The Global Distribution of Yellow Fever and Dengue

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Abstract

Yellow fever has been subjected to partial control for decades, but there are signs that case numbers are now increasing globally, with the risk of local epidemic outbreaks. Dengue case numbers have also increased dramatically during the past 40 years and different serotypes have invaded new geographical areas. Despite the temporal changes in these closely related diseases, and their enormous public health impact, few attempts have been made to collect a comprehensive dataset of their spatial and temporal distributions. For this review, records of the occurrence of both diseases during the 20th century have been collected together and are used to define their climatic limits using remotely sensed satellite data within a discriminant analytical model framework. The resulting risk maps for these two diseases identify their different environmental requirements, and throw some light on their potential for co-occurrence in Africa and South East Asia.

1. INTRODUCTION

Yellow fever virus is the type virus of the family Flaviviridae (from the Latin flavus, meaning yellow), and is thought to have originated in West Africa (Cliff et al., 2004). It was one of the earliest viruses to be identified and linked to human disease. Although substantial variation exists among strains, they can be grouped into monophyletic geographical variants, called topotypes. African isolates are usually grouped into two topotypes, associated with East and West Africa (Deubel et al., 1986; WHO, 2001), although some studies have argued for up to five (Mutebi et al., 2001). Two more have been identified from South America, although one has not been recovered since 1974, suggesting that it may be extinct in the wild. There is no evidence for a difference in virulence between the topotypes (WHO, 2001).

Dengue virus is also a member of the family Flaviviridae, and is closely related to yellow fever virus. There are four serotypically distinct types of dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4). Although recombination occurs between strains of the same serotype, no inter-serotype recombination has been observed (Gubler and Kuno, 1997).

2. THE PATHOGENS

2.1. Yellow Fever

2.1.1. History—Yellow fever virus was probably introduced into the New World via ships carrying slaves from West Africa. The first recorded epidemics of yellow fever occurred in Mexico and Guadeloupe in 1648. Throughout the 18th and 19th centuries, regular and devastating epidemics of yellow fever occurred across the Caribbean, Central and South America, the southern United States and Europe. The impact of yellow fever prompted some American colonies to refuse entry to ships from infected areas (Pearson and Miles, 1980),
and later led to the establishment of formal quarantine arrangements (of the sort already in place in Europe as a consequence of the plague). Despite these measures, urban epidemics continued, and in 1793, approximately one in ten of the inhabitants of Philadelphia, USA (then home of the federal government) died during an epidemic of yellow fever. Mortality from yellow fever and malaria caused the failure of the French Panama Canal project in the 1880s and 1890s (McCullough, 1977; Gallup and Sachs, 2000). The Yellow Fever Commission, founded as a consequence of excessive disease mortality during the Spanish–American War (1898), concluded that the best way to control the disease was to control the mosquito. William Gorgas successfully eradicated yellow fever from Havana by destroying larval breeding sites and this strategy of source reduction was then successfully used to reduce disease problems and thus finally permit the construction of the Panama Canal in 1904. Success was due largely to a top-down, military approach involving strict supervision and discipline (Gorgas, 1915). In 1946, an intensive *Aedes aegypti* eradication campaign was initiated in the Americas, which succeeded in reducing vector populations to undetectable levels throughout most of its range.

The production of an effective vaccine in the 1930s led to a change of emphasis from vector control to vaccination for the control of yellow fever. Vaccination campaigns almost eliminated urban yellow fever but incomplete coverage, as with incomplete anti-vectorial measures previously, meant the disease persisted, and outbreaks in remote forest areas continued (Barros and Boecken, 1996; Vasconcelos et al., 2001).

### 2.1.2. Symptoms

The symptoms of yellow fever are very variable and depend on the severity of infection. Although a small proportion of infections are asymptomatic, victims typically develop a number of influenza-like symptoms including fever, joint pains and headache between three and six days after infection. Three or four days after the appearance of these symptoms they may disappear, and in most cases convalescence begins (Monath, 2001). In other cases, after a remission of 6–12 hours, febrile symptoms return accompanied by nausea, vomiting, epigastric pain, renal failure, jaundice (hence the common name for the disease) and haemorrhaging (Monath, 2001; WHO, 2001). Half of patients at this stage die within 10–14 days, but the remainder recover without significant organ damage. Immunity is lifelong following infection.

### 2.1.3. Epidemiology

Yellow fever virus circulates in both urban and sylvatic settings (Figure 1), involving several mosquito and vertebrate species. In the sylvatic cycle, mosquitoes such as *Aedes africanus* (in Africa) or *Haemagogus* species (in the Americas) act as the main vectors and monkeys as the primary host. Vertical transmission also occurs within the mosquito population, and may have an important role in maintaining the sylvatic cycle (Aitken et al., 1979; Fontenille et al., 1997). Infected mosquitoes occasionally bite unvaccinated forest workers such as hunters and loggers. This route of transmission of yellow fever is viewed as an occupational disease in parts of South America, and seldom causes epidemics.

Peridomestic mosquitoes biting both humans and monkeys are capable of sustaining small-scale epidemics of yellow fever in rural human populations. This role is played by a number of species in Africa (e.g. *Aedes simpsoni*), resulting in the epidemic form of yellow fever most commonly seen in recent decades. It is thought that *Aedes albopictus*, the Asian tiger mosquito, is capable of adopting a similar role (Gratz, 2004). From its natural distribution in south-east Asia, this species has been introduced and has become established in much of Central and South America, the Pacific, Australasia, Africa and areas of Europe during the 1980s and 1990s (CDC, 2001). When anthropophilic mosquitoes such as *Aedes aegypti* become infected, rapid human–human transmission may begin. In these circumstances, an epidemic of yellow fever may spread quickly in dense urban areas. Urban epidemics are the
form most feared by public health authorities, and may incapacitate significant proportions of the population of acity.

