Air travel and vector-borne disease movement

A. J. TATEM[1,2,3]*, Z. HUANG[1,2], A. DAS[2], Q. QI[1], J. ROTH[4] *and* Y. QIU[1,2]

[1] *Department of Geography, University of Florida, Gainesville, USA*
[2] *Emerging Pathogens Institute, University of Florida, Gainesville, USA*
[3] *Fogarty International Center, National Institutes of Health, Bethesda, USA*
[4] *School of Public Health and Health Services, The George Washington University, Washington DC, USA*

(*Received 28 November 2011; revised 7 February 2012; accepted 8 February 2012; first published online 23 March 2012*)

SUMMARY

Recent decades have seen substantial expansions in the global air travel network and rapid increases in traffic volumes. The effects of this are well studied in terms of the spread of directly transmitted infections, but the role of air travel in the movement of vector-borne diseases is less well understood. Increasingly however, wider reaching surveillance for vector-borne diseases and our improving abilities to map the distributions of vectors and the diseases they carry, are providing opportunities to better our understanding of the impact of increasing air travel. Here we examine global trends in the continued expansion of air transport and its impact upon epidemiology. Novel malaria and chikungunya examples are presented, detailing how geospatial data in combination with information on air traffic can be used to predict the risks of vector-borne disease importation and establishment. Finally, we describe the development of an online tool, the Vector-Borne Disease Airline Importation Risk (VBD-Air) tool, which brings together spatial data on air traffic and vector-borne disease distributions to quantify the seasonally changing risks for importation to non-endemic regions. Such a framework provides the first steps towards an ultimate goal of adaptive management based on near real time flight data and vector-borne disease surveillance.

Key words: Air transport network, imported disease, malaria, chikungunya, *Aedes albopictus*.

INTRODUCTION

Initially, infectious diseases could spread only as fast and far as people could walk, then as fast and far as horses could gallop and ships could sail. With the advent of truly global travel, the last five centuries have seen more new diseases become potential pandemics (Karlen, 1995), with the rate of diseases that are 'emerging' increasing (Jones *et al*. 2008). The current reach, volume and speed of travel are unprecedented, with human spatial mobility increasing in high income countries by over 1000-fold since 1800 (Wilson 1995, 2003). Aviation in particular has expanded rapidly as the World economy has grown, with worries about its potential for spreading disease arising with the establishment of commercial aviation (Massey, 1933).

Air travel has changed the epidemiological landscape of the world over the last half century, providing routes from one side of the Earth to the other that can be traversed by an infected person in significantly shorter times than the incubation period of the majority of infectious diseases. This epidemiological impact has prompted a rethinking of global disease management (World Health Organisation, 2007), with pandemic control relying less and less on conventional spatial barriers as the global air network continues to expand. Moreover, the speed of air travel has meant that prompt surveillance and rapid reporting now play a critical role in preventing the spatial spread of a disease, while mathematical models are becoming more central in identifying unusual behaviour in disease trends. Finally, the high cost of surveillance makes sampling design and the development of cost effective monitoring and testing approaches vitally important in effective epidemic early-warning systems (Haggett, 2000). While work on these factors is becoming sophisticated for directly-transmitted infections, our understanding of the role of modern air travel in global vector-borne disease epidemiology remains relatively poor. In this paper, we review existing knowledge, and highlight the potential of interdisciplinary geospatial approaches to fill gaps and provide a basis for adaptive management tools.

AIR TRAVEL EXPANSION

Today, more than two billion passengers take commercial flights every year (IATA, 2010). Passenger numbers have grown at nearly 9% per annum since 1960, with air-freight traffic showing similar changes (Upham *et al*. 2003). While the recent global economic downturn resulted in a slow-down of growth in many parts of the world, the level of air traffic is still now 4% above the pre-recession peak of early 2008 (IATA, 2010). Moreover, many regions are still showing rapid expansion, such as India

* Author for correspondence: Dr Andrew J Tatem, Emerging Pathogens Institute, University of Florida, Gainesville, FL. USA. E-mail: Andy.Tatem@gmail.com; Tel: 352-273-9373. Fax: 352-273-9496

Parasitology (2012), **139**, 1816–1830. © Cambridge University Press 2012
doi:10.1017/S0031182012000352

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

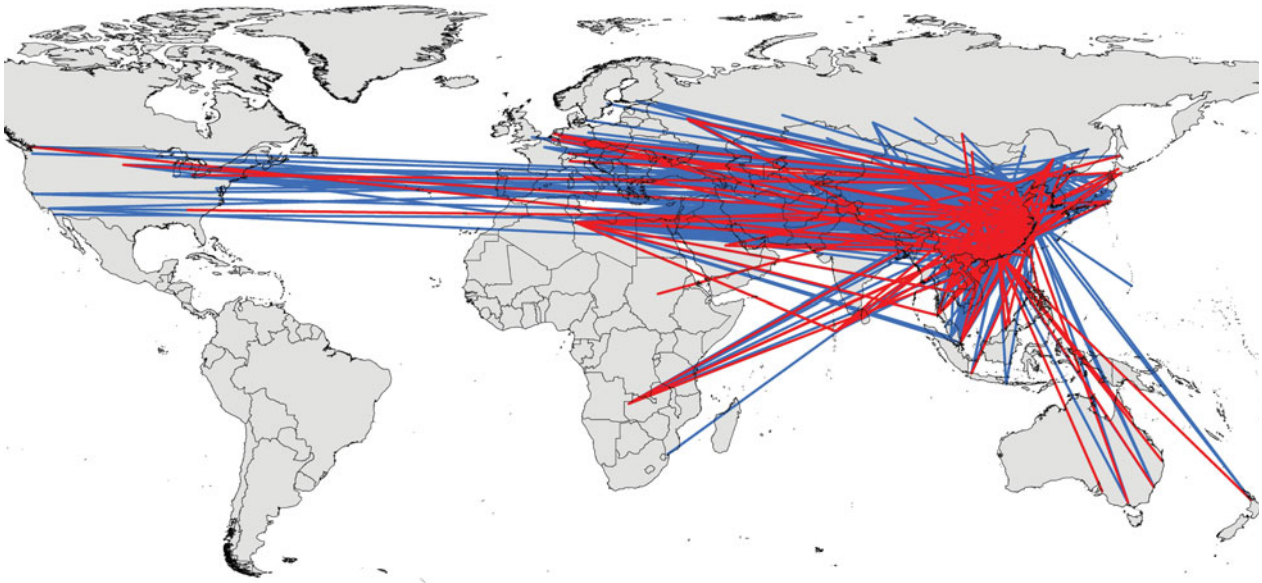

Fig. 1. Direct flight connections to and from China in 2010 and 2011. Routes operating in 2010 are shown in blue, while new routes added in 2011 are overlaid on top in red. For clarity, all routes are shown as straight lines, rather than actual great circle routes and trans-Pacific routes to/from China are shown as connecting in the opposite direction to avoid broken lines on the map.

and China, as their economies continue to grow. Fig. 1 demonstrates such trends for China, showing the large number of new routes initiated in 2011 as the country continues to expand its influence abroad. Though not shown in Fig. 1, this expansion also includes more frequent and larger capacity flights operating on existing routes. Globally, the interconnectivity brought about by air travel has had a profound impact on epidemiological dynamics, and continued growth will almost certainly result in more significant changes.

AIR TRAVEL AND DIRECTLY TRANSMITTED DISEASES

The air transportation system is responsible, indirectly, for the global propagation of directly-transmitted diseases such as influenza and severe acute respiratory syndrome (SARS). It plays a role for certain diseases that is analogous to that of the web of human sexual contacts for the propagation of HIV and other sexually transmitted infections (Guimera *et al*. 2005). Previous studies have suggested that data on air travel can be used to predict the spread of newly emerged human pathogens and better target public health measures (Colizza *et al*. 2006).

Numerous approaches have been developed which attempt to capture the possible future movements of newly-emergent communicable diseases through global and local transport networks (Thomas, 1992; Haggett, 2000). While the movements of pandemics are notoriously unpredictable (Thomas, 1992), those models that can be calibrated using data from previous epidemic events are perhaps the ones that stand the best chance of being used to predict the spread of communicable diseases in the future, enabling the construction of early warning systems and forming a basis for the planning of control strategies (Haggett, 2000). Such an approach was demonstrated by Rvachev and Longini (1985) who showed the diffusion of the 1968–9 influenza pandemic to be predictable through a model based on the air travel network of the time. Incidence data from the pandemic origin, Hong Kong, were used to estimate model parameters, such as contact level between susceptible and infectious individuals, time taken in latent and infectious states and fraction of people susceptible to the virus. Annual average daily air passenger numbers between 52 cities were then used to derive probabilities of travel between the cities. Finally, the seasonality of influenza was taken into account by applying a scaling factor to northern and southern hemisphere city contact level parameters to mimic the hemispheric swing of influenza epidemics. This model was later updated to provide the basis for predictive models of the spread of influenza, smallpox, SARS and other infectious agents through the global transportation network (Longini *et al*. 1986; Dye and Gay, 2003; Grais *et al*. 2003; Vogel, 2003; Hufnagel *et al*. 2004).

More recently, the H1N1 pandemic, development of network modelling approaches and increasing computing power have prompted both more sophisticated modelling and a better understanding of the role of global air travel in directly transmitted disease spread. Studies have examined the interplay between commuting flows and air travel flows in impacting pandemic influenza (Balcan *et al*. 2009), the role of air network structure on the predictability of global epidemics (Colizza *et al*. 2005, 2006), the impacts

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

of vaccination (Kenah *et al*. 2011) and the effects of travel restrictions on pandemic spread (Bajardi *et al*. 2011). Moreover, research has expanded in scope to include examination of the role of trade and health-care resources in addition to air traffic (Hosseini *et al*. 2010), and the development of publicly available models that draw on a wide range of datasets (Van den Broeck *et al*. 2011). Finally, recent work demonstrated the need for more complete data on air travellers and the handling of such data in mathematical models of disease spread (Johansson *et al*. 2011).

