerly *Aedes aegypti*) (14) may be responsible for epidemic spread (urban yellow fever). In Africa certain other vector species may also play a role in interhuman epidemic transmission.

The lethality of the disease, the complexities of the transmission cycle, the vast geographical areas across which enzootic
yellow fever is active, and the potential to spread to distant areas infested by the urban vector, provide a compelling mandate for preventive immunization. Although an effective vaccine (yellow fever 17D) has been available since the late 1930s, utilization is incomplete in many areas, particularly in Africa, with the result that yellow fever epidemics still occur. Epidemiological data on disease incidence are required to model costs and benefits and to make public health decisions about vaccine intervention. One study on this question has been published (10), and a more recent analysis has been completed and awaits publication. Suffice it to say that both analyses conclude that, in endemic areas, the models favor routine childhood and catch-up mass vaccination campaigns. An important consideration is the occurrence of ‘silent’ endemic transmission which results in a disease burden that cannot be directly measured for lack of surveillance, accurate case counting, and availability of specific diagnostic testing. That problem has long vexed yellow fever workers. In 1928, for example, an investigator noted that “... there is great difficulty... making the diagnosis of endemic yellow fever... Such instances are rare and isolated, and within two or three days patients are either cured or dead, so that in a country like Africa... a doctor will not even hear of them, and

Figure 1. Endemic areas (shaded) of South America and Africa (from: International Travel and Health, World Health Organization, Geneva, 2001).


Figure 2. Endemic area of Brazil (shaded) and areas with case of yellow fever in humans or detected in monkeys, 2003. The areas highlighted (boxes) represent excursion of virus activity outside the endemic zone.

Zone endémique au Brésil (ombrée) et zones avec cas de fièvre jaune chez l’homme ou détecté chez les singes en 2003. Les zones sélectionnées (encadré) représentent le champ d’activité du virus en dehors de la zone endémique.

*Other yellow fever has been reported or the presence of vectors and animals reservoirs creates potential risk of infection (considered to be endemic areas).
generally they will be considered as suffering from one of the everyday fevers so long as an exact laboratory diagnosis cannot be made of each case” (3).

A difficult consideration in setting public health policy is the occurrence within many countries of both endemic areas in which jungle/sylvatic transmission occurs and areas outside the endemic zone, which are susceptible to the introduction and spread of urban yellow fever (5). In many cases, the latter areas are large and densely populated, such as coastal regions of South America from which yellow fever has been absent for many decades. The decision to vaccinate these large populations against the theoretical threat of urban yellow fever epidemics has been controversial, as will be discussed later on.

The geography of yellow fever

Vaccination policy should be based on a clear understanding of geographical risk. The boundaries of endemic yellow fever (figure 1) have been derived from reports of cases and epidemics, and from serological surveys of monkeys and humans, most of which were conducted 60-70 years ago. The serological methods used during these surveys could have measured cross-reacting antibodies to other flaviviruses. Inspection of the maps reveals many anomalous features. Political demarcations either underestimate the endemic region or, in many cases, entire countries are shaded whereas only a delimited region of the country should be designated as falling within the endemic zone (e.g. Kenya, Tanzania, Angola). Some countries, such as Somalia and Zambia should be removed from the list of endemic countries entirely. Importantly, yellow fever epizootics may frequently broach the borders of the endemic area, a repeated feature in both South America and Africa. Examples include:

– Brazil (figure 2), where jungle yellow fever cases recently occurred in Sao Paulo, Rio Grande do Sul, Sao Paulo, and Minas Gerais States well outside the endemic area;

– southern Mauritania.

As mentioned above, an important consideration for vaccine policy makers are areas infected with the urban vector (St. aegypti) that are juxtaposed to the endemic region and are thus at risk of introduction and spread of urban yellow fever (5).

The incidence of yellow fever, based on disease reporting

The only sources of data are official notifications to the World Health and Pan American Health Organizations, and occasional descriptions of yellow fever epidemics in the literature. The figure recurrently used to estimate disease burden is 200,000 cases per year (15). The fact is, however, we do not have a clear quantitative measure of endemic disease burden, and it is clear that official case reporting is clearly the tip of a larger iceberg, at least in Africa. The very fact that severe epidemics continue to emerge is proof enough of a significant underlying problem of endemic yellow fever disease. It is also clear that cases reports during epidemics have historically underestimated the true incidence by a factor of 30-100:1, and only where an on-site intensive investigation has been performed have most cases come to light (7).

Official reports of yellow fever between 1965 and 2004 in South America and Africa number over 33,000 cases (figure 3). The overall incidence in Africa has been nearly 5 times higher than in South America, reflecting both higher backgrounds of vaccine immunity and the fact that all South American cases are of the jungle type. In contrast, large outbreaks involving interhuman transmission by St. aegypti and other vectors have occurred in Africa. The most striking aspect of the incidence data is the large peak in Africa between 1987 and 1994, which reflects a series of concurrent annual epidemics in West Africa, principally Nigeria (13). Given the recent introduction of routine childhood immunization in Africa, the low coverage levels, and the large susceptible population of persons over 5 years of age, there is a high likelihood of such conflagrations occurring again. If case reporting had been as efficient in the 1960s as it was during the 1990s, a similar peak would have been observed in the official data between 1962-65 and in 1969-70 when very large epidemics of similar scale occurred in Ethiopia, Senegal and Nigeria.