2.1.4. Distribution and Impacts—It was acknowledged by the Health Organization of the League of Nations (the forerunner to the World Health Organization (WHO)) that yellow fever was a severe burden on endemic countries. The work of Soper and the Brazilian Cooperative Yellow Fever Service (Soper, 1934, 1935a, b) began to determine the geographical extent of the disease, specifically in Brazil. Regional maps of disease outbreaks were published by Sawyer (1934), but it was not until after the formation of the WHO that a global map of yellow fever endemicity was first constructed (van Rooyen and Rhodes, 1948). This map was based on expert opinion (United Nations Relief and Rehabilitation Administration/Expert Commission on Quarantine) and serological surveys. The present-day distribution map for yellow fever is still essentially a modified version of this map.

At the beginning of the 21st century yellow fever has been estimated to affect as many as 200 000 people annually in the tropics of Africa and South America (Vainio and Cutts, 1998), and causes an estimated 30 000 deaths each year (Division of Epidemiological Surveillance and Health Situation and Trend Assessment, 1992). Approximately 2.5 billion people live within the current range of *Aedes aegypti* (Gubler, 1998), and must be considered at risk of either or both yellow fever and dengue. The rapid spread of *Aedes albopictus* in recent years has also increased the risk of epidemics (Knudsen, 1995; Tatem et al., this volume, pp. 293–343). Figure 2 presents the known global distribution of these two important vector species. In the past, the mortality rate arising from infection with yellow fever was much higher than it is today, due to inappropriate health care, or a lack of it altogether, but such death rates are now avoidable, although they are not always avoided. Urban health services may be overwhelmed by large numbers of patients, and this is likely to occur when levels of human immunity are low.

Yellow fever is conspicuously absent from Asia, despite multiple opportunities for introduction. This absence does not seem to be attributable to differences in the susceptibility of vectors, and all components of a suitable transmission cycle appear to be present (Vainio and Cutts, 1998). Race appears to affect susceptibility to dengue (Guzman et al., 1990), but there are no adequate comparable epidemiological studies of yellow fever susceptibility (Vainio and Cutts, 1998). Although there is some evidence that other flaviviruses may offer cross-protection against yellow fever (Gordon-Smith et al., 1962), why yellow fever does not occur in Asia is still unexplained.

2.1.5. Control—The first live-attenuated vaccine for yellow fever was developed between 1934 and 1935 in French West Africa (Durieux, 1956), and its use achieved a dramatic reduction in incidence within about five years of its introduction (Figure 3). Unfortunately, it was associated with a high risk of encephalitic reaction in children (3–4/1000, with a fatality rate of 38%), and its production was discontinued in 1980. The 17D live-attenuated vaccine still in use today was developed in 1936, and a single dose confers immunity for at least ten years in 95% of the cases. In a bid to contain the spread of the disease, travellers to countries within endemic areas or those thought to be ‘at risk’ require a certificate of vaccination; these countries are shown in Figure 4. The yellow fever certificate is the only internationally regulated certification supported by the WHO. The effectiveness of the vaccine reduces the need for anti-vectorial campaigns directed specifically against yellow fever. As the same major vector is involved, control of *Aedes aegypti* for dengue reduction will also reduce yellow fever transmission where both diseases co-occur, especially within urban settings.
2.2. Dengue

2.2.1. History—Probable epidemics of dengue fever have been recognised since at least 1779 (Rush, 1789), and have been recorded from Africa, Asia, Europe and the Americas since the early 19th century (Armstrong, 1923). Although it is rarely fatal, up to 90% of the population of an infected area can be incapacitated during the course of an epidemic (Armstrong, 1923; Siler et al., 1926). Widespread movements of troops and refugees during and after World War II introduced vectors and viruses into many new areas, and this trend has continued (Calisher, 2005) with the growth of global transport networks (Tatem et al., this volume, pp. 293–343). By the end of the 20th century, annual epidemics of dengue were occurring in many parts of Central and South America (Pinheiro, 1989; Rodriguez-Roche et al., 2005), throughout the Pacific Islands (Effler et al., 2005) and South East Asia and with occasional outbreaks in North Australia (Doherty et al., 1967) and Africa.

2.2.2. Symptoms—Infection with any of the four dengue serotypes may result in a spectrum of clinical manifestations. After an incubation period of around five to six days (Siler et al., 1926; Innis et al., 1988), patients develop symptoms including joint pain, fever and headaches (Halstead, 1997; Nisalak et al., 2002). Dengue fever has unsurprisingly been mistaken for yellow fever as well as other diseases including influenza, measles, typhoid and malaria (Hare, 1898; Siler et al., 1926; Lopez-Correa et al., 1979; Holmes et al., 1998). Although highly uncomfortable, dengue fever is rarely fatal and survivors appear to have lifelong immunity to the homologous serotype.

Far more serious is dengue haemorrhagic fever (DHF), where additional symptoms develop, including haemorrhaging and shock. The mortality from DHF can exceed 30% if appropriate care is unavailable. The most significant risk factor for DHF is when secondary infection with a different serotype occurs in people who have already had, and recovered from, a primary dengue infection. It is suggested that virus infection is enhanced by the presence of pre-existing heterotypic antibodies (Halstead, 1970, 1988; Halstead et al., 1980). Under this ‘antibody-dependent enhancement’ hypothesis, pre-existing antibodies bind to the heterotypic dengue virus particles but fail to neutralise them once cross-reactive antibodies have decayed below a certain level. These infectious antibody–virus complexes bind to receptors on macrophages more easily, resulting in a higher level of viral uptake. The presence of antibodies to a heterotypic serotype has been demonstrated to increase the ability of dengue virus particles to infect monocytes in both in vitro (Halstead and O’Rourke, 1977) and in vivo (Halstead, 1979) primate models, and enhancement appears in the sera of recently infected patients—i.e. those with neutralising levels of antibodies—if the sera are diluted (Kliks et al., 1989). As yet, a link has not been firmly established between increased viraemia and the pathophysiological changes seen in DHF (Halstead, 1979) and others have suggested that these may be related to T-cell activation (Rothman and Ennis, 1999; Zivna et al., 2002; Mongkolsapaya et al., 2003).

