# UNIVERSITY OF SOUTHAMPTON

FACULTY OF SOCIAL, HUMAN AND MATHEMATICAL SCIENCES

School of Geography and Environment

**Spatiotemporal patterns, driving factors and seasonal risk of mosquito-borne disease importation into China**

by

**Shengjie Lai**

Thesis for the degree of Doctor of Philosophy

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# ABSTRACT

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Health Geography

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## SPATIOTEMPORAL PATTERNS, DRIVING FACTORS AND SEASONAL RISK OF MOSQUITO-BORNE DISEASE IMPORTATION INTO CHINA

Shengjie Lai

With the rapid increase of Chinese international travel, labour service and business, the pressure of imported mosquito-borne infectious diseases into China is also on the rise, and a better understanding of this phenomenon is required to enable appropriate public health actions. The main purpose of this thesis is to examine the spatiotemporal patterns, driving factors and seasonal risk of the importation and onward transmission for two mosquito-borne diseases, malaria and dengue, in China. Multidisciplinary approaches have been used and a variety of datasets has been integrated, including disease incidence, air travel, environment, and international investment. The analyses presented demonstrate that the spatiotemporal patterns of malaria and dengue have changed significantly in mainland China over the last decade, with an expanded geographic range and increasing incidence of imported infections. However, the geographic extent of autochthonous malaria in China has shrunk significantly due to malaria control and elimination activities, while the incidence of locally transmitted dengue has increased dramatically since 1990. The importation of mosquito-borne diseases is driven by transmission rates in origin countries, increasing travel, as well as investment patterns and economic ties. Taking dengue as an example, the seasonally changing risk and geographic expansion of mosquito-borne disease spread from Southeast Asia into China has been quantified, with emerging routes highlighted. These findings have important public health significance in formulating strategies and technical guidance for mitigating infections in travellers, improving the capacity of screening, diagnosis and treatment, reducing the risk of morbidity, and strengthening surveillance and investigation capabilities, so as to enable timely interruption of the seasonal onward transmission of imported mosquito-borne diseases.

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I, Shengjie Lai, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Spatiotemporal patterns, driving factors and seasonal risk of mosquito-borne disease importation into China

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
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Signed:

Date:

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# Abbreviations

ACT, artemisinin-based combination therapy;

ADE, antibody-dependent enhancement;

AIDS, acquired immune deficiency syndrome;

AUC, area under ROC curve;

BRT, boosted regression tree;

CDC, Centres for Disease Control and Prevention;

CED, climatic Euclidean distance;

CI, confidence interval;

DALYs, disability-adjusted life years;

DENV, dengue virus;

DF, dengue fever;

DHF, dengue haemorrhagic fever;

DNA, deoxyribonucleic acid;

DSS, dengue shock syndrome;

EIP, extrinsic incubation period;

ELISA, enzyme-linked immunosorbent assay;

EU, the European Union;

EVI, enhanced vegetation index;

GDP, gross domestic product;

GLM, generalized linear model;

GPS, Global Positioning System;

HIV, human immunodeficiency virus;

IATA, International Air Transport Association;

IQR, interquartile range;

IRS, indoor residual spraying;

ITN, insecticide-treated net;

LLIN, long-lasting insecticidal net;

MERS, Middle East Respiratory Syndrome;

MESIS, Malaria Enhanced Surveillance Information System;

NIDRIS, National Notifiable Infectious Disease Reporting Information System;

NMEP, national malaria elimination programme;

NS, non-structural protein;

OD, origin-destination;

ODA, official development assistance;

OR, odds ratios;

PCR, polymerase chain reaction;

*Pf*$PR_{2\text{-}10}$, *P. falciparum* parasite prevalence estimates in 2-10 year-olds;

$R_0$, basic reproduction number;

RDT, rapid diagnostic test;

RNA, ribonucleic acid;

ROC, receiver operating characteristic;

SARS, severe acute respiratory syndrome;

SD, standard deviation;

SEA, South-East Asia;

SIR, susceptible-infected-recovered

SSA, sub-Saharan Africa;

UI, uncertainty interval;

UK, the United Kingdom;

US, the United States;

USD, US dollars;

VBD, vector-borne disease;

VFR, visiting friends and relatives;

World Health Organization, WHO;

WMR, World Malaria Report.

# Chapter 1 Introduction

## 1.1 Chapter summary

The first chapter of this thesis begins by introducing the background of mosquito-borne diseases, in particular malaria and dengue. Then the global efforts of controlling and eliminating mosquito-borne infections have been summarized and highlight that the global dispersal of mosquito-borne diseases has been accelerated by the substantial growth in the reach and rates of human travel by contemporary transport. It is of importance to determine spatiotemporal patterns and driving factors of mosquito-borne disease importations networks, based on feasible data sources, indicators and methods. Moreover, this chapter reviews and discusses the strengths and weaknesses of different modelling approaches for quantifying the risks of importation and onward transmission of mosquito-borne diseases to guide the choice of appropriate models in this study. Finally, a brief introduction of the current situation and recent research on mosquito-borne disease importation into China has been given, leading to the aims of this study and specific research questions.

## 1.2 Background to mosquito-borne diseases

Mosquito-borne diseases are illnesses in human populations caused by bacteria, viruses or parasites transmitted by mosquitoes. For instance, many species of the genus *Anopheles* mosquitoes carry *Plasmodium* parasites, which cause malaria ( World Health Organization [WHO], 2017e), and the viruses of dengue, chikungunya, yellow fever, and Zika are transmitted mostly by *Aedes* mosquitoes (WHO, 2014b). Another important vector of mosquito-borne disease is the genus *Culex*, which carries West Nile virus, Japanese encephalitis virus, and *Wuchereria bancrofti* that causes lymphatic filariasis (**Table 1-1**).

Mosquito-borne diseases have been reported in many parts of the world, resulting in heavy health and economic burdens. Globally, more than one billion people are estimated to be infected by vector-borne diseases every year (WHO, 2014b), and mosquito-borne diseases are responsible for nearly 700 million episodes of illness and more than one million deaths annually worldwide. Malaria and dengue are two of the most prevalent mosquito-borne diseases (G. B. D. Disease and Injury Incidence and Prevalence Collaborators, 2016; Murray et al., 2014; Stanaway et al., 2016; Caraballo and King, 2014), which are introduced below.

**Table 1-1. Examples of mosquitoes and the diseases that they can transmit.**

| Mosquitoes | Mosquito-borne diseases |
|---|---|
| *Anopheles* (more than 60 known species can transmit diseases) | Malaria, lymphatic filariasis (in Africa) |
| *Aedes aegypti* | Dengue, yellow fever, chikungunya, and Zika |
| *Aedes albopitctus* | Chikungunya, dengue, and West Nile virus |
| *Culex quinquefasciatus* | Lymphatic filariasis |
| *Culex tritaeniorhynchus* | Japanese encephalitis |
| *Haemagogus* | Yellow fever |

### 1.2.1 Malaria

*Plasmodium* malaria, transmitted via the bites of female *Anopheles* mosquitoes, is one of the most prevalent parasitic diseases affecting mankind. Five species of *Plasmodium* including *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* cause malaria in humans, and two of them - *P. falciparum* and *P. vivax* – pose the greatest threat (White et al., 2014).

#### 1.2.1.1 Disease burden

It has been estimated that 212 million new cases occurred worldwide (uncertainty interval [UI]: 148-304 million) in 91 countries and territories with malaria transmission in 2015 (WHO, 2016a), and the years lived with disability (YLDs) were 3358.2 (2356.9-4703.9) thousands in 2015 (G. B. D. Disease and Injury Incidence and Prevalence Collaborators, 2016). Among them, 35 countries implemented national malaria-eliminating programme in 2015 (Newby et al., 2016; Feachem et al., 2010). Most malaria cases in 2015 were reported in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%) (WHO, 2016a). Most cases are caused by *P. falciparum* malaria, and only about 4% of estimated cases globally are due to *P. vivax*, but the proportion of *P. vivax* infections is 41% in non-African countries (**Figure 1-1** and **Figure 1-2**).

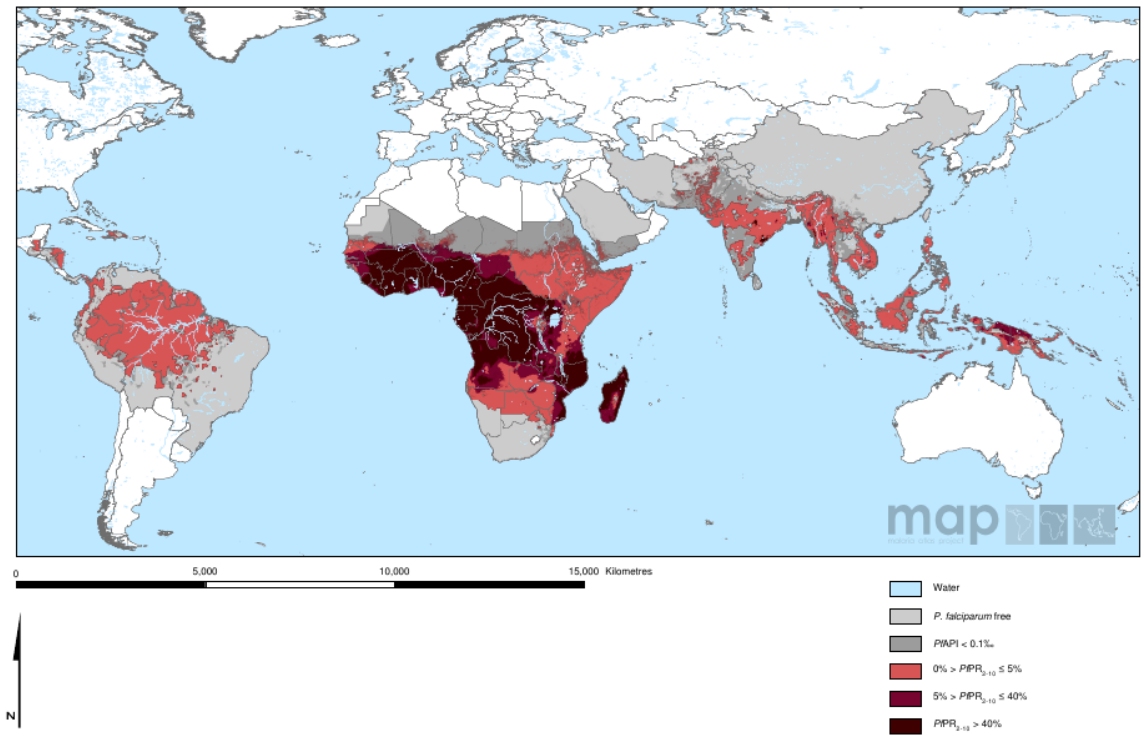



**Figure 1-1. Global spatial distribution of Plasmodium falciparum malaria stratified by endemicity class map in 2010.**

Data source: Malaria Atlas Project (Gething et al., 2011a).

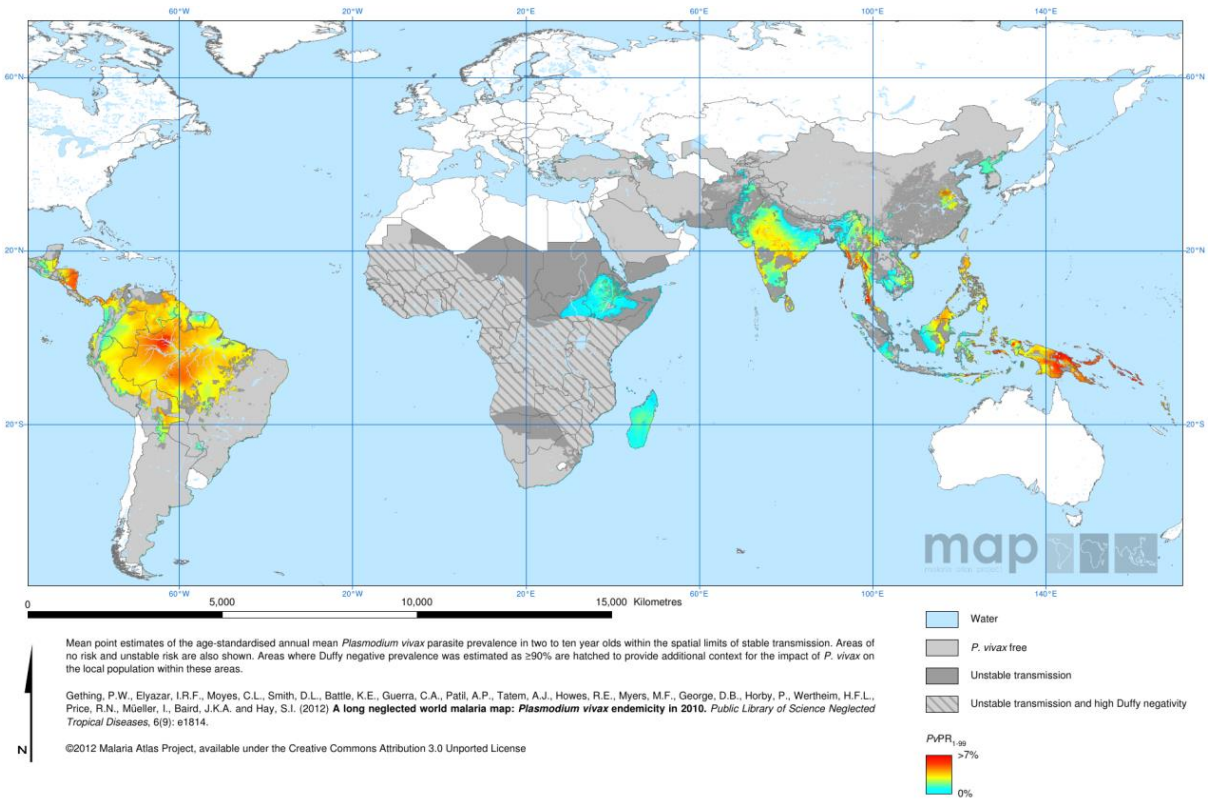



**Figure 1-2. Global spatial distribution of *Plasmodium vivax* malaria endemicity map in 2010.**

Data source: Malaria Atlas Project (Gething et al., 2012).

In 2015, it was estimated that there were 429 000 deaths from malaria globally (UI: 235 000–639 000) (WHO, 2016a). Of these, an estimated 303 000 malaria deaths (UI: 165 000–450 000) occurred in children aged under 5 years, which is equivalent to 70% of the global total. The vast majority of deaths (99%) are due to *P. falciparum* malaria, and *P. vivax* is only estimated to have been responsible for 3,100 deaths in 2015 (UI: 1800–4900), with 86% occurring outside Africa (WHO, 2016a). However, following the increasing effects of malaria intervention and elimination, the global burden of malaria has declined along with the shrinking geographic range of malaria, e.g. the global incidence of malaria has decreased by 15.4% from 2005 to 2015 (G. B. D. Disease and Injury Incidence and Prevalence Collaborators, 2016), and the prevalence of *P. falciparum* malaria in Africa was halved between 2000 and 2015 (Bhatt et al., 2015).

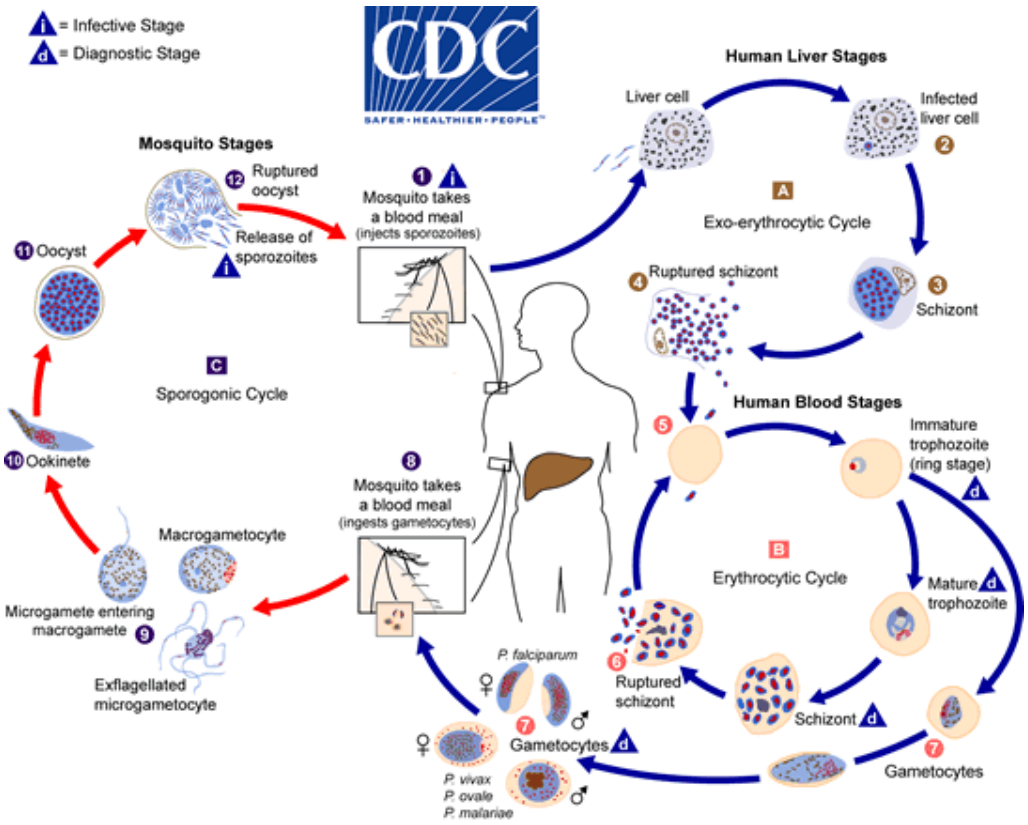



**Figure 1-3. Life cycle of malaria parasites.**

Data source: Centers for Disease Control and Prevention (CDC). Biology of malaria. www.cdc.gov/malaria/about/biology/

### 1.2.1.2 Life cycle

The *Plasmodium* parasite has a very complex life cycle (**Figure 1-3**). As a transmission vector and definitive host, a female *Anopheles* mosquito can cause infection by taking a blood meal and transmitting sporozoites into the human host ❶ in **Figure 1-3**. In the exo-erythrocytic cycle Ⓐ, sporozoites enter the bloodstream, and migrate to the hepatocytes (liver cells) ❷, where they reproduce asexually to produce thousands of merozoites ❹, which then rupture the liver cells

and return to the bloodstream. The merozoites infect red blood cells 5, where they initiate a series of asexual multiplication cycles B, develop into ring forms, trophozoites and schizonts, and produce new infective merozoites when the cells burst (CDC, 2017b). Then, some merozoites develop into a male or female gametocyte form at a sexual stage 7. If gametocytes from the blood of an infected person are taken up by the bite of a fertilized mosquito 8, they mature in the mosquito gut C. Next, the male and female gametocytes fuse and form an ookinete 10. Ookinetes develop into new sporozoites 12 that migrate to the salivary gland of mosquito, and will infect humans and continue a new life cycle, when the mosquito takes a subsequent blood meal (Cowman et al., 2012). Additionally, malaria parasites can also be transmitted by blood transfusions, although this is rare (Owusu-Ofori et al., 2010).

#### 1.2.1.3 Clinical features

The signs and symptoms of malaria usually begin 8–25 days following infection by a mosquito bite (White et al., 2014). Initial manifestations of the disease are similar to flu-like symptoms, and the presentation may include fever, fatigue, vomiting, headache, shivering and joint pain. The typical symptom of malaria is paroxysm, a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating. Generally, *P. falciparum* infection can cause recurrent fever every 36–48 hours, or a less pronounced and almost continuous fever, while tertian fever (two-day intervals) occurs in *P. vivax* and *P. ovale* infections, and quartan fever (three-day intervals) for *P. malariae*. Severe malaria with complications is usually caused by *P. falciparum* infection: this may result in cerebral malaria that frequently exhibits neurological symptoms (White et al., 2014).

Symptoms of malaria may recur after varying symptom-free periods due to: 1) Recrudescence, caused by parasites surviving in the blood as a result of inadequate or ineffective treatment; 2) Relapse, or when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in hepatocytes, commonly seen with *P. vivax* and *P. ovale* infections; or 3) Reinfection, which means a new parasite was introduced after parasites in the past infection were eliminated from the body (White, 2011; Nadjm and Behrens, 2012; WHO, 2015b).

#### 1.2.1.4 Diagnosis and treatment

Patients with suspected malaria should have parasitological laboratory-confirmed diagnosis by microscopic examination of blood films, or with antigen-based rapid diagnostic tests (RDT) (CDC, 2017). The polymerase chain reaction (PCR) technique has been developed to detect the deoxyribonucleic acid (DNA) of parasites, but is not widely used due to its cost and complexity.

Malaria is an entirely treatable disease with antimalarial medications. Treatment based on clinical manifestation should only be given if diagnostic tests are not immediately accessible within 2 hours of patients presenting for treatment (WHO, 2015b). The primary objective of prompt diagnosis and treatment with an effective and safe antimalarial within 24 hours of fever onset is to rapidly eliminate the parasite from blood in order to prevent life-threatening complications, or chronic infection that leads to malaria-related anaemia. From a public health perspective, treatment also interrupts transmission of parasite to other susceptible hosts, by reducing the reservoir and by preventing the spread of antimalarial drug resistant strains (WHO, 2015b).

The use of antimalarial medications depends on the species of parasite and severity of the disease. Simple or uncomplicated malaria may be treated with oral medications. For the treatment of uncomplicated malaria caused by *P. falciparum*, artemisinin-based combination therapies (ACTs), combining two active ingredients with different mechanisms of action, are the most effective antimalarial medicines available currently and are recommended by WHO (WHO, 2015b). The choice of ACT should be based on the results of therapeutic efficacy studies against local strains of *P. falciparum* malaria. For the treatment of *P. vivax* infections of blood stages, patients should be treated with chloroquine in areas where it remains effective, but in areas where chloroquine-resistant *P. vivax* have been found, infections should be treated with an ACT. In order to prevent relapses, primaquine should be added to the treatment for clearance of liver forms. Additionally, severe malaria should be treated with injectable artesunate (intramuscular or intravenous) for at least 24 hours and followed by a complete 3-day course of an ACT once the patient can tolerate oral medicines (WHO, 2015b).

Drug resistance in malaria treatment is now common against all classes of antimalarial drugs apart from artemisinins, which has raised a growing concern worldwide (Sinha et al., 2014). Artemisinin-resistant *P.falciparum* malaria has emerged in the Greater Mekong Subregion. (Ashley et al., 2014; Ataide et al., 2017). Moreover, malaria strains identified on the Cambodia–Thailand border are resistant to combination therapies that include artemisinins, and may, therefore, be untreatable (Carrara et al., 2013; Ataide et al., 2017).

#### 1.2.1.5 Vectors

Human malaria is transmitted only by females of the genus *Anopheles*, and approximately 40 *Anopheles* species are able to transmit malaria well enough to cause significant human illness and death. Anophelines are found worldwide, not only in malaria-endemic areas, but also in areas where malaria has been eliminated and thus are constantly at risk of re-introduction of the disease (Hay et al., 2010; Sinka et al., 2010a; Sinka et al., 2010b; Sinka et al., 2011).

The blood meals of *Anopheles* link the human and the mosquito hosts in the parasite life cycle. The female mosquito usually starts searching for a meal at dusk to carry out egg production, and prefers to feed at night. To be effective at transmitting malaria between people, a mosquito species needs to have several characteristics:

1) Abundance - the mosquito needs to exist in numbers high enough to ensure individuals encounter an infectious human to be infected by the parasite.
2) Longevity - individual mosquitoes need to survive long enough to allow the parasite to complete its lifecycle in the mosquito host ("sporogonic" or "extrinsic" cycle, duration 10 to 18 days).
3) Capacity – each mosquito needs to be able to carry enough malaria parasites (from the "gametocyte" stage to the "sporozoite" stage) in the salivary glands to ensure the parasite is transmitted to the next human;
4) Contact with humans – the species needs to be able to survive and breed in places close to homes, and be able to find and bite human.

Additionally, differently from the vertebrate hosts, the mosquito host does not suffer noticeably from the presence of the parasites (Hay et al., 2010).

#### 1.2.1.6 Preventive interventions

Vector control is one of the key measures for preventing malaria in endemic areas with the goals of protecting individual people against infective mosquito bites, and reducing the intensity of transmission at the community level. The most powerful and broadly applied interventions are insecticide-treated net (ITN), long-lasting insecticidal net (LLIN) and indoor residual spraying (IRS) with insecticides. In a few specific settings and circumstances, these may be complemented by other methods, e.g. larval control by draining standing water. Preventive chemotherapy of full antimalarial treatment can be applied intermittently or seasonally to reduce malaria morbidity and mortality in a specific high-risk target population, e.g. pregnant women and infants. However, there are currently only a recombinant protein-based malaria vaccine, the RTS, S/AS vaccine, approved for use by Europe in July 2015, and recommended by WHO to conduct a pilot programme for widely testing in Ghana, Kenya, and Malawi beginning in 2018 (WHO, 2015a; Rietveld and Newman, 2015).

Personal preventive measures are also recommended for international travellers who visit an endemic area during the malaria transmission season and who are exposed to mosquito bites. Because of the severity of malaria, the risks for nonimmune travellers and the large number of such travellers who visit endemic regions, personal protective measures taken by travellers are of utmost importance. Depending on the malaria risk in the area visited, the recommended

prevention method may be mosquito bite prevention only or mosquito bite prevention in combination with chemoprophylaxis or standby emergency treatment (WHO, 2015a; Rietveld and Newman, 2015).

### 1.2.2 Dengue

Dengue is one of the most common viral diseases in human transmitted by arthropods (Guzman and Harris, 2015; Rodenhuis-Zybert et al., 2010). It is common in more than 110 countries, and the incidence of dengue increased 30 fold between 1960 and 2010 (WHO, 2012a; WHO, 2009b).

#### 1.2.2.1 Disease burden

There are an estimated 390 million dengue infections per year in this decade, among an estimated 2.5–4 billion people living in countries where dengue virus (DENV) transmission occurs (Figure 1-4) (Bhatt et al., 2013; Brady et al., 2012). In 2013 dengue was estimated to cause about 60 million symptomatic infections worldwide (Stanaway et al., 2016), of which 18% were admitted to hospital and about 13,600 deaths resulted, with the loss of 1,600 disability-adjusted life years (DALYs) per million population and the cost of 9 billion US dollars (USD) worldwide (Shepard et al., 2016). More than 70% of people at risk reside in the Asia Pacific region (Organization, 2012), making this region the global epicentre of dengue activity (WHO, 2012a; Bhatt et al., 2013). In addition, the global incidence of dengue has increased by 143% from 2005 to 2015 (G. B. D. Disease and Injury Incidence and Prevalence Collaborators, 2016).

Compared with other diseases and their respective burdens, dengue can cause as much or greater human suffering than other communicable diseases in some of the most affected regions. Southeast Asia was estimated to have about 3 million infections and 6,000 deaths each year during 2000-2010 (Shepard et al., 2013; Shepard et al., 2004). The burden of the disease in Southeast Asia was comparable with that of meningitis, having twice the burden of hepatitis and one third of the burden of HIV/AIDS (Shepard et al., 2013; Shepard et al., 2004). In Latin America and the Caribbean, by the 1990s dengue was causing a similar burden of disease as meningitis, hepatitis, malaria, the childhood cluster of diseases (polio, measles, pertussis, diphtheria and tetanus) or tuberculosis (Meltzer et al., 1998). For Africa, there are insufficient data from endemic countries to make even rough estimates of burden. At least 22 countries in Africa have reported dengue transmission, and it is likely that African countries contain 20% of the global population at risk of dengue transmission (Amarasinghe et al., 2011; WHO, 2012a). In addition, severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries (WHO, 2017a; Ranjit and Kissoon, 2011).

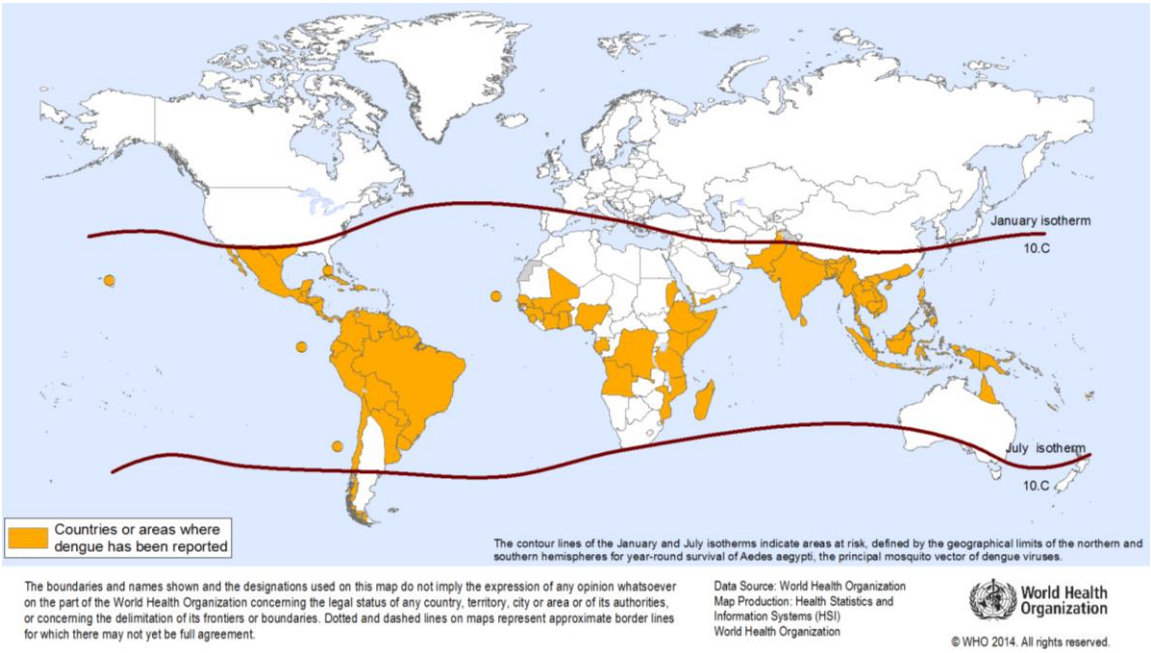



**Figure 1-4. Countries or areas where dengue has been reported**.
Data source: WHO (WHO, 2014a).

#### 1.2.2.2 Aetiology

DENV is an ribonucleic acid (RNA) virus of the *flaviviruses* that also include many other mosquito-borne pathogens, e.g. yellow fever, Zika, West Nile, and Japanese encephalitis viruses (Gould and Solomon, 2008). The genome of dengue virus codes for three types of protein molecules (C, prM and E) that form the virus particle, and seven types of non-structural proteins (NS 1, 2a, 2b, 3, 4a, 4b and 5) that are found in cells of infected host only for virus replication (Rodenhuis-Zybert et al., 2010; Guzman et al., 2010). Based on the antigenicity of dengue virus, five strains (serotypes) are identified, of which the first four are referred to as DENV-1, DENV-2, DENV-3 and DENV-4 (WHO, 2009b), and the fifth type was announced in 2013 (Normile, 2013). DENV serotypes can be further defined into genotypes based on differences in the envelope gene sequence, and molecular epidemiologic studies may assist in tracking disease transmission patterns (Margolis et al., 2015).

When a person is bitten by a mosquito carrying dengue virus, the virus enters the skin together with the saliva of mosquito. It binds to and enters white blood cells, and reproduces inside the cells while they move throughout the human body. The infected white blood cells produce several signalling proteins, such as cytokines and interferons, which are responsible for many symptoms, such as fever, flu-like symptoms and severe pains. In severe infection, the production of dengue virus is greatly increased inside human body, and many more organs, e.g. liver and bone marrow, can be affected. Due to capillary permeability, fluid from the bloodstream leaks through the wall of small blood vessels into body cavities. Thus, less blood in the vessels results in lower blood pressure, which cannot supply sufficient blood to vital organs. Furthermore, due to infection of

the stromal cells, the dysfunction of bone marrow can reduce the production of platelets that are necessary for blood clotting, and this increases the risk of bleeding (Martina et al., 2009).

Infection with one serotype is thought to produce lifelong immunity to that type, but there is no long-term, cross-protective immunity following infection (WHO, 2009b). All DENV serotypes can cause dengue and have been associated with severe infections, including dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), from a secondary infection when someone has been previously exposed (Guzman et al., 2010). It is not entirely clear why secondary infection with a different strain of dengue virus places people at risk of DHF and DSS. The most widely accepted hypothesis is that of antibody-dependent enhancement (ADE). An increased risk of severe dengue is associated with the presence of heterotypic antibody and with viral strains that have greater virulence and /or epidemic potential (WHO, 2017a; Guzman and Harris, 2015).

#### 1.2.2.3 Clinical features

The majority of people infected with dengue virus are asymptomatic (80%) or have only mild symptoms in both children and adults. The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, commonly 4 to 7 days, and it generally takes 2 to 9 days to recovery (Kularatne, 2015; Guzman and Harris, 2015). The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), vomiting, muscle and joint pains, and a characteristic skin rash, with a clinical course usually following three phases: febrile, critical, and convalescent.

**Febrile phase**: Patients with dengue often have sudden onset of fever, which lasts for 2-7 days and may be biphasic. Other signs and symptoms include intense headache, generalized pain, nausea, vomiting, macular or maculopapular rash, and minor haemorrhagic manifestations, including petechia (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries), ecchymosis (bleeding from broken blood vessels into surrounding tissue), purpura (a condition in which bleeding under the skin causes purplish blotches to appear on the skin), epistaxis, bleeding gums, haematuria, or a positive tourniquet test. Warning signs of progression to severe dengue may occur in the late febrile phase (WHO, 2009b).

**Critical phase**: This phase begins at defervescence and typically lasts 24-48 hours (Simmons et al., 2012). Most patients clinically improve during this period, but those with significant leakage of plasma, typically lasting one to two days, develop severe dengue as a result of a marked increase in vascular permeability (WHO, 2009b). This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased blood supply to

vital organs. This critical phase occurs relatively more commonly in children and young adults, with DHF and DSS occurring in less than 5% of all cases of dengue (Ranjit and Kissoon, 2011).

**Convalescent phase**: This recovery phase occurs with resorption of the leaked fluid into the blood vessel, usually lasting 2 to 3 days (WHO, 2009b). The improvement is often striking, and can be accompanied with severe itching and a slow heart rate. Patients may develop a generalized erythematous rash with circular areas of nonerythematous skin, and a feeling of fatigue may last for weeks in adults (Ranjit and Kissoon, 2011).

#### 1.2.2.4 Diagnosis and treatment

Clinical diagnosis of dengue is typically made in endemic areas on the basis of reported symptoms and physical examination. However, early disease can be difficult to differentiate from other infections with similar symptoms, e.g. chikungunya, Zika, malaria, measles, and influenza, etc (Chen and Wilson, 2010; WHO, 2009b). The diagnosis should be considered in anyone who develops a fever within two weeks of being in the tropics or subtropics (Simmons et al., 2012). Laboratory confirmation of dengue infections can be done by virus isolation in cell cultures, nucleic acid detection by polymerase chain reaction (PCR), viral antigen detection (such as for NS1) or specific antibodies (serology) (WHO, 2009b; Guzman and Harris, 2015). Tests for dengue virus-specific antibodies, types IgG and IgM, can also be useful in confirming a diagnosis in the later stages of the infection. In general, the choices of testing are based on the timing and types of samples, sensitivity of assays, and the capacity and cost to conduct the tests.

There is no specific antiviral therapy for dengue, however maintaining proper fluid balance is important (WHO, 2009b). During the febrile phase, patients should be kept well hydrated and avoid use of aspirin. Additional supportive care is required if the patient becomes dehydrated or develops warning signs for severe dengue. Early recognition of shock and intensive supportive therapy for severe disease can reduce risk of death from approximately 10% to less than 1%. During the critical phase, maintenance of fluid volume and hemodynamic status is central to management of severe cases, and patients should be monitored for early signs of DHS or DSS (WHO, 2009b).

#### 1.2.2.5 Vectors

Dengue virus is spread by several species of *Aedes* mosquito, principally *Ae. aegypti*, and to a lesser extent, *Ae. albopictus*, which also transmits chikungunya, yellow fever and Zika viruses, and these mosquitoes usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 metres (**Figure 1-4**) (Vega-Rua et al., 2013; Brady et al., 2014; Bhatt et al., 2013; Evans et al., 2017; Messina et al., 2016). The *Ae. aegypti* mosquito, a day-time feeder, lives in

urban habitats and breeds mostly in man-made containers filled with water, with peak biting periods in the early morning. *Ae. albopictus*, a highly adaptive and secondary dengue vector, has become a significant pest in many communities because it closely associates with humans (rather than living in wetlands), and typically flies and feeds in the daytime in addition to at dusk and dawn (Brady et al., 2013; Rodrigues Mde et al., 2015; Reiner et al., 2016).

An infected female mosquito can transmit the virus to humans after an extrinsic incubation period for 4–8 days (WHO, 2009b; Margolis et al., 2015). A female mosquito that takes a blood meal from a person infected with dengue virus, during the initial 2- to 10-day febrile period, becomes itself infected with the virus in the cells lining its gut. About 8–10 days later, the virus spreads to other tissues including the salivary glands of mosquito and is subsequently released into its saliva, but it seems that the virus has no detrimental effect on the mosquito, which remains infected for life. In addition, dengue can also be transmitted via infected blood products and through organ donation (Wilder-Smith et al., 2009). Vertical transmission during pregnancy or at birth has also been reported (Wiwanitkit, 2009).

#### 1.2.2.6 Preventive interventions

Several vaccine candidates are in clinical or pre-clinical development (Aguiar and Halstead, 2016; WHO, 2017b; Saez-Llorens et al., 2017). In late 2015 and early 2016, the first dengue vaccine, *Dengvaxia* by Sanofi Pasteur, was licensed by a small number of countries for use in populations aged between 9 and 45 years of age living in endemic areas (WHO, 2017c). The WHO Strategic Advisory Group of Experts (WHO, 2017c) recommended countries consider introduction of the vaccine only in geographic settings (national or subnational) with high endemicity.

For most countries, prevention of bites from the vector mosquito is the only means of prevention. The primary method of controlling vector is getting rid of larval habitats, including water-holding containers, e.g. old tires, flowerpots, trash, or water storage containers, close to or inside houses (WHO, 2012a). If removal of open sources of water is not possible, insecticides or biological control agents can be used. Community surveys to investigate the density of vector and identify larval habitats should complement plans for the elimination, management, or treatment of mosquito production sites. Communities should be educated about personal protection, e.g. repellents, screening, and protective clothing, against day-biting mosquitoes. Prevention measures are required year-round, and it is usually too late for reactive vector control activities to be effective once increase dengue activity is identified.

Because vector control and personal protection generally appear not to be sufficiently effective in preventing or mitigating dengue seasonal and epidemic increases once it has begun, timely

identification of cases and good clinical management of dengue patients to prevent mortality and morbidity is essential. This should include ongoing education of the public about dengue and warning signs, ongoing education of health care professionals in best clinical practices, evaluation of health care practices related to clinical outcomes, and planning by health care facilities to meet demands placed upon them by the annual seasonal increase in cases or by periodic epidemics (Margolis et al., 2015).

Overall, regarding the high disease burden and complex transmission mechanism of mosquito-borne diseases, feasible strategies should be formulated and implemented to control these diseases, especially malaria and dengue, and if applicable, national programmes should be adopted to interrupt the locally transmission of pathogens and ultimately eliminate the diseases.

## 1.3 Controlling and eliminating mosquito-borne diseases

The current global efforts of mosquito-borne disease control, taking malaria and dengue as examples, are summarised to understand the actions, achievements and challenges of controlling and eliminating diseases transmitted by mosquitoes. Commonly, disease control refers to a reduction in the incidence, prevalence, morbidity or mortality of an infectious disease to a locally acceptable level, whereas elimination is defined as the reduction to zero incidence of the disease or infection in a defined geographical area or country, but not worldwide; and eradication as the permanent reduction to zero incidence worldwide of the infection through deliberate measures such as vaccines (Dowdle, 1998; Heymann, 2006). Often, the first step toward disease elimination is disease control.

### 1.3.1 Malaria elimination and its challenges

Regional malaria elimination campaigns were first conducted in the late 1940s, and this campaign succeeded in eliminating malaria from Europe, North America, the Caribbean and parts of Asia and South-Central America, but no major success occurred in sub-Saharan Africa (Carter and Mendis, 2002; Lopez et al., 2006). The Global Malaria Eradication Program raised in 1955 was abandoned in 1969, and the main reasons for failure were technical challenges of executing the strategy especially in Africa (Tanner and de Savigny, 2008). By 1992, the combination of a worsening malaria situation and promising technical developments led to renewed global focus on malaria control. The Roll Back Malaria initiative, launched by WHO in 1998, led to the Abuja Declaration in 2000, which defined progressive targets of intervention coverage to eliminate malaria (WHO, 2000). Increased resources from the Global Fund to Fight AIDS, Tuberculosis and Malaria, the World Bank, the US President's Malaria Initiative, government commitments and

many others have improved the intervention coverage for malaria control and elimination (Tanner and de Savigny, 2008).

Due to the increased efforts in malaria interventions, the global malaria map continues to shrink with economic development and increasing political and financial support for elimination, and the toolkit of innovative technologies and interventions to defeat malaria continues to expand (Newby et al., 2016). Between 2007 and 2013, there were four countries certified as malaria-free by WHO (Armenia, Morocco, Turkmenistan, and United Arab Emirates), eight countries moved into the prevention of reintroduction phase after sustaining at least 3 years of zero local malaria transmission (Argentina, Egypt, Iraq, Georgia, Kyrgyzstan, Oman, Syrian Arab Republic, and Uzbekistan), and five others interrupted local transmission (Azerbaijan, Costa Rica, Paraguay, Sri Lanka, and Turkey) (Newby et al., 2016). The incidence rate of malaria is estimated to have decreased by 41% globally from 2000 to 2015, and *P. falciparum* infection prevalence in endemic Africa halved and the incidence of clinical disease fell by 40% between 2000 and 2015 (Bhatt et al., 2015). As of 1 January 2016, there are 17 countries having eliminated malaria (i.e. attained zero autochthonous cases for 3 years or more) with six of these countries having been certified as malaria free by WHO (2016a). All countries in the WHO European Region reported zero indigenous cases in 2016, and Kyrgyzstan and Sri Lanka were certified malaria free in 2016 (WHO, 2017e) (**Figure 1-5**).

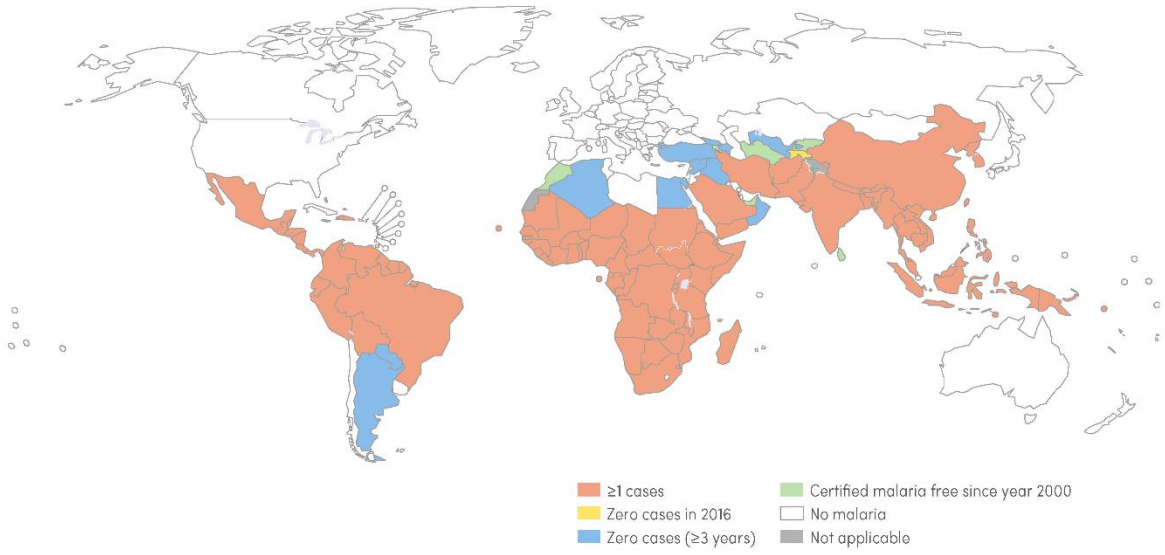



**Figure 1-5. Countries and territories with indigenous cases in 2000 and their status by 2016**. Data source: World malaria report 2017 (WHO, 2016a; 2017e). Countries with zero indigenous cases over at least the past 3 consecutive years are eligible to request certification of malaria free status from WHO.

Elimination is now considered an attainable goal by most national malaria programmes, with more than 100 countries having eliminated malaria in the past century. Moreover, malaria has not

been re-established in any of the countries where it was eliminated between 2000 and 2015 (WHO, 2016a), and 40 countries have achieved a reduction in incidence rates of 40% or more between 2010 and 2015 (Newby et al., 2016; Feachem et al., 2010).

To accelerate global progress towards malaria eradication, the Global Technical Strategy for Malaria 2016–2030 was adopted by the World Health Assembly in May 2015 to provides a comprehensive framework for reducing global malaria incidence and mortality rates (WHO, 2015a). It sets the target of reducing global malaria incidence and mortality rates by at least 90% by 2030 compared with 2015 levels; to eliminate malaria from at least 35 countries in which malaria was transmitted in 2015; and to prevent re-establishment of malaria in all countries that are malaria-free (WHO, 2017e). The strategy emphasizes the need for universal coverage of core malaria interventions for all populations at risk, including autochthonous and imported risk, and highlights the importance of using high-quality surveillance data for decision-making. It also identifies areas where innovative solutions will be essential for attaining the goals, and summarizes the estimated global costs of implementation (WHO, 2015a; 2016a). Due to this incredible progress of malaria control and elimination, the malaria eradication also back on the global agenda to achieve by a theoretical end date of 2040 (Gates, 2014; Newby et al., 2016; WHO, 2015a).

Despite excellent progress, serious challenges to further reducing malaria transmission in endemic countries in Africa and Asia and achieving malaria elimination remain as a result of (Newby et al., 2016):

1) The waning political commitment and decreasing budgets. Although the many declarations from national, regional, and global stakeholders to eliminate and eradicate malaria are promising, if political and financial commitment is not sustained, the goals will not be met (Cohen et al., 2012). Consequently, the resurgence of malaria might happen again in regions where the residual burden remains high, e.g. Sub-Saharan Africa.
2) The reintroduction of malaria from endemic areas to low transmission or non-endemic areas by increasing human mobility, along with the dispersal of increasing drug and insecticide resistance, e.g. artemisinin resistance in Thailand and Cambodia (Danis et al., 2013).

The identification of an optimum mix of interventions, improvement of intervention targeting, and elimination of local reservoirs of drug resistant parasites could help slow the spread of insecticide and drug resistance in the meantime (Smith Gueye et al., 2014; WHO, 2015a).

### 1.3.2 Dengue control and its challenges

Since the second World War, dengue has become a global problem with more than 110 countries reporting the disease (WHO, 2017a; Guzman et al., 2010). As one of eighteen neglected tropical diseases (WHO, 2017d), dengue is regarded as one of the most prevalent and rapidly spreading mosquito-borne diseases affecting human beings, with about half of the world's population now at risk (WHO, 2017a).

Global, regional, and national strategies, including guidance or toolkits for dengue prevention and control, have been issued in the last decade (WHO Regional Office for the Western Pacific, 2017b; Ooi et al., 2006; WHO, 2012a). The objectives of the WHO global strategy for dengue prevention and control during 2012–2020 are to reduce mortality and morbidity from dengue by 2020 by at least 50% and 25% respectively (using 2010 as the baseline) (WHO, 2012a). This global strategy provides the technical elements and enabling factors for implementation that are necessary to reverse the growing trend in the number of dengue cases, and the morbidity of dengue can be reduced by: 1) Implementing improved outbreak prediction and detection through coordinated epidemiological and entomological surveillance; 2) Promoting the principles of integrated vector management; 3) Deploying locally-adapted vector control measures, including effective urban and household water management; and 4) Communication to achieve behavioural outcomes in prevention programmes.

Dengue mortality will also be reduced via: 1) Implementing early case detection and referral systems for patients; 2) Managing severe cases with appropriate treatment; 3) Reorienting health services to cope with dengue outbreaks; and 4) Training health personnel at all levels of the health system. As a global threat, thus, dengue requires a global response involving all possible partners, and applying existing knowledge for dengue prevention and control, which are in need of the collaboration among partners, organizations and countries, leadership by WHO and increased funding.

However, over the last five decades from 1960 to 2010 the rates of dengue infection have increased 30-fold (WHO, 2012a), and morbidity has continued to increase in recent years, which indicates that previous control efforts may not be sufficient or sustainable. Since the first isolation of DENV in 1943, detection of four types of DENV has expanded worldwide together with growing hyperendemicity, particularly in Latin America and Asia (Messina et al., 2014). This spatial spread as well as increasing burden of dengue is believed to be due to a combination of increased vector spread, international travel, urbanization, population growth, and global warming (Gubler, 2011; Ebi and Nealon, 2016). Dengue infections are most commonly acquired in urban and semi-urban environment of tropical and sub-tropical climates, with local variations in risk influenced by

rainfall, temperature and unplanned rapid urbanization (WHO, 2017a). Moreover, *Ae. albopictus* is a competent vector for dengue viruses, expanding the territories from Southeast Asia to North America and European Region, and it has established in more countries than *Ae. aegypti* by international trade of goods (e.g. used tyres as a breeding habitat) due to its tolerance to freezing temperatures and ability to shelter in microhabitats (**Figure 1-6**) (Brady et al., 2013; Rodrigues Mde et al., 2015; Reiner et al., 2016).

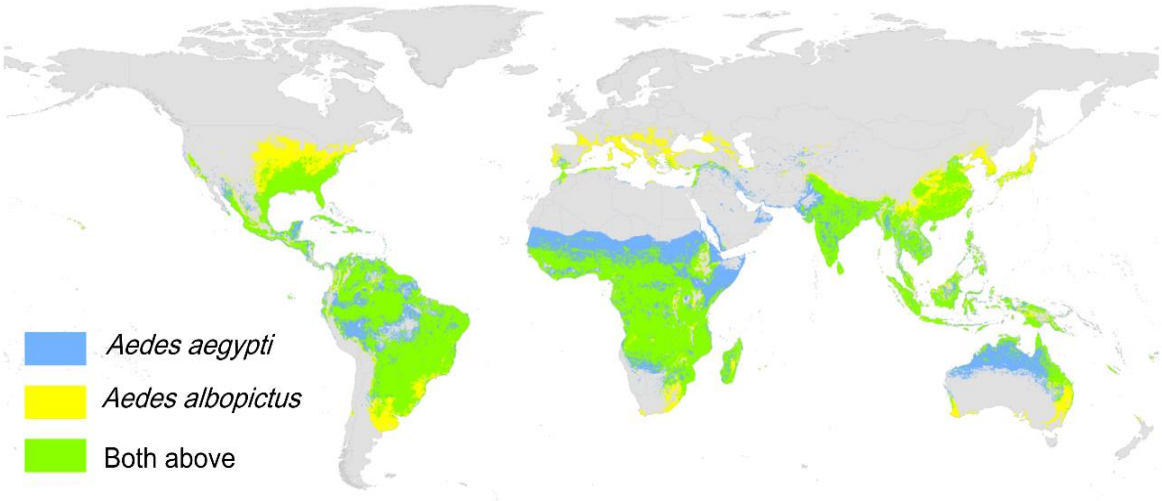



**Figure 1-6. Potential global distribution of the arbovirus vectors *Aedes* mosquitoes.**
Data source: Kraemer et al., 2015.

As the world effectively shrinks in terms of physical distance and isolation, the earth continually moves towards a globalized community (Smith et al., 2007). The increased mobility of populations has also contributed to the increasing number of outbreaks and circulating viruses, and also increased the risk of severe dengue due to the alternate transmission of different dengue strains. The importation of dengue by travellers has been widely reported in Europe, North America, and East Asia. Along with vector spread, therefore, dengue that was once endemic in Southeast Asia has spread to countries in the Pacific Ocean and America (Brathwaite Dick et al., 2012; Reiter, 2010; Lai et al., 2015).

In summary, while malaria prevalence has decreased dramatically through intense control and elimination efforts, dengue incidence is still increasing rapidly, and more control actions and investments are needed for dengue. Both face the challenges of pathogen importation from endemic areas via population movement, which threatens the successful control and elimination of mosquito-borne diseases.

## 1.4 Population movement and mosquito-borne disease transmission

This section briefly reviews the movement of population and dispersal of mosquito-borne diseases through global human transport, and outlines the approaches and data sources for determining routes and driving factors of disease importation networks.

### 1.4.1 Human travel and global disease dispersal

The substantial growth in the reach and rates of human travel in recent decades has accelerated the global spread of infectious diseases (Gushulak and MacPherson, 2004; Tatem et al., 2012; Franco-Paredes and Santos-Preciado, 2006; Tatem et al., 2006a), particularly the air traffic network (**Figure 1-7**) that allows human hosts or carriers of pathogens to move long distances within the incubation period for virtually all infections (Stoddard et al., 2009). In the last two decades, for instance, cross-continental transmission of a variety of emerging or re-emerging infectious diseases has occurred, such as: the global dispersal of severe acute respiratory syndrome in 2003 and influenza A H1N1 in 2009 (Brockmann and Helbing, 2013; Khan et al., 2009); outbreaks and dispersal of Middle East Respiratory Syndrome (MERS) (Park et al., 2015; Wu et al., 2015); Ebola in West African countries with cases transmitted to Europe and the United States (US) (Dudas et al., 2017; Cowling and Yu, 2015); Zika in American countries in 2016, which triggered a public health emergency of international concern (Rasmussen et al., 2016); yellow fever with cross-border transmission in Africa in 2016, caused by the large-scale movements of susceptible individuals into high yellow fever risk zones and by the neglect of control procedures (Kraemer et al., 2017); and lastly, the on-going seventh cholera pandemic (Hu et al., 2016a; Mutreja et al., 2011).

**Figure 1-7. The global air travel networks.**

Data source: IATA and the BlueDot (bluedot.global).

The rising volume of travel to and from endemic areas has resulted in imported mosquito-borne diseases being frequently reported in non-endemic countries. In a meta-analysis of nationally reported statistics on imported malaria from 40 non-endemic countries during 2005-2015, substantial geographical heterogeneities were found in reported malaria case numbers and compositions in non-endemic countries, and certain routes from endemic to non-endemic countries carry substantially more infections than others, with evidence of tight couplings that reflect historical, language, or travel ties (Tatem et al., 2017).

These patterns of importation also highlight the risks for secondary transmission following imported infections. A successful reintroduction depends on the arrival of the pathogen and suitable local ecology for transmission (Cohen et al., 2012). Malaria, for instance, was eliminated from the US in the early 1950's, but the species of *Anopheles* mosquitoes required for malaria transmission prior to elimination are still prevalent, and approximately 1,700 cases of malaria are reported every year in the US, almost all in recent travellers. Thus, there is a constant risk that malaria could be reintroduced in the US, and a total of 63 outbreaks of locally transmitted mosquito-borne malaria have occurred between 1957 and 2015 (CDC, 2017), including secondary transmission in Virginia in 2002 (Robert et al., 2005; CDC, 2002) and Florida in 2003 (CDC, 2003). The reintroduction of malaria through air travel has also occurred in some other previous malaria-free countries (Pindolia et al., 2012), e.g. Greece in 2011 (Andriopoulos et al., 2013; Danis et al., 2011). Further, malaria resurgence may occur in low transmission scenarios after control measures were relaxed in some countries (Chiyaka et al., 2013). Meanwhile, growing concerns have been raised about the possible spread of artemisinin resistance from the Greater Mekong subregion in Southeast Asia to other endemic regions due to the increasing global malaria connectivity through air travel (Huang and Tatem, 2013).

With regard to dengue, a similar situation has also been occurring, and the global air transport network is not only aiding the spread of both dengue vectors and virus within tropical regions suitable for transmission, but also facilitating a substantial increase of imported cases elsewhere (Tatem et al., 2006c). Imported cases of viremic travellers have been frequently reported in non-endemic countries in recent years with secondary transmission. In Europe, after the last dengue outbreak reported from 1927 to 1928 in Greece (Halstead and Papaevangelou, 1980), autochthonous dengue outbreaks reoccurred in September 2010 in Nice, south-east France, where *Ae. albopictus* is established (La Ruche et al., 2010; Semenza et al., 2014). In the US, nearly all dengue cases reported in the 48 continental states were acquired elsewhere by travellers or immigrants (Mohammed et al., 2010; CDC, 2005). Though contact between *Aedes* and people is

infrequent in the continental US, the secondary transmission by introduced dengue was reported in south Texas in 2005 (Ramos et al., 2008; CDC, 2007). After 70 years with no confirmed autochthonous dengue in Japan, 19 cases of locally acquired infection with dengue virus serotype 1 were reported in Tokyo during August–September 2014 (Kutsuna et al., 2015), and several cases were further exported to England and Germany (Kojima, 2015; Schmidt-Chanasit et al., 2014).

However, the increasing mobility by air travel expansion has not been ubiquitous, with historical and economic ties between regions and countries driving growth along certain routes far more than others, resulting in uneven pathogens movement which needs to be further investigated to define networks of disease importations (Huang and Tatem, 2013).

### 1.4.2 Population movement and its typology

The unprecedented level of population movement is attributed to several reasons. Firstly, sophisticated forms of transport, i.e. airplane and high-speed trains, now permit the swift movement of people over huge distances. Secondly, fast urbanization in the developing world is leading to major population redistribution, which particularly involves the movement from rural to urban areas, or migration flows from low or middle-income to high-income countries.(Saker et al., 2004; Abel and Sander, 2014) Thirdly, interstate war, internal conflicts, political and economic instability and natural disasters have led to mass movements of refugees and displaced persons.(Korfmacher and George, 2012)

Various datasets have been used for quantifying human mobility (Pybus et al., 2015), including volume of global air travellers (Brockmann and Helbing, 2013; Huang et al., 2013; Bogoch et al., 2016a), population census data (Wesolowski et al., 2013; Sorichetta et al., 2016), survey data using Global Positioning System (GPS) data-logger (Vazquez-Prokopec et al., 2009; Morales et al., 2010), marked banknotes movements (Brockmann et al., 2006), and anonymized call detail records and location-based service data of mobile phones (Gonzalez et al., 2008). These data sources have the potential to untangle human mobility following disasters (Wilson et al., 2016; Bengtsson et al., 2011), define the influence of seasonal population fluxes on infectious disease dynamics (Wesolowski et al., 2015a; Wesolowski et al., 2012) and support the planning of disease control and elimination strategies (Tatem et al., 2014). Although human population movement has been described using various spatial and temporal dimensions in the context of disease control and elimination (Guyant et al., 2015), a clear classification of population movement in disease transmission is also needed (Martens and Hall, 2000) (**Figure 1-8**).

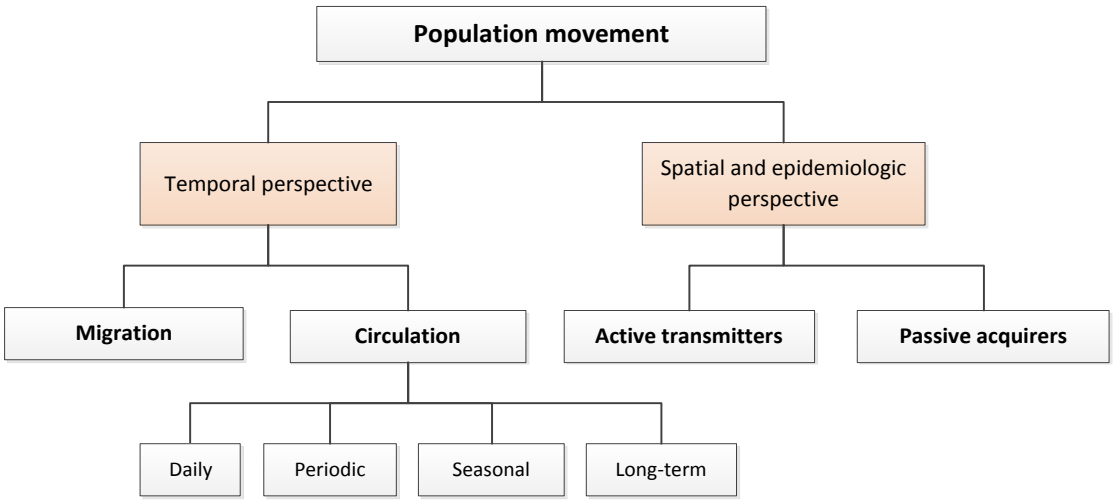



**Figure 1-8. The classification of population movement.**

In terms of a temporal perspective, population movement can be categorized as: 1) Migration, involving a permanent change of residence, including people in the transit phase of migration (Gould and Prothero, 1975; Lynch and Roper, 2011); or 2) Circulation, which encompasses movements of a short-term or cyclical nature and involving no longstanding change of residence. Moreover, circulation can be subdivided into daily, periodic, seasonal, and long-term movements. Daily circulation refers to leaving the residential location for up to 24 hours. Periodic circulation involves population who are absent from their permanent homes from one night to one year. Seasonal circulation is a type of periodic circulation but usually longer than periodic circulation, and defined as absence from the place of residence during a season or seasons of the year in the physical or economic environment. Long-term circulation involves people who are absent from their permanent residence for more than one year, and who generally maintain tight social-economic links with their home location, with an intention to return, i.e. wage labourers and traders (Saker et al., 2004).

In spatial dimensions and the epidemiologic perspective of the movements to and from endemic regions of contagion, travellers can be defined as:

1) Active transmitters who harbour pathogens and transmit the disease when they move to areas of low or sporadic transmission; or
2) Passive acquirers who are exposed to the disease through movement from one environment to another, and may lack immunity against pathogens, which increases their risk of infections (Prothero, 1977).

Based on the above definitions, human movement can be identified by different categories, and various forms, conditions and patterns of human mobility may have very different influences on the distribution and spread of infectious diseases (Gubler, 2011; Saker et al., 2004). This study

would focus on the circulation of population movement including both active and passive transmitters in mosquito-borne disease importation networks.

### 1.4.3 Mosquito-borne disease importation networks

In the context of global, air-traffic–mediated epidemics, the global spread of many emerging infectious diseases can be regarded as dynamic processes of pathogens driven by the host and/or vector movement networks (Brockmann and Helbing, 2013), and the cross-border transmission of mosquito-borne diseases can be abstractly presented as a complex network or matrix (Huang and Tatem, 2013). The complex network has elements represented by nodes (or vertices), i.e. countries, cities or airports, and the connections between the nodes as edges (or links), i.e. numbers of individuals infected by pathogens travelling between two nodes (Gross et al., 2005). However, the mobility rates and patterns of infections in the origin-destination networks are often difficult to understand due to overlapping flows. Network community or modularity structure analysis, one of the most common and important topological attributes of complex networks, has been used to measure the density of links inside communities (Vincent et al., 2008; Newman, 2004). Networks with high modularity have dense connections between the nodes within communities but sparse connections between nodes in different communities (**Figure 1-9**).

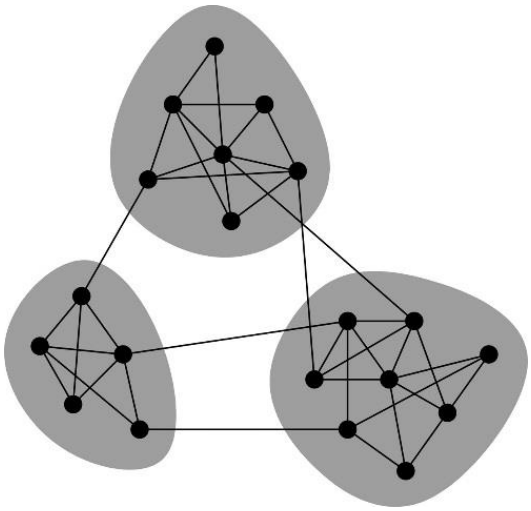


**Figure 1-9. A theoretical diagram of network communities.**

Defining communities of connectivity is valuable for identifying which regions tend to import cases from certain endemic areas more than others (Huang and Tatem, 2013). For instance, malaria importation networks can be divided into communities or groups with dense connections between the origins (in endemic regions) and the destinations (nodes) in non-endemic or other endemic regions (Huang and Tatem, 2013; Lai et al., 2016; Tatem et al., 2017). Where local health facilities are aware of these connectivity related risks, it can allow earlier diagnoses, proactive interventions (e.g. prophylaxis for high risk travellers to specific regions) and tailored public health

awareness campaigns. The identification of communities of pathogen importation networks has been applied to inform the design of malaria elimination strategies, accounting for human movement in introducing infections to areas targeted for elimination (Tatem and Smith, 2010; Huang et al., 2012).

Based on network modularity analysis tools, some studies (Tatem and Smith, 2010; Huang et al., 2012) analysed census-based migration data with information on the geographical range of *P. falciparum* malaria transmission and global population databases to map communities of countries linked by relatively high levels of movements of infected people. Principal sources and destinations of imported cases in each region indicate that certain groups of countries, e.g. countries in West Africa and central Asia, have much higher connectivity than others. Furthermore, the assembled spatial datasets on modelled global disease and vector distributions, as well as climatic and air network traffic data have been combined to reconstruct the importation networks of vector-borne infections, including malaria, dengue, yellow fever and chikungunya, and presented by a web-portal tool for vector-borne disease, VBD-AIR (www.vbd-air.com), with dynamic query of the spatial databases to provide relevant information (Huang et al., 2012). Defining the network structure for pathogen movement can help to identify potential high-risk groups of travellers, supporting the tailoring of interventions and prevention of local transmission.

### 1.4.4 Defining driving forces of imported mosquito-borne infections

There are various factors driving the dispersal of pathogens, with heterogeneous risks of infections in different populations and scenarios (**Figure 1-10**) (Salje et al., 2016). The importation of mosquito-borne diseases, i.e. malaria and dengue, are a function of several factors including the transmission intensity of origin location, number of travellers visiting that location, activities undertaken in the location, and prophylaxis availability and adherence, with some demographic groups having substantially higher risks of infection (Tatem et al., 2012; Freedman et al., 2006; Tatem et al., 2017). For example, malaria importation in Europe is often reported in migrants returning from visiting friends and relatives (VFR) or in travellers returning from (or migrants coming from) endemic areas of Africa and Asia, with children who are VFR being particularly at risk (Pavli and Maltezou, 2010). In US, first- and second-generation immigrants from malaria-endemic countries returning to their “home” countries to visit friends and relatives tend not to use appropriate malaria prevention measures and thus are more likely to become infected with malaria (CDC, 2017).

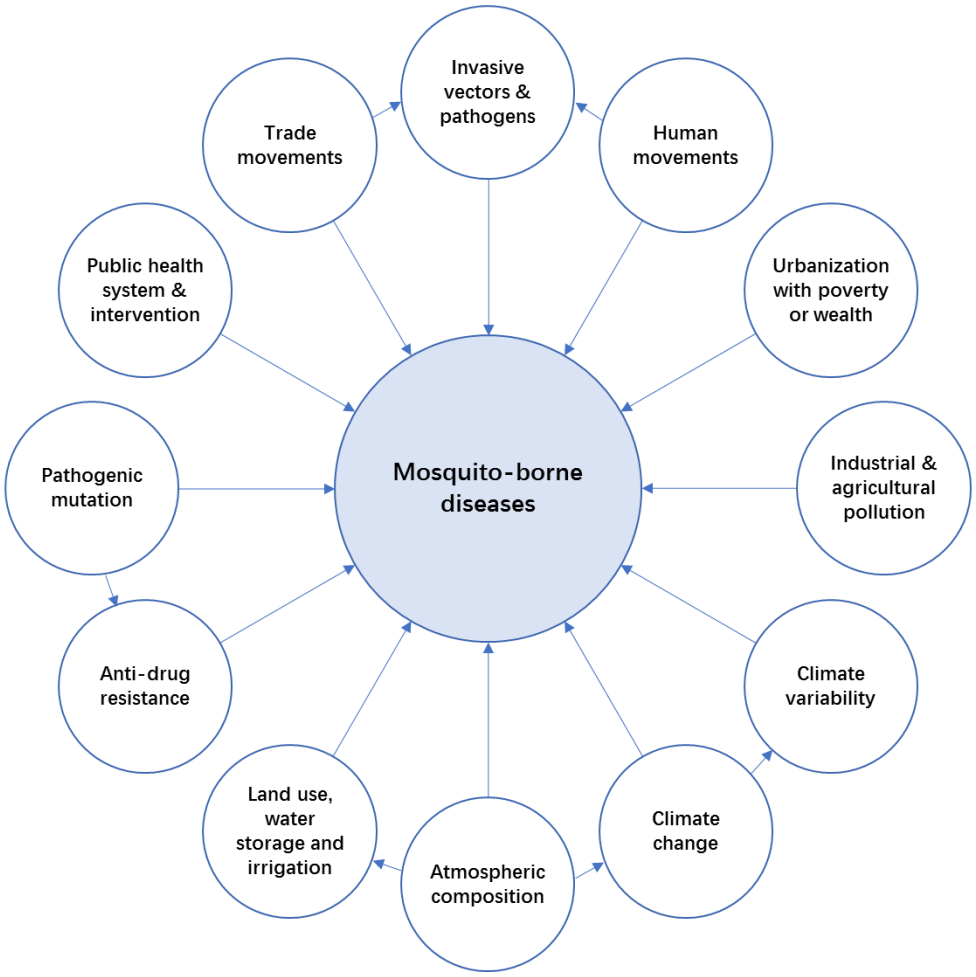



**Figure 1-10. The potential factors driving the transmission of mosquito-borne infections.**

In the UK, Smith et al (2008) used 20-year national malaria reference laboratory surveillance data from 1987 to 2006 to identify temporal, geographic, and sociodemographic trends of malaria importation, as well as high risk groups and case fatality. Despite the availability of highly effective preventive measures, they found that the preventable burden from *P. falciparum* malaria has steadily increased in the UK while *P. vivax* malaria has decreased. Travellers visiting friends and relatives, usually in a country in Africa or Asia from which members of their family migrated, accounted for 64.5% of all malaria reported, and reports were geographically concentrated in areas where migrants from Africa and South Asia to the UK have settled (Smith et al., 2008). Furthermore, Checkley et al (2012) determined the risk factors for mortality of imported *P. falciparum* malaria in the UK by comparing the age, reason for travel, country of birth, time of year diagnosed, and malaria prophylaxis used between fatal and non-fatal cases. Among them, most travellers acquiring malaria are of African heritage visiting friends and relatives. In contrast, the risks of dying from malaria once acquired are highest in the elderly, tourists, and those presenting in areas in which malaria is seldom seen.

In a subsequent study of *P. vivax* malaria imported into the UK from 1987 to 2013, Broderick et al (2015) measured mortality, sociodemographic details (age, purpose of travel, country of birth and residence, and UK region), destination, and latency (time between arrival in the UK and onset of illness). Results indicated that travellers visiting friends and family in India and Pakistan have the highest risk of acquiring *P. vivax*, and older patients (especially those >70 years) are most at risk of dying. The risk of acquiring Vivax malaria is year-round but higher during summer monsoons, masked by latency. The latency of time to clinical presentation of imported vivax malaria in the UK is highly seasonal; seasonal latency has implications for pre-travel advice, and also for the control of malaria in India and Pakistan (Broderick et al., 2015). Therefore, these high-risk groups for malaria importation and fatality should be targeted for advice before travelling.

For dengue, a variety of factors have also driven the importation of dengue virus from endemic areas to non-endemic areas. For instance, Nunes et al (2014) applied a statistical framework and genome sequencing to investigate the spatial dynamics of dengue virus. By the joint statistical analysis of evolutionary, epidemiological and ecological data, they found that aerial transportation of humans and/or vector mosquitoes determine dengue virus spread in Brazil, and the introduction of new lineages was estimated to occur within 7 to 10-year intervals, most likely from the Caribbean region to the North and Northeast regions of Brazil, and then to disperse at a rate of approximately 0.5 km/day. Among Southeast Asian countries, the synchronicity and cross-border transmission of dengue are associated with climate change (e.g. El Niño) and intercity distance in Southeast Asia (van Panhuis et al., 2015). Similarly, dengue cases imported into the US from 1996 to 2005 were commonly found to have originated in regions of the Caribbean, Mexico and Central America, and Asia (Mohammed et al., 2010). Additionally, Tian et al (2017) found that increasing airline travel may facilitate co-circulation of multiple dengue virus serotypes in Asia, and the hubs of air traffic network, e.g. the international airports of Thailand, India, China, Cambodia, Indonesia, and Singapore, may establish viral diffusion links with multiple countries in Asia.

Therefore, the geographical features of imported mosquito-borne diseases show that the air network, historical ties, demographics of travellers and endemicity status have all driven the variations of numbers, routes, and species composition of pathogen dispersal from endemic to non-endemic countries (Tatem et al., 2017). Understanding the clinical, geographical, temporal and social-economical risk factors associated with imported infections and their outcomes are of importance for mosquito-borne disease mitigation, control and prevention in travellers.

### 1.4.5 Data sources to define patterns of disease importations

Based on different temporal, geographic or demographic perspectives, epidemiological patterns of imported mosquito-borne diseases can be analysed by using a variety of data sources with various indicators for demographic features and epidemiological characteristics of infected individuals.

Firstly, statutory notification of cases of specific diseases, along with information on travel history, is conducted by hospitals, clinics, port health or public health departments. These notification systems have been implemented to understand epidemiological features of malaria infections and potential origin countries in the UK, US, China, and many other countries (Van and Abrahamian, 2005; Tatem et al., 2017; Zhou et al., 2016; Muentener et al., 1999; Checkley et al., 2012; Broderick et al., 2015; Mohammed et al., 2010). However, there is little epidemiological surveillance for dengue anywhere outside endemic areas, and for instance, none on a national scale in Europe or at the state level in the US (Gardner and Sarkar, 2013).

Secondly, a sentinel surveillance system is used when high-quality data are needed about a particular disease that cannot be obtained through a passive system. Selected reporting units, with a high probability of seeing cases of the disease in question, good laboratory facilities and experienced well-qualified staff, identify and notify on certain diseases. Whereas most passive surveillance systems receive data from as many health workers or health facilities as possible, a sentinel system deliberately involves only a limited network of carefully selected reporting sites. The sentinel surveillance of the EuroTravNet, for instance, found that the main source of imported dengue into Europe is the countries in Southeast Asia, followed by the Americas (Neumayr A, 2017).

Lastly, the increasing availability of genetic and geospatial data with advances in computational techniques are helping to address questions around pathogen evolution and transmission in an ever more connected world by integrating spatial incidence, host mobility and genetic diversity (Pybus et al., 2015; Bozick and Real, 2015; Salje et al., 2017; Tian et al., 2017). Additionally, a variety of investigations of outbreaks and surveys have also been conducted to identify the causes, risk factors or origins of importation phenomena (Li et al., 2015; Wu et al., 2017; Li et al., 2016b). In the absence of disease monitoring data, however, a number of studies have been based on travel networks or population migrant data to estimate the possible transnational communication network for infectious diseases (Sorichetta et al., 2016).

### 1.4.6 Weaknesses of using reporting data to define importation risks

Global dispersion of mosquito-borne disease has been accelerated by the substantial growth in the reach and rates of human travel by contemporary transport options. Air travel has increased rapidly in the last 30 years with 3.8 billion air travellers in 2016, and the International Air Transport Association (IATA) predicted that 7.2 billion passengers will travel in 2035, a near doubling of the volume in 2016 based on a 3.7% annual compound average growth rate (IATA, 2016; WHO, 1996). The expansion of the air traffic network and substantial growth of passengers to and from endemic areas, has resulted in imported mosquito-borne diseases, e.g. malaria and dengue, being frequently reported in non-endemic countries (Andriopoulos et al., 2013; CDC, 2017).