The distribution of officially notified yellow fever cases by country in South America and Africa (1990-2004) is shown in figure 4. In South America, Peru has the highest reported incidence, and this is a consistent finding for many years, reflecting in part the relatively lower vaccine coverage there. In Africa, the highest incidence is in West Africa, a fact recognized as early as 1907. Countries reporting the highest numbers of cases include Nigeria, Ghana, Côte d’Ivoire, Liberia, Guinea, and Senegal. The disease occurs principally in the moist savanna vegetational zone where a variety of mosquito species are responsible for transmission, and in surrounding dry areas where urban type transmission occurs. St. aegypti is found throughout the region because of the practice of storing

Water storage jars, western Nigeria, that serve as breeding sites for the urban yellow fever vector, Stegomyia aegypti. Réserves d’eau, Nigeria occidental, servant de site d’élevage du vecteur de la fièvre jaune urbaine, Stegomyia aegypti.
water in containers in and around houses (photo 1), which provide breeding sites for larval mosquitoes (20). Population densities of sylvatic vectors which breed in tree-holes and a variety of natural sites near human habitations reach high levels, and biting rates up to 35 bites/day (2) illustrate the potential for intense virus transmission.

Figure 5 shows the countries affected over the last 15 years by epidemic yellow fever. Again, with the exception of an outbreak in western Kenya (1992) and southern Sudan (2004), epidemics have occurred in West Africa. In this century, the largest outbreak occurred in Guinea in 2000-2001, with approximately 700 cases officially reported. The true number was undoubtedly greater, since some districts reported 100% fatal cases.

The incidence of yellow fever virus infection during various epidemics has been estimated based on serological testing of populations affected by the outbreaks. Across different outbreaks, there has been a remarkable consistency in these estimates, which average ~30% and illustrate the extreme danger to an unvaccinated or non-immune individual who is exposed to vector mosquitoes in a region affected by epidemic yellow fever (7). Data on infection and disease rates during outbreak investigations have allowed estimates of the ratio of sub-clinical to clinical cases. In two examples (Nigeria, the ratio was estimated to be between 3.9 and 6.9, consistent with an earlier report (table I) (8). For non-immune individuals the risk* of acquiring yellow fever disease during a one-week

* R = [r/ik]p, where R=risk of yellow fever/week of exposure, r=rate of infection/epidemic interval, i=infection:illness ratio, k=weeks exposed/epidemic interval, p=proportion of population susceptible
period of exposure during an epidemic period (assumed to be 3 months) may be estimated as 1/280.

Incidence of endemic yellow fever

In South America, all reported cases are considered the result of endemic transmission of jungle yellow fever by tree-hole breeding Haemagogus spp. mosquitoes that had acquired infection by feeding on an infected monkey in the forest canopy. Periods of intense epizootic transmission in monkeys may be associated with an increased incidence of human cases, and occasionally the epizootic wave (and associated human cases) extends beyond the perimeter of the classical area (shaded in figure 1) as happened recently in Brazil (figure 2). The annual incidence of endemic jungle yellow fever in South America has varied from 46 to 524 cases between 1990–2004, for an average incidence of 168 cases.

The sensitivity of surveillance for case ascertainment cannot be determined with accuracy. In Bolivia, Brazil, Peru and Colombia, which report the vast majority of cases, 12% of cases that were investigated were confirmed by laboratory tests or histopathologic examination (table II). The relatively large number of cases investigated but not confirmed suggests that surveillance is relatively sensitive. However, some investigated cases could be yellow fever but were not confirmed for lack of specific laboratory tests or autopsy specimens. Indeed, the case-fatality rate in South America is quite high (43–54%, table II), suggesting that there may have been missed (nonfatal) cases, possibly twice the number officially reported each year.

Quantifying the endemic disease burden in Africa is more difficult. It is clear that yellow fever virus infections occur unnoticed during periods between epidemics (11, 17). Serological surveys indicate that the annual incidence of endemic infection approximates 1% (9), the incidence being highest in the forest zone and diminishing across moist and dry savanna zones.

Table II.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Cases Investigated</th>
<th>Cases Confirmed</th>
<th>Deaths</th>
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<td>143</td>
<td>68</td>
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<tr>
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<td>15</td>
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<td>55</td>
<td>54</td>
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<tr>
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<td></td>
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<td>63</td>
<td>29</td>
</tr>
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<td>subtotal</td>
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<td>119</td>
<td>43</td>
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<tr>
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<td>58</td>
<td>24</td>
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<tr>
<td></td>
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<td></td>
<td>2003</td>
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Figure 6 shows the age structure of the West African population (2004) and of the population adjusted for vaccine immunity based on vaccine coverage data (18) and natural immunity based on an annual incidence of infection of 1%. Using the estimated infection rate and inapparent/apparent infection ratio, it is possible to estimate disease burden. Assuming that the entire West African population is annually exposed, the incidence of disease in the adjusted (immunologically susceptible) population exposed to endemic transmission at a rate of 1%, with an inapparent/apparent disease ratio if 7:1 would be 244,224 cases, or 131/100,000 population (figure 7).