2.2.3. Epidemiology—As with yellow fever, dengue is thought to have originally been a sylvatic virus, and a complex sylvatic cycle involving multiple mosquito and vertebrate species still exists in the forests of South-East Asia (Knudsen, 1977) and West Africa (Diallo et al., 2003). Dengue has adapted to changes in human demography very effectively. The main vector of dengue is the anthropophilic Aedes aegypti, which is found in close association with human settlements throughout the tropics, breeding mainly in containers in and around buildings (Christophers, 1960; Sheppard et al., 1969; Southwood et al., 1972; Trpis and Hausermann, 1986), and feeding almost exclusively on humans (Christophers, 1960; Scott et al., 1993). As a result, dengue is essentially a disease of tropical urban areas, although occasional sylvatic outbreaks do still occur in areas of West Africa (Diallo et al., 2003). Both vertical (Rosen et al., 1985) and sexual (Rosen, 1987) transmissions of dengue
are possible in *Aedes aegypti*, but they occur at extremely low rates and are not thought to be epidemiologically significant. *Aedes albopictus* also transmits dengue in parts of Asia but is not as important, at present, as is *Aedes aegypti*.

DHF first came to attention in the 1950s and has since spread rapidly throughout the tropical world (Halstead, 2005). The first DHF epidemic was reported in Manila in 1953–1954, but cases of probable DHF can be found in the literature stretching back to 1779 (Rush, 1789; Halstead, 1997). Before 1970, only nine countries had experienced DHF epidemics, but by 1995 this number had increased fourfold (WHO, 2001). The appearance of DHF stimulated large amounts of dengue research, which established the existence of the four serotypes and the range of competent vectors, and led to the adoption of *Aedes aegypti* control programmes in some areas (particularly South-East Asia) (Kilpatrick *et al.*, 1970).

There is currently some debate over the taxonomy and nomenclature of Aedine mosquitoes (Diptera: Culicidae). A recent phylogenetic analysis suggested elevating the subgenus *Stegomyia* to full generic status, and *Aedes* to a supergenus (Reinert *et al.*, 2004), in which case *Aedes aegypti* would become *Stegomyia aegypti*. This proposal has attracted criticisms of both a theoretical and a practical nature, and the Walter Reed Biosystematics Unit has established a Mosquito Taxonomy Review Committee to help resolve the issue [http://wrbu.si.edu/forums/]. In this review, and others in this volume, the more familiar name, *Aedes*, is retained to avoid confusion until the situation is resolved.

**2.2.4. Distribution and Impacts**—Dengue case numbers have increased considerably since the 1960s; by the end of the 20th century an estimated 50 million cases of dengue fever and 500 000 cases of DHF were occurring every year (WHO, 2001). There have been several attempts to estimate the economic impact of dengue: the 1977 epidemic in Puerto Rico was thought to have cost between $6.1 and $15.6 million ($26–$31 per clinical case) (Von Allmen *et al.*, 1979), while the 1981 Cuban epidemic (with a total of 344 203 reported cases) cost about $103 million (around $299 per case) (Kouri *et al.*, 1989). Costs of non-epidemic dengue, including dengue fever, are difficult to estimate (Clark *et al.*, 2005; Meltzer *et al.*, 1998). Dengue is essentially an urban problem in the tropics, and urban populations are projected to increase from three to five billion by 2030, with much of this increase occurring in less-developed countries (United Nations, 2004; Hay *et al.*, 2005).

Large numbers of asymptomatic dengue infections have been confirmed in South-East Asia (Sangkawibha *et al.*, 1984; Burke *et al.*, 1988; Chen *et al.*, 1996; Porter *et al.*, 2005), the South Pacific (Maguire *et al.*, 1974) and South America (Kochel *et al.*, 2002; Teixeira *et al.*, 2002), and are suspected in areas of Africa (Saluzzo *et al.*, 1986). These asymptomatic cases may conceal the true extent of infection incidence and virus diversity in a population.

**2.2.5. Control**—There is no cure for dengue fever or for DHF. Currently, the only treatment is symptomatic, but this can reduce mortality from DHF to less than 1% (WHO, 2002). Unfortunately, the extent of dengue epidemics means that local public health services are often overwhelmed by the demands for treatment.

Vaccine development has been complicated by the potential risk of vaccination resulting in antibody-dependent enhancement of future heterotypic infection (Vaughn, 2000; Halstead and Deen, 2002), although a tetravalent vaccine is presently undergoing clinical trials (Bhamarapravati *et al.*, 2003).

The most common historical approach to limiting dengue was source control of *Aedes aegypti*. Although such programmes are capable of achieving significant reductions in the house index (the percentage of buildings positive for immature vectors) (Mendes Luz *et al.*,...
2003), they are labour-intensive, expensive to sustain and appear to be less effective than expected at preventing dengue transmission. An informative review of the pitfalls and progress experienced by *Aedes aegypti* control programmes is presented in Reiter and Gubler (1997).

Modern *Aedes aegypti* control programmes such as those in Singapore (Goh, 1995, 1997; Wilder-Smith *et al*., 2004) and Cuba (Spiegel *et al*., 2002) are also based on locating and eliminating domestic breeding sites, but growing prosperity in many areas has led communities to resent the invasion of their homes by control officials. Furthermore, short-term success generally lowers public perceptions of disease risk, and generates increased hostility to continued control attempts.

3. MATERIALS AND METHODS

3.1. Existing Maps

No serious attempts to update the yellow fever distribution map have been made since the first global map was produced in 1948, although part of the map for Africa was slightly amended in 1986 (WHO, 1986). The most recent global map, for the situation in 2003, was released in 2004 [http://www.who.int/ith/en]. Despite the implementation of vaccination programmes, attempts to eradicate the mosquito vectors and a substantially altered human population distribution and socio-economic status over the last 50 years, this map is still based on the earlier maps with relatively few significant changes. Endemicity is reported mostly at country level, and some countries are included that have not had reported outbreaks for at least two or three decades. While it is obviously wise to avoid underestimating the extent of a zoonosis such as yellow fever, overestimation of the current situation may lead to a dilution of control efforts through their application in places where they are not really required.