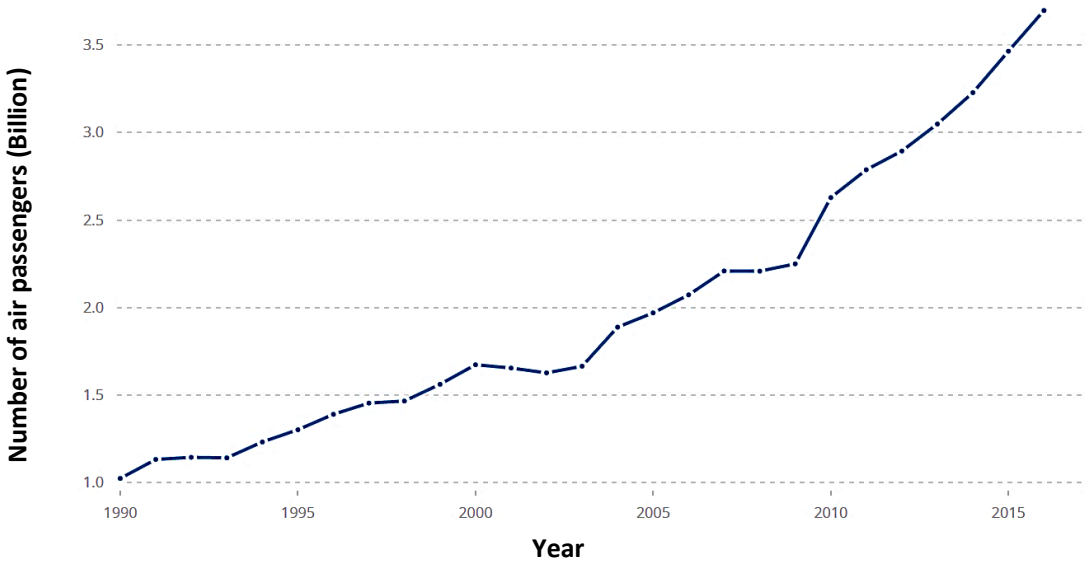



**Figure 1-11. Global air passenger traffic trend, 1990-2016.**

Data source: The World Bank (data.worldbank.org/indicator/IS.AIR.PSGR?end=2016&start=1990).

However, the number of imported human infections found by routine and passive disease surveillance in health facilities or ports of entry, e.g. international airports, usually underestimates the actual number of infected travellers for the following reasons.

1) A high proportion of infections are asymptomatic. For instance, most people infected with dengue virus are asymptomatic (80%) or have only mild symptoms such as an uncomplicated fever (Guzman and Harris, 2015; WHO, 2009b), and asymptomatic malaria infections (70%) are individuals who have not received recent antimalarial treatment and with the malarial parasitemia of any density but without fever or other acute symptoms (Lindblade et al., 2013; Chen et al., 2016). From the sentinel surveillance of returning travellers by the European Travel Medicine Network between September 2011 and December 2014, up to 36% of travellers infected with dengue while travelling returned during the acute phase of the infection (up to 7

days after symptom onset) or became symptomatic after returning to Europe, and 58% of the patients with acute dengue infection were viraemic when seeking medical care (Neumayr A, 2017). Diagnosing asymptomatic mosquito-borne diseases is not as straightforward due to the obvious lack of clinical manifestations or the undetectable level of parasites or viruses or antibody.

2) The incubation periods of mosquito-borne diseases are commonly longer than the duration of travel, and international travellers may not present symptoms when they are in transit or enter into a country. For example, dengue has an incubation period of 3-14 days, usually 4-8 days, and therefore only a small proportion of imported infections in the points of entry into a country are likely to be found (Tatem et al., 2012).

3) Underreporting occurs in both endemic and non-endemic regions. In tropical and subtropical endemic countries, under-reporting may be due to misdiagnosis, limitations of criteria of case classification, and a lack of laboratory infrastructure and resources, etc. In non-endemic regions, the actual number of imported infections is greatly underestimated by doctors due to an unfamiliarity with the disease (Gardner and Sarkar, 2013). Additionally, the mild or non-typical manifestations of dengue and malaria infections may closely mimic flu symptoms and lead to misdiagnosis.

Determining spatiotemporal features and driving factors of mosquito-borne disease importation networks is important, based on feasible data sources, indicators and methods. However, a lack of accurate infection data and questions about data access and quality make it difficult to assess the true extent of mosquitoes-borne disease prevalence and the risk of importation for developing appropriate control strategies (Gardner and Sarkar, 2013; Shepard et al., 2016). Therefore, to estimate the risk of disease importation, a variety of models have been constructed to predict the number or relative risk of imported infections across geographic frontiers by integrating datasets of air travel, disease incidence, vector distribution, climate, etc (Andraud et al., 2012; Bianco and Shaw, 2011; Gardner and Sarkar, 2013; Bogoch et al., 2016a; Bogoch et al., 2015; Tatem et al., 2012; Huang and Tatem, 2013; Lopez et al., 2016).

## 1.5 Quantifying the risks of pathogen importation via air travel

Quantifying the patterns and risks of the global spread of pathogens has become one of the major challenges in the 21st century due to the complexity of global multiscale mobility networks, the spatiotemporal heterogeneity of infections in endemic countries, the various demographic features of travellers, and a variety of factors driving international population movements (Brockmann and Helbing, 2013; Balcan et al., 2009; Stoddard et al., 2013). In the last three

decades, different models have been applied to the understanding infectious disease dynamics, including various models of mosquito-borne pathogen transmission (Heesterbeek et al., 2015; Reiner et al., 2013; Andraud et al., 2012). Given the vast range of complicating factors, no model can be expected to predict the spread of an infectious disease with complete accuracy, but quantifying the risks of disease importation through modelling enables tailoring of feasible interventions for a range of scenarios, spanning the range of uncertainties of key parameters (Tatem et al., 2012; Khan et al., 2012; Ferguson et al., 2003; Tatem et al., 2006c). For example, estimated importation risk has been used to evaluate the potential effect of air travel restrictions, and the efficiency of airport-based traveller screening at international ports of entry and exit, to mitigate the potential global health and economic impacts of introduced pathogens, e.g. H1N1 pandemic, dengue, Ebola, MERS, and Zika, etc (Khan et al., 2013; Bogoch et al., 2015; Bogoch et al., 2016b).

This section briefly reviews and demonstrates common approaches to estimate the numbers and/or relative risk of mosquito-borne disease importation via air travel (**Figure 1-12**), and the benefits and drawbacks of these models to guide the choice of appropriate models for this study (**Table 1-2**).

### 1.5.1 Estimating the numbers of imported infectious travellers

#### 1.5.1.1 Importation index model

The importation index model is a simple, widely-used empirical model, defined as the incidence rate of infections in the country of origin multiplied by the volume of travellers from origin to destination. For example, the monthly number of travellers infected by a specific pathogen from an endemic country can be estimated by (Wilder-Smith et al., 2012):

(number of monthly new cases or infections/country population) × monthly number of international outbound air travellers.

Based on air travel volume and reported dengue cases, the basic importation index model has been applied to explore the origin of a dengue outbreak in Madeira (Wilder-Smith et al., 2014), thereby showing that this model can be an effective additional tool to identify the risks and pathways of dengue importation. Additionally, to predict potential international spread of emerging infectious diseases, this model has also been employed to estimate the number of internationally exported Ebola virus infections via air travel, coupled with Ebola virus surveillance data and air travel itinerary data (Bogoch et al., 2015; Cowling and Yu, 2015).

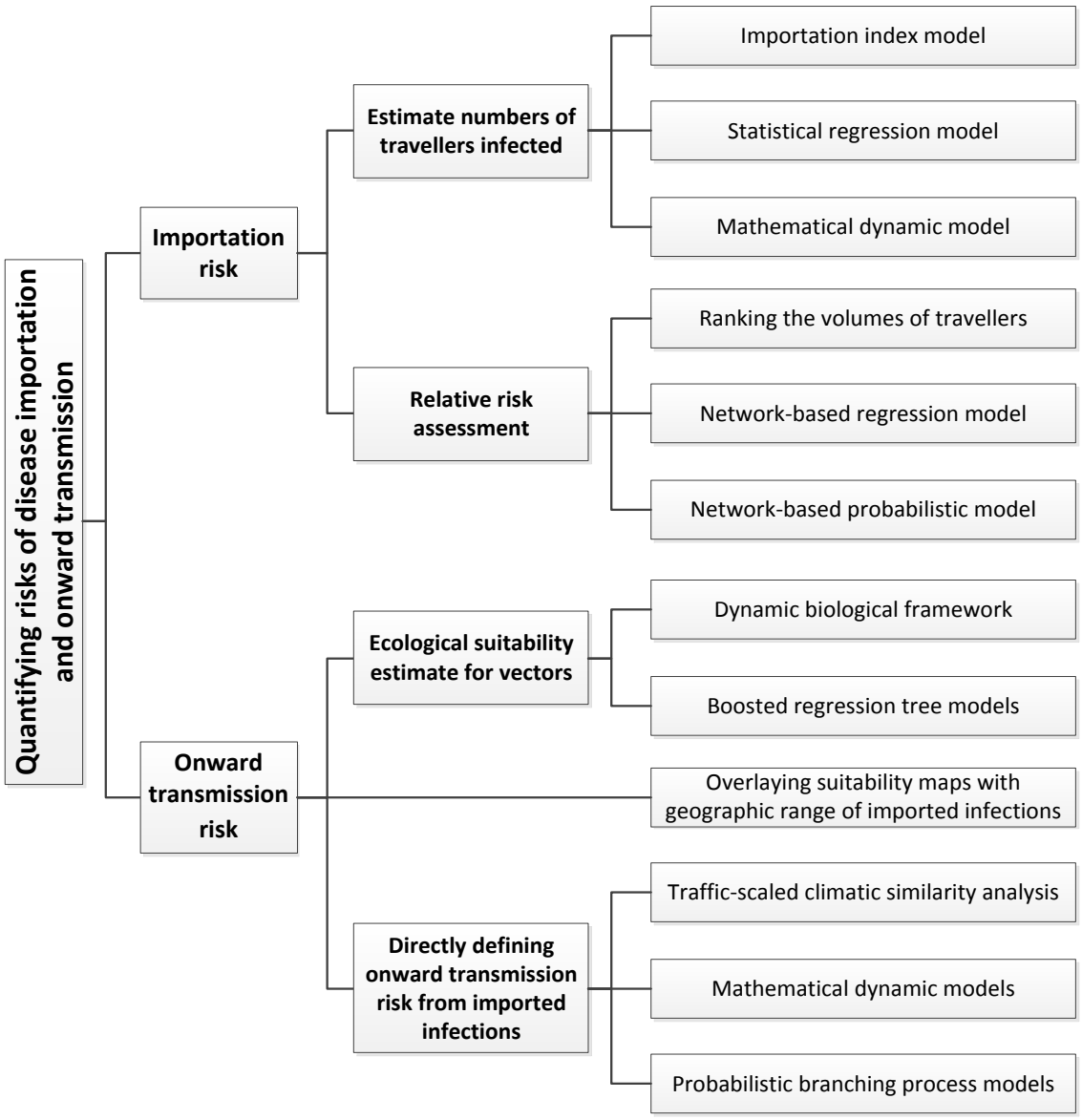



**Figure 1-12. The diagram of main methods to quantify risks of mosquito-borne disease importation and onward transmission via air travel.**

Some comprehensive epidemiological parameters have been integrated into the models to improve their performance. For instance, to estimate air travel–associated quarterly "apparent" and "inapparent" dengue infections imported into Rome, Italy between 2005 and 2012, Quam et al (2015) designed an importation index model that included not only the volume of air traffic and the estimates of dengue incidence in the countries of disembarkation, but also the probability of infection coinciding with travel. Moreover, to assess the risk of importing dengue and chikungunya viruses to the European Union (EU), Seyler et al. (2009) developed a more complex model with a Monte Carlo approach using the number of viraemic person-days among air travellers arriving in the Europe, taking into account the probability distributions based on quarterly incidences in endemic countries, passenger flow from endemic to EU countries, duration of viraemia, probability of being viraemic upon arrival, and distribution and period of vector activity in the EU (Seyler et al., 2009).

**Table 1-2. Models for measuring risks of pathogen importation via air travel.**

| Methods and diseases | Description | Strengths | Weaknesses |
|---|---|---|---|
| **Estimate the numbers of imported infectious travellers** | | | |
| Importation index<br>i.e. Dengue (Wilder-Smith et al., 2012; Wilder-Smith et al., 2014; Quam et al., 2015) and Ebola (Bogoch et al., 2015; Cowling and Yu, 2015) | Commonly defined as the incidence rate of infections in the country of origin multiplied by the volume of travellers from origin to destination, i.e., (number of active cases/country population) × monthly number of international outbound air travellers. | ● A simple model to calculate expected absolute numbers of infection exportations;<br>● The expected time in months/days for one air traveller infected to depart can be estimated (i.e. 1/expected number of Ebola virus exportations per month);<br>● Can be parameterized with some epidemiological features, i.e., apparent and inapparent dengue infections;<br>● More factors can be included into a more complex model, i.e., duration of viraemia, probability of being viraemic upon arrival, and distribution and period of vector activity. | ● A crude estimate depends on the dengue activity in the country of origin, which are commonly underreported in the surveillance;<br>● Absence of demographic data for air travellers or their intended purpose for travel, which is related to the risk of disease acquisition;<br>● The risk of exposure to pathogens are assumed to be uniform across the entire population and geographically across the country of origin, and to be similar for travellers and non-travellers;<br>● How to validate the results of this model is a challenge due to the lack of true number of importation infections. |
| Statistical regression model<br><br>i.e. Dengue (Semenza et al., 2014) and malaria (Tatem et al., 2012; Lai et al., 2016) | The number of imported infections<br>(dependent variable) was modelled using multilevel mixed-effects regression for count outcomes with the month of reporting and monthly volume of travellers from endemic areas and other factors as independent variables (predictors). | ● Monthly number or incidence rate ratio of importation infections with 95% CI can be estimated;<br>● Many more covariates (e.g. traveller demographics) can be included to improve the performance of model;<br>● Different distributions, i.e. negative binomial distribution, and link function can be used to take into account the features or drawbacks of the outcome variable, i.e. over-dispersion. | ● The performance of the model depends on the high data accuracy of dengue notifications. Based on passive surveillance, the incidence data (dependent variable) only including the apparent infection are commonly underestimated;<br>● The model does not account for stopovers or length of stopovers;<br>● Appropriate distribution and link function should be chosen to take into account over-dispersion of the outcome variable; |

| Methods and diseases | Description | Strengths | Weaknesses |
|---|---|---|---|
| | | | ● Assumes homogenous risk across country of origin;<br>● Should incorporate more known determinants of imported vector-borne diseases into existing regression models. |
| Mathematical dynamic model<br><br>i.e. Dengue (Pongsumpun et al., 2004; Wesolowski et al., 2015b),<br>Ebola (Lopez et al., 2016) and<br>Zika virus infections (Massad et al., 2016) | Commonly used difference or differential equations to model the establishment and spread of pathogens. The SIR model is one of the basic mathematical epidemic models and commonly abstracts the population (human and/or vector) into compartments under certain assumptions, which represent their health status with respect to the dynamics of pathogen. | ● Provides time-specific estimates of travellers infected and imported from endemic countries;<br>● The numbers of travellers infected are commonly calculated as a function of the incidence rate and the length of time the tourist stays in the endemic region;<br>● More factors, e.g. demographic features, endemicity, population size, immunization coverage rates, infectious period, the asymptomatic-to-symptomatic ratio, can be integrated into models to improve the performance. | ● Commonly assumes that travellers are subject to the same risk of infection as local residents in endemic areas, and the force of infection at the visited/source country were known and homogeneous;<br>● Heavily depends on the estimation/surveillance data of local dynamics of the infections at risk of being spread to other parts of the world; and estimation of the parameters related to transmission in the host country, e.g. the vectors' density and biting habits;<br>● The deterministic nature of the common used models does not allow estimation of many uncertainties related to parameter estimation among others. |
| **Estimate relative risk of pathogen importation** | | | |
| Ranking the volumes of travellers<br><br>i.e. Dengue (Sessions et al., 2013; Semenza et al., 2014),<br>Zika (Rocklov et al., 2016; Bogoch et al., 2016a),<br>Chikungunya (Khan et al., | Used to order the numbers of international air travellers from endemic or epidemic areas into the cities or airports of destinations to indirectly inform the risks of importation. | ● Simple and easy to understand;<br>● The potential number of travellers needed to be screened at exit- and entry-points;<br>● The volume of stopover can be also considered. | ● An indirect and descriptive indicator of the raw risk of pathogens introduction;<br>● Only considers the volume of airline travel to and from source countries, without taking into account the risk of acquiring the infection in endemic areas;<br>● Assuming a homogeneous risk of disease acquisition in origin. |

| Methods and diseases | Description | Strengths | Weaknesses |
|---|---|---|---|
| 2014), Ebola (Bogoch et al., 2015) and MERS (Zhang et al., 2016) | | | |
| Network-based regression model<br><br>i.e. Dengue (Gardner et al., 2012; Gardner and Sarkar, 2013),<br>malaria and other vector-borne disease (Huang and Tatem, 2013; Tatem et al., 2012) | Uses a link-based functional form to quantify the expected number and relative risk of spread of infections at each stopover airport and destination airport via the global air transport network by passengers with travel-acquired infections. | ● Combines the international passenger travel volumes, travel routes, travel distances, regional populations, and predictive species distribution models to prioritize optimal locations (i.e., airports) for targeted dengue surveillance at city or airport level;<br>● Can be easily extended to other geographical regions and vector-borne diseases, as well as other network-based processes. | ● The most critical issue of this model is determining the link-based functional form. The process that the function attempts to model is too complex to determine a functional form a priori;<br>● Needs the rich of datasets, and directional infection data (i.e., the source of infection for travel acquired dengue cases) is commonly not available.<br>● The risk may be underestimated due to the underreport of infections via surveillance. |
| Network-based probabilistic model<br><br>i.e. SARS and H1N1 (Brockmann and Helbing, 2013),<br>Ebola (Brockmann et al., 2014), Yellow Fever, dengue and Chikungunya (Johansson et al., 2011; Johansson et al., 2012; Johansson et al., 2014) | Combining the network and probability analysis | ● The timing and relative distance for emerging relative distance can be identified for the spread of emerging pathogens into a new area;<br>● Used to predict probable locations and seasonal risks for the arrival of travellers with mosquito-borne infections;<br>● Estimate risk with uncertainty;<br>● Easy to integrate with onward transmission model in destinations. | ● Needs the rich of datasets, e.g. transportation network, incidence data in origin, epidemiological parameters of pathogens, etc.;<br>● The challenges to validation of probabilistic models remains, especially based on the occurrence of imported infections to empirically validate the relative risk estimated by the models. |

However, the importation index model is a simple formula to make a crude estimate with some limitations:

1) The model depends on the dengue activity in the country of origin, which is commonly underreported in surveillance;
2) A lack of demographic data exists for air travellers or their intended purpose for travel, which is related to the risk of disease acquisition;
3) Despite the existing heterogeneity of infections in origins, the risk of exposure to pathogens is still assumed to be uniform across the entire population and similar for travellers and non-travellers;
4) How to validate the results of this model is a challenge due to the lack of true number of importation infections.

To overcome some of the drawbacks and account for the existing uncertainty of parameters in models, sensitivity analyses can be conducted to explore different scenarios, e.g. increasing case burden (2×, 5×, 10×), or exponential risk in case burden over time, and decreasing international air traffic capacity due to flight cancellations, travel restrictions, or changes in travel behaviours (Bogoch et al., 2015; Cowling and Yu, 2015).

#### 1.5.1.2 Statistical regression model

In statistical modelling, regression analysis is a process for estimating the relationships between a dependent variable and one or more independent variables or predictors (**Figure 1-13**). Regression models are widely used for prediction and forecasting, and many techniques for carrying out regression analysis have been developed to predict the risks of pathogen importation. For instance, a hierarchical regression model for dengue importation risk assessment was designed by Semenza et al (2014) to quantify the relationship between the number of reported dengue cases imported into Europe and the volume of airline travellers arriving from dengue-affected areas internationally, then predict the numbers of imported infections for 2010. In this empirical model, the number of dengue cases imported into European countries (dependent variable) was modelled using multilevel mixed-effects regression for count outcomes with the month of reporting and monthly volume of travellers from dengue-affected areas worldwide as independent variables (predictors). Considering the group structure of the data at the country level, a hierarchical count model was performed by reporting the regression coefficients, the number of importation infections fitted and incidence rate ratio with 95% confidence interval (CI). However, no country-specific importation and exportation risk were estimated, and no dengue incidence rates in origin countries were incorporated in the model to improve the performance of prediction. Additionally, a negative binomial distribution and log-link

function have been used in this model to take into account the over-dispersion of the outcome variable (Semenza et al., 2014).

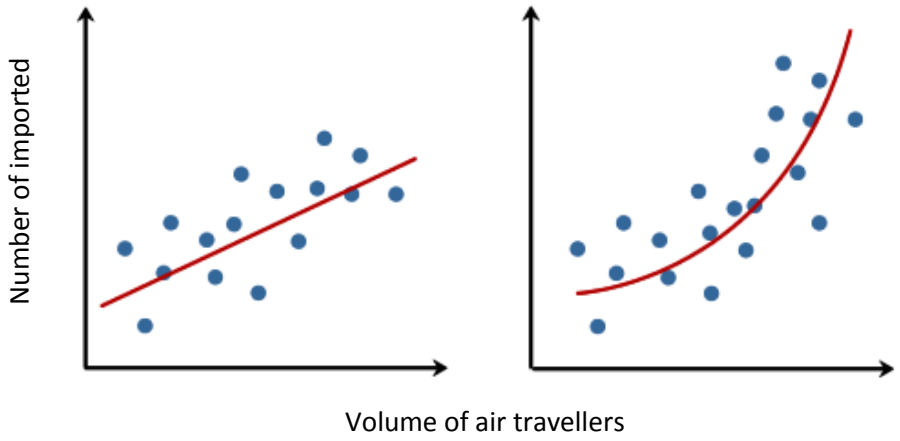


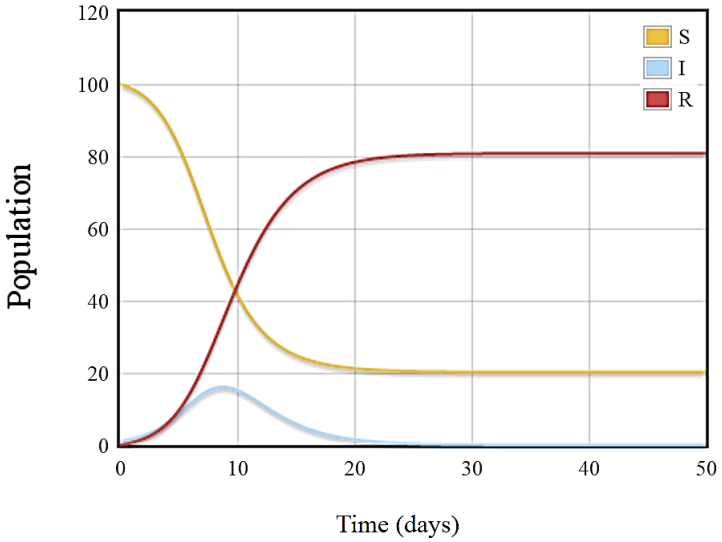

**Figure 1-13. A concept of regression analysis for disease importation via air travellers with linear (left) or no linear (right) relationship.**

More relevant variables can be included in the model to improve the accuracy of prediction. Based on the assumption that numbers of imported cases were a function of numbers of incoming travellers and prevalence of *P. falciparum* at their origins, Tatem et al (2012) used a log-linear regression model to predict the numbers of *P. falciparum* malaria cases imported into the US from 84 origin countries. As the numbers of imported cases tend to be positively skewed and subject to outliers and a linear regression was not appropriate, a natural logarithm transformation was applied to both response and predictor variables to alleviate heteroscedasticity. The results showed that the model was statistically significant, and 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.

According to best practices of model post-estimation, the predictions, model diagnostic measures, residuals plots and detection of outliers can be examined. To assess the stability of the regression coefficient, a sensitivity analysis can also be carried out by removing outliers. However, great potential exists to improve the existing regression models of predicting importation risk by adding more sophistication in incorporating known determinants of imported mosquito-borne diseases, e.g. traveller activities, prophylaxis use and resident/immigrant/visitor status, and in turn explain a greater proportion of the variance in case numbers seen (Tatem et al., 2012). In addition, due to the limitation of the underreporting of the dependent variable, the number of diseases imported, the predictions of regression models may underestimate the volume of imported travellers, and a mathematical dynamic model might be a better approach to estimate the number of imported infections based on the knowledge of epidemiological features.

### 1.5.1.3 Mathematical dynamic model

Mathematical models for infectious disease transmission are used to model the establishment and spread of pathogens and understand the complex dynamics of infectious diseases. Some basic assumptions are used in the models to find parameters for various infectious diseases and show the likely outcome of an epidemic and help inform public health interventions. The susceptible-infected-recovered (SIR) model, one of the basic mathematical models in epidemiology, uses the notion of abstracting the population into compartments under certain assumptions, which represent their health status with respect to the dynamics of a pathogen (Kermack and McKendrick, 1991). A variety of mathematical epidemiological models have been developed to understand the transmission of mosquito-borne pathogens, especially malaria and dengue (Reiner et al., 2013; Andraud et al., 2012).




$$\begin{aligned} \frac{dS}{dt} &= -\beta\frac{SI}{N} \\ \frac{dI}{dt} &= \beta\frac{SI}{N} - \gamma I \\ \frac{dR}{dt} &= \gamma I \\ N &= S + I + R \end{aligned}$$

**Figure 1-14. A basic SIR model with ordinary differential equations to quantify the flows of people between three states.**

Note: Susceptible (S), infected (I), and recovery (R), and the number of total population (N); The parameters β and γ partially control how fast people move from being susceptible to infected and from infected to recovery.

Regarding mosquito-borne disease importation, the deterministic SIR approach has been applied to formulate the transmission of dengue in an endemic region into where tourists enter (Pongsumpun et al., 2004). This study introduced different population groups into the model: two human populations, hosts and travellers, and one mosquito population. Each human population was divided into three classes, susceptible, infected and recovered respectively, while the mosquito population is divided into two classes, susceptible and infected. The dynamics of the travellers was incorporated into the systems of first order differential equations in the SIR model describing the dynamics of the transmission in the host region. The time rate of change in the

number of subjects in each group was equal to the number of subjects entering the group minus the number leaving the group. Using standard dynamic analysis methods, the numbers of travellers who become infected with the dengue virus were calculated as a function of the length of time a tourist stays in the endemic region. The time-specific estimates of travellers infected and imported from endemic countries have been estimated in high spatiotemporal resolution.

Additionally, the force of infection is a key component in mathematical dynamic models, which commonly is defined as the fraction of susceptible individuals that will become the number of reported cases in a given time unit, and estimated by fitting a continuous function to the time distribution of notified cases. For instance, based on the force of infection with variations over time depending upon the time of stay in Singapore and season of arrival, Massad and Wilder-Smith (2009) used a mathematical dynamic model to estimate the risk of nonimmune persons in acquiring dengue when traveling to Singapore. Additionally, the concept of the force of infection was also used to estimate monthly Zika virus importations to Europe by travellers from Brazil in 2015, based on the travel volume, the probability of being infected at the time of travel, the population size of Brazil, and the estimated incidence of Zika virus infections (Massad et al., 2016).

However, these models commonly assume that travellers are subject to the same risk of infection as local residents in the case of disease importation, and the force of infection at the visited/source country is known. These models heavily depend on the estimation/surveillance data of local dynamics of the infection, and also depend on estimation of the parameters related to transmission in the host country, e.g. the vectors' density and biting habits. Although the performance of models can be improved by parameterizing with endemicity, population size, immunization coverage rates, infectious period, the asymptomatic-to-symptomatic ratio, and the probability of a traveller being infectious at the time of travel, the deterministic nature of commonly used models does not allow estimation of many uncertainties related to parameter estimation among others (Wilder-Smith et al., 2015). Therefore, the estimate of relative risk might be a better way to quantify the risk of disease importation than the absolute number of predicted infectious travellers.

### 1.5.2 Relative importation risk assessment

#### 1.5.2.1 Ranking the volumes of travellers

As an indicator of the relative risk of pathogen introduction, the simplest descriptive approach is to rank the numbers or proportions of travellers from endemic or epidemic areas into different cities or airports of destination. This has been widely used in previous studies of importation risk assessment for a wide range of diseases, for example, in defining the potential for international

spread of Ebola from West Africa (**Table 1-3**) (Bogoch et al., 2015), during the 2013 dengue outbreak in Luanda, Angola (Sessions et al., 2013) , investigating potential spread of Zika Virus from the Americas (Rocklov et al., 2016; Bogoch et al., 2016a), and Chikungunya virus from the Caribbean (Khan et al., 2014), and the 2015 MERS outbreak in the Republic of Korea (Zhang et al., 2016). This approach provides the potential number of travellers needed to be screened at exit- and entry-points, and the volume of travellers with stopovers can be also presented (Bogoch et al., 2015; Geng et al., 2016; Lai et al., 2014). However, this method only gives an indirect and descriptive indicator of the raw risk of pathogens introduction, assuming all travellers have a homogeneous risk of disease acquisition at the origin.

**Table 1-3. The example of ranking the volumes of air travellers.**

| Rank | Country | Number of travellers | % total volume |
|---|---|---|---|
| 1 | Ghana | 4,626 | 13.39% |
| 2 | Senegal | 3,903 | 11.29% |
| 3 | France | 3,161 | 9.15% |
| 4 | Cote D'Ivoire | 2,844 | 8.23% |
| 5 | United Kingdom | 2,808 | 8.13% |
| 6 | Gambia | 1,898 | 5.49% |
| 7 | Mali | 1,617 | 4.68% |
| 8 | Nigeria | 1,413 | 4.09% |
| 9 | South Africa | 1,383 | 4.00% |
| 10 | Morocco | 1,280 | 3.70% |
| 11 | Belgium | 1,196 | 3.46% |
| 12 | United States | 855 | 2.47% |
| 13 | China | 730 | 2.11% |
| 14 | Canada | 531 | 1.54% |
| 15 | Germany | 510 | 1.48% |
| 16 | Italy | 493 | 1.43% |
| 17 | Lebanon | 456 | 1.32% |
| 18 | Portugal | 337 | 0.98% |
| 19 | Kenya | 332 | 0.96% |
| 20 | Spain | 320 | 0.93% |
| All Others | | 1,765 | 11.21% |
| Total | | 34,558 | 100% |

Note: To understand the potential for international spread of Ebola from West Africa in 2014, the data are the final destinations of individuals initiating air travel from airports within Guinea,

Liberia and Sierra Leone in August 2012, obtained from the International Air Transport Association.

#### 1.5.2.2 Network-based regression model

To complement the qualitative risk analysis of ranking the volumes of travellers, mathematical network models of air travel linked with disease and vector distribution maps can offer great potential for infection importation risk assessment and the modelling of vector-borne disease spread (Tatem et al., 2012; 2006a). In network structure analysis, geographic areas/airports are commonly represented as nodes, belonging to either the set of endemic nodes, or the set of susceptible nodes globally, and the links in the network represent direct air travel connections between geographic areas/airports (**Figure 1-15**).

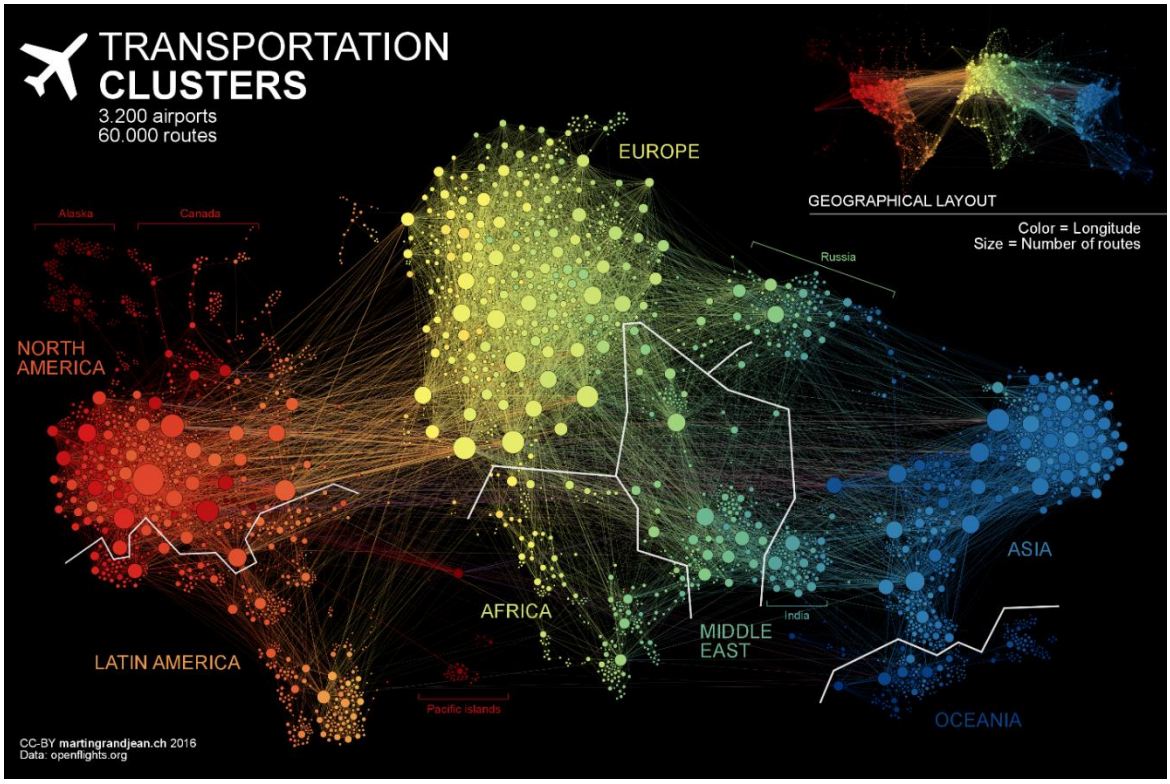



**Figure 1-15. The clusters of global air transportation network.**

Note: Based on OpenFlights.org data, this "map" is the result of a force-directed layout algorithm on a graph of 3,275 airports (37,153 single routes), with a geographic layout on the top-right corner (www.martingrandjean.ch/connected-world-air-traffic-network/).

The network-based regression model uses a link-based functional form to estimate the risk of passengers with travel-acquired dengue infections via the global air transport network (Gardner et al., 2012; Gardner and Sarkar, 2013). This model computes the expected number of imported infections (per origin-destination link), which can then be normalized by dividing by the highest

value computed over all pairs to give estimates of relative risk. The importation risk posed by each airport includes:

1) stopover risk, defined as the total expected harm (or cost) posed by a given stopover airport to regions other than this airport. The stopover risk is a function of the volume of passengers traveling through stopover airport, and the origin-destination pairs they were traveling between; and
2) destination risk, defined as the total expected harm posed to a destination airport by all passengers arriving at this airport. The destination risk is a function of the volume of passengers traveling to the destination airport, and their route origins (Gardner et al., 2012; Gardner and Sarkar, 2013).

This model offers some advantages. This global airport-based risk regression model combines the international passenger travel volumes, travel routes, travel distances, regional populations, and predictive species distribution models, e.g. Maxent (Phillips et al., 2006; Phillips and Dudik, 2008), to prioritize optimal locations (i.e., airports) for targeted dengue surveillance at the city or airport level to monitor importations and to avoid ongoing transmission following an introduction. The model can be extended to other geographical regions and vector-borne diseases, as well as other network-based processes.

However, some drawbacks of this method also exist. The most critical issue of this model is determining the link-based functional form. The process that the function attempts to model is too complex to determine a functional form *a priori*, and directional infection data (i.e., the source of infection for travel acquired dengue cases) is commonly not available. In addition, a variety of functional forms are usually examined to identify a link-based function that best replicate the number of reported imported cases at each airport or city (Gardner et al., 2012; Gardner and Sarkar, 2013), but the risk may be underestimated due to underreporting of infections from routine surveillance that is used as a dependent variable in the regression model.

#### 1.5.2.3 Network-based probabilistic model

To complement the potential underestimation of relative risk by regression models using imported infections data through routine disease reporting, and to estimate the importation risk of emerging infectious diseases where epidemiological data are lacking or represent areas without robust surveillance systems to monitor importations, mathematical probabilistic models combining network analysis and statistical analysis have been used. For instance, Brockmann and Helbing (2013) showed that probabilities of global spreading patterns can be obtained by a geometric approach using complex network theory, and found that firstly, effective distance is a reliable predictor of epidemic arrival times, and, secondly, that the contagion phenomena in a

complex and strongly heterogeneous transportation network are dominated by the most probable pathways a disease can take through the network.

Furthermore, to estimate risk for the 2014 Ebola outbreak, a stochastic model was used predicting the probabilities of ensembles of paths an infected individual entering a source node in the network (e.g. one of the airports in the outbreak region), thereby estimating the probability of importation risk and effective distance (**Figure 1-16**) (Brockmann et al., 2014). For every path (potentially via a sequence of intermediate locations), the probability for every step along the path and the probability that the current location is the destination were calculated. Both types of quantities are computed from traffic flux across the worldwide air transportation. Every simulated individual reaches a destination somewhere in the network (Brockmann et al., 2014). This approach is commonly used for risk estimation of timing and relative distance for emerging pathogens spreading to a new territory.

To estimate the persistent importation risk and the seasonality of transmission of common infectious diseases from endemic to non-endemic areas, a sophisticated network-based probabilistic model developed by Johansson et al (Johansson et al., 2012; 2014) has been used to predict probable locations and seasonal risks for the arrival of travellers with mosquito-borne infections, by integrating travel patterns, local infection prevalence, climate-dependent transmission factors, and associated uncertainty. The model simulations could be used to estimate the relative risk of infection spread due to limitations of available data during outbreaks. In addition, this model framework can be further adjusted and parameterized to “traveller” submodels and “migration” submodels, to account for infection and importation risk of different groups (Johansson et al., 2011). Moreover, these probabilistic models have also been used to compare the probabilities of *P. falciparum* and dengue virus introduction by mosquitoes and by humans via aircraft (Mier et al., 2017). The probability of introduction of pathogens via infected human travellers sounds far more likely than introduction by infected mosquitoes. However, the validation of probabilistic models is a challenge. The occurrence of imported infections has been commonly used to empirically validate the relative risk estimated by the models, but the underreporting or the lack of imported travellers infected with pathogens reported via routine surveillance hinders this approach to evaluating the models. Moreover, expanding the approach to longer time series, different diseases, other countries and more sophisticated modelling will likely improve reliability and utility further.

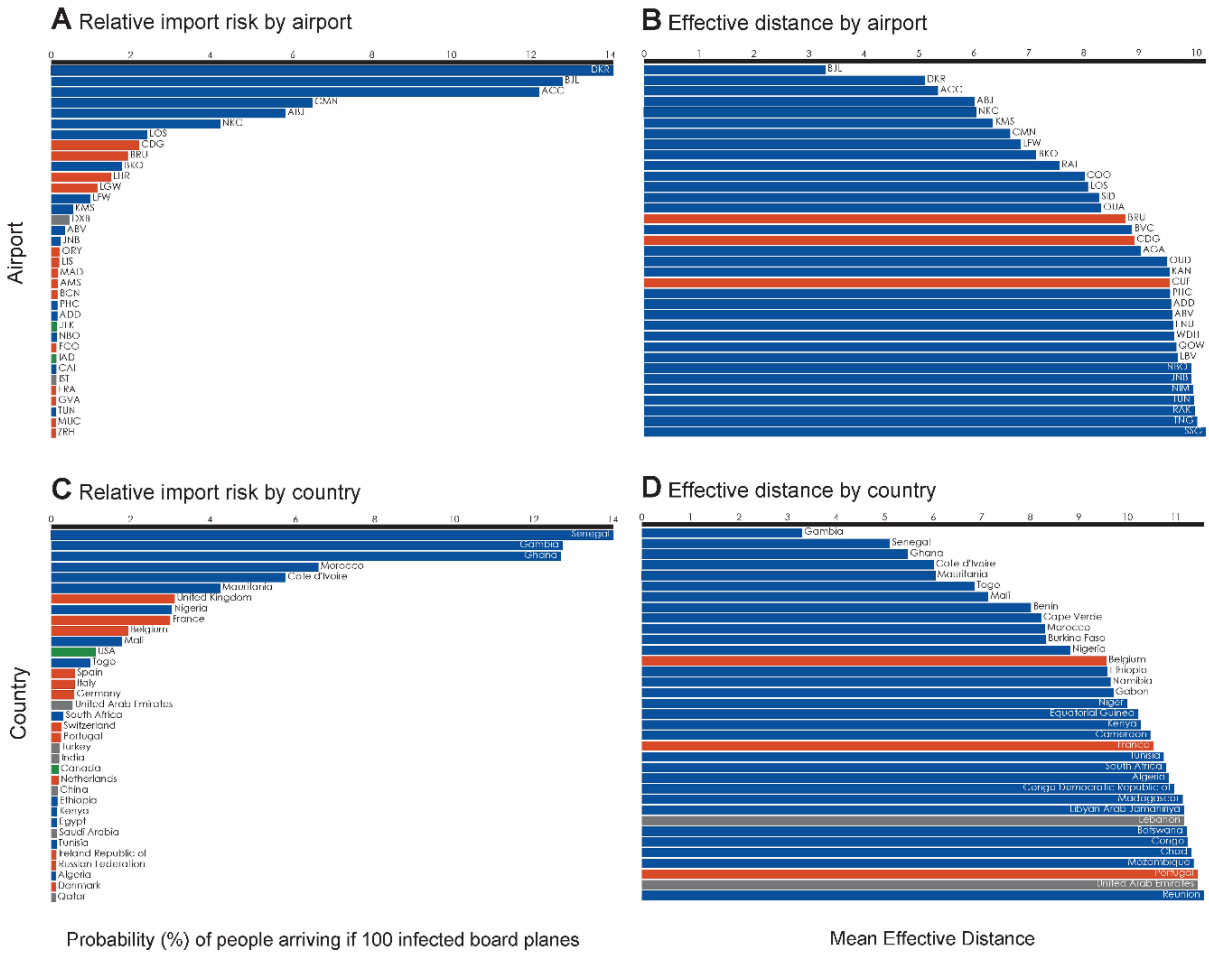



**Figure 1-16. Relative import risk and effective distance from Ebola affected West African countries to other locations worldwide via air travel ranked by airport or country.**

Data source: Research on Complex Systems (rocs.hu-berlin.de/projects/ebola/index.html) (Brockmann et al., 2014). Three West African countries, Guinea, Sierra Leone and Liberia, were included. The IATA codes of airports are showed in panels A and B. The colours of bars represent the continents in where the airports or countries located.

## 1.6 Estimating onward transmission risks from introduced infections

Assessing the risk of importation is only the first step. Often more critical is assessing whether introduction will lead to autochthonous transmission. A better understanding of the risk of onward transmission by imported mosquito-borne infections can improve interventions to mitigate this risk. As the vectors are key component in the local transmission of vector-borne infections, it is important to understand the geographic range of competent vectors and their seasonal dynamics. One basic method is conducting entomological surveillance and evaluating the effect of control measures (Liu Qiyong, 2016; Guo et al., 2015; Mendenhall et al., 2017). However, due to the lack of long-term and high-quality monitoring data in many countries, several approaches have been applied to model the distribution of or environmental suitability for vectors. The resulting maps can then be combined with connectivity networks or risks of introduced infections to estimate the onward transmission risk of imported mosquito-borne infectious disease by air travel. The relevant approaches have been summarized (**Table 1-4**).

### 1.6.1 Ecological suitability estimate for local transmission risk

The risk for the establishment of mosquito-borne disease and potential cases of disease in an originally non-endemic area depends fundamentally on the ability of a vector to establish itself in that area, or the ecological conditions for the vector there. When these ecological conditions are suitable, the disease can transmit locally in two ways: 1) If the vector is already established, it can become infected from a person infected with pathogens arriving in that area; 2) Infected mosquitoes can be transported into such an area and establish themselves. For this process, habitats in the area of interest must be ecologically suitable for the vector. A quantitative relative measure of the suitability of one area compared to another defines the relative ecological risk of that area (Gonzalez et al., 2010; Moffett et al., 2007; Gardner and Sarkar, 2013). If the ecological risk is low, such an establishment is highly unlikely. If that risk is high, then other factors, such as the (temporally) immediate ambient environmental conditions and the size of the founder population or the availability of hosts, become critical for establishment. Two commonly used approaches to map the ecological suitability of mosquito-borne diseases are introduced below.

**Table 1-4. Models for measuring onward transmission risks of mosquito-borne disease imported by air travel.**

| Methods and diseases/vectors | Description | Strengths | Weaknesses |
|---|---|---|---|
| **Ecological suitability estimates and local transmission risk** | | | |
| Dynamic biological framework<br><br>i.e. *P. falciparum* and *P. vivax* (Gething et al., 2011b); *Ae. aegypti* and *Ae. albopictus* for dengue *(Gething et al., 2011b; Weiss et al., 2014)* and Zika (Kraemer et al., 2015) | Elucidates the environmental limits with an index proportional to vectorial capacity in the mosquito-borne disease transmission cycle. | ● The predictive maps produced can be used as more biologically-appropriate covariates than typical temperature averages in statistical modelling of dengue and as an informative subcomponent to link vector and human models of dengue virus transmission;<br>● Model the seasonal variation. | ● Based on the priori knowledge on the relationships between vectors and ecological factors, e.g. temperature;<br>● The climatic suitability models cannot capture factors such as differences in transmission efficiency of locally dominant vector species, as well as the impact of human activities;<br>● Output does not represent a metric of contemporary endemicity of mosquito-borne diseases. |
| Boosted regression tree models<br><br>i.e. Dengue, Chikungunya and Zika (Bhatt et al., 2013; Messina et al., 2016; Kraemer et al., 2015), *Ae. aegypti* and *Ae. albopictus* (Kraemer et al., 2015), avian influenza H5N1 and H7N9 (Elith et al., 2008) (Artois et al., 2016), and Ebola (Gilbert et al., 2014; Pigott et al., 2014) | Using a machine-learning approach with strong predictive performance to model interactions between variables as well as non-linear relationships between the outcome and predictor variables. | ● Include a set of high-resolution globally gridded environmental and socioeconomic covariates hypothesised to affect disease transmission;<br>● Mapping global environmental suitability for disease lacking the basic epidemiological information;<br>● Gain a better understanding of the factors driving spread of disease and the potential for geographic expansion beyond the disease's currently limited geographical extents. | ● Non-informative predictors are largely ignored;<br>● Seasonal maps are commonly unpredictable to due to the lack of the high resolution of land-cover and environmental variables |

| Methods and diseases/vectors | Description | Strengths | Weaknesses |
|---|---|---|---|
| Overlaying suitability maps with imported infections geographic range<br><br>i.e. Dengue (Wesolowski et al., 2015b), Zika (Bogoch et al., 2016a; Rocklov et al., 2016), and malaria, Yellow Fever and Chikungunya (Huang and Tatem, 2013) | Combine the geographic range of imported infections with the suitability maps of vectors that have full competence to transmit the pathogens. | ● An easy way to highlighting specific geographic areas and timing of risk for pathogens introduction and possible spread. | ● Qualitatively combine the maps to present the potential risks of onward transmission by imported pathogens commonly without the magnitude or probability of this risk. |
| **Directly defining onward transmission risk from imported infections** | | | |
| Traffic-scaled climatic similarity analysis<br><br>i.e. *Ae. albopictus* (Tatem, 2009; Tatem and Hay, 2007) and Chikungunya (Tatem et al., 2012) | Estimate the relative risk of importation and establishment of vectors and pathogens importation by traffic-scaled climatic Euclidean distance (CED) between origins and destinations. | ● Examine the likely directions and magnitudes of changes in climatically sensitive organism invasion risk across the worldwide airline network;<br>● High traffic-scaled CED represents a greater possibility of biological invasion. | ● Model validation remained qualitative;<br>● CED addresses the risk of importation and establishment of the vector but not the likelihood of infection directly;<br>● How to interpret and act upon the kind of relative risks identified is a challenge yet to be overcome. |
| Mathematical dynamic models<br><br>i.e. malaria(Le Menach et al., 2011) and dengue (Wesolowski et al., 2015b; Lopez et al., 2016) | Directly quantify the rates of onward transmission from imported vector-borne infections with an ento-epidemiological framework. | ● Estimate the numbers of infections importation and onward transmission;<br>● Estimate the dynamics of introduction and transmission of different strains and interaction. | ● Rich data are required to parameterize the models;<br>● Assumes that all returning infectious travellers arrive at their home country homogeneously distributed, that is, all the susceptible local inhabitants had the same probability of being infected by them; |

| Methods and diseases/vectors | Description | Strengths | Weaknesses |
|---|---|---|---|
| | | | ● Accurate data on outbreak locations and sizes are difficult to obtain to validate the models. |
| Probabilistic branching process models<br><br>i.e. Yellow Fever, dengue, and Chikungunya (Johansson et al., 2011; Johansson et al., 2012; Johansson et al., 2014) | Mechanistically calculate the probability of introduction and autochthonous transmission of mosquito-borne diseases by two submodels. | ● Highly sensitive and specific for the prediction for the probability of onward transmission from imported infections based on the latest best understanding of the dynamics of vectors, infections, and global travel;<br>● Estimate the timing and seasonal patterns of the introduction and onward transmission;<br>● Estimate R0 with the pathogen transmission components from vector to human and from human to vector;<br>● Uncertainties of estimates are provided by global sensitivity analysis. | ● Rich data are required for the parameterizations of the travel network and model validation;<br>● Parameters of mosquito-borne diseases transmission dynamics should be captured for the different scenarios. |

#### 1.6.1.1 Dynamic biological framework

Based on the principal mechanisms of environmental dependency in the mosquito-borne disease transmission cycle, this framework elucidates the environmental limits with an index proportional to the basic reproductive number (R0) for mosquito-borne diseases transmission in targeted areas. The concept of R0, the number of secondary cases that will arise from a single infectious human in a totally susceptible population, is a natural framework for evaluating relative changes in transmission potential for a variety of vector-borne diseases. The entomological, and thus strongly environmentally dependent, components of R0 can be summarised by the equation for vectorial capacity (defined as the inherent ability of the mosquito to transmit pathogens, the vector's lifespan, and the extrinsic incubation period).

For instance, Gething et al (2011b) has designed a dynamic biological model and mapped the temperature suitability index of malaria vectors to define the constraints of temperature on transmission of *P. falciparum* and *P. vivax*. This model incorporated the principal mechanisms of temperature dependency in the mosquito-borne transmission cycle and, using fine spatial and temporal resolution temperature data, they temporally evaluated temperature suitability for transmission of *P. falciparum* and *P. vivax* throughout an average year. Time-series analyses were calculated for all 1 km resolution land pixels globally, and were summarised to create high-resolution maps for each species delineating those regions where temperature precludes transmission throughout the year. Within suitable zones they mapped for each pixel the number of days in which transmission is possible and an integrated measure of the intensity of suitability across the year (Gething et al., 2011b).

This dynamic biological framework (Gething et al., 2011b; Weiss et al., 2014) has also been used to define global temperature constraints on *Ae. aegypti* and *Ae. albopictus* persistence and competence for dengue virus transmission at a high spatial and temporal resolution using an empirically-parameterised mechanistic model that explicitly considers the interplay between temperature-dependent extrinsic incubation period (EIP) and adult vector survival (**Figure 1-17**) (Brady et al., 2014). Based on the given temperature-based relationships (Chan and Johansson, 2012), this modelling framework evaluated the cumulative effects of changing temperature regimes on an index proportional to vectorial capacity of *Aedes* mosquitoes. The predictive maps produced can be used as more biologically-appropriate covariates than typical temperature averages in statistical modelling of dengue and as an informative subcomponent to link vector and human models of dengue virus transmission.

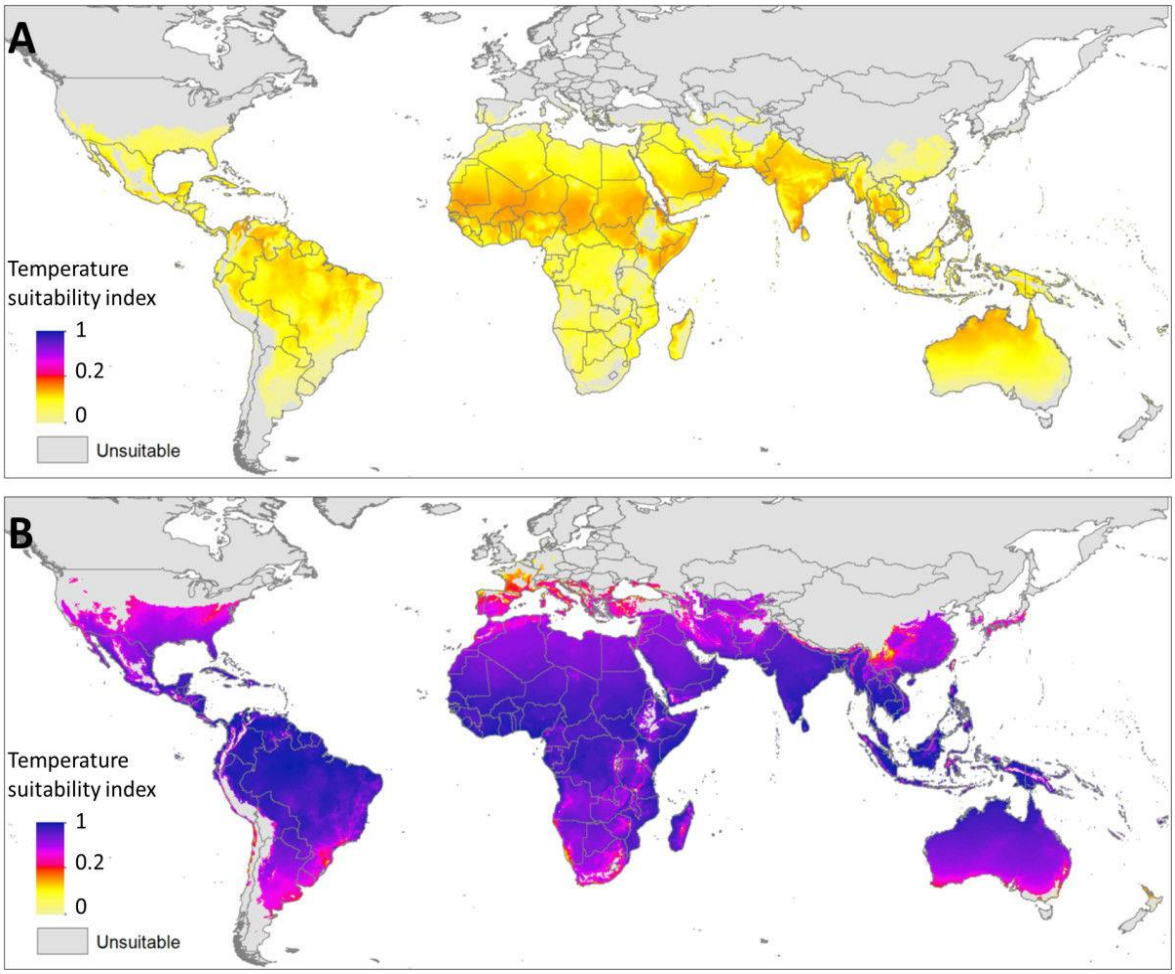



**Figure 1-17. Comparative temperature suitability of Ae. aegypti (A) and Ae. albopictus (B).**
Note: The annualised temperature suitability index normalised relative to the maximum value of both species and plotted on a logarithmic scale.

Furthermore, to understand seasonal variation in the global geographical range of vector suitability for Zika virus transmission, Bogoch et al (2016a) used mosquito species distribution models for *Ae. aegypti* and *Ae. albopictus* (originally fitted to annual data and covariates) (Lambrechts et al., 2011) to make monthly predictions by use of new monthly covariates for temperature-persistence suitability, relative humidity, and precipitation. Then they refined these seasonal maps by scaling their values so that the sum of all monthly maps equalled to the previous annual mean map (Kraemer et al., 2015), accounting for relative changes in suitability throughout the year and between regions. Continuous seasonal maps were produced for each month of the year to delineate different suitability scenarios, and converted into binary range maps for each species. Finally, monthly vector maps showed predictions of areas with a high likelihood for observation or detection of mosquito populations, which were assumed to be sufficiently abundant to enable transmission of disease to humans.

The performance of these frameworks is constrained by the knowledge on the relationships between vectors and ecological factors. Based on *a priori* knowledge, temperature has been

included in previous studies as an important factor affecting the vectorial capacity, but in many regions of the world temperature is not the primary climatic limitation on transmission, and the insufficient moisture for breeding habitats limits the survival of vectors regardless of the suitability of ambient temperature regimes. The climatic suitability models cannot capture factors such as differences in transmission efficiency of locally dominant vector species, as well as the impact of human activities that, for example, have had a dramatic effect on the global malaria landscape over the past century (Gething et al., 2010). Therefore, the modelled outputs do not represent a metric of contemporary endemicity of mosquito-borne diseases.

#### 1.6.1.2 Boosted regression tree models

Taking into account a variety of covariates such as climate, urbanisation and economy on diseases transmission, boosted regression tree (BRT) models use a machine-learning approach which has strong predictive power to model interactions between variables as well as non-linear relationships between the outcome and predictor variables (Elith et al., 2008). BRT models are increasingly used in probabilistic species distribution modelling and show strong predictive capacity due to their ability to handle complex non-linear relationships between probability of species occurrence and multiple environmental correlates (Elith et al., 2008), such as vectors of arboviruses, i.e. dengue, Chikungunya, and Zika (Bhatt et al., 2013; Messina et al., 2016; Kraemer et al., 2015) and zoonotic diseases, e.g. avian influenza H5N1 and H7N9 (Artois et al., 2016; Gilbert et al., 2014) and Ebola (Pigott et al., 2014).

Taking the *Aedes* mosquito as an example, Kraemer et al (2015) employed the BRT approach to estimate the global distribution of the arbovirus vectors, *Ae. aegypti* and *Ae. albopictus*. They compile a large contemporary database for both species and pair it with relevant environmental variables to predict probabilistic global environmental risk maps for *Ae. aegypti* and *Ae. albopictus*. In order to make accurate predictions of the distribution of these two species, the model required the suitability mask defining the fundamental limits of species, globally comprehensive datasets of geocoded occurrence points for species (**Figure 1-18**), appropriate environmental covariate datasets to explain the current distribution of the species (**Figure 1-19**), and a set of species absence records that further refine the species range and reduce sampling bias. These predictive maps help to define the spatial potential of autochthonous transmission of dengue viruses (Kraemer et al., 2015).

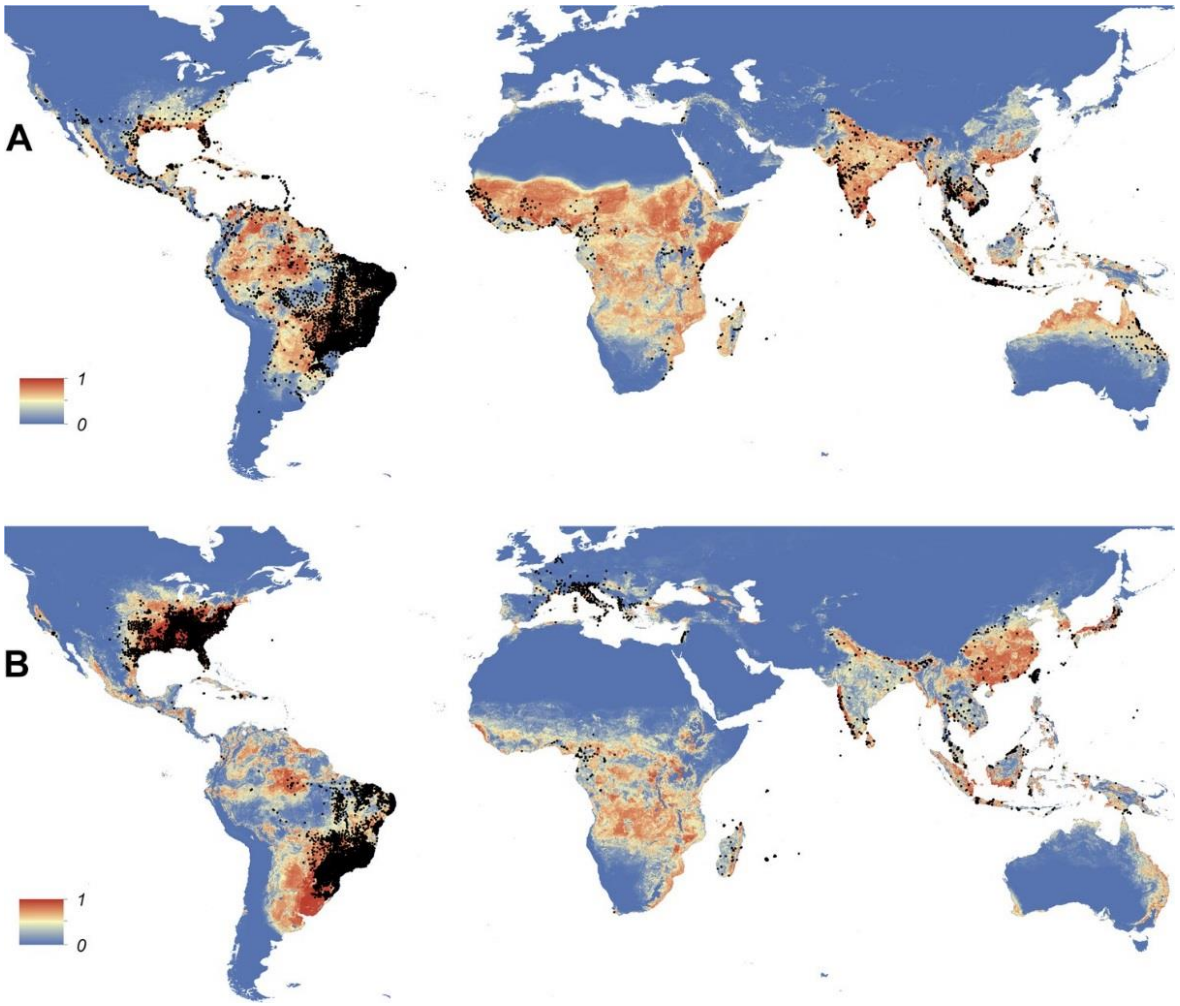



**Figure 1-18. The distribution of the occurrence database for *Ae. aegypti* (A) and *Ae. albopictus* (B) plotted on the underlying prediction surface.**

Data source: Kraemer et al., 2015.

Moreover, despite lacking a great deal of basic epidemiological information specific to a disease at the early stage of an epidemic, the BRT methodology has good performance to predict the potential geographic range of transmission. For instance, BRT has been employed to map global environmental suitability for Zika based on the known locations of disease occurrence in humans, background points representing locations where Zika has not yet been reported, and a set of high-resolution globally gridded environmental and socioeconomic covariates hypothesised to affect Zika transmission (Messina et al., 2016). The resulting model produces a high spatial-resolution global map of environmental suitability for Zika transmission to humans.

However, in a BRT, non-informative predictors are largely ignored, and due to the lack of time series of disease, land-cover and environmental variables, the existing studies based on BRT does not directly infer seasonal patterns of geographic distributions which might be of importance on the periphery of the species distributions. With a more temporally resolved dataset it may be

possible to capture the effects of intra-annual seasonality on the species' distributions (Kraemer et al., 2015).

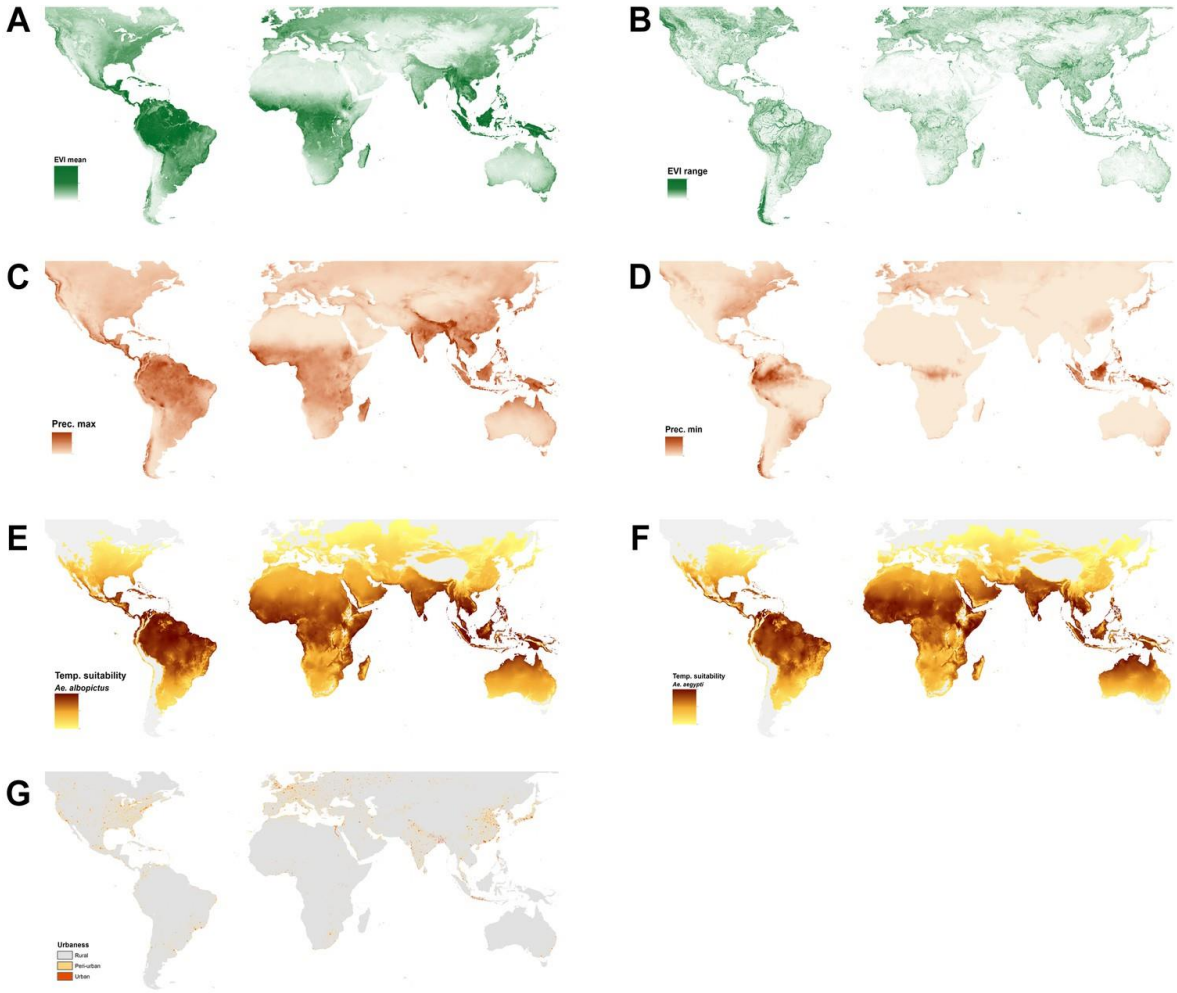



**Figure 1-19. Set of covariate layers to predict ecological niche of *Ae. aegypti* and *Ae. albopictus*.** Note: (A) enhanced vegetation index (EVI) annual mean; (B) EVI annual range; (C) annual monthly maximum precipitation; (D) annual monthly minimum precipitation; (E) temperature suitability for *Ae. albopictus*; (F) temperature suitability for *Ae. aegypti*; (G) rural, peri-urban and urban classification layer. Data source: Kraemer et al., 2015.

#### 1.6.1.3 Overlaying suitability maps with geographic range of importation infections

To define the onward transmission risk by imported mosquito-borne diseases, a common approach is to combine the geographic range of imported infections with suitability maps of vectors that have full competence to transmit the pathogens, and sometimes, further overlap with the distribution of population density to estimate the number of population at risk. For example, to predict the potential for Zika virus introduction and transmission in Africa and the Asia-Pacific region, Bogoch et al (2016a) overlaid monthly flows of airline travellers arriving to Africa and the Asia-Pacific region from areas of the Americas suitable for year-round transmission

of Zika virus with monthly maps of climatic suitability for mosquito-borne transmission of Zika virus within Africa and the Asia-Pacific region.

Similarly, to assess seasonal risks for the introduction and mosquito-borne spread of Zika virus in Europe, Rocklov et al (2016) produced a map to highlight specific geographic areas and timings of risk for Zika virus introduction and possible spread within Europe. This was carried out by overlaying the monthly flows of airline travellers arriving into European cities from Zika affected areas across the Americas, the geographic range of monthly R0 of Zika virus in areas where *Ae.* mosquito populations reside in Europe, and human populations living within areas where mosquito-borne transmission of Zika virus may be possible. Additionally, the VBD-Air tool (www.vbd-air.com) has been developed to present the global connectivity through air travel in the transmission and spread of four vector-borne diseases including malaria, dengue, yellow fever and chikungunya with aims of improving access to such datasets and combining them for initial assessments of risk of vector-borne pathogen importation and onward spread, or vector importation and establishment (**Figure 1-20**) (Huang and Tatem, 2013). However, these approaches only simply qualitatively combine the maps to present the potential risks of onward transmission by imported pathogens without the magnitude or probability of this risk.

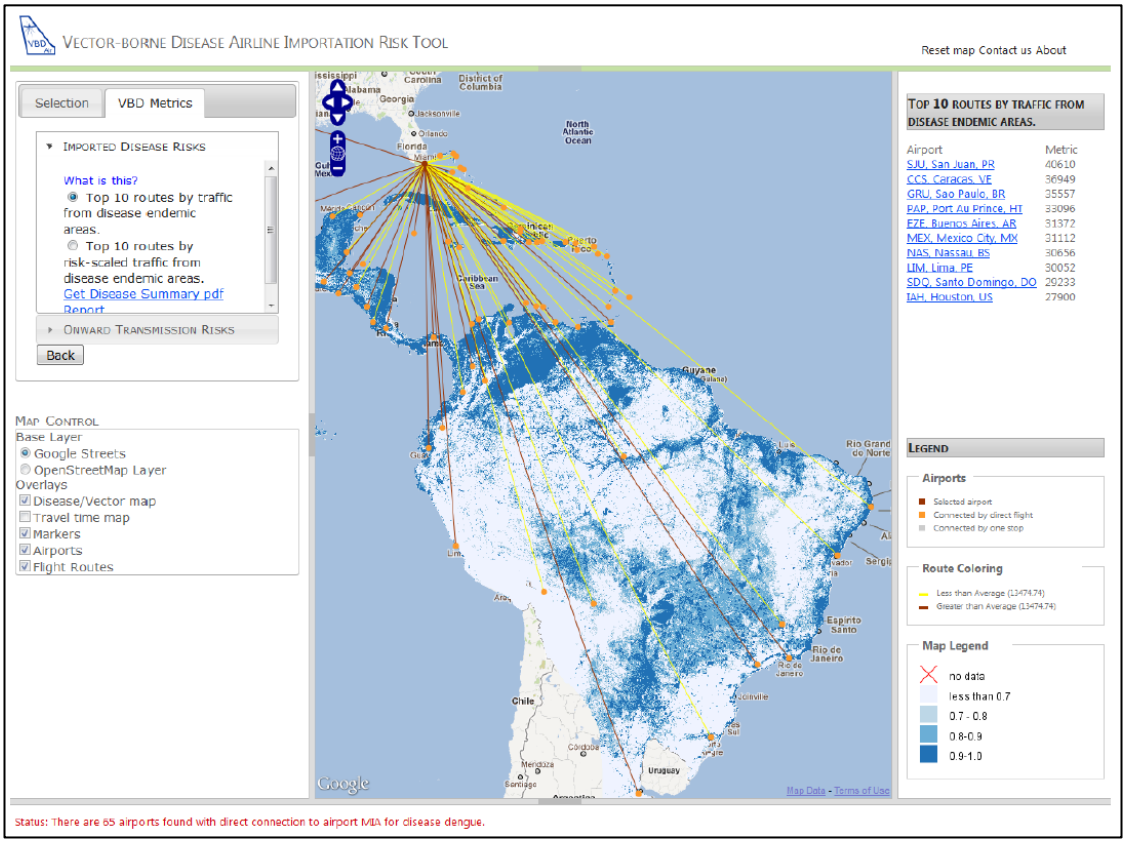



**Figure 1-20. A web-based tool for the vector-borne disease airline importation risk.**

Note: The selected airport (Miami) was connected by direct and one-stop flights in dengue endemic areas defined by overlapping with predicted suitability (0-1 scale) for dengue transmission.

### 1.6.2 Directly defining onward transmission risk from imported infections

#### 1.6.2.1 Traffic-scaled climatic similarity analysis

The international spread of many vector-borne diseases could be explained using data on both traffic volumes and the climatic similarity between source and potential invasion points (Tatem et al., 2006b; 2006c). A climatic Euclidean distance (CED) has been applied to estimate the relative risk of importation and establishment of vectors and pathogens imported by sea or air routes (Tatem, 2009; Tatem and Hay, 2007). The climatic similarity of an air route connecting two airports is defined by the Euclidean distance between the climatic conditions at these two airports. The Euclidean distance in climatic space can be calculated to produce 12 symmetrical "climatic dissimilarity" matrices, one for each month of the year, with each cell representing a CED between one airport and the other (**Figure 1-21**). Moreover, to examine the general combined effect of climatic similarity and traffic volume for each route, the CED for each flight route is scaled by the passenger capacities on those routes. The traffic-scaled CED between airports $i$ and $j$ is defined as

$$\mathrm{CED}t_{ij} = \left(\frac{1}{\mathrm{CED}_{ij}}\right) t_{ij}$$

where $\mathrm{CED}t_{ij}$ is the CED between airports $i$ and $j$, and $t_{ij}$ is the total traffic volume or seat capacity on the route from airport $i$ to airport $j$. A relatively low $\mathrm{CED}t_{ij}$ indicates that the traffic volume and climatic similarity between the connected regions is low, while a relatively high $\mathrm{CED}t_{ij}$ on a route shows there to be high levels of traffic between climatically similar regions.

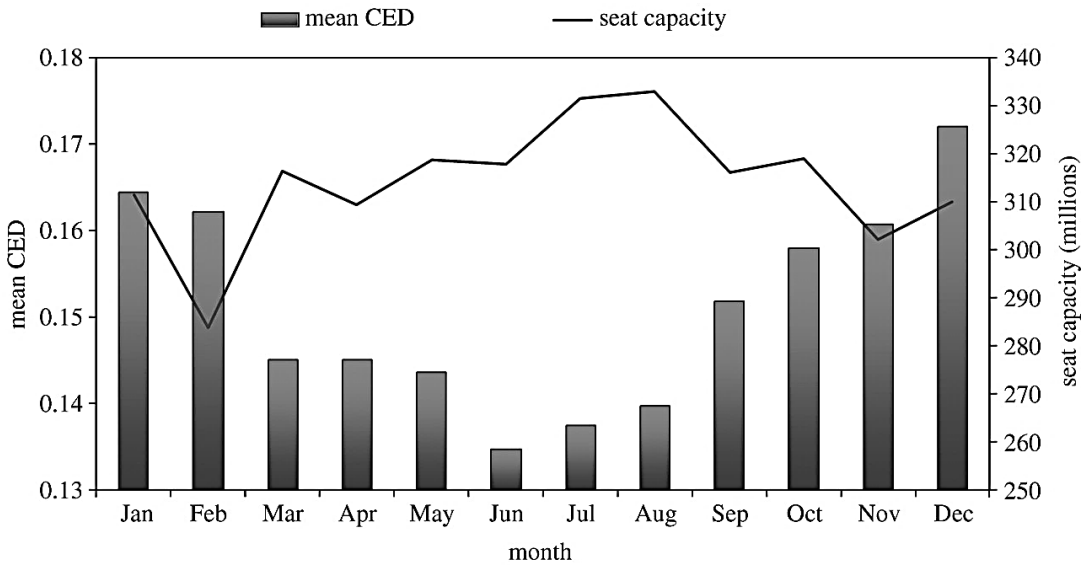



**Figure 1-21. Mean monthly CEDs and monthly total seat capacities across the worldwide airline transportation network in 2005-2006.**

Data source: Tatem and Hay, 2007.

