**Title**: The use of air travel data for predicting dengue importation to China: a modelling study

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**Abstract**

**Background**: Dengue virus importation from abroad is still the main driver of dengue incidence in China. Using global flight data to model importation may improve our understanding and prediction of dengue virus importation and onward transmission.

**Methods**: A retrospective analysis was performed of surveillance cases of dengue infections imported to China and volume of air traffic to China for the years 2005 through 2014, inclusive. The data were aggregated by year, destination province, and source country. Descriptive statistics were calculated, and a random effects negative binomial model was created to predict the number of imported cases based on the volume of travelers from dengue-endemic countries.

**Results**: There were 1,822 cases of imported dengue infections over the study period. Most imported cases are from a small number of high-incidence countries with a large volume of travel to China, most notably Myanmar (22% of cases). The number of imported cases of dengue infections increased by 5.9% for every 10% increase in travel volume from dengue-endemic countries.

**Conclusion**: Patterns of air travel have a measurable impact on the importation of dengue to China. Modelling dengue importation risk may be a useful strategy to direct public health surveillance and interventions.

**1. Introduction**

Infection with Dengue virus (DV) remains the most important viral disease spread by mosquito vectors with over half the world’s population at risk for infection, approximately 75% of whom live in the Asia-Pacific region [1]. There are over 100 endemic countries and estimated 50-100 million cases per year [1]. Transmission is through urban-adapted *Aedes aegypti* and *Ae*. *albopictus* mosquitoes, leading to a febrile illness that can be associated with severe and potentially lethal complications such as in cases of severe dengue [2].

Dengue continues to reemerge as an infectious disease of global health significance, with locally-acquired cases now detectable in regions previously free of the disease, such as the United States and Japan [3,4]. In China, dengue reemerged in 1978 after a 30-year absence, most likely due to decreasing economic isolation and increasing international trade and travel [5,6]. Epidemics have become frequent, though it is still considered an imported epidemic disease rather than endemic in mainland China [7].

As Southeast and Pacific Asia’s economies have grown, so too have the rates of travel and human migration, contributing to the reemergence of dengue in China and elsewhere. Infected individuals have the potential to transmit dengue to mosquito vectors for up to two weeks after exposure, which is ample time to travel to a distant locale. This may lead to outbreaks if a viremic individual is bitten by a competent vector in that new region [1]. With the increase in global air travel, the risks of importing new strains of dengue are also increasing [8].

Dengue currently has no specific antiviral treatment and there is no widely available vaccine [9], so current efforts at disease control are primarily focused on vector control. Evaluating vector dynamics, environmental factors, and human movement allow for the modelling and prediction of outbreaks and targeted public health measure. Recent studies have focused on temperature and climate change effects on *Ae. aegypti* populations and distribution and used these to target vector therapy with improved results [10–13]. A less-studied but potentially important risk factor has been human air travel. Outbreaks of dengue in China appear to be dependent on importation from neighboring and nearby countries[8], and rates of importation from other countries in southeast Asia varies with the volume of air travel from those countries [14]. Evaluation of passenger volumes through air travel data has the potential to identify regions at risk of importing vector-borne illnesses, for example with dengue and other arboviruses [15,16]. This paper, therefore, examines the relationship of travel data, passenger volumes and the risk of dengue virus importation to mainland China.

**2. Methods**

*Data sources*: Dengue has been a reportable disease in mainland China since 1989, with all probable or confirmed cases reported to the Center for Disease Control and Prevention in Beijing using their standardized case definition. It was only in 2005, however, that data related to importation or autochthonous cases began to be recorded. All clinically diagnosed or laboratory-confirmed cases of dengue from 2005 to 2014 calendar years were included in this study. Imported cases were initially defined as when the patient reported being bitten by mosquitoes in a dengue-affected country or province of mainland China within 15 days of the onset of the illness [17]. This definition changed in October 2014 to no longer require a history of mosquito bites. Data were aggregated to number of imported cases per year for further analysis.

Anonymous passenger-level itinerary data were acquired from the International Air Transport Association (IATA) for the years 2005 to 2014 inclusive. Data were aggregated to the total annual volume of passengers from external countries to each province of mainland China. A list of dengue-endemic countries was created based on Bhatt *et al* [18]. The National Bureau of Statistics of China data was used to determine the population of each province for each year [19].