The latest distribution map for ‘all cause dengue’ (dengue risk irrespective of serotype) reports the global situation in 2003 [http://www.who.int/ith/en], but it is not clear how this map was derived. As with the yellow fever map, the dengue map provides an indication of the historical occurrence of this disease and again includes large areas (especially in Africa) that may indeed have the disease, but have never reported any cases of it. Thus, both the yellow fever and dengue maps could be improved upon, most efficiently through the use of modern mapping and modelling techniques. Attempts using climate data and logistic regression have been made for dengue with some success (Hales *et al*., 2002), but the global climate datasets used for this modelling have relatively coarse spatial resolution, as do the resultant maps. This paper applies discriminant analytical methods within an information theoretic approach (Rogers, this volume, pp. 1–35) to point records gleaned from archived reports and literature surveys, and high spatial resolution environmental information derived from satellites to create risk maps of environmental suitability for both diseases.

3.2. Archive and Literature Searches

A detailed search of the WHO library archives identified point records for yellow fever outbreaks between 1900 and 1959 (Boyce, 1906; Great Britain Colonial Office Yellow Fever Commission, 1915a,b and c; Noguchi *et al*., 1924; General Government of French West Africa, 1929; Sawyer, 1934; Soper, 1934, 1935a, b, 1955; Jorge, 1938; Bustamante, 1958; WHO, 1971). Serological data were not included because they confuse populations infected naturally with those protected by vaccination coverage. The location data were either digitised using ESRI ArcView 3.2 or geo-located using an online gazetteer [http://www.traveljournals.net/explore/index.html]. Between 1900 and 1959, a total of 450
locations of yellow fever outbreaks in Africa were identified, with a further 707 locations in the Americas.

Point records for yellow fever and dengue infections between 1960 and 2005 were gathered by querying the PubMed archives [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi] in conjunction with country names obtained from the GEOnet Names Server (GNS) [http://earth-info.nga.mil/gns/html/cntry_files.html]. This query was initially restricted to articles in English and with abstracts. The references were loaded into RefViz [http://www.adeptscience.co.uk/products/refman/refviz/info.html], which automatically groups them into clusters depending upon their key words. Clusters judged to be unlikely to contain spatial information were deleted. The abstracts of papers surviving this initial cull were then checked and references discarded that did not contain data that could be geo-referenced. A second reference search was later undertaken for both diseases, with no language restrictions and only in those countries that looked promising after the first search round. RefViz was again applied to filter the results. For yellow fever, a total of 663 references were initially downloaded from PubMed, reduced by 395 when unpromising keyword groups were deleted and a further 96 when the abstracts were read. The remaining 172 references provided 281 geo-referenced points of yellow fever occurrence. For dengue, a total of 1735 references were downloaded from PubMed, reduced by 781 when unpromising keyword groups were considered and by a further 77 after reading their abstracts. The remaining 877 references provided 897 geo-referenced dengue points.

The geo-referenced data points are shown in Figure 5 (yellow fever) and 6 (dengue). It is convenient to split the yellow fever map into two, for the periods 1900–1959 and 1960–2005, but the records for dengue are more sparse in the early years of the last century and so only a single map is shown, covering the period 1960–2005.

3.3. Yellow Fever Data

At the beginning of the 20th century, a large number of yellow fever epidemics were recorded in both African and American cities, and these occurred against a background of annual cases. Documentation for this period is relatively complete because there was a concerted effort at the time to eradicate the disease.

In Africa yellow fever was mainly a problem of the sub-Saharan countries of West Africa, but reached as far east as central Sudan and Kenya (Soper, 1955; Haddow, 1965; Reiter et al., 1998; Bell, 1999). There is little reason to think that the recorded distribution is an artefact of colonial data reporting. In the New World, a large number of outbreaks were reported in eastern Mexico and other Central American countries. At this time, yellow fever was an epidemic disease mainly of port cities, although a large number of inland reports came from south-eastern Brazil. These cases, and those from Columbia, were recorded at very high spatial densities with many fewer reports from the Amazon Basin.

The period between about 1950 and the 1970s was one of complacency about the control of yellow fever, probably arising from the feeling that yellow fever vaccination had solved the problem. Aedes aegypti control was reduced and overall disease record keeping appears to have diminished.

For the period 1960–2005, only 110 yellow fever points were recorded in Africa and 171 in South America. In both regions, these records more or less fall within the same areas of risk shown for the first half of the last century (Figure 5b compared with Figure 5a), although there is a noticeable lack of new records in Central America and proportionately more cases within the Amazon basin.
3.4. Dengue Fever Data

For the first half of the last century and up until 1960, there was little control directed specifically at dengue, although some control was achieved through the collateral impacts of yellow fever vector eradication programmes (most notably in the Americas). Information for this period is difficult to obtain, although known outbreaks are recorded predominantly in coastal ports. Large movements of susceptible populations during the Second World War led to a rise in recorded dengue cases (Gubler, 1997), especially, for countries in South-East Asia (Gubler, 2004). Dengue point records since 1960 are shown in Figure 6 (n = 897). Dengue has now firmly established itself in three geographical areas; South-East Asia, Latin America and throughout the Pacific islands, and seems to be consolidating itself in these areas, benefiting from local, large human populations. Reported outbreaks are clustered around the Caribbean, in southern Brazil, western India and Bangladesh and in countries surrounding the South China Sea. Dengue has long been thought to be widespread in Africa but case reporting remains very poor. In the absence of laboratory test facilities, it is likely that dengue fever, as opposed to DHF, would often be mistaken for other diseases such as malaria.

For both yellow fever and dengue, all presence records from 1960 to 2005 were used to construct the risk maps. For each disease, it was also necessary to identify areas of absence and this was done by sampling at random regions no closer than 0.5° and no farther than 10° from any recorded presence site. A total of 3500 absence points for yellow fever and 9000 absence points for dengue were selected in this way.