As greater traffic volumes equate to greater propagule pressure and climatic similarity results in a greater chance of exotic organism survival, the high $\mathrm{CED}t_{ij}$ represents a greater possibility of biological invasion. For instance, based on normalized measures of traffic volume and climatic similarity through obtaining measures of rainfall, temperature and humidity between the origin and destination, Tatem et al (2009; 2007) used CED to examine the likely directions and magnitudes of changes in climatically sensitive organism invasion risk across the worldwide airline network for *Ae. albopictus*, and furthermore assessed regions most at risk for onward transmission of chikungunya importation into Italy (Tatem et al., 2012).

This CED approach is a simple risk analysis to provide insight into the pathogen importation and onward transmission process, but model validation remains qualitative. Moreover, CED addresses the risk of importation and establishment of the vector but not the likelihood of infection directly, and how to interpret and act upon the kind of relative risks identified is a challenge yet to be overcome.

#### 1.6.2.2 Mathematical dynamic models

As mentioned in the previous section on importation risk estimates, mathematical dynamic models have been further adopted to directly quantify the rates of onward transmission from imported vector-borne infections with an ento-epidemiological framework (**Figure 1-22**) (Wesolowski et al., 2015b). For instance, to assess travel risk, malaria importation and malaria transmission in Zanzibar, Le Menach et al (2011) used a dynamic model to estimate importation and transmission rates based on mobile phone usage data and ferry traffic between Zanzibar and mainland Tanzania. They found that the malaria importation rate was estimated to be 1.6 incoming infections per 1,000 inhabitants per year, but local transmission was estimated too low to sustain transmission in most places.

Additionally, based on an SIR model framework, Lopez et al (2016) estimated the risk of dengue importation and secondary transmission by travellers from Thailand to Europe. Assuming the travellers' home country had a sufficiently high density of *Aedes* mosquitoes, and R0 was approximately 0.3 for Europe and the number of travellers visiting Thailand during summer was 10,000, the expected number of individuals returning still infectious was 30 and they would generate nine autochthonous secondary dengue cases. However, the above calculation assumed that all returning infectious travellers arrived at their home country in a homogeneously distributed way; that is, all the susceptible local inhabitants had the same probability of being infected by the infectious travellers.

Model validation is another challenge for dynamic models. The observed occurrence of imported infections and onward transmission has been commonly used to empirically validate the estimates of the models. However, accurate data on outbreak locations and sizes are difficult to obtain to be sure of comprehensive assessments of risk, and the underreporting or the low accessibility of imported infections data hinders model evaluation, but the simulation of outbreaks in different scenarios are widely used in model validation and comparison.

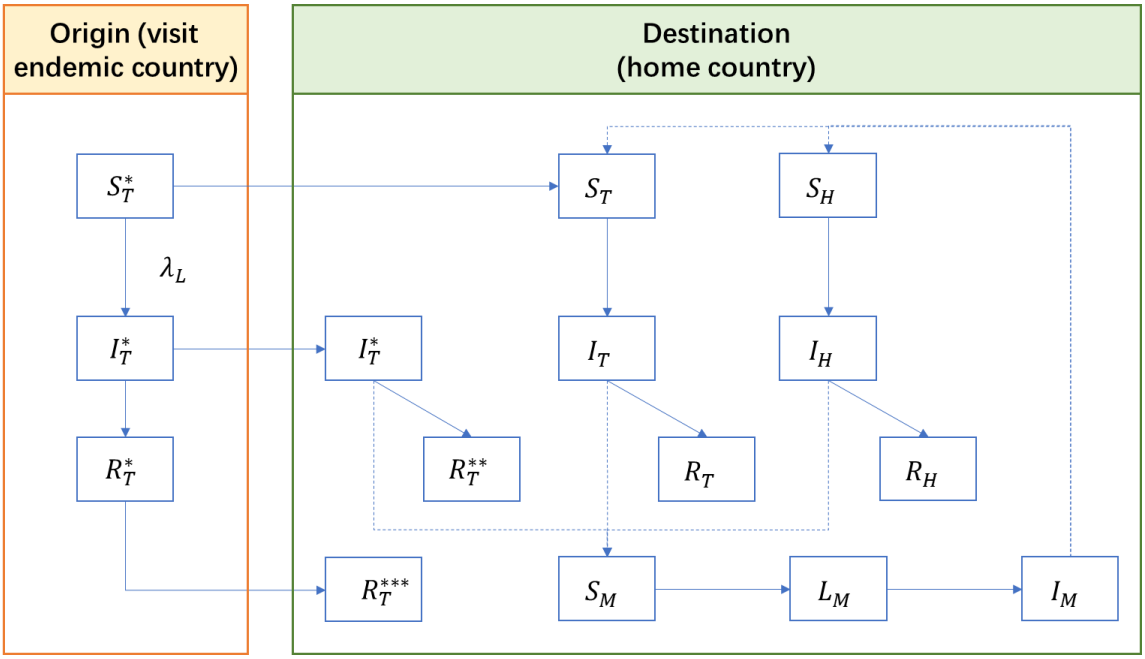



**Figure 1-22. The flow of individuals in a basic mathematical dynamic model for disease introduction and onward transmission**.

Note: $S_H$ - Susceptible individuals in home country that never travelled to the endemic country; $I_H$ - Infectious individuals in home country that acquired the infection locally in their home country (autochthonous infections from the $S_H$ class); $R_H$ - Recovered individuals in home country, from the autochthonous infections $I_H$ class; $S_T$ - Susceptible travellers that returned susceptible to their home country; $I_T$ - Infectious travellers, infected locally in home country after returning (autochthonous infections from the $S_T$ class); $R_T$ - Recovered individuals from the autochthonous infections $I_T$ class; $S_T^*$ - Susceptible travellers visiting an endemic country; $I_T^*$ - Infectious travellers, that acquired the infection at the visited country and return infectious; $R_T^*$ - Recovered travellers, that were infected and recovered in the visited country before returning home; $R_T^{***}$ - Individuals $R_T^*$ that returned to their home country; $I_T^{**}$ - Individuals $I_T^*$ that returned to their home country; $R_T^{**}$ - Recovered travellers, that were infected in the visited country, returned home infected, and recovered there; $S_M$ - Susceptible mosquitoes (disease vectors in the home country); $L_M$ - Latent mosquitoes, disease vectors which have been infected locally by $I_H$, $I_T$ and $I_T^*$ but are not yet infectious; $I_M$ - Infectious mosquitoes, disease vectors which have survived to the incubation period and can transmit the disease.

#### 1.6.2.3 Probabilistic branching process models

Regarding the probability of introduction and autochthonous transmission of vector-borne diseases, probabilistic branching process models have been used to mechanistically address the potential for mosquito-borne pathogens to spread around the world through infected airline travellers. This approach directly integrates the risk of imported infections with the suitability for vectors for pathogen transmission from humans to mosquitoes and from mosquitoes to humans at destinations (Johansson et al., 2012; 2014). Probabilistic branching process models have two sub-models:

1) The first estimates the probability of at least one infected traveller arriving somewhere as a binomial process, dependent on the risk of infection in endemic locations, the probability of those individuals travelling, and the duration of infection.
2) The second mechanistically estimates the probability of introduction leading to autochthonous transmission as the probability of infected travellers arriving, infected travellers infecting mosquitoes, and infected mosquitoes infecting at least one human.

These models can be designed using the latest understanding of vector dynamics, infections, and global travel to assist in assessing the probabilities of pathogen spread for different transmission scenarios representing drastically different estimations of transmissibility and epidemic/pandemic potential. Furthermore, the probabilistic branching process models estimate the timing, in terms of both actual time and the number of people infected, and seasonal patterns of the introduction and onward transmission for mosquito-borne infections (Johansson et al., 2014). Moreover, findings from previous studies show that the models were highly sensitive and specific for the prediction of introduction in the simulations and tended to predict introduction before actual introduction (Johansson et al., 2012; 2014).

Using simulations and probability generating functions to estimate the probability of one or more autochthonous infections, Johansson et al (2014) showed the models reliably predicted the probability of autochthonous transmission occurring in other cities based solely on the cumulative number of infectious person-days in a source city, and found that the probability of autochthonous transmission depends on both the probability of introduction and the efficiency of local transmission (**Figure 1-23**). The stochasticity of these processes contributes to the high degree of variability in the city where the earliest autochthonous infections occurred. Furthermore, the R0 with the pathogen transmission components from vector to human and from human to vector can also be estimated with associated uncertainties incorporated into the models using global sensitivity analysis (Johansson et al., 2014), and the area under the receiver

operating characteristic curve has been widely used as a measurement of the discriminatory capacity of models and parameters (Elith et al., 2008).

However, some important limitations exist for probabilistic branching process models as well as other models:

1) More data are required for the parameterizations of the travel network;
2) The parameters of mosquito-borne diseases transmission dynamics should be captured for the different scenarios;
3) Travellers are commonly treated with identical risk of infections, but the simple fact is that not all airline travellers are equivalently at risk (Johansson et al., 2011);
4) The assumption for local transmission is a mass action-based process treating each city or airport in the destination as a single pool of individuals all experiencing equal exposure risk, which masks significant underlying heterogeneity.

Additionally, there are few previous studies and probabilistic models to quantitatively define the long-term and seasonal relative risk of importation and onward transmission via air travel for mosquito-borne diseases, which will be further investigated in this study.

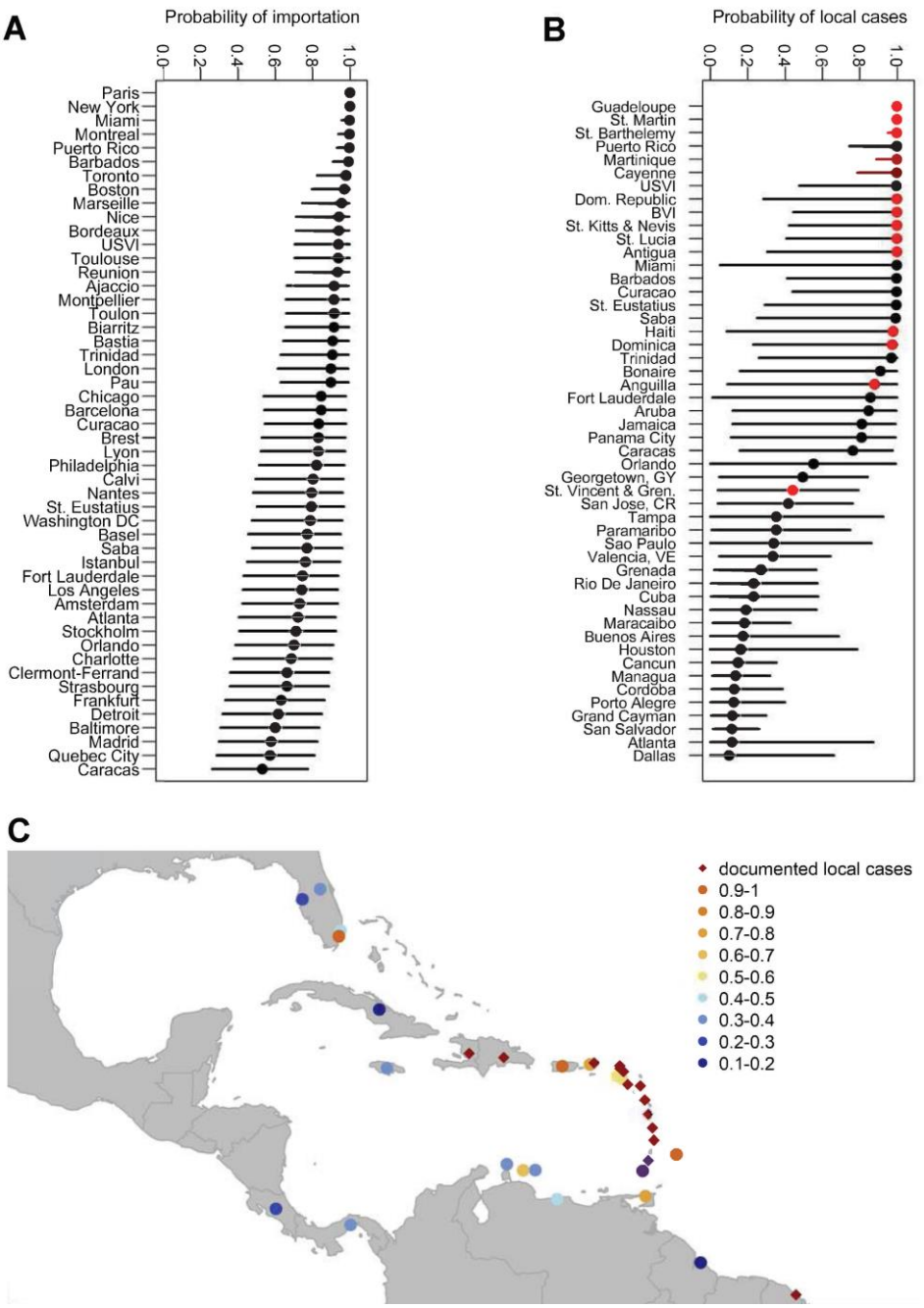



**Figure 1-23. Probability of importation and local transmission of chikungunya virus by location in Americas, 2013-2014.**

Note: (A) Probability of chikungunya virus importation for select locations, April 2014. Location-specific mean estimates (points) and 95% percentiles (lines) for the predicted probability of the arrival of at least one chikungunya infected traveller for the 50 locations most likely to have had imported cases in April 2014. (B) The cumulative predicted probabilities of local transmission for the 50 locations most likely to have had introduced transmission over the time period December 2013–April 2014, with location-specific mean estimates (points) and 95% percentiles (lines). Locations which had reported locally-acquired cases as of 2 May 2014, are marked in red. (C)The mean probabilities of local transmission for all locations in the Americas with p>0.1 in April. BVI: British Virgin Islands; USVI: U.S. Virgin Islands. Data source: (Johansson et al., 2014).

## 1.7 Mosquito-borne diseases and importations in China

Among all 39 notifiable infectious diseases of mainland China (31 provinces), there are three mosquito-borne diseases: malaria, dengue and Japanese encephalitis. As a vaccine-preventable disease, the incidence of Japanese encephalitis has decreased dramatically in China since 1990 to lower than 1 case per 100,000 persons, and reached a historical low of 0.46 per 1 million persons in 2015 (Chinese Center for Disease Control and Prevention [China CDC], 2016). However, the accumulated numbers of malaria and dengue cases rank them the top two notifiable mosquito-borne diseases in China during 2004-2015, with thousands of cases imported from other countries (Yang et al., 2017; China CDC, 2015; 2016). At the same time, some other mosquito-borne diseases were also reported to have been sporadically imported into China from other countries, e.g. Zika fever, Chikungunya fever, Yellow fever and Rift Valley fever, following the increasing connectivity between China and other countries (**Figure 1-24**) (Xiang et al., 2017; Zheng et al., 2010; Ling et al., 2016; Yang et al., 2017). A study for monitoring mosquito-borne diseases in febrile travellers in Shenzhen of Guangdong province of China in 2013 found that dengue, Japanese encephalitis, Chikungunya viruses, and *Plasmodium* malaria were detected, with dengue mainly having been imported from Southeast Asia and malaria from Africa (Shi et al., 2016).

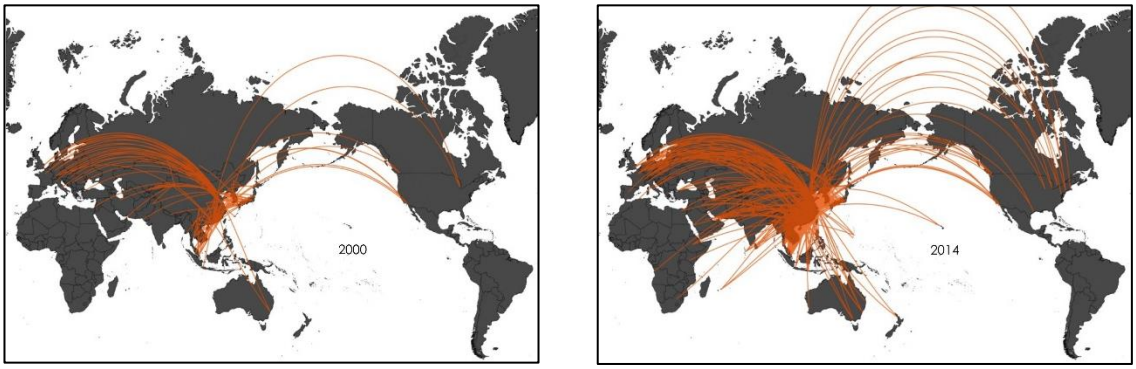



**Figure 1-24. The expanding networks of non-stop international airlines from mainland China in 2000 (left) and 2014 (right).**

Data source: IATA and the BlueDot (bluedot.global).

These imported pathogens also impose threats of potential local transmission in suitable environments. The Chikungunya virus, for instance, was likely imported from Southeast Asia and probably evolved from a strain that originated in Thailand (Wu et al., 2012), and has caused the first outbreak of Chikungunya of China in Dongguan city of Guangdong province in 2010 (Qiaoli et al., 2012; Li et al., 2012a). International travellers with mosquito-borne infections can accelerate the spread of pathogens. Thus, early identification of imported mosquito-borne infections to prevent onward transmission should become a high priority. Considering the significance and the

intensity of importations into China, the situation for malaria and dengue in China are detailed below.

### 1.7.1 Malaria and its importation in China

Historically, malaria had a wide geographical distribution in China for both *P. falciparum* and *P. vivax* malaria, with high incidence. Unlike in Africa, where *An. Gambiae* is the predominant vector of malaria, the *Anopheles* mosquitoes as vectors of malaria in China include *An. sinensis*, the most widespread malaria vector, followed by *An. dirus*, *An. minimus*, *An. candidiensis*. Additionally, *An.kunmingensis*, *An. messeae* and *An. sacharovi* may also transmit *Plasmodium* malaria (Sinka et al., 2012; Pan, 2003).

Before 1949, it was estimated that 30 million malaria cases occurred yearly and 70% of counties in China were endemic for malaria (Zhou, 1981). In recent decades, malaria control has achieved remarkable success in China. The annual number of malaria cases has decreased from 24 million in the early 1970s to less than 26,000 by 2000 (Tang, 2000), and the spatial extent of the malaria epidemic has narrowed significantly. After 2000, malaria in some regions of China rebounded, but with the implementation of the 2006-2015 National Malaria Prevention and Control Program, increased support and investment for malaria prevention and control from the central and local governments facilitated comprehensive intervention measures. These included enhanced surveillance activities, identification of the source of infections, control of outbreaks, and provision of treatment. This has effectively curbed the resurgence of malaria. By 2010, the incidence of malaria in 95% of counties within the 24 malaria endemic provinces in mainland China had dropped to less than one per ten thousand residents (**Figure 1-25**) (Zhang et al., 2014b).

In response to the global initiative to eliminate malaria at the High Level Meeting of the United Nations Millennium Development Goals, the national malaria elimination programme (NMEP) was launched by Chinese Central Government in May 2010, with aims of interrupting malaria transmission in most Chinese counties by 2015, and malaria elimination by 2020 (National Health and Family Planning Commission of China, 2010).

Zhang et al (2014b) found that the epidemiological characteristics of both *P. vivax* and *P. falciparum* malaria in China changed between the control stage (pre-2010) and the elimination stage (2010 onwards) in China (**Figure 1-25**). Since the initiation of NMEP, autochthonous malaria cases have numbered in the hundreds annually and significantly narrowed to several provinces, e.g. Yunnan and Hainan.

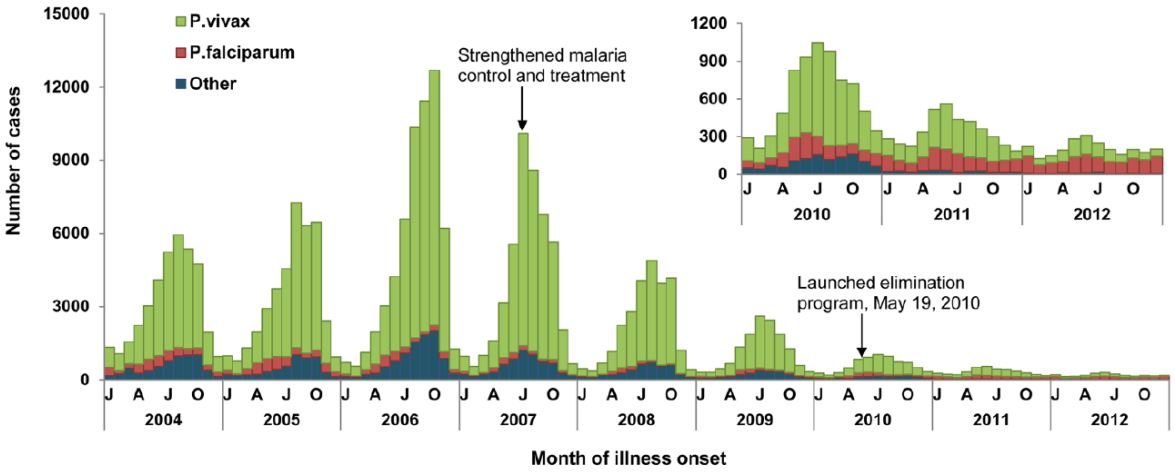



**Figure 1-25. The epidemic curve of cases by *Plasmodium* species**.

Note: Others contained *P. ovale*, *P. malariae*, mixed infections and untyped cases (Zhang et al., 2014b).

Although the areas affected by *P. vivax* malaria shrunk considerably, areas affected by *P. falciparum* malaria (autochthonous and imported) expanded from 294 counties in 2004 to 600 counties in 2012, especially among cases imported from Africa (Lai et al., 2016; Zhang et al., 2014b). The incidence of *P. falciparum* increased nearly threefold from 0.08 to 0.21 per 100,000 population from 2010 to 2014 (Zhou et al., 2016). Among 11,331 (64 % of all cases) imported malaria cases during 2010-2014, 90 % of *P. falciparum* infections were imported into China from Africa, while 77 % of *P. vivax* infections originated from Asia. The majority (94 %) of imported malaria cases had a labour-related travel history (Zhou et al., 2016).

During May-August 2013, an unusual, large-scale outbreak of imported malaria among Chinese travellers returning from overseas was detected among 4,052 returners in Shanglin County, China, with 874 cases and an attack rate of 216/1,000 persons. Most of those cases were infected with *P. falciparium* (94.6%). Ghana was the predominant origin country, and 92.3% of these malarial infections occurred in gold miners (Li et al., 2015).

However, the awareness of malaria prevention and symptoms are weak in Chinese travellers, and prophylactic measures against malaria are lacking for migrant labourers. In an epidemiological investigation of imported malaria cases in nine provinces of China, a total of 1420 imported malaria cases were recorded from 1 November 2013 to 30 October 2014, with *P. falciparum* (50.9 %) and *P. vivax* (44.3 %) being two predominant species (Li et al., 2016b). However, only 27.8 % imported cases had taken prophylactic anti-malarial drugs, and 27.7 % of the cases had experienced two or more episodes of malaria infection oversea. Additionally, the awareness of clinical manifestations and the capacity for malaria diagnosis were weak in private clinics and primary healthcare facilities of non-endemic regions in China (Li et al., 2016b). Considering the remarkable increase in volumes of cross-border travellers, malaria elimination in China faces the

challenge of imported parasites, especially those carried by Chinese workers returning from other malaria endemic countries.

### 1.7.2 Dengue and its importation in China

In 1978 dengue re-emerged in mainland China, reported in Foshan City of Guangdong province, after being absent for around 30 years (Zhao, 1981; Fan et al., 1989). Since then, outbreaks of dengue fever involving hundreds of thousands of people occurred in Guangdong and Guangxi provinces and on Hainan island in 1980s with the transmission of all four types of dengue virus. Cases of dengue haemorrhagic fever in both children and adults were also found sequentially in these outbreaks. Epidemics in 1980 caused by DENV-3 and 1985-1986 by DENV-2 resulted in more than 600,000 cases with 475 deaths overall in Hainan (Qiu et al., 1991; Li et al., 1986).

Partly in response to the dengue outbreaks in the 1980s, dengue became a notifiable disease on September 1$^{st}$, 1989 in China. Although the magnitude of dengue epidemics remained at low lever in the 1990s, the incidence of dengue in the 21$^{th}$ century has increased steadily and reached a historical high in 2014 (47,056 cases and 6 deaths) after the disease was made statutorily notifiable in 1989 (**Figure 1-26**) (Ooi, 1989; Sun et al., 2017; Lai et al., 2015). Locally transmitted dengue has not been limited to Hainan and Guangdong provinces, but has spread gradually from southern coastal tropical or subtropical regions (Guangdong, Guangxi, Hainan) to the neighbouring northern and western regions (Fujian, Zhejiang, and Yunnan), and even to the central part of China, such as Henan province, which has a generally warm climate (Fan et al., 1989; Qiu et al., 1991; Lai et al., 2015; Wu et al., 2010; Huang et al., 2014).

Compared to the major epidemic in the 1980s, Hainan showed a dramatically decreased incidence of dengue, but Guangdong had the highest incidence of indigenous dengue over the last 25 years from 1990 to 2014 with expanding geographic range (Lai et al., 2015; Li et al., 2012b). Dengue transmission has become evident in some previously unaffected areas, i.e. the central and north of Zhejiang province in 2004 and 2009 (Xu et al., 2007; Sun et al., 2011), and the central and north-eastern area of Fujian in 2014 and 2016 (Lai et al., 2015; Mu et al., 2017). In 2013, the first dengue outbreak in central China was reported in the centre of Henan province, located at northern temperate regions, and 106 suspected dengue cases were reported and 73 patients were confirmed with DENV-3 infections (Huang et al., 2014).

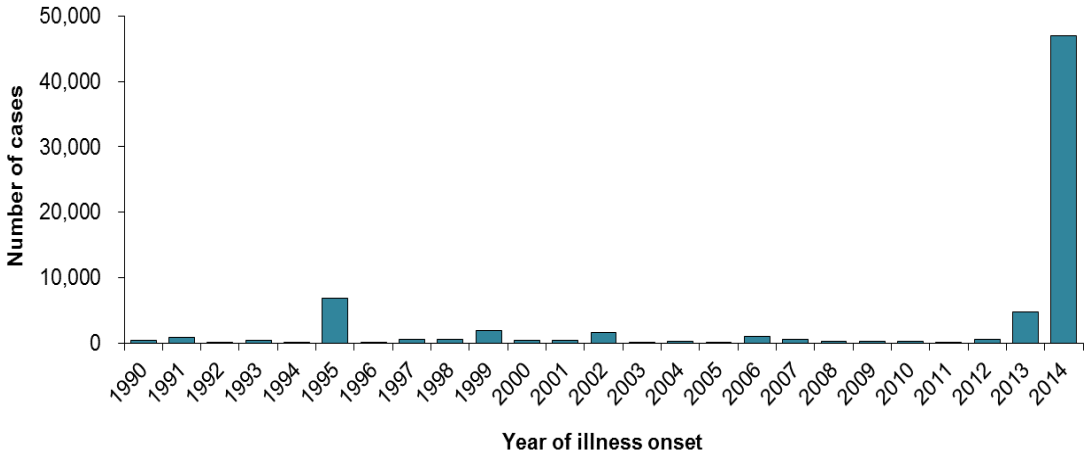



**Figure 1-26. The number of dengue cases reported in mainland China from 1990 to 2014**.

*Ae. aegypti* was the predominant vector in southern coastal areas, e.g. Hainan island, while *Ae. albopictus* was the most widespread vector in mainland China. However, a previous study (Guo et al., 2016) found that *Ae. aegypti* and *Ae. albopictus* has gradually coexisted in Jinghong city of Yunnan province, which confirms that the geographic distribution of *Ae. aegypti* has expanded, and the vector has invaded and colonized in into the place where *Ae. albopictus* was the predominate vector previously.

Following China's reform and opening-up policy since late-1970s, China has been facing the pressure of dengue virus importation and introduced transmission, with Southeast Asian countries being the main source (Sang et al., 2016; Jing et al., 2012). The evidence of previous studies suggests that the re-emergence of dengue in late-1970s and 1980s in Guangdong and Guangxi provinces and on Hainan Island resulted from the introduction of the infection by travellers from Asian countries where dengue is endemic (Fan et al., 1989).

The molecular fingerprints of strains often suggest that the outbreak is likely due to viruses imported from other countries (Jiang et al., 2013; Sang et al., 2015a; Yang et al., 2014). Since 2004, most (>80%) of imported dengue was transmitted from Southeast Asia, with all four serotypes of dengue virus being found (Guzman et al., 2010). The outbreak of DENV-1 infection in Ningbo city of Zhejiang province in 2004 was associated with a traveller from Thailand, when autochthonous dengue infections have not been reported in Ningbo since 1929 (Xu et al., 2007). In 2009, a DENV-3 outbreak was reported in Yiwu city of Zhejiang, a city famous for the largest small commodity wholesale market in the world, and the outbreak might have been triggered by DENV-3 imported from India or Saudi Arabia (Sun et al., 2011). None of the strains or genotypes identified from dengue virus infections in Guangzhou during 2001–2010 were found to be predominant, and DENV strains from different years had different origins with the strains from each year belonged to different serotypes and/or genotypes (Jiang et al., 2013). The unprecedented outbreak in Guangzhou in 2014 can also be explained using imported cases and

climatic factors (Sang et al., 2015c). Therefore, based on the evidence of molecular epidemiology and the geographic and seasonal restriction of cases, dengue in mainland China is still characterized as an imported disease and not recognized as endemic.

### 1.7.3 Research on mosquito-borne disease importation into China

Imported mosquito-borne diseases, e.g. malaria and dengue, have become a public health concern in China. However, prior to this work which began in 2015, only a few analyses focusing on imported malaria infections had been published, and most of them were descriptive analyses of imported parasites at a sub-national level or at a national level for a single year. For instance, Xia et al (2014) and Feng et al (2014) preliminarily revealed the epidemic situation of imported malaria in China in 2011 and in 2012, respectively. Some provinces have investigated the patterns and trends of malaria importation, e.g. Ning et al (1999) analysed the characteristics of imported *P. falciparum* malaria cases in Sichuan provinces and their origins, and the demographic features and sources of imported malaria in overseas labourers in Jiangsu province during 2000-2012 were presented by Liu et al (Liu et al., 2013; Liu et al., 2014). In addition, Yunnan, Guangxi, Guangdong, Henan and some other provinces also carried out the epidemiological studies to present the features and sources of the imported parasites (Yang et al., 2013; Hu et al., 2016c; Chen et al., 2012; Zhang et al., 2010).

Several regional surveys were also conducted in China, especially in the areas bordering with Southeast Asia, to investigate the vector distribution screen sources of imported malaria, and assess the diagnosis and treatment of patients. For example, Hu et al (2016c) analysed seasonal dynamics and microgeographical spatial heterogeneity of malaria along the China-Myanmar border. Although the majority of imported *P. falciparum* malaria cases in China have been reported in those with a history of labour-related travel to Africa (Zhou et al., 2016; Li et al., 2015; Liu et al., 2014; Li et al., 2016b), China has only been grouped with neighbouring countries in Asia in the communities detected for *P. falciparum* malaria importation networks in previous studies (Tatem and Smith, 2010; Huang and Tatem, 2013).

In a provincial analysis of imported malaria in overseas labourers of Jiangsu province in China during 2001–2011, Liu et al (2014) found the investments to African countries from Jiangsu was related to the annual number of cases imported from other countries, and the increasing annual number of labourers exported from Jiangsu to Africa was also positively correlated with the increase of imported malaria. A study was also conducted to assess the risk of local transmission caused by imported *P. vivax* malaria in three villages in the China-Myanmar Border Region Yunnan (Wang et al., 2015).

However, the studies on the epidemiology and origin-destination connectivity of imported dengue are even less than malaria, and most of them are regional studies or cases studies for outbreaks in Guangdong and Yunnan provinces (Zhang et al., 2013; Yang et al., 2009; Wang et al., 2009; Luo et al., 2008; Du and Pan, 2010). Few studies have investigated the correlations between the number of autochthonous disease and the number of imported cases for the dengue outbreak in Guangzhou in 2014 (Xu et al., 2016; Sang et al., 2015b; Cheng et al., 2016; Li et al., 2016a).

There are also few studies to quantitatively define the importation risk of infections for China. Tu et al (2016) conducted a risk assessment to identify the risk of importation and autochthonous transmission of Zika Virus Disease in mainland China from March to December, 2016. Due to the lack of travel data, they assumed that the Zika virus might have similar transmission patterns as dengue virus, and the numbers of imported dengue in mainland China from 2011 to 2015 were analysed for inferring the importation of Zika virus travelling between China and those areas with Zika virus autochthonous transmission by using a ratio of dengue to Zika for imported cases. Based on the air travel and disease epidemiological data, Lai and collaborators (Lai et al., 2014; Geng et al., 2016) have estimated the relative importation risk of Ebola from west Africa in 2014 and MERS from South Korea in 2015 by ranking the volume and proportion of air travel passengers from origin to destination and using the importation index models.

Overall, comprehensive national, long-term studies are needed for malaria and dengue to define the epidemiological characteristics of imported mosquito-borne diseases and origin-destination communities of importation networks for China. Quantitative and nationwide studies on the drivers and risk factors of dengue and malaria importation into China are also rare. The studies on the nationwide risk of importation and local transmission by introduced pathogens through air travel are also needed for China, which would also contribute to the understanding of seasonal and long-term variations of vector-borne disease spread.

In conjunction with emerging international trade and travel, more and more imported diseases have been reported in China. From 2002 to 2015, China's total net outward direct investment has increased from 2.7 billion USD to 145.7 billion USD (Chinese Ministry of Commerce, 2015), and more than 127.9 million Chinese citizens travelled abroad in 2015 (**Figure 1-27** and **Figure 1-28**) (National Tourism Administration Data Center, 2014). This results in an increased risk of infectious diseases spreading to East Asia, in particular mosquito-borne disease (Chinese Ministry of Commerce, 2015; Kitano and Harada, 2015; Strange et al., 2015). For instance, China imported its first cases of yellow fever and rift valley fever by Chinese workers from Angola in 2016 (WHO, 2016b), and thousands of malaria importations from Africa and dengue importations from Southeast Asia have been reported in China in the last several years (Chinese Ministry of

Commerce, 2015; Kitano and Harada, 2015; Strange et al., 2015). China's recent development strategy of the Silk Road Economic Belt and the 21st-century Maritime Silk Road, also known as 'One Belt, One Road', may further increase overseas investment and Chinese international travel.

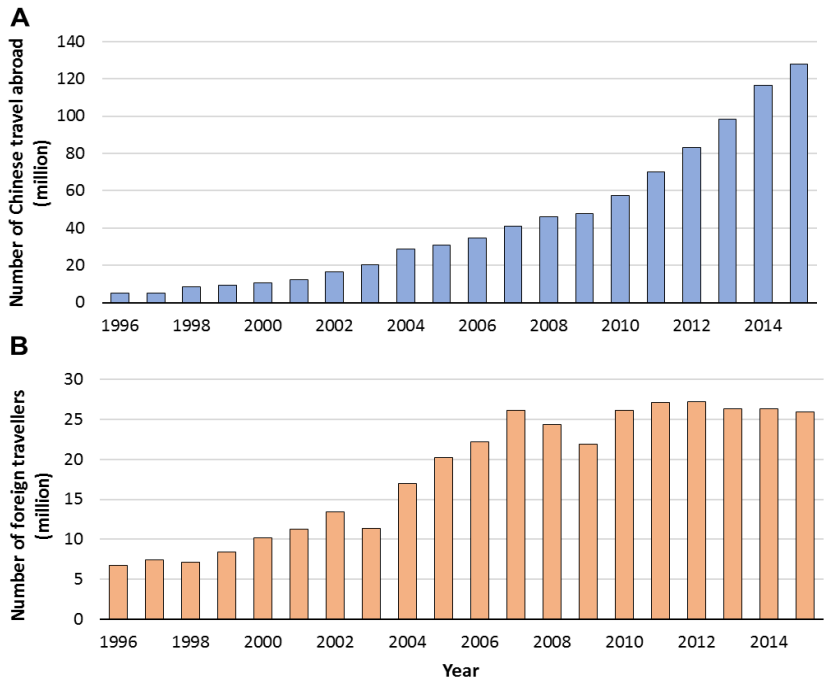



**Figure 1-27. The number of Chinese citizens travel abroad (A) and foreigners travel into mainland China (B).**

Data source: National Bureau of Statistics of China (data.stats.gov.cn).

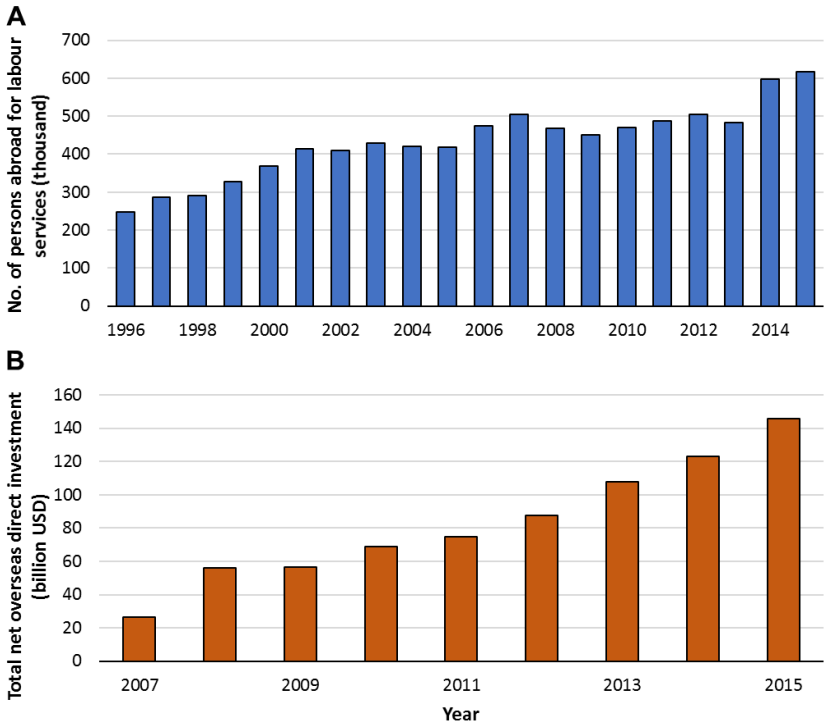



**Figure 1-28. The number of Chinese travel abroad for labour services by the end of year (A) and total net overseas direct investment from mainland China (B)**.

Data source: National Bureau of Statistics of China (data.stats.gov.cn).

Moreover, with the rapid growth of the economy and urbanization in China, the scale of urbanization and migration to cities in China has been unprecedented. Large populations have moved away from their original residences, especially from central China, to coastal provinces, and from poor rural areas to urbanized regions (**Figure 1-29**): the total urban share of the population has increased from 17.9% to 53.7% during 1978-2013 (The Central Committee of the Communist Party of China and the State Council, 2014; United Nations Development Program, 2013). The movement of humans, the host of a variety of pathogens, changes epidemiological dynamics and environments, and can promote transmission domestically, increasing the population at risk of infections, and creating major challenges for prevention and control (Gong et al., 2012; Wesolowski et al., 2015b).

Two mosquito-borne diseases, malaria and dengue, have a substantial number of imported cases in China each year with a growing public health concern of onward transmission in China. Additionally, malaria is on the way towards elimination under the Action Plan of China Malaria Elimination (2010-2020), whilst dengue has an increasing threat in urban areas in China (Lai et al., 2015). Further, both face an increasing risk of importation from other countries to China in terms of the huge volume of Chinese international travel. Quantifying the connectivity and driving factors of infectious diseases importation and its risk onward transmission has significance for diseases management in receiving areas and the development of mitigation strategies (Talisuna et al., 2012; Askling et al., 2012; Tatem et al., 2014). However, quantitative analyses on China's malaria and dengue importation patterns, networks and its drivers, as well as the risk of onward transmission are scarce.

In summary, the nationwide spatiotemporal patterns, connectivity network and driving factors of mosquito-borne diseases importation for China are less well understood, as well as the seasonal risk of importation and onward transmission by air travel. With the rapid increase of Chinese international mobility of tourism, labour service and business, the pressure of imported mosquito-borne infectious diseases, e.g. dengue and malaria, into China is also on the rise, and studies using multidisciplinary approaches and technologies are required to understand the phenomena of contagions importation by combine a variety of datasets of disease surveillance, air travel, environment, and investment, etc. These findings will have important public health significance for understanding the importation patterns and risk and for mosquito-borne disease prevention and control.

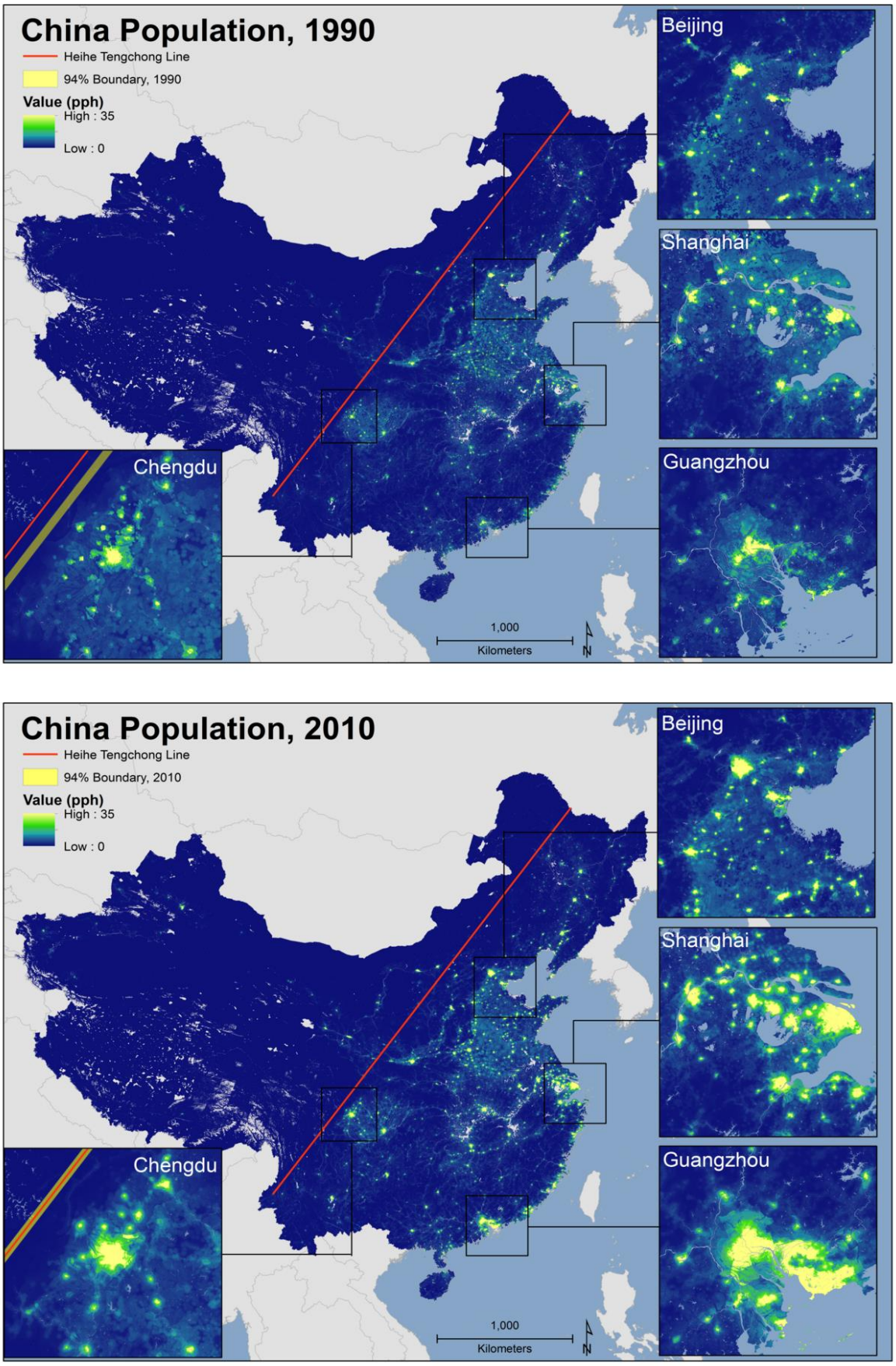



**Figure 1-29. The population density in mainland China in 1990 and 2010.**

Data source: The Worldpop project (Gaughan et al., 2016).

## 1.8 Aims of this study and research questions

To understand the challenges of increasing population mobility as well as the emerging threats of malaria and dengue importations in China, this study focuses on understanding the spatiotemporal patterns, driving factors and seasonal introduced and onward transmission risk of the importation of two principal mosquito-borne diseases, malaria and dengue in China. The specific objectives of this study are:

**1) To determine the spatiotemporal patterns and demographic features of mosquito-borne disease importation into China (Chapter 2 and Chapter 3).**

The questions which need to be answered for this objective are:

i) What are the spatiotemporal patterns of malaria and dengue importation in China?

ii) Are the epidemiological patterns different between autochthonous and imported cases?

I assume that surveillance data has high coverage and quality to represent the epidemiological patterns of malaria and dengue, and there is not a significant difference between the spatiotemporal and demographic features of symptomatic and asymptomatic infections.

**2) To define the network communities and driving factors of diseases importation into China (Chapter 4).**

Taking the increasing *P. falciparum* malaria importation from Africa into China during 2011-2015 as an example, the questions which need to be answered for this objective are:

i) What are the structures and communities of malaria importation networks from Africa into China?

ii) Do correlations exist between the number of imported malaria cases and potential driving factors, e.g. Chinese overseas investment, air travel from Africa into China and malaria endemicity in Africa?

iii) What are the risk factors of death in imported cases?

I hypothesize that: the importation malaria is a function of various factors, including volume of air travellers, parasite prevalence in Africa, and investments from China, and the demographic features, social-economic status of cases and healthcare capacity in different regions of China play a key role on the mortality of imported *P. falciparum* malaria cases.

**3) To quantify seasonal importation and onward transmission risk of mosquito-borne diseases in China (Chapter 5).**

Taking dengue as an example, which has increasing locally transmitted outbreaks caused by imported viruses from Southeast Asia into China, this analysis tries to answer the following questions:

i) How high is the risk of dengue importation and onward transmission from Southeast Asian endemic countries into cities of China during 2005-2015?

ii) Did the risk of dengue importation and onward transmission in China have seasonal variation during 2005-2015?

iii) How much did the risk of dengue importation and onward transmission change from 2005 to 2015?

These analyses rest on the assumptions that human movement by air travel has a key impact on the dengue importation, and the population travelling by air has same infection risk as travellers using other transportations, and that imported infections play a key role in initiating outbreaks in China.

## 1.9 Organisation of the thesis and contribution in published papers

This thesis starts with an introduction of vector-borne diseases, including a literature review about methodologies of population movement and disease importation, and the objective and research problems of the study (**Chapter 1**). Then **Chapter 2** and **Chapter 3** will present the analysis of the spatiotemporal patterns for malaria and dengue respectively. In **Chapter 4**, the network communities and driving factors of disease importation into China will be explored by analysing the *P. falciparum* malaria importation phenomenon from Africa into China during 2011-2015 and its covariates. **Chapter 5** will determine the seasonal risk of disease importation and onward transmission, focusing on dengue imported from Southeast Asian endemic countries into cities of China during 2005-2015. Finally, **Chapter 6**, consists of a summary and discussion of the main conclusions, providing insight into importation phenomena and mitigation approaches for mosquito-borne diseases.

This thesis follows the 'Three-Paper' format with three published papers and one publishable paper to form four chapters, from **Chapter 2** to **Chapter 5** respectively, as the main body of thesis. My contribution to the three published papers is declared as below:

### 1.9.1 The first paper (Chapter 2)

**Shengjie Lai**†, Zhuojie Huang†, Hang Zhou†, Katherine L Anders, T Alex Perkins, Wenwu Yin, Yu Li, Di Mu, Qiulan Chen, Zike Zhang, Yanzi Qiu, Liping Wang, Honglong Zhang, Linjia Zeng, Xiang Ren, Mengjie Geng, Zhongjie Li, Andrew J Tatem, Simon I Hay & Hongjie Yu. The Changing Epidemiology of Dengue in China, 1990-2014: a descriptive analysis of 25 years of Nationwide Surveillance Data. *BMC Medicine* 2015, 13:100. DOI:10.1186/s12916-015-0336-1 (†Contributed equally)

**Contributions**: I led this work, including designing the study, collecting and collating the dataset, conducting the analysis, interpreting the findings, and writing and submitting the drafts of the manuscript.

### 1.9.2 The second paper (Chapter 3)

**Shengjie Lai**, Zhongjie Li, Nicola A Wardrop, Junling Sun, Michael G Head, Zhuojie Huang, Sheng Zhou, Jianxing Yu, Zike Zhang, Shui-Sen Zhou, Zhigui Xia, Rubo Wang, Bin Zheng, Yao Ruan, Li Zhang, Xiao-Nong Zhou, Andrew J Tatem & Hongjie Yu. Malaria in China, 2011-2015: an observational study. *Bulletin of the WHO* 2017, 95(8):564-573. DOI:10.2471/BLT.17.191668

**Contributions**: I led research design, data gathering, processing and analysis. I interpreted findings, wrote the first draft of manuscript, submitted to journal and revised drafts of the manuscript.

### 1.9.3 The third paper (Chapter 4)

**Shengjie Lai**, Nicola A. Wardrop, Zhuojie Huang, Claudio Bosco, Junling Sun, Tomas Bird, Amy Wesolowski, Sheng Zhou, Qian Zhang, Canjun Zheng, Zhongjie Li, Andrew J. Tatem & Hongjie Yu. *Plasmodium falciparum* malaria importation from Africa to China and its mortality: an analysis of driving factors. *Scientific Reports* 2016, 6:39524. DOI:10.1038/srep39524

**Contributions**: I led this work, including designing the study, collecting data, finalising the analysis, interpreting the findings, writing and submitting the manuscript.

### 1.9.4 The fourth paper (publishable manuscript, Chapter 5)

**Shengjie Lai**, Michael A Johansson, Wenwu Yin, Nicola A Wardrop, Willem G van Panhuis, Amy Wesolowski, Moritz U G Kraemer, Isaac I Bogoch, Dylain Kain, Aidan Findlater, Marc Choisy, Zhuojie Huang, Di Mu, Yu Li, Yangni He, Qiulan Chen, Kamran Khan, Andrew J Tatem, Hongjie Yu.

Quantifying seasonal and interannual risks of dengue introduction from endemic countries via air travel.

**Contributions**: I led this work, including designing the study, collecting data, finalising the analysis, interpreting the findings and writing the manuscript.

## 1.10 Ethical approval

The ethical clearance of collecting and using secondary data for this study has been 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.

# Chapter 2 Spatiotemporal patterns of dengue in China

## 2.1 Chapter summary

Dengue has been a notifiable disease in China since 1 September 1989. Cases have been reported each year during the past 25 years of dramatic socio-economic changes in China, and reached a historical high in 2014. This study describes the changing epidemiology of dengue in China during this period, to identify high-risk areas and seasons and to inform dengue prevention and control activities.

This Chapter describes the incidence and distribution of dengue in mainland China using notifiable surveillance data from 1990-2014, which includes classification of imported and autochthonous cases from 2005-2014. From 1990-2014, 69,321 cases of dengue including 11 deaths were reported in mainland China, equating to 2.2 cases per one million residents. The highest number was recorded in 2014 (47,056 cases). The number of provinces affected has increased, from a median of three provinces per year (range: 1 to 5 provinces) during 1990-2000 to a median of 14.5 provinces per year (range: 5 to 26 provinces) during 2001-2014. During 2005-2014, imported cases were reported almost every month and 28 provinces (90.3%) were affected. However, 99.8% of autochthonous cases occurred between July and November. The regions reporting autochthonous cases have expanded from the coastal provinces of southern China and provinces adjacent to Southeast Asia to the central part of China. Dengue virus serotypes 1, 2, 3, and 4 were all detected from 2009-2014.

In China, the area affected by dengue has expanded since 2000 and the incidence has increased steadily since 2012, for both imported and autochthonous dengue. Surveillance and control strategies should be adjusted to account for these changes, and further research should explore the drivers of these trends.

## 2.2 Background

Dengue is an acute infectious disease caused by infection with any one of four serotypes of dengue virus (DENV 1-4), which are transmitted by *Aedes* mosquitoes (Guzman and Harris, 2015; WHO, 2009b). There are an estimated 390 million dengue infections per year, of which 96 million manifest clinically (any level of disease severity) (Bhatt et al., 2013), among an estimated 2.5 to 4 billion people living in over 100 countries where DENV transmission occurs (WHO, 2009b; Bhatt et al., 2013; Brady et al., 2012). More than 70% of people at risk reside in the Asia Pacific region,

making this region the global epicentre of dengue activity (Bhatt et al., 2013; Simmons et al., 2012; WHO, 2012a). Susceptibility to dengue in humans is universal. Recovery from infection with one serotype confers lifelong homologous immunity, but only short-term protection against other serotypes, and sequential infections put people at greater risk for severe illness (Halstead and O'Rourke, 1977; Halstead et al., 1977; Vaughn et al., 2000; Dejnirattisai et al., 2010). Because the vaccine for dengue is not currently widely available, the effective protective measures are those that suppress vector populations and prevent exposure to *Aedes* mosquito biting (Capeding et al., 2014; Wilder-Smith, 2014; Villar et al., 2015; Achee et al., 2015).

In 1978 dengue fever re-emerged in mainland China, in Foshan City of Guangdong province, after being absent for around 30 years (Zhao, 1981). Dengue became a notifiable disease on 1 September 1989 in China, partly in response to outbreaks of dengue fever, with cases of dengue haemorrhagic fever being reported sequentially in Hainan, Guangxi, Fujian, Zhejiang, and Yunnan provinces during the 1980s (Fan et al., 1989; Wu et al., 2010; Qiu et al., 1991). All of these provinces are located in the southeast coastal regions or around the national border with Myanmar, Laos, and Vietnam in Southeast Asia. Based on the notifiable reporting data, the magnitude and distribution of dengue in mainland China is described here, focusing on seasonal and geographical patterns from 1990 to 2014, and characteristics of imported and autochthonous cases from 2005 to 2014, so as to identify high-risk areas and seasons and thereby help plan resource allocation for dengue prevention and control.

## 2.3 Methods

### 2.3.1 National dengue surveillance program

On 1 September 1989, dengue was made statutorily notifiable in China. Dengue cases are diagnosed according to the unified diagnosis criteria issued by the Chinese Ministry of Health, including clinically diagnosed and laboratory confirmed cases (Wang et al., 2008; Ministry of Health of the People's Republic of China, 2008; Ministry of Health of the People's Republic of China, 2001; Ministry of Health of the People's Republic of China, 1988). All probable or laboratory confirmed cases are reported to the Chinese Centre for Disease Control and Prevention (China CDC) in Beijing. Two datasets were used in this study. One includes monthly number of dengue cases, aggregated by gender and 5-year age group in 1990-2004 and 2015-2016 by provinces in mainland China, which includes 22 provinces, four municipalities, and five autonomous regions. The other consists of individual dengue cases reported by doctors within 24 hours of diagnosis to the online National Notifiable Infectious Disease Reporting Information System at the China CDC from 2005 to 2014. The individual data include gender, age, address,

nationality, type of diagnosis, imported or autochthonous case, serotype, hospitalization, date of illness onset, and various potential risk factors (appendix **Table A-1**). All the data used in this study were anonymized; the identity of any individual case cannot be uncovered.

### 2.3.2 Case definition

Three editions of criteria/guidelines for dengue diagnosis issued by the Chinese Ministry of Health in 1988, 2001, and 2008 were successively used from 1990 to 2014 (appendix **Table A-2**) (Ministry of Health of the People's Republic of China, 1988; Ministry of Health of the People's Republic of China, 2001; Ministry of Health of the People's Republic of China, 2008). Dengue cases are classified as probable or confirmed based on whether they are clinically diagnosed or laboratory confirmed. Probable cases are those diagnosed by local experienced physicians according to cases' epidemiologic exposure and clinical manifestations; confirmed cases are clinically diagnosed cases for which any of the following laboratory results are reported by the local public health institutes: fourfold or greater increase in DENV-specific IgG antibody titre between paired samples, or positive PCR test, or positive virus isolation and identification (Ministry of Health of the People's Republic of China, 1988; Ministry of Health of the People's Republic of China, 2001; Ministry of Health of the People's Republic of China, 2008). Before 1 September 2008, a DENV-IgM positive laboratory result was classified as a confirmed case, but since then has been classified as probable. In the notifiable disease database, dengue cases are not reported with information about their disease severity, and classification as either a probable or confirmed case was not recorded before 2005.

At the provincial level, an imported case of dengue is defined as a dengue case for which the patient had travelled to a dengue-affected foreign country or province of mainland China, and reported being bitten by mosquitoes within 15 days of the onset of illness (Li et al., 2012b; Ministry of Health of the People's Republic of China, 2005). In some cases, importation is defined based on laboratory results showing that the infecting dengue virus had a high sequence similarity in the preM/E region compared with viruses isolated from the putative source region where the patient had travelled (Ministry of Health of the People's Republic of China, 2005). Otherwise, a dengue case is considered to be an autochthonous case. All imported cases in the datasets were classified as importations either from other countries or from other provinces. A determination about whether a case in the individual-level dataset from 2005 to 2014 was imported or autochthonous was made by local public health institutes, following epidemiological investigations after a dengue case was diagnosed and reported by local physicians.

### 2.3.3 Data analysis

All cases with illness onset from 1 January 1990, to 31 December 2014 were included in the analysis. The crude incidence rate was estimated as the number of probable and confirmed cases divided by the population at each year-end, which was extracted from the China population and employment statistics yearbook 2013 of the National Bureau of Statistics of China. The population data in 2014 were estimated from the population data and growth rates in 2013. The epidemiologic characteristics of imported and autochthonous cases in China from 2005-2014 were also summarized. The *Kruskal-Wallis* test was used to examine whether the median age was significantly different between imported and autochthonous cases, with a significance level of $\alpha = 0.05$.

To analyse the time series of dengue cases, I created heat maps of the proportion of cases reported in each month from 1990 to 2014 by province, standardized by the total number of cases in each province over the 25-year period, and ordered by latitude of capital city of each province (appendix **Figure A-1** and **Table A-3**). To compare seasonal patterns of dengue by imported and autochthonous cases, heat maps of the mean value of the proportion of cases in each week from 2005 to 2014 were also created. Version 3.0.1 of the *R* statistical software (R Foundation for Statistical Computing, Vienna, Austria) (R Development Core Team, 2010) was used to produce the graphs and heat maps and conduct statistical analyses, and *ArcGIS* 10.0 (ESRI, Redlands, CA, USA) was used to plot the geographical distribution of cases.

## 2.4 Results

### 2.4.1 Overall incidence

During the 25-year period from 1990 to 2014, 69,321 cases of dengue including 11 deaths were reported to the national dengue surveillance system in China, with an average of 2.2 cases per one million residents each year in mainland China. Annual case numbers displayed striking variations, with the lowest in 1992 and 1996 (only two cases) and the highest recorded in 2014 (47,056 cases), then decreasing to 4,230 cases in 2015 and 2,049 in 2016 (**Figure 2-1**).

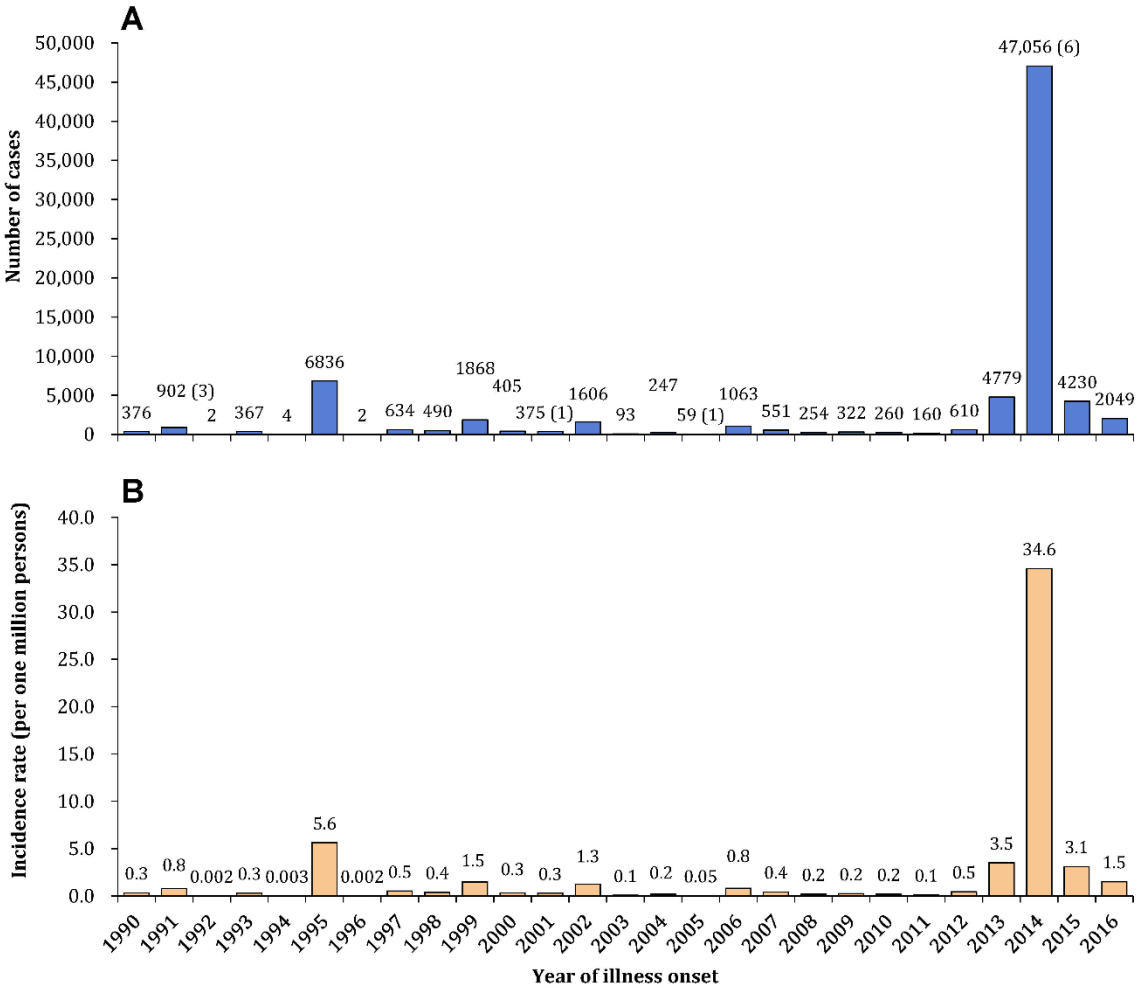



**Figure 2-1**. **Incidence of dengue cases reported in mainland China, 1990-2016**.

Note: (A) The aggregated number of cases by year with the numbers of deaths in parentheses. (B) The morbidity of dengue per one million residents of mainland China at the end of each year.

During 2005-2014, 55,114 cases including 7 deaths were reported, of which 2,061 (3.7%) were imported and 53,053 (95.3%) were autochthonous (appendix **Table A-4**, **Table A-5**, and **Table A-6**). The annual incidence rate of imported cases was relatively stable, with a median of 0.2 case per one million residents of affected provinces per year (interquartile range [IQR]: 0.1-0.2 cases/1,000,000), except for a slight increase in 2013 (0.4 case/1,000,000) and 2014 (0.5 case/1,000,000) (**Figure 2-2**). Autochthonous cases were reported each year from 2006 to 2014, with a median annual incidence of 2.5 cases per one million residents of affected provinces (IQR: 0.6-9.1 cases/1,000,000), decreasing from 2006 to 2011, and increasing from 2012 to 2014 with a peak of 155.3 cases/1,000,000 and 6 deaths in 2014 (**Figure 2-2** and appendix **Figure A-2**).

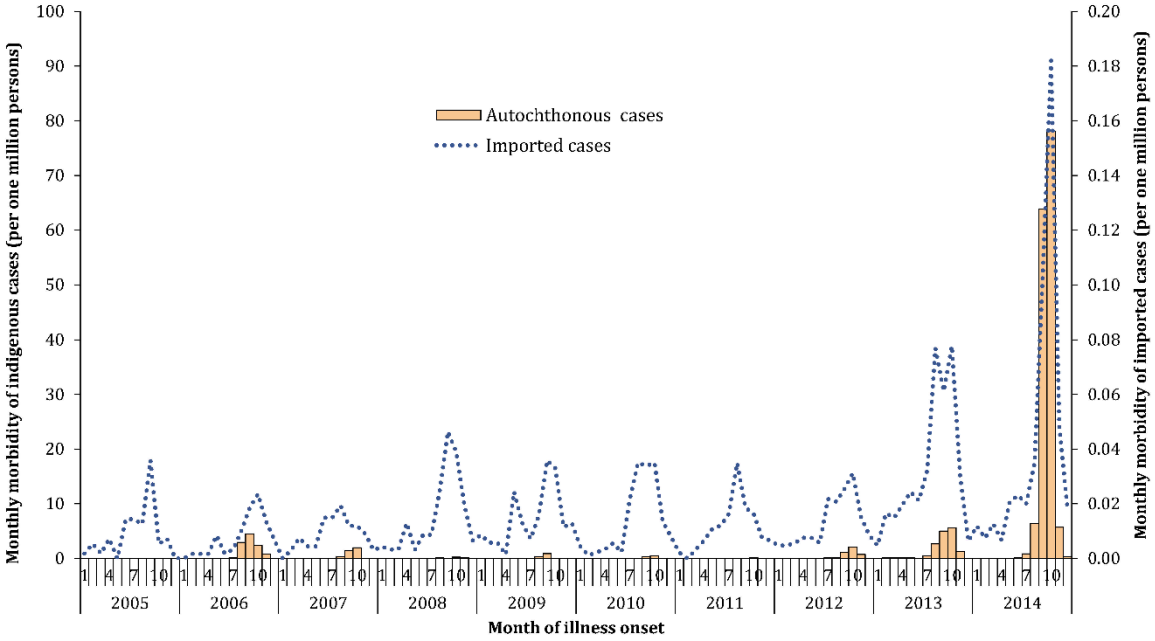



**Figure 2-2**. **Incidence of imported and autochthonous dengue by month in China, 2005-2014**.
Note: The morbidity is the number of cases per one million residents of affected provinces at the end of each year.

### 2.4.2 Demographic and virologic features

The overall male-to-female ratio was even from 1990 to 2014. However, there was a strong male predominance (2:1) among imported cases during 2005-2014 and an almost equal gender distribution for autochthonous cases. The age distribution differed significantly between imported and autochthonous cases during 2005-2014 (*Kruskal-Wallis* statistic = 228.3, *df* = 1, $P < 0.001$), with a younger median age of 32.5 years (IQR: 25.6-42.0) for imported cases and an older median age of 39.0 years (IQR: 26.3-53.7) for autochthonous cases (**Figure 2-3**, and appendix **Figure A-3**).

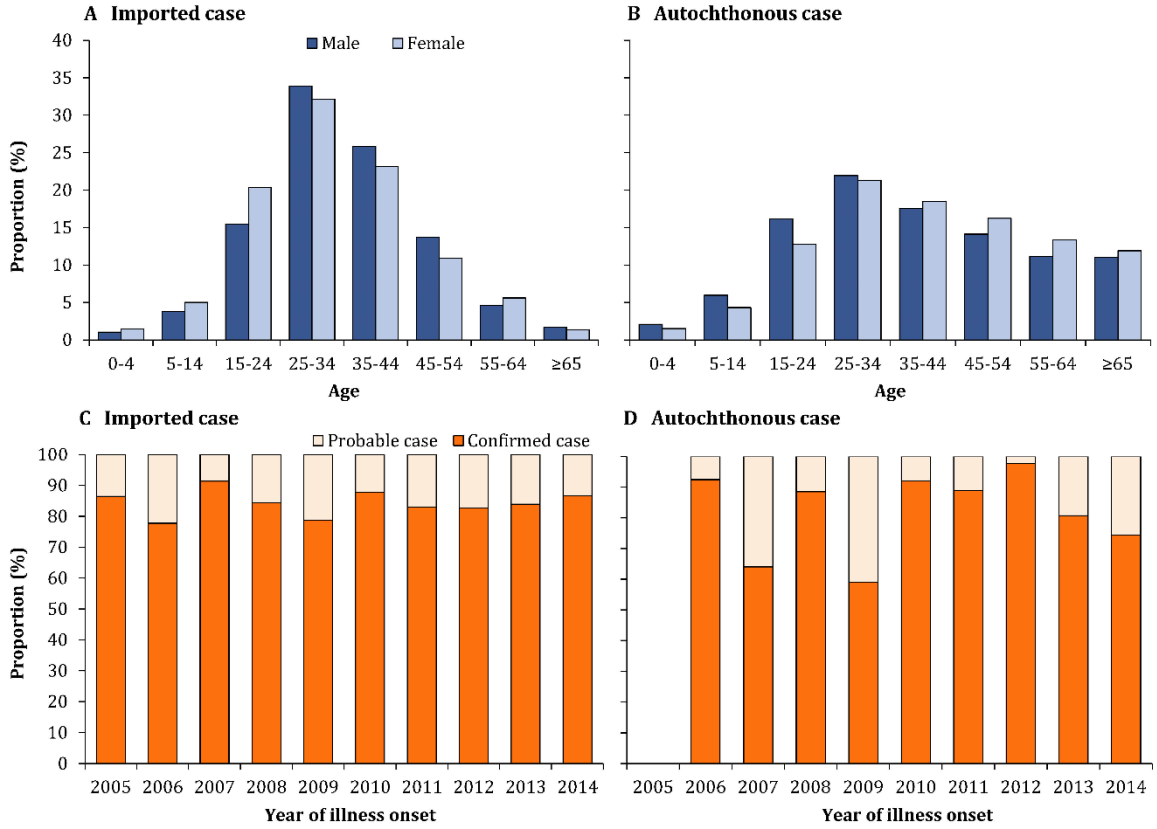



**Figure 2-3**. **Age and gender distribution and proportion of imported and autochthonous dengue cases that were laboratory confirmed by year, 2005-2014.**

Note: (A) The age distribution of male and female imported cases. (B) The age distribution of male and female autochthonous cases. (C) The proportion of imported cases that were laboratory confirmed each year. (D) The proportion of autochthonous cases that were laboratory confirmed each year.

During 2005-2014, 75.8% (41,783/55,114) of reported dengue cases were laboratory confirmed; 84.7% (1,746/2,061) of imported cases and 75.5% (40,037/53,053) of autochthonous cases. Of cases without laboratory confirmation, 89.4% were reported in 2014 (**Figure 2-3**). Data on serotypes were only available for 415 (0.8%) autochthonous cases during 2005-2014: 362 (87.2%) cases with DENV-1 in Guangdong during 2011-2014, 40 (9.6%) DENV-2 in Guangdong during 2013-2014, and 13 (3.1%) DENV-3 in Zhejiang in 2009 and Guangdong during 2012-2013. Among 18 (0.9%) imported cases with serotype data, all four serotypes were reported: DENV-1 (11 cases), DENV-2 (2), DENV-3 (3), and DENV-4 (2) during 2009-2014 (appendix **Figure A-4**). More demographic and epidemiologic results are shown in the Supplementary information for Chapter 2.

### 2.4.3 Geographical distribution

The number of provinces reporting dengue cases has increased since 1990, from a median of 3 provinces per year (range: 1 to 5 provinces) during 1990-2000 to a median of 14.5 provinces per year (range: 5 to 26 provinces) during 2001-2014. The provinces affected have also expanded geographically from the southern to the northern parts of China (**Figure 2-4**). During 2005-2014, except for Ningxia, Qinghai, and Tibet, all the other 28 provinces in mainland China had imported cases; the top provinces were Yunnan (28.8% of all imported cases), Guangdong (18.3%), Fujian (11.2%), Zhejiang (6.4%), and Hunan (5.4%) in southern China and the municipality of Beijing (4.4%) in northern China (**Figure 2-4** and **Figure 2-5**). The suspected country of origin was recorded for 1,488 (81.5%) of all 1,826 dengue cases imported from other countries: 82.7% came from Southeast Asia, 8.3% from South Asia, and 5.6% from Africa. There were 235 cases exported from four domestic provinces of mainland China to other provinces: Guangdong (96.2%), Yunnan (2.1%), Guangxi (1.3%), and Hainan (0.4%). Of those interprovincial case movements, most (96.6%) occurred in 2014.

During 2005-2014, all 53,053 autochthonous cases were limited to just seven provinces: 94.3% were reported in Guangdong from 2006 to 2014, 3.0% in Yunnan (3 years), 1.6% in Guangxi (2 years), 0.7% in Fujian (5 years), 0.4% in Zhejiang (2 years), 0.05% in Henan in 2013, and 0.004% in Hainan in 2014. The affected regions expanded gradually over the 10-year period, from the coastal provinces (Hainan, Guangdong, Fujian, and Zhejiang) of southern China and provinces (Guangxi and Yunnan) adjacent to Southeast Asian countries to the central provinces of China (Henan) (**Figure 2-4**, **Figure 2-5**, **Figure 2-6** and appendix **Figure A-5**).