Figure 7.

Number of cases of endemic malaria (2005) based on the adjusted population (figure 6), the incidence of infection (1%) and the infection: illness ratio (7:1), West Africa (see legend figure 6 for countries). The top line indicates the case incidence assuming that the entire population is exposed, the middle line assumes 25% of the population exposed, and the bottom line assumes 10% of the population is exposed (see text).
No adjustment was made for emergency mass immunizations that may have been conducted in West Africa in the past. The estimate is not far off the 200,000 cases estimate previously published (15). However, yellow fever transmission is most certainly not uniform within countries and across sub-continental regions, such as West Africa. During the rainy season, the virus is thought to emerge from the forested vegetational zone across the moist savanna, but these emergences vary greatly in intensity form year to year, as shown by longitudinal studies in Senegal (12, 16). Since no data are available on which to base a true picture of endemic yellow fever virus activity, a sensitivity analysis provides some insights. For example, if the annual endemic expansion affects 25% or 10% of the population across the endemic region of West Africa, the annual incidence would be 61,056 and 24,422 cases, respectively (figure 7).

Since 2001, efforts by WHO have centered on increasing the sensitivity of surveillance by using a clinical case definition (fever with jaundice appearing within 14 days) and by improving specific laboratory diagnosis (19). By 2004, the number of countries undertaking case-based surveillance increased to 15, serological testing was established in 22 laboratories, and over 2000 specimens from suspected cases were tested. The proportion of samples from suspected cases that had IgM antibody indicative of recent yellow fever infection between 2001 and 2004 has been 0.5-8%, but it is uncertain what proportion of these reports represent epidemic versus endemic transmission. It is clear that yellow fever is responsible for a small proportion of cases presenting with fever and jaundice, consistent a previous study in Nigeria indicating that 2-5% of hospitalized cases with jaundice were caused by yellow fever (11).

Immunization programs

Yellow fever vaccine has been introduced into the Expanded Program of Immunization (EPI) in South America and Africa. In South America a high level of immunity exists in older children and adults in the endemic region, by virtue of long-standing policies of mass campaigns in most countries. This presents a significant obstacle to yellow fever urbanization, despite the continuing encroachment of St. aegypti mosquito into towns and cities. However, there is still a significant problem of immigration of unvaccinated persons from non-endemic (coastal) regions to the interior.

Recently, a policy of routine immunization at 9 months of age was adopted in South America, which would afford a seamless maintenance of the immune barrier. Implementation has been spotty, however. In 2004, only Ecuador, Venezuela and Trinidad achieved a high coverage of the target population (9 mo. old children).

As shown recently in Brazil, the virus can periodically invade non-endemic regions with unvaccinated populations, resulting in emergency immunization campaigns and a policy in some areas for ‘blocking’ immunization of towns in the transitional or border areas between the endemic area and receptive zone (5). However, the occurrence of serious adverse events has raised concern about over-utilization of the vaccine in areas at low risk of yellow fever. A recent analysis using a model for the proportion of the population residing in such areas that should be vaccinated to prevent a yellow fever outbreak while minimizing severe adverse events was lower than the proportion needed to prevent a yellow fever outbreak (6). Since advanced age is a significant risk factor for severe adverse events, limiting vaccinations to infants mini-
mizes the risk of these events (4) while ultimately providing a barrier to yellow fever (6).

In Africa, despite recommendations for introducing yellow fever vaccine to the Expanded Programme of Immunization (EPI) going back to 1988, little progress was made until 2000, when Global Alliance for Vaccines and Immunization (GAVI) undertook support for vaccine purchases. In 2000, 12 countries in the endemic region of Africa were implementing yellow fever vaccinations and coverage rates were generally low (figure 8) (18, 19). Five years later, the picture has changed dramatically, with 22 of the 33 countries having established a policy for yellow fever immunization, and 3 having achieved coverage of the target population of >80%, the minimum that would afford significant protection against an epidemic (1). Since catch-up immunization has not been performed, it will take many years to provide a barrier to epidemic spread.

Potential for spread of yellow fever

The possibility cannot be ignored that yellow fever will be introduced to densely populated coastal regions of South America infested with *Ae. aegypti*, or to areas in Asia, the Caribbean, Central or North America. The likelihood of such an occurrence, in which a viremic human (or possibly infected mosquitoes) serves as the source of introduction, is enhanced by rapid air travel. The disease is so lethal and relatively easily diagnosed that little delay is expected in recognizing it and mounting a mass immunization effort. WHO has pre-qualified vaccine produced by the major manufacturers, and production now totals 70 million doses/year. In addition, GAVI has funded the establishment of an emergency stockpile of 6 million doses, thus facilitating emergency control efforts and avoiding temporary shortages (19). Although scenarios can be constructed that would require a larger quantity of vaccine over a short period, this theoretical risk is balanced by surge capacity of vaccine manufacture to meet such emergencies.

Références bibliographiques