Clearly, the air transport network plays a much more indirect role in the spread of vector-borne diseases, due to the requirements for not only movement of infected passengers or vectors, but also the availability of competent vectors upon arrival to facilitate onward spread. Nevertheless, increases in reported rates of imported vector-borne infections around the world, the establishment of exotic vectors and occasional outbreaks of vector-borne disease sparked by incoming air travellers, are all evidence of the role that air travel is playing in a changing global epidemiology. The size and predictability of this impact remains poorly understood compared to directly-transmitted diseases however, and in the remainder of this article, we discuss current understanding, modelling approaches and knowledge gaps still to be filled regarding the role of air travel in the movement and spread of vector-borne diseases.

MOVEMENTS OF VECTORS VERSUS DISEASE

Substantial evidence exists documenting examples of both vector-borne diseases and the vectors that carry them being transported between distant locations via air travel. The rates of importation of disease vectors (infected or non-infected) versus infected passengers appear to be very different however. While imported vector-borne disease infections in air travellers are common and number tens of thousands each year into non-endemic high income countries (Jelinek *et al*. 2002; Wichmann and Jelinek, 2004), disease vectors appear to be relatively rarely imported, and their establishment in a new location is an even rarer event (Lounibos, 2002).

Aircraft and ships are believed to be directly responsible for rapid expansion in the range of many plants and animals via inadvertent transport (Perrings *et al*. 2005), including some of the World's principal disease vectors (Lounibos, 2002). The global air network enables many of the World's most isolated and diverse ecosystems to become connected and aids the movement of organisms, including disease vectors, to new habitats where they can become damaging invasive species, economically and health-wise (Tatem *et al*. 2006*a*; Tatem and Hay, 2007). Aircraft were recognized as a mechanism of transport of undesirable insects, especially mosquitoes, not long after the implementation of commercial, transcontinental flights (Massey, 1933; Griffits and Griffits, 1931). Fumigation, or 'disinsection' of aircraft arriving from the tropics, as well as insect control at receiving airports, were recommended to prevent the establishment of undesirable pests and disease vectors that might hitchhike aboard flights (Williams, 1940). Malaria epidemics in northeastern Brazil vectored by *Anopheles gambiae*, possibly transported on aircraft, though more likely a steamship from Dakar (Killeen, 2003), heightened concerns about the dangerous consequences of vector arrivals aboard international flights. Mosquitoes representing five genera were identified from inspections of aircraft arriving in northeastern Brazil from Africa in 1941–1942 (Soper and Wilson, 1943), while more recently, inspections of aircraft during a three week period in 1994 produced estimations that 2000–5000 anopheline mosquitoes were imported into France at a rate of 8–20 mosquitoes per flight (Gratz *et al*. 2000). Given such findings and the ever-increasing volume of air traffic, it is perhaps surprising that very few disease epidemics have been associated with the arrival of vectors via aircraft, though the establishment of West Nile virus in the US has been linked to the possibility of infected mosquito importation by air (Kilpatrick, 2011). Mosquitoes can survive moderately high atmospheric pressures aboard aircraft (Laird, 1984) and can be transported alive between international destinations, even in wheel bays (Russell, 1987). However, the reason behind the lack of establishment or epidemics is likely a case of sheer numbers. Those disease vectors that make it onto a flight, survive it, then disembark to a new location are likely comprised of very small numbers of adults – this contrasts with examples from cargo shipping of the discoveries of large numbers of eggs, and the long list of cases of mosquito invasion success through ship-borne introductions (Lounibos, 2002).

Air travel likely plays a much more significant role in moving the vector-borne disease (via infected passengers) than in moving the vector itself. It provides rapid and wide-reaching connections between outbreaks or high levels of endemicity and susceptible vector populations elsewhere in the world. The numbers of reported imported cases of notifiable vector-borne infections in non-endemic countries provide an indication of the rate at which infected travellers are arriving, but this likely involves significant under-reporting in terms of actual case numbers. For malaria, around 10,000 imported cases imported to high-income countries are reported each year, but the true figure may be over 25,000 (Franco-Paredes and Santos-Preciado, 2006). Up to 8% of travellers to the developing world become ill enough to seek health-care upon returning home, with a relatively substantial proportion of these suffering from vector-borne infections (Freedman *et al*. 2006). Imported case rates also vary significantly by traveller group, with migrant residents of high income

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

countries who return home to visit friends and relatives being particularly at risk, especially for malaria (Franco-Paredes and Santos-Preciado, 2006). The expansion of air travel has fuelled many of these trends, with case numbers often mirroring trends in travel to certain high risk locations (see example malaria analysis later in this article), modified only by efforts to promote awareness of risks, as well as prophylaxis, bed-net and insecticide use. With imported vector-borne infections placing a financial and operational burden on health systems in non-endemic countries, as well as the risk of onward transmission and even establishment, as in the case of West Nile virus (Kilpatrick, 2011), the development of tools for assessing the spatiotemporal risks of importation could bring substantial benefits.

VECTOR-BORNE DISEASE DISTRIBUTIONS AND CONNECTIVITY

Defining the extent of infectious diseases as a public health burden and their distribution and dynamics in time and space are critical to disease monitoring, control and decision-making. The epidemiology of many vector-borne diseases makes health system-based surveillance-based methods for estimating populations at risk and disease burden problematic because a large proportion of cases do not seek treatment, and in many resource-poor areas there is significant under-reporting anyway (Gething *et al*. 2006; Health Metrics Network, 2005; Murray *et al*. 2004). Meanwhile susceptibility and transmissibility of diseases can vary across differing population densities, and demographic and socioeconomic groups due to differences in immunity, mobility, contact patterns and health status (Riley, 2007; Kubiak *et al*. 2010). Cartographic and spatial modelling approaches have proven to be effective in tackling these factors, through using community surveys to assess prevalence rates, and geostatistical approaches combined with covariates to predict prevalences at unsampled locations (Brooker *et al*. 2002; Ferguson *et al*. 2005; Hay *et al*. 2010). Such approaches can help characterize large-scale patterns of disease spread to evaluate intervention impact (Riley, 2007) and produce globally consistent measures of morbidity of known fidelity, often the only plausible method in many African countries where surveillance data are incomplete, unreliable and inconsistent (Gething *et al*. 2006; Cibulskis *et al*. 2007; World Health Organization 2008).

The spatial modelling of vector and vector-borne disease distributions is reliant upon the collation of georeferenced samples informing on either the presence of a disease or vector, or its prevalence. Examples of such datasets are those from global surveillance (Brownstein *et al*. 2008), or collected from field surveys on vector presence (Moffett *et al*. 2009), or disease prevalence (Guerra *et al*. 2007). Relationships between the presence/prevalence of a disease or vector and environmental, climatic and physical covariates (Hay *et al*. 2006; Scharlemann *et al*. 2008; Tatem *et al*. 2008) can then be exploited to build statistical predictive distribution models (Rogers, 2006; Elith *et al*. 2006). Moreover, by setting these in a Bayesian framework, full predictive posterior distributions can be obtained, facilitating explicit measures of mapping uncertainty (Patil *et al*. 2011). Examples of global distribution maps include *P. falciparum* malaria (Hay *et al*. 2009; Gething *et al*. 2011), dengue and yellow fever (Rogers *et al*. 2006) and Anopheles species (Sinka *et al*. 2010*a*, *b*, 2011). Such predicted global distribution maps, when combined with data on human movements, can then form the basis for models of infection movement risk (Tatem *et al*. 2009; Tatem and Smith, 2010; Le Menach *et al*. 2011).

The linkage of disease and vector distribution maps with air travel network data offers great potential for infection importation risk assessment and the modelling of vector-borne disease spread, and this is explored in the remainder of this article. Such distribution maps, however, represent static pictures of relatively long term (>1 year) disease prevalence and vector presence. Ideally, the substantial climate-driven seasonal fluctuations in disease risk and vector densities should be accounted for. Exploiting the richness of spatial climate data now available offers solutions here. The current architecture of the global air network provides links between regions of high climatic similarity, but that are spatially distant (Tatem and Hay, 2007). These linkages change seasonally, showing greatest overall climatic similarity in June, July and August, when long-haul routes link climatically similar regions around the globe (Tatem and Hay, 2007). If a vector or an infected individual arrives in a new location via air travel, the risk of the vector establishing or the infection being passed on to local vector populations is often dependent upon the time of year of arrival. The arrival of an individual infected in a chikungunya outbreak occurring in February in Reunion (the time of year climatically suitable for *Aedes albopictus* activity there) in Milan will present no risk of onward transmission, due to the cold February climate in Italy being not conducive for *albopictus* activity. However, a similar arrival from India (where climatic conditions are suitable for year-round transmission) in July presents a much greater risk (Charrel *et al*. 2008). By utilizing gridded climate data to measure climatic similarity between origin and destination locations with known presence of a suitable vector, and adjusting for flight passenger numbers as an additional measure of risk, these factors can be accounted for (Tatem *et al*. 2006*a*, *b*). The potential for undertaking such analyses, making use of the range of datasets now available and described briefly above, is explored in the following sections.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

SPATIAL APPROACHES TO UNDERSTANDING AND PREDICTING RISK

Given the vast range of complicating factors, no model can be expected to predict the spread of an infectious disease pandemic with complete accuracy. Modelling can, however, improve our understanding of the driving factors behind epidemiological processes, offer quantitative assessments of risk for improved targeting of surveillance and identify possible interventions for a range of scenarios, spanning the range of uncertainties of key parameters. A recent illustration of the potential for combining mathematical modelling with air travel data to assess the risks of spread of a vector-borne disease is provided in Johansson *et al*. (2012). This, and the previous section here have outlined how new approaches and datasets are providing us with a more complete understanding of the global distributions of vectors and the diseases they carry, and how combining these maps with air traffic and climate data can enable us to better parameterize the risks of vector-borne disease and vector importation and spread risk. In the following sections, we outline two novel examples where the simple combination of data on air travel passengers with spatial data on vector-borne disease risk offers potential for improved risk assessment.