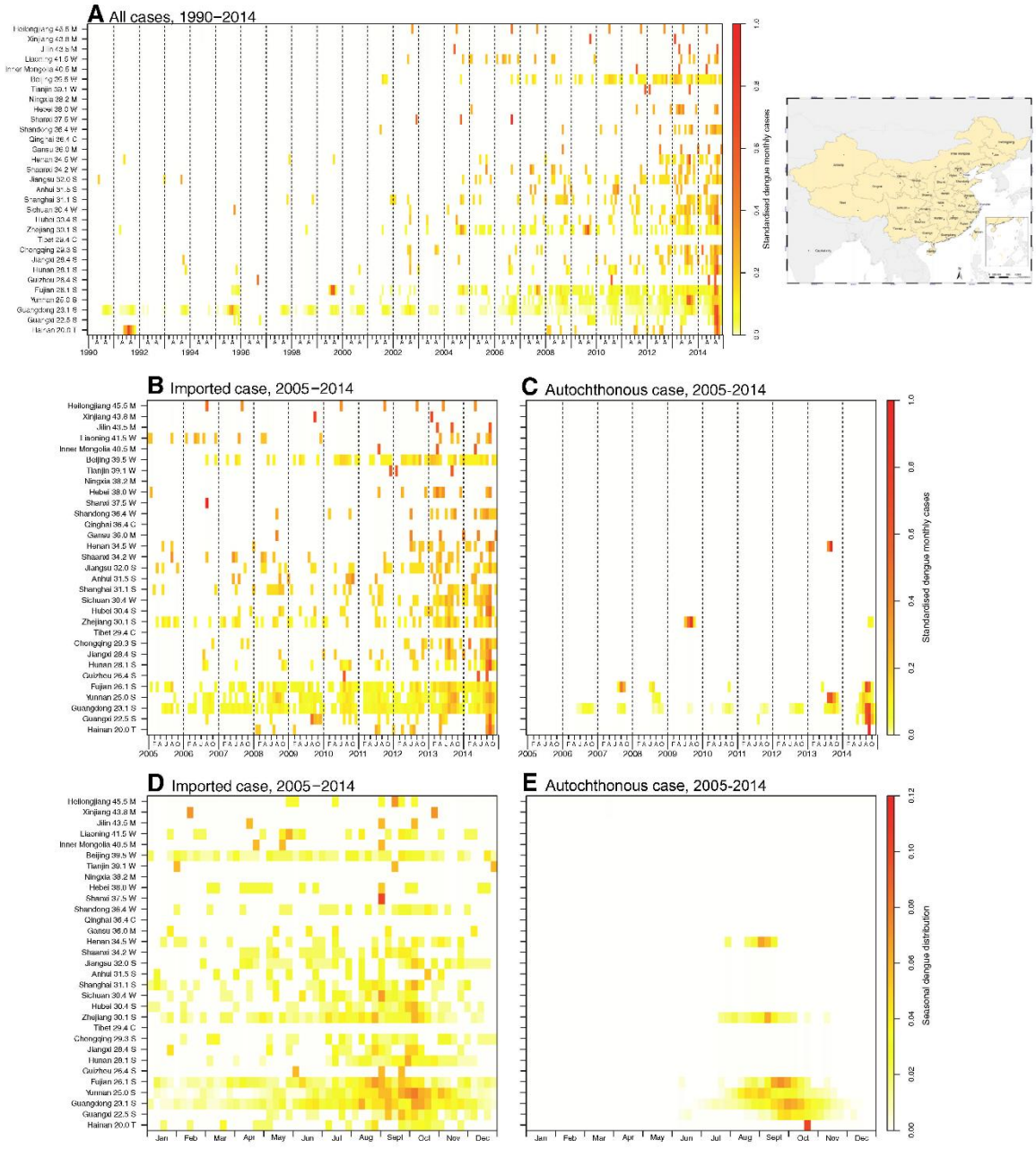



**Figure 2-4. Heat map of dengue by province, sorted by latitude of capital city, 1990-2014.**

Note: On the Y-axis is listed the name of the province with the latitude of the capital city and a general classification of climate zone for each province. M: Mid-temperate; W: warm-temperate; C: cold; S: subtropical; T: tropical. A thumbnail map of all the provinces of China is provided at the end of the figure. (A) Time series of monthly dengue cases, 1990-2014, standardized by the number of total cases reported by each province. (B) Time series of monthly imported dengue cases, 2005-2014, standardized by the number of total cases reported by each province. (C) Time series of monthly autochthonous dengue cases, 2005-2014, standardized by the number of total cases reported by each province. (D) Seasonal distribution of imported dengue cases, plotted as the mean value of the proportion of cases in each week of the year from 2005 to 2014. (E)

Seasonal distribution of autochthonous dengue cases, plotted as the mean value of the proportion of cases in each week of the year from 2005 to 2014.

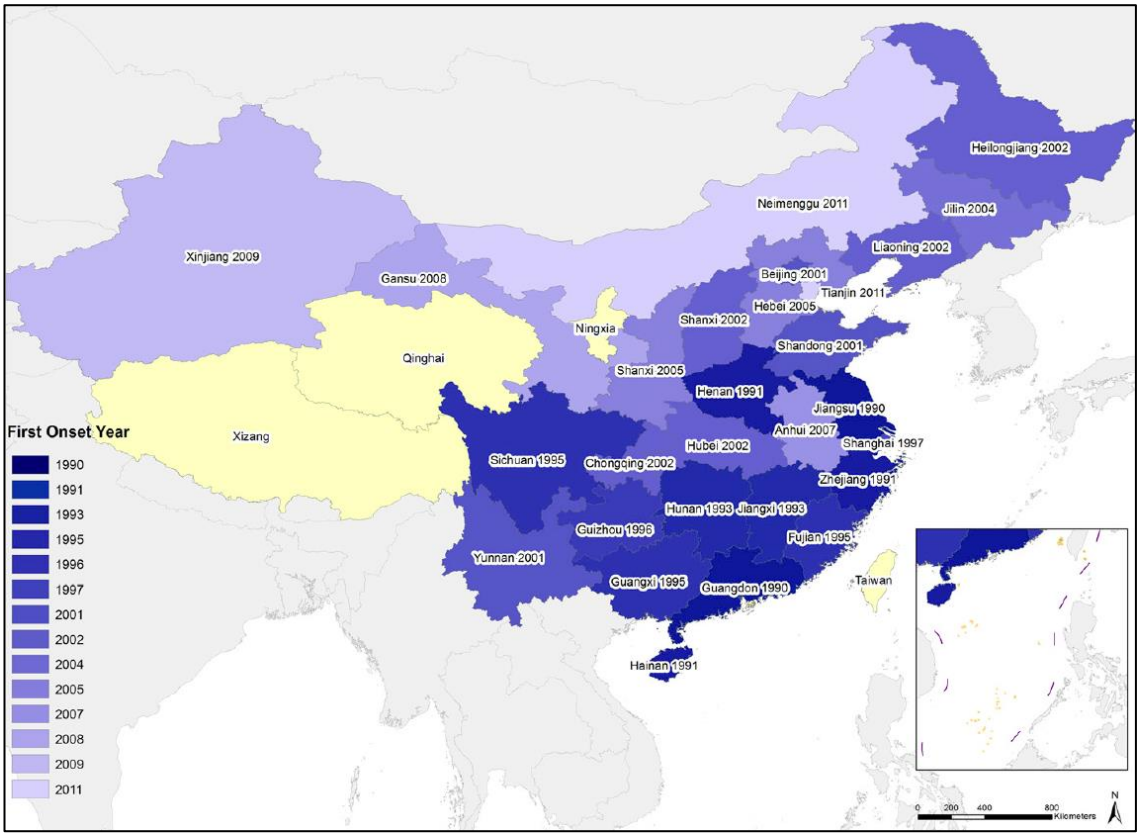
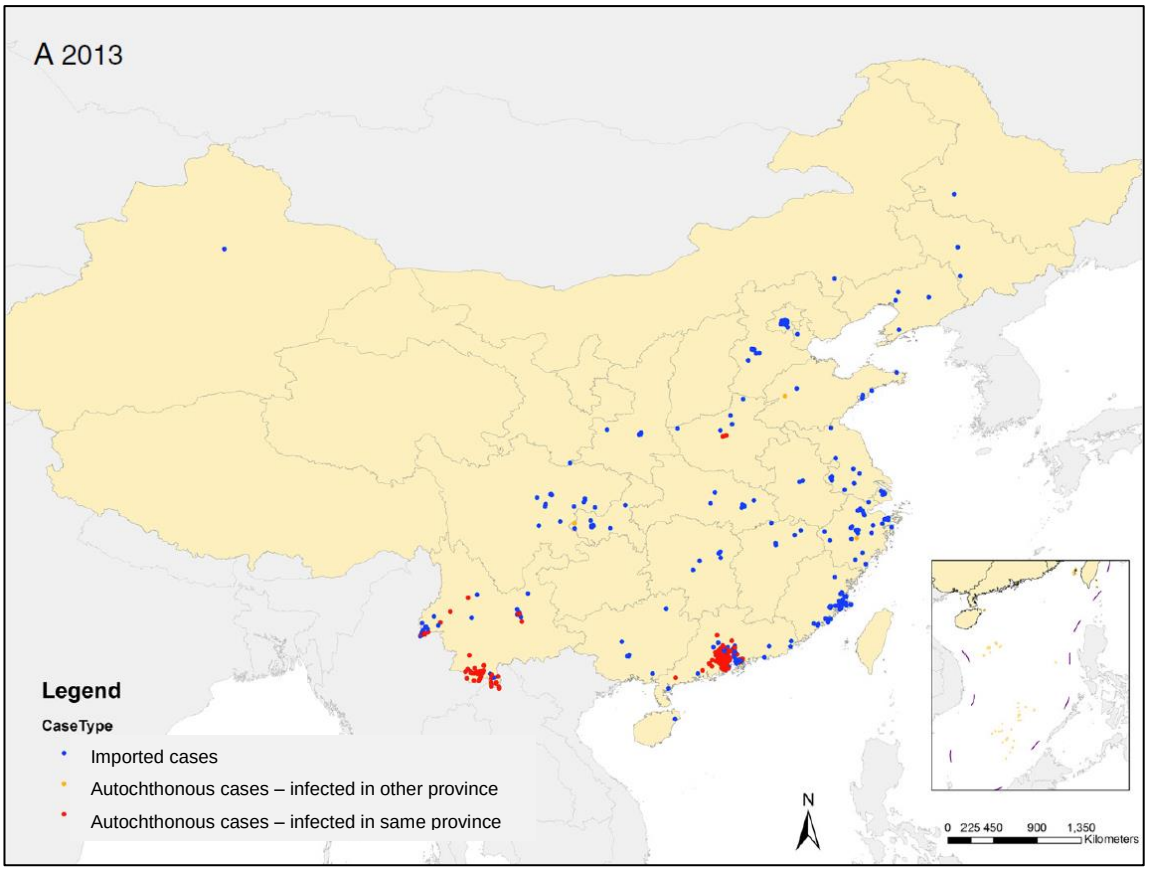



**Figure 2-5. Years in which the first case of dengue was reported in each province of mainland China, 1990-2014.**

### 2.4.4 Seasonality

During 2005-2014, 74.5% of imported cases were reported between July and November with a peak in October (24.6%) (**Figure 2-2** and **Figure 2-4**). Generally, there was a subpeak of imported cases before the epidemic of autochthonous cases each year, with a median lag of 2 months (IQR: 1-3 months) from the peak of imported cases to the month of the first autochthonous case onset. Except for one autochthonous case that occurred in April of 2010 in Guangdong, no autochthonous cases were reported from January to May during 2005-2014, and 99.8% of autochthonous cases occurred in the July to November period, peaking in September (40.4%) and October (48.6%). However, autochthonous cases in the provinces with higher latitudes (Henan, Zhejiang, and Fujian), which were limited in their warm season duration, showed earlier peaks and shorter epidemic periods than the provinces at lower latitudes, such as Guangdong and Yunnan (**Figure 2-4E**).



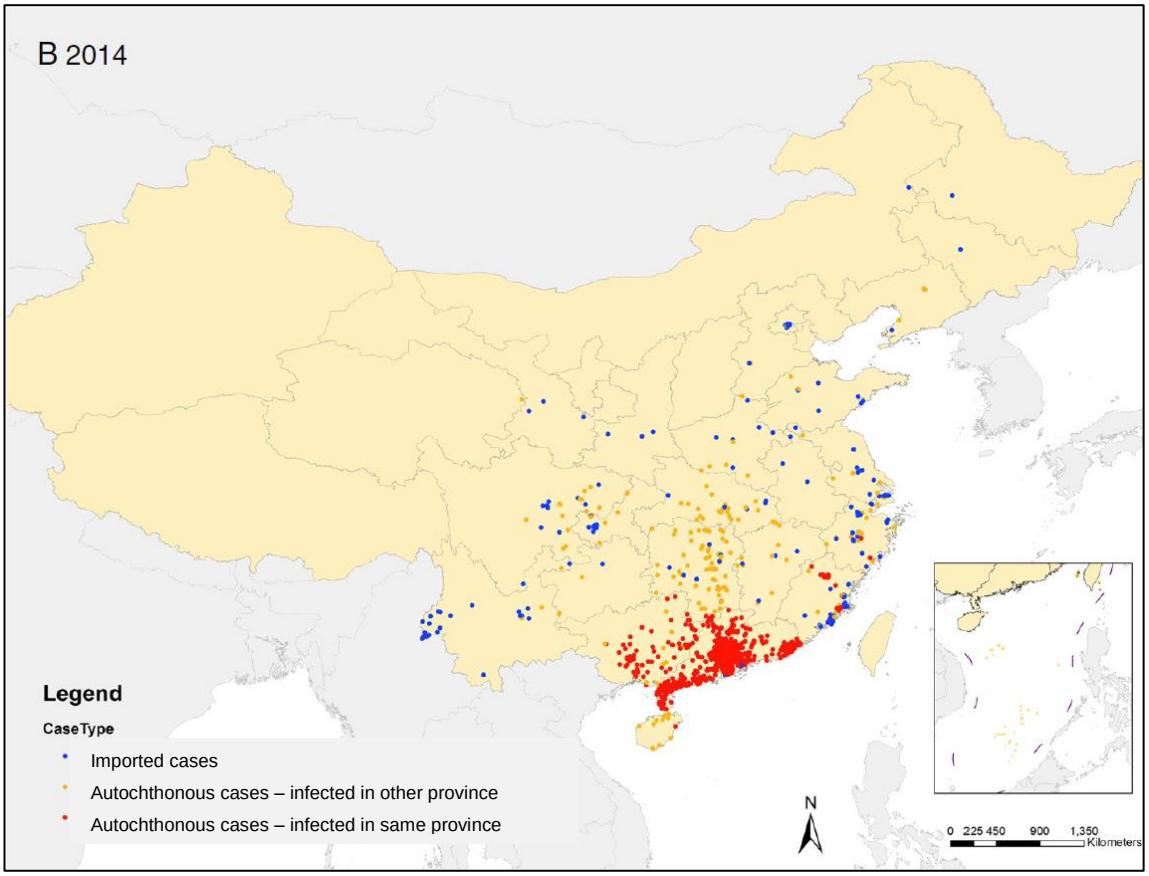




**Figure 2-6. Geographic distribution of dengue cases in mainland China, 2013 and 2014.**

Note: (A) The distribution of dengue cases in 2013 (N = 4,779). (B) The distribution of dengue cases in 2014 (N = 47,056).

## 2.5 Discussion

In this study, a longitudinal surveillance dataset spanning 25 years in China was used to investigate changes in the epidemiological characteristics of imported and autochthonous dengue during the period of dramatic social-economic changes that has occurred in China over the last three decades. This analysis found that the geographic distribution of provinces affected by imported and autochthonous dengue has expanded, especially since 2000, and recently the incidence rate of autochthonous dengue has increased dramatically with a peak in the most recent recorded year.

### 2.5.1 Magnitude and geographic extent of autochthonous dengue

The incidence of dengue in China during the period 1990-2014 was lower than the epidemics in 1980 and 1985-1986, which resulted in more than 600,000 cases with 475 deaths overall in Hainan (Qiu et al., 1991; Li et al., 1986). However, since 1990, autochthonous dengue has not been limited to Hainan and Guangdong provinces, but has spread gradually from southern coastal tropical or subtropical regions (Guangdong, Guangxi, Hainan) to the neighbouring northern and western regions (Fujian, Zhejiang, and Yunnan), and even to the central part of China - Henan province with a generally warm climate (**Figure 2-5**) (Fan et al., 1989; Wu et al., 2010; Wang et al., 2009). Compared to the major epidemic in the 1980s, Hainan showed a dramatically decreased incidence of dengue with a few autochthonous cases reported only in 1991 and 2014. Guangdong had the highest incidence of autochthonous dengue over the last 25 years, with cases reported each year since 1997. Dengue transmission has also become evident in some previously unaffected areas, such as Ningbo city in the north of Zhejiang in 2004, Yiwu city in the inland part of Zhejiang in 2009, the central region of Henan province in 2013, and Nanping city in the central region of Fujian in 2014 (Xu et al., 2007; Sun et al., 2011; Huang et al., 2014). However, the hot spots with locally transmission have shifted from Guangzhou city of Guangdong province to Chaozhou city of Guangdong and Xishuangbanna city of Yunnan province in 2015 and Fuzhou city of Fujian province in 2016 (Mu et al., 2017). This highlights the fact that the geographic range of dengue has apparently expanded in China, which is valuable information for consideration in national planning on dengue prevention and outbreak response. If dengue does continue to expand in China, this will need to be acknowledged in control planning, which currently focuses on Guangdong, Hainan, and Yunnan provinces in south China (Lai et al., 2015).

However, the number of reported dengue cases might be influenced by the change of diagnosis criteria and case definitions, especially through the introduction of more sensitive and rapid laboratory tests between 1990 and 2014, which could result in an increased number of reported

cases without increased transmission. Compared to the 1988 criteria, the 2001 edition introduced the enzyme-linked immunosorbent assay (ELISA), immunofluorescence method, and dengue blot for serologic testing, RT-PCR for nucleic acid detection, and monoclonal antibody immunofluorescence for antigen detection. Then, the 2008 edition included MAC-ELISA for serologic testing and real-time fluorescence quantitative PCR for detecting nucleic acids, and classified a positive DENV-IgM result from a confirmed to a probable dengue case (appendix Table A-2) (Ministry of Health of the People's Republic of China, 1988; Ministry of Health of the People's Republic of China, 2001; Ministry of Health of the People's Republic of China, 2008).

### 2.5.2 Demographic features of imported and autochthonous dengue

The age and gender distributions of imported and autochthonous cases in China differ in a number of ways. Imported cases were younger than autochthonous cases, and were more likely to be male. This may reflect a population of younger working male adults who tend to travel more domestically and regionally and thereby have more exposure risk to dengue. In addition, the autochthonous cases occurred across all age groups, including the elderly, which is different from other countries in Southeast Asia where dengue is endemic and where most dengue cases occur in children or younger adults (WHO, 2009a). This pattern most likely is due to the fact that the population in China has very low seroprevalence of dengue antibodies, and is therefore broadly susceptible to dengue infection, whereas the population in dengue endemic countries has higher rates of immunity, especially in adults and the elderly (Xu et al., 2007; Guo et al., 2014; Huang et al., 2014). However, the history of “mosquito bites” as part of the definition of imported case was impractical and likely introduced recall bias, which therefore probably underestimated the numbers and proportions of imported cases. A new guideline was issued in October 2014, which excludes “mosquitoes bite" in the definition of an imported case (Ministry of Health of the People's Republic of China, 2005; China CDC, 2014).

### 2.5.3 Dengue and *Aedes* mosquitoes

*Ae. albopictus* has been found in nearly one third of China and is the most predominant species in south China except in Hainan province, which has both types of *Aedes* mosquitoes (Wu et al., 2010). *Ae. aegypti* was implicated in outbreaks in Hainan in 1980 and 1985-1986 (Qiu et al., 1991). However, *Ae. albopictus* was the only vector species present in the outbreaks reported in Guangdong, Fujian, and Zhejiang from 2004 to 2010 (Peng et al., 2012; Xu et al., 2007). The importance of *Ae. albopictus* in dengue outbreaks appears to be increasing in China, which is worrisome because *Ae. albopictus* seems to adapt easily to new environments, even in a temperate climate, and to be associated with the huge population migration and urbanization in

China and climatic change (Wu et al., 2010; Rezza, 2012). However, under a national sentinel vector surveillance project for dengue, only 16 counties out of 483 counties in the five provinces in south China conducted *Aedes* mosquito surveillance between June and October since 2005, and China did not have a national vector control program for dengue (Ministry of Health of the People's Republic of China, 2008). Therefore, it may be prudent for China to put more effort into mosquito surveillance and control for *Ae. albopictus.*

### 2.5.4 Dengue virus serotypes

This study found all four serotypes of dengue virus in dengue patients in China, all of which are capable of causing dengue of any clinical severity (Wu et al., 2010; WHO, 2009a). DENV-3 was the first serotype documented in Guangdong in 1978 and in Hainan in 1980 (Zhao, 1981; Li et al., 1986). Then, in 2009 and 2010, DENV-3 was isolated again in Guangdong from imported cases, but the 2010 outbreak was not a re-emergence of the 2009 strain (Liang et al., 2013). DENV-3 was also isolated during the outbreak in Zhejiang in 2009, in Yunnan in 2013, including from severe cases, and in the first outbreak in central China in 2013 (Sun et al., 2011; Zhang et al., 2014a; Huang et al., 2014). DENV-1 has become the predominant serotype since the 1990s (Xu et al., 2007; Yang et al., 2014). During 2005-2011, DENV-1 was the predominant serotype in circulation in Guangdong, while all four serotypes have been identified in autochthonous patients from different outbreak localities since 2009 (Jiang et al., 2013; Guo et al., 2014). In addition, after an absence of 20 years since the DENV-4 outbreak in 1990, DENV-4 was detected during the outbreak in Guangzhou in 2010, in a Guangzhou resident who travelled back from Thailand (Jing et al., 2012). DENV-2 was confirmed in Hainan in 1985-1986 (Qiu et al., 1991), and a few cases were reported in 2013 and 2014. The increasing diversity in DENV strains imported to China, especially in 2013 and 2014, might increase the risk of DENV outbreaks and their severity in the near future, as well as the difficulty of dengue control. Therefore, monitoring this viral diversity should be considered in the design of surveillance and control strategies for China.

### 2.5.5 Is dengue an endemic disease in China?

Because of the geographic and seasonal restriction of cases, dengue in mainland China is still characterized as an imported disease and is not recognized as endemic (Luo, 2007). This characterization rests on the assumption that imported cases play a key role in initiating outbreaks in China (Xu et al., 2007; Chen, 2011). From this study, imported cases were reported in nearly every month during 2005 to 2014. However, autochthonous cases were mainly reported from July to November, which indicates a strong seasonality to dengue transmission in China, with peak transmission occurring mostly in the hot and humid seasons. Two factors are likely to

contribute to this pattern. Firstly, the large amount of rainfall from July to October increases the availability of breeding habitats of mosquitoes, thereby causing increases in mosquito population densities and the potential for dengue transmission (Sang et al., 2014). Secondly, transmission intensity can also fluctuate with temperature due to concomitant fluctuations in the length of the incubation period in the mosquito or mosquito mortality or blood feeding rates (Chan and Johansson, 2012; Brady et al., 2013; Brady et al., 2014).

The dengue case data presented here represent only the clinically apparent infections which presented to health care facilities. Previous studies have shown that a large and variable proportion of DENV infections are clinically inapparent or mildly symptomatic (Endy et al., 2011; Yoon et al., 2012), though adults are more likely to experience symptomatic illness than children (Egger and Coleman, 2007). This suggests that there is likely a larger pool of DENV infections and cases in China than is represented in this dataset. However, the overall incidence likely remains low compared to that in neighbouring endemic countries (Simmons and Farrar, 2009; Cuong et al., 2013).

In addition, most of the first local dengue outbreaks in each city and year can be traced back to imported cases that sparked the outbreaks (Xu et al., 2007; Peng et al., 2012; Jing et al., 2012). Although for some outbreaks initial imported cases cannot be identified, the molecular fingerprints of strains often suggest that the outbreak is likely due to viruses imported from other countries (Yang et al., 2014; Sun et al., 2011). Molecular epidemiological analysis in the last three decades also did not identify any new variants of viruses that are unique to mainland China (Wu et al., 2010). Although DENV-1 was predominant in most years in Guangzhou city during 2001-2010, the strains from each year belonged to different genotypes and none of them was found to be predominant, though Southeast Asian countries were generally found to be the most likely source (Jiang et al., 2013). This suggests that dengue in China is due to localized transmission sparked by regular virus importations from returned travellers or visitors, rather than endemic transmission. Therefore, more attention should be directed toward the early identification of imported cases from other countries, especially from Southeast Asia.

### 2.5.6 Challenge of dengue control in mainland China

The expansion of global air travel and seaborne trade, and the huge population movements in China overcome geographic barriers for both disease vectors and pathogens, enabling them to move great distances in short periods of time (Tatem et al., 2006a; Cowling and Yu, 2015; Messina et al., 2014). With the rapid growth of the economy and urbanization in China, more and more people in China have moved away from their original residences, especially from central China to

coastal provinces, and from poor rural areas to urban centres (Gaughan et al., 2016; Ma, 2014). This migration changes epidemiological dynamics and environments and can promote the transmission of dengue virus, increasing the population at risk of infection, and creating major challenges for prevention and control. Further, the increasing labour movements in and out of China to dengue endemic countries all over the world are driving changes in imported dengue dynamics.

The exceptionally high number of dengue cases in 2014 - a historical record since dengue became a notifiable disease in China in 1989 - serves as a reminder that even if dengue is not yet endemic in China, the possibility exists that the receptivity and vulnerability of certain areas to outbreaks could be increasing. Exploring the role of putative drivers of this huge outbreak, modelling and mapping the risk of importation and local transmission, and extracting lessons about how it could have been averted should be pursued immediately so as to inform future outbreak prediction and mitigation.

### 2.5.7 Limitations and conclusions of this analysis

There are some limitations in this study. Firstly, the data used were collected from passive public health surveillance. The data quality may be influenced by the key steps in surveillance including changing case definitions, reporting methods, availability of health facilities and laboratory diagnostics, under reporting, and completeness and accuracy of data over the years. Secondly, the individual case data were not reported before 2005, so demographic characteristics, laboratory confirmation, and the distribution of autochthonous versus imported cases could only be analysed from 2005-2014, and cases were not reported by the classification of disease severity.

In conclusion, based on notifiable surveillance data in mainland China from 1990-2014, the area affected by dengue has expanded since 2000 and the incidence has increased steadily since 2012, for both imported and autochthonous dengue. Surveillance and control strategies should be adjusted to account for these changes, and further research should explore the drivers of these trends.

# Chapter 3 Spatiotemporal patterns of malaria in China

## 3.1 Chapter summary

To ascertain the trends and burden of malaria in China and the costs of intervention for 2011-2015 while experiencing transitions between funders during a national plan launched to interrupt malaria transmission in most counties by 2015 and ultimately eliminate malaria by 2020.

I analysed the spatiotemporal and demographic features of autochthonous and imported malaria using disaggregated surveillance data on malaria from 2011 to 2015, covering the range of dominant malaria vectors in China. The total and mean costs for malaria elimination were calculated by funding sources, interventions, and population at risk.

A total of 17,745 malaria cases, including 123 deaths (0.7%), were reported in mainland China from 2011-2015, with 89% being imported cases, mainly from Africa and Southeast Asia. Most counties (99.9%) have achieved their elimination goals by 2015, and autochthonous cases dropped from 1,469 cases in 2011 to 43 cases in 2015, mainly occurring in the regions bordering Myanmar where *An. minimus* and *An. dirus* are the dominant vector species. A total of 134.6 million USD was spent in efforts to eliminate malaria during 2011-2015. The average annual investment per person at risk was 0.05 USD (SD 0.03) with the highest (0.09 USD) in 2012 and subsequent reductions between 2013 and 2015 after the Global Fund ceased providing investments.

The autochthonous malaria burden in China has decreased significantly, and malaria elimination is an achievable prospect in China. The key challenge is to address the remaining autochthonous transmission, as well as simultaneously reducing importation from Africa and Southeast Asia. Continued efforts and appropriate levels of investment are needed in the 2016-2020 period to achieve elimination.

## 3.2 Background

Malaria remains one of the most serious public health issues globally, with an estimated 214 million cases and 438,000 deaths in 2015 (WHO, 2015e; Dalrymple et al., 2015; Lai et al., 2016). Historically, malaria has been widespread in China with 24 malaria-endemic provinces, and over 24 million cases being reported in the early 1970s, with *P. vivax* and *P. falciparum* the main parasite species responsible (National Health and Family Planning Commission of China, 2010; Zhou, 1981). After control efforts were intensified, incidence has been substantially reduced with

95% of the counties in China having an incidence rate under 1/10,000 in 2009 (Zhang et al., 2014b). The Chinese government launched a National Malaria Elimination Programme (NMEP) in May 2010, aimed at reducing the number of autochthonous malaria cases across the majority of China to zero by 2015 (except some border areas of Yunnan province where the goal is elimination by 2017), and achieve certification of malaria elimination for China by 2020 (National Health and Family Planning Commission of China, 2010; WHO, 2015a). Comprehensive intervention policies and strategies have been adopted (appendix **Table B-1**), e.g. the "1-3-7" approach: reporting cases within one day, investigation within three days, and response to prevent further transmission within seven days (China CDC, 2011; Cao et al., 2014), and autochthonous malaria infections were only found in Yunnan and Tibet Provinces in 2014 (Hu et al., 2016b). Additionally, China is one of the 35 malaria-eliminating countries that are in the process of moving from controlled low-endemic malaria to elimination (Newby et al., 2016), and the progress in China is a major contributor towards the goal of elimination of malaria in all of the Greater Mekong Subregion countries by 2030 (WHO, 2015d).

Both international and domestic funds have been used to implement the NMEP to achieve the goal of malaria elimination. The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) has supported China to progress from control to elimination between 2003 and 2012 (Hu et al., 2016b; The Global Fund). The Global Fund disbursed approximately 113 million USD to China for malaria-related support during 2003-2012, and the coverage of Global Fund-supported projects expanded from 47 high malaria-burden counties (within 10 provinces) in 2003 to 762 high and lower malaria-burden counties (within 20 provinces) in 2010 (Hu et al., 2016b). The Global Fund accounted for all documented operational malaria funding in China between 2005 and 2010 (Zelman et al., 2014), and the National Strategy Application project for malaria elimination from the Global Fund consolidated previous grants and other resources to align with the NMEP in China since 2010. However, changes to eligibility criteria in November 2011 meant that China was no longer eligible for renewals of grants, due to categorisation as an upper middle income country and the malaria burden being sufficiently low (Hu et al., 2016b; The Global Fund). The National Strategy Application project was closed ahead of schedule on June 30, 2012, and the financial commitment of the Chinese central government has since been utilised to cover the investment gaps (Hu et al., 2016b).

There are few comprehensive analyses of the changing epidemiology of malaria in China, or of the achievement of the NMEP by 2015 and challenges for the halfway point goals of the NMEP, and the evidence in favour of these actions has been more descriptive than quantitative (Li et al., 2015; Li et al., 2016b; Liu et al., 2014; Zhou et al., 2016; Hu et al., 2016b). Both donors and policy makers should ideally have information about the costs and benefits of interventions, especially

during the transition of funders from international to domestic sources (Fan et al., 2013; Haque et al., 2014; Wangdi et al., 2016a). A robust epidemiological and cost–benefit analysis is crucial to support the design and update of national strategies and future needs for malaria elimination (WHO, 2015c; Haque et al., 2014; Wangdi et al., 2016a). Here I have conducted an observational situation analysis to determine (1) the epidemiological trends and burden of malaria, (2) areas and populations with residual transmission, and (3) the costs of interventions from different donors for malaria elimination from 2011 to 2015 in China. This work identifies the achievements and challenges and thereby helps to plan resource allocation for the second-half (2016-2020) of the elimination plan and the ultimate goals of NMEP in China.

## 3.3 Methods

### 3.3.1 Data sources

Data on individual malaria cases, including clinically diagnosed and laboratory-confirmed cases reported in all 31 provinces of mainland China during 2011–2015, were obtained from the Malaria Enhanced Surveillance Information System (MESIS). The MESIS was developed as a part of the NMEP to actively collect demographic and epidemiological information including age, gender, occupation, diagnosis, treatment, outcome, classification, and travel history (appendix **Table B-2**), using the unified form for case investigation required by the Technical Scheme of China Malaria Elimination (Sun et al., 2016; China CDC, 2011). Laboratory-confirmed malaria cases refer to patients with a positive result from one of the laboratory tests including RDTs, microscopy, or PCR (National Health and Family Planning Commission of China, 2006). RDTs were the primary diagnostic tools in the remote villages, townships and counties; microscopy was used in county, prefectural and provincial levels as the gold standard method for case verification; and PCR was mainly used for case verification at provincial levels because of its higher sensitivity than microscopy and RDTs. Clinically diagnosed cases were defined as patients with malaria-like symptoms but no parasites detected in blood examination. A malaria patient was classified as an imported case if the individual travelled to malaria-endemic areas outside China within the month prior to illness onset, and the last country visited was taken as the potential origin of infection (China CDC, 2011).

I extracted data on costs of malaria control and the estimated yearly population at risk in 2011-2015 from the annual World Malaria Report (WMR) in 2012-2016 of the WHO (2015e; 2016a), the China Annual Report of Malaria Elimination, the National Programme Office for malaria of the Global Fund in China, and information publicly available through the Global Fund website (appendix **Table B-3**) (The Global Fund, 2016). This study included the costs from the Global Fund

(2011-2012) and Chinese Central Government (2011-2015). Other sources of international malaria funding (e.g. the President's Malaria Initiative, the United Nations International Children's Emergency Fund, and the World Bank) were checked but excluded here because no funding for malaria was allocated to China from these sources in 2011-2015. The costs incurred by the governments at sub-national levels are also not included here because the Chinese Central Government plays a major role in domestic funding to the NMEP. From the WMR and the China Annual Report of Malaria Elimination, I also collected the number of long-lasting insecticidal nets (LLINs) and insecticide-treated nets (ITNs) distributed, the number of people protected by indoor residual spraying (IRS), and the number of blood samples collected and tested for malaria using these funds. All the funds documented in Chinese Yuan were converted into US dollars using the average exchange rate from the year of the award/funding, and the values were adjusted for the annual average inflation rate (2.65% in 2012, 2.62% in 2013, 1.99% in 2014 and 1.44% in 2015) in China through comparison to 2011, in order to measure funding/spending trends in real terms.

The geographic distributions of dominant *Anopheles* vectors of human malaria in China were obtained from the Malaria Atlas Project (Sinka et al., 2012) to define high risk areas for malaria residual transmission. The population data at national and sub-national level for each year were obtained from the National Statistical Bureau of China (2016a), to estimate the incidence rate and population living in counties with malaria transmission by different dominant *Anopheles* mosquitoes.

### 3.3.2 Data analyses

All cases reported in all 2858 counties of 333 prefectures in 31 provinces of mainland China were included in this analysis, with illness onset from January 1, 2011, to December 31, 2015. The epidemiologic characteristics of malaria cases were summarized. I estimated the incidence rate for each year at national and county levels, and calculated the case-fatality rate of malaria (number of deaths divided by number of probable and confirmed cases), overall, and stratified by autochthonous and imported cases. All counties in mainland China have been classified into four categories with different goals for malaria elimination in the NMEP (**Table 3-1** and appendix **Figure B-1**). The achievement of the NMEP for 2011-2015 was defined by comparing the incidence of malaria with the mid-way goals of the four categories of counties by 2015. The population living in the counties with autochthonous *P. falciparum* and *P. vivax* each year were stratified by the different dominant *Anopheles* vectors.

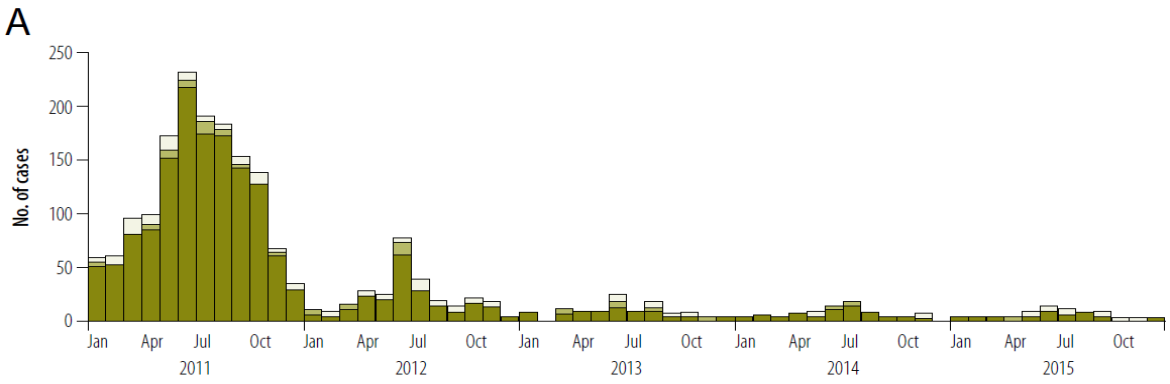
The values of disbursed funds for malaria elimination was calculated by the source of the Global Fund and the Chinese Central Government in 2011-2015. The costs of different interventions and

management (e.g. insecticidal nets, diagnostic testing, insecticide and spraying materials, antimalarial medicines, monitoring and evaluation, human resources and technical assistance, management and "other" costs) were summarized for each year, and stratified by sources of funding. The coverage of nets (LLINs and ITNs) and IRS were estimated using the corresponding at-risk population in China. Test positivity proportion was calculated by dividing the total number of laboratory-confirmed malaria cases by the number of blood samples tested, multiplied by 100 (and expressed as a percentage). Version 3.3.1 of the *R* statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct statistical analyses, and ArcGIS 10.3 (ESRI, Redlands, CA, USA) was used to plot the geographical distribution of cases and conduct spatial analyses.

## 3.4 Results

### 3.4.1 Overall incidence and achievements for malaria elimination

From 2011 to 2015, a total of 17,745 malaria cases, including 123 deaths (0.7%) were reported in mainland China, of which 15,840 (89%) were imported and 1,905 (11%) were autochthonous (**Figure 3-1** and appendix **Figure B-2**). The number of autochthonous malaria cases dropped from 1,469 cases (1.1 cases per one million persons) in 2011 to 43 (0.03 cases per one million persons) cases in 2015, with most (94%) autochthonous cases being infected with *P. vivax* (appendix **Table B-4**). Compared with the goals set for different counties in the NMEP by 2015, most counties (99.9%) had achieved their goals by 2015, and all counties in the border areas of Yunnan had an annual incidence rate less than the target of one case per 10,000 persons since 2013. However, three areas failed to achieve their goal (reducing autochthonous case to zero) by 2015, including Motuo county in Tibet, Sanya City in Hainan Island and Donggang City in Liaoning Province (**Table 3-1**, **Figure 3-2**, and appendix **Figure B-1** and **Figure B-3**).



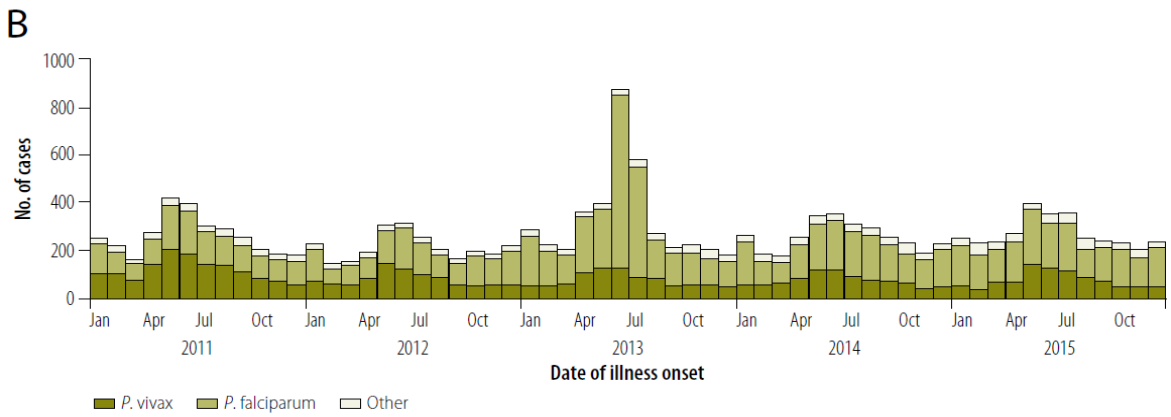



**Figure 3-1. Epidemic curves of *Plasmodium* malaria in mainland China, 2011-2015.**

Note: (A) Autochthonous cases (n=1,905) including 1708 *P. vivax* cases, 92 *P. falciparum*, 4 *P. malariae*, 1 *P. ovale*, 5 mixed infections and 95 untyped. (B) Imported cases (n=15,840) including 9754 *P. falciparum* cases, 4,882 *P. vivax*, 524 *P. ovale*, 188 *P. malariae*, 202 mixed infections and 290 untyped.

### 3.4.2 Remaining locally transmitted malaria and vector distribution

The residual transmission by 2015 might reflect the spatial variability and complexity of *Anopheles* vectors in China (**Figure 3-3**). Among the counties with only *An. sinensis* and/or *An. lesteri* as dominant vectors, the number of *P. vivax* and *P. falciparum* cases have been reduced substantially, with only one county reporting the occurrence of autochthonous *P. vivax* (**Table 3-2**). However, among the counties with other dominant vectors (e.g. *An. minimus s.l.*, *An. dirus s.l.*, *An. stephensis*, and *An. Maculatus*), there were still more than 10 counties (with a combined population of 3.7 million) reporting autochthonous *P. vivax* annually in 2013-2015, and two countries (with a combined population of 569,000) reporting autochthonous *P. falciparum* in 2015.

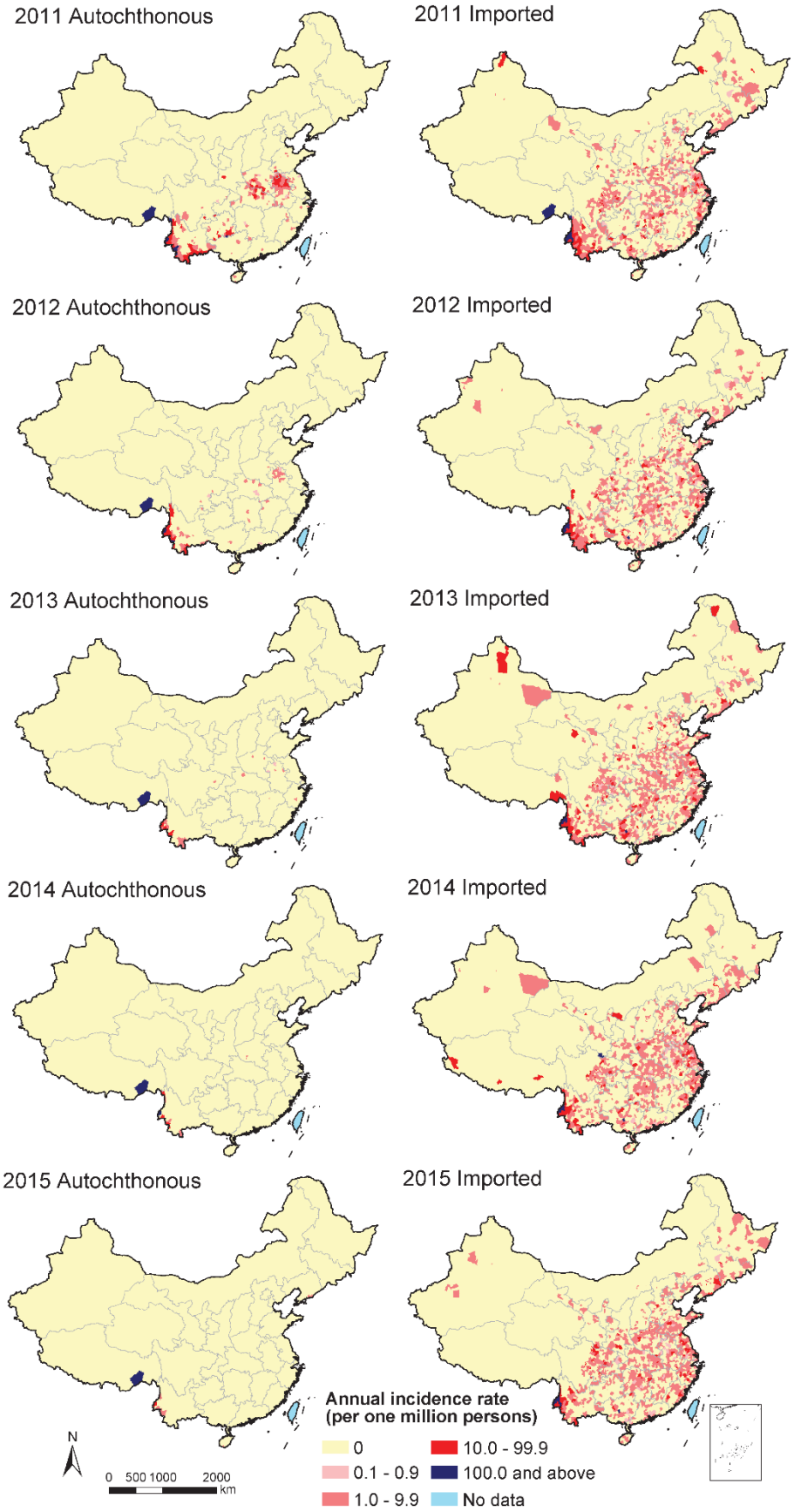



**Figure 3-2. Changing geographic distribution of autochthonous and imported malaria by county in mainland China, 2011-2015.**

**Table 3-1. Four categories of counties and their goals and achievements for malaria elimination in mainland China**.

| Category definition | No. (%) of counties (n = 2858[a]) | Goals by 2015 | Goals in 2016-2020 | Achievements for the goals by 2015 |
|---|---|---|---|---|
| **Type I:** Local infections detected in 3 consecutive years and annual incidence ≥ 1 per 10,000 persons for each year. | 75 (2.6%) | Counties in border areas of Yunnan: annual incidence < 1 per 10,000 persons. | The counties in border areas of Yunnan: no local infections detected by 2017; malaria elimination by 2020. | Yes. Annual incidence in each county was < 1 cases per 10,000 persons. |
| | | Other counties: no local infections detected by 2015. | Other counties: malaria elimination by 2018. | Partly. Motuo county in Tibet (bordering with India) and Sanya City in Hainan in tropic reported locally transmitted cases in 2015. Motuo county had ≥ 1 cases per 10,000 persons for each year in 2011-2015. |
| **Type II**: Local infections detected in the last three years and at least the annual incidence < 1 per 10,000 persons in one of the three years. | 687 (24.0%) | No local infections detected by 2015. | Malaria elimination by 2018. | Partly. Donggang City in Liaoning Province (bordering with Democratic People's Republic of Korea) reported locally transmitted cases in 2015. |
| **Type III**: No local infections reported in the last three years. | 1432 (50.1%) | Malaria elimination by 2015. | Maintaining malaria-free status. | Yes. Pass the subnational malaria elimination assessment. |
| **Type IV**: Non-malaria-endemic area. | 664 (23.3%) | Maintaining malaria-free status. | Maintaining malaria-free status. | Yes. Maintained malaria-free status. |

[a] Only the counties of 31 provinces in mainland China are included in the national malaria elimination programme. Note: The counties are categorized by the malaria incidence data reported in mainland China from 2006 to 2008, obtained from the Action Plan of China Malaria Elimination (2010–2020) and the National Notifiable Infectious Disease Reporting Information System in China.

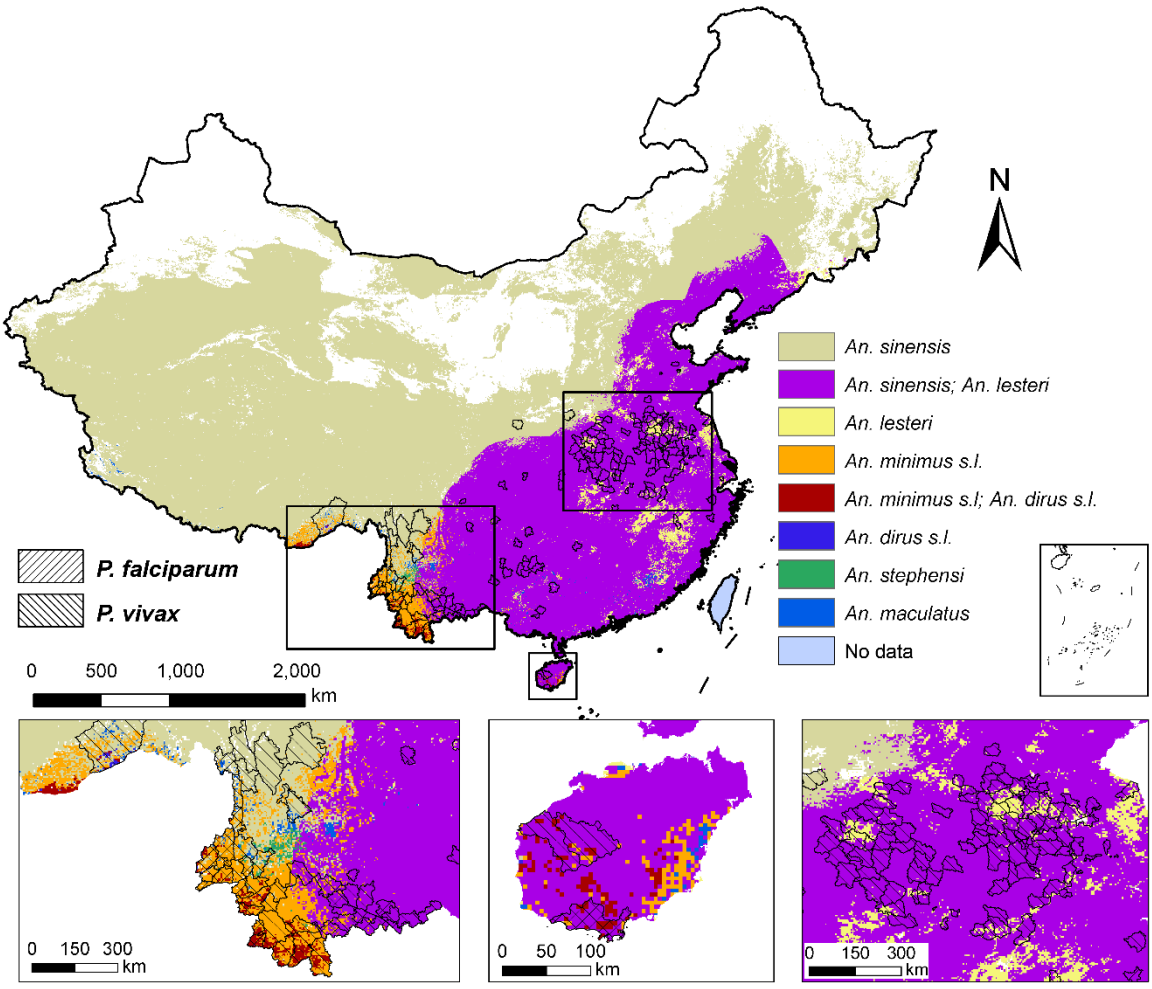



**Figure 3-3. Geographic distribution of autochthonous *Plasmodium* malaria and *Anopheles* mosquitoes by county in China, 2011-2015**.

Note: Autochthonous *P. vivax* cases were only found in 172 counties (87.8% of all 196 counties with autochthonous cases) with 104,852,176 persons; autochthonous *P. falciparum* cases in three counties (1.5%) with 1,442,755 persons; and 21 counties (10.7%) with 5,765,053 persons reported both species. A total of 130 counties (66.3% of all 196 counties with autochthonous cases) have only *An. sinensis* and/or *An. lesteri* as dominant vector, whereas the remaining 66 counties (33.7%) have co-existence of other *Anopheles* mosquitoes and/or *An. sinensis*, *An. lesteri* as dominant vectors.

### 3.4.3 Spatiotemporal features of imported malaria

Imported cases have been reported in all 31 provinces of mainland China, with a median of 3,091 cases (IQR: 3,049-3,221 cases) from 2011 to 2015. The imported cases originated from 69 countries, in Africa (44 countries), Southeast Asia (18) and other regions (7) (**Figure 3-4** and appendix **Table B-5**). Most imported cases were male (95%) and Chinese (94%) migrant workers with a longer stay in Africa than in Southeast Asia (median 320 days; IQR 171-515 vs 120 days; IQR 59-229). Most cases (80%) imported from Africa were infected with *P. falciparum*, whereas a high proportion (78%) of cases from Southeast Asia were cause by *P. vivax*. Yunnan province imported the most cases (68%) from Southeast Asia, while Guangxi (17%), Jiangsu (15%) and Sichuan (8%) provinces imported the most cases from Africa. The co-occurrence of autochthonous and imported malaria was mainly found in the border areas of Yunnan and Tibet, and the provinces of central China (appendix **Figure B-6** and **Figure B-7**).

**Table 3-2. Trends in locally transmitted *Plasmodium vivax* and *P. falciparum* malaria infections in mainland China, 2011–2015**.

| Variable | Year | | | | |
|---|---|---|---|---|---|
| | **2011** | **2012** | **2013** | **2014** | **2015** |
| **Total population, thousands** | **1 347 350** | **1 354 040** | **1 360 720** | **1 367 820** | **1 374 620** |
| ***P. vivax and P. falciparum* malaria** | | | | | |
| Total no. of cases | 1396 | 231 | 78 | 59 | 36 |
| No. of cases per 1 000 000 persons | 1.04 | 0.17 | 0.06 | 0.04 | 0.03 |
| No. of counties affected | 183 | 50 | 21 | 10 | 11 |
| Population of counties, thousands | 104 499 | 25 940 | 9202 | 1872 | 3945 |
| ***P. vivax* malaria** | | | | | |
| Total no. of cases | 1344 | 212 | 65 | 53 | 34 |
| No. of cases per 1 000 000 persons | 1.00 | 0.16 | 0.05 | 0.04 | 0.02 |
| No. of counties affected (% of total) | | | | | |
| Total | 182 (100) | 50 (100) | 18 (100) | 10 (100) | 10 (100) |
| Only *Anopheles sinensis* and/or *An. lesteri* mosquitoes | 119 (65) | 24 (48) | 5 (28) | 0 (0) | 1 (10) |
| Other *Anopheles* mosquitoes[a] | 63 (35) | 26 (52) | 13 (72) | 10 (100) | 9 (90) |
| Population in counties affected, thousands (% of total) | | | | | |
| Total | 104 242 (100) | 25 940 (100) | 7622 (100) | 1872 (100) | 3766 (100) |
| Only *An. sinensis* and/or *An. lesteri* mosquitoes | 84 376 (81) | 18 199 (70) | 3937 (52) | 0 (0) | 627 (17) |

| Variable | Year | | | | |
|---|---|---|---|---|---|
| | 2011 | 2012 | 2013 | 2014 | 2015 |
| Other *Anopheles* mosquitoes[a] | 19 866 (19) | 7741 (30) | 3685 (48) | 1872 (100) | 3139 (83) |
| ***P. falciparum* malaria** | | | | | |
| Total no. of cases | 52 | 19 | 13 | 6 | 2 |
| No. of cases per 1 000 000 persons | 0.04 | 0.01 | 0.01 | 0.00 | 0.00 |
| No. of counties affected (% of total) | | | | | |
| Total | 17 (100) | 9 (100) | 6 (100) | 2 (100) | 2 (100) |
| Only *An. sinensis* and/or *An. lesteri* mosquitoes | 2 (12) | 0 (0) | 3 (50) | 0 (0) | 0 (0) |
| Other *Anopheles* mosquitoes[a] | 15 (88) | 9 (100) | 3 (50) | 2 (100) | 2 (100) |
| Population in counties affected, thousands (% of total) | | | | | |
| Total | 4391 (100) | 2941(100) | 2246 (100) | 484 (100) | 569 (100) |
| Only *An. sinensis* and/or *An. lesteri* mosquitoes | 362 (8) | 0 (0) | 1 581 (70) | 0 (0) | 0 (0) |
| Other *Anopheles* mosquitoes[a] | 4029 (92) | 2941 (100) | 665 (30) | 484 (100) | 569 (100) |

[a] Other *Anopheles* mosquitoes includes *An. minimus s.l.*, *An. dirus s.l.*, *An. stephensis* and *An. maculatus*. Notes: 11 counties in 5 provinces (Yunnan, Tibet, Hainan, Guangxi and Liaoning) reported locally transmitted cases in 2015.

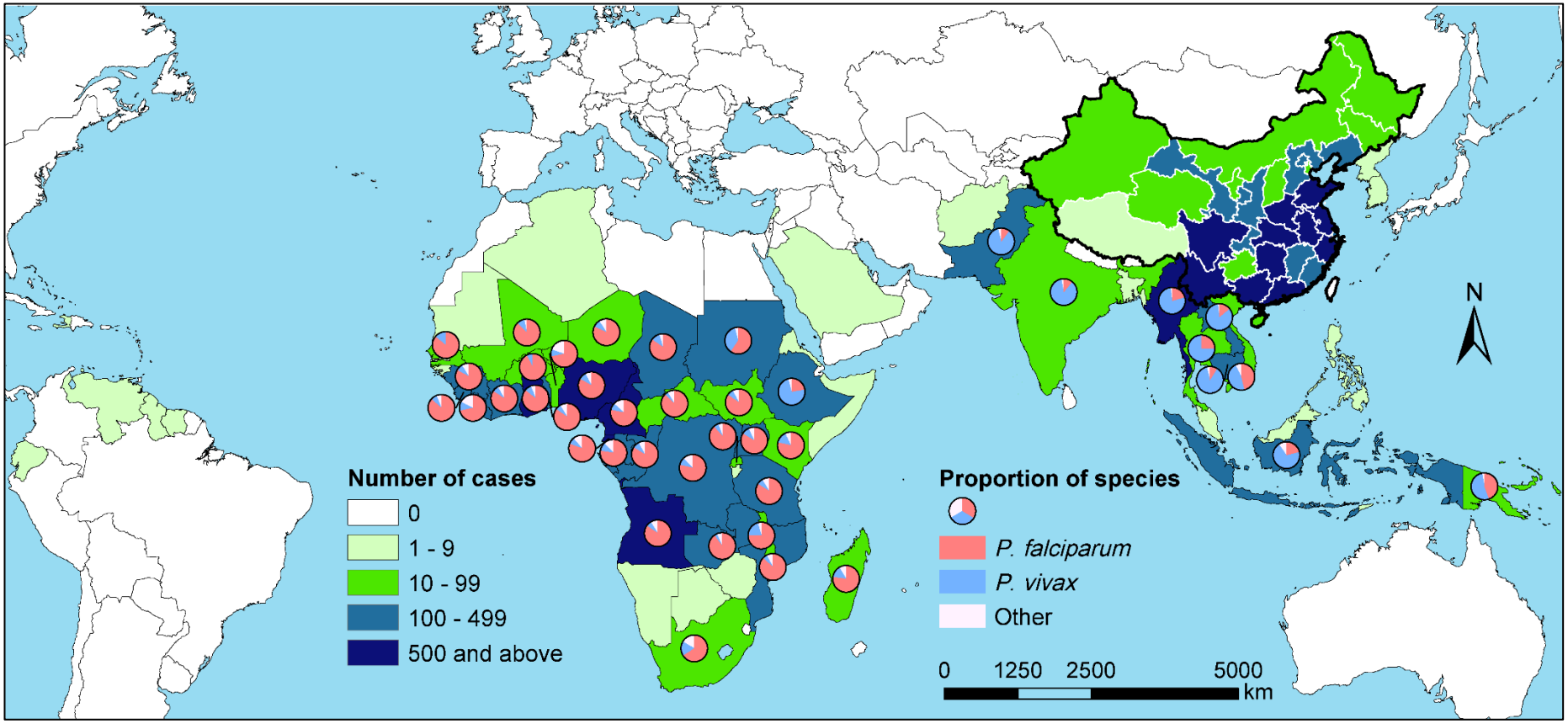



**Figure 3-4. Origin-destination and species of imported *Plasmodium* malaria reported in mainland China, 2011-2015.**

Note: The imported cases (15,840) included 9,754 *P. falciparum* cases, 4,882 *P. vivax*, 524 *P. ovale*, 188 *P. malariae*, 202 mixed infections and 290 untyped, of which 15,524 cases (97.4%) reported with travel information. The last countries visited by patients before returning to China were recorded as the potential origins of infections. The cases were exported from 69 countries located in Africa (10,949 cases), Southeast (4,340) and South Asia (175), and other regions (60), into all 31 provinces in mainland China. The proportion of *Plasmodium* species are presented for countries with ≥10 cases.

### 3.4.4 Costs for malaria elimination

China spent US$134.6 million on malaria elimination efforts during 2011-2015, including $57.2 million (42.5%) from the Global Fund in 2011-2012 and $77.3 million (57.5%) from the Central Government of P. R. China in 2011-2015 (**Table 3-3**). The value of funding varied each year, with the highest ($51.5 million) provided in 2012, and subsequent reductions between 2013 and 2015 after the Global Fund ceased providing investments. The level of funding from the Chinese central government increased to fill the gap during the transition of funders, but the annual values were still lower than that previously provided by the Global Fund. The annual investment per person at risk varied during the study period with an average of $0.05 (SD 0.03) and the highest ($0.09) in 2012.

The expenditure by intervention varied between international and domestic funding. The expenditure on management and "other" (e.g. vehicle, small refrigerators and computers) costs accounted for 57% of the $24.4 million from the Global Fund in 2011, followed by the costs of human resources and technical assistance (26%, $6.3 million) for providing township hospitals and village clinics with incentives to improve case management and reporting. However, the financing for interventions from the Chinese Central Government from 2013 to 2015 was predominantly allocated for diagnostic testing (57.4%, $29.6 million), and management and "other" costs (28.7%, $14.8 million). The costs of ITNs and LLINs, insecticide and spraying materials, and antimalarial medicines accounted for small proportions of both international (4%) and domestic (12.7%) funders. A large number of blood samples (30,119,108) were collected for laboratory-diagnostic testing with a positive rate of 0.06% (16,579). A total of 1,274,548 nets were purchased with 509,333 LLINs (40%) and 765,215 ITNs (60%), with the annual numbers of nets purchased each year decreased from 2011 to 2014, and the high-risk populations (> 1 case per 1000 persons) were covered by IRS during 2011-2015 (**Table 3-3**).

**Table 3-3. Interventions and costs for malaria elimination in mainland China, 2011–2015**.

| Variable | Year | | | | |
|---|---|---|---|---|---|
| | 2011 | 2012 | 2013 | 2014 | 2015 |
| **Population, thousands (% of total)** | | | | | |
| **Total** | **1 347 350 (100)** | **1 354 040 (100)** | **1 360 720 (100)** | **1 367 820 (100)** | **1 374 620 (100)** |
| At risk of malaria[b] | 563 574 (42) | 575 911 (42) | 579 467 (42) | 575 985 (42) | 575 985 (42)[a] |
| At high risk of malaria[b] | 192 (0.01) | 196 (0.01) | 197 (0.01) | 196 (0.01) | 196 (0.01) |
| **Funding, US$ millions (% of total)** | | | | | |
| Total | 31.5 (100) | 51.5 (100) | 16.0 (100) | 19.4 (100) | 16.2 (100) |
| The Global Fund | 24.4 (77) | 32.8 (64) | 0.0 (0) | 0.0 (0) | 0.0 (0) |
| Central government of China | 7.1 (23) | 18.6 (36) | 16.0 (100) | 19.4 (100) | 16.2 (100) |
| **Spending per person at risk, US$** | 0.06 | 0.09 | 0.03 | 0.04 | 0.03 |
| **Spending on interventions, US$ millions (% of total)[c]** | | | | | |
| Total | 24.4 (100) | N/A | 16.0 (100) | 19.4 (100) | 16.2 (100) |
| Insecticide and spraying materials | 0.5 (2) | N/A | 1.1 (7) | 0.8 (4) | 0.7 (4) |
| Insecticide-treated nets and long-lasting insecticidal nets | 0.4 (1) | N/A | 1.4 (9) | 1.1 (6) | 0.9 (6) |
| Diagnostic testing | 0.7 (3) | N/A | 13.3 (83) | 8.9 (46) | 7.5 (46) |
| Antimalarial medicines | 0.0 (0) | N/A | 0.2 (1) | 0.2 (1) | 0.2 (1) |
| Monitoring and evaluation | 2.7 (11) | N/A | 0.0 (0) | 0.0 (0) | 0.0 (0) |
| Human resources and technical assistance | 6.3 (26) | N/A | 0.0 (0) | 0.3 (2) | 0.3 (2) |
| Management and other costs | 13.8 (57) | N/A | 0 (0) | 8.1 (42) | 6.6 (41) |

| Variable | Year | | | | |
|---|---|---|---|---|---|
| | 2011 | 2012 | 2013 | 2014 | 2015 |
| **Nets coverage, no. of nets purchased** | | | | | |
| Total | 656 674 | 509 490 | 58 874 | 19 899 | 29 611 |
| Long-lasting insecticidal nets | 149 394 | 251 555 | 58 874 | 19 899 | 29 611 |
| Insecticide-treated nets | 507 280 | 257 935 | 0 | 0 | 0 |
| **Indoor residual spraying coverage, no. of people protected** | 1 043 963 | 1 092 158 | 447 639 | 504 936 | 1 697 188 |
| **Laboratory-confirmed malaria, no. of blood samples** | | | | | |
| Total collected | 9 189 270 | 6 918 657 | 5 554 960 | 4 403 633 | 4 052 588 |
| Positive (% of total)[d] | 3629 (0.04) | 2633 (0.04) | 4029 (0.07) | 3065 (0.07) | 3223 (0.08) |
| Positive, by species (% of positive samples) | | | | | |
| *P. falciparum* | 1467 (40) | 1460 (55) | 2892 (72) | 1879 (61) | 1977 (61) |
| *P. vivax* | 2087 (58) | 1068 (41) | 915 (23) | 919 (30) | 910 (28) |
| Other[e] | 75 (2) | 105 (4) | 222 (6) | 267 (9) | 336 (11) |

N/A: data not available; The Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria; US$: United States dollars. [a] Risk areas (counties) were those with malaria transmission. High-risk areas (counties) were those with > 1 case per 1000 persons. [b] Using the estimates of population at risk in 2014 from the world malaria report 2015. [c] Expenditure by interventions in 2011 only included the cost of the Global Fund. Cost calculations did not include: salaries of department of health staff at county level or above; direct costs of eliminating malaria incurred by the governments at sub-national levels; costs of treatment of malaria provided by physicians; or expenditure on malaria treatment by patients. All the funds documented in Chinese yuan were converted into US$ using the average exchange rate from the year of the award or funding, and the values were adjusted for the annual average inflation rate in China (2.65% in 2012, 2.62% in 2013, 1.99% in 2014 and 1.44% in 2015) through comparison to 2011. [d] Malaria cases were confirmed by diagnostic tests of microscopy, rapid diagnostic tests or polymerase chain reaction tests. [e] Other included *P. ovale*, *P. malariae*, and mixed infections. Notes: The conversion rates were US$ 100 to Chinese Yuan: 645.88 in 2011; 631.25 in 2012; 619.32 in 2013; 614.28 in 2014; and 622.84 in 2015.

## 3.5 Discussion

### 3.5.1 Dramatically reduction on locally transmitted malaria

The prevalence of autochthonous malaria has decreased in mainland China following the first 5 years of elimination efforts, which began in May 2010. The geographic range of endemic areas with *P. falciparum* and *P. vivax* transmission has shrunk dramatically, with most counties having achieved their NMEP goals by 2015. Malaria is on the verge of elimination in central China. This reduction corresponded with the implementation of the NMEP and continuous investments from international and domestic funders to support diagnosis and treatment, indoor residual spraying, and the distribution of insecticidal nets (Wang et al., 2014b; Zelman et al., 2014). This success also could be attributed, at least in part, to robust surveillance systems that rapidly detected and responded to individual cases (Cao et al., 2014). This study also suggests that the greatest threats to successful elimination efforts in China are the residual malaria transmission in the regions with dominant vectors of *An. minimus s.l.*, and *An. dirus s.l.*

### 3.5.2 Challenges of malaria elimination imposed by importation

In areas where malaria transmission has been interrupted, the challenge is to maintain malaria-free status and prevent reintroduction. In contrast, in areas with ongoing local transmission (i.e. Yunnan and Tibet), the main challenges are the higher malaria burdens and lack of healthcare and malaria control services in malaria endemic areas of Myanmar and India which border China, and the importation of cases from mobile and migrant populations (Wang et al., 2014a). High incidence of clinical malaria has been reported from the villages in Yunnan along the border, and the risk increases with decreasing distance from the international border (Wang et al., 2015; Hu et al., 2016c; Sinka et al., 2012; Sinka et al., 2011). There is also a risk of malaria parasites being carried across the borders by infected mosquitoes, due to the very close proximity of villages along the border on both sides (Wang et al., 2015; Hu et al., 2016c).

Additionally, malaria importation from beyond neighbouring countries in Africa and southeast Asia also remains a serious challenge, because only a few countries in Africa and southeast Asia are expected to eliminate malaria by 2020. Therefore, addressing cross-border malaria carried by travellers, especially Chinese migrant workers, to/from Africa and nearby countries in Southeast Asia is crucial to eliminate malaria and maintain the gains that have been achieved by China so far (Tatem and Smith, 2010; Wangdi et al., 2016b; Chinese Ministry of Commerce, 2015; National Tourism Administration Data Center, 2014; Liu et al., 2014; Huang and Tatem, 2013; Tatem et al., 2017).

### 3.5.3 Investment on malaria intervention

The cost per person at risk in China was low compared with other countries (WHO, 2013; Haque et al., 2014). Among 87 malaria-endemic countries that received financial support from international donors to control malaria from 2008 to 2012, China (>56 million people living in endemic districts) ranked 2nd in terms of the size of population at risk of malaria, but it ranked 82nd in terms of the amount of international funding invested per person (WHO, 2013; Haque et al., 2014).

Furthermore, as international support wanes due to the decreasing burden of malaria, it is the central and local governments of China who will continue to fund malaria elimination activities, and ensure that the universal coverage of interventions is maintained for the second-half of the elimination program and post-elimination era. Resurgence of malaria may occur if control and surveillance measures are scaled back too early following elimination, and consistent financing is necessary to avoid this (Zhang et al., 2014b; Cohen et al., 2012; Chiyaka et al., 2013). Malaria elimination in China may be currently underfunded relative to the frequency of parasite importation and the size of the population living in areas at risk of malaria, and increased funding could be crucial for elimination efforts.

### 3.5.4 Limitations and conclusions of this Chapter

This study had some limitations. It is possible that not all improvements in the malaria situation were attributable to the elimination activities. For example, it is known that socioeconomic development can be associated with reduced malaria in urban areas (Tusting et al., 2013), and China has undergone substantial socioeconomic growth and unprecedented urbanization (Gaughan et al., 2016). These changes could have contributed to a decrease in malaria prevalence, irrespective of malaria control and elimination activities. The number of malaria cases identified in the present study might be an underestimate if some cases did not seek treatment, or imported malaria was misdiagnosed in malaria-free areas or hard-to-reach areas, even though the individual case-based malaria surveillance system in China operated well during the malaria elimination stage (Sun et al., 2016).

Furthermore, the cost calculations do not include funding from governments at national and sub-national levels to support the salaries of department of health staff at county level or above who were responsible for most of the malaria elimination activities (e.g. surveillance, data collection, vector control and diagnosis). Additionally, the costs of treatment of malaria provided by physicians and the costs of patients for malaria related expenditure were not included in the study because of difficulties in obtaining adequate data.

The results of this study show that the malaria burden in China fell substantially during the study period, with substantial financial support from international and domestic funds. Elimination is a realistic aim, and the benefits are not only local, but also international if elimination in China acts to reduce or delay the spread of artemisinin resistance from the Mekong region. However, the foreseeable challenges presented here need national attention to achieve the goal of malaria elimination in China by 2020. Investment needs to be maintained and ideally increased to target resources towards the remaining high-burden and high importation regions, and strong surveillance and response systems need to be maintained to monitor residual transmission in endemic areas. Monitoring the risk of importation and the transmission potential in importation risk areas will ensure that elimination is sustained and will form a cornerstone of post-2015 elimination strategies in China (WHO, 2015a).

# Chapter 4 Driving factors of mosquito-borne disease importation into China

## 4.1 Chapter summary

In this Chapter, taking *Plasmodium falciparum* malaria as an example, an analysis has been conducted to explore the driving factors of mosquito-borne pathogen importation into China during 2011-2015 and its mortality in imported cases. *P. falciparum* malaria importation from Africa to China is rising with increasing Chinese overseas investment and international travel. Identifying networks and drivers of this phenomenon as well as the contributors to high case-fatality rate is a growing public health concern to enable efficient response.

I compiled and analysed a comprehensive database including individual cases, air travel, parasite prevalence, and official development assistance (ODA) from China as potential economic driver to examine the connectivity and driving factors of *P. falciparum* malaria importation, with the likely origins and destinations defined. Multivariate logistic regression was also conducted to explore the risk factors for mortality.

From 2011-2015, 8653 *P. falciparum* cases leading to 98 deaths (11.3 per 1000 cases) were imported from 41 sub-Saharan countries into China, with most cases (91.3%) occurring in labour-related Chinese travellers. Four strongly connected groupings of origin African countries with destination Chinese provinces were identified, and the number of imported cases was significantly associated with the volume of air passengers to China ($P=0.006$), parasite prevalence in Africa ($P<0.001$), and the amount of ODA from China ($P<0.001$) with investment in resource extraction having the strongest relationship with parasite importation. Risk factors for deaths from imported cases were related to the capacity of malaria diagnosis and diverse socioeconomic factors.

The spatial heterogeneity uncovered, principal drivers explored, and risk factors for mortality found in the rising rates of *P. falciparum* malaria importation to China can serve to refine malaria elimination strategies and the management of cases. High risk groups and regions should be targeted to prevent malaria importation, tackle the risks of onward transmission, and reduce case-fatality rates.

## 4.2 Background

The international spread of infectious diseases including *Plasmodium falciparum* malaria has been accelerated by increasing human mobility via air travel over recent decades (Gushulak and MacPherson, 2004; Tatem et al., 2012; Franco-Paredes and Santos-Preciado, 2006). With many countries moving towards national malaria elimination (Wangdi et al., 2016a; Haque et al., 2014), global eradication has risen up the international agenda (Newby et al., 2016; Bhatt et al., 2015). However, *P. falciparum* malaria importation from endemic regions and the threat of spreading drug resistance remains a problem for many eliminating or malaria-free countries due to the difficulty of diagnosis, substantial burden of treatment, relatively high mortality rates, and potential secondary local transmission (Hanscheid, 2003; Checkley et al., 2012). The importation of malaria from Africa has been common over the past decades in non-endemic countries such as the UK and France, that have historical, language and cultural ties (Askling et al., 2012; Leder et al., 2006), and certain demographic groups exhibit substantially higher infection rates, such travellers visiting friends and relatives in endemic countries (Checkley et al., 2012; Broderick et al., 2015; Pavli and Maltezou, 2010).

An emerging route of *P. falciparum* infection movements recently is from Africa to China by Chinese migrant workers (Zhou et al., 2016; Li et al., 2016b). This rise has been witnessed over the past decade, corresponding with increased investment and movement of workers from China (Chinese Ministry of Commerce, 2015; National Tourism Administration Data Center, 2014). Historically, malaria has been widespread in China, with an estimate of approximately 30 million cases occurred annually in the 1940s (Zhou, 1981). Since the initiation of a national control program in May 2010, which aims to eliminate malaria by 2020, autochthonous malaria cases have numbered in the hundreds annually, and the spatial distribution of locally acquired *P. falciparum* malaria in China has been significantly narrowed to Yunnan and Hainan provinces (WHO Western Pacific Region, 2016; Zhang et al., 2014b). However, imported *P. falciparum* malaria is on the rise, with a higher case-fatality rate reported than that for countries in north America and Europe (Zhou et al., 2016; Li et al., 2016b; Pavli and Maltezou, 2010; Checkley et al., 2012), leading to a threat to the health of travellers and challenges to the Chinese healthcare system, as well as increasing the potential for re-introduction and onward transmission in malaria-free receptive areas (Zhou et al., 2016; Li et al., 2015; Liu et al., 2014; Li et al., 2016b; Zhang et al., 2014b).

Quantifying the connectivity and drivers of international movements of malaria across continents and its risk factors for mortality has significance for the management of imported cases in receiving areas and development of mitigation strategies (Talisuna et al., 2012; Askling et al.,

2012). For example, identifying which regions tend to import cases from certain parts of Africa more than others means that local health facilities can be aware of risks and make more rapid diagnoses to save lives, undertake proactive interventions, such as prophylaxis to high risk travellers, and tailoring public health awareness campaigns (Tatem and Smith, 2010; Huang and Tatem, 2013). The majority of imported *P. falciparum* malaria cases in China have been reported in those with a history of labour-related travel to Africa (Zhou et al., 2016; Li et al., 2015; Liu et al., 2014; Li et al., 2016b), and thus, identifying potential high risk groups of travellers and the factors driving these risks facilitates both the tailoring of interventions (Walker et al., 2016; Mbacham et al., 2014) and an understanding of how these risks might impact future importation rates, supporting strategy design.