*Analysis:* Total cases of imported dengue and volume of air travelers were calculated in aggregate, by year, and by country of origin. Volume of air travelers was aggregated based on travel from dengue-endemic and non-endemic countries, based on Bhatt *et al* [18]. To account for possible overdispersion in the data, a negative binomial regression model was used to model the rate of the imported cases for each year and province, using the log-transformed annual volumes of air travelers from dengue-endemic and non-endemic countries to that province in that year as the main predictors. The covariance of the residuals was modelled as Toeplitz(1) and random effects by province to account for the spatial autocorrelation. A year term was also added as a covariate to capture any secular trends in the data. Descriptive statistics were performed in R and model analysis in SAS [20,21].

**3. Results**

Between 2005 and 2014, there were 1,822 cases of imported dengue into mainland China (excluding Hong Kong Special Administrative Region [SAR], Macau SAR, and Taiwan), peaking in 2013 (Figure 1). Of those, the source country was not identified in 349 cases (19%). The number of imported cases grew from 58 in 2005 to 432 in 2014. Over that time, Myanmar was the source country with the greatest number of cases (408 cases; 22%), followed by Thailand (164; 9%), Indonesia (136; 7%), and Laos (135; 7%) (Table 1). Cases of imported dengue were detected throughout the year, though the incidence was highest in September and October (Figure 2).

Between 2005 and 2014, there were 306,313,978 international air travel itineraries whose final destination was mainland China. This more than doubled over ten years, increasing from 20 million in 2005 to 47 million in 2014 (Figure 1). The countries with the highest risk per traveler of importing a case of dengue to China were Papua New Guinea (126 cases per 100,000 travelers) and Myanmar (62 cases per 100,000 travelers). Hong Kong SAR was notable in that it has a very high number of travelers to mainland China, but has a very low rate of dengue exportation into mainland China.

The result of the negative binomial model found a statistically significant relationship between the log of the annual number of passengers from dengue-endemic countries and the risk of detecting imported cases of dengue (p<0.01). There was also a statistically significant year-on-year increase in the number of detected cases not accounted for by the increase in travelers (p<0.01). The model predicts that a 10% increase in the volume of air travelers from dengue-endemic countries will be associated with a 5.9% increase in detected cases of imported dengue (Table 3).

**4. Discussion**

The spread of dengue both into China and globally is a complex process influenced by many factors including temperature, precipitation, and vector competence [11–13]. However, there are limited data examining the relationship between globalization and flight patterns and their effect on dengue outbreaks. We demonstrate that flight data can be used to model the number of imported dengue cases into China by evaluating the source and volume of air travelers. Based on the negative binomial model used, there is an estimated 5.9% increase in the number of imported cases for a 10% increase in air travelers from dengue-endemic countries. This relationship appears to be robust and may be a useful tool in guiding focused public health responses such as surveillance and vector control efforts.

These findings are consistent with a growing body of literature demonstrating the direct relationship between air travel and importation of infectious diseases, such as the increase in imported cases of dengue with increasing air travel that was seen in South Korea [22] and Italy [23], and the spread of dengue serotypes predicted by air travel that was seen in Brazil [24] and Asia [25]. Our analysis, as compared to these, uses a large data set in terms of cases but also the total population at risk, has relatively granular data at the province level of a single large country, and uses a simple model that could be easily applied to other countries or diseases.

Our analysis is strengthened by the relatively long timeframe that captures many seasons over several years. Additionally, the close integration between Chinese local health care systems and the national surveillance program help ensure that the data is reflective of imported symptomatic cases of dengue who sought healthcare after their travel to China [14]. Finally, the statistical model used in the analysis is simple and flexible. It has the potential to be readily adapted to other countries, as well as other arboviral diseases such as Zika and Chikungunya viruses.

Still, the data used in the analysis have some limitations. The dengue case data required a history of mosquito bites in the country of origin to qualify as an imported case for almost the entire time period studied, likely leading to systematic underestimation of the number of imported cases. Only in the last few months of the data set did the definition change to no longer require this history of mosquito bites, which likely increased the number of cases identified in the final year of data. As well, the surveillance capacity of the government most likely increased over the time period, although this was at least partially captured by the linear year component of the model. This linear component also should capture some of the rise globally in both dengue and air travel. Lastly, only reported cases were captured in the data set. Since as many as 80% of individuals infected with dengue will be asymptomatic [26], this will further underestimate the number of imported cases. The overall increase in detected cases of imported dengue, therefore, is likely a combination of the spread of dengue in source endemic countries, increased volume of travelers, broadened case definition, and increased surveillance capacity. Finally, the travel data only included air travel, and therefore systematically underestimates the total number of travelers for countries that share a land border, where many or most travelers would cross by land rather than by plane. This potentially overestimates the per-traveler risk of dengue importation for countries like Myanmar and Laos, which import a large number of cases and share a land border with China.