Example 1: The use of global malaria maps for imported malaria origin and case number prediction

Despite over fifty countries having achieved malaria elimination over the past century, the disease remains a problem to many countries that are certified as 'malaria free' through cases imported from endemic regions each year. Cases remain expensive to treat and can occasionally spark secondary local transmission (e.g. Zucker, 1996; MacArthur *et al*. 2001). While the numbers and origins of cases seen in a non-endemic country are a result of a complex interplay of factors, broad patterns are evident, relating to the number and origin of incoming travellers and level of risk at these locations. The recent construction of a global evidence-based map of *P. falciparum* malaria transmission intensity (Hay *et al*. 2009) provides valuable data on the spatial variation in risk of acquiring a *P. falciparum* infection. Here we examine the potential of combining these maps with data on numbers of people arriving in the US to explore the relationship to numbers and origins of reported imported malaria cases.

Data on the number and country of origin of reported imported *P. falciparum* malaria cases from 2000–07 were obtained from the CDC's Morbidity and Mortality Weekly Reports (e.g. Solomon *et al*. 2009). It should be noted that these numbers may not completely capture the true number of imported cases since there is the potential for long delays to onset and diagnosis, and more importantly, these only represent reported cases, thus a large proportion may be missed. The case numbers were averaged across years to obtain a mean number of imported *P. falciparum* cases from each country of origin. Next, estimates of *P. falciparum* malaria prevalence in each endemic country were obtained from the World malaria map recently published by the Malaria Atlas Project (Hay *et al*. 2009, www.map.ox.ac.uk). To produce a single measure of malaria risk for each country, enabling comparison with the imported malaria statistics, a gridded population dataset (Balk *et al*. 2006) was used to calculate population-weighted mean prevalence for each country. This was undertaken because taking a single mean prevalence value across the country often incorporates large unpopulated areas, so weighting by population density produces a more relevant value of the average level of prevalence that each person is residing under. Ideally, a range of measures should be calculated to exploit the richness of data in the malaria map, but for this simple illustrative analysis, just the population-weighted mean was used. Moreover, the potential exists to use recently developed mathematical transmission models (Smith *et al*. 2010) to convert the map to represent force of infection, a more relevant risk measure for the case of non-immune US residents visiting endemic areas. Finally, the numbers of foreign national travellers by country of national origin to the United States from 2000–07, i.e. non-US citizens entering the US for any reason, were obtained from the US Office of Travel and Tourism Industries (http://tinet.ita.doc.gov/outreachpages/inbound.general_information.inbound_overview.html), and an average per year was calculated.

We next explored the simple assumption that numbers of imported *P. falciparum* cases by origin country to the US were a function of numbers of incoming travellers and the *P. falciparum* prevalence at their origins. A log-linear model was constructed to investigate this relationship:

$$\ln(\gamma_i) = \beta_0 + \beta_1 * \ln(\Lambda_i) + \beta_2 * \ln(P_i) + \varepsilon_i$$

Where i denotes the country of origin, γ_i is the imported malaria cases from country i, Λ_i is the number of international arrivals from country i, and P_i is the population-weighted mean *P. falciparum* prevalence in country i. Linear regression was not appropriate here as the approach suffers from the fact that the numbers of imported cases tend to be positively skewed and subject to outliers. Thus, a natural logarithm transformation was applied to both response and predictor variables to alleviate heteroscedasticity. The mean number of imported cases for each origin was adjusted by adding one before logarithmic transform to eradicate zero values and make full use of the imported case dataset.

A total of 84 countries was included in the modelling. The results of the log-linear model

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Table 1. Results of a log-linear model for the estimation of imported *P. falciparum* malaria case numbers to the US by origin country (PR = Parasite Rate)

Variables	Coefficient	Std. Error	Z value	*P* value
Intercept	0·1004	0·2848	0·352	0·725
P. falciparum PR	0·3842	0·0429	8·948	< 0·001
Arrivals	0·2745	0·0397	6·911	< 0·001

estimation (Table 1) showed that the model was statistically significant, with an adjusted R-squared of 0·497, indicating that approximately 50% of the variance of the response variable (imported case numbers) was accounted for by the explanatory variables (arrivals and *P. falciparum* prevalence at origin). The estimated coefficients of both explanatory variables were significant ($P < 0{\cdot}001$) with values of 0·3842 and 0·2745, respectively. Thus, we may expect around a 3·7% increase in the number of imported malaria cases to the US when the *P. falciparum* Parasite Rate increases by 10% at the origin, or a 2·7% increase in the number of imported *P. falciparum* malaria cases when the number of incoming arrivals increases by 10% (holding the other predictor constant).

Results show that the simple scaling of spatial data on malaria transmission by incoming traveller numbers can broadly replicate the patterns of imported *P. falciparum* case numbers and origins. Such findings offer promise for the construction of a tool for forecasting trends in imported malaria case numbers and origins, as incoming traveller numbers continue to be monitored and global malaria risk maps continue to be updated and refined (www.map.ox.ac.uk). Finally, this example outlines an extremely simple model, and great potential exists to improve and add more sophistication in incorporating known determinants of imported malaria, and in turn explain a greater proportion of the variance in case numbers seen. Information on traveller activities, prophylaxis use and resident/immigrant/visitor status are important factors to include. Moreover, expanding the approach to longer time series, different diseases, other countries and more sophisticated modelling will likely improve reliability and utility further.

Example 2: Predicting the movement of a vector-borne disease: Chikungunya in Italy

In 2006, India and several Indian Ocean states experienced outbreaks of chikungunya virus infection, where the vector was *Aedes albopictus* in at least some areas (Schuffenecker *et al*. 2006; Bodenmann and Genton, 2006). At the end of August 2007, Italy notified its EU partners of an outbreak of chikungunya in the Emilio-Romagna region of north-eastern Italy (Rezza *et al*. 2007). The index case of the epidemic was a resident of the region, who travelled to the state of Kerala, India, in June, and presented with two episodes of fever on 15 June and 23 June. Eventually, over 200 cases were recorded during the summer of 2007, mostly in two villages in the Province of Ravenna. The outbreak of chikungunya in northern Italy was the first recorded in a temperate country. The drivers behind its occurrence were many and varied, but were principally related to a confluence of five factors: (1) The global spread from east Asia of *Aedes albopictus* (the 'Asian tiger mosquito') during the past 30 years through the global trade in used tires (Tatem *et al*. 2006*a*), including widespread establishment of populations in Italy (Rezza *et al*. 2007). (2) The chikungunya virus strains introduced in Italy contained a mutation in the E1 glycoprotein which was responsible for a single amino acid substitution (A226 V) able to increase the infectivity of the virus for *Aedes albopictus* (Tsetsarkin *et al*. 2007). (3) The spread of chikungunya outbreaks from Indian Ocean states in the southern hemisphere, where outbreaks were occurring in the warmer months of December to March (asynchronous to the principal vector activity months of June–September in Italy), to India in the northern hemisphere, where vector activity occurred year-round, providing synchrony with northern hemisphere *albopictus* activity (Charrel *et al*. 2007). (4) An unusually prolonged hot spell in the Northern Italy summer that apparently promoted intense *Aedes albopictus* activity. (5) A traveller taking advantage of recently established air travel connections between India and Italy.

Though the second factor remains difficult to predict, data on the remaining factors were here assembled in a simple framework, following similar previous retrospective analyses (Tatem *et al*. 2006*a*, *b*), to assess whether the relative risk of an outbreak occurring in northern Italy over other locations could have been predicted at the time using readily available datasets. Table 2 documents these datasets and their sources.

Firstly, field data on the presence of *Aedes albopictus* were gathered from a range of sources (Table 2), and used with satellite-derived environmental and climatological covariates (Scharlemann et al. 2008) within a boosted regression tree species distribution mapping algorithm (Elith *et al*. 2008), following similar approaches adopted for *Anopheles* distribution mapping in Sinka et al (Sinka *et al*. 2010*a*, *b*, 2011). The resulting distribution map, showing predicted suitability for *albopictus* presence, is shown in Fig. 2. Areas that were predicted as suitable for *albopictus*, but known to be free of the mosquito (e.g. Australia, New Zealand), were masked from the map for the remainder of the analyses.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Table 2. Principal factors that determined the occurrence of the 2007 chikungunya outbreak in Italy, the datasets used to represent them in the modeling exercise and the source of the datasets

Factor	Dataset	Source
Presence of *Aedes albopictus*	Predicted *Aedes albopictus* distribution	Multiple georeferenced datasets on confirmed *albopictus* field presence (e.g. Benedict *et al*. 2007; Moffett *et al*. 2009; European Centers for Disease Control, 2009).
Chikungunya virus mutation	N/A	N/A
Large outbreaks elsewhere	Mapped surveillance report data	Promed-mail (www.promedmail.org), Healthmap (www.healthmap.org)
Climatic conditions	Climatic similarity between outbreak regions and those connected by flights	NCEP reanalysis gridded data: temperature, rainfall, humidity (Kanamitsu *et al*. 2002)
Incoming travellers from outbreak regions	Global flight schedules and monthly route capacities	2007 database on flight schedules (www.oag.com)

Following this, reports of outbreaks occurring in the first half of 2007 were collected and mapped, and passenger capacity information for all flight routes originating in outbreak regions were extracted.