Despite the public health relevance, existing analyses of *P. falciparum* malaria connectivity and importation have only considered China in the context of neighbouring countries in Asia (Tatem and Smith, 2010; Huang and Tatem, 2013), and the patterns and driving factors of *P. falciparum* malaria importation from Africa to China have not been addressed. This analysis therefore sought to quantify the patterns of malaria importation to China from Africa and explore these as a function of key driving factors, including volume of air travellers, parasite prevalence in Africa, and investments from China. In addition, I examined the factors behind the high mortality rates in imported cases. Improved understanding of the importation phenomenon can enable the development of rational, evidence based interventions in China to reduce levels of importation, lower mortality rates and design strategies to limit onward transmission risks.

## 4.3 Methods

A comprehensive database of individual malaria cases imported from sub-Saharan Africa (SSA) to China between 2011 and 2015 was constructed. I also compiled covariate datasets covering Chinese investment in African countries, air travel volumes between China and African countries and malaria endemicity across SSA. These data were used to describe *P. falciparum* malaria importation networks from SSA to China and to examine driving factors for malaria importation and its mortality. The data assembly and analysis were described here, with further details provided in **Appendix C**.

### 4.3.1 Database compilation

The individual *P. falciparum* malaria case records reported during 2011–2015 in China were compiled (appendix **Table C-1**): cases were diagnosed according to the unified national diagnostic criteria, including clinically diagnosed and laboratory-confirmed cases (Wang et al., 2008). A

malaria patient was classified as an imported case if the individual travelled to a malaria-endemic country within the month prior to diagnosis, and the last country visited was taken as the origin of infection (China CDC, 2011).

To examine driving factors for malaria importation from SSA to China, data describing malaria endemicity, population movements and investments were collated. *P. falciparum* parasite prevalence estimates in 2-10 year-olds ($Pf PR_{2-10}$) across Africa from 2010 to 2015, were obtained from the Malaria Atlas Project (Bhatt et al., 2015), as an indicator of risk of infection for Chinese travellers lacking acquired immunity. Mean $Pf PR_{2-10}$ was calculated for each country after weighting by population density (using data acquired from the WorldPop project; www.worldpop.org) (Linard and Tatem, 2012). The volume of air passengers from SSA to China, predicted based primarily on publicly available datasets from 2010 under a generalized linear model framework in previous studies, was acquired (Linard and Tatem, 2012; Huang and Tatem, 2013). Travel data for direct, one-stop and two-stop flights were aggregated with the assumption that the air travel patterns, in terms of relative strength of connections from SSA to mainland China, were consistent during 2010-2015.

Investment data relating to Chinese ODA to SSA between 2006 and 2013 were obtained from AidData (china.aiddata.org), which collates information using a systematic and replicable approach to generate open-source, project-level data (Strange et al., 2015). Private-sector data are not available, and this study assume that investment from official and private sectors from China will follow the same patterns. The ODA flows used in this study include grants, technical assistance, concessional and non-concessional loans, debt relief, export credits, and other financial instruments. The ODA data were further grouped into six sectors: resource extraction (energy, mining and agriculture), infrastructure (transport, communications and utilities), health, education, multi-sector, and "other". The monetary amount was deflated from reported currency to 2011 U.S. Dollars (appendix **Table C-2**).

### 4.3.2 Statistical analyses

The epidemiologic characteristics of imported *P. falciparum* cases were summarized, and the crude 5-year incidence rates were estimated as the total number of cases divided by the population at 2010 year-end from census data in China. Based on the travel history of each case, the connectivity between SSA countries (origins) exporting *P. falciparum* and Chinese provinces (destinations) were defined by network modularity analysis (appendix **Table C-3**) (Newman, 2004). By mapping communities on the importation network, this analysis aimed to identify

groups of origin-destination pairs that show strong links in terms of movements of infected travellers.

The *Spearman's* rank correlation coefficient (ρ) (Lehman, 2005) was employed to test the relationship between the counts of imported cases and covariates (investment value from China, volume of air travellers from origin country to China, and *Pf*$PR_{2-10}$ in origin country) by sub-Saharan country. To explore the impact of ODA in each investment category on malaria importation from SSA, a generalized linear regression model was constructed, adjusting for parasite prevalence at origin and volume of air travellers from origin country to China. The Quasi-Poisson distribution was used due to over-dispersion (the counts of imported cases were positively skewed and subject to outliers) (Wedderburn, 1974). Model validation was performed using cross-validation with repeated random sub-sampling, iterated 1000 times (80% training and 20% testing). The strength of relationships was examined using R-square ($R^2$).

To examine potential risk factors (**Table 4-1**) for case fatality, bivariate and multivariate logistic regression were used, with mortality as a binary outcome from all imported *P. falciparum* malaria cases from SSA. All covariates found to be significantly associated with mortality (P<0.05) in univariate analysis were included in a multivariable logistic regression model, controlling for confounders age, sex and nationality. Version 3.2.3 of the *R* statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct statistical analyses, and the ArcGIS 10.3 (ESRI, Redlands, CA, USA) was used to plot the geographical distribution of cases and conduct spatial analyses.

## 4.4 Results

### 4.4.1 Characteristics of *P. falciparum* imported from SSA to China

From 2011 to 2015, a total of 8,653 *P. falciparum* malaria cases recorded in China were imported from SSA, with an overall 5-year incidence rate of 6.5 cases per one million persons. The median age of patients was 40 years (IQR: 31–46) with a strong male predominance (27.7:1) (appendix **Figure C-1** and **Table C-4**). Most cases were Chinese (97.0%) with a median duration of stay in SSA of 317 days (IQR 168–496), and 91.3% of cases were Chinese migrant workers. The distribution of imported cases in China varied, with the highest density in the counties of Guangxi province of southern China, Jiangsu and Anhui provinces in eastern China, and Sichuan provinces in western China (≥ 50 cases per one million persons) (**Figure 4-1** and appendix **Figure C-2**).

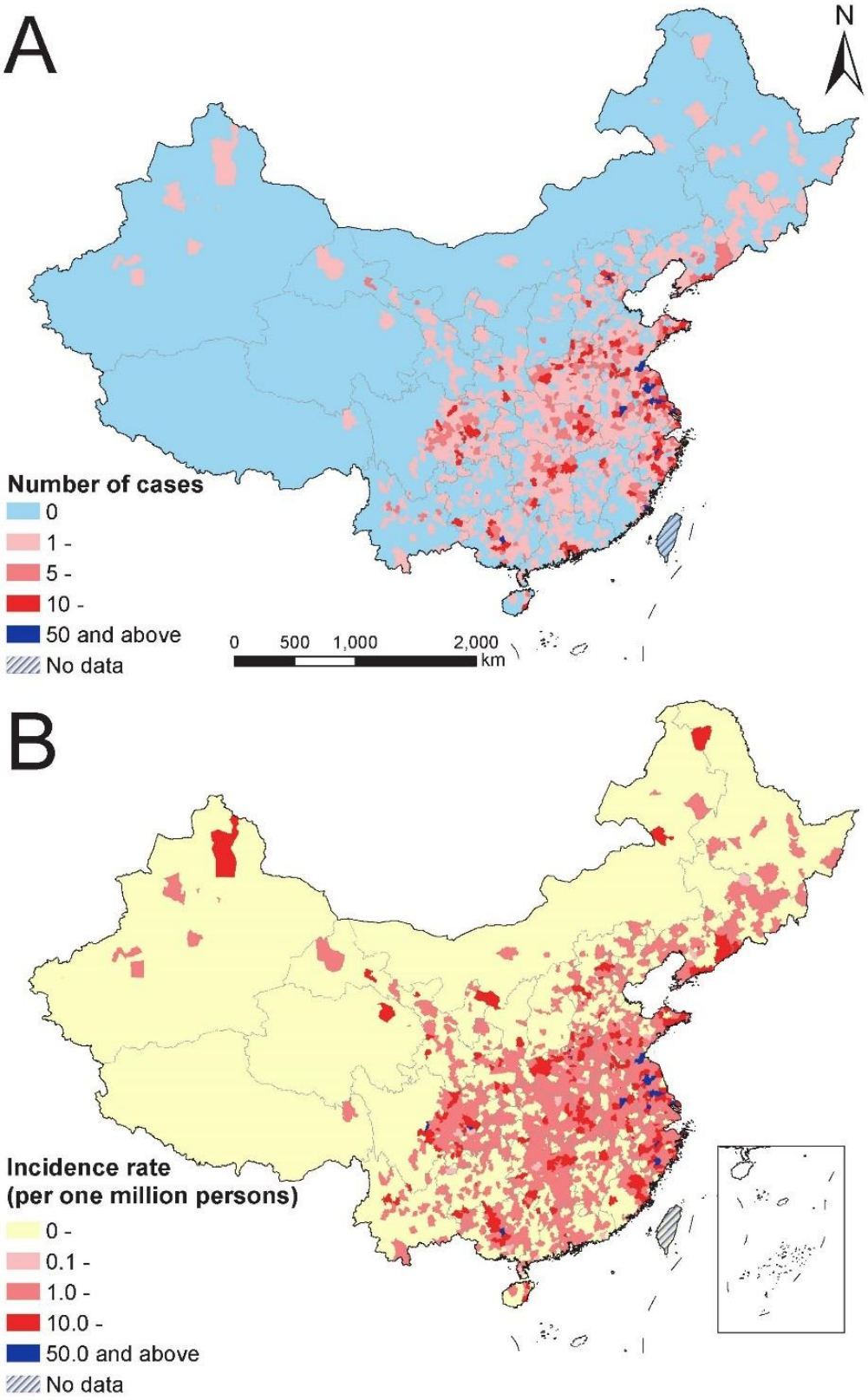



**Figure 4-1. Geographic distribution of imported *P. falciparum* malaria cases in China, 2011-2015**.

Note: (A) Number of cases by county. (B) Overall 5-year incidence rate per one million persons by county.

### 4.4.2 Connectivity and community of *P. falciparum* importation

In terms of connectivity, 41 sub-Saharan countries exported *P. falciparum* into China, with Ghana (20.0%, 1734 cases), Angola (15.4%, 1333), and Nigeria (12.4%, 1076) being the top three origins. All 31 provinces in mainland China reported imported cases, with Guangxi (17.9%, 1548), Jiangsu (15.7%, 1355), and Henan (7.8%, 677) provinces as top three destinations (appendix **Figure C-3**). The median number of imported cases was 4 cases (IQR 2–11) for each origin-destination pair, and four distinct communities were identified in this imported malaria flow matrix (**Figure 4-2** and appendix **Table C-3**). The first community included Ghana and Guangxi province: this link constituted the largest number of malaria case importations between SSA and Africa (1311 cases). The second community included five countries (Sudan, Ethiopia, Sierra Leone, Togo, and Rwanda) in Africa and two provinces (Xinjiang and Sichuan) in China; the third had ten countries with most in southern Africa and nine provinces with most in eastern China; others constituted the fourth community.

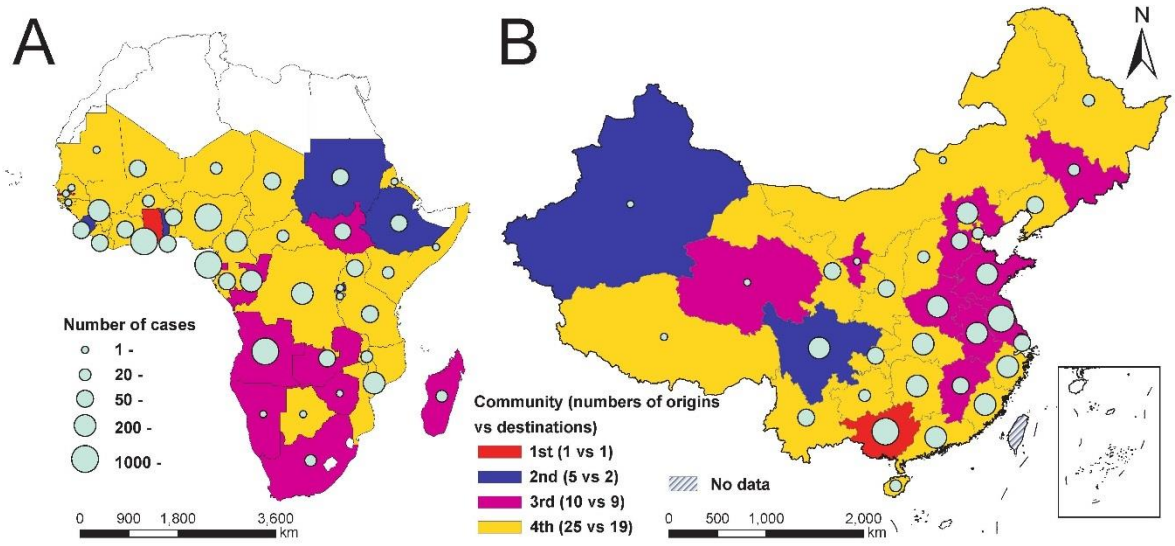



**Figure 4-2. Four communities of origin-destination networks of *P. falciparum* malaria importation from SSA to China.**

Note: (A) Origins (41 countries) in sub-Saharan Africa. (B) Destinations (31 provinces) in mainland China. The origin countries linked to a median of 18 provinces (IQR 8–23) in mainland China, with Angola was the most connective country linking to 30 provinces. Conversely, destination provinces in mainland China linked to a median of 21 countries (IQR 13–26), with Guangdong province was the most connective destination receiving cases from 34 countries. The score of modularity is 0.219 with a resolution of 0.9, and the list of origin-destination communities is provided in appendix **Table C-3**.

### 4.4.3 Driving factors of the importation phenomena

According to *Spearman*'s correlation coefficient, the number of *P. falciparum* cases exported from each SSA country to China was significantly associated with the volume of air passengers (median 2,080 persons, IQR 405-34,600; ρ=0.425, P=0.006), $PfPR_{2\text{-}10}$ (10.7%, 2.5%–30.6%; ρ=0.639, P<0.001), and total ODA from China (610.4 million $, 219.7–4,654.0; ρ=0.679, P<0.001) (**Figure 4-3** and appendix **Table C-5**). By sector of ODA, significant correlations were found between the numbers of cases and investment in natural resource extraction (P<0.001), infrastructure (P=0.002), health (P=0.001), education (P=0.054), multi-sector (P=0.034), and "other" (P=0.011) (appendix **Figure C-4** and **Table C-5**). Adjusting for the volume of air travellers and $PfPR_{2\text{-}10}$, the quasi-Poisson regression model fitted by total ODA explained 65.9% (IQR 63.3%-69.8%) of the deviance of the number of cases in the training dataset, and 57.7% (23.7%-79.7%) in cross-validation. In the model, the total ODA and $PfPR_{2\text{-}10}$ were positively correlated with numbers of cases with coefficients of 1.0 (IQR 0.96-1.13) and 0.70 (IQR 0.64-0.8), while volume of travellers had a negative coefficient of -0.45 (IQR -0.54 to -0.41) (appendix **Table C-6** and **Figure C-5**).

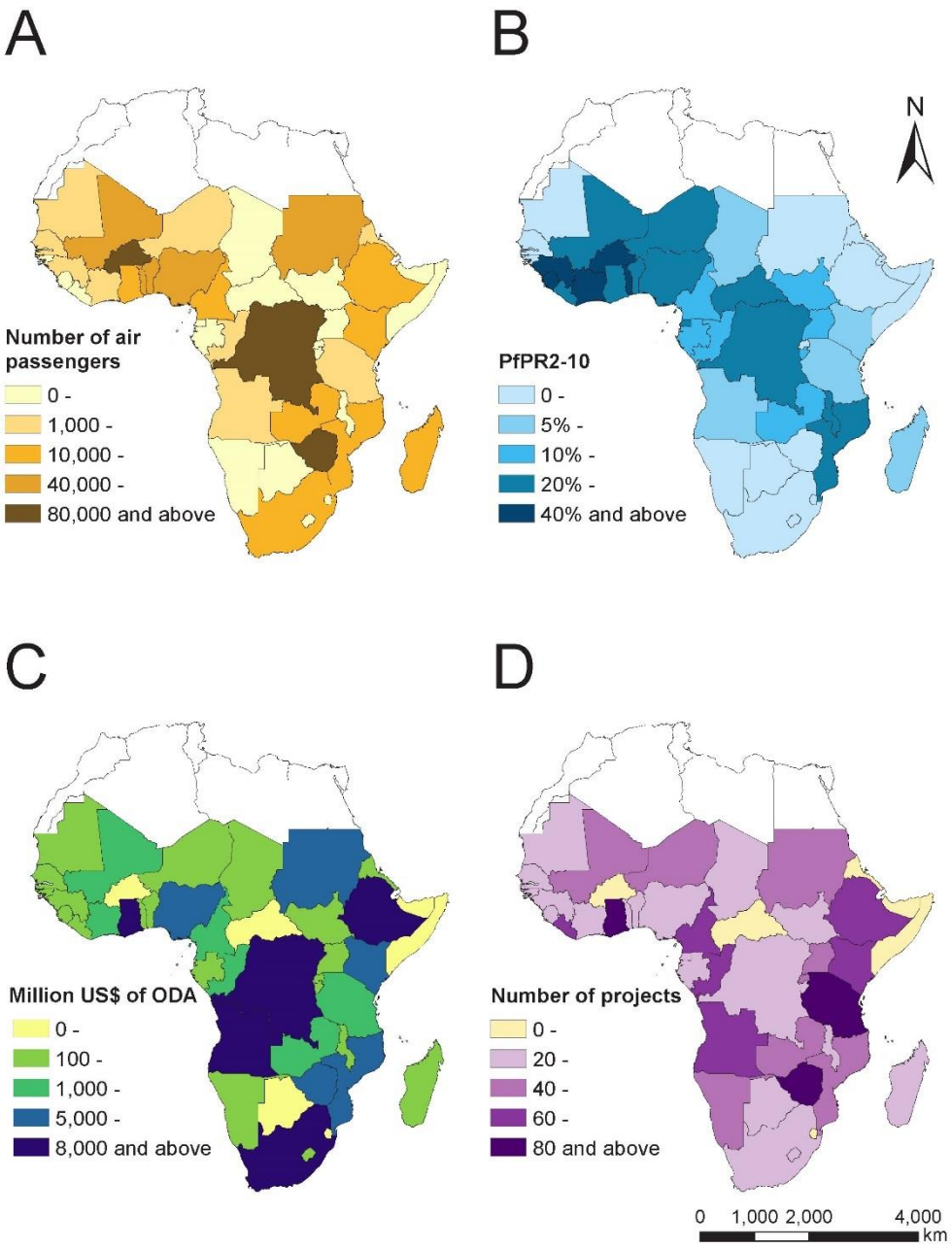



**Figure 4-3. Geographic distribution of air travellers from sub-Saharan Africa to China, malaria risk in Africa, and official development assistance from China by country.**

Note: (A) Number of air passengers from sub-Saharan countries to China. (B) Mean of *P. falciparum* malaria prevalence ($PfPR_{2\text{-}10}$) by country from 2010 to 2015. (C) The total amount of official development assistance (ODA) from China into sub-Saharan countries in 2006-2013. The monetary amount was deflated from reported currency to U.S. Dollars in 2011. (D) The numbers of projects of ODA from China into sub-Saharan countries in 2006-2013.

### 4.4.4 Risk factors for deaths in imported cases

The case-fatality rate was 11.3 per 1,000 cases (98 deaths in 8653 *P. falciparum* imported cases), and potential mortality risk factors with adjusted odds ratios (OR) and 95% CI are summarised in appendix **Table C-7**. The significant mortality risk factors identified by multivariable logistic regression model were mainly related to the capacity of malaria diagnosis and socio-economic status of cases , including the first-visit health institution at township level or lower (OR 2.6, 95%CI 1.5-4.2), >3 days between onset and diagnosis (2.2, 1.3-4.0), onset in January and February (2.3, 1.4-3.7), age > 50 years (2.4, 1.2-4.4), and cases from provinces with GDP per capita <=12,000 US$ (1.9, 1.0-3.9), low education (1.8, 1.0-3.3), and cases from communities 2$^{nd}$ to 4$^{th}$ identified by network modularity analysis above (**Table 4-1**).

**Table 4-1. Factors associated with risk of death in *P. falciparum* malaria cases imported from sub-Saharan countries to mainland China, 2011-2015.**

| Factor | OR (95% CI) | P value |
|---|---|---|
| Gender - Male | 2.1 (0.4, 37.4) | 0.469 |
| Age >50 years | 2.4 (1.2, 4.4) | 0.009 |
| Nationality - Chinese | 1.5 (0.3, 27.8) | 0.675 |
| Education - Primary or lower | 1.8 (1.0, 3.3) | 0.055 |
| Community 2$^{nd}$ of origin-destination | 6.2 (1.5, 41.2) | 0.022 |
| Community 3$^{rd}$ of origin-destination | 3.8 (1.1, 24.6) | 0.072 |
| Community 4$^{th}$ of origin-destination | 5.7 (1.6, 35.7) | 0.020 |
| GDP per capita by province <=12000 US$ | 1.9 (1.0, 3.9) | 0.048 |
| Onset in January and February | 2.3 (1.4, 3.7) | 0.001 |
| Duration from onset to diagnosis > 3 days | 2.2 (1.3, 4.0) | 0.006 |
| $PfPR_{2\text{-}10}$ in origins of SSA in 2010-2015 <= 20% | 1.5 (0.9, 2.4) | 0.140 |
| First-visit health institution at township level or lower | 2.6 (1.5, 4.2) | <0.001 |

OR: odds ratio; CI: confidence interval. Note: All potential risk factors (appendix **Table C-7**) statistically associated with mortality (P<0.05) found in univariate analysis and potential confounders (factors age, sex, and nationality) were introduced into multivariable logistic regression model to explore the significant risk factors. A total of 7,025 cases (81.2% of 8,653 cases) with complete data were included in this model. Communities of origin-destination were identified by network modularity analysis.

## 4.5 Discussion

The data and analyses presented here highlight an emerging route of infectious disease importation for *P. falciparum* malaria from Africa to China over the last half decade. The level of importation from SSA to China is contrary to the previous perception that China's imported malaria mainly originates in neighbouring countries of southeast Asia (Tatem and Smith, 2010; Huang and Tatem, 2013). Volume of air travel from African countries to China, prevalence of malaria in origin countries and Chinese investments in African countries were all associated with the number and distribution of imported cases, with diverse risk factors for mortality found. Malaria elimination strategies in China should account for these trends and challenges, and malaria diagnosis efforts and healthcare should target high risk groups and regions to reduce case-fatality rates.

### 4.5.1 Network modularity and drivers of malaria importation from Africa

The heterogeneity of communities mapped between origin SSA countries and destination Chinese provinces (e.g. the strongest linkage was between Ghana and Guangxi province), reflects the variability of connections and driving factors that exist. The presence of four distinct communities relates to patterns in investments and volume of workers moving between specific provinces in China and specific countries in SSA (Liu et al., 2014; Li et al., 2015). Moreover, the magnitude of importation from sub-Saharan countries was significantly correlated with the volume of air passengers (although the coefficient was negative in the regression model, after inclusion of other covariates), $PfPR_{2\text{-}10}$, and ODA. Recent ODA investments (in particular natural resource extraction projects) by Chinese companies (Monath, 2007), mainly state-owned enterprises, has led to growth in the number of migrant Chinese labourers in SSA, and those engaged in outdoor activities are at particularly high risk for malaria infection (Zhou et al., 2016; Li et al., 2015; Liu et al., 2014; Li et al., 2016b).

Furthermore, the lack of acquired immunity in Chinese citizens increases their vulnerability to *P. falciparum*, and their long stays (median 317 days) also increase the risk of exposure. Additionally, the labourers are generally poorly educated and lack awareness of the risk of malaria and personal protection against mosquito bites, and the majority of workers do not obtain anti-malarial medication prior to overseas travel (Zhang et al., 2011; Li et al., 2016b). Thus, targeting these workers, especially employees in resource extraction related businesses, with malaria awareness messages and provision of prophylaxis is likely to be an efficient strategy.

### 4.5.2 Risk factors of high mortality in infected travellers

I found that socio-economic factors were associated with case fatality in imported *P. falciparum* cases, with a higher fatality rate in those with a lower education level or from the provinces with lower GDP per capita. Most cases were migrant workers from less developed regions in China, who might lack knowledge of malaria prevention, experience poor healthcare accessibility, and delay treatment seeking behaviour (Tusting et al., 2013). Care-seeking from hospitals at county or higher levels in the first instance might reduce the risk of fatality as the low capacity for malaria diagnosis at township or lower levels, especially in non-endemic areas, is likely to contribute to high fatality rates. Moreover, higher case fatality rates occurred in imported cases were found during January and February, which normally covers the Chinese New Year holidays. In this period, delayed presentation to medical services, lower levels of hospital staffing over the holiday period, and delays in communication of malaria diagnosis from laboratory to physician may be contributory factors, and other possibilities include initial misdiagnosis of a febrile illness as influenza-like illness in the winter-spring epidemic season (Checkley et al., 2012; Legros et al., 2007). The results here therefore point towards the need to increase malaria diagnostic capacity in rural, low-level facilities, improve staffing over holidays, and provide health messages to encourage seeking treatment if ill after travel to Africa.

### 4.5.3 Destinations at risk of importation and onward transmission

There is heterogeneity in destination provinces for imported *P. falciparum* cases, with a high density in the Yangzi-river delta areas, the centre of Guangxi, and the east of Sichuan province (appendix **Figure C-2**). Further, Yunnan and Hainan provinces, where autochthonous transmission of *P. falciparum* malaria occurs, also have imported cases (WHO Western Pacific Region, 2016), which poses a challenge for national malaria elimination. *Anopheles* that can transmit malaria are found in both malaria-endemic areas of China and in areas where malaria has already been eliminated (Kiszewski et al., 2004), and climate change may change habitats and predominant vector species (Ren et al., 2016). Therefore, malaria importation is a continual and evolving threat which may undermine elimination efforts in China, especially in areas historically endemic for *P. falciparum* malaria and areas with high transmission suitability, where the vector may be present. It also becomes increasingly important to ensure that surveillance systems capture data on imported cases, and designing intervention strategies that target areas of high importation and have had past transmission. Future work should be focussed on estimating transmission potential in areas of high parasite importation.

### 4.5.4 Limitations and suggestions

There are some limitations to this study. First, the case data used were collected from passive public health surveillance. The data quality may be influenced by the key steps in surveillance including reporting methods, availability of health facilities and laboratory diagnostics, under reporting, completeness and accuracy of data over the years. Second, the economic data only include Chinese official financing without data of private-sector investments, and the original data source is likely of variable accuracy. Third, this analysis cannot capture the movement and detailed location of air travellers: a modelled travel dataset was used, although the relative patterns of air travel might have changed from 2010 to 2015. Moreover, the importation calculations are non-seasonal, constrained by the available malaria prevalence estimates, air travel and economic data.

Strategies for targeting *P. falciparum* importation from SSA related to Chinese investment-related travel will likely be different from those that concentrate on local transmission in China. The evidence of this study, by mapping these emerging routes and defining drivers of parasite dispersal by human carriers, suggests that national malaria elimination programs should account for labour travel-mediated malaria spread. Interventions for reducing this importation pathway should communicate risks to travellers to alter their behaviours and improve regional capacity for diagnosis and treatment to prevent death. Strong surveillance systems need to be maintained to sustain the status of elimination in malaria-free regions by monitoring the risk of importation and the transmission potential in risk areas and form a cornerstone of post-2015 elimination strategies in China (WHO, 2015a; Wesolowski et al., 2012).

# Chapter 5 Seasonal risks of mosquito-borne disease importation and onward transmission

## 5.1 Chapter summary

The global dispersal of infectious disease has accelerated due to increased human mobility. Few studies have quantified and validated changes in seasonal and long-term risks of international spread for mosquito-borne viral diseases. Taking dengue as an example, this Chapter presents an integrated series of analyses including examining seasonality and synchrony of dengue in South-East Asia (SEA) and China; modelling mobility using monthly international flight data; estimating the probability (0-1 scale) of dengue importation from SEA and leading to autochthonous transmission (introduced transmission) in China; and finally validating models using dengue incidence data.

This study found that the annual number of airline travellers from SEA into China has quadrupled over a decade (2005-2015). The probability of dengue importation from SEA into China each month has increased from 0.33 in 2005 to 0.73 in 2015, and the probability of introduced transmission has increased threefold. Malaysia, Singapore and Thailand were consistently amongst the highest risk countries for dengue importation into China, while Philippines, Sri Lanka and Maldives have been emerging as origins. The new destinations of potential introduced transmission in China were located at central and middle coastal areas. This analysis also found substantial seasonal variation and geographic expansion of the introduction: 295.1 million people live in cities with a risk of introduced transmission greater than 0.5 as of July 2015.

Following the huge growth of air traffic, dengue introductions from SEA into China have more than doubled over a decade, and cities across China are increasingly vulnerable to dengue importation and local transmission. Mitigation strategies should be tailored to tackle the increasing seasonal threats of imported infections into the neglected regions.

## 5.2 Background

The substantial growth and reach of human travel in recent decades has contributed to the global spread of infectious diseases (Gushulak and MacPherson, 2004; Tatem et al., 2012; Franco-Paredes and Santos-Preciado, 2006; Tatem et al., 2006a). In particular, air travel has allowed human hosts or carriers of pathogens to move long distances within the incubation period of infections (Stoddard et al., 2009), such as in the case of severe acute respiratory syndrome, swine

flu H1N1, Ebola virus disease, Zika virus disease, and Yellow Fever (Brockmann and Helbing, 2013; Khan et al., 2009; Rasmussen et al., 2016; Kraemer et al., 2017; Cowling and Yu, 2015). In addition, air travel has contributed to malaria importations from endemic into non-endemic countries (Tatem et al., 2017). Understanding the global dynamics of infectious disease has become a major 21st-century challenge, and mathematical models of the actual and potential spread of specific diseases can assist public health planning (Brockmann and Helbing, 2013; Bogoch et al., 2016a).

Three key factors are relevant in evaluation of the risk of disease importation into a host country: 1) the risk of a person acquiring the disease in the origin country; 2) the risk of a person traveling to an international destination while contagious; and 3) the likelihood of subsequent local transmission in the destination country. Previous modelling studies have generally focused on only one of these components, and the seasonal and long-term risks of international spread of infectious diseases are rarely quantified (Brockmann and Helbing, 2013; Bogoch et al., 2016a; Jelinek et al., 2002; Seyler et al., 2009; Massad et al., 2016; Gardner et al., 2012; Semenza et al., 2014). These three components were integrated in a single model of dengue, an acute viral disease transmitted by *Aedes* mosquitoes, from SEA into China.

Given the global expansion of *Aedes* mosquitoes (Tatem et al., 2006a), dengue has established itself worldwide in both endemic and epidemic transmission cycles, causing significant morbidity and occasional mortality (Shepard et al., 2016; Bhatt et al., 2013). In China, dengue remains a seasonally transmitted disease occasionally triggered by imported dengue virus (DENV). More than 90% of imported cases between 2005 and 2014 originated from SEA (Wu et al., 2010; Lai et al., 2015; Li et al., 2017; Sang et al., 2015a; Yang et al., 2014). Following China's economic boom in the last two decades, the number of Chinese citizens travelling abroad has increased from 5 million in 1996 to 128 million in 2015 (National Tourism Administration Data Center, 2014). The recent Belt and Road Initiative of China may further boost overseas investment and international travel (National Development and Reform Commission et al., 2015), which could also increase the number of importations of pathogens including DENV.

However, the seasonal patterns and changing risks of importation and subsequent transmission of dengue and other mosquito-borne pathogens over the last decade have rarely been quantified (Brockmann and Helbing, 2013; Khan et al., 2009; Kraemer et al., 2017). Based on the assumption that human mobility via commercial air travel is an important conduit for the spread of infectious diseases internationally, I examine the relationship between airline travel and DENV importation from dengue endemic countries in SEA into China between 2005 and 2015. I quantified and validated the seasonal risks and the trends of DENV importation and downstream transmission in

China, and identified geographic and seasonal patterns of emerging origin-destination (OD) routes. With rising concerns about global pathogen dispersal, this study provides evidence that could be used to mitigate the spread of other mosquito-borne viral infections including Zika, chikungunya, and Yellow Fever.

## 5.3 Methods

First, I analysed the incidence and seasonality of dengue in the origin (SEA) countries and in China. I then modelled human mobility using monthly international traveller flight data, and estimated the seasonal risk of DENV importation from SEA and the probability of importation leading to autochthonous transmission (introduced transmission) in China. Finally, I tested models using dengue incidence data reported in China.

### 5.3.1 Dengue incidence in SEA

Dengue surveillance data reported by 17 SEA countries (Cambodia, Bangladesh, Bhutan, India, Indonesia, Laos, Malaysia, Maldives, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Thailand, Timor-Leste, and Vietnam) in 2005-2015 were collated from Project Tycho and other publicly available sources (appendix **Table D-1**). Monthly data were available for nine countries: Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam. The monthly dengue data from these nine countries were used to estimate the risk of dengue importation into China. The wavelet analysis was performed to understand the periodicity of dengue transmission, the seasonal risk of DENV infection in SEA, and the coherency of seasonal patterns between SEA and China. To prepare data for wavelet analysis, the time-series data were detrended after imputing missing monthly data estimated from the annual number of cases and the average monthly proportion of cases in the same month of other years (**Appendix D** materials and methods) (van Panhuis et al., 2015; Torrence and Compo, 1998; Cazelles et al., 2008).

### 5.3.2 Dengue incidence in China

The data of imported and autochthonous dengue cases reported in China for 2005-2015 were obtained from the China Public Health Science Data Centre (www.phsciencedata.cn). As described previously (Lai et al., 2015), an imported case was defined as a dengue case for which the patient had travelled to a dengue-affected foreign country within 15 days prior to the onset of illness. As some cases in border regions may have been imported to China via land travel, cases reported by cities without an airport in border areas of Yunnan, Guangxi, Tibet and Xinjiang province bordering SEA countries were excluded.

### 5.3.3 International air travel from SEA into China

The flight itineraries of all travellers initiating trips from any airport in SEA with a destination in China between January 2005 and December 2015 were analysed, using data obtained from the International Air Transport Association (IATA). These itineraries included data on the initial airports of embarkation in SEA and all flight connections up to the travellers' final airport destination in China. The *Spearman*'s rank correlation coefficient was used to test the relationship between the volume of air travellers and the number of imported dengue cases by year and by country of origin. As most travels are temporary, and local residents of SEA and Chinese travellers returning from SEA might have different risks of dengue infection in SEA (Johansson et al., 2011), The yearly statistics of the nationality of travellers into China were obtained from the China National Tourism Administration to estimate the monthly volume of air travellers by nationality to further delineate the risk (**Appendix D** materials and methods).

### 5.3.4 Importation and introduced transmission risk estimates

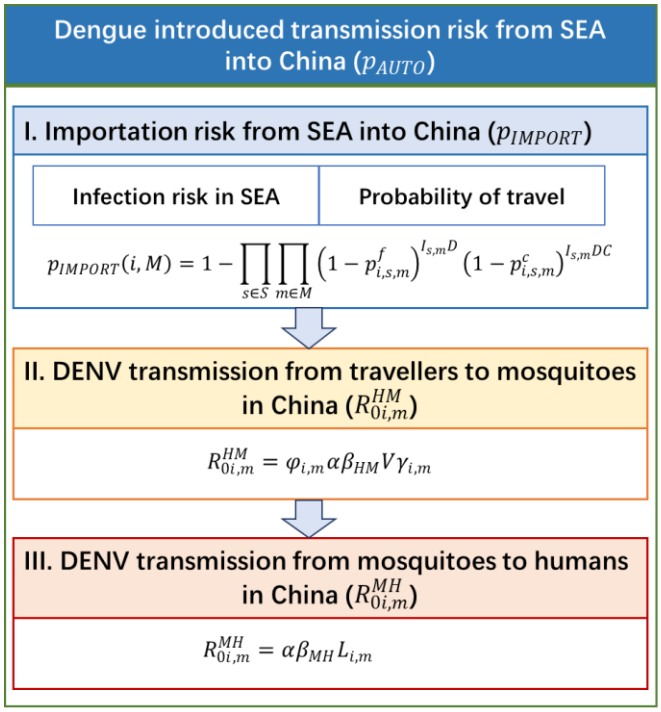
To quantify the seasonality and the risk of DENV importation and spreading within China, a branching process model was constructed for both importation and onward autochthonous transmission risk estimates (**Figure 5-1**). The probabilistic risk ranged from the lowest (0) to the highest (1) with the levels of likelihood for occurrence defined as: almost certain (a probability of 0.95-1.0), highly likely (0.70-0.94), likely (0.30-0.69), unlikely (0.05-0.29) and very unlikely (<0.05) (appendix **Table D-2**) (WHO, 2012b). More details on these models and parameters used are available in the **Appendix D**.

#### 5.3.4.1 Importation risk

The probability ($p_{IMPORT}$) of at least one DENV-infected traveller importation from SEA into China and being infectious after arriving China was estimated as a single-step binomial process. The probability of importation was dependent on: (1) the risk of infection in SEA country where dengue transmission has occurred, defined by the incidence of dengue in each month and duration of stay in each country; (2) the monthly probability of non-Chinese residents in SEA traveling into China and that of Chinese residents travelling to and returning from SEA; and (3) the duration of infection in humans as the length of the intrinsic incubation period for DENV plus the infectiousness period after onset, referring to the duration when an infected person could travel and still be infectious after traveling (Johansson et al., 2012; Johansson et al., 2014).

#### 5.3.4.2 Introduced transmission risk

The monthly risk ($p_{AUTO}$) of an introduced DENV infection leading to autochthonous transmission in China was defined as the probability in a three-step process (**Figure 5-1**): (1) infected airline travellers from each SEA country entering provinces or cities in China (importation risk, $p_{IMPORT}$); (2) mosquitoes acquiring the virus from that traveller in China; and (3) infected mosquitoes infecting at least one other person in China (Johansson et al., 2012; Johansson et al., 2014). The basic reproduction number ($R_0$) of DENV in China was characterized as a *Poisson* process of infectious mosquitoes produced per infected human ($R_{0i,m}^{HM}$) and humans infected per infectious mosquito ($R_{0i,m}^{MH}$). Additionally, global *Aedes* mosquito suitability maps were also used to exclude areas in China unsuitable for the vector (Kraemer et al., 2015).




| Parameters | |
|---|---|
| $I_{s,m}$ | Incidence in origin $s$ and month $m$ |
| $D$ | Average duration of infection in humans |
| $C$ | Duration of Chinese stay in SEA |
| $p_{i,s,m}^{c}$ | Prob. of Chinese travelling to SEA and returning home |
| $p_{i,s,m}^{f}$ | Prob. of SEA residents travelling to China |
| $\varphi_{i,m}$ | Mosquitoes per person in location $i$ and month $m$ |
| $\alpha$ | Daily biting rate |
| $\beta_{HM}$ | Human-to-mosquito transmissibility |
| $\beta_{MH}$ | Mosquito-to-human transmissibility |
| $V$ | Human infectious time |
| $\gamma_{i,m}$ | Proportion of mosquitoes surviving the extrinsic incubation period in $i$ and $m$ |
| $L_{i,m}$ | Period of an infectious mosquito surviving in $i$ and $m$ |

**Figure 5-1. The structure of model and its parameters.**

#### 5.3.4.3 Model Parameters

Parameters included infection probability in SEA, travel capacity, infectious period, and entomological indicators of *Aedes* mosquitoes, and temperature-dependent parameters (**Figure 5-1**) were estimated using average monthly minimum temperature data obtained from the China Meteorological Data Service Centre (Johansson et al., 2012; Johansson et al., 2014). The uncertainties of parameters were incorporated into models using a global sensitivity analysis by sampling 10,000 sets of parameters from likely ranges. Then $p_{IMPORT}$ and $p_{AUTO}$ were computed with all 10,000 parameter sets and reported the mean and SD to account for uncertainties (**Appendix D** materials and methods).

#### 5.3.4.4 Validation

The risks defined by models were compared with the occurrence of imported and locally acquired DENV infections reported in the corresponding location and month in China. A receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to measure the accuracy of models and illustrate their diagnostic ability with a prioritized cut-off of risks.

## 5.4 Results

### 5.4.1 Overall incidence of dengue in SEA and China

The volume of airline travellers from 17 SEA countries into China nearly quadrupled from 3.6 million in 2005 to 13.8 million in 2015, and has a positive correlation with corresponding dengue importation by year and by origin (both $p<0.001$) (**Figure 5-2** and appendix **Figure D-1**). Seasonal patterns of dengue transmission in SEA were seen with annual amplitude positively correlated to latitude of each country ($p=0.01$), and there was a significant synchrony between dengue infection in SEA and importation to China (**Figure 5-3** and appendix **Figure D-2**, **Figure D-3** and **Figure D-4**). Moreover, seasonal epidemics in China, with an apparent one-month lag, were also highly coherent with dengue transmission in SEA and importation into China (appendix **Figure D-2** and **Figure D-3d**).

### 5.4.2 Importation risk of dengue from SEA into China

Nine countries with available monthly incidence data had a total of 63.4 million travellers (85.8% passengers from SEA) into 165 cities in China from 2005 to 2015. Malaysia, Singapore and Thailand were consistently amongst the highest probability countries for DENV importation. Philippines, Sri Lanka and Maldives are emerging as origin of importation due to increasing travel (appendix **Figure D-5**, **Figure D-6** and **Figure D-7**). The average provincial importation risk in China increased from likely (0.33, SD 0.35) in 2005 to highly likely (0.73, SD 0.33) in 2015 with a jump since 2013 (**Figure 5-4a**). Moreover, the number of cities with an average monthly risk greater than 0.5 (importation occurs likely) increased from 16 (9.7% of 165 cities) in 2005 to 42 (25.5%) in 2015 with most emerging destinations in central and western China (**Figure 5-5**). Meanwhile, the OD routes with risk greater than 0.5 have risen from 23 (1.5% of all 1485 OD pairs) in 2005 to 92 (6.2%) in 2015 (**Figure 5-6** and appendix **Table D-3** and **Table D-4**). The highest importation risk was in August (mean 0.50, SD 0.39) when 29 (17.6%) cities had an average risk greater than 0.5 (**Figure 5-4c** and appendix **Figure D-8**).

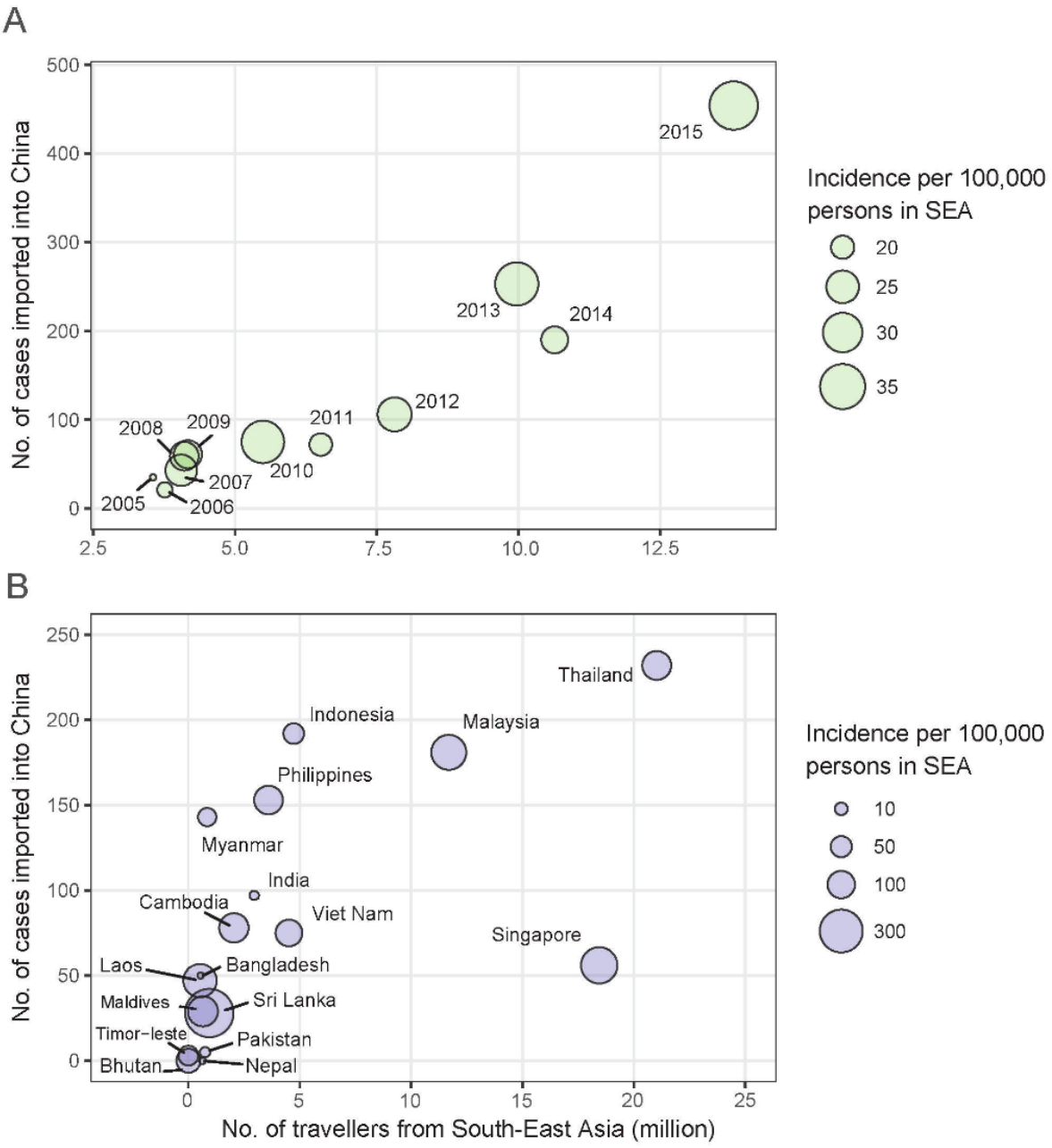



**Figure 5-2. Airline travellers and dengue importation from SEA into China, 2005-2015**.

Note: (A) Yearly volume of airline travellers vs number of dengue cases imported from SEA into China; (B) Airline travellers vs dengue cases imported from SEA into China, aggregated by country.

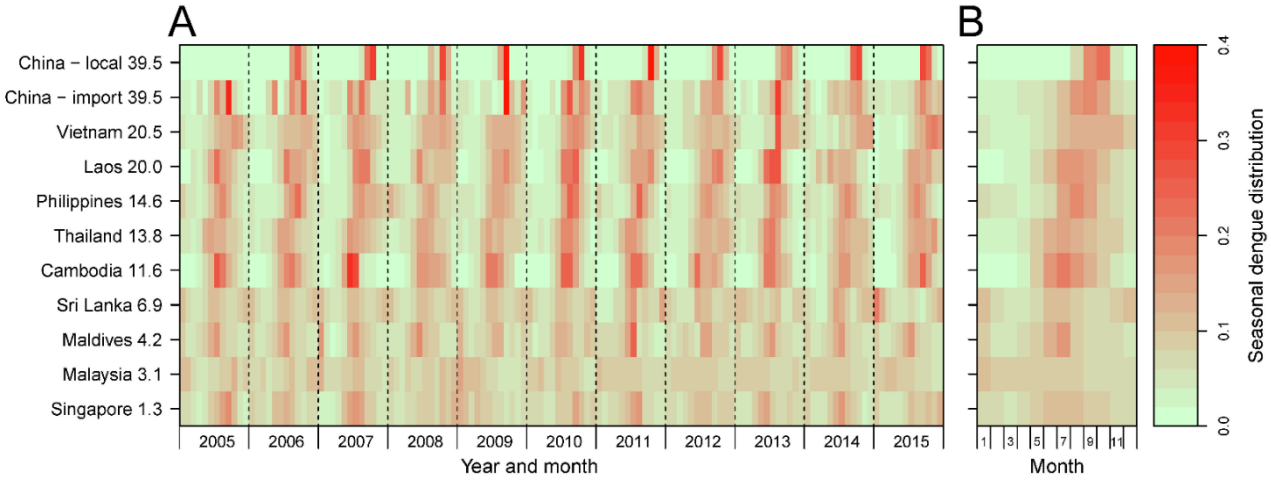



**Figure 5-3. Heatmaps of dengue monthly incidence data reported in SEA countries and China, sorted by the latitude of capital city of each country, 2005-2015**.

Note: (A) Time series of monthly dengue cases, standardized by the total number of cases reported in each year and country. (B) Average seasonal distribution of dengue by country, plotted as the proportion of cases reported in each week of the year from 2005 to 2015. The data of "China – import" represents the cases imported from nine SEA countries. The data of "China – local" represents the autochthonous cases in China.

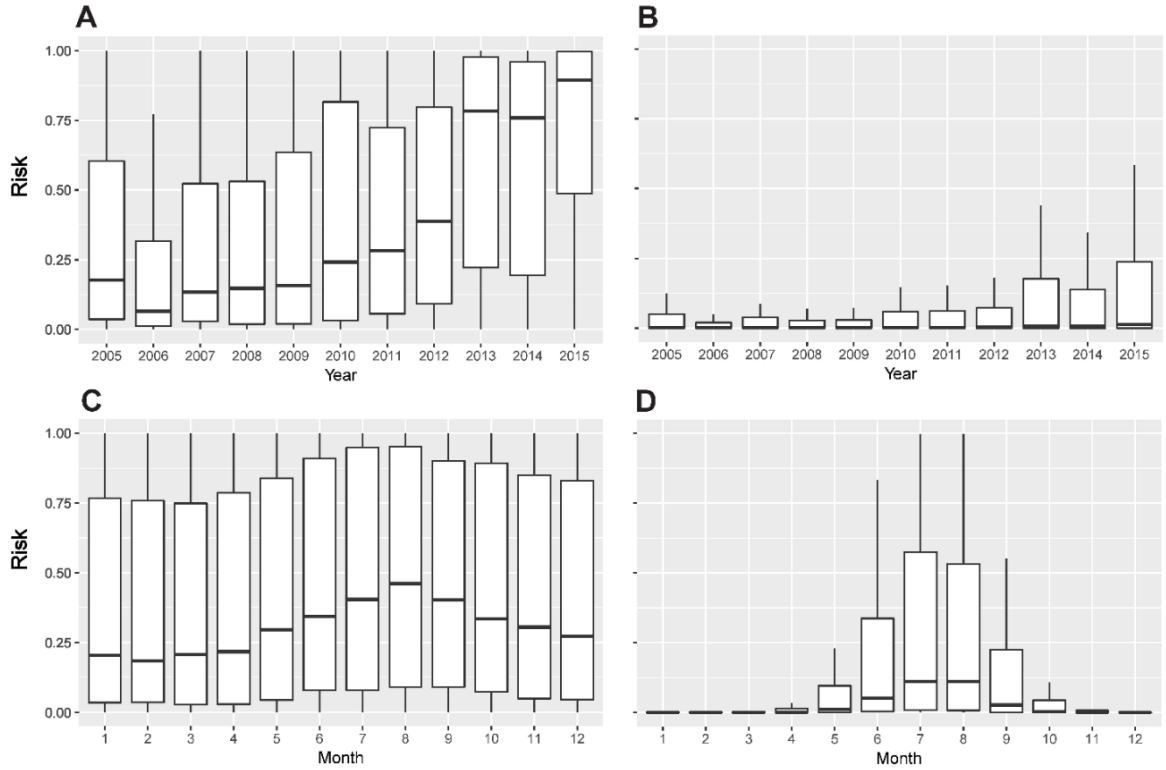



**Figure 5-4. Boxplots of dengue importation and introduced transmission risks from SEA into mainland China, 2005-2015**.

Note: (A) Importation risk by year. (B) Introduced transmission risk by year. (C) Importation risk by month. (D) Introduced transmission risk by month. The probabilistic risk presented here is the

likelihood of occurrence, ranging from 0 (the lowest probability) to 1 (the highest). Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) in SEA with available data of monthly DENV incidence were included here.

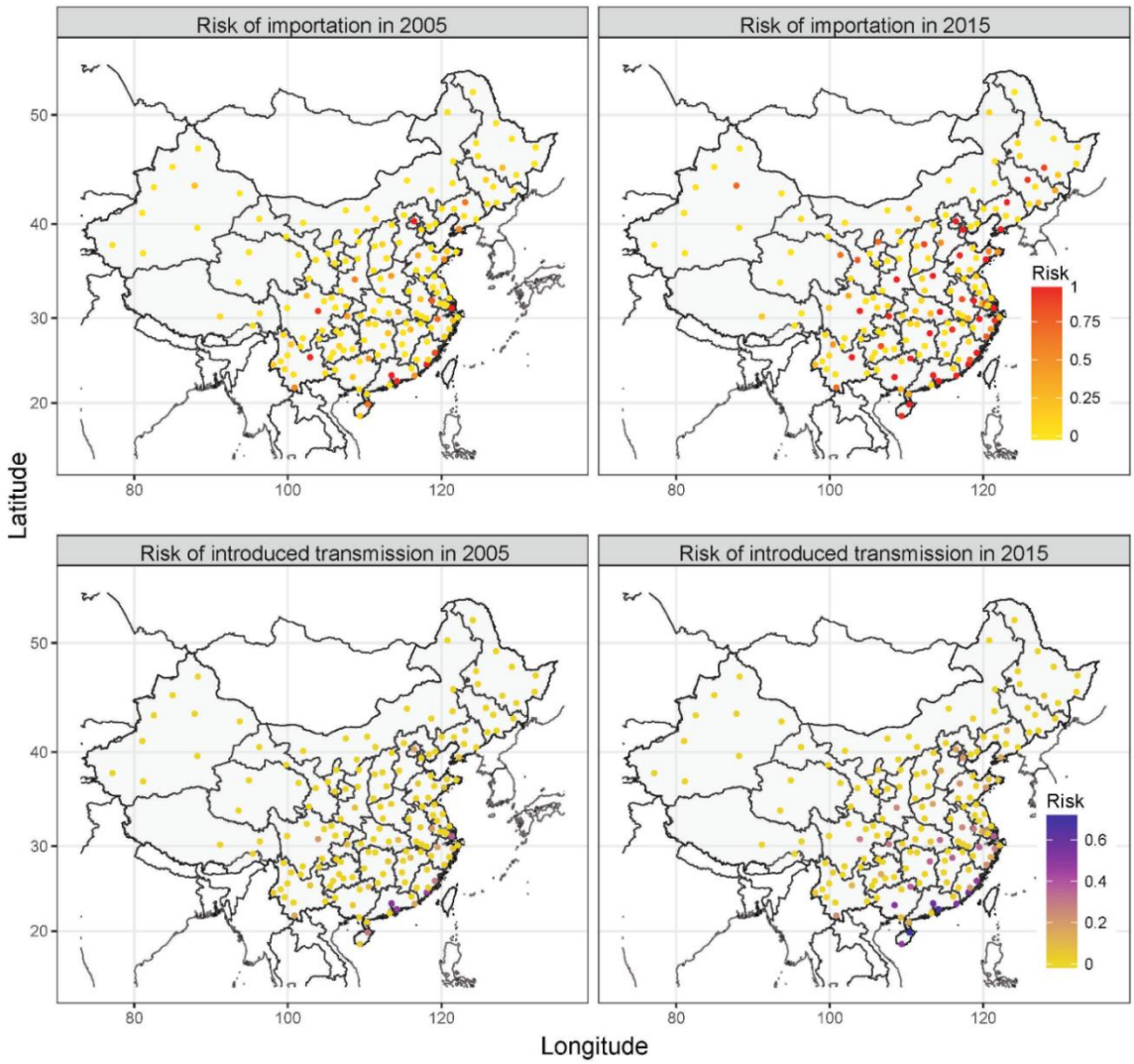



**Figure 5-5. Risks of dengue importation and introduced transmission from SEA into cities of mainland China in 2005 and 2015**.

Note: The probabilistic risk (0-1 scale) is the likelihood of importation and introduced transmission. Nine SEA countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

### 5.4.3 Seasonal risk of introduced transmission in China

Subsequently, the average provincial monthly risk of dengue introduced transmission has also risen, tripling from a low of 0.06 (SD 0.17) in 2006 to 0.18 (SD 0.30) in 2015 (**Figure 5-4b**). In 2005, Guangzhou was the only city with a risk greater than 0.5, while in 2015, seven other cities (Shenzhen, Haikou, Xiamen, Nanning, Shantou, Sanya and Fuzhou) had a risk greater than 0.5 (**Figure 5-5**). Significant seasonal variation was also found, with high risk during warm season of

May-October, but very unlikely transmission in other months (**Figure 5-4d** and appendix **Figure D-9**). Compared to cities with intensive importation in cold regions of northern China, e.g. Beijing and Shenyang, the lower latitude cities such as Guangzhou, Shenzhen and Haikou had higher risk and wider seasonal period of introduced transmission (**Figure 5-7** and appendix **Figure D-10**). Moreover, there were 295.1 million people in 31 cities with an introduced transmission risk greater than 0.5 in July of 2015, increasing from 80.3 million in nine cities with the same risk in July of 2005.

The dynamics of dengue in SEA, air travel from SEA, and the $R_0$ of DENV local transmission in China have been changing the high-risk routes for introduced transmission. For instance, Thailand-Fuzhou and Malaysia-Hangzhou routes have had increasing risks since 2010, and cities in central China and middle coastal regions, e.g. Chengdu, Fujian and Hangzhou, have been emerging as destinations with an increasing risk of introduced transmission (appendix **Figure D-11** and **Table D-5** and**Table D-6**). Additionally, comparing model outputs with dengue incidence reported in China at a provincial level, the models performed robustly with a AUC of 0.85 and a prioritized cut-off risk of 0.86 (sensitivity: 0.77; specificity: 0.82) to diagnose DENV importation from SEA into China, and with an AUC of 0.92 and a cut-off of 0.14 (0.88; 0.83) for introduced transmission estimate (appendix **Figure D-12**).

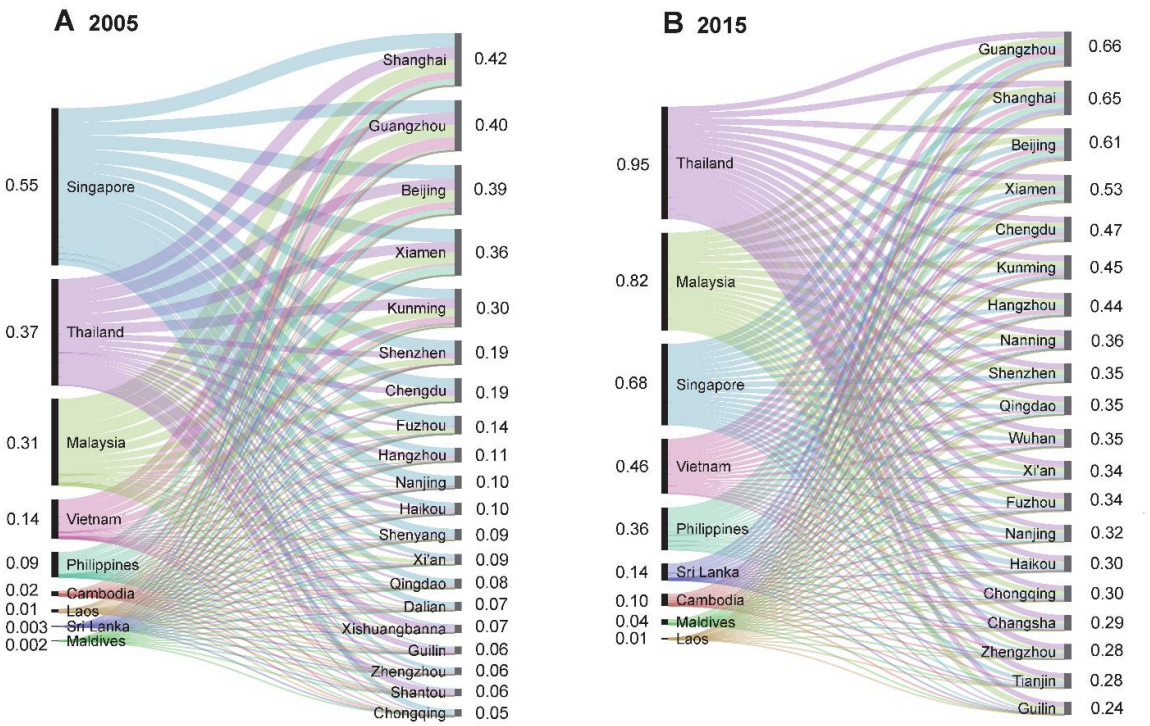



**Figure 5-6. Origin-destination routes of dengue importation from SEA into top 20 high-risk cities of China in 2005 and 2015.**

Note: (A) Importation routes and risks in 2005. (B) Importation routes and risks in 2015. The risk means the likelihood of occurrence, ranging from 0 (the lowest probability) to 1 (the highest). The

numbers in the figures are the average risk of all exportation/importation routes from each origin/destination. The thickness of line for each route is scaled to the importation risk from the lowest (thinnest) to highest (thickest) within each figure.

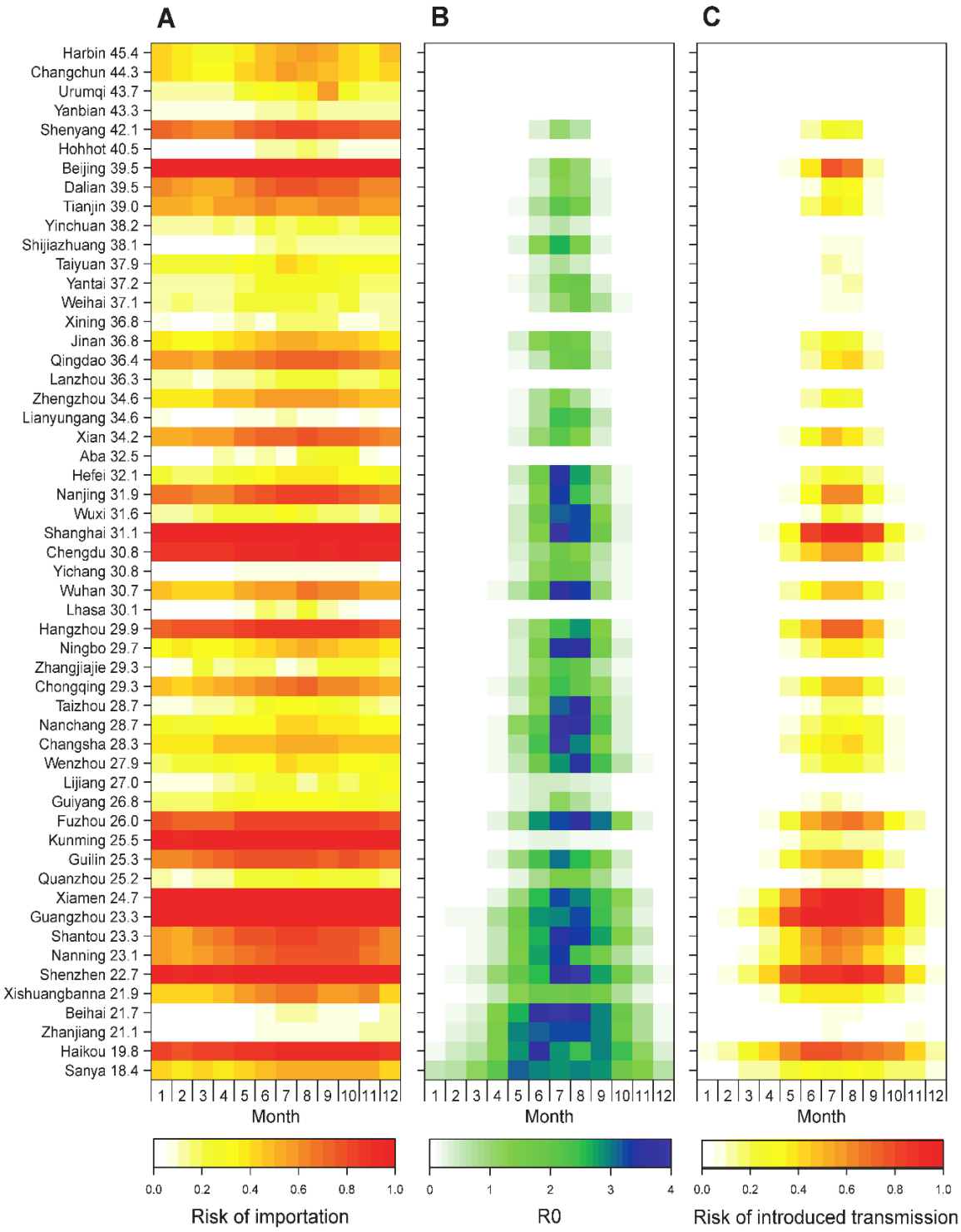



**Figure 5-7. Average monthly risks of dengue importation and introduced transmission from SEA into cities of China in 2005-2015, sorted by the latitude of cities**.

Note: Only cities with the average monthly importation risk >0.05 from 2005 to 2015 were presented here. The number behind the name of each city is the north latitude. (A) Risk of importation. (B) Basic reproduction number (R0). (C) Risk of introduced transmission.

## 5.5 Discussion

Being able to identify areas at risk for introduction and spread of pathogens in a timely manner is critical for tailoring strategies for preparedness and response, e.g. allocation of finite health and human resources, and to alerting people to the risk of disease (Lai et al., 2015). This study has identified likely locations in China that are most susceptible to dengue importation from SEA and onward transmission, and revealed the seasonal patterns and increasing risks as well as the highlights of the heterogeneity in OD network of DENV spread by air travel over a decade. The spatiotemporal explicit introduced transmission risks from particular routes identified here are valuable evidence for designing a mitigation strategy, in particular for, currently neglected, high-risk destinations, such as Chengdu, Wuhan, Nanjing.

### 5.5.1 Dengue infection risk in SEA and importation into China by air travel

The geographic, historical, and cultural ties between SEA countries and China, as well as the increasing economic and tourism links, likely contributes to the volume of international travellers. This analysis found the epidemiological significance of these ties has been demonstrated in the context of dengue importation from these countries into China in the last 11 years. The accelerated increases in the volume of international Chinese travellers over time have also increasingly facilitated dengue importation from SEA. Additionally, the dramatically increasing risk of dengue importation from Sri Lanka since 2010 might be attributed to the increasing investment and workers from China (Kitano and Harada, 2015), while the rising risk from Maldives might be related to the increasing tourists from China (National Tourism Administration Data Center, 2014).

The seasonal risk of dengue infection in SEA for travellers might relate to changing density of *Aedes* mosquitoes and their capacity for DENV transmission, along with the seasonal fluctuation of temperature and precipitation. Hence, travellers from low-latitude countries might have less seasonal variation of dengue infection risk due to less variability in meteorological conditions (van Panhuis et al., 2015). Comparing to local residents in SEA, Chinese travellers with shorter stays in SEA should presumably have a lower risk of infection. Moreover, the megacities in China, e.g. Beijing, Shanghai and Guangzhou with regional aviation hubs, have consistently received large volumes of international air passengers, leading to high risk of dengue importation from SEA. However, the rapid growth of travel abroad for tourism, business and migrant workers from cities in central and southwest China could promote pathogen importation: this phenomenon has been seen for malaria importation from Africa and SEA into these areas (Lai et al., 2016).

### 5.5.2 Increasing introduced transmission risk in China

The increase in imported DENV from SEA has also escalated the subsequent transmission risk in China, with Guangdong, Yunnan and Fujian province frequently reporting outbreaks following dengue importation, and now, other provinces, (e.g. Henan, Shandong and Shanghai) reporting autochthonous cases of dengue for the first time in the last decade (Lai et al., 2015; Shanghai Municipal Commission of Health and Family Planning, 2017). Moreover, the increasing importation risk, climate change and spatial spread of *Aedes* aegypti are all raising concerns about the potential for year-round autochthonous transmission of dengue and other flaviviruses in several tropical and subtropical regions of China (e.g. Hainan, Guangdong and Yunnan) (Guo et al., 2016). The variation in DENV serotypes introduced from different origins over time is especially relevant considering the potential for adverse effects from dengue haemorrhagic fever after infection with a different serotype of DENV (Lai et al., 2015). Public health authorities and partners in areas with high risk of onward transmission should consider implementing appropriate interventions at an early stage of potential seasonal transmission, e.g. intensive surveillance, vector control, laboratory diagnosis, clinical management, and health education in travellers.

### 5.5.3 Limitations and conclusions

The findings in this study must be considered in the context of several assumptions and data limitations. First, the quality of incidence data of dengue in SEA and China might be influenced by key steps in public health surveillance or reports including the case definitions, reporting methods, availability of healthcare and laboratory diagnosis, under reporting, and the completeness and accuracy of data reported. Second, the risk of dengue infection in SEA was assumed to be identical across each country for each month, regardless of the levels of immunity in Chinese travellers and local residents. Third, *Ae. albopictus* was regarded as an equally competent vector as *Ae. aegypti* for dengue virus, with similar temperature dependency and extrinsic incubation period. Fourth, this study did not account for the importation by different DENV serotypes from SEA and internal travel by land or by water in China. Furthermore, the estimates of this study did not address variability in the public health and health-care capacity and resources for different years and locations in China and SEA countries in response to dengue. For instance, clinicians in newly-affect locations might have never seen a dengue case before due to the high proportion of asymptomatic infections and potentially insufficient capacity for testing and diagnosis, all of which may cause a lag between the observed extent of spread and the true extent of spread estimated here.

Nonetheless, the models and findings presented here leverage previous work suggesting that a branching process model of spread over a heterogeneous network could capture most of the variability in a more complex stochastic simulation model (Johansson et al., 2012; Johansson et al., 2014). Moreover, the retrospective validation showed the predicted seasonal risk of DENV into China coincided with a surge in the number of imported cases and volume of airline travellers arriving into China from SEA countries with reported dengue virus activity. The model framework of this study is flexible to incorporate new forms of data and vector-borne diseases, and may be used to project into the future given different scenarios and to illustrate the effects of different control methods. In addition, it is crucial for making relevant high-quality data available and accessible for up-to-date importation risk assessment and prompt response at national, regional, and global level.

In conclusion, the findings in this Chapter indicate that dengue importation and onward transmission risks in China have increased since 2005, with significant spatiotemporal heterogeneity. This offers valuable information to support time-sensitive public health decision-making, especially for the high-risk regions with emerging OD routes of dengue importation and onward autochthonous transmission. As global populations become increasingly mobile, pathogens are continuing to emerge and spread into novel populations at risk. Modelling frameworks, such as the one outlined in this study, are needed to help combat this spread by moving from purely reactive measures, to proactively pre-empting outbreaks. Furthermore, understanding vulnerable areas and populations allows for efficient use of scarce resources for surveillance, preventative measures and treatment.

# Chapter 6 Conclusions and recommendations

## 6.1 Conclusions

Based on comprehensive longitudinal datasets and a contemporary multidisciplinary approach, the analyses presented here demonstrate that the spatiotemporal patterns for two mosquito-borne diseases, malaria and dengue, have changed significantly in mainland China. The geographic extent of autochthonous malaria in China has shrunk significantly due principally to malaria elimination activities, while the incidence of locally transmitted dengue has increased dramatically since 1990. However, the incidence of imported malaria and dengue has increased with an expanded geographic range. The importation of mosquito-borne diseases into China is driven by transmission rates and patterns in origin countries, increasing travel due to tourism and migrant workers, as well as investment patterns and economic ties. Moreover, taking dengue as an example, increasing seasonal risk and spatiotemporal heterogeneity of disease importation has been found, with increasing onward transmission risk following importation from Southeast Asia into China. These findings provide valuable evidence to support the allocation of resources and formulate strategies to mitigate the risks associated with mosquito-borne disease introduction.

## 6.2 Limitations of this study

The limitations in this study have been detailed in the research chapters, but several points are summarized and emphasized here. Firstly, the incidence data used here were collected from routine passive public health surveillance. The data quality might be influenced by key steps in surveillance including case definitions, reporting methods, availability of health care and laboratory diagnostics, treatment seeking behaviours, classification of disease severity, and the completeness and accuracy of data reported or announced. These might influence the recognition of spatiotemporal patterns of mosquito-borne disease in China. Secondly, a limited set of driving factors and covariates for disease importation and transmission were explored in this study due to data availability constraints. For instance, economic data only included Chinese official financing without data of private-sector investments into Africa, which might overemphasise the factors included here and ignoring other factors, e.g. the socioeconomic growth and urbanization in China. Thirdly, with the assumption that airports mainly service the population in their cities or provinces, this study did not capture the onward movement of air travellers landing in China. Moreover, international overland and shipping travel flows were not considered here, which might also contribute to local, regional and global connectivity and spread of infectious diseases.

Fourthly, all travellers were assumed to be susceptible to all species or strains of pathogens investigated here, regardless of the levels of immunity in travellers, which might overestimate the risks of infection and importation in travellers. Finally, different travel patterns (e.g. length of stay) and the travel purpose (e.g. business, tourism, labour) might be associated with different demographic and behavioural features of travellers, e.g. gender, age, education and occupation, which could also influence risk of infection and importation, but were not included in the models to estimate importation risk.

## 6.3 Recommendations for mitigating mosquito-borne disease importation

The evidence presented in this study highlights real progress in understanding the changing epidemiology of imported and indigenous malaria and dengue in China, the role of different factors in the importation of mosquito-borne diseases, and the changing seasonal risks of disease importation and onward transmission. This provides valuable evidence to support the allocation of resources and strategic planning to mitigate the risks associated with pathogen importation. In view of the growing threat of imported mosquito-borne diseases and invasion of vectors, China should formulate corresponding prevention and control strategies and technical guidance for mitigating infections in travellers, improving the capacity of screening, diagnosis and treatment, reducing the risk of morbidity, hospitalization and death, and strengthening surveillance and investigation capabilities to enable timely interruption of potential local spread (WHO Regional Office for the Western Pacific, 2017a; 2017b). Here, a set of strategic approaches are proposed (**Table 6-1**):

**Table 6-1. Principal strategic approaches and core activities for mitigating mosquito-borne diseases importation and onward transmission in China.**

| Strategic approach | Core activity |
|---|---|
| 1. Preventing infections in travellers | • Health notices for travellers<br>• Protecting travellers against mosquito bites<br>• Prophylaxis and preventive therapies<br>• Awareness-raising and health promotion in travellers<br>• Healthier staff - Working with major companies or organisations that are involved in overseas labour |
| 2. Early detection of imported infections at entry points | • Screening at entry points for imported infections<br>• Risk communications to cabin crew and travellers |

| Strategic approach | | Core activity | |
|---|---|---|---|
| | | • | Disinsection on high-risk routes and seasons |
| 3. | Enhanced integrated surveillance | • | Entomological surveillance |
| | | • | Epidemiological surveillance |
| | | • | Risk factor identification |
| 4. | Prevention and control of local transmission | • | Preparation for disease outbreak response |
| | | • | Improvement of diagnosis and case management |
| | | • | Sustainable vector control |
| 5. | Capacity development and international cooperation | • | Development of human capacity and resources |
| | | • | Regional and bilateral coordination |

### 6.3.1 Preventing infections in travellers

By identifying high-risk origins and defining drivers of pathogen dispersal by human carriers in this study, interventions for reducing travellers' infection risk in endemic countries should be communicated to alter their behaviours. Targeted education and awareness campaigns in travellers are potentially one of the most cost-effective approaches to reducing numbers of mosquito-borne disease infections and mitigating the potential impacts. In terms of risk of exposure in endemic countries, public health communication should also target to travellers with different travel purpose (business, tourism, and labour, etc.). These can involve focusing on:

Travel notice: Based on the findings of the seasonal risk of infection and importation from endemic countries, travel notices relating to specific travel destinations should be designed and disseminated to travellers at the early stage of and during the high-risk season, along with up-to-date risk assessment by collating and monitoring the epidemics of mosquito-borne diseases in endemic regions. For example, different levels of notice (i.e. watch, alert, and warning) could be provided with both levels of risk to travellers and recommended preventive measures to take at each level of risk (**Table 6-2**).