3.5. Environmental Data from Satellites

The environmental data used to describe the distributions of yellow fever and dengue were derived from the Advanced Very High Resolution Radiometer (AVHRR) on board the National Oceanographic and Atmospheric Administration (NOAA) satellites and cover the period from 1982 to 1999. These data are described in detail in Hay et al. (this volume, pp. 37–77) and are provided on the DVD accompanying this volume. Briefly, monthly maximum value composited AVHRR Channel 3, the derived Land Surface Temperature (LST) and the Normalized Difference Vegetation Index (NDVI) data were temporal Fourier processed to extract annual, bi-annual and tri-annual seasonal signals, which were captured as separate images showing the amplitudes and phases or timing of the first peak of each of the three signals (Rogers, 2000). In addition, the signal means, maxima, minima and variances were also available, as was a single digital elevation surface (DEM) derived from the GTOPO30 coverage [http://edcdaac.usgs.gov/gtopo30/gtopo30.asp]. All AVHRR data were originally produced and made available at a spatial resolution of 8 × 8 km in the Goode’s Interrupted Homolosine projection (James and Kalluri, 1994) and after Fourier processing were projected by bi-linear interpolation to latitude/longitude format at 0.10° spatial resolution. The DEM data at an original 30 arc second resolution (1/120th of a degree) were re-sampled to 0.1° resolution by averaging. Satellite and DEM data were later extracted for each of the disease presence and absence points and these data formed the training sets for model construction.

3.6. The Modelling Approach

The modelling approach followed that described by Rogers (this volume, pp. 1–35) and Rogers (2000). Briefly, non-linear discriminant analysis captured the covariance characteristics of sites of disease presence and absence and these were used to define the location within multivariate space of any point within the risk-mapped area. On this basis, the probability with which the point belonged to the category of disease presence or absence was calculated and this probability was entered into the final risk map. Disease presence and absence data were separately clustered before analysis into between one and eight clusters,
but the final results presented here used only three clusters each in all the models. Clustering splits data that may be non-multivariate normal in their overall characteristics into groups that are more nearly multivariate normal, and thus make the data comply with the assumptions of the discriminant methods used. It is often the case that the resulting clusters occupy separate geographical regions or areas where different vector species are important, so that what is initially a mathematical requirement of the methods used can also be justified on ecological and biological grounds.

During discriminant analysis ten variables were selected for each model in a step-wise inclusion fashion, using the corrected Akaike Information Criterion (AICc) as the basis for choosing the next variable to add to the model (Rogers, this volume, pp. 1–35). The AICc is one of a number of criteria that might be used for variable selection, and is a measure of the Kullback–Leibler information or distance statistic that measures how well the current model fits the data (Burnham and Anderson, 2002); the smaller the value of the AICc, the more accurate the model.

As was the case with a set of Rift Valley Fever data (Rogers, this volume, pp. 1–35) derived using the same literature search criteria as were used here, the point records for yellow fever and dengue are likely to be incomplete to a lesser or greater degree. Rogers (this volume, pp. 1–35) describes two ways of extracting maximum information from such sparse datasets—bootstrap sampling and environmental envelope expansion—and the former was used here. For each disease, 100 bootstrap samples were taken, with replacement, from the training set (300 presence and 300 absence points for Yellow Fever and 900 of each for dengue) and a separate model was constructed for each bootstrap sample, producing one output risk map. The 100 risk maps were then averaged to produce the results given here. Each risk map shows the average predicted maximum likelihood posterior probabilities of environmental suitability for the disease in question, i.e. the probability with which each pixel belongs to the category of disease presence. Areas of high probability of disease presence are more likely to harbour the disease than are areas of lower probability, or are at greater risk of invasion by the disease if it is not already present. Conventionally, risk maps of this sort are thresholded at a probability of 0.5 to produce a binary presence/absence map, but the continuous scale more appropriately captures the variable risk of disease occurrence. Diseases may occur in areas of low predicted risk, but they should do so only infrequently, and they should not persist. The thresholded versions of the maps were used to calculate the kappa index (κ) of model fit (Congalton, 1991; Ma and Redmond, 1995), which is based on the matrix of observed and predicted presences and absences of each model’s bootstrap sample of the training set data. Kappa varies from −1 (predictions completely opposite to observations) through 0 (model fit no better than random) to 1 (perfect fit) and Landis and Koch (1977) suggest the following ranges of agreement for the kappa statistic: poor, κ<0.4; good, 0.4<κ<0.75 and excellent, κ>0.75.

4. RESULTS

4.1. Risk Maps for Yellow Fever and Dengue

The predicted distribution maps are shown in Figure 7 (yellow fever) and 8 (dengue). Figure 7 (Figure 7 is Plate 6.7 in the Separate Colour Plate Section) for yellow fever shows that the predicted high-risk areas are quite localised within the broad boundaries of the 2003 WHO map for this disease, and that there are predicted areas of high risk outside these boundaries, most notably in parts of the Minas Gerais region, south east of Brasilia in Brazil, the common border region between the Democratic Republic of Congo and western Zambia, the eastern border region of Zimbabwe and in Swaziland. Regions of high risk well outside these boundaries are also predicted in Malagasy, Thailand and parts of Malaysia and Indonesia.
Figure 8 (Figure 8 is Plate 6.8 in the Separate Colour Plate Section) for dengue shows a similar patchy distribution of high-risk areas within WHO’s 2003 map for this disease, and high-risk areas outside these boundaries in the New World, most notably in southern Mexico. Given that some of the database points fall in these areas, it is clear that the WHO map should be extended to include more of this country. As expected, the predicted high-risk areas of Africa are much more extensive than the WHO map indicates, and are well outside any of the database records for this disease. This suggests an underreporting of dengue in Africa, for the reasons already mentioned. In India and South-East Asia the predictions more or less fill in the gaps between the database records. In Pakistan and India the predicted high-risk areas are well within the north-western boundary of the WHO map. Much of the northern part of the South-East Asian limits on the WHO map also seems to be at very low risk.

4.2. Overall Model Accuracy

The 100 bootstrap models for each disease were ranked in order of their AICc values, lowest (best fit) to highest (worst fit). Although there is no exact correspondence between the AICc values and the kappa index of agreement (since the former are based on probabilities and the latter on categorical assignment of those probabilities), there was, nevertheless, overall agreement between the figures. Thus, the mean kappa value for the top ten yellow fever models was 0.742 (s.d. = 0.023) and for the bottom ten was 0.644 (s.d. = 0.049). The equivalent figures for the dengue models were 0.700 (s.d. = 0.017) and 0.680 (s.d. = 0.011), respectively. These values indicate a good to excellent fit of the models to the point data.