Climatic Euclidean Distances (CEDs) (Tatem and Hay, 2007) between the nearest international airport to each outbreak region within the predicted distribution of *Aedes albopictus* (defined by >90% predicted probability of presence), and every other airport within the predicted distribution of *Aedes albopictus* that was connected by direct flights, were then calculated for each month using the 2007 gridded climate data. CEDs are a measure of similarity in climatic regime between one location and another, and in this case were calculated through obtaining measures of rainfall (r), temperature (t) and humidity (h) for each airport location. The CED between airport i and j is then calculated by $\sqrt{((r_i - r_j)^2 + (t_i - t_j)^2 + (h_i - h_j)^2)}$ (Tatem and Hay, 2007). The CEDs for each flight route were scaled by the passenger capacities on those routes, following previous approaches (Tatem *et al*. 2006*b*; Tatem and Hay, 2007; Tatem, 2009). Thus for each flight route, this gave a relative measure of the probability of imported chikungunya-infected travellers entering regions with no chikungunya activity, but *Aedes albopictus* presence and similar climatic conditions to the origin region, where the climate was suitable for sufficient *albopictus* activity to spark an epidemic. For each month, the routes were ranked by these traffic-scaled CEDs to give a relative assessment of regions most at risk for importation and onward transmission of chikungunya, based on the factors considered (Table 2). The top ten risk routes for June (out of a total of 57 routes), when the Italian outbreak was seeded by a traveller from India, are shown in Table 3. While the highest ranked routes are unsurprisingly the shorter distance, regional flights to Sri Lanka and Bangladesh, the highest ranked longer distance route was Mumbai to Milan. Milan was the nearest international airport to Ravenna Province that had connections to chikungunya outbreak regions, suggesting that at the time, the elevated risk of chikungunya importation and establishment through this route, relative to other routes, was actually predictable using readily available spatial datasets.

The results show that a multi-disciplinary approach, which draws on a variety of spatial data on factors known to influence the spread of vectors and the diseases they carry, offers potential for assessing the risk of disease importation. How to interpret and act upon the kind of relative risks identified is a challenge yet to be overcome. However, the approach presented here is a simple, proof of concept analysis, and clearly would benefit from improvements to datasets and methods, many of which are covered in the future directions section below. Here we have examined only direct flights, and their capacities, rather than actual passenger numbers or stopovers. Moreover, in the distribution modelling we have treated *Aedes albopictus* as a single homogenous type of mosquito, yet competition, competence, adaptation and preferences can vary widely across its global distribution (Gratz, 2004). Finally, accurate data on outbreak locations and sizes, as with many diseases, are difficult to obtain to be sure of comprehensive assessments of risk, however, improvements in global surveillance and the rapid availability of data are improving (e.g. Brownstein *et al*. 2008). Despite these issues, the results of this first-iteration spatial framework show promise in terms of being able to conduct rapid risk assessments and prioritise surveillance for a range of vector-borne diseases in the future. The next section documents the first steps in the construction of an online tool to do this.

THE VECTOR-BORNE DISEASE AIRLINE IMPORTATION RISK (VBD-AIR) TOOL

The two examples in the previous section, as well as previous studies (Tatem *et al*. 2006*a*, *b*, *c*) have demonstrated the potential that exists in combining

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

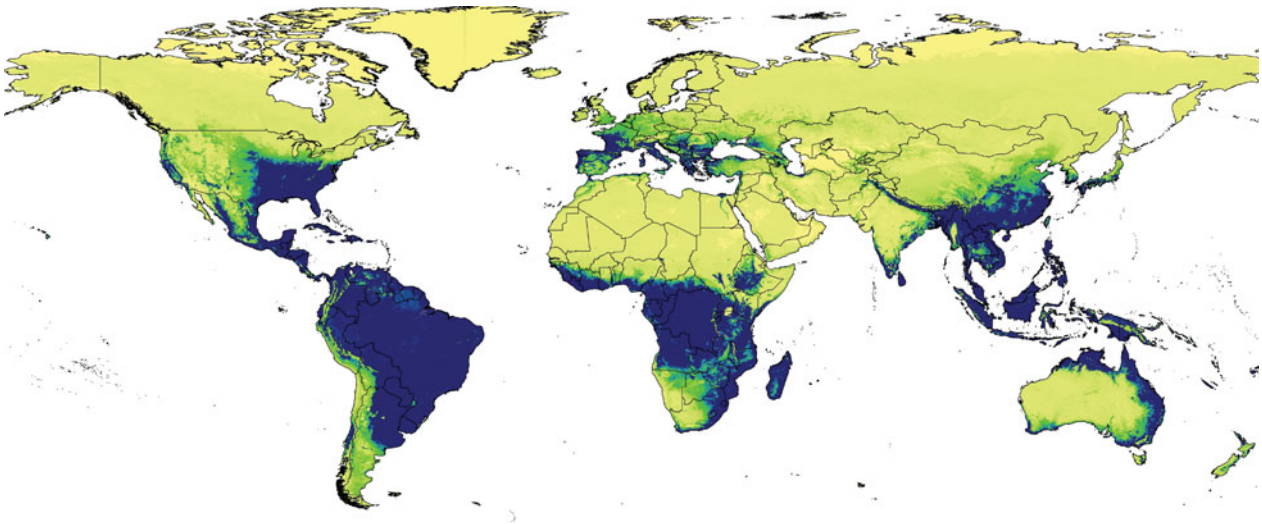

Fig. 2. The predicted distribution of climatic and environmental suitability for *Aedes albopictus* presence based on field survey data combined with satellite-derived environmental covariates within a boosted regression tree species distribution prediction model. The colour scale shows predicted unsuitable to suitable conditions as a continuous scale from yellow to dark blue.

spatial data on disease distributions and climatic seasonality with routinely collected data on flight traffic within a simple modelling framework. To improve access to such datasets and the benefits of combining them for initial assessments of risk of vector-borne pathogen importation and onward spread, or vector importation and establishment, the Vector-Borne Disease Airline Importation Risk (VBD-Air) tool has been developed by the authors.

The VBD-Air tool aims to help better define the roles of airports and airlines in the transmission and spread of vector-borne human diseases. It represents a flexible tool that combines multiple geospatial datasets to estimate the relative risks between differing airports, flight routes, times of year, diseases and their vectors, in promoting the movement of passengers infected by vector-borne diseases and the vectors that spread these diseases. These datasets include global disease risk maps, vector presence maps, 2010 and 2011 air travel network and capacity information, and global climatic datasets. Airports are considered as nodes in the air travel network, with attributes extracted from these datasets based on the locations of the airports. For disease risk, the maximum risk value within a two hour travel time mask around each airport (defined using methods outlined here: http://bioval.jrc.ec.europa.eu/products/gam/index.htm) is used to reflect local accessibilities for infected passengers. The calculations and outputs of the tool rely on the assumptions that the levels of imported vector and vector-borne disease risk via air travel are related to (1) the presence of flight routes connecting to endemic regions (promoting the movement of people, pathogens and vectors), (2) the level of traffic between origin and destination (increasing the probability of infected passenger and vector carriage), and (3) the monthly climatic similarity between origin and destination (since vector activity is required at both locations to firstly provide infected passengers, and secondly prompt onward transmission or vector establishment at the selected destination). These all represent first-step risk assessments based on available global data, and many additional factors for which data are sparse, or which are locally-specific are not included in the tool. At present, VBD-Air focuses on four vector-borne diseases that are the cause of high burden and imported case numbers globally, or that have been readily spread by air travel previously: malaria, dengue, yellow fever and chikungunya. However, extension to other vector-borne diseases is anticipated.

The VBD-Air tool takes the form of an interactive online interface (Fig. 3), and is targeted to users with interests in specific airports or regions, and the risks to those locations of vector-borne disease importation and onward spread, or exotic vector importation and establishment. Users initially select an airport of interest, then make further selections regarding the disease, month and whether only direct flights should be examined. The selections prompt database queries to return a map of the selected disease distribution with direct (or one-stop) flight routes from endemic regions of the selected disease to the airport in question overlaid. The flight routes are coloured by passenger capacity for the selected month, and each route and airport can be selected to examine various statistics on its predicted disease prevalence, climate and traffic in the selected month. The top ten routes ranked by incoming traffic in the selected month from disease endemic regions are also listed to provide an initial assessment of risk, and users can click on any listed airport to view its location on the map. Following this, options for further calculations are available, categorized by (1) imported disease risk,

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Table 3. The top ten predicted risk routes for chikungunya importation and onward transmission in June 2007. Origin airports are chosen from international airports within or near to ongoing chikungunya outbreaks and predicted as suitable for *Aedes albopictus* presence (Fig. 2). Destination airports are those with direct flights to the origin airports and predicted to have *Aedes albopictus* present in their vicinity. The routes are ranked by traffic-scaled climatic Euclidean distance (CED) (Tatem and Hay, 2007) from largest to smallest

Ranking	Origin airport	Destination airport	Traffic-scaled CED
1	Chennai, India	Colombo, Sri Lanka	10,516
2	Thiruvananthapurum, India	Colombo, Sri Lanka	9,885
3	Mumbai, India	Colombo, Sri Lanka	8,777
4	Mumbai, India	Dhaka, Bangladesh	8,561
5	Chennai, India	Dhaka, Bangladesh	8,148
6	Kozhikode, India	Colombo, Sri Lanka	7,477
7	Mumbai, India	Milan, Italy	6,919
8	Mumbai, India	Newark New York, USA	6,145
9	Mumbai, India	Atlanta, USA	4,472
10	Chennai, India	Singapore	4,218