**Table 6-2. Levels of notice for international travellers.**

| Notice Level | Traveller Action | Risk to Traveller |
|---|---|---|
| **Level 1:** Watch | Reminder to follow usual precautions for this destination | Usual baseline risk or slightly above baseline risk for destination and limited impact to the traveller |
| **Level 2:** Alert | Follow enhanced precautions for this destination | Increased risk in defined settings or associated with specific risk factors |
| **Level 3:** Warning | Reduce or delay travel to specific destination | High risk to travellers, and certain high-risk populations may wish to delay travel to these destinations |

Adapted from: Centres for Disease Control and Prevention, USA. Travel Health Notices. 4 Nov 2017 wwwnc.cdc.gov/travel/notices#travel-notice-definitions

(1) Protecting travellers against mosquito bites: As most imported cases in China were Chinese travellers or workers, it is important to inform and protect Chinese against mosquito bites while travelling to endemic countries, to reduce the risk of infection, including choosing screened or air-conditioned holiday accommodation, sleeping under a bed net, using repellent and wearing long, light coloured, loose clothing, when possible. Particularly, these measures should be promoted and implemented in the Chinese workers who generally have a long stay abroad in sites of construction or energy extraction.

(2) Prophylaxis and preventive therapies: Before travelling overseas to endemic regions, travellers are suggested to seek medical advice, e.g. appropriate vaccinations for yellow fever. Moreover, due to the high risk of mortality of *P. falciparum* in Chinese workers found in this study, guidelines on malaria chemoprophylaxis for international travellers should be developed in China, and travellers may be prescribed antimalarial medicines as prophylaxis if travelling to malaria-endemic areas to reduce malaria infection risk.

(3) Health promotion and campaigns: To increase awareness regarding malaria and dengue importation and potential transmission in China, public information campaigns can be conducted in high-risk regions estimated in this study. This approach could be also useful for both prospective travellers and health care providers of returning travellers (Semenza et al., 2014). Moreover, because air travel is one of principal approaches of disease importation which has been examined in this study, travel agency and airline could inform outgoing passengers to specific destinations with elevated risk for mosquito-borne

disease when air tickets are purchased, so as to prompt prophylaxis acquisition for malaria or to increase awareness of bed net usage and insecticide application.

(4) Healthier workers: Chinese labourers usually work overseas on construction sites and experience poor living conditions with a lack of access to mosquito control measures, and they generally lack the knowledge of mosquito-borne infections and personal protection against mosquito bites (Li et al., 2016b). They should be trained on the prevention for mosquito-borne diseases by local health departments. Additionally, this approach could also include working with major companies/organisations that are involved in overseas labour to build health promotion activities, or supply of preventative measures to staff, which is a win-win approach: more healthy staff more productive workers.

### 6.3.2 Early detection of imported infections at entry points

If a particular route is identified as a high-risk source of imported mosquito-borne diseases, the fever screening program (e.g. self-reported fever, infrared thermal camera scanning, or tympanic temperature) of arriving passengers, is as a means of stopping or slowing the spread of disease (Kuan and Chang, 2012; Cho and Yoon, 2014; Monge-Maillo et al., 2015). Such an approach has been implemented for dengue, malaria, Ebola and many other diseases, whereby blood samples were taken and tested for pathogens from incoming air travellers, though it often represents a costly and often inconvenient option, especially for the detection of asymptomatic infections in travellers (Monge-Maillo et al., 2015; Selvey et al., 2015). Moreover, the asymptomatic infections or the latent stages will not be captured by entry screening, but outbreak-associated communications for travellers at border entry points or on incoming flights may be a more effective approach to mitigate the international spread of communicable diseases (Selvey et al., 2015).

(1) Cabin crew should be informed about specific routes and times of year where the risks of passengers harbouring mosquito-borne infections may be relatively high, by making them aware of symptoms and treatments, and raising vigilance for identifying potential sick passengers.

(2) As the seasonal risk of importation found in this study, passengers returning from specific destinations at certain times of year of the potential elevated risks of contracting mosquito-borne diseases should be informed on incoming flights or entry points about how to report their travel-mediated health issues and contact local health department. These may improve treatment seeking behaviour and facilitate rapid diagnosis in travellers, should them become sick upon return home.

(3) Disinsection is unlikely to impact the spread of mosquito-borne pathogens by air travellers, but it may serve a role in preventing the spread of vector species and other invasive insects (Mier et al., 2017), and the practice is likely to make more economic and logistical sense on certain routes and seasons found here regarding to the importation of disease-carrying mosquitoes and invasion of vectors.

### 6.3.3 Enhanced integrated surveillance

Strong surveillance systems for mosquito-borne diseases are needed to monitor the risk of importation and the onward transmission potential by detecting infected travellers, vector distribution and local outbreaks, as contemporary surveillance data are essential for the design and evaluation of preventive or control action, and for measuring the effectiveness of interventions (WHO, 2017e). As *Anopheles* and *Aedes* mosquitoes are widely distributed in China, China should establish integrated surveillance systems, including entomological surveillance, epidemiological surveillance and risk factor identification, for the early detection of epidemics, monitoring of vector populations and risk factors and measurement of the disease burden (**Figure 6-1**).

(1) For malaria, a capable surveillance system should be maintained to monitor residual transmission in endemic areas, and ensure the sustainment of the elimination status in malaria-free regions to form a cornerstone of post-2015 elimination strategies in China.

(2) For dengue, the risk of onward transmission is related to the number of imported infections and the entomological and environmental variables. Therefore, the regions with high risk but still in the absence of locally transmitted cases should conduct routine surveillance of vectors and other risk factors to monitor the probability of local transmission. In regions with sporadic and seasonal locally transmitted infections, rapid case investigation and active surveillance are needed to determine whether the infection is imported or locally acquired, which should be accompanied by locally focused vector surveillance and control to limit the risk of transmission to other residents at the early stage of the event.

Moreover, seasonal or sentinel integrated surveillance can be enhanced and tailored to certain regions and time periods. The findings in this study can also help to pragmatically schedule case (importation and introduced transmission) and vector surveillance (vector presence, absence, recent introduction, and density) in the most crucial time and at high-risk areas, as well as formulating a mechanism for prioritising in space and time if relative resources are limited.

Additionally, an integrated strengthened surveillance can benefit control of malaria, dengue and many other mosquito-borne diseases at the same time (Berg et al., 2013).

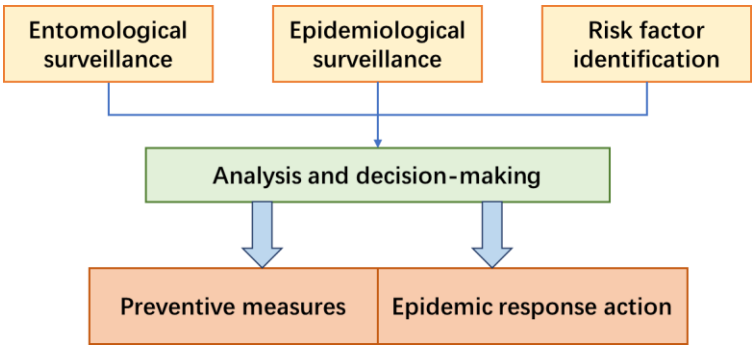



**Figure 6-1. The role of integrated surveillance in the planning for disease prevention and control.**

### 6.3.4 Prevention and control of local transmission

In areas where *Anopheles* and *Aedes* mosquitoes have become firmly established with endemic malaria historically reported and locally transmitted dengue sporadically occurred respectively, it is important to minimize the impact of imported infections and risk of local transmission by core activities as below.

(1) In areas with high risks of importation and onward transmission, local physicians and clinical practices should be informed in terms of vigilance for specific illnesses in patients with certain travel histories to enable rapid diagnosis, early reporting and reduce the risk of local secondary transmission. If introduced infections are found, effective communication with clinicians and communities should be conducted to implement effective control measures.

(2) Preparation for outbreak response: Cities where the competent vector for malaria and dengue are established should have preparedness plans to respond to early signs of outbreaks as soon as locally transmitted cases have been confirmed. Preparedness plans should cover hospitalization plans, emergency vector control, advocacy, community mobilization, logistics, and monitoring and evaluation, which should be field-tested together with partners from local government and other sectors (WHO, 2012a; Berg et al., 2013).

(3) Improvement of diagnosis, case management and notification: Early diagnosis and effective treatment is central to reducing the severity and mortality of mosquito-borne infections and achieving a successful clinical outcome. Laboratory confirmation is important to exclude other diseases and to ensure proper symptomatic and supportive

treatment. Moreover, the information of cases and their geo-locations collected by clinics and hospitals should be communicated to the emergency response unit to assist in detection and management of outbreaks. Additionally, the capacity of molecular and morphological techniques is critical for differentiating between indigenous and introduced species and for determining the origin of pathogens (WHO, 2012a; Berg et al., 2013).

(4) Sustainable vector control to prevent transmission: In the direct vicinity of autochthonous cases, emergency vector control will be necessary to stop transmission. Proactive reduction of vector populations and human-vector contact in the high-risk season will reduce the risk of seasonal transmission of mosquito-borne diseases. To achieve a gradual and sustainable reduction in vector breeding and human-vector contact, a combination of top-down and bottom-up approaches should be deployed to integrate chemical, mechanical and biological vector control methods and personal protection methods with the active participation of communities and involvement of relevant sectors and agencies (WHO, 2012a; Berg et al., 2013). Additionally, vector control by larvicide and larval habitat management around airports at specific times of year may represent a relatively cheap option to reduce the risk of the establishment of invasive vectors.

In addition, communities and local residents should also be mobilized (for example, by the health sector and nongovernmental organizations) to help prevent the spread of infection through source reduction campaigns and education on disease symptoms and personal protection measures.

### 6.3.5 Capacity development and international cooperation

The implementation of mitigating measures depends on the existing institutional infrastructure, financial resources and human capacity to conduct and coordinate prevention, surveillance and control activities, and international cooperation is also necessary to address the cross-border problem.

(1) Development of human capacity and resources: A needs assessment should be carry out first to identify the existing capacity and resources could be utilized for prevention, surveillance and control of imported and locally transmitted mosquito-borne diseases and their vectors. Then, the requirements in terms of additional training, staffing and infrastructure development could be further identified (WHO, 2012a; Berg et al., 2013). In accordance with the outcome of the needs assessment, central and local governments in China should mobilize adequate human and financial resources and training for

developing and strengthening the core capacity. Additionally, investment needs to be maintained and ideally increased to target resources towards the remaining high-burden or high-risk regions of introduced transmission.

(2) Regional and bilateral coordination: The introduction of mosquito-borne diseases and invasions of vectors are cross-border problems. Coordination between countries and at regional level is, therefore, necessary to prevent the problem spreading into new territories. Rapid communication between origin-destination countries and international agencies (WHO and Member States) is crucial for setting up a prompt emergency response, and regional organizations (such as WHO regional office) play an important role in the provision of technical support and establishing or strengthening the collaborative networks (WHO Regional Office for the Western Pacific, 2017a; 2017b; WHO, 2012a).

Additionally, stakeholder engagement is crucial to implement the strategic approaches proposed in this study. To increase the impact of this thesis, a 2-page brief of the main findings and conclusion and recommendations can be summarised and disseminated to the relevant stakeholders including the health authorities or institutes, e.g. Chinese MOH, China CDC and WHO, and funding agencies, e.g. Global Fund, China Natural Research Foundation, Wellcome Trust, and Gates Foundation. Beside the publications of this study, attending relevant national and international conferences to present research results are also necessary.

## 6.4 Future research

Further multi-disciplinary studies on the dynamics of mosquito-borne disease, population movement and vector and pathogen introductions are required. In particular, future work should aim to incorporate information on temporal variations in passenger numbers, human populations at risk, stopover risks, climate change, urbanization, intra-species competition, breeding site availability, disinsection and onward land transport. The impact and interactions of different strains or species of vector and diseases should also be quantified, and methods for the early detection and control of mosquito-borne disease importation and onward transmission should be developed and tested (Tatem et al., 2012). More sophisticated statistical and mathematical models should be developed to integrate spatially explicit data on pathogen evolution, population movement, vector invasion and environmental variability. This could provide a means to describe, explain and predict the phenomena of disease importation, as well as deepen our understanding of fundamental evolutionary and ecological processes for mosquito-borne disease, which is also vital for tailoring mitigation strategies (Huang and Tatem, 2013). In particular, the aspects listed below could be further investigated:

(1) Defining the correlation between importation and autochthonous malaria by field investigation and modelling, and quantifying the impact of importation on the residual transmission and elimination of malaria in China.

(2) Exploring the role of putative drivers of the large outbreak of dengue in 2014 - a historical record since dengue became a notifiable disease in China in 1989. This could incorporate modelling and mapping of the risk of importation and local transmission, and extracting lessons about how it could have been averted so as to inform future outbreak prediction and mitigation.

(3) Investigating the distribution, invasion and dynamics of vectors in China and their entomological parameters. Little is known about the mechanisms of vectors for malaria and dengue to adapt to new environmental conditions or their potential to invade new areas in China.

(4) The importation and onward transmission risks for different serotypes of dengue virus or species of *Plasmodium* malaria and their impacts on the clinical severity or potential co-infections during onward transmission in China.

(5) The mechanism and control strategy of cross-border importation for mosquito-borne disease and further spread by road, especially in the regions along the China-Myanmar border.

(6) Defining the potential impact of the Belt and Road Initiative on the dispersal of mosquito-borne diseases and their transmission risks.

(7) Defining the impact of climate change and the massive urbanization, land use change, health care reform and increases in wealth of China on the transmission of mosquito-borne diseases.

(8) As the threat of antimalarial drug resistance and anti-microbial resistance grows, identifying the potential routes of drug-resistant malaria and insecticide-resistance vector spread.

(9) Developing up-to-date online risk assessment tools or mobile phone apps to provide travellers with near seasonal risk mapping for early quantification of mosquito-borne disease infection risk in endemic area and importation.

(10) Developing and formulating comprehensive and new strategy to tackle the challenges of increasing pathogens and vectors importation, by incorporating medical and physical

science, and a more multi-disciplinary outlook/approaches that may cover behavioural and social sciences, financing and economics, management science, etc.

(11) Modelling to explore the costs/benefits of all the different options of control and prevention outlined in the sections above.

In conclusion, based on longitudinal data and a contemporary modelling approach, my study presents initial efforts for China to integrate disparate data (disease incidence, vector distribution, air travel network and itinerary, climate data, and investment etc.), to investigate the patterns and risks of mosquito-borne disease importation from other countries into China. This study represents the first research for China to integrally define the spatiotemporal patterns, complex network analysis and driving factors of vector-borne infectious disease importation, together with how the importation and introduced risk changed seasonally over last decade.

# Appendices

# Appendix A Supplementary information for Chapter 2

**Table A-1. Variables in the individual dataset of dengue cases from 2005 to 2014.**

| Variables | Definition/classification | Completeness |
|---|---|---|
| ID | A unique 8-digital number for each case. | 100% reported |
| Gender | Male and Female | 100% reported |
| Age | The interval time from the date of birth to the date of onset | 100% reported |
| Address | The living address (township level) of case when the case was recorded. | 100% reported |
| Address code | A unique 8-digital number for each town | 100% reported |
| Type of diagnosis | Probable case (clinical diagnosed case) and confirmed case (laboratory confirmed case) | 100% reported |
| Serotype | DENV-I, II, III and IV (if applicable) | 0.8% reported |
| Hospitalization | Inpatient or outpatient (Non-mandatory report) | 30.9% reported |
| Nationality | Chinese or foreigner | 100% reported |
| Type of case | Autochthonous case, or case imported from other country, or case imported from other province in China | 100% reported |
| Origin Country | The country where the case infected with dengue virus or had an exposure history during incubation period. | 99.4% reported |
| Origin province of China | For case imported from other province in China, the province where the case infected with dengue virus or had an exposure history during incubation period. | 100% reported |
| Date of onset | The date of illness onset | 100% reported |
| Date of diagnosis | The date of diagnosis as a probable or confirmed dengue case | 100% reported |

| | | |
|---|---|---|
| Date of report | The first date of reporting to dengue surveillance system | 100% reported |
| Date of Death | The date of case death, if applicable. | 100% reported |

**Table A-2. Summary of diagnosis criteria and classification for dengue.**

| Variable | Guidelines for Diagnosis, Treatment, Prevention and Control for Dengue Fever | Diagnostic Criteria and Principle of Management of Dengue Fever | Diagnostic Criteria for Dengue Fever |
|---|---|---|---|
| **Issued by** | Chinese Ministry of Health | Chinese Ministry of Health | Chinese Ministry of Health |
| **Date issued** | 20 June 1988 | 23 November 2001 | 28 February 2008 |
| **Date enforced** | 20 June 1988 | 1 May 2002 | 1 September 2008 |
| **Epidemiologic linkage** | **1.1** Living in or travel to a dengue endemic country/region or presence at location with ongoing outbreak within previous 15 days of dengue-like illness. | **1.1** Living in or travel to a dengue endemic country/region or presence at location with ongoing outbreak within previous 15 days of dengue-like illness, and reported being bitten by mosquito within 5-9 days of illness onset. | **1.1** Travel to a dengue endemic country/region within previous 14 days of dengue-like illness<br>**1.2** Around the place of residence or place of work (e.g. 100m radius), there have been dengue case(s) within one month. |
| **Clinical description** | **2.1** **Dengue fever (DF)**: Sudden onset, chills and fever (39-40°C within 24-36h, a small number of patients showed a biphasic fever). Headache, retro-orbital pain, joint pain, myalgia, arthralgia and lumbago, and a few patients develop abdominal pain. Fatigue and loss of appetite. Flushed skin on face, neck and chest, and conjunctival congestion, superficial lymphadenopathy, and tourniquet test positive. A total white blood cell and platelets | **2.1** Sudden onset, chills and fever (39-40°C within 24-36h, a small number of patients showed a biphasic fever), with symptoms such as fatigue, nausea and/or vomiting.<br>**2.2** Aches and pains (e.g., headache, retro-orbital pain, joint pain, myalgia, arthralgia).<br>**2.3** Flushed skin on face, neck and chest, and conjunctival congestion.<br>**2.4** Superficial lymphadenopathy. | **2.1** Sudden onset, fever (39-40°C within 24-36h, someone shows biphasic fever); severe headache, retro-orbital pain, myalgia, arthralgia and fatigue; flushed skin on face, neck and chest, and conjunctival congestion, etc.<br>**2.2** Rash: measles-like rash, scarlatiniform rash, and/or needle-like hemorrhagic rash in the limbs, trunk, head and face in the course of illness (days 5-7); itching; no scaling; continued 3-5d. |

| Variable | Guidelines for Diagnosis, Treatment, Prevention and Control for Dengue Fever | Diagnostic Criteria and Principle of Management of Dengue Fever | Diagnostic Criteria for Dengue Fever |
|---|---|---|---|
| | counts are normal or decrease. Diversity-rash in limbs and trunk, some patients with bleeding tendency.<br>**2.2 Dengue hemorrhagic fever (DHF)**: a dengue fever case develops the following symptoms: sporadic bleeding points in the limbs, face, armpits, mucous membrane after 2-3 days of illness onset, then become ecchymosis; bleeding of nose and mouth, bleeding in more than one organ of gastrointestinal tract, uterine, vaginal and urinary tract. Liver enlargement. Hematocrit increased more than 20%; Low platelets (< 100,000 cells per $mm^3$).<br>**2.3 Dengue shock syndrome (DSS)**: a dengue hemorrhagic fever case develops worse condition: clammy skin, restlessness, cyanotic lip, rapid and weak pulse, narrow pulse pressure ≤20mm Hg (2.7kPa) and undetectable in blood pressure, etc. | **2.5** Measles-like rash, scarlatiniform rash, and/or petechiae in the limbs, trunk, head and face in the course of illness (days 5-7); itching; no scaling; continued 3-5d.<br>**2.6** Encephalitis, encephalopathy, or meningitis-like neurological disorders.<br>**2.7** Bleeding tendency (tourniquet test positive): occurs in the course of illness (days 5-8) with gingival bleeding, nose bleeding, gastrointestinal bleeding, subcutaneous hemorrhage, hematuria, hemoptysis, and vaginal bleeding, and/or chest and abdominal cavity bleeding, etc.<br>**2.8** Multiple organ bleeding.<br>**2.9** Liver enlargement.<br>**2.10** Shock. | **2.3** Bleeding tendency (tourniquet test positive): petechia, ecchymoses, purpura and injection site bleeding, or bleeding from the mucous membranes of mouth and nose, gastrointestinal bleeding, hemoptysis, hematuria and vaginal bleeding in the course of illness (days 5-8).<br>**2.4** Massive hemorrhage of gastrointestinal tract, or chest and abdominal cavity bleeding, or intracranial hemorrhage.<br>**2.5** Liver enlargement, pleural or pericardial effusion.<br>**2.6** Shock syndrome: clammy skin, restlessness, rapid and weak pulse and narrow pulse pressure < 20mm Hg (2.7kPa) and undetectable in blood pressure, oliguria etc. |

| Variable | Guidelines for Diagnosis, Treatment, Prevention and Control for Dengue Fever | Diagnostic Criteria and Principle of Management of Dengue Fever | Diagnostic Criteria for Dengue Fever |
|---|---|---|---|
| **Laboratory tests** | **3.1** Clinical routine tests of complete blood count, platelet, bleeding and clotting time; for severe cases, test hematocrit, and do additional tests according to the conditions.<br>**3.2** Cell culture isolation of dengue virus (DENV) by *Ae. albopictus* C6/36 cell, or 1-3 day-old newborn mice, or the larvae of Toxorhynchites.<br>**3.3** Serologic tests positive: for paired acute and convalescent serum specimens, ≥4-fold rise in titer by complement fixation (CF), hemagglutination inhibition (HI), or neutralization test (NT); for a single acute phase serum specimen, 1:32 or higher in titer by CF, or 1:1280 or higher in titer by HI, or index ≥50 by NT. | **3.1** Thrombocytopenia (< $100x10^9$/L). White blood cell count decrease, lymphocytes and mononuclear cell count increase.<br>**3.2** Hematocrit increased more than 20%.<br>**3.3** IgG anti-DENV positive in a serum specimen.<br>**3.4** IgM anti-DENV positive in a serum specimen.<br>**3.5** IgG anti-DENV ≥4-fold rise in titer in paired acute and convalescent serum specimens.<br>The serologic tests included enzyme-linked immunosorbent assay (ELISA), HI, CF, immunofluorescence method (FA/IFA), Dengue blot (DB), and NT.<br>**3.6** Cell culture isolation of DENV by *Ae. albopictus* C6/36 cell or 1-3 day-old newborn mice; or detection of DENV nucleic acid by RT-PCR; or detection of antigens by monoclonal antibodies immunofluorescence (mbAb-FIA) in serum, cerebrospinal fluid (within 5 days of illness course), other body fluid or tissue. | **3.1** A total white blood cell count decrease.<br>**3.2** Thrombocytopenia (< $100x10^9$/L).<br>**3.3** Hemoconcentration (an increase in hematocrit ≥20% above average for age or a decrease in hematocrit ≥20% of baseline following fluid replacement therapy); hypoproteinemia.<br>**3.4** IgG or IgM anti-DENV positive in a serum specimen.<br>**3.5** Cell culture isolation of DENV by *Ae. albopictus* C6/36 cell or 1-3-day-old newborn mice in acute serum, cerebrospinal fluid, blood, or other tissue specimens.<br>**3.6** IgG anti-DENV ≥4-fold rise in titer in paired acute and convalescent serum samples.<br>The serologic tests included ELISA, mac-ELISA, HI, FA/IFA, NT.<br>**3.7** Detection of DENV nucleic acid by RT-PCR or real-time fluorescence quantitative PCR. |

| Variable | Guidelines for Diagnosis, Treatment, Prevention and Control for Dengue Fever | Diagnostic Criteria and Principle of Management of Dengue Fever | Diagnostic Criteria for Dengue Fever |
|---|---|---|---|
| **Diagnosis and classification** | **4.1 Probable case:** a clinically compatible case of DF, DHF, or DSS with an epidemiologic linkage, as defined above.<br>**4.2 Confirmed case:** a probable case with a positive result of dengue virus isolation or serologic tests. The index case(s) of an outbreak or a new affected area should be a confirmed case. | **4.1 Suspected case**: a patient with item 1.1, 2.1 and 2.2, and one of item 2.3 to 2.7, as defined above.<br>**4.2 Probable case**: a suspected case with item 3.1 in a confirmed outbreak, or a suspected case with item 3.1 and 3.3 in an unconfirmed outbreak or presented as a sporadic case.<br>4.3 Confirmed case:<br>**DF**: a probable case with one of item 3.4, 3.5 and 3.6.<br>**DHF**: a confirmed DF case with item 2.8, 2.9 and 3.2.<br>**DSS**: a confirmed DHF case with item 2.10. | **4.1 Suspected case:** a patient with item 1.1 and 2.1, or a patient with item 2.1, 3.1 and 3.2, as defined above.<br>**4.2 Probable case**:<br>**DF**: a suspected case with 1.2, 3.1 and 3.2; or a suspect case with item 2.1, 3.1, 3.2 and 3.4<br>**DHF**: a probable case of DF with item 3.2, 3.3 and one of item 2.3 to 2.5.<br>**DSS**: a probable case of DHF with item 2.6.<br>**4.3 Confirmed case**: a probable case with one of item 3.5 to 3.7. |

**Table A-3. Summary of the geography and climate of each province in mainland China.**

| No. | Province | Zone code | Climate [a] | Inland or coastal province | Northern or southern | Adjacent country | Capital city | Latitude [b] | Longitude [b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Heilongjiang | 230000 | Mid-Temperate | Inland | Northern | Russia | Harbin | 46.1138 | 126.185 |
| 2 | Jilin | 220000 | Mid-Temperate | Inland | Northern | Russia and North Korea | Changchun | 44.1156 | 125.352 |
| 3 | Xinjiang | 650000 | Mid-Temperate | Inland | Northern | Russia, Mongolia, Kazakhstan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan and India | Urumqi | 43.7878 | 87.574 |
| 4 | Inner Mongolia | 150000 | Mid-Temperate | Inland | Northern | Russia and Mongolia | Huhhot | 40.7632 | 110.82 |
| 5 | Liaoning | 210000 | Warm-temperate | Coastal | Northern | North Korea | Shenyang | 40.6843 | 122.589 |
| 6 | Beijing | 110000 | Warm-temperate | Inland | Northern | None | Beijing | 39.94 | 116.41 |
| 7 | Tianjin | 120000 | Warm-temperate | Coastal | Northern | None | Tianjin | 39.16 | 117.2 |
| 8 | Hebei | 130000 | Warm-temperate | Coastal | Northern | None | Shijiazhuang | 38.1269 | 115.078 |
| 9 | Shanxi | 140000 | Warm-temperate | Inland | Northern | None | Taiyuan | 37.8098 | 112.8 |
| 10 | Ningxia | 640000 | Mid-Temperate | Inland | Northern | None | Yinchuan | 37.6234 | 106.026 |
| 11 | Qinghai | 630000 | Cold | Inland | Northern | None | Xining | 36.6401 | 101.835 |
| 12 | Shandong | 370000 | Warm-temperate | Coastal | Northern | None | Jinan | 36.313 | 118.368 |
| 13 | Gansu | 620000 | Mid-Temperate | Inland | Northern | Mongolia | Lanzhou | 35.5751 | 104.657 |
| 14 | Henan | 410000 | Warm-temperate | Inland | Northern | None | Zhengzhou | 34.707 | 113.058 |
| 15 | Shaanxi | 610000 | Warm-temperate | Inland | Northern | None | Xi'an | 34.3038 | 108.849 |
| 16 | Jiangsu | 320000 | SubTropic | Coastal | Southern | None | Nanjing | 32.8614 | 118.575 |
| 17 | Anhui | 340000 | SubTropic | Inland | Southern | None | Hefei | 31.8527 | 117.543 |
| 18 | Shanghai | 310000 | SubTropic | Coastal | Southern | None | Shanghai | 31.28 | 121.46 |
| 19 | Hubei | 420000 | SubTropic | Inland | Southern | None | Wuhan | 30.8781 | 112.606 |
| 20 | Sichuan | 510000 | SubTropic | Inland | Southern | None | Chengdu | 30.2459 | 103.978 |

| No. | Province | Zone code | Climate [a] | Inland or coastal province | Northern or southern | Adjacent country | Capital city | Latitude [b] | Longitude [b] |
|---|---|---|---|---|---|---|---|---|---|
| 21 | Zhejiang | 330000 | SubTropic | Coastal | Southern | None | Hangzhou | 29.9769 | 120.444 |
| 22 | Tibet | 540000 | Cold | Inland | Northern | India, Bhutan, Nepal, Myanmar and Pakistan | Lhasa | 29.65 | 91.13 |
| 23 | Chongqing | 500000 | SubTropic | Inland | Southern | None | Chongqing | 29.59 | 106.55 |
| 24 | Jiangxi | 360000 | SubTropic | Inland | Southern | None | Nanchang | 28.2274 | 115.261 |
| 25 | Hunan | 430000 | SubTropic | Inland | Southern | None | Changsha | 27.3878 | 113.006 |
| 26 | Guizhou | 520000 | SubTropic | Inland | Southern | None | Guiyang | 27.3627 | 106.816 |
| 27 | Fujian | 350000 | SubTropic | Coastal | Southern | None | Fuzhou | 25.337 | 118.827 |
| 28 | Yunnan | 530000 | SubTropic | Inland | Southern | Vietnam, Laos and Myanmar | Kunming | 24.8119 | 103.034 |
| 29 | Guangdong | 440000 | SubTropic | Coastal | Southern | None | Guangzhou | 22.9286 | 113.414 |
| 30 | Guangxi | 450000 | SubTropic | Coastal | Southern | Vietnam | Nanning | 22.85 | 108.37 |
| 31 | Hainan | 460000 | Tropic | Coastal | Southern | None | Haikou | 19.5855 | 110.101 |

Note: [a] The general climate of each province, which is available on the website of China Meteorological Administration (www.cma.gov.cn). [b] The latitude and longitude of capital city of each province.

**Table A-4. Characteristics of dengue cases from 2005 to 2014.**

| Characteristics | Total (n=55,114) | Imported cases (n=2,061) | Autochthonous cases (n=53,053) |
|---|---|---|---|
| Type of cases | | | |
| Lab-confirmed case | 41783 (75.8%) | 1746 (84.7%) | 40037 (75.5%) |
| Probable case | 13331 (24.2%) | 315 (15.3%) | 13016 (24.5%) |
| Gender | | | |
| Female | 27611 (50.1%) | 687 (33.3%) | 26924 (50.7%) |
| Male | 27503 (49.9%) | 1374 (66.7%) | 26129 (49.3%) |
| Age | | | |
| Median (yrs, range) | 39 (0.01, 107) | 32 (0.5, 80) | 39 (0.01, 107) |
| Age group | | | |
| 0-4 | 988 (1.8%) | 24 (1.2%) | 964 (1.8%) |
| 5-14 | 2814 (5.1%) | 86 (4.2%) | 2728 (5.1%) |
| 15-24 | 8012 (14.5%) | 347 (16.8%) | 7665 (14.4%) |
| 25-34 | 12156 (22.1%) | 687 (33.3%) | 11469 (21.6%) |
| 35-44 | 10089 (18.3%) | 517 (25.1%) | 9572 (18%) |
| 45-54 | 8323 (15.1%) | 264 (12.8%) | 8059 (15.2%) |
| 55-64 | 6614 (12%) | 103 (5%) | 6511 (12.3%) |
| 65 and above | 6118 (11.1%) | 33 (1.6%) | 6085 (11.5%) |
| Nationality | | | |
| Chinese | 54608 (99.1%) | 1571 (76.2%) | 53037 (100%) |
| Foreigner | 506 (0.9%) | 490 (23.8%) | 16 (0.03%) |
| Hospitalization | | | |
| Yes | 6408 (11.6%) | 172 (8.3%) | 6236 (11.8%) |
| No | 10611 (19.3%) | 54 (2.6%) | 10557 (19.9%) |
| Unknown | 38095 (69.1%) | 1835 (89%) | 36260 (68.3%) |
| Year of onset | | | |
| 2005 | 59 (0.1%) | 59 (2.9%) | 0 (0) |
| 2006 | 1063 (1.9%) | 54 (2.6%) | 1009 (1.9%) |
| 2007 | 551 (1%) | 70 (3.4%) | 481 (0.9%) |
| 2008 | 254 (0.5%) | 167 (8.1%) | 87 (0.2%) |
| 2009 | 322 (0.6%) | 122 (5.9%) | 200 (0.4%) |
| 2010 | 260 (0.5%) | 147 (7.1%) | 113 (0.2%) |

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| Characteristics | Total (n=55,114) | Imported cases (n=2,061) | Autochthonous cases (n=53,053) |
|---|---|---|---|
| 2011 | 160 (0.3%) | 124 (6%) | 36 (0.1%) |
| 2012 | 610 (1.1%) | 168 (8.2%) | 442 (0.8%) |
| 2013 | 4779 (8.7%) | 491 (23.8%) | 4288 (8.1%) |
| 2014 | 47056 (85.4%) | 659 (32%) | 46397 (87.5%) |
| Month of onset | | | |
| January | 44 (0.1%) | 44 (2.1%) | 0 (0) |
| February | 50 (0.1%) | 50 (2.4%) | 0 (0) |
| March | 61 (0.1%) | 61 (3%) | 0 (0) |
| April | 73 (0.1%) | 72 (3.5%) | 1 (0.002%) |
| May | 110 (0.2%) | 110 (5.3%) | 0 (0) |
| June | 135 (0.2%) | 113 (5.5%) | 22 (0%) |
| July | 584 (1.1%) | 158 (7.7%) | 426 (0.8%) |
| August | 3363 (6.1%) | 290 (14.1%) | 3073 (5.8%) |
| September | 21824 (39.6%) | 399 (19.4%) | 21425 (40.4%) |
| October | 26278 (47.7%) | 507 (24.6%) | 25771 (48.6%) |
| November | 2434 (4.4%) | 182 (8.8%) | 2252 (4.2%) |
| December | 158 (0.3%) | 75 (3.6%) | 83 (0.2%) |
| Median of time delay (days, range) | | | |
| From illness onset to diagnosis | 5 (0, 196) | 6 (0, 196) | 5 (0, 141) |
| From diagnosis to report [a] | 0.3 (-196, 31) | 0.2 (-196, 31) | 0.3 (-122, 15) |
| From illness onset to report | 6 (0.3, 82) | 6 (0.3, 82) | 6 (0.3, 64) |
| Serotype of Dengue virus | | | |
| I | 373 (0.7%) | 11 (0.5%) | 362 (0.7%) |
| II | 42 (0.1%) | 2 (0.1%) | 40 (0.1%) |
| III | 16 (0.03%) | 3 (0.1%) | 13 (0.02%) |
| IV | 2 (0.004%) | 2 (0.1%) | 0 (0) |
| Unknown | 54681 (99.2%) | 2043 (99.1%) | 52638 (99.2%) |
| Case imported from other province in China | | | |
| Yes | 235 (0.4%) | 235 (11.4%) | 0 (0) |
| No | 54879 (99.6%) | 1826 (88.6%) | 53053 (100%) |

Note: Data are presented as no. (%) of patients unless otherwise indicated. [a] The negative number of the median from diagnosis to report means that case was reported by physician as a suspected dengue patient to the surveillance system before diagnosed as a probable or laboratory confirmed dengue cases.

**Table A-5. Demographic and epidemiologic characteristics of imported dengue cases by year from 2005 to 2014.**

| Characteristics | Total (n=2061) | 2005-2013 (n=1402) | 2014 (n=659) |
|---|---|---|---|
| Type of cases | | | |
| Lab-confirmed case | 1746 (84.7%) | 1177 (84%) | 569 (86.3%) |
| Probable case | 315 (15.3%) | 225 (16%) | 90 (13.7%) |
| Gender | | | |
| Female | 687 (33.3%) | 452 (32.2%) | 235 (35.7%) |
| Male | 1374 (66.7%) | 950 (67.8%) | 424 (64.3%) |
| Age | | | |
| Median (yrs, range) | 32 (0.5, 80) | 32 (0.6, 80) | 33 (0.5, 76) |
| Age group | | | |
| 0-4 | 24 (1.2%) | 14 (1%) | 10 (1.5%) |
| 5-14 | 86 (4.2%) | 48 (3.4%) | 38 (5.8%) |
| 15-24 | 347 (16.8%) | 252 (18%) | 95 (14.4%) |
| 25-34 | 687 (33.3%) | 478 (34.1%) | 209 (31.7%) |
| 35-44 | 517 (25.1%) | 363 (25.9%) | 154 (23.4%) |
| 45-54 | 264 (12.8%) | 160 (11.4%) | 104 (15.8%) |
| 55-64 | 103 (5%) | 68 (4.9%) | 35 (5.3%) |
| 65 and above | 33 (1.6%) | 19 (1.4%) | 14 (2.1%) |
| Nationality | | | |
| Chinese | 1571 (76.2%) | 1066 (76%) | 505 (76.6%) |
| Foreigner | 490 (23.8%) | 336 (24%) | 154 (23.4%) |
| Hospitalization | | | |
| Yes | 172 (8.3%) | 116 (8.3%) | 56 (8.5%) |
| No | 54 (2.6%) | 19 (1.4%) | 35 (5.3%) |
| Unknown | 1835 (89%) | 1267 (90.4%) | 568 (86.2%) |
| Month of onset | | | |
| January | 44 (2.1%) | 28 (2%) | 16 (2.4%) |
| February | 50 (2.4%) | 40 (2.9%) | 10 (1.5%) |
| March | 61 (3%) | 44 (3.1%) | 17 (2.6%) |
| April | 72 (3.5%) | 63 (4.5%) | 9 (1.4%) |
| May | 110 (5.3%) | 82 (5.8%) | 28 (4.2%) |

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| Characteristics | Total (n=2061) | 2005-2013 (n=1402) | 2014 (n=659) |
|---|---|---|---|
| June | 113 (5.5%) | 82 (5.8%) | 31 (4.7%) |
| July | 158 (7.7%) | 131 (9.3%) | 27 (4.1%) |
| August | 290 (14.1%) | 243 (17.3%) | 47 (7.1%) |
| September | 399 (19.4%) | 259 (18.5%) | 140 (21.2%) |
| October | 507 (24.6%) | 262 (18.7%) | 245 (37.2%) |
| November | 182 (8.8%) | 117 (8.3%) | 65 (9.9%) |
| December | 75 (3.6%) | 51 (3.6%) | 24 (3.6%) |
| Median of time delay (days, range) | | | |
| From illness onset to diagnosis | 6 (0, 196) | 6 (0, 196) | 5 (0.3, 140) |
| From diagnosis to report [a] | 0.2 (-196, 31) | 0.3 (-196, 31) | 0.1 (-137, 1) |
| From illness onset to report | 6 (0.3, 82) | 6 (0.4, 82) | 5 (0.3, 48) |
| Serotype of Dengue virus | | | |
| I | 11 (0.5%) | 9 (0.6%) | 2 (0.3%) |
| II | 2 (0.1%) | 1 (0.1%) | 1 (0.2%) |
| III | 3 (0.1%) | 3 (0.2%) | 0 (0) |
| IV | 2 (0.1%) | 2 (0.1%) | 0 (0) |
| Unknown | 2008 (99.1%) | 1387 (98.9%) | 621 (99.5%) |
| Case imported from other province in China | | | |
| Yes | 235 (11.4%) | 8 (0.6%) | 227 (34.4%) |
| No | 1826 (88.6%) | 1394 (99.4%) | 432 (65.6%) |

Note: Data are presented as no. (%) of patients unless otherwise indicated. [a] The negative number of the median from diagnosis to report means that case was reported by physician as a suspected dengue patient to the surveillance system before diagnosed as a probable or laboratory confirmed dengue cases.

**Table A-6. Demographic and epidemiologic characteristics of autochthonous dengue by year from 2005 to 2014.**

| Characteristics | Total (n=53 053) | 2005-2013 (n=6656) | 2014 (n=46 397) |
|---|---|---|---|
| Type of cases | | | |
| Lab-confirmed case | 40037 (75.4%) | 5466 (82.1%) | 34571 (74.5%) |
| Probable case | 13016 (24.6%) | 1190 (17.9%) | 11826 (25.5%) |
| Gender | | | |
| Female | 26924 (50.7%) | 3505 (52.7%) | 23419 (50.5%) |
| Male | 26129 (49.3%) | 3151 (47.3%) | 22978 (49.5%) |
| Age | | | |
| Median (yrs, range) | 39 (0.01, 107) | 38 (0.2, 96) | 39 (0.01, 107) |
| Age group | | | |
| 0-4 | 964 (1.8%) | 56 (0.8%) | 908 (2%) |
| 5-14 | 2728 (5.1%) | 396 (5.9%) | 2332 (5%) |
| 15-24 | 7665 (14.4%) | 1115 (16.8%) | 6550 (14.1%) |
| 25-34 | 11469 (21.6%) | 1399 (21%) | 10070 (21.7%) |
| 35-44 | 9572 (18%) | 1288 (19.4%) | 8284 (17.9%) |
| 45-54 | 8059 (15.2%) | 1052 (15.8%) | 7007 (15.1%) |
| 55-64 | 6511 (12.3%) | 770 (11.6%) | 5741 (12.4%) |
| 65 and above | 6085 (11.5%) | 580 (8.7%) | 5505 (11.9%) |
| Nationality | | | |
| Chinese | 53037 (100%) | 6656 (100%) | 46381 (100%) |
| Foreigner | 16 (0%) | 0 (0) | 16 (0%) |
| Hospitalization | | | |
| Yes | 6202 (11.7%) | 749 (11.3%) | 5453 (11.8%) |
| No | 10537 (19.9%) | 155 (2.3%) | 10382 (22.4%) |
| Unknown | 36164 (68.4%) | 5752 (86.4%) | 30412 (65.8%) |
| Month of onset | | | |
| January | 0 (0) | 0 (0) | 0 (0) |
| February | 0 (0) | 0 (0) | 0 (0) |
| March | 0 (0) | 0 (0) | 0 (0) |
| April | 1 (0.002%) | 1 (0.02%) | 0 (0) |
| May | 0 (0) | 0 (0) | 0 (0) |
| June | 22 (0.04%) | 4 (0.1%) | 18 (0.04%) |

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| Characteristics | Total (n=53 053) | 2005-2013 (n=6656) | 2014 (n=46 397) |
|---|---|---|---|
| July | 426 (0.8%) | 170 (2.6%) | 256 (0.6%) |
| August | 3073 (5.8%) | 1161 (17.4%) | 1912 (4.1%) |
| September | 21425 (40.4%) | 2333 (35.1%) | 19092 (41.1%) |
| October | 25771 (48.6%) | 2431 (36.5%) | 23340 (50.3%) |
| November | 2252 (4.2%) | 552 (8.3%) | 1700 (3.7%) |
| December | 83 (0.2%) | 4 (0.1%) | 79 (0.2%) |
| Median of time delay (days, range) | | | |
| From illness onset to diagnosis | 5 (0, 141) | 6 (0, 141) | 5 (0, 95) |
| From diagnosis to report [a] | 0.3 (-122, 15) | 0.1 (-122, 15) | 0.3 (-84, 8) |
| From illness onset to report | 6 (0.3, 64) | 6 (0.4, 62) | 5 (0.3, 64) |
| Serotype of Dengue virus | | | |
| I | 362 (0.7%) | 61 (0.9%) | 301 (0.6%) |
| II | 40 (0.1%) | 1 (0%) | 39 (0.1%) |
| III | 13 (0.02%) | 13 (0.2%) | 0 (0) |
| Unknown | 52638 (99.2%) | 6581 (98.9%) | 46057 (99.3%) |

Note: Data are presented as no. (%) of patients unless otherwise indicated. [a] The negative number of the median from diagnosis to report means that case was reported by physician as a suspected dengue patient to the surveillance system before diagnosed as a probable or laboratory confirmed dengue cases.


**Figure A-1. General climate of each province in mainland China.**

Note: The data is from the China Meteorological Administration (www.cma.gov.cn).

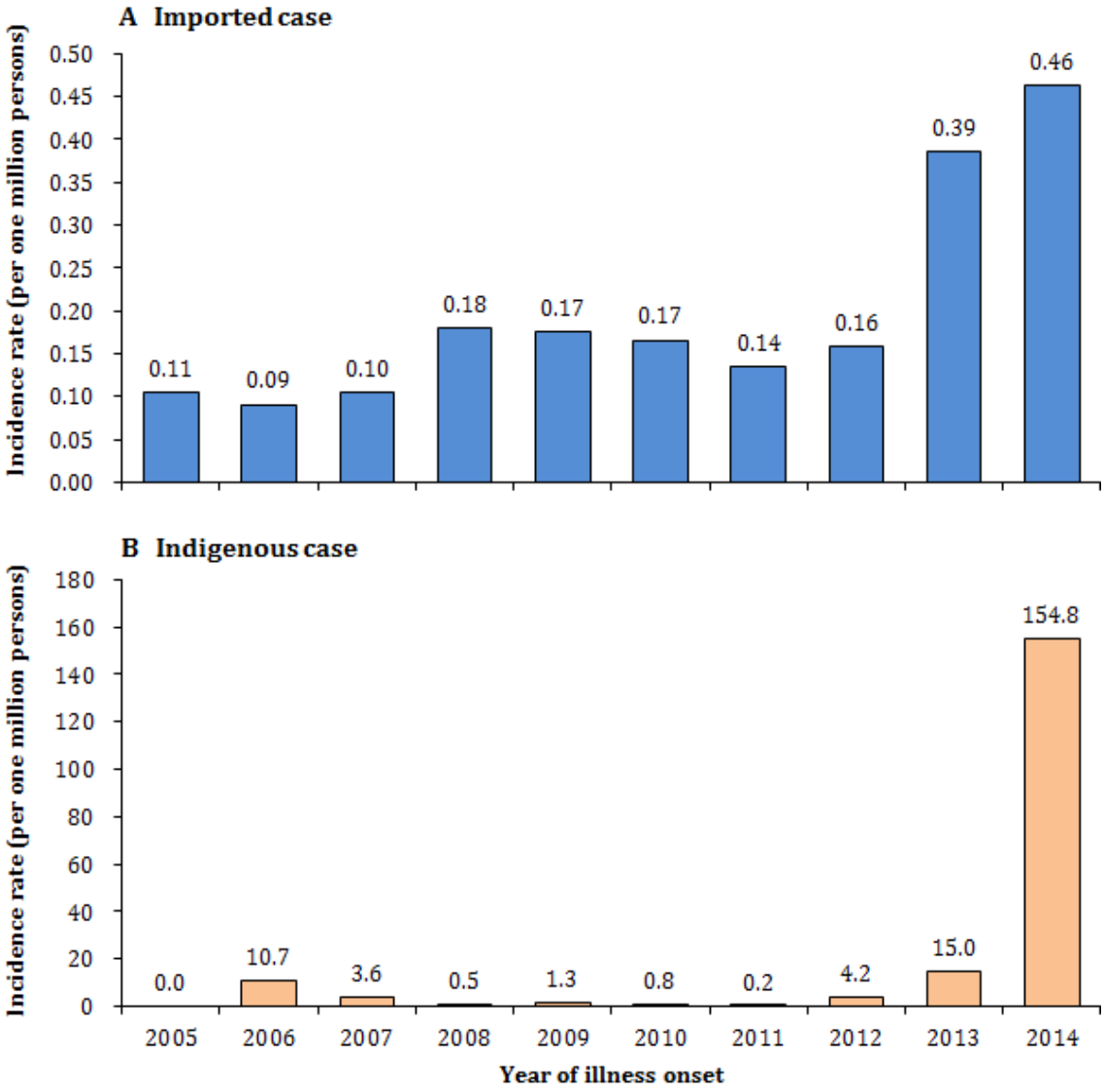



**Figure A-2. Morbidity of imported and autochthonous dengue cases in mainland China, 2005-2014.**

Note: Panel A: The morbidity of imported cases per one million persons of affected provinces at each year-end. Panel B: The morbidity of autochthonous cases per one million persons of affected provinces at each year-end.

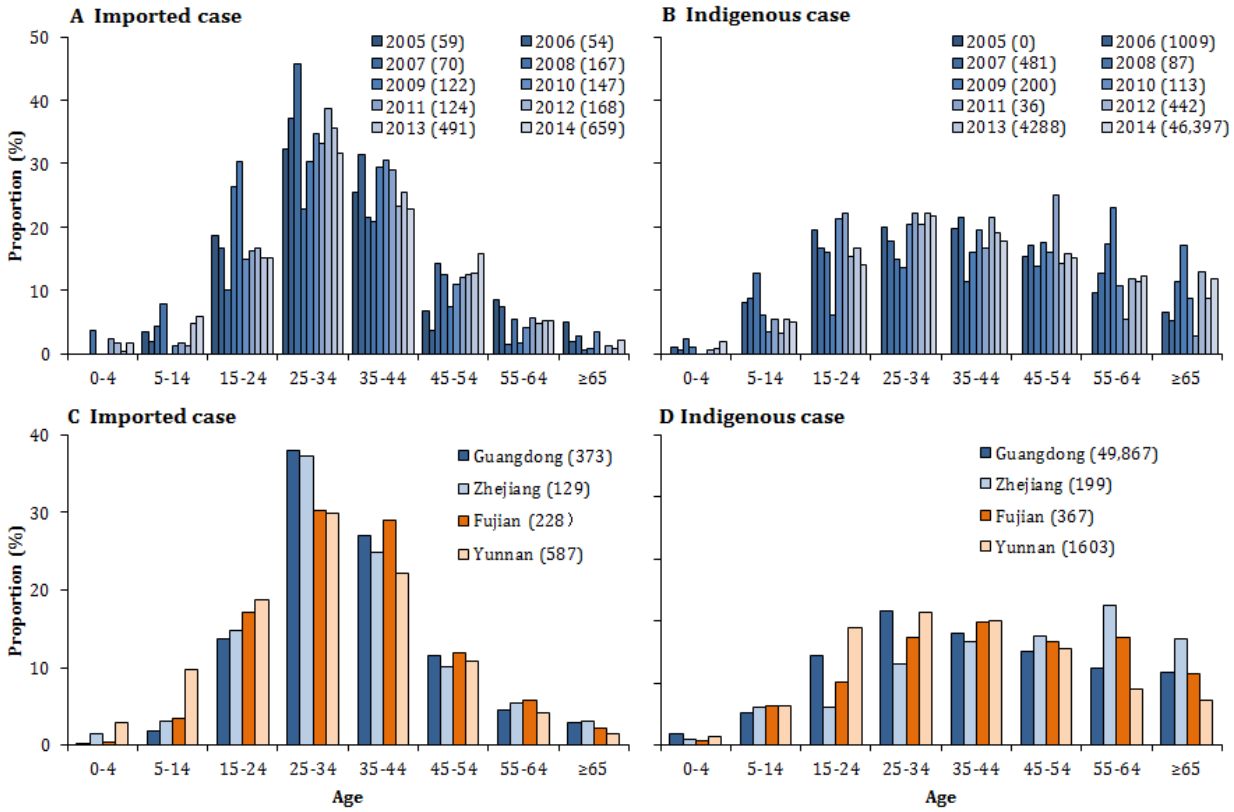



**Figure A-3. Age distribution of imported and autochthonous dengue cases by year and province.**

Note: (A) The proportion of imported cases by age and year. (B) The proportion of autochthonous cases by age and year. (C) The proportion of imported cases by age and top four provinces reported cases. (D) The proportion of autochthonous cases by age and top four provinces reported cases. The number of cases is shown in parentheses in the legend.

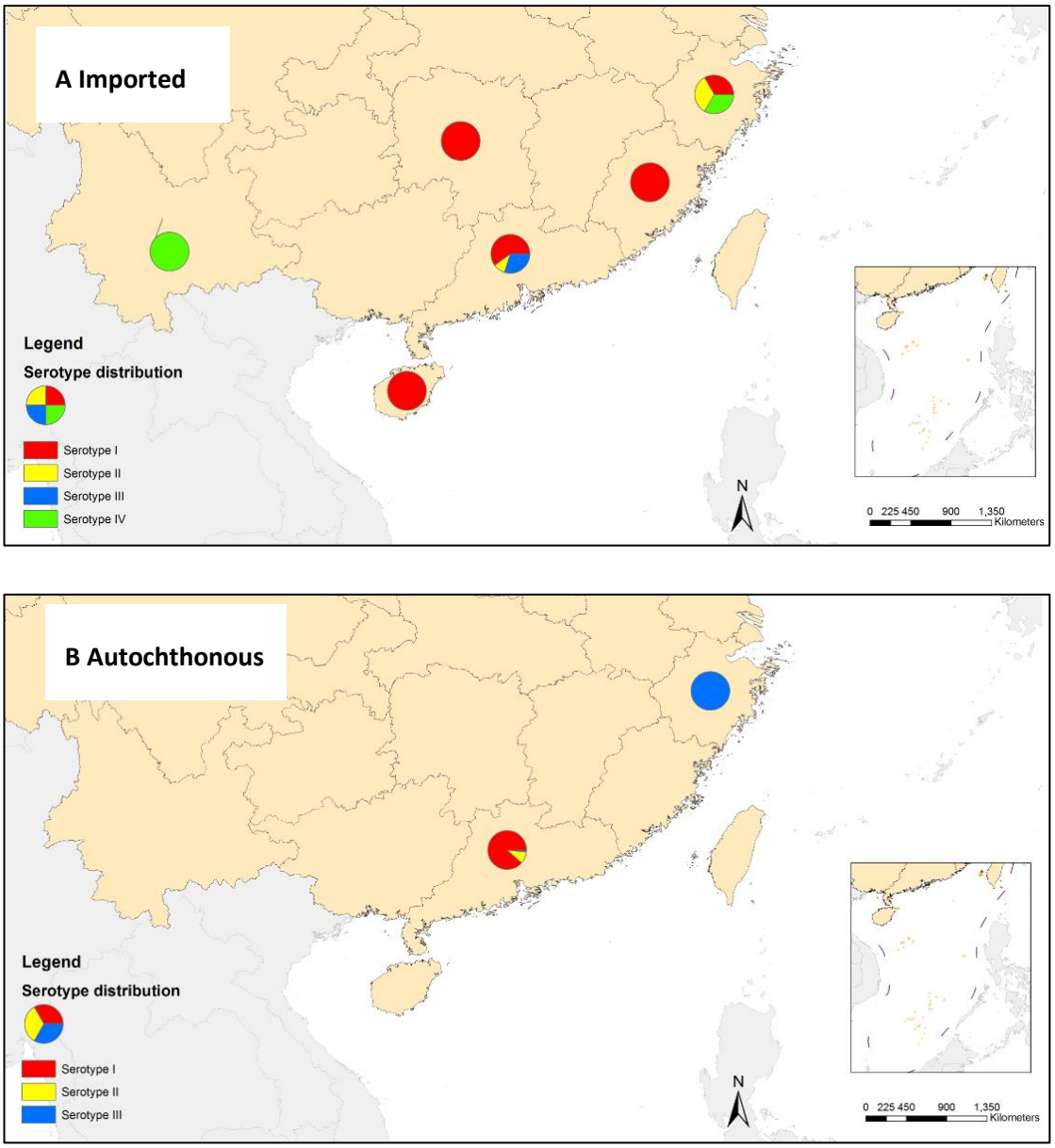
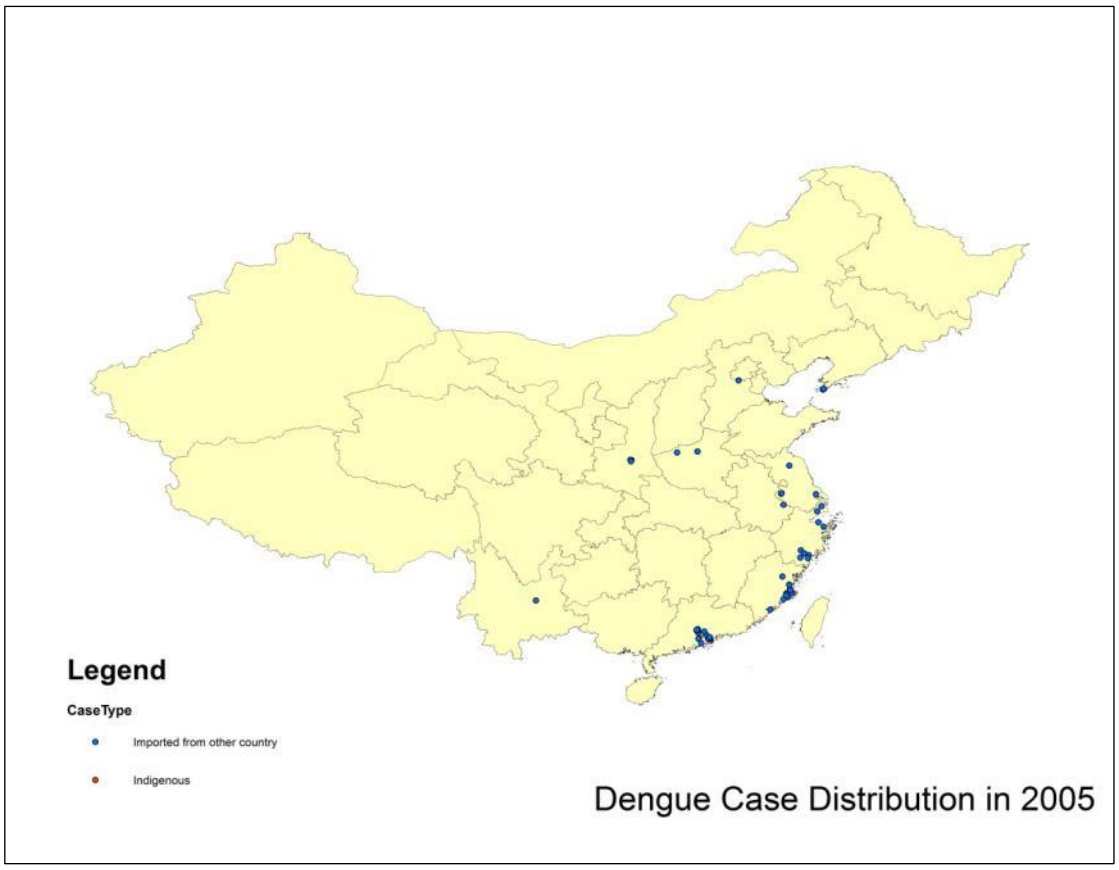
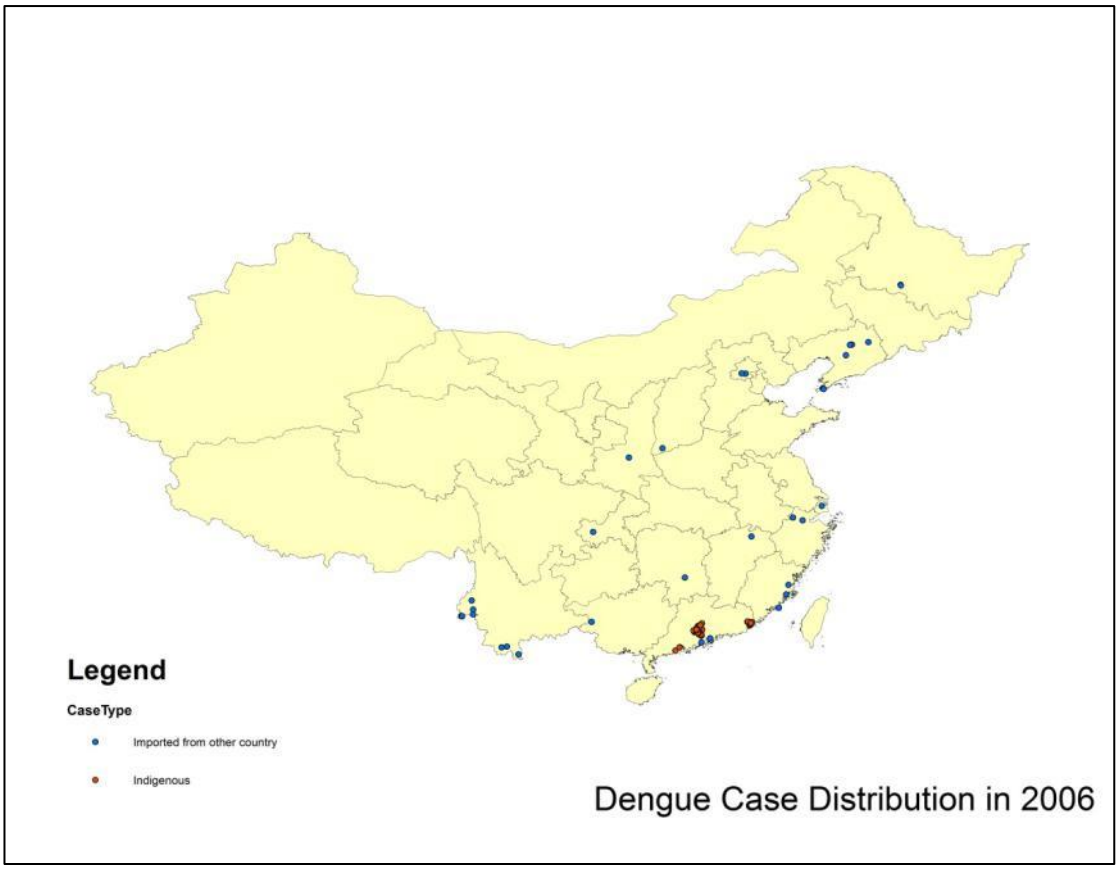



**Figure A-4. Serotype distribution of imported and autochthonous dengue cases by province, 2009-2014.**

Note: (A) Serotype distribution of imported cases. Among 18 imported cases with serotype data, all four serotypes were reported: DENV-1 (11 cases), DENV-2 (2), DENV-3 (3), and DENV-4 (2) during 2009-2014. (B) Serotype distribution of autochthonous cases. Data on serotypes were only available for 415 autochthonous cases during 2005-2014: 362 (87.2%) cases with DENV-1 in Guangdong during 2011-2014, 40 (9.6%) DENV-2 in Guangdong during 2013-2014, and 13 (3.1%) DENV-3 in Zhejiang in 2009 and Guangdong during 2012-2013.


Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2005


Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2006

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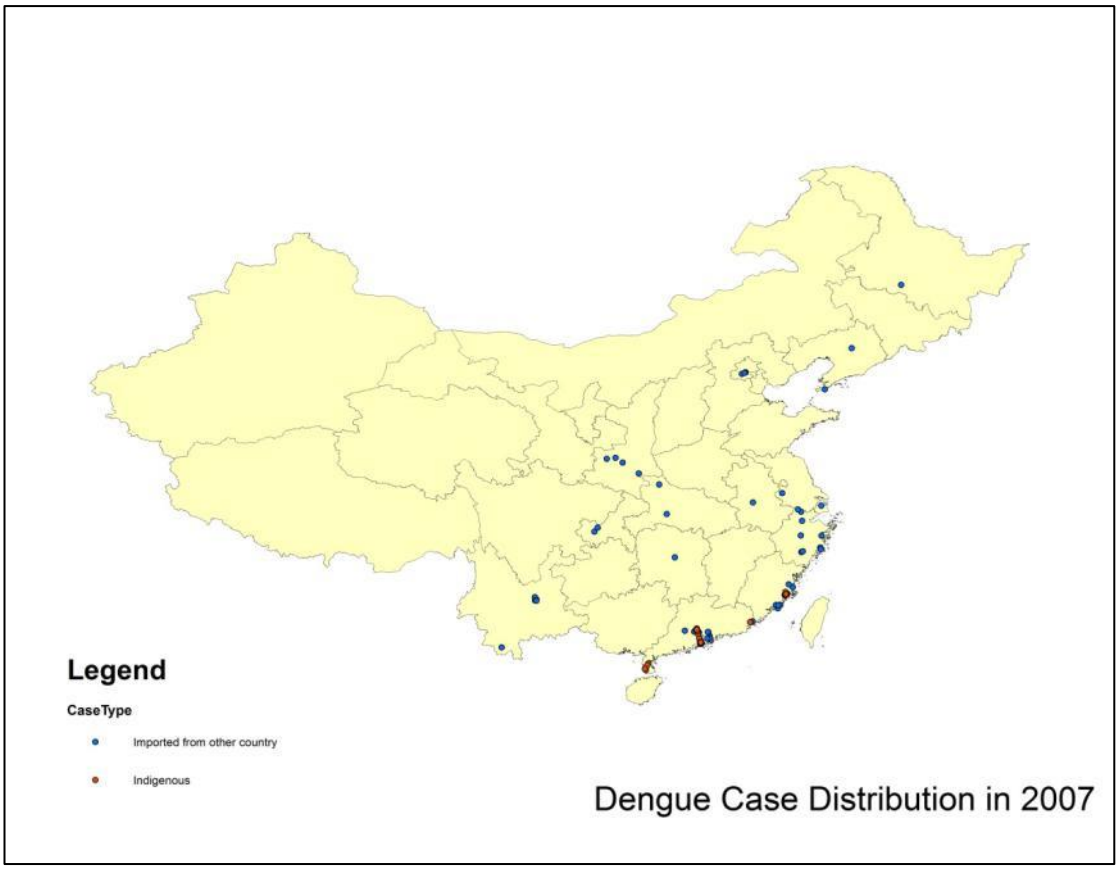
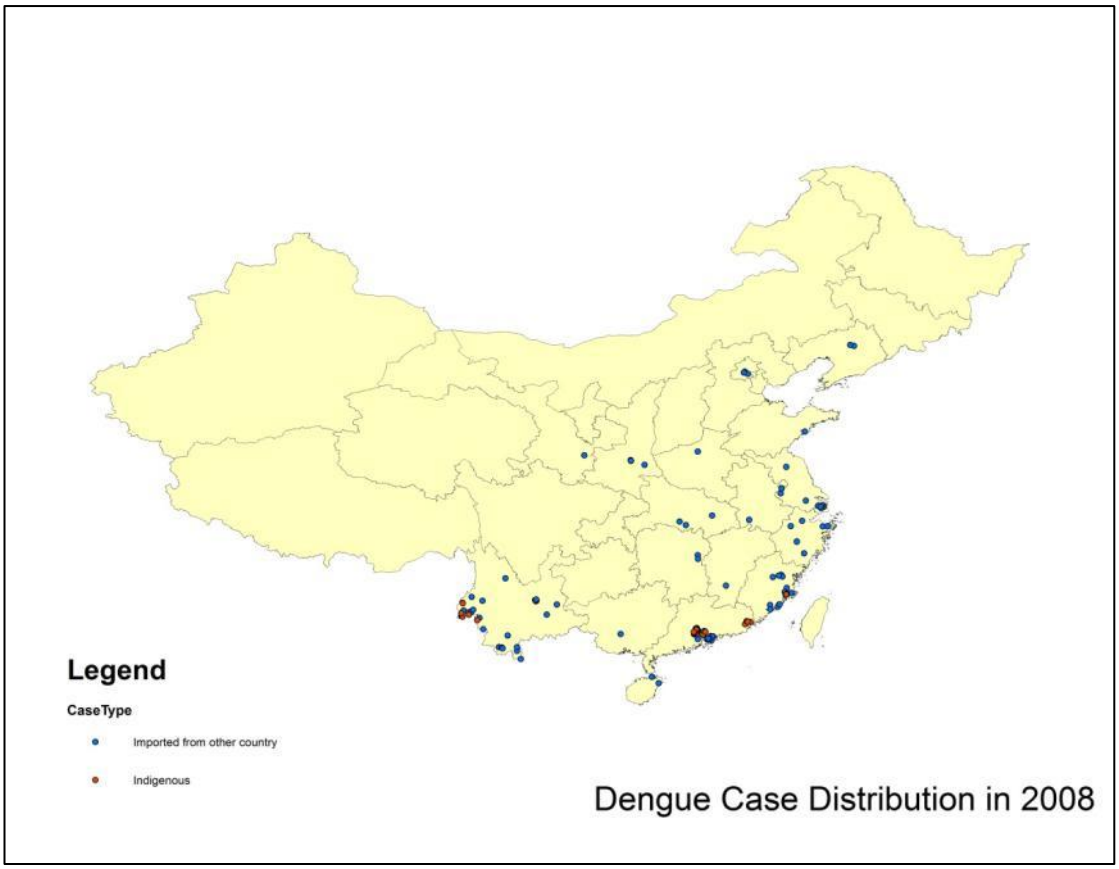
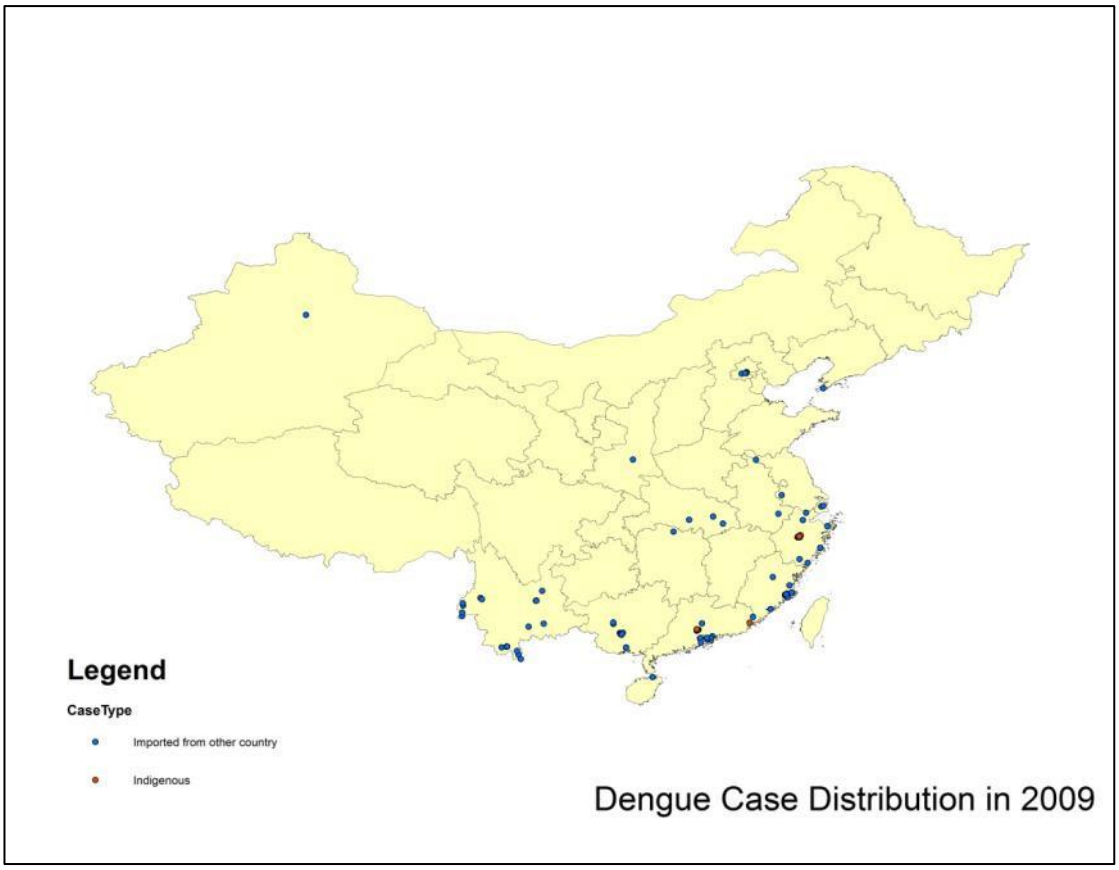
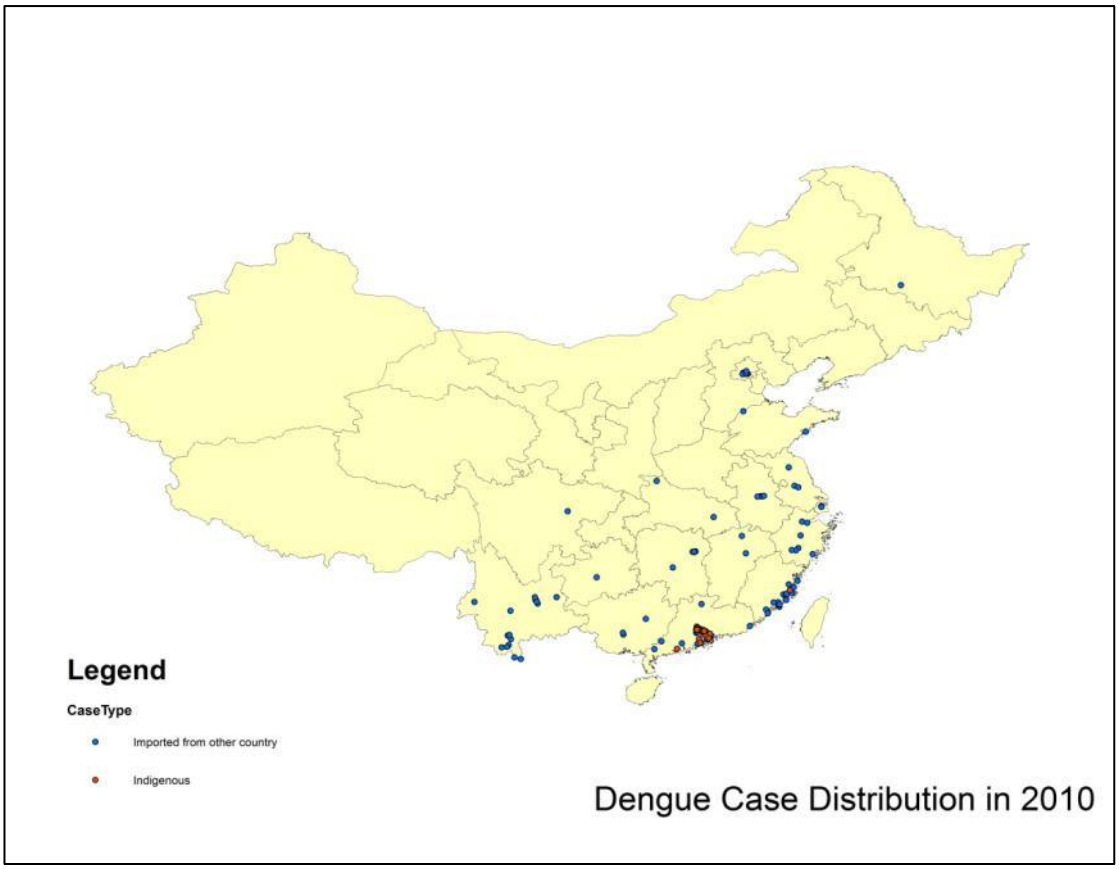
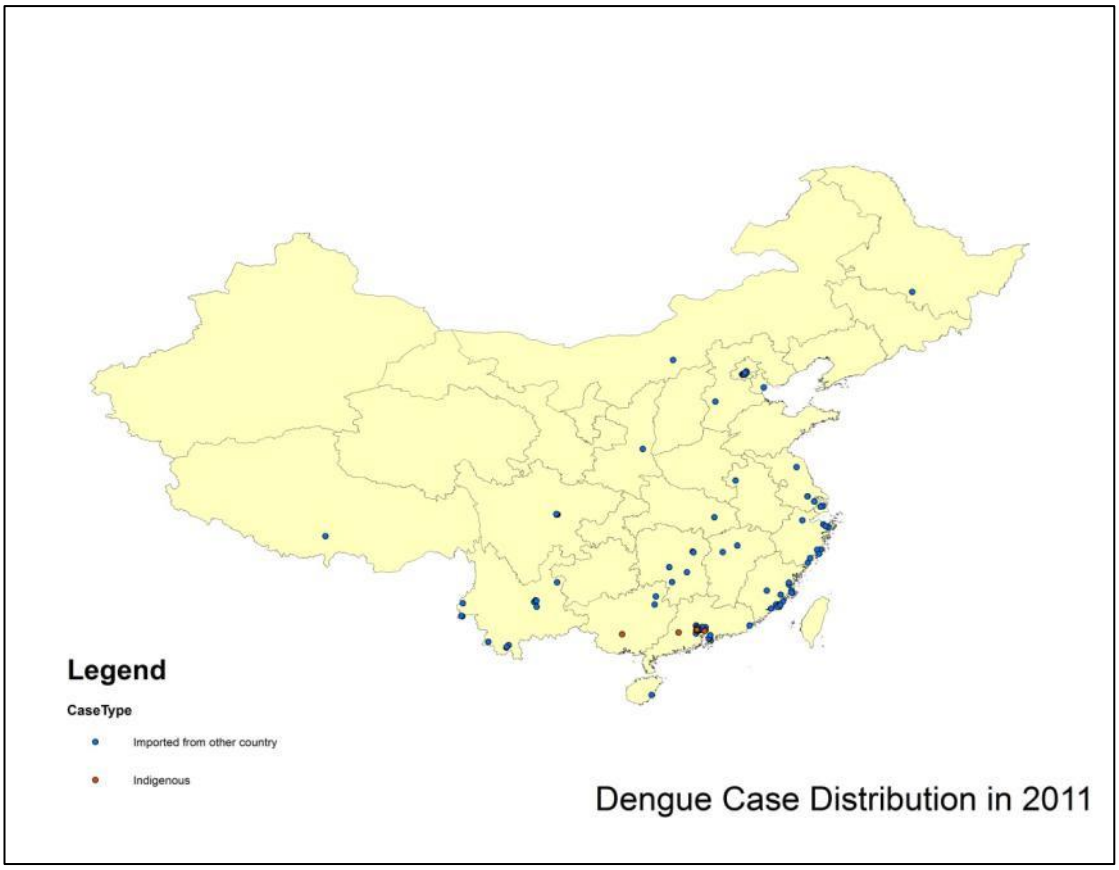

Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2007


Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2008


Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2009


Legend
CaseType
Imported from other country
Indigenous
Dengue Case Distribution in 2010



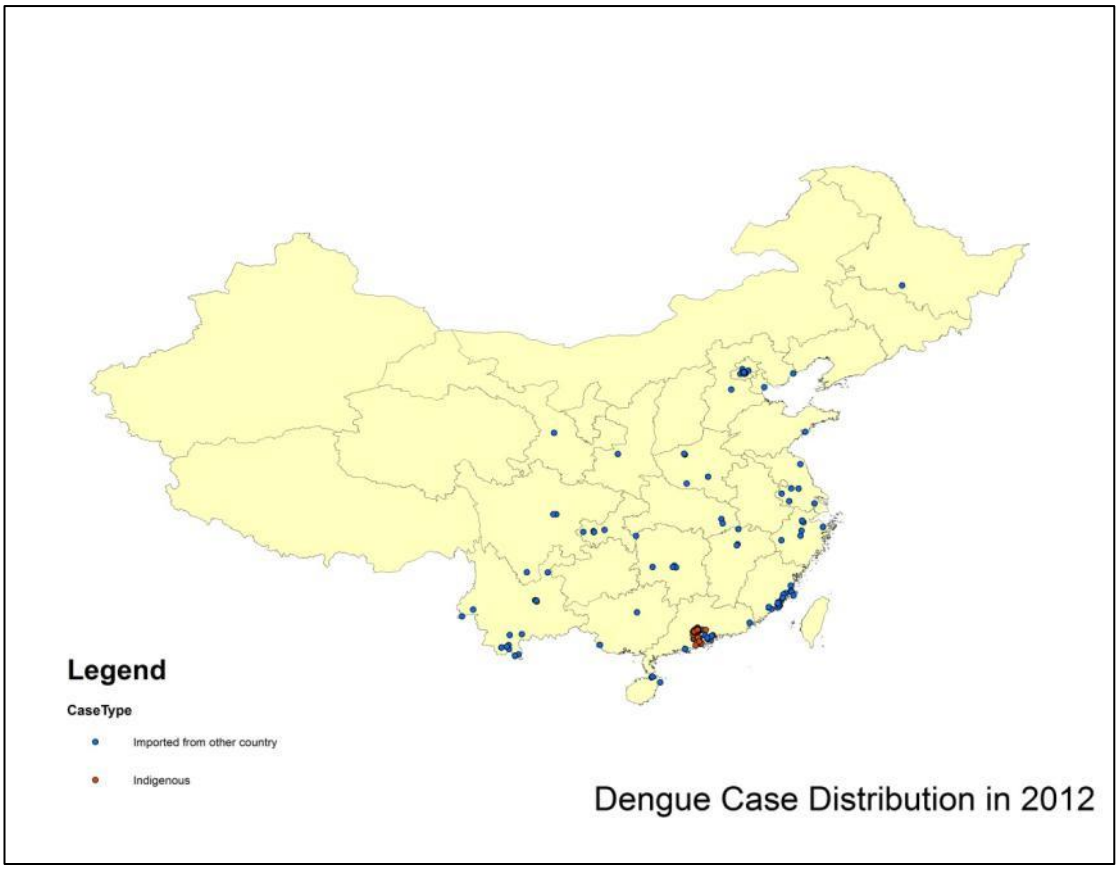




**Figure A-5. Geographic distribution of dengue cases by year in mainland China, 2005-2012.**

# Appendix B Supplementary information for Chapter 3

**Table B-1. Intervention policies and strategies of malaria elimination in mainland China.**

| Intervention | Policies/strategies | Yes/No/Medicine | Adopted |
|---|---|---|---|
| **ITN** | ITNs/LLINs distributed free of charge | Yes | 2003 |
| | ITNs/LLINs distributed to all age groups | Yes | 2000 |
| **IRS** | IRS is recommended | Yes | 2000 |
| | DDT is authorized for IRS | No | - |
| **Larval control** | Use of larval control recommended | No | - |
| **Diagnosis** | Patients of all ages should receive diagnostic test | Yes | 2000 |
| | Malaria diagnosis is free of charge in the public sector | No | - |
| **Treatment** | ACT is free for all ages in public sector | Yes | 2006 |
| | Sale of oral artemisinin-based monotherapies | Is banned | |
| | Single dose of primaquine is used as gametocidal medicine for *P. falciparum* | Yes | 2013 |
| | Primaquine is used for radical treatment of P. vivax | Yes | 1970 |
| | G6PD test is a requirement before treatment with primaquine | No | - |
| | Directly observed treatment with primaquine is undertaken | Yes | 1970 |
| | System for monitoring of adverse reactions to antimalarials exists | Yes | 1970 |
| **Surveillance** | ACD for case investigation (reactive) | Yes | 2010 |
| | ACD of febrile cases at community level (pro-active) | Yes | 2010 |
| | Mass screening is undertaken | Yes | 2010 |
| | Uncomplicated P. falciparum cases routinely admitted | No | - |
| | Uncomplicated P. vivax cases routinely admitted | No | - |

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| Intervention | Policies/strategies | Yes/No/Medicine | Adopted |
|---|---|---|---|
| | Foci and case investigation undertaken | Yes | 2010 |
| | Case reporting from private sector is mandatory | Yes | 1956 |
| **Antimalarial treatment policy** | First-line treatment of unconfirmed malaria | - | - |
| | First-line treatment of P. falciparum | ART+NQ; ART-PPQ; AS+AQ; DHA-PPQ | 2009 |
| | Treatment failure of P. falciparum | - | - |
| | Treatment of severe malaria | AM; AS; PYR | 2009 |
| | Treatment of P. vivax | CQ+PQ (8d) | 2006 |
| | Dosage of primaquine for radical treatment of P. vivax | - | 0.75mg/kg (8d) |

**Table B-2. The list of variables in the individual dataset of malaria cases in this study.**

| Variables | Definition/classification | Completeness (N = 17,745) |
|---|---|---|
| Type of diagnosis | Clinical diagnosed or laboratory-confirmed case | 100% reported |
| Age | The interval time from the date of birth to the date of onset | 99.96% reported |
| Nationality | Chinese or foreigner | 100% reported |
| Origin country | The last countries with malaria transmission and visited by imported cases before returning to China were recorded as the potential origins of infections. | 97.5% reported |
| Education | Illiteracy, Primary (6-year education), Junior secondary (9-year), Senior secondary (12-year), or Higher education (>12-year) | 89.2% reported |
| Date of onset | The date of illness onset | 100% reported |
| Date of diagnosis | The date of diagnosis as malaria | 100% reported |
| Date of report | The date of report to surveillance system | 100% reported |
| Date of Death | The date of case death, if applicable. | 100% reported |
| Purpose of travel of Chinese imported cases | Labour service or other | 98.4% reported |
| Duration in other countries of Chinese cases | Days in other countries | 23.4% reported |
| Hospitalization | Inpatient or outpatient | 94.8% reported |
| Address of illness onset | The address (community/village) of case with illness onset | 100% reported |

Appendix B

| **Variables** | **Definition/classification** | **Completeness (N = 17,745)** |
|---|---|---|
| Coordinates of address | Latitude and longitude of address of case with illness onset | 100% produced |
| Admin level of hospitals for final diagnosis and report | Province, prefecture, county, or township and lower | 99.97% reported |
| County's code of hospital | A unique 8-digital number for each county | 99.97% reported |
| Onset location vs. report (hospital) location | In same county, in different counties of same province, or in different provinces | 100% reported |
| Report (hospital) location vs. home/living location | In same county, in different counties of same province, or in different provinces | 100% reported |

**Table B-3. Data sources of cost analysis of malaria elimination in China, 2011-2015.**

| Sources | Period | Cost | Data sources |
|---|---|---|---|
| The Global Fund | 2011-2012 | 57.2 million USD | • The World Malaria Report (WMR) of the WHO from 2011 to 2016.<br>• The China Annual Report of Malaria Elimination.<br>• The National Programme Office for Malaria in the National Institute of Parasitic Diseases Control and Prevention, China CDC in Shanghai.<br>• The website of the Global Fund. |
| The Chinese Central Government | 2011-2015 | 77.3 million USD | • The WMR of the WHO from 2011 to 2016.<br>• The China Annual Report of Malaria Elimination.<br>• The Division of Infectious Diseases, and the National Institute of Parasitic Diseases Control and Prevention, China CDC. |

Note: Data taken from the WMR included country-reporting government and external funding for the period of 2011–2015, and did not include ‘‘Contributions reported by donors’’. The costs of Chinese Central Government for malaria in 2011-2012 was obtained from the Division of Infectious Diseases, and the National Institute of Parasitic Diseases Control and Prevention, China CDC. When the data from different sources were conflicting, the information reported by Chinese government in the WMR was taken. Other sources of international malaria funding (e.g. the President’s Malaria Initiative, the United Nations International Children’s Emergency Fund, and the World Bank) were also checked but excluded here because of no funding for malaria was reported to allocate into China from these sources in 2011-2015. The costs incurred by the governments at sub-national levels are also not included here because the Chinese Central Government plays a major role of domestic funding in NMEP and the costs of sub-national levels are not publicly available. All the funds using Chinese Yuan have been converted into US$ using the average exchange rate from the year of the award/funding, and the annual values were adjusted for the annual average inflation rate (2.65% in 2012, 2.62% in 2013, 1.99% in 2014 and 1.44% in 2015) from China comparing to 2011 in order to measure funding/spending trends in real terms.