We have also not accounted for seasonal variation in risk of importing dengue. The seasonality that is seen in the imported cases, with a peak in September, most likely corresponds to the seasonality of the source countries of imported cases. The predictive power of flight data would likely be improved, therefore, if data were available on the seasonality of dengue in the source country. Unfortunately, surveillance data for dengue are poorly reported in many countries. The analysis focusses exclusively on imported cases and does not predict overall incidence of dengue, which can include locally-acquired cases as well as those imported from other provinces of China. It also does not include several variables that have previously been shown to be important for modeling dengue incidence, including seasonality and climate [8]. Future research should explore how international travel patterns can be added to existing forecasting models to potentially increase their accuracy. Additionally, future research should also focus on the potential for autochthonous transmission of imported cases, with a focus on large urban centers, based on vector competency and climate capacity.

**5. Conclusion**

The annual volume of air travel arriving to China from dengue-endemic countries is useful for predicting the risk of detecting imported cases of dengue. This represents a novel risk factor that, with further refinement, could be a useful adjunct in forecasting models.

**Competing Interests**

The authors declare that they have no competing interests.

**Ethics approval and consent to participate**

It was determined by the National Health and Family Planning Commission, China, that the collection of malaria case reports was part of continuing public health surveillance of a notifiable infectious disease. The ethical clearance of collecting and using second-hand data from the surveillance was also granted by the institutional review board of the University of Southampton, UK (No. 18152). All data were supplied and analysed in an anonymous format, without access to personal identifying information.

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Figure 1. Total number of air travelers arriving (left axis) and number of imported cases of dengue (right axis) to mainland China from 2005 to 2014.

Figure 2. Boxplots of the monthly number of imported cases of dengue identified in mainland China between 2005 and 2014.

Table 1. Total volume of travelers to mainland China (2005 – 2014) and number of imported cases of dengue identified, by country of origin.

| Origin Country | Cases | Travel volume | Cases per 100,000 travelers |
| --- | --- | --- | --- |
| Myanmar | 408 (22.4%) | 658,599 (0.2%) | 62.0 |
| Thailand | 164 (9.0%) | 15,203,732 (5%) | 1.08 |
| Indonesia | 136 (7.5%) | 3,777,180 (1%) | 3.60 |
| Laos | 135 (7.4%) | 406,147 (0.1%) | 33.2 |
| Philippines | 114 (6.3%) | 3,124,811 (1.0%) | 3.65 |
| Malaysia | 110 (6.0%) | 10,159,135 (3.3%) | 1.08 |
| India | 73 (4.0%) | 2,575,407 (0.8%) | 2.83 |
| Viet Nam | 61 (3.3%) | 3,725,543 (1.2%) | 1.64 |
| Cambodia | 52 (2.9%) | 1,521,464 (0.5%) | 3.42 |
| Singapore | 47 (2.6%) | 16,155,080 (5.3%) | 0.29 |
| Angola | 41 (2.3%) | 197,908 (0.06%) | 20.7 |
| Bangladesh | 28 (1.5%) | 445,879 (0.1%) | 6.28 |
| Maldives | 14 (0.8%) | 709,714 (0.2%) | 1.97 |
| Papua New Guinea | 12 (0.7%) | 9,550 (<0.01%) | 126 |
| Other (32 countries) | 78 (4.3%) | 75,757,649 (25%) | 0.10 |
| Unknown | 349 (19.2%) | – | – |
| Total | 1,822 (100%) | 306,313,978 (100%) | – |

Table 2. Summary of the results of a multivariable negative binomial regression model predicting cases of imported dengue from annual totals of air travelers from dengue-endemic and non-endemic countries.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Coefficient | SE | 95% confidence interval | p-value |
| Log of travelers from endemic countries | 0.60 | 0.18 | (0.24 , 0.96) | <0.01 |
| Log of travelers from non-endemic countries | 0.03 | 0.20 | (-0.37 , 0.44) | 0.9 |
| Year | 0.23 | 0.06 | (0.12 , 0.34) | <0.01 |

Table 3. Predictions from a negative binomial model of the increase in number of detected cases of imported dengue based on increase in volume of air travel from dengue-endemic countries, aggregated to year.

|  |  |
| --- | --- |
| Increase in annual air travel volume from dengue-endemic countries (%) | Increase in imported cases of dengue with 95% confidence interval (%) |
| 1 | 0.6 (0.4 to 0.8) |
| 5 | 3.0 (1.8 to 4.1) |
| 10 | 5.9 (3.6 to 8.2) |