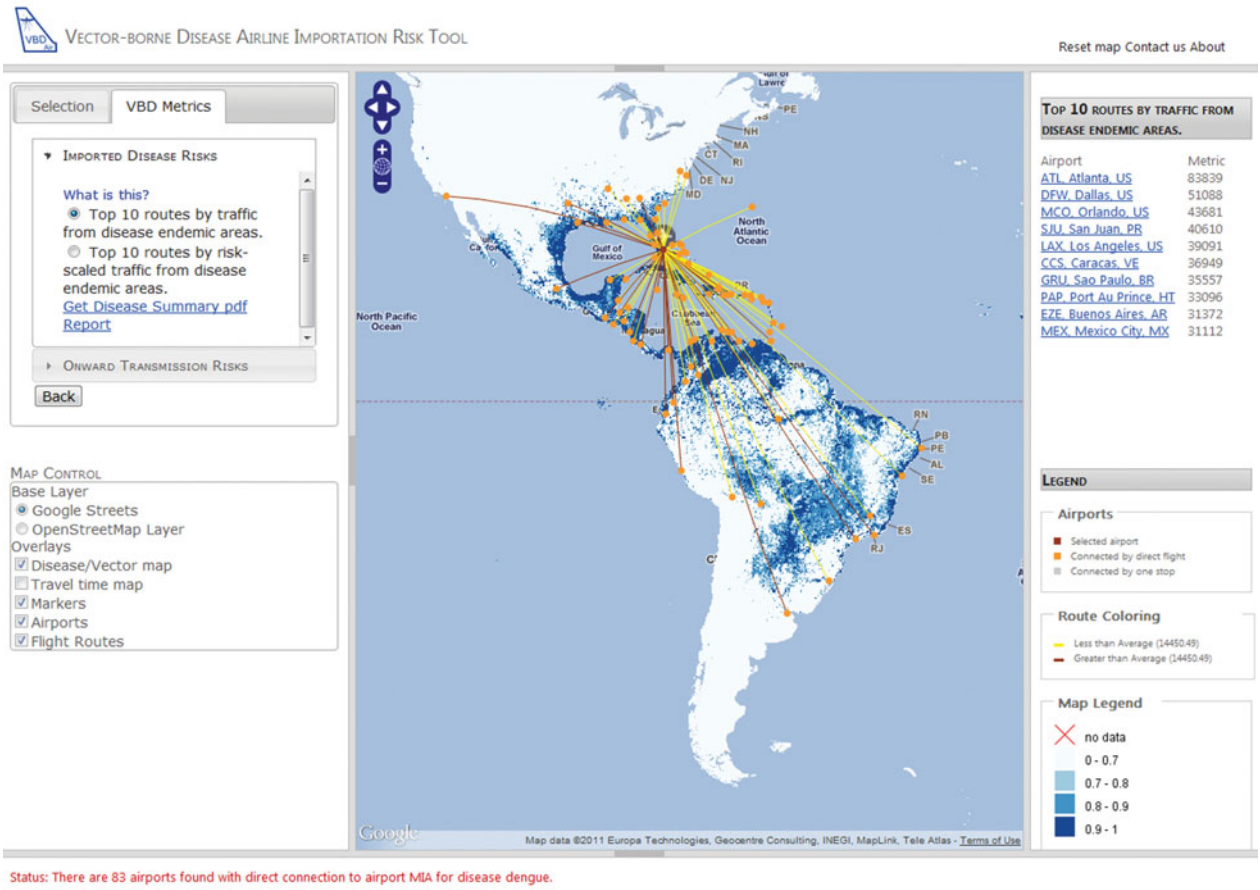

Fig. 3. Example output screen from the VBD-Air tool. Here the user has chosen to examine direct flight routes into Miami airport originating in regions that have previously seen dengue transmission or are predicted to be suitable for transmission. The routes are coloured by high/low 2011 passenger capacities, and the top ten routes by traffic from endemic areas are listed in the top-right window.

(2) onward transmission risk and (3) imported vector risk. Each section provides more detailed metrics and the option to produce a report in PDF format that summarises differing risk metrics throughout the year for the airport in question.

The imported disease section enables users to explore further statistical summarizations for their airport of interest, including air traffic levels from endemic regions, and traffic levels rescaled by disease prevalence or risk at the origin. This section follows similar assumptions to the imported malaria example above – that rates and origins of imported cases are likely a function of numbers incoming and disease risk at the origin. The onward transmission section

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

enables similar calculations to be undertaken, but extends analyses to include vector distributions and climatic similarity between origin and destination regions, in a similar fashion to that undertaken for the chikungunya example above. Finally, the imported vector section makes use of the predicted vector distribution maps and climatic similarity indices to undertake calculations on flight routes and climatic similarity between origins and destinations at different times through the year, following metrics outlined and applied in previous studies (Tatem *et al*. 2006*a*; Tatem and Hay, 2007; Tatem 2009).

The tool is currently in its final stages of development at the time of writing, and anyone wishing to test it or obtain further details should contact Dr Tatem (Andy.Tatem@gmail.com).

MITIGATION

The data and approaches presented so far highlight how far we have come in understanding the role of air travel in the spread of vector-borne diseases, and how spatial information on a variety of factors can be combined to assess the risks of disease and vector importation and spread. Such approaches are valuable for allocating sparse surveillance resources or for strategic planning, but once these risks have been characterized, the question remains on how to mitigate them. A range of options exist, and each have been applied in a variety of settings and to varying degrees of intensity and expense. Here we highlight briefly some of the more widely used air travel-specific approaches:

Disinsection

Disinsection (in-cabin spraying with insecticide at take-off or landing (Gratz *et al*. 2000)) used to be widely recommended and practised (World Health Organisation, 1998; Aitio, 2002). Studies have suggested that, where used, routine disinsection can prove effective in reducing 'airport malaria' (Tatem *et al*. 2006*b*) risk (Hutchinson *et al*. 2005), although the number of countries implementing such procedures is in decline (Russell and Paton, 1989; Woodyard, 2001). The practice is likely to make more economic and logistical sense on certain routes and at certain times of the year in terms of reducing risk from the import of disease-carrying insects. Alternative approaches that avoid the application of insecticides have been developed, such as the use of air curtain barriers (Carlson *et al*. 2006). These approaches are likely to be of little impact in terms of reducing numbers of imported cases in infected travellers though.

Vector control

Vector control through larviciding and larval habitat management around airports (Guillet *et al*. 1998) at specific times of year likely represents a relatively cheap option, should a particular gateway airport be considered a risk for the establishment of invasive, non-native insect vectors. The technique is again likely to be of little use in reducing numbers of imported cases in infected travellers, and only of use in limiting onward transmission in the vicinity of the airport.

Screening and treatment

If a particular route is identified as a likely source of imported insect-borne disease cases, then the implementation of targeted, random or full screening (followed by treatment if infections are found) of arriving passengers represents a costly and often inconvenient option, but potentially an effective one. Such an approach has been implemented by the malaria control programme in Mauritius as a tool for maintaining the island's malaria-free status, whereby blood samples were taken and tested for parasites from incoming air travellers, though questions about its cost effectiveness remain (Tatarsky *et al*. 2011). A less intrusive approach uses infrared thermometers (Maurice, 2009) to screen for passengers with fever, and has been implemented at some airports during the SARS and influenza epidemics and occasionally for vector-borne diseases, such as dengue (Shu *et al*. 2005) and chikungunya (Shu *et al*. 2008). Such an approach may only be cost-effective for specific routes and at times when a known large outbreak is occurring at origin regions. Moreover, passengers who are infected, but at latent stages of infection, or are asymptomatic, will not be captured by such approaches.

Awareness and education

Potentially the most cost-effective approaches to reducing numbers of imported vector-borne disease cases and mitigating the potential impacts are targeted education and awareness campaigns. These can involve focusing on a range of groups: (1) Informing airport staff, cabin crew and particularly medical staff about specific routes and times of year where the risks of passengers harbouring vector-borne infections may be relatively high. By making them aware of symptoms and treatments, and raising vigilance, the possibility for identifying and rapidly treating sick passengers is higher. (2) Similarly, informing local physicians and clinical practices in terms of vigilance for specific illnesses in those with certain travel histories can enable rapid diagnosis and reduce the risk of local secondary transmission. (3) Informing passengers returning from specific destinations at certain times of year of the potential elevated risks of contracting vector-borne diseases. This can improve treatment seeking behaviour and

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

facilitate rapid diagnosis, should travellers become sick upon return home. (4) Informing outgoing passengers to specific destinations of elevated risk for vector-borne disease. This can include advance warning when tickets are purchased to prompt prophylaxis acquisition, and onboard the flight to increase awareness of bednet usage and insecticide application, for example.

FUTURE DIRECTIONS

Compared to our understanding of the role of air travel in the spread of directly transmitted infections such as influenza, much is still to be discovered, explored and analysed in terms of vector-borne diseases. A set of possible future research directions exist as clear extensions to the work outlined in this paper, and these are discussed below.

Real time risk assessment

Ultimately, being able to map rapidly vector-borne disease risks as they change, then link these contemporary risks to actual air travel ticket purchase records and occupancy rates will take the types of analyses presented here a step further towards near real-time assessments of disease importation risk. Projects such as Bio.diapsora (www.biodiaspora.com) and GLEAM (www.gleamviz.org) aim to provide frameworks for integrating air travel data with disease surveillance data and mathematical modelling, respectively, to better quantify risks for directly-transmitted infections. The increasing availability of rapidly reported and georeferenced data on disease outbreaks through projects such as Healthmap (Brownstein *et al*. 2008) and the development of statistical disease and vector distribution mapping techniques make the possibility of near real-time vector-borne disease risk mapping within reach, however. Through combining these with information on human movement, for (1) air travel through actual ticket sales, passenger logs or modelled data (see below) and (2) land-based and travel through a variety of datasources and models (e.g. www.thummp.org), and linking these movement data to disease-specific stochastic models (see below), the goal of real-time adaptive management and surveillance for vector-borne disease importation and spread could become a reality.