4.3. Importance of Individual Variables

The summed Akaike weights of the models in which each variable occurred are given in Table 1 (yellow fever) and 2 (dengue). These sums are an indication of the importance of the individual variables regardless of the particular models in which, and other variables with which, they occurred (Rogers, this volume, pp. 1–35). Due to the ‘best’ model in each case being so much better than the second best, these summed weights depend a great deal on whether the variables were chosen in the best model. For example, the third variable in the list for yellow fever is the phase of the bi-annual cycle of the AVHRR channel 3 (MIR) variable (Table 1). This was selected in only 9 of the top 25 models, while the two variables above it in the list were selected 19 and 18 times in the same models. The summed Akaike weights for all 3 variables are the same (1.0) because they were all selected for the top two models. The seven variables following these three all have the same Akaike weight (0.99906); they too were selected by the top model but not by the second- and third-best models. Vegetation index variables occupy four of the top five positions in Table 1, suggesting that yellow fever is particularly sensitive to the greenness or humidity of the environment. The fact that the NDVI variance is the most important variable also suggests that the variability of greenness or humidity is key to the distribution of this disease.

For dengue the situation with regard to the importance of the top few variables is the same (Table 2), but in this case LST variables occupy three of the top five slots. Once again, the most important variable appears to be the variance of this variable. In the case of dengue, the variability of environmental temperature rather than of moisture appears to be key to its distribution.

4.4. Variability of Bootstrap Results

Some ideas of the different sets of variables selected during bootstrapping, and also of differences between the two diseases, are given in Figure 9a (yellow fever) and b (dengue). Each row in each image in Figure 9 (Figure 9 is Plate 1.3 (middle and right) in the Separate Colour Plate Section) refers to one of the bootstrap models that are arranged in rank order,
with 1 (lowest AICc value) at the top and 100 (highest AICc value) at the bottom. Each of the 31 columns on the right of the image indicates one of the satellite predictor variables available to describe the disease. The first column of these 31 columns is for the digital elevation layer (DEM), followed by three sets of 10 columns referring to the Fourier-processed AVHRR MIR, LST and NDVI imagery, respectively. Within each set, the Fourier layers are in the following order, from left to right: mean, phase of annual cycle, amplitude of annual cycle; phase of bi-annual cycle, amplitude of bi-annual cycle; phase of tri-annual cycle, amplitude of tri-annual cycle; maximum of fitted Fourier cycles (summed annual to tri-annual), minimum of fitted Fourier cycles and variance of the original signal. In any single model (row) the predictor variable selected first is coloured red, the second selected variable is coloured orange and so on according to the rainbow colour scale to the right of the image. Variables not chosen in any model are not coloured at all in that row. Images like these are able to show visually both any consistent changes (if they occurred) in the suites of variables chosen by models of increasing overall accuracy and whether or not individual variables were consistently selected within those suites. For yellow fever and dengue (as was also the case with Rift Valley fever—Rogers, this volume, pp. 1–35), there do not appear to be any gradual changes in the suites of chosen variables, but (different) individual variables are consistently chosen.

In the case of yellow fever (Plate 1.3 (middle)), the predominantly red line down the right-most column of the image indicates variable 31 in the variable list, which is the NDVI variance. Not only is this variable overall the most important in the 100 models, it is also often selected first in the step-wise selection process; the annual amplitude of NDVI (variable 24 in the list) sometimes replaces it as the first-selected variable.

In the case of dengue (Plate 1.3 (right)) the predominantly red line down the middle of the image indicates variable 10 in the variable list, which is the minimum of AVHRR channel 3 (MIR). This variable is often selected first, but LST variance (number 21 in the sequence) is also often selected first, second or third. Crucially, LST variance was selected first in the best model; hence its highest overall summed Akaike weight (see above).

4.5. Populations at Risk

To be at all useful, risk maps must also contribute to initiatives aimed at public health intervention. To do this it is first necessary to relate the risk maps to the human populations in the ‘at risk’ regions. The GRUMP human population surface (Balk et al., this volume, pp. 119–156) was aggregated to the same 0.1° resolution as the risk maps and the populations within each category of risk were read off from the resulting image. Figure 10 shows both the total human populations living within each risk category (Figure 10a) and the mean human population density per 0.10° grid square related to the same risk categories (Figure 10b). The total number of grid squares globally that fall within each category of risk is indicated by the dashed lines in Figure 10a. The first point to be noted is that large portions of the globe—the colder, temperate regions—are free of any risk from either disease (note that the graph does not show the total human population at zero risk of either disease, because it is so large). Taking the 0.50 probability of risk as the cut-off between disease absence (p<0.5) and presence (p≥0.5) reveals that approximately 33.3% of the Earth’s 6.05 billion people are at risk of dengue infection and 7.01% at risk of yellow fever infection (Figure 10a). Figure 10b shows that areas with the highest human population densities are associated with the higher risk categories for dengue and the lower risk categories for yellow fever. It seems that dengue is a disease associated with populous places of the globe, whereas yellow fever is associated with places where humans are relatively scarce. Curiously, the very highest risk categories of all are associated with low human population densities in the case of dengue (possible rural dengue in South-East Asia?), but high
population densities in the case of yellow fever (possible urban yellow fever in South America?) (Figure 10b).

These results allow further interpretations of Figures 7 and 8. These figures were produced using only the environmental conditions associated with yellow fever or dengue infections in the past; the human population map was not an input data layer to the models. Figure 7 shows parts of Asia that are climatically suitable for yellow fever (which does not occur there); these include populous areas, and it is possible that the pressures of the human population exclude this disease. This could be for a number of reasons, including the exclusion by high population densities of humans of critical sylvatic maintenance hosts of yellow fever and the bridge mosquito vectors that transfer infections to the urban transmission cycle. Conversely, Figure 8 shows that many areas of Africa are climatically suitable for dengue, which is seldom reported from the continent. It was suggested previously in this review that this may be because of underdiagnosis of dengue in Africa, but a further possibility is that the low human population density across much of Africa (compared with India and South-East Asia) in some way precludes the occurrence of dengue. The essentially domestic vector, *Aedes aegypti*, may not exist at the levels required to transmit dengue, except in heavily populated places that provide just the right sorts of conditions for this vector species. If this is the case, any future increase of human populations in Africa, and their increasing urbanisation, may be associated with an increase in dengue across the continent, which is clearly already climatically suitable for this disease (Figure 8).