**Table B-4. Characteristics of *Plasmodium* malaria cases reported in mainland China, 2011-2015.**

| Characteristics | Total (n=17,745) | Imported cases (n=15,840) | Autochthonous cases (n=1,905) |
|---|---|---|---|
| Type of diagnosis | | | |
| Laboratory-confirmed | 16,579 (93.4%) | 15,354 (96.9%) | 1,225 (64.3%) |
| Clinically diagnosed | 1,166 (6.6%) | 486 (3.1%) | 680 (35.7%) |
| Sex | | | |
| Male | 16,193 (91.3%) | 14,972 (94.5%) | 1,221 (64.1%) |
| Female | 1,552 (8.7%) | 868 (5.5%) | 684 (35.9%) |
| Outcome | | | |
| Non-fatal | 17,622 (99.3%) | 15,718 (99.2%) | 1,904 (99.9%) |
| Fatal | 123 (0.7%) | 122 (0.8%) | 1 (0.1%) |
| Age | | | |
| Median (yrs, IQR) | 38.7 (29.0, 46.0) | 38.1 (29.0, 45.4) | 42.0 (26.4, 58.0) |
| Nationality | | | |
| Chinese | 16,754 (94.4%) | 14,849 (93.7%) | 1,905 (100%) |
| Foreigner | 991 (5.6%) | 991 (6.3%) | 0 (0) |
| Hospitalization | | | |
| Yes | 8,651 (48.8%) | 8,314 (52.5%) | 337 (17.7%) |
| No | 8,174 (46.1%) | 6,701 (42.3%) | 1,473 (77.3%) |
| Unknown | 920 (5.1%) | 825 (5.2%) | 95 (5.0%) |
| Median of time lag (days, IQR) | | | |
| From illness onset to diagnosis | 3.6 (1.7, 6.7) | 3.5 (1.6, 6.6) | 4.4 (2.5, 7.6) |
| From diagnosis to report | 0.1 (0.02, 0.7) | 0.1 (0.02, 0.7) | 0.1 (0.03, 0.6) |
| From illness onset to report | 3.7 (1.7, 6.6) | 3.6 (1.7, 6.5) | 4.6 (2.7, 7.8) |
| Species of *Plasmodium* | | | |
| *P. falciparum* | 9,846 (55.5%) | 9,754 (61.6%) | 92 (4.8%) |
| *P. vivax* | 6,590 (37.1%) | 4,882 (30.8%) | 1,708 (89.6%) |

| Characteristics | Total (n=17,745) | Imported cases (n=15,840) | Autochthonous cases (n=1,905) |
|---|---|---|---|
| *P. ovale* | 525 (3.0%) | 524 (3.3%) | 1 (0.1%) |
| *P. malariae* | 192 (1.1%) | 188 (1.2%) | 4 (0.2%) |
| Mixed infections | 207 (1.2%) | 202 (1.3%) | 5 (0.3%) |
| Untyped | 385 (2.1%) | 290 (1.8%) | 95 (5.0%) |
| Report location vs home/living location | | | |
| In same county | 9,200 (51.8%) | 7,591 (47.9%) | 1,609 (84.5%) |
| In different counties of same province | 5,829 (32.8%) | 5,611 (35.4%) | 218 (11.4%) |
| In different provinces | 1,725 (9.7%) | 1,647 (10.4%) | 78 (4.1%) |
| Foreigner | 991 (5.7%) | 991 (6.3%) | 0 (0) |
| The admin level of hospitals for diagnosis and report | | | |
| Province | 2,382 (13.4%) | 2,350 (14.8%) | 32 (1.7%) |
| Prefecture | 4,730 (26.7%) | 4,604 (29.1%) | 126 (6.6%) |
| County | 8,020 (45.2%) | 7,412 (46.8%) | 608 (31.9%) |
| Township and lower | 2,607 (14.7%) | 1,471 (9.3%) | 1,136 (59.6%) |
| Unknown | 6 (0.03%) | 3 (0.02%) | 3 (0.2%) |

Note: Data are presented as no. (%) of patients unless otherwise indicated. The autochthonous cases also included six cases of transfusion infections (3 *P. falciparum*, 2 *P. malariae*, and 1 *P. ovale*) and one suspected vertical transmission for *P. vivax.*

**Table B-5. Characteristics of *Plasmodium* malaria cases imported from Africa and southeast Asia into mainland China, 2011-2015.**

| Characteristics | Total (n=15,289) | Africa (n=10,949) | Southeast Asia (n=4,340) |
|---|---|---|---|
| Type of cases | | | |
| Laboratory-confirmed | 14913 (97.5%) | 10699 (97.7%) | 4214 (97.1%) |
| Clinically diagnosed | 376 (2.5%) | 250 (2.3%) | 126 (2.9%) |
| Sex | | | |
| Male | 14492 (94.8%) | 10577 (96.6%) | 3915 (90.2%) |
| Female | 797 (5.2%) | 372 (3.4%) | 425 (9.8%) |
| Age | | | |
| Median (yrs, IQR) | 38.3 (29.0, 45.5) | 40.0 (31.0, 46.0) | 34.0 (25.4, 43.0) |
| Nationality | | | |
| Chinese | 14399 (94.2%) | 10619 (97%) | 3780 (87.1%) |
| Foreigner | 890 (5.8%) | 330 (3%) | 560 (12.9%) |
| Hospitalization | | | |
| Yes | 8038 (52.6%) | 6754 (61.7%) | 1284 (29.6%) |
| No | 6544 (42.8%) | 3848 (35.1%) | 2696 (62.1%) |
| Unknown | 707 (4.6%) | 347 (3.2%) | 360 (8.3%) |
| Complications | | | |
| Yes | 1559 (10.2%) | 1222 (11.2%) | 337 (7.8%) |
| No | 12679 (82.9%) | 9062 (82.8%) | 3617 (83.3%) |
| Unknown | 1051 (6.9%) | 665 (6.1%) | 386 (8.9%) |
| Year of onset | | | |
| 2011 | 2818 (18.4%) | 1407 (12.9%) | 1411 (32.5%) |
| 2012 | 2413 (15.8%) | 1511 (13.8%) | 902 (20.8%) |
| 2013 | 3904 (25.5%) | 3193 (29.2%) | 711 (16.4%) |

| Characteristics | Total (n=15,289) | Africa (n=10,949) | Southeast Asia (n=4,340) |
|---|---|---|---|
| 2014 | 2980 (19.5%) | 2304 (21.0%) | 676 (15.6%) |
| 2015 | 3174 (20.8%) | 2534 (23.1%) | 640 (14.7%) |
| Month of onset | | | |
| January | 1223 (8.0%) | 972 (8.9%) | 251 (5.8%) |
| February | 958 (6.3%) | 718 (6.6%) | 240 (5.5%) |
| March | 878 (5.7%) | 636 (5.8%) | 242 (5.6%) |
| April | 1309 (8.6%) | 815 (7.4%) | 494 (11.4%) |
| May | 1789 (11.7%) | 998 (9.1%) | 791 (18.2%) |
| June | 2217 (14.5%) | 1522 (13.9%) | 695 (16.0%) |
| July | 1734 (11.3%) | 1272 (11.6%) | 462 (10.6%) |
| August | 1224 (8.0%) | 878 (8.0%) | 346 (8.0%) |
| September | 1037 (6.8%) | 808 (7.4%) | 229 (5.3%) |
| October | 1014 (6.6%) | 814 (7.4%) | 200 (4.6%) |
| November | 920 (6.0%) | 714 (6.5%) | 206 (4.7%) |
| December | 986 (6.4%) | 802 (7.3%) | 184 (4.2%) |
| Median of time delay (days, IQR) | | | |
| From illness onset to diagnosis | 3.5 (1.6, 6.6) | 3.3 (1.5, 6.5) | 3.7 (2.0, 6.7) |
| From diagnosis to report | 0.1 (0.02, 0.7) | 0.1 (0.01, 0.7) | 0.1 (0.03, 0.7) |
| From illness onset to report | 3.6 (1.7, 6.4) | 3.4 (1.6, 6.4) | 4.0 (2.5, 6.7) |
| Median of duration abroad (days, IQR) | 304 (150, 475) | 320 (171, 515) | 120 (59, 229) |
| Infected with malaria before | | | |
| Yes | 7205 (47.1%) | 6135 (56.0%) | 1070 (24.7%) |
| No | 8084 (52.9%) | 4814 (44.0%) | 3270 (75.3%) |
| Types | | | |
| P. falciparum | 9623 (62.9%) | 8756 (80.0%) | 867 (20.0%) |

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| Characteristics | Total (n=15,289) | Africa (n=10,949) | Southeast Asia (n=4,340) |
|---|---|---|---|
| P. vivax | 4590 (30.0%) | 1228 (11.2%) | 3362 (77.5%) |
| P. ovale | 516 (3.4%) | 503 (4.6%) | 13 (0.3%) |
| P. malariae | 187 (1.2%) | 169 (1.5%) | 18 (0.4%) |
| Mixed infections | 200 (1.3%) | 152 (1.4%) | 48 (1.1%) |
| Untyped | 173 (1.1%) | 141 (1.3%) | 32 (0.7%) |
| Onset location vs report location | | | |
| In same county | 9180 (60.0%) | 5860 (53.5%) | 3320 (76.5%) |
| In different counties of same province | 5354 (35.0%) | 4536 (41.4%) | 818 (18.8%) |
| In different provinces | 755 (4.9%) | 553 (5.1%) | 202 (4.7%) |
| Report location vs home/living location | | | |
| In same county | 7435 (48.6%) | 5166 (47.2%) | 2269 (52.3%) |
| In different counties of same province | 5383 (35.2%) | 4352 (39.7%) | 1031 (23.8%) |
| In different provinces | 1581 (10.3%) | 1101 (10.1%) | 480 (11.1%) |
| Foreigner | 890 (5.8%) | 330 (3.0%) | 560 (12.9%) |
| The admin level of hospitals for diagnosis and report | | | |
| Province | 2211 (14.461%) | 2017 (18.4%) | 194 (4.5%) |
| Prefecture | 4401 (28.8%) | 3858 (35.2%) | 543 (12.5%) |
| County | 7231 (47.3%) | 4788 (43.7%) | 2443 (56.3%) |
| Township and lower | 1445 (9.4%) | 286 (2.6%) | 1159 (26.7%) |
| Unknown | 1 (0.01%) | 0 (0) | 1 (0.01%) |

Note: Data are presented as no. (%) of patients unless otherwise indicated.

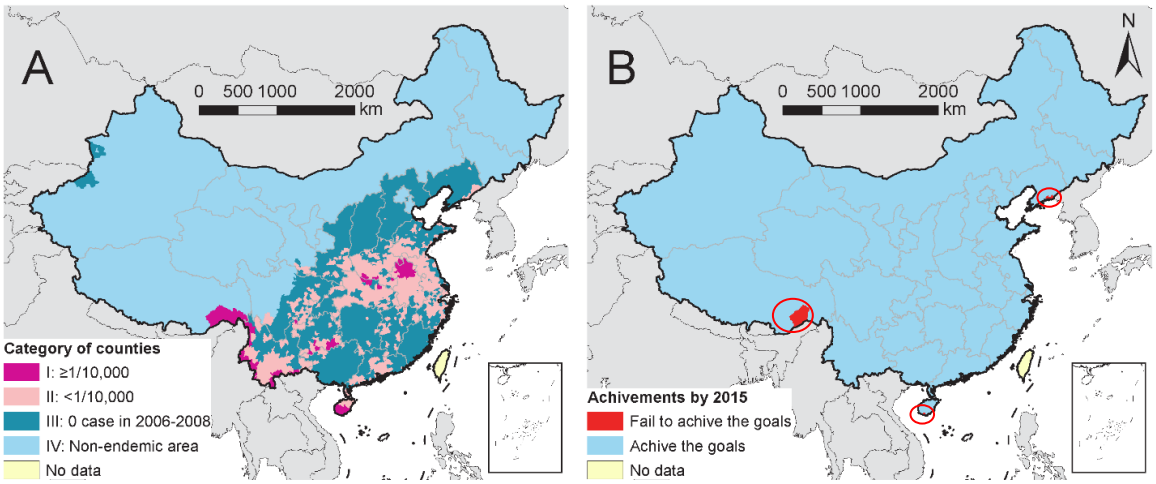


**Figure B-1. Category of counties in NMEP and their achievements by 2015 in China.**

Note: (A) Geographic distribution of counties by category in national malaria elimination programme. (B) Achievements of counties for malaria elimination by 2015. The counties were categorized by malaria incidence in China from 2006 to 2008, with their specific goals for malaria elimination by 2015. Three areas, Motuo county (Type I) in Tibet, Sanya City (Type I) in Hainan, and Donggang City (Type II) in Liaoning, failed to achieve their goals (zero case) by 2015.

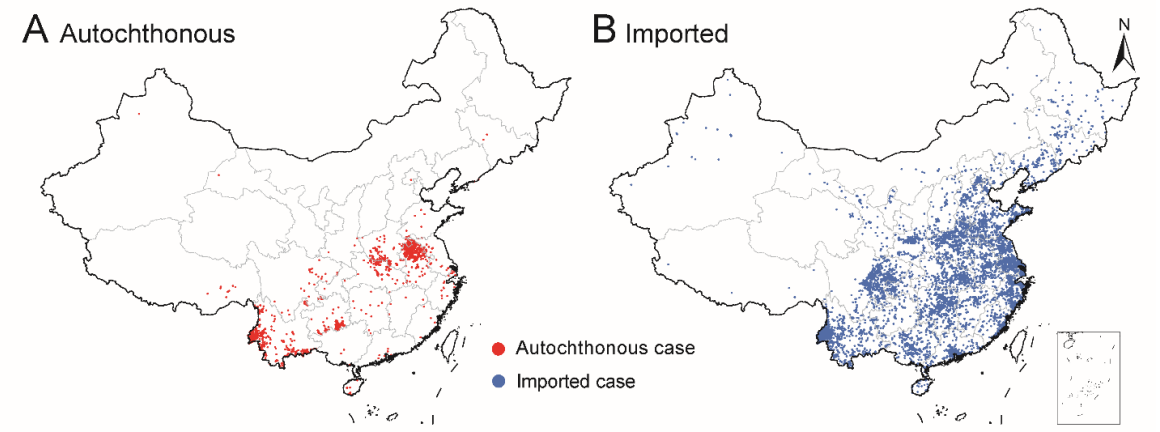


**Figure B-2. Geographic distribution of individual malaria cases in mainland China, 2011-2015**.

Note: (A) Geographic distribution of autochthonous cases. (B) Geographic distribution of imported cases.

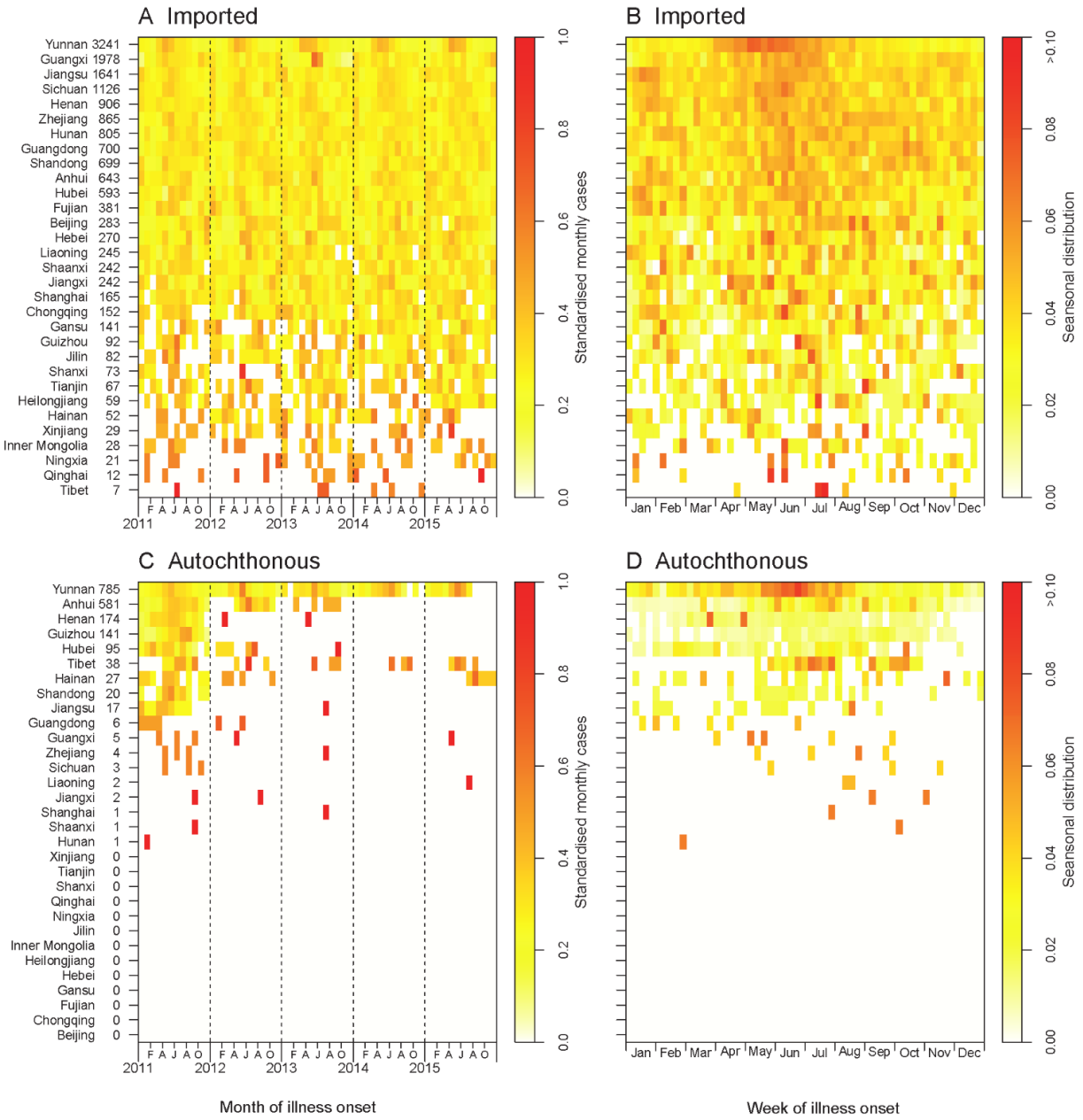


**Figure B-3. Heat map of malaria by province in mainland China, 2011-2015.**

Note: On the Y-axis is listed the name of each province with the number of cases, sorted by number of cases reported in each province, 2011-2015. (A) Time series of monthly imported cases, standardized by the number of total imported cases reported by each province. (B) Seasonal distribution of imported cases, plotted as the mean value of the proportion of cases in each week of the year from 2011 to 2015. (C) Time series of monthly autochthonous cases, standardized by the number of total autochthonous cases reported by each province. The autochthonous malaria also included six cases of transfusion infection (3 *P. falciparum*, 2 *P. malariae*, and 1 *P. ovale*) and one suspected vertical transmission for *P. vivax*. (D) Seasonal distribution of autochthonous cases, plotted as the mean value of the proportion of cases in each week of the year from 2011 to 2015.

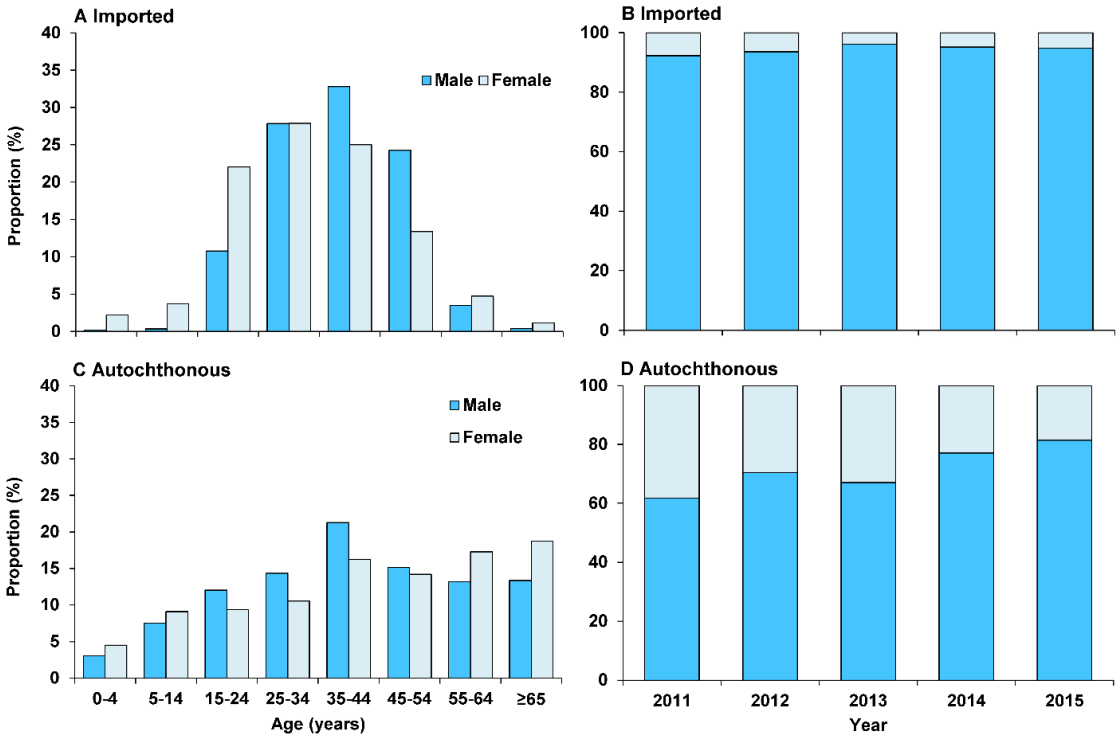


**Figure B-4. Age and gender distribution of imported and autochthonous *Plasmodium* malaria cases in mainland China, 2011-2015.**

Note: (A) Age of imported male (n=14,972) and female cases (n=868). (B) Gender of imported cases by year. (C) Age of autochthonous male (n=1,221) and female cases (n=684). (D) Gender of autochthonous cases by year.

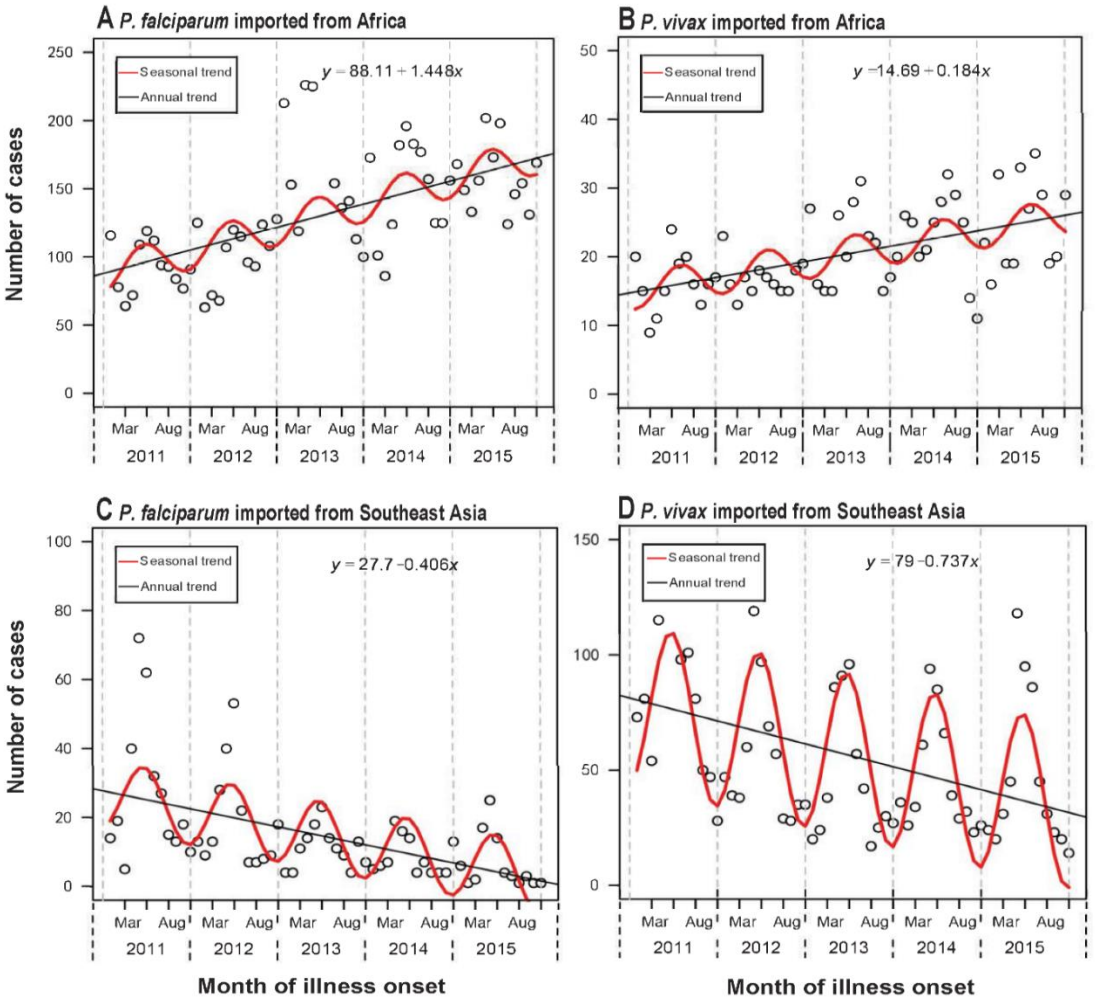


**Figure B-5. Trend of imported *Plasmodium* malaria cases by origins and species, 2011-2015.**

Note: The monthly counts of cases were aggregated by origin and species for 8,756 *P. falciparum* cases and 1,228 *P. vivax* imported from Africa, and 867 *P. falciparum* cases and 3,362 *P. vivax* imported from Southeast Asia. The seasonality of imported cases was fitted by nonlinear regression with cosine function proposed in a previous study (Naumova EN et al. Seasonality in six enterically transmitted diseases and ambient temperature. *Epidemiol Infect* 2007; 135(2): 281-92), and a linear regression model was also employed to explore the annual trend.

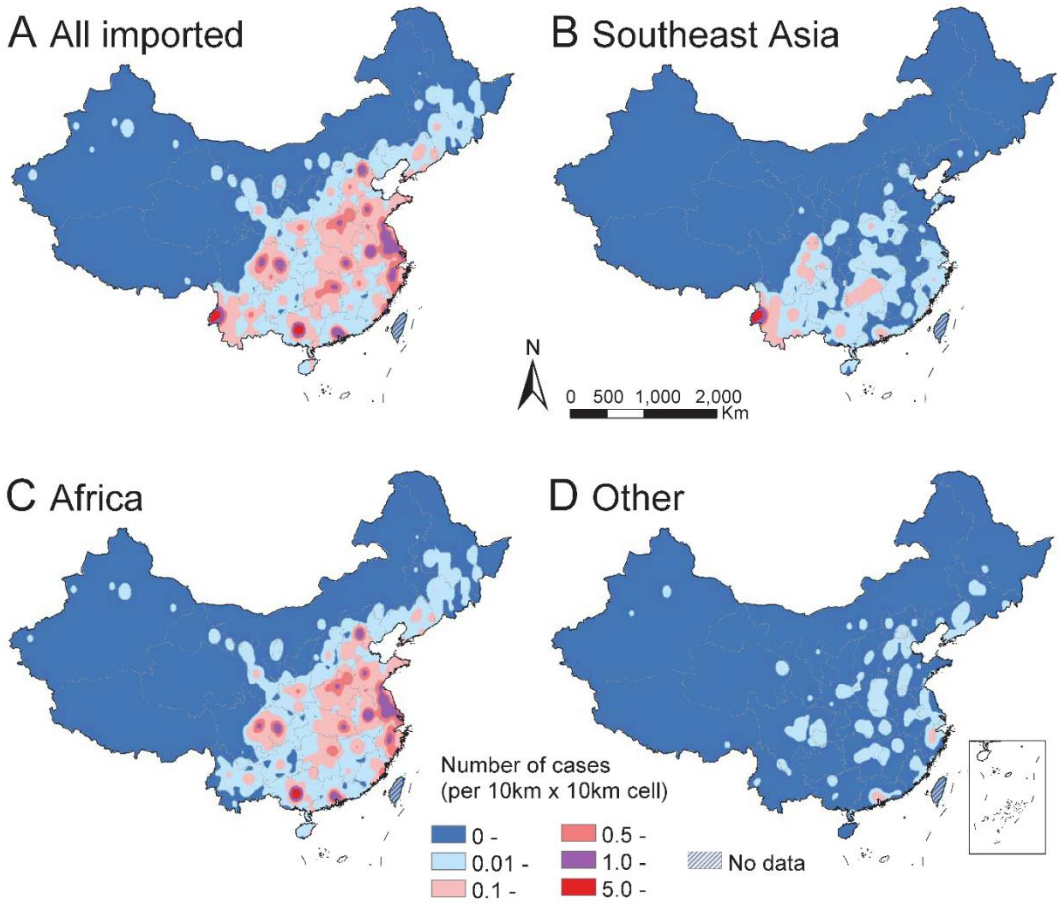


**Figure B-6. Geographic distribution of imported *Plasmodium* malaria in China by origins, 2011-2015.**

Note: (A) All imported cases (n=15,840). (B) Cases imported from Africa (n=10,949). (C) Cases imported from southeast Asia (n=4,340). (D) Cases imported from other regions (n=235). To visualize the geographic distribution of imported cases based on the location of illness onset, density maps were created and smoothed by kernel density estimation at a spatial resolution of 0.083333 decimal degrees per pixel (approx. 10km at the equator).

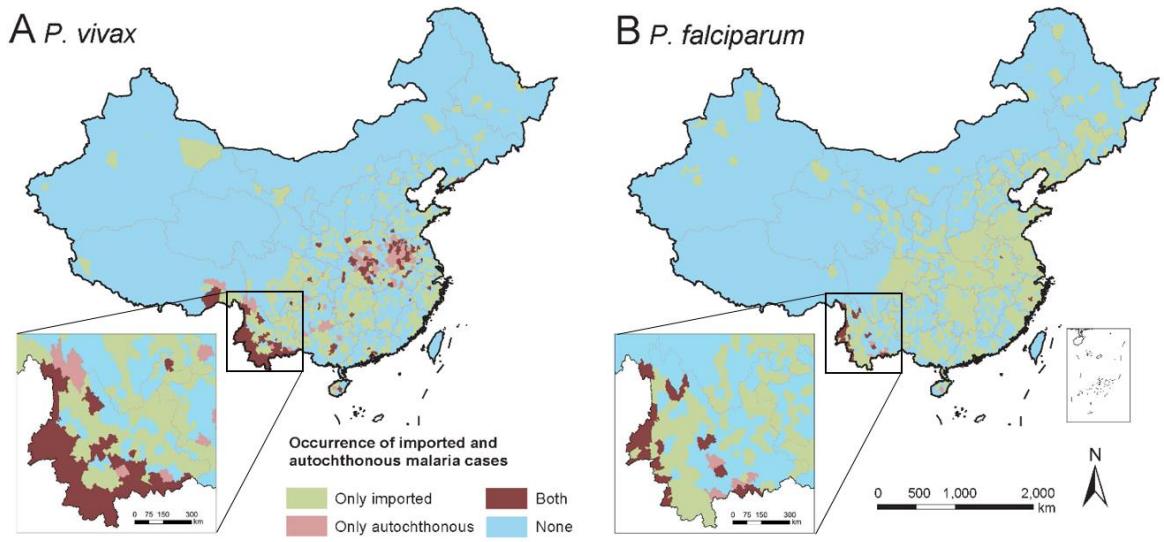


**Figure B-7. Geographic distribution of autochthonous and imported *P. vivax* and *P. falciparum* cases by county in mainland China, 2011-2015.**

Note: (A) Autochthonous (n=1,708) and imported *P. vivax* (n=4,882) with 1536 counties (53.8% of total 2854 counties) only reported imported cases, six counties (0.2%) only reported autochthonous cases, and 18 counties (0.6%) had both cases. (B) Autochthonous (n=92) and imported *P. falciparum* (n=9,754) with 857 counties (30.0%) only reported imported cases, 90 counties (3.2%) only reported autochthonous cases, and 103 counties (3.6%) had both cases.

# Appendix C Supplementary information for Chapter 4

## Materials and Methods

### Database compilation

#### *Malaria case definition and data sources*

This study included all records of *P. falciparum* malaria cases during 2011–2015 imported from sub-Saharan Africa (SSA) to all provinces in mainland China, which includes 22 provinces, four municipalities, and five autonomous regions. Laboratory-confirmed malaria cases refer to patients with any positive result in the following diagnostic tests: malaria parasites confirmed by microscopy, rapid diagnostic tests, or polymerase chain reaction tests. All other cases with malaria-like symptoms and a history of travelling to a malaria endemic area in malaria transmission season, or a history of blood transfusion in past 2 weeks, but without positive laboratory test results, were identified as clinically diagnosed malaria cases (National Health and Family Planning Commission of China, 2006).

Two data sources of individual *P. falciparum* cases were used in this study. One includes demographic information, date of onset, date of diagnosis, date of reporting, and reporting institute, obtained from the National Notifiable Infectious Disease Reporting Information System (NIDRIS). The other consists of epidemiological information on the course of diagnosis, history of travel, treatment, classification (autochthonous or imported case), collated from MESIS (Sun et al., 2016). The MESIS was developed in 2010 as an effort of National Malaria Elimination Action Plan, and the same individual case recorded in NIDRIS and MESIS is linked by unique code. The cases have been checked in NIDRIS and MESIS by the variables of name, identity number and gender to avoid the duplicative reporting, and only case with new infection is reported in the surveillance systems.

#### *P. falciparum malaria prevalence data in Africa*

To assess the impact of malaria endemicity on the importation, parasite rate of *P. falciparum* in 2- to 10-year-olds ($Pf\mathrm{PR}_{2\text{-}10}$) in Africa from 2010 to 2015 were obtained from the Malaria Atlas Project (www.map.ox.ac.uk). The methods behind their construction are presented by Bhatt et al (Bhatt et al., 2015). In brief, a large database of malaria infection prevalence survey points (n= 27,573) were combined with intervention data, and environmental and sociodemographic covariates within a spatiotemporal Bayesian geostatistical model to map the yearly prevalence of *P. falciparum* in children age 2-up-to-10 at 5 × 5 km resolution across sub-Saharan Africa from

2000 to 2015. A map of mean *Pf*$PR_{2-10}$ during 2010-2015 was created and weighted by the averaged population density in 2010 and 2015 of each country which were obtained from the WorldPop Project (www.worldpop.org). Then an average value of *Pf*$PR_{2-10}$ was aggregated for each country and used in the statistical analysis of this study. Because most Chinese cases had a long stay in SSA (median: 317 days) and might be infected in previous year, the data of *Pf*$PR_{2-10}$ in 2010 were also included in this analysis.

***Air travel flow data from Africa to China***

The flow matrix from SSA to mainland China were obtained from an open-access modelled passenger flow matrix of the global air networks for the Vector-borne Disease Airline Importation Risk Tool (www.vbd-air.com). This dataset was modelled based primarily on publicly available datasets in 2010 under a generalized linear model framework (Huang and Tatem, 2013; Huang et al., 2013). To construct the matrix, topological characteristics of the air travel network, city population, and local area GDP, amongst others, were utilized as covariates, and the actual travel volumes were extracted and assembled for training and validation. A log linear model controlling for random effects on origin, destination and the airport hierarchy was then built to predict passenger flows on the network. The model outperformed existing air travel passenger flow models in terms of prediction accuracy (Huang and Tatem, 2013; Huang et al., 2013).

The vector imported was not taken into account due to few direct flights from Africa to China, and air travel likely plays a much more significant role in moving the vector-borne disease (via infected passengers) than in moving the vector itself. Additionally, as the long geographic distance from Africa to China and few travel by road and water, only air travel data were included in this study. The number of air passengers of direct, one-stop and two stops flights from airports in SSA to airports in China were aggregated for each sub-Saharan country.

***Official financial flow data from China to Sub-Saharan Africa***

To define the impact of investment from China on malaria importation, the dataset of Official Development Assistance (ODA) from the People's Republic of China to Africa between 2006 and 2013 were obtained from the AidData Project (china.aiddata.org). China is fundamentally changing the development finance landscape; however, there are few statistical data reported officially, and China does not participate in existing global reporting systems, such as the Organization for Economic Cooperation and Development's Creditor Reporting System and the International Aid Transparency Initiative. Therefore, the AidData has collated official financing from China to Africa using a systematic and replicable approach to generate open-source, project-level data of international development finance (Strange et al., 2015). The official development

finance flows included grants, technical assistance, concessional and non-concessional loans, debt relief, export credits, and other financial instruments.

The methodology of data collation in the AidData was divided into two stages (Strange, 2015). In Stage One, researchers followed a step-by-step guide to identify potential sources of project-level information from the Factiva (global.factiva.com), publicly available official data and documentation from donor/creditor and recipient/borrower governments. Projects were given unique identification numbers as they were discovered and entered into the database. All available project information was input into database, including links to the underlying source documentation. The primary objective of Stage One was to identify and record as many potential projects as possible. In Stage Two, each project record created in Stage One was carefully assessed and enhanced through targeted Google and Google Scholar searches, using a corpus of relevant search terms developed by the AidData. Researchers compiled and triangulated information from these diverse sources in order to accurately populate as project fields as possible. This process of stage-two refinement was designed to minimize reliance upon "sole-sourced" records.

The unit of record in dataset is the “project”, broadly defined, which is a discrete transfer of goods, services or cash. The pledges or cancelled/suspended projects were not included in the aggregate amounts of Chinese official financing. The monetary amount was deflated from reported currency to 2011 U.S. Dollars. In addition, the duration of each project is unavailable, and normally projects need several years to conduct, this analysis therefore included the data since 2006, five years before the study period of 2011-2015, with the assumption that each project will last 5 years.

***Other data***

To quantify the impact of social-economic factors on the risk of mortality in malaria cases, I collected the data of GDP per capita of each province in mainland China in 2015 (National Bureau of Statistics of China, 2016b; National Bureau of Statistics of China, 2016a), referring to the development level of provinces where malaria cases came from (address of onset).

## Data analyses

***Mapping the distribution of P. falciparum cases in China***

To visualize the geographic distribution of imported cases in China, using the coordinate of each case’s location of illness onset in China (appendix **Figure C-2**), I fitted a smoothly tapered density surface to the coordinate of individual cases at a magnitude-per-unit area based on the quartic

kernel function described by Silverman (Silverman, 1986). Conceptually, a smoothly curved surface is fitted over each point, and the surface value is highest at the location of the point and diminishes with increasing distance from the point, reaching zero at the search radius distance from the point. The algorithm used to determine the search radius, also known as the bandwidth is:

$$SearchRadius = 0.9 \times min\left(SD, \sqrt{\frac{1}{\ln(2)}} D_m\right) n^{-0.2}$$

where $D_m$ is the median distance from the mean center for all points, $SD$ is the standard distance, and $n$ is the number of points. The density at each output raster cell is calculated by adding the values of all the kernel surfaces where they overlay the raster cell centre. The output density surface was compiled at a spatial resolution of 0.083333 decimal degrees per pixel (approx. 10km at the equator).

***Identifying communities of malaria importation networks***

The communities of malaria importation networks were detected by modularity analysis. The modularity of a partition is a scalar value between -1 and 1 that measures the density of links inside communities as compared to links between communities (Vincent et al., 2008). The score of modularity is defined by Newman and Girvan (2004) as

$$Q = \frac{1}{2m} \sum_{i,j} \left[A_{ij} - \frac{k_i k_j}{2m}\right] \delta(c_i, c_j)$$

where $A_{ij}$ represents the weight of the edge between $i$ and j, $k_i = \sum_j A_{ij}$ is the sum of the weights of the edges attached to vertex $i$, $c_i$ is the community to which vertex $i$ is assigned, the δ-function $\delta(u, v)$ is 1 if $u = v$ and 0 otherwise and $m = \frac{1}{2}\sum_{ij} A_{ij}$.

Networks with high modularity have dense connections between the nodes within communities but sparse connections between nodes in different communities. This study divided the *P. falciparum* importation networks into communities of densely connected the origins (nodes) of sub-Saharan countries and the destinations (nodes) of provinces in China. To generate suitable number of communities in the networks, the resolution of modularity was tested from 0.1 to 2.0, and 0.9 and 1.1 were set to produce four and three communities respectively to visualize and understand the connectivity between African countries and provinces in China (**Figure 4-2** and appendix **Figure C-6**) (Lambiotte et al., 2014).

Additionally, Ghana in 2013 began to strictly regulate the gold mining industry, which forced many Chinese gold miners returning to hometowns in Guangxi province within a short time, and a

substantial proportion of them (21.6%) infected with malaria (Li et al., 2015). To account for this special event, this analysis therefore exploited the communities of networks again after removing the cases of Ghana-Guangxi pair in January - October 2013 (N = 1,057) during this special event of. This study found that the remained data formed similar three communities (appendix **Figure C-6**) as the original data except for Ghana-Guangxi community (appendix **Figure C-3**).

***Exploring driving factors of malaria importation***

The relations between the number of cases and covariates were explored by the *Spearman*'s rank correlation coefficient (ρ), which is a nonparametric measure of statistical dependence between the ranking of two variables (Lehman, 2005). The *Spearman*'s coefficient ρ assesses how well the relationship (whether linear or not) between two variables can be described using a monotonic function, while *Pearson*'s correlation only assesses linear relationships (Stigler, 1989). The *Spearman* correlation between two variables is equal to the *Pearson* correlation between the rank values of those two variables, and if there are no repeated data values, a perfect *Spearman* correlation of 1 or −1 occurs when each of the variables is a perfect monotone function of the other (Fieller et al., 1957). Because the relationship of two variables without transformation might be linear or not in this study, *Spearman*'s correlation ρ was explored here.

Since the counts of cases tend to be positively skewed and subject to outliers, a generalized linear model with quasi-Poisson distribution function was constructed to fit the numbers of cases from each sub-Saharan country with covariates (Wedderburn, 1974). The quasi-Poisson function differs from the Poisson function only in that the dispersion parameter is not fixed at one, it therefore can model over-dispersion for count data of occurrences in fixed amount of time/space (Enki et al., 2013). To understand the impact of investments, the models were fitted by each of the aggregated ODA covariates, while adjusting for *Pf*$PR_{2\text{-}10}$ and number of air passengers. To make full use of the dataset, the number of imported cases for each origin was adjusted by adding one before logarithmic transform to eradicate zero values (Tatem et al., 2012). Moreover, to compare model's coefficients of covariates that were measured on different scales, Z-scores standardization was applied for covariates (Lukacs, 1942). Z-scores are expressed in terms of standard deviations from their means with a distribution of a mean of 0 and a standard deviation of 1. The formula of Z-scores is

$$z = \frac{x - \mu}{\sigma}$$

where $x$ is an observation of a covariate, $\mu$ is the mean of observations of this covariate, while $\sigma$ is SD. A repeated random sub sampling validation was conducted, with 80% observations were randomly sampled as train set to build the models, and remaining 20% observations as validation set. Due to the low number of aggregated data (41 observations), a high number of iterations

(1000 times) was applied to fully explore the dataset for avoiding the outliers have a too big effect on the final results in validation. The strength of relationships was examined by the median of the $R^2$ calculated for each of the iterations, and the coefficients of models with highest median of $R^2$ were plotted.

***Defining risk factors of mortality in imported P. falciparum***

Bivariate analysis and multivariable logistic regression were conducted, with OR, 95% CI, and a significance level of α=0.05, to examine potential risk factors for case fatality, by comparing deaths from *P. falciparum* malaria with the denominator of all imported *P. falciparum* malaria cases from SSA to mainland China. Potential risk factors for death from imported falciparum malaria were studied by univariate analysis with unadjusted and adjusted OR. The biologically likely potential confounding factors, age, sex, and nationality were included as potential confounding factors for adjusted OR. Additionally, all risk factors found to be associated with mortality with a probability value $p<0.05$ in univariate analysis and potential confounding factors (age, sex, and nationality) were introduced into a multivariable logistic regression model to explore the significant risk factors.

**Table C-1. Variables in the dataset of *P. falciparum* malaria cases imported from SSA to mainland China, 2011-2015**.

| Variables | Definition/classification | Completeness (N = 8,653) |
|---|---|---|
| Type of diagnosis | Clinical diagnosed or laboratory-confirmed case | 100% reported |
| Age | The interval time from the date of birth to the date of onset | 100% reported |
| Nationality | Chinese or foreigner | 100% reported |
| Origin country | The country where the case infected with *P. falciparum* malaria | 100% reported |
| Education | Illiteracy, Primary (6-year education), Junior secondary (9-year), Senior secondary (12-year), or Higher education (>12-year) | 92.5% reported |
| Date of onset | The date of illness onset | 100% reported |
| Date of diagnosis | The date of diagnosis as malaria | 100% reported |
| Date of report | The date of report to surveillance system | 100% reported |
| Date of Death | The date of case death, if applicable. | 100% reported |
| Purpose of travel | Labour service or other | 98.3% reported |
| Duration in Africa of Chinese cases | Days in Africa for Chinese cases | 30.7% reported |
| Hospitalization | Inpatient or outpatient | 97.3% reported |
| County of address | The address (county level) of case with illness onset | 100% reported |
| County's code of address | A unique 8-digital number for each county | 100% reported |
| Coordinates of address | Latitude and longitude of living address of case with illness onset | 100% reported |
| Admin level of first-visit health institution | Province, prefecture, county, or township and lower | 85.3% reported |

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| Variables | Definition/classification | Completeness (N = 8,653) |
|---|---|---|
| First diagnosis as malaria | Yes, or No | 86.2% reported |
| Admin level of hospitals for final diagnosis and report | Province, prefecture, county, or township and lower | 100% reported |
| County's code of hospital | A unique 8-digital number for each county | 100% reported |
| Coordinates of hospital | Latitude and longitude of address of hospital for final diagnosis and report | 100% reported |
| Onset location vs. report (hospital) location | In same county, in different counties of same province, or in different provinces | 100% reported |
| Report (hospital) location vs. home/living location | In same county, in different counties of same province, or in different provinces | 100% reported |

**Table C-2. Amount of ODA by sector from China to sub-Saharan Africa between 2006 and 2013**.

| Sector and subsector | Number of projects | Million U.S. Dollars |
|---|---|---|
| **1 Resource extraction** | **263** | **28,566.06** |
| **1.1 Energy** | **99** | **17,541.91** |
| Energy generation and supply | 99 | 17,541.91 |
| **1.2 Mining** | **46** | **7,245.99** |
| Mining industry and construction | 46 | 7,245.99 |
| **1.3 Agriculture** | **118** | **3,778.16** |
| Agriculture, forestry and fishing | 118 | 3,778.16 |
| **2 Infrastructure** | **319** | **35,732.79** |
| **2.1 Communications** | **72** | **4,619.94** |
| Communications | 72 | 4,619.94 |
| **2.2 Transport** | **140** | **26,654.02** |
| Transport and storage | 140 | 26,654.02 |
| **2.3 Utilities** | **107** | **4,458.83** |
| Water supply and sanitation | 36 | 2,889.33 |
| Other social infrastructure and services | 71 | 1,569.50 |
| **3 Education** | **206** | **961.53** |
| Education | 206 | 961.53 |
| **4 Health** | **365** | **1,624.05** |
| Health | 351 | 1,612.13 |
| Women in development | 9 | 10.52 |
| Population policies/programmes and reproductive health | 5 | 1.41 |
| **5 Multi-sector** | **68** | **20,700.02** |
| Other multisector | 68 | 20,700.02 |
| **6 Other** | **510** | **17,860.19** |

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| Sector and subsector | Number of projects | Million U.S. Dollars |
|---|---|---|
| Unallocated / unspecified | 179 | 7,595.64 |
| Banking and financial services | 10 | 2,271.47 |
| Government and civil society | 172 | 2,199.18 |
| General budget support | 5 | 1,487.06 |
| Trade and tourism | 29 | 1,486.67 |
| Action relating to debt | 31 | 1,456.13 |
| Emergency response | 41 | 1,267.40 |
| Developmental food aid/food security assistance | 26 | 63.77 |
| Business and other Services | 6 | 20.45 |
| Support to non-governmental organizations and government organizations | 5 | 10.66 |
| General environmental protection | 3 | 1.73 |
| Non-food commodity assistance | 3 | 0.03 |
| **Total** | **1731** | **105,444.64** |

Note: The classification of subsector for each project was defined by the Development Assistance Committee of the Organization for Economic Cooperation and Development (Organization for Economic Cooperation and Development, 2015). This study aggregated the subsector into sector (in bold). The monetary amount was deflated from reported currency to 2011 U.S. Dollars.

**Table C-3. Communities of origin-destination networks of *P. falciparum* malaria imported from SSA to mainland China, 2011-2015**.

| Community | Sub-Saharan country (n=41) | Province in mainland China (n=31) |
|---|---|---|
| 1 | Ghana (1) | Guangxi (1) |
| 2 | Sudan, Ethiopia, Sierra Leone, Togo, and Rwanda (5) | Xinjiang and Sichuan (2) |
| 3 | Angola, Equatorial Guinea, Republic of Congo, Gambia, Namibia, Zambia, South Africa, Zimbabwe, South Sudan, and Madagascar (10) | Qinghai, Ningxia, Henan, Jiangxi, Hebei, Anhui, Shandong, Jiangsu, and Jilin (9) |
| 4 | Senegal, Mauritania, Guinea Bissau, Guinea, Liberia, Mali, Ivory Coast, Burkina Faso, Niger, Benin, Nigeria, Gabon, Cameroon, Chad, Democratic Republic of the Congo, Central African Republic, Botswana, Burundi, Mozambique, Uganda, Malawi, Kenya, Eritrea, United Republic of Tanzania, and Somalia (25) | Beijing, Chongqing, Fujian, Gansu, Guangdong, Guizhou, Hainan, Heilongjiang, Hubei, Hunan, Liaoning, Inner Mongolia, Shanghai, Shanxi, Shaanxi, Tianjin, Tibet, Yunnan, and Zhejiang (19) |

Note: The data in parentheses is the number of countries or provinces. The score of modularity is 0.219 with a resolution of 0.9.

**Table C-4. Characteristics of *P. falciparum* malaria cases imported from SSA to mainland China, 2011-2015**.

| Characteristics | Total (n=8,653) | Non-fatal cases (n=8,555) | Fatal cases (n=98) |
|---|---|---|---|
| **Type of diagnosis** | | | |
| Laboratory-confirmed | 8,530 (98.6%) | 8,433 (98.6%) | 97 (99.0%) |
| Clinically diagnosed | 123 (1.4%) | 122 (1.4%) | 1 (1.0%) |
| **Sex** | | | |
| Male | 8,351 (96.5%) | 8,259 (96.5%) | 92 (93.9%) |
| Female | 302 (3.5%) | 296 (3.5%) | 6 (6.1%) |
| **Age** | | | |
| Median (yrs, IQR) | 40.0 (31.0, 46.0) | 40.0 (31.0, 46.0) | 44.2 (36.4, 49.5) |
| Age group | | | |
| 0-4 | 7 (0.1%) | 7 (0.1%) | 0 (0) |
| 5-14 | 6 (0.1%) | 6 (0.1%) | 0 (0) |
| 15-24 | 688 (8.0%) | 685 (8.0%) | 3 (3.1%) |
| 25-34 | 2,275 (26.3%) | 2,257 (26.4%) | 18 (18.4%) |
| 35-44 | 3,022 (34.9%) | 2,993 (35.0%) | 29 (29.6%) |
| 45-54 | 2,324 (26.9%) | 2,283 (26.7%) | 41 (41.8%) |
| 55-64 | 307 (3.4%) | 302 (3.4%) | 5 (5.1%) |
| 65 and above | 24 (0.3%) | 22 (0.3%) | 2 (2.0%) |
| **Nationality** | | | |
| Chinese | 8,395 (97.0%) | 8,298 (97.0%) | 97 (99.0%) |
| Foreigner | 258 (3.0%) | 257 (3.0%) | 1 (1.0%) |
| **Education** | | | |
| Illiteracy | 516 (6.0%) | 504 (5.9%) | 12 (12.2%) |
| Primary | 880 (10.2%) | 862 (10.1%) | 18 (18.4%) |
| Junior secondary | 4,091 (47.3%) | 4,061 (47.5%) | 30 (30.7%) |
| Senior secondary | 1,276 (14.6%) | 1,257 (14.7%) | 19 (19.4%) |
| Higher education | 1,244 (14.4%) | 1,232 (14.4%) | 12 (12.2%) |
| Unknown | 646 (7.5%) | 639 (7.4%) | 7 (7.1%) |
| **Travel purpose** | | | |
| Labour | 7,770 (89.8%) | 7,679 (89.8%) | 91 (92.9%) |
| Other | 738 (8.5%) | 731 (8.5%) | 7 (7.1%) |

| Characteristics | Total (n=8,653) | Non-fatal cases (n=8,555) | Fatal cases (n=98) |
|---|---|---|---|
| Unknown | 145 (1.7%) | 145 (1.7%) | 0 (0) |
| **Hospitalization** | | | |
| Yes | 5,525 (63.9%) | 5,441 (63.6%) | 84 (85.7%) |
| No | 2,894 (33.4%) | 2,884 (33.7%) | 10 (10.2%) |
| Unknown | 234 (2.7%) | 230 (2.7%) | 4 (4.1%) |
| **Year of onset** | | | |
| 2011 | 1,057 (12.2%) | 1,033 (12.1%) | 24 (24.5%) |
| 2012 | 1,197 (13.8%) | 1,184 (13.8%) | 13 (13.3%) |
| 2013 | 2,724 (31.5%) | 2,703 (31.6%) | 21 (21.4%) |
| 2014 | 1,779 (20.6%) | 1,757 (20.5%) | 22 (22.4%) |
| 2015 | 1,896 (21.9%) | 1,878 (22.0%) | 18 (18.4%) |
| **Month of onset** | | | |
| January | 786 (9.1%) | 763 (8.9%) | 23 (23.5%) |
| February | 533 (6.2%) | 526 (6.1%) | 7 (7.1%) |
| March | 469 (5.4%) | 459 (5.4%) | 10 (10.2%) |
| April | 641 (7.4%) | 638 (7.5%) | 3 (3.1%) |
| May | 817 (9.4%) | 805 (9.4%) | 12 (12.2%) |
| June | 1,305 (15.1%) | 1,295 (15.1%) | 10 (10.2%) |
| July | 1,047 (12.1%) | 1,042 (12.2%) | 5 (5.1%) |
| August | 635 (7.3%) | 628 (7.3%) | 7 (7.1%) |
| September | 618 (7.1%) | 615 (7.2%) | 3 (3.1%) |
| October | 619 (7.2%) | 613 (7.2%) | 6 (6.1%) |
| November | 548 (6.3%) | 543 (6.3%) | 5 (5.1%) |
| December | 635 (7.3%) | 628 (7.3%) | 7 (7.1%) |
| **Median of time (days, IQR)** | | | |
| From illness onset to diagnosis | 3.0 (1.4, 6.0) | 3.0 (1.4, 6.0) | 6.3 (3.6, 7.8) |
| From diagnosis to report | 0.1 (0.02, 0.7) | 0.1 (0.02, 0.7) | 0.2 (0.01, 0.7) |
| From illness onset to report | 3.3 (1.6, 5.7) | 3.0 (1.5, 5.7) | 6.2 (3.7, 7.7) |
| In sub-Saharan Africa | 317 (168, 496) | 318 (168, 497) | 175 (47.5, 320.8) |
| **Onset location vs report location** | | | |
| In same county | 4,589 (53.0%) | 4,554 (53.2%) | 35 (35.7%) |
| In different counties of same province | 3,625 (41.9%) | 3,573 (41.8%) | 52 (53.1%) |

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| Characteristics | Total (n=8,653) | Non-fatal cases (n=8,555) | Fatal cases (n=98) |
|---|---|---|---|
| In different provinces | 439 (5.1%) | 428 (5.0%) | 11 (11.2%) |
| **Report location vs home/living location** | | | |
| In same county | 4,083 (47.2%) | 4,056 (47.4%) | 27 (27.6%) |
| In different counties of same province | 3,477 (40.2%) | 3,418 (40.0%) | 59 (60.2%) |
| In different provinces | 835 (9.6%) | 824 (9.6%) | 11 (11.2%) |
| Foreigner | 258 (3.0%) | 257 (3.0%) | 1 (1.0%) |
| **The admin level of first-visit health institution** | | | |
| Province | 898 (10.4%) | 886 (10.4%) | 12 (12.2%) |
| Prefecture | 1,928 (22.3%) | 1,915 (22.4%) | 13 (13.2%) |
| County | 3,227 (37.3%) | 3,210 (37.5%) | 17 (17.4%) |
| Township and lower | 1,325 (15.3%) | 1,297 (15.1%) | 28 (28.6%) |
| Unknown | 1,275 (14.7%) | 1,247 (14.6%) | 28 (28.6%) |
| **The admin level of hospitals for final diagnosis and report** | | | |
| Province | 1,625 (18.8%) | 1,588 (18.5%) | 37 (37.8%) |
| Prefecture | 3,044 (35.2%) | 3,000 (35.1%) | 44 (44.9%) |
| County | 3,769 (43.5%) | 3,752 (43.9%) | 17 (17.3%) |
| Township and lower | 215 (2.5%) | 215 (2.5%) | 0 (0) |

Note: Data are presented as n (%) of patients unless otherwise indicated.

**Table C-5. *Spearman*'s rank correlation coefficients between the number of *P. falciparum* malaria cases and covariates**.

| Covariate | Correlation coefficient (ρ) | P value |
|---|---|---|
| **1 Number of air passengers** | 0.425 | 0.006 |
| **2 *Pf*PR$_{2-10}$** | 0.639 | <0.001 |
| **3 Total amount of ODA** | 0.679 | <0.001 |
| **3.1 Resource extraction** | 0.668 | <0.001 |
| - Energy generation and supply | 0.629 | <0.001 |
| - Mining industry and construction | 0.350 | 0.025 |
| - Agriculture, forestry and fishing | 0.542 | <0.001 |
| **3.2 Infrastructure** | 0.475 | 0.002 |
| - Transport and Storage | 0.470 | 0.002 |
| - Communications | 0.361 | 0.020 |
| - Utilities | 0.373 | 0.016 |
| **3.3 Health** | 0.503 | 0.001 |
| **3.4 Education** | 0.303 | 0.054 |
| **3.5 Multi-sector** | 0.331 | 0.034 |
| **3.6 Other** | 0.393 | 0.011 |

Note: The analysis was based on the aggregated data by sub-Saharan country.

**Table C-6. Performance of generalized linear models fitting the number of *P. falciparum* malaria cases by the amount of each ODA sector, adjusting for *Pf*PR$_{2\text{-}10}$ and number of air passengers**.

| Formula in GLM models | With quasi-Poisson distribution function | |
|---|---|---|
| | $R^2$ in train (IQR) | $R^2$ in cross-validation (IQR) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + ODA (total) | 0.659 (0.633, 0.698) | 0.577 (0.237, 0.797) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Resource | 0.335 (0.314, 0.429) | 0.303 (0.096, 0.654) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Infrastructure | 0.171 (0.137, 0.208) | 0.132 (0.021, 0.374) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Health | 0.489 (0.455, 0.536) | 0.116 (0.018, 0.507) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Education | 0.310 (0.267,0.356) | 0.110 (0.020, 0.478) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Multi-sector | 0.493 (0.428, 0.622) | 0.257 (0.051, 0.691) |
| Case ~ Passengers + *Pf*PR$_{2\text{-}10}$ + Other | 0.280 (0.220, 0.351) | 0.056 (0.011, 0.269) |

Note: The analysis based on the aggregated data by sub-Saharan country. In the cross-validation approach, 80% observations were randomly sampled as train set with remaining 20% as validation set, and the process was iterated 1000 times.

**Table C-7. Factors associated with risk of death in *P. falciparum* malaria cases imported from sub-Saharan countries to mainland China between 2011 and 2015**.

| Risk factor | No (%) of fatal cases | Odds ratio (95% CI) of death | | | |
|---|---|---|---|---|---|
| | | Crude OR | *P* | Adjusted OR[a] | *P* |
| **Gender** | | | | | |
| Female | 92/8351 (1.10) | 1.9 (0.7, 4.0) | 0.153 | 2.0 (0.8, 4.4) | 0.095 |
| Male | 6/302 (1.99) | | | | |
| **Age** | | | | | |
| 0-50 years | 83/7969 (1.04) | 2.1 (1.2, 3.6) | 0.006 | 2.2 (1.2, 3.7) | 0.007 |
| >50 years | 15/684 (2.19) | | | | |
| **Nationality** | | | | | |
| Chinese | 97/8395 (1.16) | 2.6 (0.6, 60.8) | 0.373 | 3.5 (0.8, 61,9) | 0.218 |
| Foreigner | 1/258 (0.39) | | | | |
| **Purpose of visit to sub-Saharan Africa** | | | | | |
| Labour service | 91/7770 (1.17) | 1.2 (0.6, 2.9) | 0.588 | 1.2 (0.6, 3.1) | 0.597 |
| Other | 7/738 (0.95) | | | | |
| **Education** | | | | | |
| Primary or lower | 30/1396 (2.15) | 2.4 (1.5, 3.6) | <0.001 | 2.3 (1.5, 3.5) | <0.001 |
| Secondary or higher | 61/6611 (0.92) | | | | |
| **Modularity of destination province** | | | | | |
| Community 1st | 2/1548 (0.13) | Reference | | | |
| Community 2nd | 14/597 (2.35) | 17.4 (4.8, 121.2) | <0.001 | 18.2 (5.1, 116,4) | <0.001 |
| Community 3rd | 39/3422 (1.14) | 8.3 (2.5, 54.9) | <0.001 | 8.7 (2.7, 53,7) | <0.001 |
| Community 4th | 43/3086 (1.39) | 10.2 (3.1, 67.2) | <0.001 | 10.6 (3.3, 65,4) | <0.001 |
| **GDP per capita of each province in 2015 (onset location)** | | | | | |
| <=12,000 US dollars | 80/6293 (1.27) | 1.7 (1.0, 2.9) | 0.046 | 1.7 (1.1, 3.0) | 0.036 |

| | | | | | |
|---|---|---|---|---|---|
| >12,000 US dollars | 18/2360 (0.76) | | | | |
| **Month of onset** | | | | | |
| January - February | 40/1788 (2.24) | 2.7 (1.8, 4.0) | <0.001 | 2.7 (1.8, 4.0) | <0.001 |
| March – December | 58/6865 (0.84) | | | | |
| **Duration from onset to diagnosis** | | | | | |
| >3 days | 74/4163 (1.78) | 3.4 (2.1, 5.4) | <0.001 | 3.4 (2,1, 5.4) | <0.001 |
| <=3 days | 24/4490 (0.53) | | | | |
| ***PfPR*$_{2-10}$ in sub-Saharan countries in 2010-2015** | | | | | |
| <=20% | 44/2863 (1.54) | 1.7 (1.1, 2.5) | 0.012 | 1.7 (1.1, 2.5) | 0.013 |
| >20% | 54/5790 (0.93) | | | | |
| **First-visit health institution** | | | | | |
| Township level or lower | 28/1325 (2.11) | 3.1 (1.9, 5.0) | <0.001 | 3.0 (1.9, 4.9) | <0.001 |
| County level or higher | 42/6053 (0.69) | | | | |

[a] The odds ratio was adjusted for gender, age and nationality if applicable.