Flight passenger modelling

The analyses here and prior studies (Tatem *et al*. 2006*a*, *b*, *c*) have focused solely on scheduled direct flights and relied on flight capacities as a surrogate for actual passenger traffic. In reality, stopovers are common, flights rarely operate at full capacity and chartered flights still carry large numbers of people. Aside from obtaining full records of all passenger itineraries, which generally remain confidential and expensive to obtain, a number of steps can be explored to rectify this, firstly focused on deriving models based on widely available and reliable US data. These likely include the processing of DB1B data and T-100 data (http://www.transtats.bts.gov) to compare purchased tickets (which include full routes including stopovers) and flight occupancy on routes against flight capacity. Moreover, analysis of T-100 data and its cross-referencing against enhanced traffic management system operator codes can enable the inclusion of chartered flights. Finally, approaches to model the potential area of dispersal of any VBD brought in by an infected human could be developed through spatial quantification of airport accessibility by overland travel in combination with vector-borne disease and vector distribution datasets. Previously developed approaches for quantifying spatially the ease of access of differing locations globally have shown application in describing the movement of directly transmitted infections (Gray *et al*. 2009; Talbi *et al*. 2010), and could be extended to provide estimates of airport catchment areas and potential routes of onward transmission.

Vector-borne disease and vector-specific parameters

The risks of long-distance spread for differing vector-borne diseases are partially dependent upon their respective epidemiological features. For instance, the differing incubation times and prevalence of asymptomatic carriers means that some vector-borne diseases have greater opportunities to be carried beyond their region of entry to a country than others, before symptoms appear, treatment is sought and the disease presence is alerted to control authorities. Moreover, the length of parasite lifecycle stages (Guerra *et al*. 2008), vector development times (Sinka *et al*. 2010*a*, *b*, 2011) and diapause (Hawley *et al*. 1987) all impact upon the timings of risk, while larval site preferences and human population densities (Tatem *et al*. 2008) affect locations of risk. Incorporation of these factors into existing air network model frameworks, including VBD-Air, should be a priority.

Stochastic models

The simple model frameworks presented in this paper and previously (Tatem *et al*. 2006*a*, *b*, *c*) use single mean estimates of monthly traffic per route, environmental suitability, disease endemicity/presence and vector presence to estimate long-distance vector-borne disease spread risk. In reality, this spread is a stochastic process, and each of these variables can (1) exhibit substantial variations from the mean and (2) include uncertainty in the way they are measured. These encompass, for example,

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

interannual climatic variability, monthly variations in traffic on flight routes, the uncertainties inherent in mapping vector-borne disease transmission (Patil *et al*. 2011) and vector suitability from species distribution models (Sinka *et al*. 2010*a*,*b*, 2011), and past histories of outbreaks. Future work should focus on deriving probability distributions for each model parameter. By simulating risks of importation from these probability distributions, improved and more informative model outputs can be produced that will provide a better understanding of the uncertainties inherent in forecasts and more realistic scenarios for guiding management decisions.

Validation

The testing and validation of any models designed to assess vector-borne disease importation and establishment risk against detailed and reliable data on previous vector-borne disease-spread events should represent an important component of future research. The imported malaria and chikungunya outbreak examples presented here, as well as previous work on airport malaria (Tatem *et al*. 2006*b*) and *Aedes albopictus* (Tatem *et al*. 2006*a*) represent first steps towards achieving this, but more detailed and rigorous assessments will increase confidence in the forecasting abilities of such models.

Phylogeography

The analysis of phylogenetic data is increasingly uncovering patterns and information on the timing and global spread routes of pathogens (Lemey *et al*. 2009). While such analyses offer valuable insights into global epidemiological dynamics, the driving factors behind them remain unquantified. Recent work, however, is focused on building in candidate driving factors (including air traffic data) into Bayesian phylodynamic frameworks to quantify the possible role of each one in describing spread patterns seen (Lemey *et al*. 2009; Talbi *et al*. 2010; Gray *et al*. 2011). This multidisciplinary approach offers a potentially powerful framework for understanding, modelling and forecasting the dynamics of pathogens spread through air travel.

CONCLUSIONS

Increases in global travel are happening simultaneously with many other processes that favour the emergence of disease (Wilson 1995, 2003). Air travel is a potent force in disease emergence and spread, and the speed and complexity of modern aviation makes both geographical space and the traditional 'drawbridge' strategy of disease control and quarantine increasingly irrelevant (Haggett, 2000). With no apparent end in sight to the continued growth in global air travel, we must expect the continued appearance of communicable disease pandemics, disease vector invasions and vector-borne disease movement. Approaches that can model, predict and explain such events can be used to focus surveillance and control efforts more efficiently. This paper has shown that the risk of movement of vector-borne diseases through the global air network can be predicted to a certain degree to provide such information. Future challenges include incorporating information on temporal variations in passenger numbers, stopover risks, intra-species competition, human populations at risk, breeding site availability, climate change, disinsection and onward land transport, as well as quantifying the relative importance of all types of transport for vector and disease movement. The development and application of statistical and mathematical models based on spatially explicit data, with a particular focus on air transport connectivity have the potential to aid in reaching an ultimate goal of real-time adaptive management and surveillance.

ACKNOWLEDGMENTS

The authors thank Dr Simon Hay, Prof David Rogers, Dr Peter Gething and Dr Anand Patil for sharing global disease risk datasets used in the construction of the VBD-Air tool.

FINANCIAL SUPPORT

AJT, ZH, AD and YQ acknowledge support from the Transportation Research Board of the National Academy of Sciences, through contract #ACRP02-20. AJT also acknowledges funding support from the RAPIDD program of the Science & Technology Directorate, Department of Homeland Security, and the Fogarty International Center, National Institutes of Health, and is also supported by grants from the Bill and Melinda Gates Foundation (#49446 and #1032350).

REFERENCES

Aitio, A. (2002). Disinsection of aircraft. *Bulletin of the World Health Organization* **80**, 257.

Bajardi, P., Poletto, C., Ramasco, J., Tizzoni, M., Colizza, V. and Vespignani, A. (2011). Human mobility networks, travel restrictions, and the global spread of 2009 H1N1 pandemic *PLoS ONE* **6**, e16591.

Balcan, D., Colizza, V., Goncalves, B., Hu, H., Ramasco, J. J. and Vespignani, A. (2009). Multiscale mobility networks and the spatial spreading of infectious diseases. *Proceedings of the National Academy of Sciences, USA* **106**, 21484–21489.

Balcan, D., Hu, H., Goncalves, B., Bajardi, P., Poletto, C., Ramasco, J. J., and Paolotti, D., (2009). Seasonal transmission potential and activity peaks of the influenza A (H1N1): a Monte Carlo likelihood analysis based on human mobility. *BMC Medicine* **7**, 45.

Balk, D. L., Deichmann, U., Yetman, G., Pozzi, F., Hay, S. I. and Nelson, A. (2006). Determining global population distribution: methods, applications and data. *Advances in Parasitology* **62**, 119–156.

Benedict, M. Q., Levine, R. S., Hawley, W. A. and Lounibos, L. P. (2007). Spread of the tiger: global risk of invasion by the mosquito Aedes albopictus. *Vector Borne and Zoonotic Diseases* **7**, 76–85. doi:10.1089/vbz.2006.0562.

Bodenmann, P. and Genton, B. (2006). Chikungunya: an epidemic in real time. *The Lancet* **368**, 258.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Brooker, S., Hay, S. I. and Bundy, D. A. (2002). Tools from ecology: useful for evaluating infection risk models? *Trends in Parasitology* **18**, 70–74. doi:S1471492201022231.

Brownstein, J. S., Freifeld, C. C., Reis, B. Y. and Mandl, K. D. (2008). Surveillance Sans Frontières: Internet-based emerging infectious disease intelligence and the HealthMap project. *PLoS Medicine* **5**, e151. doi:10.1371/journal.pmed.0050151.

Carlson, D. A., Hogsette, J., Kline, D. L., Geden, C. D. and Vandermeer, R. K. (2006). Prevention of mosquitoes (Diptera: Culicidae) and house flies (Diptera: Muscidae) from entering simulated aircraft with commercial air curtain units. *Journal of Economic Entomology* **99**, 182–193.

Charrel, R. N., de Lamballerie, X. and Raoult, D. (2007). Chikungunya outbreaks – the globalization of vectorborne diseases. *New England Journal of Medicine* **356**, 769–71. doi:10.1056/NEJMp078013.

Charrel, R. N., de Lamballerie, X. and Raoult, D. (2008). Seasonality of mosquitoes and chikungunya in Italy. *Lancet Infectious Diseases* **8**, 5.

Cibulskis, R. E., Bell, D., Christophel, E. M., Hii, J., Delacollette, C., Bakyaita, N. and Aregawi, M. W. (2007). Estimating trends in the burden of malaria at country level. *American Journal of Tropical Medicine and Hygiene* **77**, 133–137.

Colizza, V., Barrat, A., Barthelemy, M. and Vespignani, A. (2005). Prediction and predictability of global epidemics: the role of the airline transportation network. *Biocomplexity* **20**, arXiv:q-bio.OT/0507029v1.

Colizza, V., Barrat, A., Barthélemy, M. and Vespignani, A. (2006). The role of the airline transportation network in the prediction and predictability of global epidemics. *Proceedings of the National Academy of Sciences, USA* **103**, 2015–2020.