5. DISCUSSION

The models presented here are based purely on outbreak data. A large number of protection test surveys were undertaken as part of the yellow fever monitoring programmes (Beeuwkes et al., 1930, 1934; Beeuwkes and Mahaffy, 1934; Sawyer and Whitman, 1936), but these data were not included in the models since some of them refer to immunity following vaccination rather than naturally acquired infection.

Future models of both diseases could be improved by incorporating information about the distributions of vector (Kumm, 1931; Whitman, 1951) and reservoir species (Balfour, 1915; Findlay et al., 1936; de Thoisy et al., 2004), either from point records or from models (Hopp and Foley, 2001) and the distribution of the human host populations (Balk et al., this volume, pp. 119–156).

The restriction of yellow fever to Africa and South America has long been a puzzle (Bell, 1999; Monath, 2001). The present models indicate an area of high suitability for yellow fever in eastern Thailand and other areas of lower suitability for this disease in parts of Malaysia and Indonesia. Dengue occurs in all of these places, but the two diseases do not appear to co-occur. Explanations for this lack of co-existence include failed introduction prior to the modern transportation era (Gubler, 2002), the restriction of yellow fever outbreaks to communities which do not undertake international travel (Monath, 2001), cross protection by hyperendemic dengue (Theiler and Anderson, 1975) and low vector competence (Beaty and Aitken, 1979). The very different human population densities under which each disease appears to thrive (Figure 10) will tend to prevent their co-existence. Africa at the present time provides a test for some of these hypotheses. Parts of West Africa are predicted to be highly suitable for both diseases, while central parts of the Democratic Republic of the Congo (aka Zaire) are predicted suitable only for dengue (Figures 7 and 8). Does dengue occur only or mostly in the latter? If dengue really only thrives in populous areas, will dengue increase as Africa’s population increases?
6. CONCLUSION

Eradication attempts, when they fail, become merely temporary control measures and when these in turn end, or are underfunded, the controlled diseases can return. Devastating outbreaks of yellow fever in the 1970s and 1980s (Gubler, 2004), an expanding distribution of *Aedes aegypti* from their post-control levels (Gubler, 1998), the appearance of DHF and a resurgence of dengue from the 1970s, all demonstrate the resilience of yellow fever and dengue in the face of our attempts to control them globally. Figure 11 shows the annual occurrences of yellow fever outbreaks in South America and Africa since 1960. It suggests a period of relative quiescence in South America in the last 20 years, but a trend to increasing frequency of outbreaks in Africa over the same period of time. In the two decades before this period, the situation was, if anything, reversed. It is unlikely that any static risk map will capture this dynamic situation, and it is suggested that the risk-mapping approach presented here not only delivers maps which more accurately reflect current disease situations, but can also become part of disease early warning systems, if the models are driven by new disease records and contemporary satellite data which are now freely available from a variety of sources (Hay *et al.*, this volume, pp. 37–77).

A major concern is that the rise of international sea and air traffic connects infected with suitable but presently uninfected regions of the globe and also connects remote infected regions in which different disease serotypes occur (Tatem *et al.*, this volume, pp. 293–343). Vector and disease spread to new regions seems almost inevitable, as are the consequences of co-circulation of different serotypes. These concerns have been in the minds of health officials for some time (Mhatre, 1934; Massad *et al.*, 2001), but have never been satisfactorily addressed. Given that we now have a semi-quantitative way of dealing with transportation network risks (Tatem *et al.*, this volume, pp. 293–343) and with habitat suitability for each disease (this review), these concerns can now be quantified and perhaps prioritised.

The maps presented in this review are based solely on a pixel’s environmental suitability for yellow fever and dengue, as judged by the locations of past cases of these diseases recorded in the literature, and the satellite measures of environmental conditions in these places. If, as Rogers points out (this volume, pp. 1–35), “All maps are wrong; but some are useful”, it is now timely to see just how useful are satellite-informed, dynamic risk maps of vector-borne diseases for use in reconnaissance, surveillance and control. The relatively large discrepancies between the present ‘standard’ WHO maps for these two diseases on the one hand, and both the databases gleaned from the literature of the past 45 years and the predicted risk maps arising from them on the other, suggest that any effort put into improving existing maps should rapidly result in improvements in the maps, the data and therefore future generations of risk maps.

**Acknowledgments**

The authors are grateful to Dr. Carlos Guerra and Alya Dabbagh (WHO) for support in yellow fever data gathering, Dr. Andy Tatem for supplying Figure 2, Ben McCormick for discussions and Dr. Bethan Purse and the series editors for comments on the manuscript. AJG was funded by European Union grant GOCE-2003-010284 EDEN and the paper is catalogued by the EDEN steering committee as EDEN0010 [http://www.eden-fp6project.net/]. The contents of this publication are the sole responsibility of the authors and do not reflect the views of the European Union. AJW is funded by a University of Oxford Newton–Abraham Studentship in the Biological Sciences. SIH is funded by a Research Career Development Fellowship from the Wellcome Trust (no. 069045). SIH and DJR thank Monica Myers for continued support through the International Research Partnership for Infectious Diseases (INTREPID).
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Figure 1.
Yellow fever transmission cycles for (a) South America and (b) Africa. Simian host species in South America include Alouatta sp., Ateles sp., Callithrix sp., Cebus sp. and Saimiri sp. while those in Africa include Colobus abyssinicus, C. polycomos, C. badius, Cercopithicus sp., Cercocebus sp., Erythrocebus sp., Papio papio, P. anubis and Pan troglodytes.
Figure 2.
Global distribution of *Aedes aegypti* (top) and *Aedes albopictus* (bottom), two important vector species of yellow fever and dengue. *Aedes albopictus* distributions are provided at national scale. Australia, New Zealand and South Africa have all reported mosquito interception at ports (see Tatem et al., this volume, pp. 293–343). Source: Center for International Earth Science Information Network (CIESIN) [http://www.ciesin.org/docs/001-613/map15.gif], supplemented with information from Gratz (2004); Gubler (2003); Lounibos (2002); Medlock et al. (2005); Moore (1999); and Moore and Mitchell (1997).
Figure 3.
Plot of the number of yellow fever cases and the number of vaccinations in French West Africa for the period of 1934–1953, demonstrating the effect of the French vaccine on case numbers. Source: Vainio and Cutts (1998).
Figure 4.
Yellow fever vaccination certificate requirements by country. □E1 requirements, □E2 requirements □E3 requirements ■E4 requirements ■E5 requirements. There are five levels of certification: E1—immunisation is an essential requirement for entry to the country concerned and a certificate is required, except for infants under one year, E2—immunisation is an essential requirement for entry to the country concerned and a certificate is required (except for infants under one year) unless arriving from non-infected areas and staying for less than two weeks, E3—immunisation is an essential requirement for entry to the country concerned and a certificate is required if the traveller arrives from an infected country or area, E4—immunisation is an essential requirement for entry to the country concerned and a certificate is required if arriving within six days of having visited an infected country, E5—immunisation is an essential requirement for entry to the country concerned and a certificate is required for entry to the country from endemic areas, travelling to Easter island. Source: From data obtained at [http://www.dh.gov.uk/PolicyAndGuidance/HealthAdviceForTravellers/GeneralHealthAdvice/Diseases/DiseasesArticle/fs/en?].
Figure 5.
Yellow fever outbreak distribution for 1900–1959 (top) and 1960–2005 (bottom). The maps are displayed between 40°N and 40°S as these latitudes encompass all known areas of the disease.
Figure 6.
All-sera dengue outbreak distribution for 1960–2005. The map is displayed between 40°N and 40°S as these latitudes encompass all known areas of the disease.
Figure 10.
(a) Total numbers of humans within each category of yellow fever or dengue risk as shown in Figures 8 and 9 (thick lines, millions scale) and numbers of 0.10° grid squares within each risk category (dashed lines, thousands scale). (b) Mean human population density per 0.10° grid square for each category of yellow fever and dengue risk.
Figure 11.
Reported number of yellow fever outbreaks per year per continent. Source: Weekly Epidemiological Record archives.
Plate 6.7.
Risk map for yellow fever. This risk map is the average of 100 bootstrap models each based on a sample of 300 presence and 300 absence pixels selected at random with replacement from the training set for this disease. Risk is on a probability scale from zero to 1.0. Probabilities from 0.0 to 0.49 are coloured green (darker to lighter) and indicate conditions not suitable for the disease (i.e. predicted absence of disease). Probabilities from 0.50 to 1.0 are coloured yellow through to dark red, indicating conditions increasingly suitable for the disease. The database observations of presence are indicated by the blue dots and the WHO 2003 map for yellow fever by the thick black outline.
Plate 6.8.
Risk map for dengue. This risk map is the average of 100 bootstrap models each based on a sample of 900 presence and 900 absence pixels selected at random with replacement from the training set for this disease. Risk is on a probability scale from zero to 1.0. Probabilities from 0.0 to 0.49 are coloured green (darker to lighter) and indicate conditions not suitable for the disease (i.e. predicted absence of disease). Probabilities from 0.50 to 1.0 are coloured yellow through to dark red, indicating conditions increasingly suitable for the disease. The database observations of presence are indicated by the blue dots and the WHO 2003 map for dengue by the thick black outline.
Plate 1.3.
Results from the 100 bootstrap models for (left) Rift Valley Fever, (middle) Yellow Fever and (right) Dengue. Each row in the image refers to one of the models, which are arranged in rank order, with 1 (lowest AIC\(_c\) value) at the top and 100 (highest AIC\(_c\) value) at the bottom. Each of the 31 columns on the right of the image indicates one of the satellite predictor variables available to describe the disease. The first column of these 31 columns is for the digital elevation layer or DEM. There then follow three sets of 10 columns referring to the Fourier-processed AVHRR MIR, LST and NDVI imagery. These layers are in the following order: mean, phase of annual cycle, amplitude of annual cycle; phase of bi-annual cycle, amplitude of bi-annual cycle; phase of tri-annual cycle, amplitude of tri-annual cycle; maximum of fitted Fourier cycles (summed annual to tri-annual), minimum of fitted Fourier cycles and variance of the original signal. In any single model (row) the top (i.e. first selected) predictor variable is coloured red, the second most important variable is coloured orange and so on according to the rainbow colour scale to the right of the image. Variables not chosen in any model are not coloured at all in that row. The red line down the first image indicates variable 14 in the variable list, which is the annual amplitude of LST. This variable is consistently chosen in all RVF models, and is usually the most important variable, but there is no other single variable which is consistently chosen second. (The left-most column refers to the model number in the sequence; this, and the grey area to the left of the variable columns should be ignored.) The other two images may be similarly interpreted (see Rogers et al., this volume, pp. 181–220, for more details).
### Table 1

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Note: Summed Akaike weights (second column) for the top predictor variables (first column) of the 100 yellow fever bootstrap models used to produce Figure 7 (see text for details). The mean ranks (i.e. the order in which the variables were selected, where rank 1 = the first selected variable, rank 10 = the tenth selected variable and all non-selected variables are given a rank of 11) are given in the third column, and the number of times (out of 100 models) each variable was selected is given in the final column.

Key to variable names: **wd10** refers to AVHRR data at 0.10° resolution in the latitude/longitude format, **03** refers to the AVHRR channel 3 (MIR), **07** to LST and **14** to Normalized Difference Vegetation Index (NDVI) data; **a1**, **a2** and **a3** refer to the amplitudes of the annual, bi-annual and tri-annual cycles, respectively, of temporal Fourier processed imagery and **p1**, **p2** and **p3** to their corresponding phases (timing of the first peak); **mn** and **mx** refer to the minimum and maximum and **vr** to the variance.
Dengue model predictor variables

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Note: Summed Akaike weights (second column) for the top predictor variables (first column) of the 100 dengue bootstrap models used to produce Figure 8 (see text for details). The mean ranks (i.e. the order in which the variables were selected, where rank 1 = the first selected variable, rank 10 = the tenth selected variable and all non-selected variables are given a rank of 11) are given in the third column, and the number of times (out of 100 models) each variable was selected is given in the final column.

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