Dye, C. and Gay, N. (2003). Modeling the SARS epidemic. *Science* **300**, 1884–1885.

Elith, J., Graham, C. H., Anderson, R. P., Dudík, M., Ferrier, S., Guisan, A., Hijmans, R. J., Huettmann, F., Leathwick, J. R., Lehmann, A., Li, J., Lohmann, L. G., Loiselle, B. A., Manion, G., Moritz, C., Nakamura, M., Nakazawa, Y., Overton, J. McC., Peterson, A. T., Phillips, S. J., Richardson, K., Scachetti-Pereira, R., Schapire, R. E., Soberón, J., Williams, S., Wisz, M. S. and Zimmermann, N. E. (2006). Novel methods improve prediction of species' distributions from occurrence data. *Ecography* **29**, 129– 151.

Elith, J., Leathwick, J. R. and Hastie, T. (2008). A working guide to boosted regression trees. *Journal of Animal Ecology* **77**, 802–813.

European Centers for Disease Control (2009). Development of *Aedes albopictus* risk maps. ECDC, Stockholm, Sweden.

Ferguson, N. M., Cummings, D. A. T., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A. and Iamsirithaworn, S. (2005). Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* **437**, 209–214.

Franco-Paredes, C. and Santos-Preciado, J. I. (2006). Problem pathogens: prevention of malaria in travellers. *The Lancet Infectious Diseases* **6**, 139–149.

Freedman, D. O., Weld, L. H., Kozarsky, P. E., Fisk, T., Robins, R., Sonnenburg, F. and Keystone, J. S. (2006). Spectrum of disease and relation to place of exposure among ill returned travelers. *New England Journal of Medicine* **354**, 119–130.

Gething, P. W., Noor, A. M., Gikandi, P. W., Ogara, E. A. A., Hay, S. I., Nixon, M. S., Snow, R. W. and Atkinson, P. M. (2006). Improving imperfect data from health management information systems in Africa using space-time geostatistics. *PLoS Medicine* **3**, e271.

Gething, P. W., Patil, A. P., Smith, D. L., Guerra, C. A., Elyazar, I. R. F., Johnston, G. L., Tatem, A. J. and Hay, S. I. (2011). A new world malaria map: *Plasmodium falciparum* endemicity in 2010. *Malaria Journal* **10**, 378.

Grais, R. F., Ellis, J. H. and Glass, G. E. (2003). Forecasting the geographical spread of smallpox cases by air travel. *Epidemiology and Infection* **131**, 849–857.

Gratz, N. G. (2004). Critical review of the vector status of *Aedes albopictus*. *Medical and Veterinary Entomology* **18**, 215–227.

Gratz, N. G., Steffen, R. and Cocksedge, W. (2000). Why aircraft disinsection? *Bulletin of the World Health Organization* **78**, 995–1004.

Gray, R. R., Tatem, A. J., Johnson, J. A., Alekseyenko, A. V., Pybus, O. G., Suchard, M. A. and Salemi, M. (2011). Bayesian phylogenetics of bacterial genomes: inferring the pandemic spread of Methicillin resistant Staphylococcus aureus ST239. *Molecular Biology and Evolution* in press. http://mbe.oxfordjournals.org/content/early/2010/12/23/molbev.msq319

Gray, R. R., Tatem, A. J., Lamers, S., Hou, W., Laeyendecker, O., Serwadda, D., Sewankambo, N. and Salemi, M. (2009). Spatial phylodynamics of HIV-1 epidemic emergence in east Africa. *AIDS* **23**, F9–F17.

Griffits, T. and Griffits, J. (1931). Mosquitoes transported by airplanes: staining methods used in determining their importation. *Public Health Reports* **46**, 2775–2782.

Guerra, C. A., Gikandi, P. W., Tatem, A. J., Noor, A. M., Smith, D. L., Hay, S. I. and Snow, R. W. (2008). The limits and intensity of *Plasmodium falciparum* transmission: implications for malaria control and elimination worldwide. *PLoS Medicine* **5**, e38.

Guerra, C. A., Hay, S. I., Lucioparedes, L. S., Gikandi, P. W., Tatem, A. J., Noor, A. M. and Snow, R. W. (2007). Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. *Malaria Journal* **6**, 17.

Guillet, P., Germain, M. C., Giacomini, T., Chandre, F., Akogbeto, M., Faye, O. and Kone, A. (1998). Origin and prevention of airport malaria in France. *Tropical Medicine and International Health* **3**, 700–705.

Guimera, R., Mossa, S., Turtschi, A. and Amaral, L. A. N. (2005). The worldwide air transportation network: anomalous centrality, community structure, and cities' global roles. *Proceedings of the National Academy of Sciences, USA* **102**, 7794–7799.

Haggett, P. (2000). *The Geographical Structure of Epidemics*. Oxford, Clarendon.

Hawley, W. A., Reiter, P., Copeland, S., Pumpuni, C. B. and Craig, G. B. (1987). *Aedes albopictus* in North America: probable introduction in used tires from northern Asia. *Science* 236, 1114–1115.

Hay, S. I., Guerra, C. A., Gething, P. W., Patil, A. P., Tatem, A. J., Noor, A. M., Kabaria, C. W. and Snow, R. W. (2009). World malaria map: *Plasmodium falciparum* endemicity in 2007. *PLoS Medicine* **6**, e1000048.

Hay, S. I., Okiro, E. A., Gething, P. W., Patil, A. P., Tatem, A. J., Guerra, C. A. and Snow, R. W. (2010). Estimating the global clinical burden of *Plasmodium falciparum* malaria in 2007. *PLoS Medicine* **7**, e100029.

Hay, S. I., Tatem, A. J., Graham, A. J., Goetz, S. J. and Rogers, D. J. (2006). Global environmental data for mapping infectious disease distribution. *Advances in Parasitology* **62**, 37–77.

Health Metrics Network. (2005). *Statistics Saves Lives: Strengthening Country Health Information Systems*. Geneva: Health Metrics Network.

Hosseini, P., Sokolow, S. H., Vandegrift, K. J., Kilpatrick, A. M. and Daszak, P. (2010). Predictive power of air travel and socio-economic data for early pandemic spread. *PloS One* **5**, e12763.

Hufnagel, L., Brockmann, D. and Geisel, T. (2004). Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences, USA* **101**, 15124–15129.

Hutchinson, R., Bayoh, M. and Lindsay, S. (2005). Risk of airport malaria in the UK. *European Mosquito Bulletin* **19**, 12–13.

IATA (2010). *World Air Transport Statistics 2010*. Montreal, IATA.

Jelinek, T., Schulte, C., Behrens, R., Grobusch, M. P., Coulaud, J. P., Bisoffi, Z. and Matteelli, A. (2002). Imported *falciparum* malaria in Europe: sentinel surveillance data from the European network on surveillance of imported infectious diseases. *Clinical Infectious Diseases* **34**, 572–576.

Johansson, M. A., Arana-Vizcarrondo, N., Biggerstaff, B. J., Gallagher, N. J., Marano, N. and Staples, J. E. (2012). Assessing the risk of international spread of Yellow Fever Virus: A mathematical analysis of an urban outbreak in Asuncion, 2008. *American Journal of Tropical Medicine and Hygiene* **86**, 349–358

Johansson, M. A., Arana-Vizcarrondo, N., Biggerstaff, B. J., Staples, J. E., Gallagher, N. J. and Marano, N. (2011). On the treatment of airline travelers in mathematical models. *PLoS One* **6**(7), e22151.

Jones, K. E., Patel, N. G., Levy, M. A., Storeyguard, A., Balk, D., Gittleman, J. L. and Daszak, P. (2008). Global trends in emerging infectious diseases. *Nature* **451**, 990–994.

Kanamitsu, M., Ebisuzaki, W., Woollen, J., Yang, S.-K., Hnilo, J. J., Fiorino, M. and Potter, G. L. (2002). NCEP–DOE AMIP-II reanalysis (R-2). *Bulletin of the American Meteorological Society* **83**, 1631–1643.

Karlen, A. (1995). *Plague's Progress*. London, Indigo.

Kenah, E., Chao, D. L., Matrajt, L., Halloran, M. E. and Longini, I. M. (2011). The global transmission and control of influenza. *PloS One* **6**, e19515.

Killeen, G. F. (2003). Following in Soper's footsteps: northeast Brazil 63 years after eradication of *Anopheles gambiae*. *Lancet Infectious Diseases* **3**, 663–666.

Kilpatrick, A. M. (2011). Globalization, land use, and the invasion of West Nile Virus. *Science* **334**, 323–327.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Kubiak, R. J., Arinaminpathy, N. and McLean, A. R. (2010). Insights into the evolution and emergence of a novel infectious disease. *PLoS Computational Biology* **6**, e1000947.

Laird, M. (1984). *Commerce and the Spread of Pests and Disease Vectors*. New York, Praeger.

Le Menach, A., Tatem, A. J., Cohen, J. M., Hay, S. I., Randell, H., Patil, A. P. and Smith, D. L. (2011). Travel risk, malaria importation and malaria transmission in Zanzibar. *Scientific Reports* **1**, 1–7.

Lemey, P., Rambaut, A., Drummond, A. J. and Suchard, M. A. (2009). Bayesian phylogeography finds its roots. *PLoS Computational Biology* **5**, e1000520.

Longini, I. M., Fine, P. E. M. and Thacker, S. B. (1986). Predicting the global spread of new infectious agents. *American Journal of Epidemiology* **123**, 383–391.

Lounibos, L. P. (2002). Invasions by insect vectors of human disease. *Annual Review of Entomology* **47**, 233–266.

MacArthur, J. R., Holtz, T. H., Jenkins, J., Newell, J. P., Koehler, J. E., Parise, M. E. and Kachur, S. P. (2001). Probable locally acquired mosquito-transmitted malaria in Georgia, 1999. *Clinical Infectious Diseases* **32**, E124–8.

Massey, A. (1933). *Epidemiology in Relation to Air Travel*. London, H. K. Lewis and Co. Limited.

Maurice, S. (2009). International travel and fever screening during epidemics. *Eurosurveillance* 1–5.

Moffett, A., Strutz, S., Guda, N., González, C., Ferro, M. C., Sánchez-Cordero, V. and Sarkar, S. (2009). A global public database of disease vector and reservoir distributions. *PLoS Neglected Tropical Diseases* **3**, e378.

Murray, C. J. L., Lopez, A. D. and Wibulpolprasert, S. (2004). Monitoring global health: Time for new solutions. *British Medical Journal* **329**, 1096–1100.

Patil, A. P., Gething, P. W., Piel, F. B. and Hay, S. I. (2011). Bayesian geostatistics in health cartography: the perspective of malaria. *Trends in Parasitology* **27**, 246–253.

Perrings, C., Dehnen-Schmutz, K., Touza, J. and Williamson, M. (2005). How to manage biological invasions under globalization. *Trends in Ecology and Evolution* **20**, 212–215.

Rezza, G., Nicoletti, L., Angelini, R., Romi, R., Finarelli, A. C., Panning, M. and Cordioli, P. (2007). Infection with chikungunya virus in Italy: an outbreak in a temperate region. *The Lancet* **370**, 1840–6.

Riley, S. (2007). Large-scale spatial-transmission models of infectious disease. *Science* **316**, 1298–1301.

Rogers, D. J. (2006). Models for vectors and vector-borne diseases. *Advances in Parasitology* **62**, 1–35.

Rogers, D. J., Wilson, A. J., Hay, S. I. and Graham, A. J. (2006). The global distribution of yellow fever and dengue. *Advances in Parasitology* **62**, 181–220.

Russell, R. C. (1987). Survival of insects in the wheelbays of Boeing 747B aircraft on flights between tropical and temperate airports. *Bulletin of the World Health Organisation* **65**, 659–662.

Russell, R. C. and Paton, R. (1989). In-flight disinsection as an efficacious procedure for preventing international transport of insects of public health importance. *Bulletin of the World Health Organization* **67**, 543–547.

Rvachev, L. A. and Longini, I. M. (1985). A mathematical model for the global spread of influenza. *Mathematical Biosciences* **75**, 3–22.

Scharlemann, J. P. W., Benz, D., Hay, S. I., Purse, B. V., Tatem, A. J., Wint, G. R. W. and Rogers, D. J. (2008). Global data for ecology and epidemiology: a novel algorithm for temporal Fourier processing MODIS data. *PloS One* **3**, e1408.

Schuffenecker, I., Iteman, I., Michault, A., Murri, S., Frangeul, L., Vaney, M.-C. and Lavenir, R. (2006). Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak. *PLoS Medicine* **3**, e263.

Shu, P.-Y., Chien, L.-J., Chang, S.-F., Su, C.-L., Kuo, Y.-C., Liao, T.-L. and Ho, M.-S. (2005). Fever screening at airports and imported dengue. *Emerging Infectious Diseases* **11**, 460–462.

Shu, P.-Y., Yang, C.-F., Su, C.-L., Chen, C.-Y., Chang, S.-F., Tsai, K.-H. and Cheng, C.-H. (2008). Two imported chikungunya cases, Taiwan. *Emerging Infectious Diseases* **14**, 1325–1326.

Sinka, M. E., Bangs, M. J., Manguin, S., Chareonviriyaphap, T., Patil, A. P., Temperley, W. H., Gething, P. W. and Hay, S. I. (2011). The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic precis. *Parasites and Vectors* **4**, 89.

Sinka, M. E., Bangs, M. J., Manguin, S., Coetzee, M., Mbogo, C. M., Hemingway, J., Patil, A. P. and Hay, S. I. (2010*a*). The dominant *Anopheles* vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic precis. *Parasites and Vectors* **3**, 117.

Sinka, M. E., Rubio-Palis, Y., Manguin, S., Patil, A. P., Temperley, W. H., Gething, P. W., Van Boeckel, T. and Hay, S. I. (2010*b*). The dominant *Anopheles* vectors of human malaria in the Americas: occurrence data, distribution maps and bionomic precis. *Parasites and Vectors* **3**, 72.

Smith, D. L., Drakeley, C. J., Chiyaka, C. and Hay, S. I. (2010). A quantitative analysis of transmission efficiency versus intensity for malaria. *Nature Communications* **1**, 108.

Solomon, S. L., Daniel, K. L., Rutledge, T. F. and Boyd, M. F. (2009). Morbidity and Mortality Weekly Report Malaria Surveillance — United States, 2007, **58**.

Soper, F. L. and Wilson, D. B. (1943). *Anopheles gambiae in Brazil: 1930 to 1940*. New York, Rockefeller Foundation.

Talbi, C., Lemey, P., Suchard, M. A., Abdelatif, E., Elharrak, M., Nourlil, J., Tatem, A. J. and Jalal, N. (2010). Phylodynamics and human-mediated dispersal of a zoonotic virus. *PLoS Pathogens* **6**, e1001166.

Tatarsky, A., Aboobakar, S., Cohen, J. M., Gopee, N., Bheecarry, A., Moonasar, D., Phillips, A. A., Smith, D. L. and Sabot, O. (2011). Preventing the reintroduction of malaria in Mauritius: A programmatic and financial assessment. *PLoS ONE* **6**, e23832.

Tatem, A. J. (2009). The worldwide airline network and the dispersal of exotic species: 2007–2010. *Ecography* **32**, 94–102.

Tatem, A. J., Guerra, C. A., Kabaria, C. W., Noor, A. M. and Hay, S. I. (2008). Human population, urban settlement patterns and their impact on *Plasmodium falciparum* malaria endemicity. *Malaria Journal* **7**, 218.

Tatem, A. J. and Hay, S. I. (2007). Climatic similarity and biological exchange in the worldwide airline transportation network. *Proceedings Biological sciences/The Royal Society* **274**, 1489–1496.

Tatem, A. J., Hay, S. I. and Rogers, D. J. (2006*a*). Global traffic and disease vector dispersal. *Proceedings of the National Academy of Sciences, USA* **103**, 6242–6247.

Tatem, A. J., Rogers, D. J. and Hay, S. I. (2006*b*). Estimating the malaria risk of African mosquito movement by air travel. *Malaria Journal* **5**, 57.

Tatem, A. J., Rogers, D. J. and Hay, S. I. (2006*c*). Global transport networks and infectious disease spread. *Advances in Parasitology* **62**, 293–343.

Tatem, A. J., Rogers, D. J. and Hay, S. I. (2006*d*). T8.5: Traffic in disease vectors: 2005, 2015 and 2030. Commissioned as part of the U.K. Government's Foresight project, Infectious Diseases: preparing for the future. London, U.K, Office of Science and Innovation.

Tatem, A. J. and Smith, D. L. (2010). International population movements and regional *Plasmodium falciparum* malaria elimination strategies. *Proceedings of the National Academy of Sciences, USA* **107**, 12222–12227.

Tatem, A. J., Qiu, Y., Smith, D. L., Sabot, O., Ali, A. S. and Moonen, B. (2009). The use of mobile phone data for the estimation of the travel patterns and imported *Plasmodium falciparum* rates among Zanzibar residents. *Malaria Journal* **8**, 287.

Thomas, R. (1992). *Geomedical Systems: Intervention and Control*. London, Routledge.

Tsetsarkin, K. A., Vanlandingham, D. L., McGee, C. E. and Higgs, S. (2007). A single mutation in chikungunya virus affects vector specificity and epidemic potential. *PLoS Pathogens* **3**, e201.

Upham, P., Thomas, C., Gillingwater, D. and Raper, D. (2003). Environmental capacity and airport operations: current issues and future prospects. *Journal of Air Transport Management* **9**, 145–151.

Van den Broeck, W., Gioannini, C., Gonçalves, B., Quaggiotto, M., Colizza, V. and Vespignani, A. (2011). The GLEaMviz computational tool, a publicly available software to explore realistic epidemic spreading scenarios at the global scale. *BMC Infectious Diseases* **11**, 37. doi:10.1186/1471-2334-11-37.

Vogel, G. (2003). SARS outbreak – Modelers struggle to grasp epidemic's potential scope. *Science* **300**, 558–559.

Wichmann, O. and Jelinek, T. (2004). Dengue in travelers: a review. *Journal of Travel Medicine* **11**, 161–170.

Williams, C. (1940). Disinsectization of aircraft. *Public Health Reports* **55**, 1005–1010.

Wilson, M. E. (1995). Travel and the emergence of infectious diseases. *Emerging Infectious Diseases* **1**, 39–46.

Wilson, M. E. (2003). The traveller and emerging infections: sentinel, courier, transmitter. *Journal of Applied Microbiology* **94**, 1S–11S.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press

Woodyard, C. (2001). Fliers fume over planes treated with pesticides. *USA Today*, October 9 2010.

World Health Organisation (1998). Recommendations of the disinsecting of aircraft. *Weekly Epidemiological Record*, **15**, 109–111.

World Health Organisation (2007). The World Health Report 2007: A safer future, global public health security in the 21st century. Geneva, World Health Organization.

World Health Organization (2008). The World Health Report 2008: Primary Health Care – Now More Than Ever. Geneva, World Health Organization.

Zucker, J. R. (1996). Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks. *Emerging infectious diseases* **2**, 37–43.

https://doi.org/10.1017/S0031182012000352 Published online by Cambridge University Press