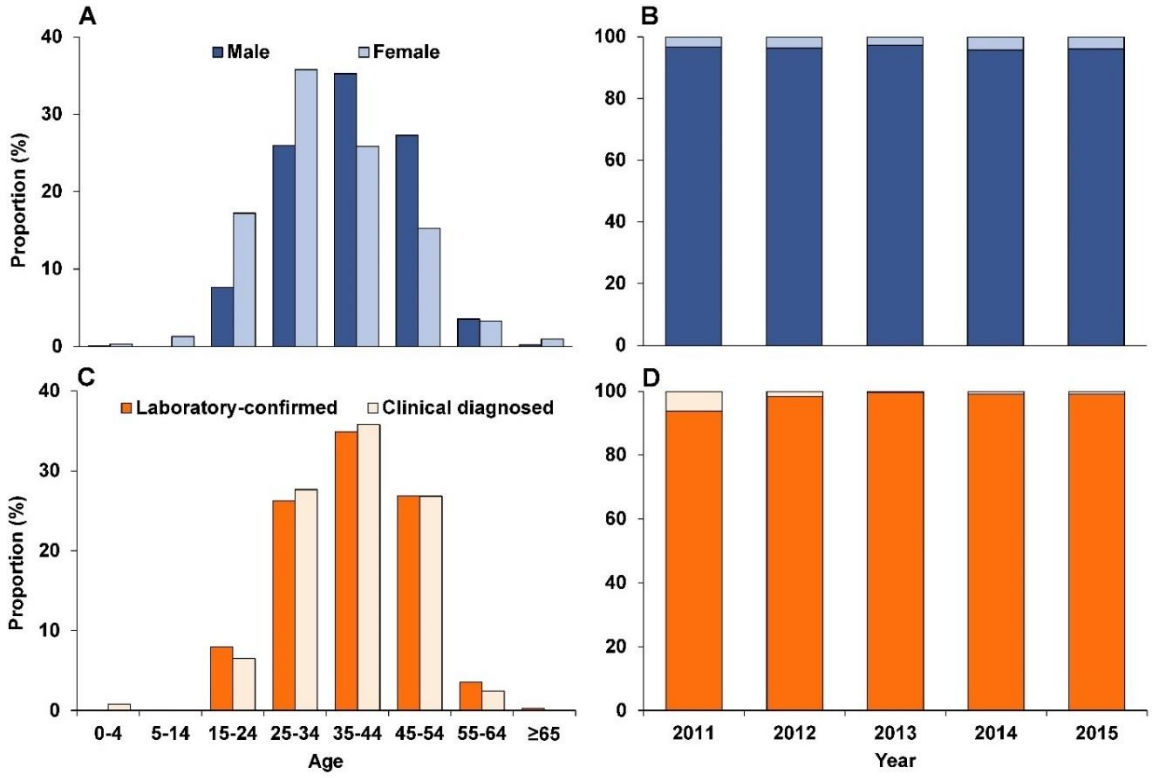


**Figure C-1. Age distribution and proportion by different characteristics of *P. falciparum* malaria cases from sub-Saharan countries to provinces in mainland China, 2011-2015**.

Note: (A) Age distribution of male and female cases. (B) Proportion of cases by sex each year. (C) Age distribution of laboratory-confirmed and clinical diagnosed cases. (D) Proportion of laboratory-confirmed and clinically diagnosed cases each year.

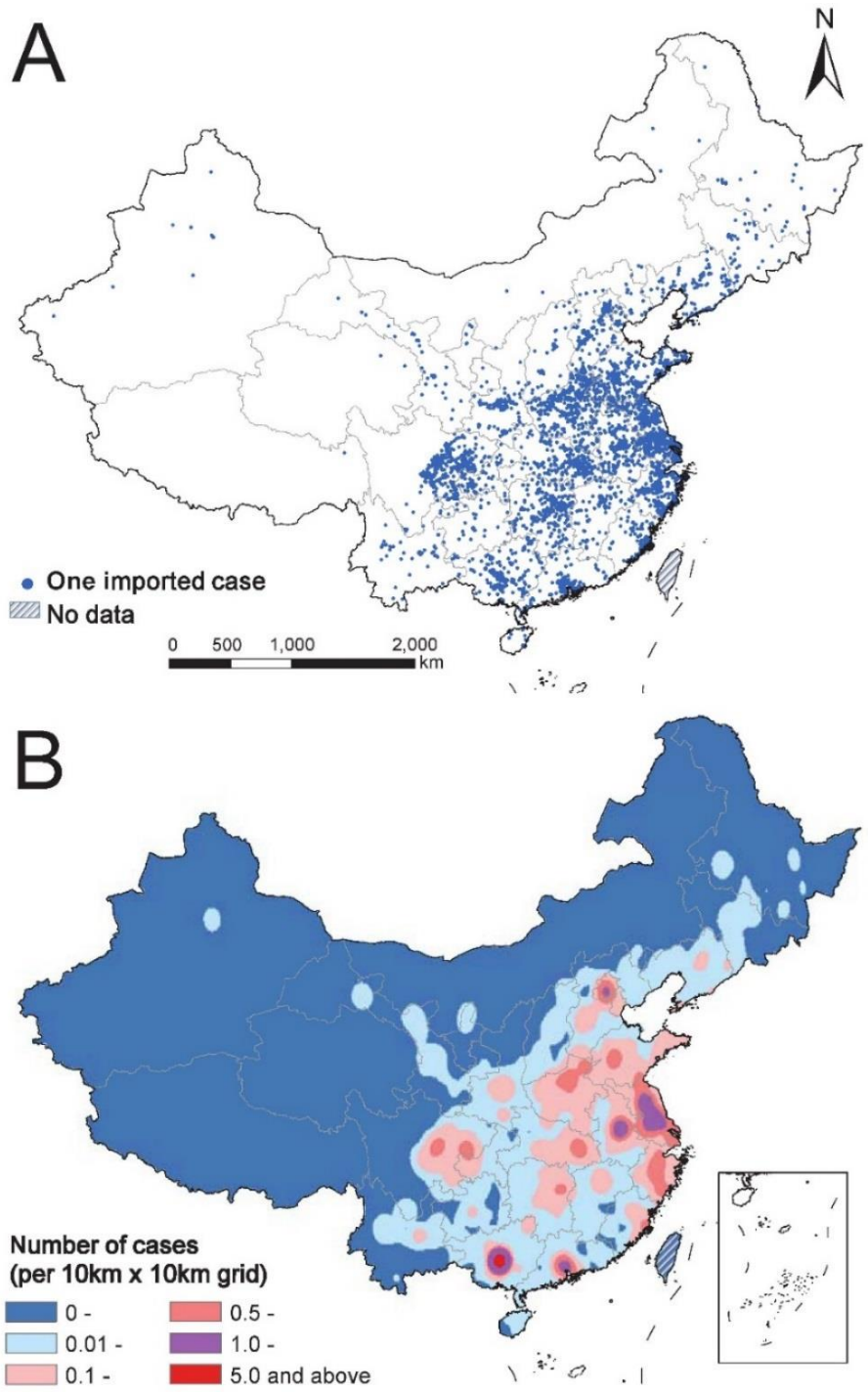


**Figure C-2. Geographic distribution of *P. falciparum* malaria cases imported from SSA into China, 2011-2015**.

Note: (A) Geographic mapping of each by location with illness onset. (B) Density of cases per 10km$^2$ by kernel estimation. The centre of Guangxi province has the highest density (≥ 5 cases per 100 km$^2$), followed by Beijing, Jiangsu, Anhui and Guangdong provinces at eastern China (1.0 to 4.9 cases per 100km$^2$), and Sichuan province in western China and Henan province in central China (0.5 -0.9 cases per 100km$^2$).

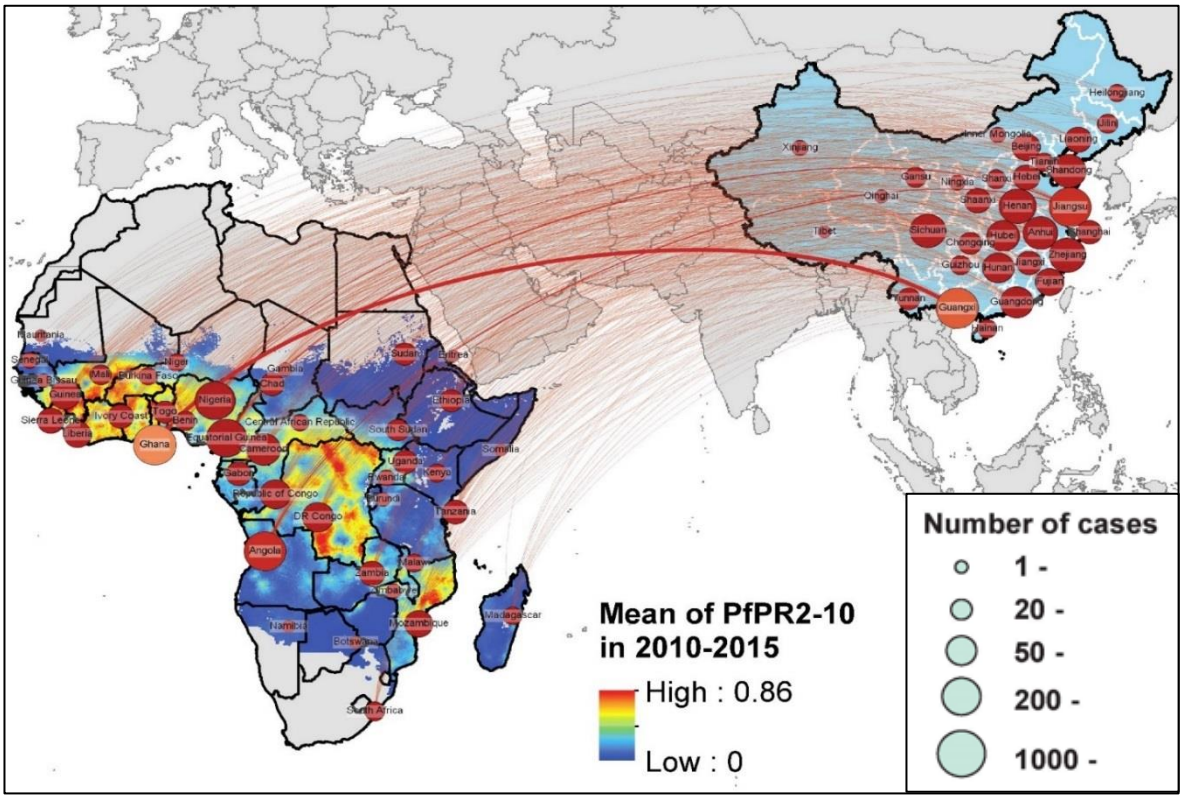


**Figure C-3. Routes of *P. falciparum* malaria cases importation from sub-Saharan countries to provinces in mainland China, 2011-2015**.

Note: Each line represents a pair of origin-destination, and the circle size and line weight represents the number of cases.

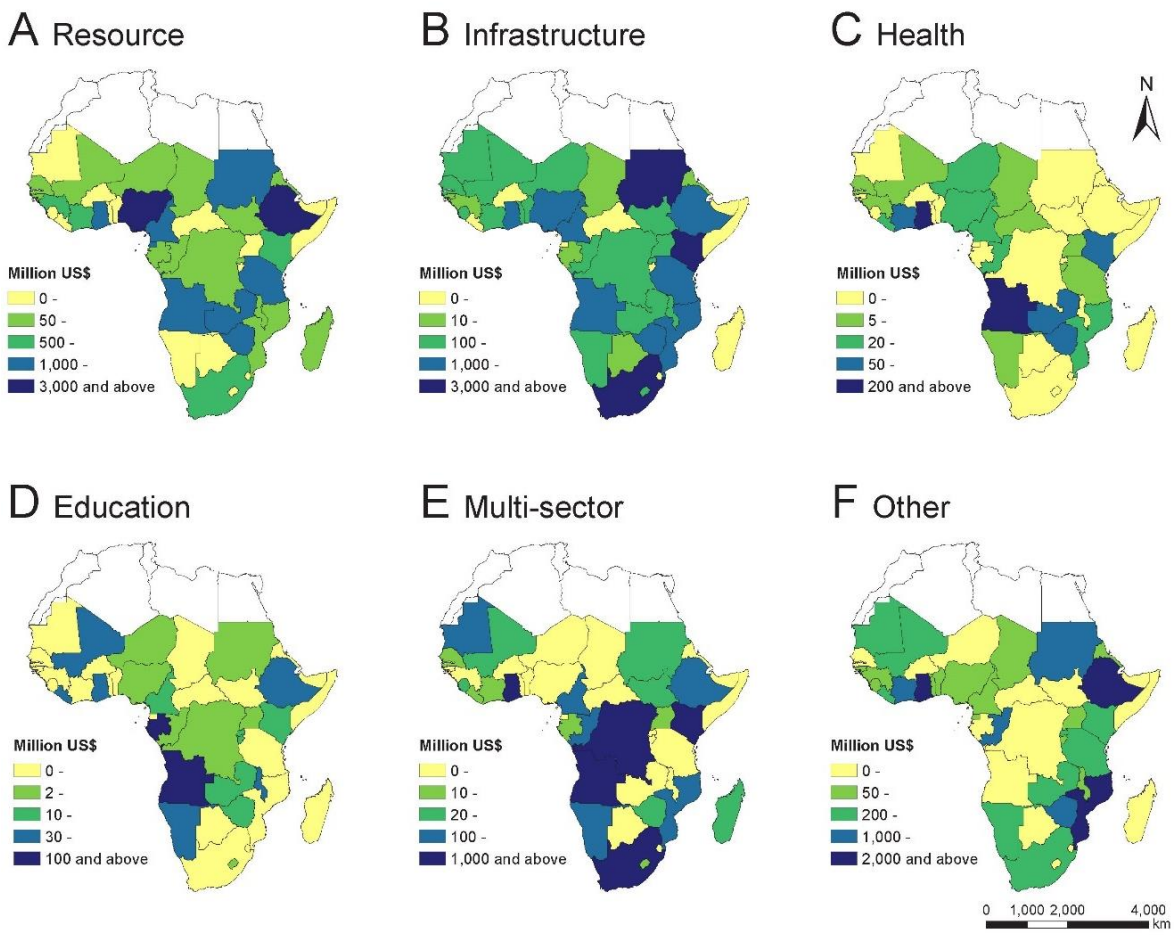


**Figure C-4. Geographic distribution of ODA by sector from China to sub-Saharan countries between 2006 and 2013**.

Note: The monetary amount of ODA was deflated from reported currency to 2011 U.S. Dollars.

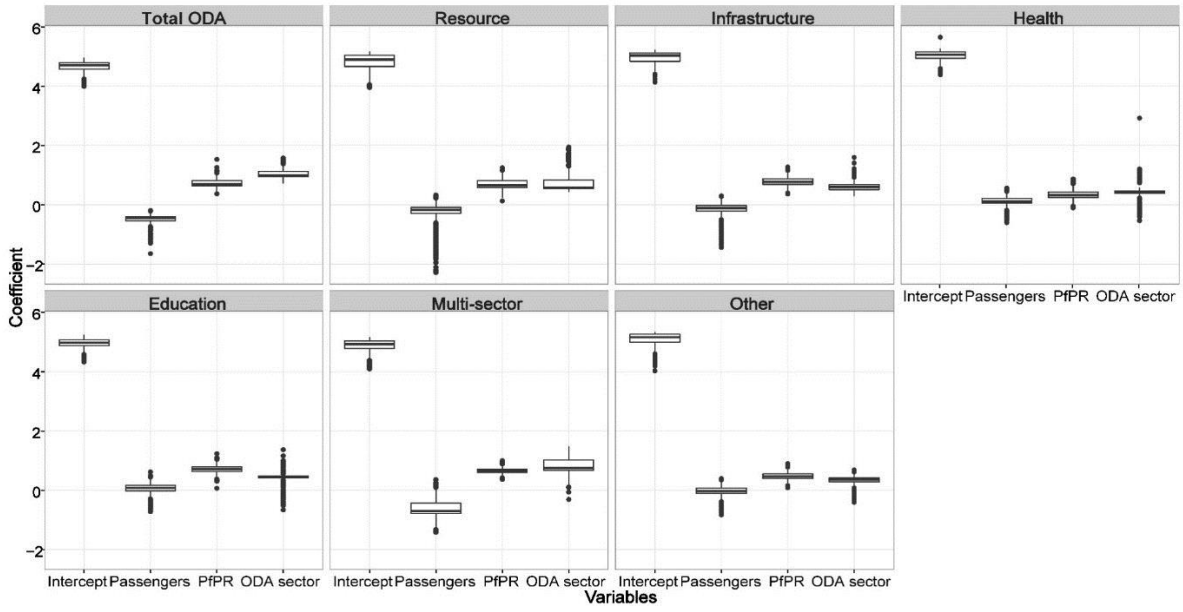


**Figure C-5. Boxplot of coefficients of covariates in generalized linear model.**

Note: The model with quasi-Poisson distribution was used to fit the number of *P. falciparum* malaria cases by the amount of each ODA sector, adjusting for *Pf*$PR_{2\text{-}10}$ and number of air passengers. Each covariate was standardized, and the process of cross-validation was iterated 1000 times.

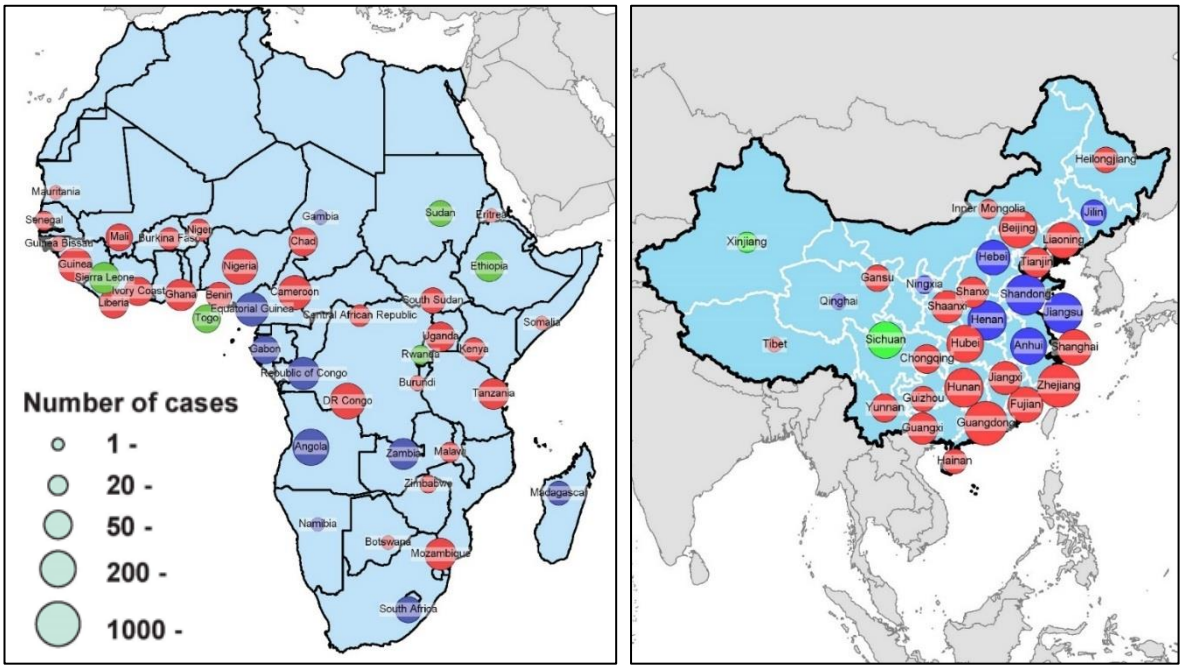


**Figure C-6. Three communities of origin-destination networks of *P. falciparum* malaria cases from sub-Saharan countries to provinces in mainland China, 2011-2015.**

Note: The cases of Ghana-Guangxi pair in January - October 2013 (N = 1,057) were removed from this figure. In 2013, Ghana began to strictly regulate the gold mining industry, which forced many Chinese gold miners to return to Guangxi province within a short time, and a substantial proportion of them (21.6%) infected with malaria (Li et al., 2015). Therefore, the communities of networks were exploited again after removing the cases returned from Ghana during this special event. The same colour of circles represents the same community of origin-destination networks detected by modularity analysis. The score of modularity is 0.206 with a resolution of 1.1.

# Appendix D Supplementary information for Chapter 5

## Materials and Methods

### Database compilation

#### *DENV incidence in the SEA*

The annual dengue surveillance data (including dengue fever, dengue haemorrhagic fever and dengue shock syndrome) between 2005 and 2015 reported in 17 SEA countries (Cambodia, Bangladesh, Bhutan, India, Indonesia, Laos, Malaysia, Maldives, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Thailand, Timor-Leste, and Vietnam) were obtained from publicly available sources (appendix **Table D-1**). This included Dengue Situation Updates of the WHO and regional offices, the websites of the ministries of health in individual countries, and dengue case data of seven SEA countries in 2005-2010 collected by the Project Tycho (www.tycho.pitt.edu) that are identical to those originally reported and have not been modified (van Panhuis et al., 2015). To complement these, I searched PubMed for relevant articles in English published from January 1, 2005 to December 31, 2016 with the query "((Dengue[Title]) AND "country name"[Title]) AND ("2005/01/01"[Date - Publication]: "2016/12/31"[Date - Publication])", and the search engine (www.google.com) was queried with keywords, such as "Dengue", year and name of country in English, to identify the aggregated data of dengue epidemics from English language news releases. The annual numbers of DENV cases were available for all 17 SEA countries, and monthly data were available for 9 countries: Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam (appendix **Table D-1**).

#### *International air travel from SEA into China and nationality of travellers*

For commercial air travel from countries in SEA into mainland China between January 1, 2005, and December 31, 2015, the airline ticket sales and flight itinerary data were obtained from the International Air Transport Association (IATA), representing an estimated 90% of all passenger trips on commercial flights worldwide (the remaining 10% of passenger data are estimates modelled by the IATA). This analysis assumed that the airports mainly service the population in their cities or provinces, and did not account for cross-province or city ground travel in China. Additionally, the itinerary data did not distinguish between Chinese residents and SEA residents. Therefore, to account for travel patterns and different risk of dengue infection and importation in Chinese and local residents of SEA, the annual number of residents from each SEA country

travelling into China were obtained from the China National Tourism Administration (CNTA) (www.cnta.gov.cn/zwgk/lysj), then divided by the yearly total volume of travellers from each country into China to estimate the proportions of Chinese travellers and local residents from SEA countries into China for each year, then the monthly proportions were computed with the assumption that the monthly figures had an standard deviation of 10% of the annual proportions.

## Data analyses

### *Wavelet transforms for dengue periodicity in the SEA and China*

To examine the seasonality of dengue transmission and importation, I used wavelet transform methods to decompose monthly dengue incidence for nine SEA countries and monthly numbers of dengue cases imported from SEA into China as well as the autochthonous cases reported in China. Wavelet transforms are appropriate to characterize epidemiological time series containing cyclical variability with periodicities that change over time (non-stationarity) and isolate the multiannual and annual periodical features from the reported incidence data (van Panhuis et al., 2015; Grenfell et al., 2001; Choisy and Rohani, 2012; Johansson et al., 2009). Detailed methods for wavelet analysis have been described previously (van Panhuis et al., 2015; Torrence and Compo, 1998; Cazelles et al., 2008).

As described previously (van Panhuis et al., 2015), the monthly incidence rates for each country were de-trended by subtracting fitted values of a linear model from the observed values. The fitted linear model:

$$\widehat{IR_{\iota,m}} = C + \beta_c \times m$$

where $\beta_c$ is the linear regression coefficient, and *m* is the study month. The de-trended incidence rates for each country (*i*) and month (*m*) are thus

$$\widetilde{IR_{\iota,m}} = IR_{i,m} - \widehat{IR_{\iota,m}}$$

where *m* refers to the month and $IR_{i,m}$ refers to the reported incidence rates for each country and month. Finally, incidence rates were centred (discounted the mean) and reduced (divided by the SD) to z scores to increase cross-country comparability.

Then, the continuous wavelet transforms with the complex Morlet wave using a nondimensional frequency $\omega_0 = 6$ and a periodicity step size $\delta_j$ of 0.25 on a linear scale were computed for each country to enable the extraction of a high resolution of the periodicity scale (1-mo intervals) and obtain phase angles to represent epidemic timing (van Panhuis et al., 2015; Cazelles et al., 2007; Torrence and Compo, 1998). For each scale *s* and time interval $\delta_t$, the continuous wavelet

transforms of a time series were defined as in the work by Torrence and Campo (Torrence and Compo, 1998):

$$W_n^X(s) = \sqrt{\frac{\delta t}{s}} \sum_{n'=0}^{N-1} x_{n'} \psi^* \left[ \frac{(n' - n)\delta t}{s} \right]$$

where *n* represents the time index, ranging from zero to the total number of time points *N*, and $\psi$ represents the Morlet wavelet function and * the complex conjugate. Statistical significance of wavelet transforms was tested by comparing the wave signal with a red noise background signal (van Panhuis et al., 2015; Torrence and Compo, 1998; Cazelles et al., 2008).

Additionally, to compute the incidence rate and probability of travel, the corresponding populations for SEA countries for 2005-2015 were obtained from the World Bank (www.worldbank.com), and the population data at national and sub-national level for each year in China were obtained from the National Statistical Bureau of China.

***Synchrony of dengue transmission in SEA and importation into China***

As a metric for synchrony over time, I measured wavelet coherency between dengue transmission time series in SEA and dengue importation time series from SEA into China. As described previously (van Panhuis et al., 2015; Cazelles et al., 2007; Grinsted et al., 2004), wavelet coherency uses wave transforms of two time-series to indicate their localized phase relationship in a time–frequency spectrum. Wavelet coherency ranges from zero to one, and high wavelet coherency requires that statistically significant cycles of a particular periodicity are detected in both time series and that these cycles are phase-dependent (positively or negatively):

$$R_n^2(s) = \frac{|S(s^{-1} W_n^{XY}(s))|^2}{S(s^{-1}|W_n^X(s)|^2) \times S(s^{-1}|W_n^Y(s)|^2)}$$

where *S* is a smoothing operator. Statistical significance of wavelet coherency was tested using Monte Carlo methods (n = 600) (van Panhuis et al., 2015; Grinsted et al., 2004). For the wavelet transform in the wave coherency function, same parameters were used as specified for the wave correlation analysis.

***Importation model***

Based on previous work (Johansson et al., 2012; 2014), the relative risk ($p_{IMPORT}$) of dengue importation from SEA into a location (*i*) of China were defined as

$$p_{IMPORT}(i, M) = 1 - \prod_{s \in S} \prod_{m \in M} \left(1 - p_{i,s,m}^f\right)^{I_{s,m}D} \left(1 - p_{i,s,m}^c\right)^{I_{s,m}DC}$$

where $I_{s,m}$ is the number of infections in origin location *s* and month *m*; *D* the average duration of infection in humans; *C* the duration of stay (divided by the number of days in each month) in SEA for Chinese; and the monthly probability of Chinese ($p^{f}_{i,s,m}$) and residents in SEA ($p^{c}_{i,s,m}$) travelling from each source location into a destination in China in a month.

Given the high dengue burden and ecological suitability of vectors in SEA (Brady et al., 2014; Stanaway et al., 2016), I assumed that the viruses were active across all geographical areas in SEA conducive to year-round transmission for 2005-2015.

***Introduced transmission model***

The probability of introduction leading to autochthonous transmission ($p_{AUTO}$) by Chinese and foreign travellers was considered as the probability of infected travellers arriving, infected travellers infecting mosquitoes, and infected mosquitoes infecting at least one human.

$$p_{AUTO}(i,M) = 1 - \prod_{s\in S}\prod_{m\in M}\left(1 - p^{f}_{i,s,m} + p^{f}_{i,s,m}e^{R^{HM}_{0i,m}\left(e^{-R^{MH}_{0i,m}}-1\right)}\right)^{Is,mD}\left(1 - p^{c}_{i,s,m} + p^{c}_{i,s,m}e^{R^{HM}_{0i,m}\left(e^{-R^{MH}_{0i,m}}-1\right)}\right)^{Is,mDC}$$

where the specific components of DENV transmission from humans to mosquitoes and from mosquitoes to humans were characterized as a *Poisson* process with means $R^{HM}_{0i,m}$ and $R^{MH}_{0i,m}$, the average number of infectious mosquitoes produced per infected human and the average number of humans infected per infectious mosquito, respectively. $R^{HM}_{0i,m}$ was defined as

$$R^{HM}_{0i,m} = \varphi_{i,m}\alpha\beta_{HM}V\gamma_{i,m}$$

where $\varphi_{i,m}$ is the number of mosquitoes per person in a location *i* and month *m*, $\alpha$ the daily biting rate, $\beta_{HM}$ the probability of transmission given an infectious blood meal, *V* the number of days a human is infectious, and $\gamma_{i,m}$ the proportion of mosquitoes surviving the extrinsic incubation period in a given location *i* and month *m*. Then, $R^{MH}_{0i,m}$ was formulated as

$$R^{MH}_{0i,m} = \alpha\beta_{MH}L_{i,m}$$

where $\alpha$ represents the daily biting rate, $\beta_{MH}$ the probability of transmission given an infectious bite, and $L_{i,m}$ the number of days an infectious mosquito survives in a place *i* and month *m*. Finally, the $R_{0i,m}$ was defined as

$$R_{0i,m}=R^{HM}_{0i,m} \times R^{MH}_{0i,m}.$$

Given the airport mainly serviced for the local regions, I assumed that the travellers with DENV infections arrived at the cities or provinces of destinations without further cross-city or province movement during infectious period.

***Model parameterization***

**Volume of Chinese and SEA travellers:** The annual number of residents from each SEA country travelling into China, then divided by the yearly total volume of travellers from each country into China to estimate the proportions of Chinese travellers and local residents from SEA countries into China for each year, then I generated the monthly proportions with the assumption that the monthly proportions of travellers between Chinese and SEA residents had a SD of 10% of the average annual proportions.

**Probability of travel (*p*):** Based the estimated nationality data of all itineraries originating from SEA countries into China, for residents in SEA I calculated the probability of travel from a specific SEA origin country to a specific city in China for each month, using the population of the origin country as the denominator. For Chinese, I assumed all Chinese will return to China, and the probability of travel from China to SEA then return to China for each month as the total number of monthly travellers for each origin-destination pair divided by the population of the origin area in China (a province or prefectural city). Additionally, these probabilities were reduced by 25–100% (uniformly distributed, mean = 62.5%) to account for the potential lower travel abilities of infected patients in the years of 2005-2015. This reduction was used to reflect possible changes in travel patterns or differences in the probability of travel for infected individuals due to different risks (e.g., higher risk of infection for non-travellers vs. travellers) or due to illness (i.e., sick individuals may be less likely to travel).

**Duration of stay in SEA for Chinese travellers (C):** This analysis assumed the all travellers were susceptive to DENV, and the risk of infection was related to the duration of stay in the SEA country. To count for the different monthly risks of exposure to DENV in Chinese travellers and residents in SEA, the duration of stay (C) for Chinese travellers in SEA for each month was parameterized as 7 days (SD 1 day) based on CNTA data, standardized by the number of days of the corresponding month.

**Infections in origin populations (*I*):** Infection by any dengue virus can produce a wide spectrum of illness, with most infections asymptomatic or subclinical, and cases reported may be under-recognized or misclassified (e.g., DENV cases misdiagnosed as another arboviral infection such as Chikungunya) (Guzman and Harris, 2015). The reported cases were assumed to represent approximately 80% (SD 10%) of all infections.

**Human infectious period (V):** Patients are typically viremic for 3-5 days, and mosquitoes are capable of becoming infected when biting viremic hosts - the model assumes a viremic duration of four days (SD 1 day) (Guzman and Harris, 2015).

**Duration of infection in humans (*D*):** I define this period as the length of time between when a human becomes infected and when that human ceases to be infectious to mosquitoes, i.e. the period when a person could travel and still be infectious after traveling. The mean intrinsic incubation period for DENV is approximately 6 days and the infectious period post-onset is 3–5 days (Guzman and Harris, 2015). *D* has a value of 10 days (SD 1 day) in this model.

**Mosquito biting rate ($\alpha$):** A detailed study of blood meals suggests that *Ae. aegypti* feed 0.63–0.76 times per day (Scott et al., 2000). This study assumed that *Ae. albopictus* behaves similarly and used a mean of 0.7 blood meals per day (SD 0.05) as previous study (Johansson et al., 2014).

**Human-to-mosquito transmissibility ($\beta_{HM}$):** $\beta_{HM}$ is the probability of a mosquito acquiring DENV while feeding on a viremic human. Because this analysis estimated the human infectious period based on the 50% infectious dose, $\beta_{HM}$ is assumed as 0.5 (SD 0.1).

**Mosquito-to-human transmissibility ($\beta_{MH}$):** Transmissibility of DENV from infected mosquitoes to humans is unknown, yet it is likely less than 100%. The probability was assumed as 0.5 (SD 0.1).

**Extrinsic incubation period (EIP):** EIP is the period in the mosquito after acquiring the virus and prior to being able to transmit the virus. Temperature-specific data for DENV are limited to the range of 26–30°C (Chan and Johansson, 2012). This study assumed that average EIP at 28°C ($EIP_{28}$) is 6 days (SD 2 days) and that the relationship with temperature is $\beta_T = -0.08$ (SD 0.02) (Chan and Johansson, 2012). This analysis sampled from both distributions to estimate the mean EIP for each location as a function of temperature using the following equation:

$$e^{(log\ EIP_{28})e^{\beta_T(T-28)}}$$

**Mosquito survival ($\gamma$ and *L*):** *Aedes* mortality in the field depends on many factors including weather and species (Brady et al., 2013). The species composition of is unknown, and the mean mortality for *Ae. albopictus* and *Ae. aegypti* across temperature was estimated by averaging mortality for each species at each temperature and fitting a polynomial curve to the relationship between temperature and average daily mortality (Brady et al., 2013; Johansson et al., 2014):

$$\mu(T) = 0.3967 - 0.03912T + 2.442e-03T^2 - 7.479e-05T^3 + 9.298e-07T^4$$

I assume that the month- and location-specific average mosquito lifespan ($L$) was $1/\mu(T)$ days (SD 2 days). The proportion of mosquitoes surviving the EIP ($\gamma$), was then calculated as $e^{-EIP/L}$, thus incorporating the uncertainty associated with both mosquito mortality and the EIP (above).

**Mosquito density ($\varphi$):** This study assumes that under ideal weather conditions there are 1–3 mosquitoes per person, an average of 2 (SD 1). To account for the population-wide effects of increased mortality at temperature extremes, the density proportional to the minimum mortality was estimated as

$$\varphi_{i,m} = \varphi(\frac{L_{i,m}}{max\ L})$$

where $\varphi$ is the density under ideal weather conditions, $L_{i,m}$ is a location- and month-specific, temperature-dependent lifespan, and max $L$ is the maximum mean lifespan, 7.9 days.

**Table D-1. Data source and collation of annual and monthly dengue incidence data in SEA, 2005-2015.**

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| **Cambodia** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The data in 2011-2015 were obtained from Cambodia Early Warning System in the Communicable Disease Control Department of the Ministry of Health (www.cdcmoh.gov.kh/surveillance/camewarn). | 1. The monthly numbers of dengue cases in 2005-2010 were obtained from the Project Tycho (www.tycho.pitt.edu).<br>2. The weekly data in 2011-2012 and 2014-2015 were obtained from the reports of the Communicable Disease Control Department of the Ministry of Health (www.cdcmoh.gov.kh/surveillance/camewarn) then aggregated to monthly incidence.<br>3. The monthly incidence of dengue in 2013 was estimated by: the total annual number of cases in 2013 × the proportion of cases in the same month of other years between 2005 and 2015. |
| **Bangladesh** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013-2015 were obtained from the Annual Health Bulletin published by the Ministry of Health and Family Welfare (www.dghs.gov.bd/index.php/en/data); and<br>3. Sharmin S, Viennet E, Glass K, Harley D. The emergence of dengue in Bangladesh: epidemiology, challenges and future disease risk. Transactions of the Royal Society of Tropical Medicine and Hygiene 2015; **109**(10): 619-27. | Unavailable |
| **Bhutan** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1). | Unavailable |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | 2. The yearly data in 2013-2015 were obtained from the online Annual Health Bulletins published by the Ministry of Health (www.health.gov.bt/publications/annual-health-bulletins). | |
| **India** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013-2015 were obtained from the national Vector Borne Disease Control Programme of the Ministry of Health and Family Welfare (nvbdcp.gov.in/DENGU1.html). | Unavailable |
| **Indonesia** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013-2015 were obtained from the Annual Indonesia Health Profile (www.depkes.go.id/folder/view/01/structure-publikasi-pusdatin-profil-kesehatan.html), and reports published by the Ministry of Health (www.depkes.go.id/article/view/15011700003/demam-berdarah-biasanya-mulai-meningkat-di-januari.html). | Unavailable |
| **Laos** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The data in 2011-2015 were obtained from the National Surveillance Weekly Report published by the National Center for Laboratory and Epidemiology of the Ministry of Health (www.ncle.gov.la/epidemiology/national-surveillance-weekly-report/). | 1. Monthly numbers of dengue cases in 2005-2010 were obtained from the Project Tycho (www.tycho.pitt.edu).<br>2. Annual data in 2011-2015 were obtained and aggregated from the National Surveillance Weekly Report published by the National Center for Laboratory and Epidemiology of the Ministry of Health (www.ncle.gov.la/epidemiology/national-surveillance-weekly-report/). |
| **Malaysia** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu). | 1. The monthly numbers of dengue cases in 2005-2010 were obtained and aggregated |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | 2. The data in 2011-2015 were obtained from the weekly Press Release of Dengue Fever Situation published by the Ministry of Health Malaysia (www.moh.gov.my/english.php/database_stores/store_view/17). | from the Project Tycho (www.tycho.pitt.edu).<br>2. The monthly data in 2011-2015 were obtained from the weekly Press Release of Dengue Fever Situation published by the Ministry of Health Malaysia (www.moh.gov.my/english.php/database_stores/store_view/17). |
| **Maldives** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The annual numbers of cases in 2013-2015 were obtained from the annual Maldives Health Statistics or Profile published on the official website of the Ministry of Health (www.health.gov.mv/Downloads). | 1. The monthly numbers of cases in 2005-2014 were obtained from the annual Maldives Health Statistics published on the website of the Ministry of Health (www.health.gov.mv/Downloads).<br>2. The monthly incidence of dengue in 2015 was estimated by: the total annual number of cases in 2015 × the proportion of cases in the same month in previous years of 2005-2014. |
| **Myanmar** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013 were obtained from: Ngwe Tun MM, Kyaw AK, Makki N, et al. Characterization of the 2013 dengue epidemic in Myanmar with dengue virus 1 as the dominant serotype. Infection, genetics and evolution: journal of molecular epidemiology and evolutionary genetics in infectious diseases 2016; **43**: 31-7.<br>3. The incidence data in 2014 were obtained from the report of the Ministry of information of Myanmar (www.moi.gov.mm/moi:eng/?q=news/29/06/2015/id-4205)<br>4. The data in 2015 were collated from the press release | Unavailable |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | (outbreaknewstoday.com/myanmar-health-minister-dengue-cases-increasing-since-april-more-than-7000-reported-27057/ and frontiermyanmar.net/en/the-dreaded-dengue-on-the-rise ). | |
| **Nepal** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1) and checked with the data in the publication: Subedi D, Taylor-Robinson AW. Epidemiology of dengue in Nepal: History of incidence, current prevalence and strategies for future control. Journal of vector borne diseases 2016; **53**(1): 1-7.<br>2. The annual numbers of dengue cases in 2013-2015 were obtained from the Annual Report 2015/2016 published by the Department of Health Services, Ministry of Health (dohs.gov.np/wp-content/uploads/2017/06/DoHS_Annual_Report_2072_73.pdf). | Unavailable |
| **Pakistan** | 1. Annual numbers of dengue cases in 2006-2010 were obtained from WHO Regional Office for the Eastern Mediterranean (www.emro.who.int/surveillance-forecasting-response/outbreaks/dengue-fever-in-pakistan.html).<br>2. Data in 2005 and 2011 were extracted from a paper: Rasheed SB, Butlin RK, Boots M. A review of dengue as an emerging disease in Pakistan. Public health 2013; **127**(1): 11-7.<br>3. The data in 2012 were extracted from a study of Principal Component Analysis to Explore Climatic Variability and Dengue Outbreak in Lahore (pjsor.com/index.php/pjsor/article/viewFile/686/362).<br>4. Data in 2013 were collated from the Weekly Epidemiological Bulletin of the WHO country office for Pakistan bulletin (www.emro.who.int/images/stories/pakistan/documents/pak_documents/DEWS/Weekly-Epidemiological-Bulletin-52- | Unavailable |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | 01012014.pdf?ua=1) and the publication: Wesolowski A, Qureshi T, Boni MF, et al. Impact of human mobility on the emergence of dengue epidemics in Pakistan. Proceedings of the National Academy of Sciences of the United States of America 2015; **112**(38): 11887-92.<br>5. Annual data in 2014-2015 were extracted from press release (aaj.tv/2016/01/32600-dengue-cases-registered-129-people-died-in-three-years/). | |
| **Philippines** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The annual data in 2011-2015 were obtained from the statistics of disease surveillance (www.doh.gov.ph/statistics) and weekly Dengue Morbidity Reports (www.doh.gov.ph/notifiable_diseases) published by the Department of Health. | 1. Monthly numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The data in 2011-2015 were obtained from the statistics of disease surveillance (www.doh.gov.ph/statistics) and weekly Dengue Morbidity Reports (www.doh.gov.ph/notifiable_diseases) published by the Department of Health, then aggregated into monthly data. |
| **Singapore** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The annual data in 2011-2015 were obtained from the Weekly Infectious Diseases Bulletin published by the Ministry of Health (www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html) | 1. The monthly data in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The data in 2011-2015 were obtained from the Weekly Infectious Diseases Bulletin published by the Ministry of Health (www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html), then aggregated into monthly data. |
| **Sri Lanka** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia | 1. The monthly numbers of dengue cases in 2010-2015 were obtained from the monthly data released by the |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The annual numbers of dengue cases in 2013-2015 were obtained and aggregated from the monthly data released by the Epidemiology Unit of the Ministry of Health (www.epid.gov.lk/web/index.php?option=com_casesanddeaths&Itemid=448&lang=en#). | Epidemiology Unit of the Ministry of Health (www.epid.gov.lk/web/index.php?option=com_casesanddeaths&Itemid=448&lang=en#).<br>2. The weekly numbers of dengue cases in 2006-2009 were obtained from the Weekly Epidemiological Report released by the Epidemiology Unit of the Ministry of Health (www.epid.gov.lk/web/index.php?option=com_content&view=article&id=163&Itemid=450&lang=en), then were aggregated into monthly data.<br>3. The monthly incidence of dengue in 2005 was estimated by: the total annual number of cases in 2005 × the proportion of cases in the same month in other years of 2006-2015. |
| **Thailand** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013-2015 were obtained from the online Summary of Dengue Annual Situation released by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health (www.boe.moph.go.th/boedb/surdata/disease.php?dcontent=old&ds=66). | 1. The monthly numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The monthly data in 2011-2015 were obtained and aggregated from the online Summary of Dengue Annual Situation released by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health (www.boe.moph.go.th/boedb/surdata/disease.php?dcontent=old&ds=66). |
| **Timor-Leste** | 1. The annual data in 2005-2012 were collated from the WHO Regional Office for South-East Asia | Unavailable |

| Country | Source of annual incidence | Source of monthly incidence |
|---|---|---|
| | (www.searo.who.int/entity/vector_borne_tropical_diseases/data/graphs.pdf?ua=1).<br>2. The data in 2013 were extracted from the website of the Ministry of Health (www.moh.gov.bn/SitePages/Information%20on%20Dengue.aspx).<br>3. The data in 2014 were extracted from the press release (modasys.net/3g/index.php/news-events/around-brunei/local-news/26251-significant-drop-in-dengue-cases-since-2014.html).<br>4. The annual data in 2015 was the average number of cases in 2012-2014. | |
| **Vietnam** | 1. The annual numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The annual data in 2011-2015 were extracted from the Dengue Situation Updates published by the WHO Regional Office for Western Pacific Region (www.wpro.who.int/emerging_diseases/documents/Dengue_Archives/en/). | 1. The monthly numbers of dengue cases in 2005-2010 were obtained and aggregated from the Project Tycho (www.tycho.pitt.edu).<br>2. The monthly data in 2011-2015 were extracted from the Dengue Situation Updates published by the WHO Regional Office for Western Pacific Region (www.wpro.who.int/emerging_diseases/documents/Dengue_Archives/en/). |

**Table D-2. Likelihood definitions for risks estimated by models.**

| Level | Definition | Probability estimated |
|---|---|---|
| Almost certain | Is expected occur in most circumstances. | A probability of 0.95 or more. |
| Highly likely | Will probably occur in most circumstances. | A probability of between 0.7 and 0.94 |
| Likely | Will occur some of the time. | A probability of between 0.3 and 0.69 |
| Unlikely | Could occur some of the time. | A probability of between 0.05 and 0.29 |
| Very unlikely | Could occur under exceptional circumstances | A probability of less than 0.05 |

Adapted from: Rapid Risk Assessment 0f Acute Public Health Events, WHO, 2012 (apps.who.int/iris/bitstream/10665/70810/1/WHO_HSE_GAR_ARO_2012.1_eng.pdf); and Microbiological Risk Assessment Series 17, WHO and Food and Agriculture Organization, 1999 (www.who.int/foodsafety/publications/micro/MRA17.pdf).

**Table D-3. Top 20 routes with the highest risk of dengue importation from SEA into provinces in China, 2005-2015.**

| Origin country | Destination province | Volume of travellers (IQR) | Importation risk (IQR) | Onward transmission risk (IQR) |
|---|---|---|---|---|
| Singapore | Shanghai | 40100 (37070, 43330) | 0.94 (0.90, 0.98) | 0.08 (0, 0.59) |
| Thailand | Shanghai | 25700 (20880, 46760) | 0.93 (0.83, 0.98) | 0.07 (0, 0.59) |
| Malaysia | Guangdong | 33340 (18770, 38660) | 0.91 (0.88, 0.96) | 0.37 (0.06, 0.66) |
| Singapore | Beijing | 24100 (22110, 26750) | 0.89 (0.82, 0.95) | 0 (0, 0.13) |
| Thailand | Beijing | 19640 (15340, 33290) | 0.88 (0.79, 0.97) | 0.01 (0, 0.13) |
| Malaysia | Shanghai | 15900 (13430, 18990) | 0.87 (0.81, 0.92) | 0.06 (0, 0.44) |
| Malaysia | Beijing | 11560 (9965, 14300) | 0.84 (0.75, 0.89) | 0 (0, 0.09) |
| Singapore | Guangdong | 19300 (15680, 32890) | 0.84 (0.74, 0.93) | 0.23 (0.04, 0.61) |
| Philippines | Shanghai | 9576 (5128, 12180) | 0.79 (0.48, 0.95) | 0.02 (0, 0.38) |
| Thailand | Guangdong | 28390 (19620, 42170) | 0.78 (0.66, 0.93) | 0.25 (0.03, 0.60) |
| Vietnam | Guangdong | 14180 (11100, 16950) | 0.75 (0.55, 0.89) | 0.16 (0.02, 0.51) |
| Singapore | Fujian | 11440 (9828, 12850) | 0.73 (0.59, 0.84) | 0.07 (0.01, 0.34) |
| Vietnam | Shanghai | 7769 (3308, 12600) | 0.67 (0.47, 0.87) | 0.03 (0, 0.30) |
| Philippines | Fujian | 6724 (5011, 8112) | 0.64 (0.37, 0.87) | 0.04 (0, 0.28) |
| Malaysia | Fujian | 5951 (5096, 7122) | 0.62 (0.52, 0.75) | 0.05 (0.01, 0.23) |
| Philippines | Beijing | 4684 (3414, 6821) | 0.61 (0.35, 0.88) | 0 (0, 0.06) |
| Malaysia | Zhejiang | 7356 (328, 9180) | 0.59 (0.07, 0.78) | 0.01 (0, 0.17) |
| Vietnam | Beijing | 4379 (2724, 6008) | 0.57 (0.36, 0.73) | 0 (0, 0.05) |
| Thailand | Yunnan | 7451 (6089, 12440) | 0.52 (0.35, 0.77) | 0.26 (0.10, 0.48) |
| Malaysia | Sichuan | 5084 (970, 7102) | 0.47 (0.17, 0.70) | 0 (0, 0.01) |

Note: The numbers in the table are the median and interquartile range (IQR) of monthly data for each origin-destination pair. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

**Table D-4. Top 20 routes with the highest risk of dengue importation from SEA into cities in China, 2005-2015.**

| Origin country | Destination city in China | Volume of travellers (IQR) | Importation risk (IQR) | Onward transmission risk (IQR) |
|---|---|---|---|---|
| Singapore | Shanghai | 40100 (37070, 43330) | 0.97 (0.94, 0.99) | 0.09 (0.01, 0.62) |
| Philippines | Xiamen | 6604 (4980, 7681) | 0.97 (0.88, 0.99) | 0.23 (0.04, 0.74) |
| Thailand | Guangzhou | 22840 (14800, 32890) | 0.97 (0.92, 0.99) | 0.41 (0.06, 0.81) |
| Thailand | Shanghai | 25700 (20880, 46760) | 0.96 (0.90, 0.99) | 0.07 (0, 0.64) |
| Malaysia | Guangzhou | 17360 (12660, 25640) | 0.96 (0.92, 0.98) | 0.38 (0.07, 0.70) |
| Vietnam | Guangzhou | 13180 (9857, 16530) | 0.95 (0.87, 0.99) | 0.33 (0.04, 0.75) |
| Singapore | Beijing | 24100 (22110, 26750) | 0.94 (0.89, 0.98) | 0.01 (0, 0.15) |
| Thailand | Beijing | 19640 (15340, 33290) | 0.93 (0.87, 0.99) | 0.01 (0, 0.13) |
| Malaysia | Shanghai | 15900 (13430, 18990) | 0.93 (0.89, 0.96) | 0.08 (0.01, 0.52) |
| Malaysia | Shenzhen | 12030 (6731, 13760) | 0.92 (0.83, 0.98) | 0.27 (0.08, 0.65) |
| Singapore | Guangzhou | 13940 (10990, 24740) | 0.92 (0.82, 0.97) | 0.27 (0.05, 0.66) |
| Malaysia | Beijing | 11560 (9965, 14300) | 0.91 (0.85, 0.94) | 0.01 (0, 0.10) |
| Singapore | Xiamen | 8466 (7596, 9725) | 0.90 (0.80, 0.96) | 0.20 (0.02, 0.56) |
| Thailand | Kunming | 6936 (5607, 11500) | 0.89 (0.79, 0.98) | 0.02 (0, 0.08) |
| Philippines | Shanghai | 9576 (5128, 12180) | 0.88 (0.60, 0.98) | 0.03 (0, 0.41) |
| Thailand | Xiamen | 3318 (2291, 4458) | 0.87 (0.68, 0.95) | 0.23 (0.02, 0.65) |
| Malaysia | Xiamen | 4197 (3516, 5114) | 0.82 (0.73, 0.91) | 0.19 (0.03, 0.42) |
| Malaysia | Hangzhou | 7040 (276, 8843) | 0.81 (0.09, 0.93) | 0.01 (0, 0.18) |
| Vietnam | Shanghai | 7769 (3308, 12600) | 0.78 (0.57, 0.93) | 0.04 (0, 0.36) |
| Singapore | Haikou | 4030 (2913, 6138) | 0.75 (0.57, 0.87) | 0.28 (0.10, 0.51) |

Note: The numbers in the table are the median and interquartile range (IQR) of monthly data for each origin-destination pair. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

**Table D-5. Top 20 routes with the highest risk of dengue introduced transmission from SEA into provinces in China, 2005-2015.**

| Origin country | Destination province | Volume of travellers (IQR) | Importation risk (IQR) | Onward transmission risk (IQR) |
|---|---|---|---|---|
| Malaysia | Guangdong | 33340 (18770, 38660) | 0.91 (0.88, 0.96) | 0.37 (0.06, 0.66) |
| Thailand | Yunnan | 7451 (6089, 12440) | 0.52 (0.35, 0.77) | 0.26 (0.10, 0.48) |
| Thailand | Guangdong | 28390 (19620, 42170) | 0.78 (0.66, 0.93) | 0.25 (0.03, 0.60) |
| Singapore | Guangdong | 19300 (15680, 32890) | 0.84 (0.74, 0.93) | 0.23 (0.04, 0.61) |
| Singapore | Hainan | 4080 (2962, 6198) | 0.47 (0.33, 0.63) | 0.17 (0.08, 0.34) |
| Vietnam | Guangdong | 14180 (11100, 16950) | 0.75 (0.55, 0.89) | 0.16 (0.02, 0.51) |
| Malaysia | Yunnan | 2287 (1566, 3417) | 0.34 (0.24, 0.44) | 0.15 (0.08, 0.23) |
| Singapore | Yunnan | 2935 (2373, 3577) | 0.32 (0.22, 0.49) | 0.14 (0.07, 0.27) |
| Singapore | Shanghai | 40100 (37070, 43330) | 0.94 (0.90, 0.98) | 0.08 (0, 0.59) |
| Thailand | Shanghai | 25700 (20880, 46760) | 0.93 (0.83, 0.98) | 0.07 (0, 0.59) |
| Singapore | Fujian | 11440 (9828, 12850) | 0.73 (0.59, 0.84) | 0.07 (0.01, 0.34) |
| Malaysia | Shanghai | 15900 (13430, 18990) | 0.87 (0.81, 0.92) | 0.06 (0, 0.44) |
| Vietnam | Yunnan | 1249 (972, 1500) | 0.16 (0.08, 0.28) | 0.05 (0.02, 0.15) |
| Malaysia | Fujian | 5951 (5096, 7122) | 0.62 (0.52, 0.75) | 0.05 (0.01, 0.23) |
| Philippines | Guangdong | 3536 (1936, 5535) | 0.35 (0.16, 0.62) | 0.04 (0.01, 0.20) |
| Thailand | Hainan | 480 (290, 722) | 0.11 (0.06, 0.30) | 0.04 (0.01, 0.13) |
| Laos | Yunnan | 1964 (1196, 4467) | 0.09 (0.03, 0.18) | 0.04 (0.01, 0.09) |
| Philippines | Fujian | 6724 (5011, 8112) | 0.64 (0.37, 0.87) | 0.04 (0, 0.28) |
| Vietnam | Shanghai | 7769 (3308, 12600) | 0.67 (0.47, 0.87) | 0.03 (0, 0.30) |
| Thailand | Guangxi | 1768 (1086, 2896) | 0.16 (0.09, 0.32) | 0.03 (0, 0.10) |

Note: The numbers in the table are the median and interquartile range (IQR) of monthly data for each origin-destination pair. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

**Table D-6. Top 20 routes with the highest risk of dengue introduced transmission from SEA into cities in China, 2005-2015.**

| Origin country | Destination city in China | Volume of travellers (IQR) | Importation risk (IQR) | Onward transmission risk (IQR) |
|---|---|---|---|---|
| Thailand | Guangzhou | 22840 (14800, 32890) | 0.97 (0.92, 0.99) | 0.41 (0.06, 0.81) |
| Malaysia | Guangzhou | 17360 (12660, 25640) | 0.96 (0.92, 0.98) | 0.38 (0.07, 0.70) |
| Vietnam | Guangzhou | 13180 (9857, 16530) | 0.95 (0.87, 0.99) | 0.33 (0.04, 0.75) |
| Singapore | Haikou | 4030 (2913, 6138) | 0.75 (0.57, 0.87) | 0.28 (0.10, 0.51) |
| Malaysia | Shenzhen | 12030 (6731, 13760) | 0.92 (0.83, 0.98) | 0.27 (0.08, 0.65) |
| Singapore | Guangzhou | 13940 (10990, 24740) | 0.92 (0.82, 0.97) | 0.27 (0.05, 0.66) |
| Thailand | Xiamen | 3318 (2291, 4458) | 0.87 (0.68, 0.95) | 0.23 (0.02, 0.65) |
| Philippines | Xiamen | 6604 (4980, 7681) | 0.97 (0.88, 0.99) | 0.23 (0.04, 0.74) |
| Thailand | Shenzhen | 3443 (2494, 4904) | 0.68 (0.50, 0.90) | 0.22 (0.04, 0.50) |
| Singapore | Shenzhen | 4874 (4169, 7182) | 0.67 (0.50, 0.87) | 0.21 (0.04, 0.47) |
| Singapore | Xiamen | 8466 (7596, 9725) | 0.90 (0.80, 0.96) | 0.20 (0.02, 0.56) |
| Malaysia | Xiamen | 4197 (3516, 5114) | 0.82 (0.73, 0.91) | 0.19 (0.03, 0.42) |
| Thailand | Shantou | 2224 (1731, 3214) | 0.66 (0.46, 0.86) | 0.16 (0.02, 0.43) |
| Thailand | Haikou | 405.5 (247.5, 621.8) | 0.38 (0.21, 0.70) | 0.12 (0.03, 0.36) |
| Philippines | Guangzhou | 3518 (1920, 5474) | 0.70 (0.39, 0.93) | 0.10 (0.02, 0.37) |
| Singapore | Shanghai | 40100 (37070, 43330) | 0.97 (0.94, 0.99) | 0.09 (0.01, 0.62) |
| Malaysia | Shanghai | 15900 (13430, 18990) | 0.93 (0.89, 0.96) | 0.08 (0.01, 0.52) |
| Thailand | Shanghai | 25700 (20880, 46760) | 0.96 (0.90, 0.99) | 0.07 (0, 0.64) |
| Singapore | Fuzhou | 2618 (1944, 3216) | 0.45 (0.33, 0.70) | 0.06 (0.01, 0.23) |
| Malaysia | Fuzhou | 1642 (1314, 1856) | 0.42 (0.34, 0.62) | 0.06 (0.01, 0.19) |

Note: The numbers in the table are the median and interquartile range (IQR) of monthly data for each origin-destination pair. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

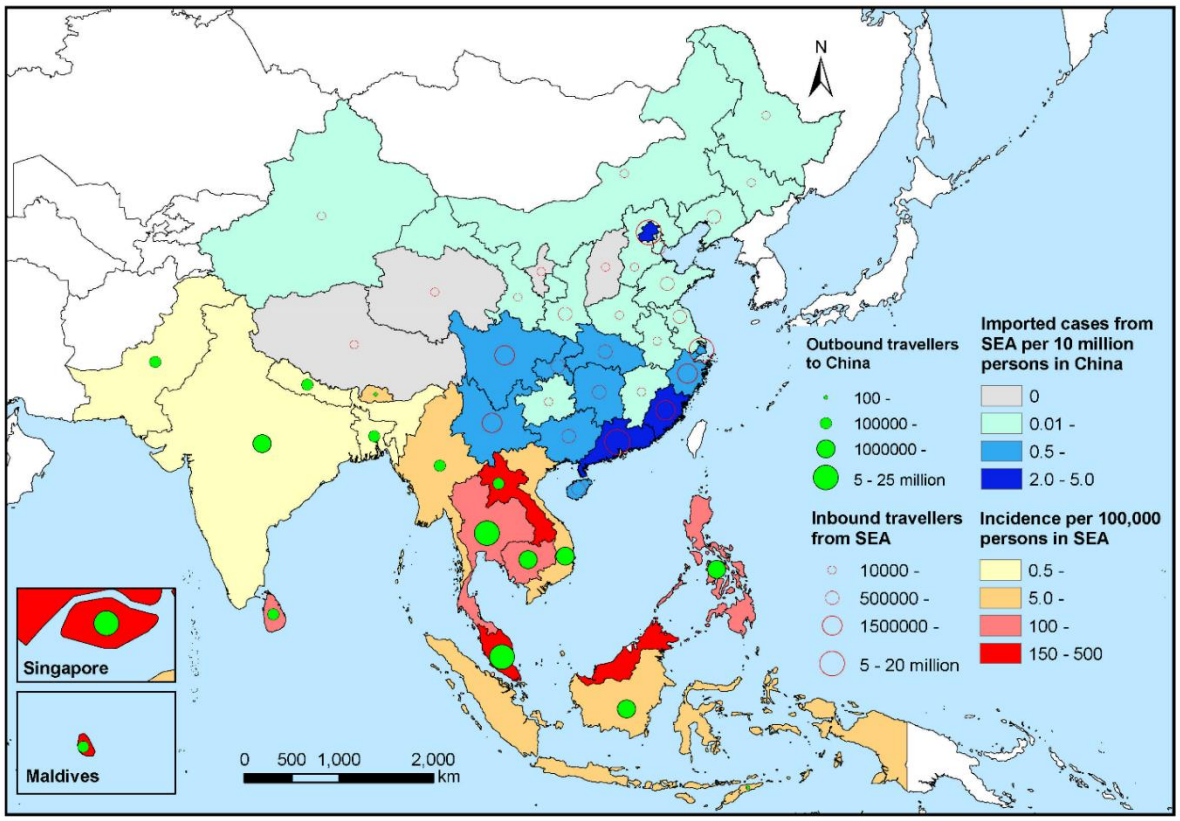


**Figure D-1. Geographic range of airline travellers and dengue from SEA into provinces of China**.

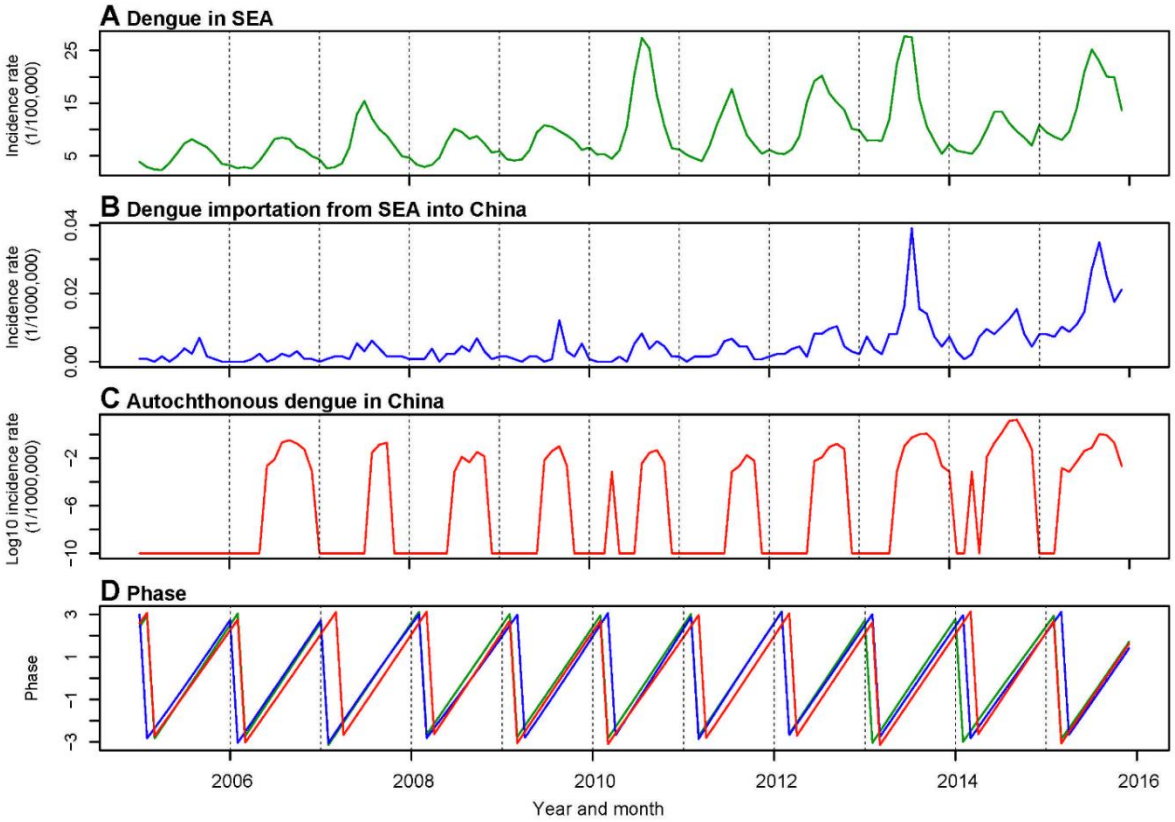


**Figure D-2. Time series and phase of dengue incidence in SEA and China.**

Note: (A) Incidence rates (per 100,000 people) of dengue reported in nine SEA countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam). (B) Incidence rates (per 1,000,000 people) of dengue importation reported in China from nine SEA countries. (C) The log-transformed incidence rates (per 1,000,000 people) of autochthonous dengue reported in China. The number of 10-10 was added into each number of the time series to replace zero before log-transforms. (D) Phase angles of three time series above by wavelet transforms and reconstruction with annual dengue cycles. Green line represents dengue incidence rate in SEA; Blue represents dengue importation from SEA into China; Red line represents autochthonous dengue incidence rate (log10-transformed) in China.

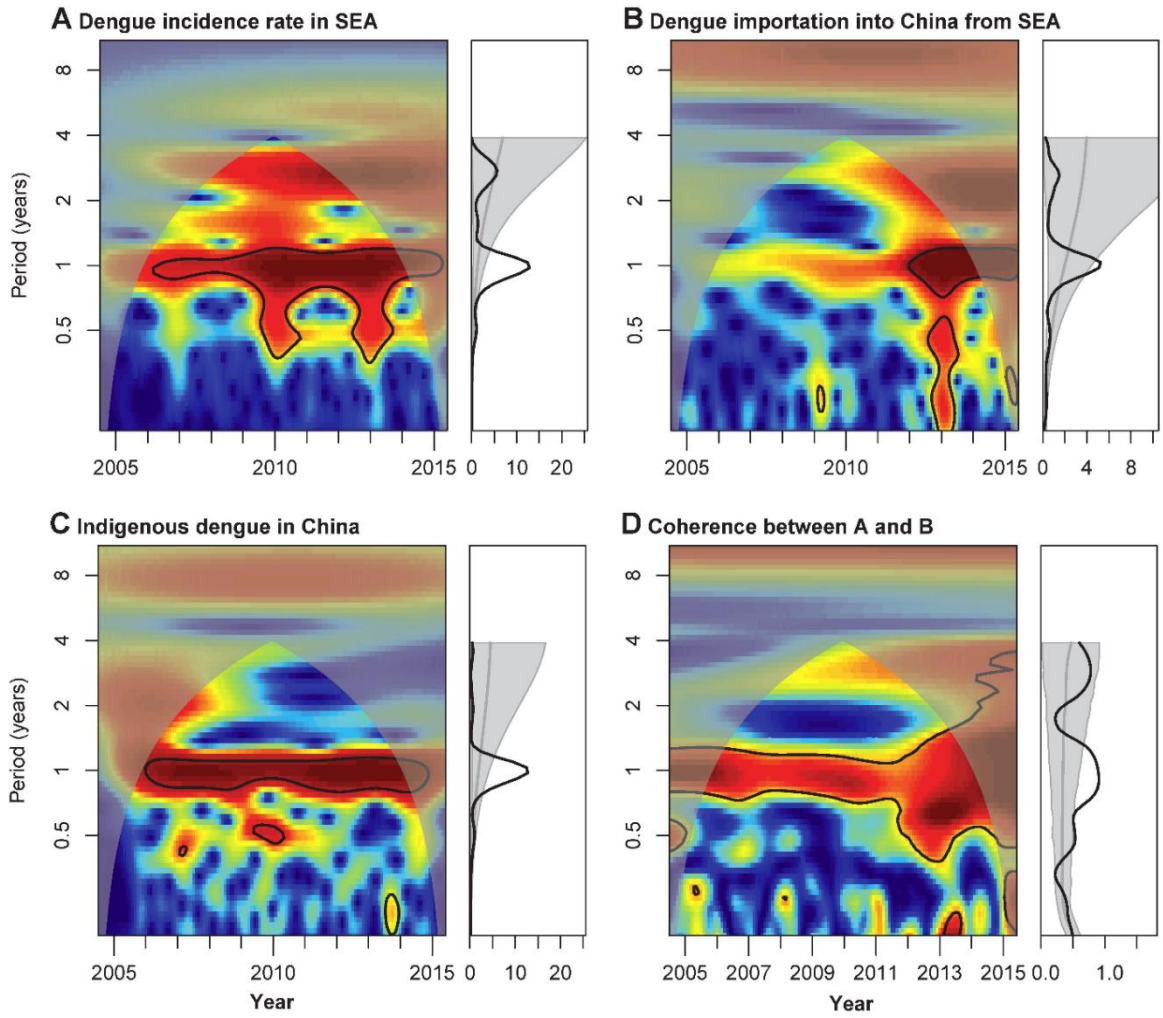


**Figure D-3. Spectrums and coherency of dengue incidence in nine SEA country and China by wavelet transforms**.

Note: The Morlet wavelet was applied to transform the time series and generate the local wavelet power spectrum. The red thick contour encloses regions of greater than 95% confidence for a red-noise process with a lag-1 coefficient of 0.72, and the shaded regions on the top and either end indicate the "cone of influence," where edge effects become important. (A) Spectrum of incidence rates (per 100,000 people) of dengue reported in nine SEA countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam). (B) Spectrum of incidence rates (per 1,000,000 people) of dengue importation reported in China from nine SEA countries. (C) Spectrum of the log-transformed incidence rates (per 1,000,000 people) of indigenous dengue reported in China. The number of 10-10 was added into each number of the time series to replace zero figures before log-transforms and wavelet transforms. (D) Synchrony between the spectrums of A and B. Wavelet coherency (ranging from zero to one) describes the phase relationship between two time series localized in a time–periodicity spectrum. For strong wavelet coherency, statistically significant cycles of a specific periodicity need to be phase-locked (positively or negatively).

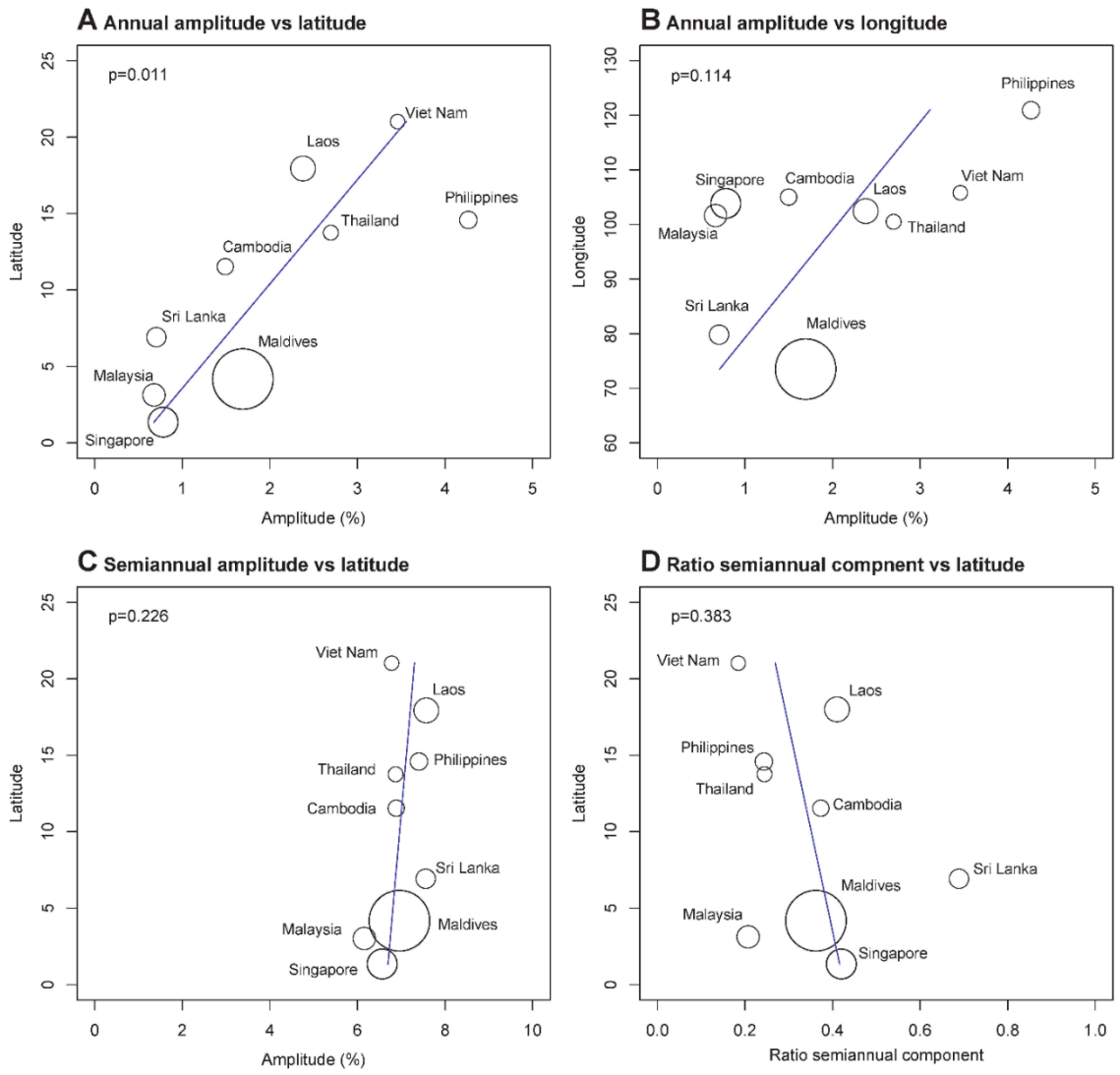


**Figure D-4. Latitudinal and longitudinal gradients in periodicity of dengue in nine SEA countries, 2005-2015.**

Note: (A) Amplitude of the annual periodicity vs the latitude of capital city of each country. (B) Amplitude of the annual periodicity vs longitude. (C) Amplitude of the semiannual periodicity vs latitude. (D) Contribution of the semiannual periodicity, measured by the ratio of the amplitude of the semiannual periodicity to the sum of the amplitudes of annual and semiannual periodicities (higher ratio suggests a stronger semiannual periodicity). Symbol size is proportional to the dengue incidence rate in each country. Blue solid lines represent linear regression fit. p values are given on the graphs.

Appendix D

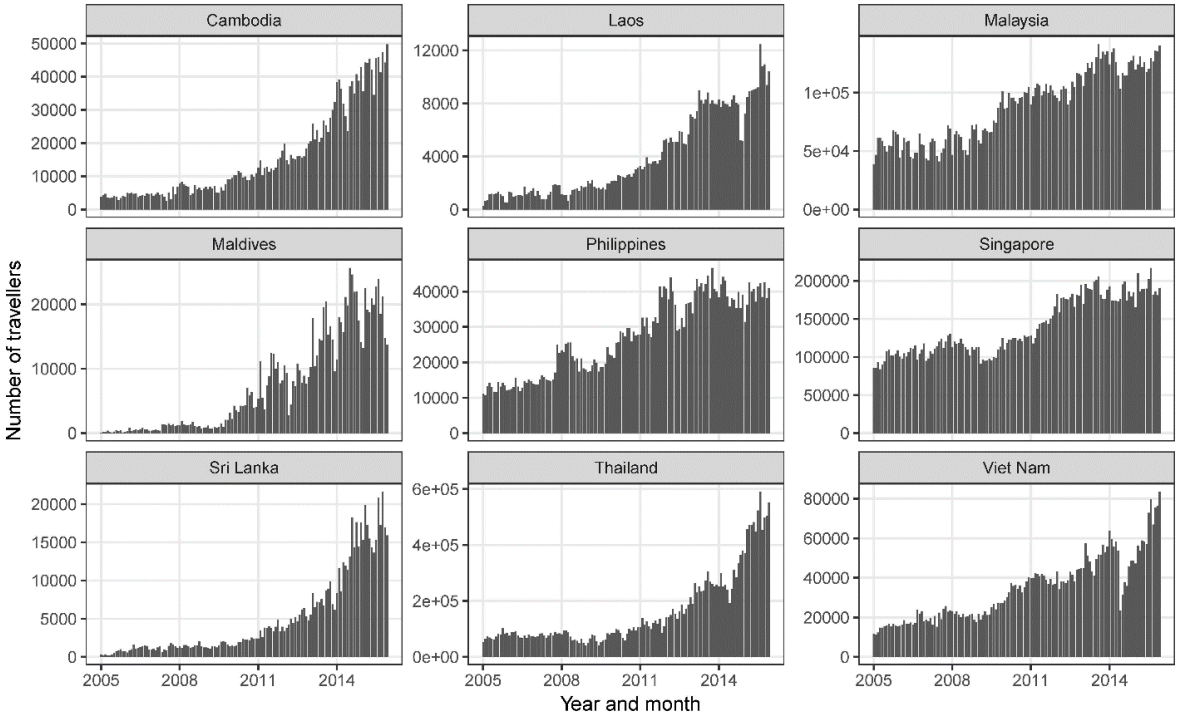


**Figure D-5. The monthly volume of air travellers from nine countries of South-East Asia into mainland China, 2005-2015.**

Note: Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were showed here.

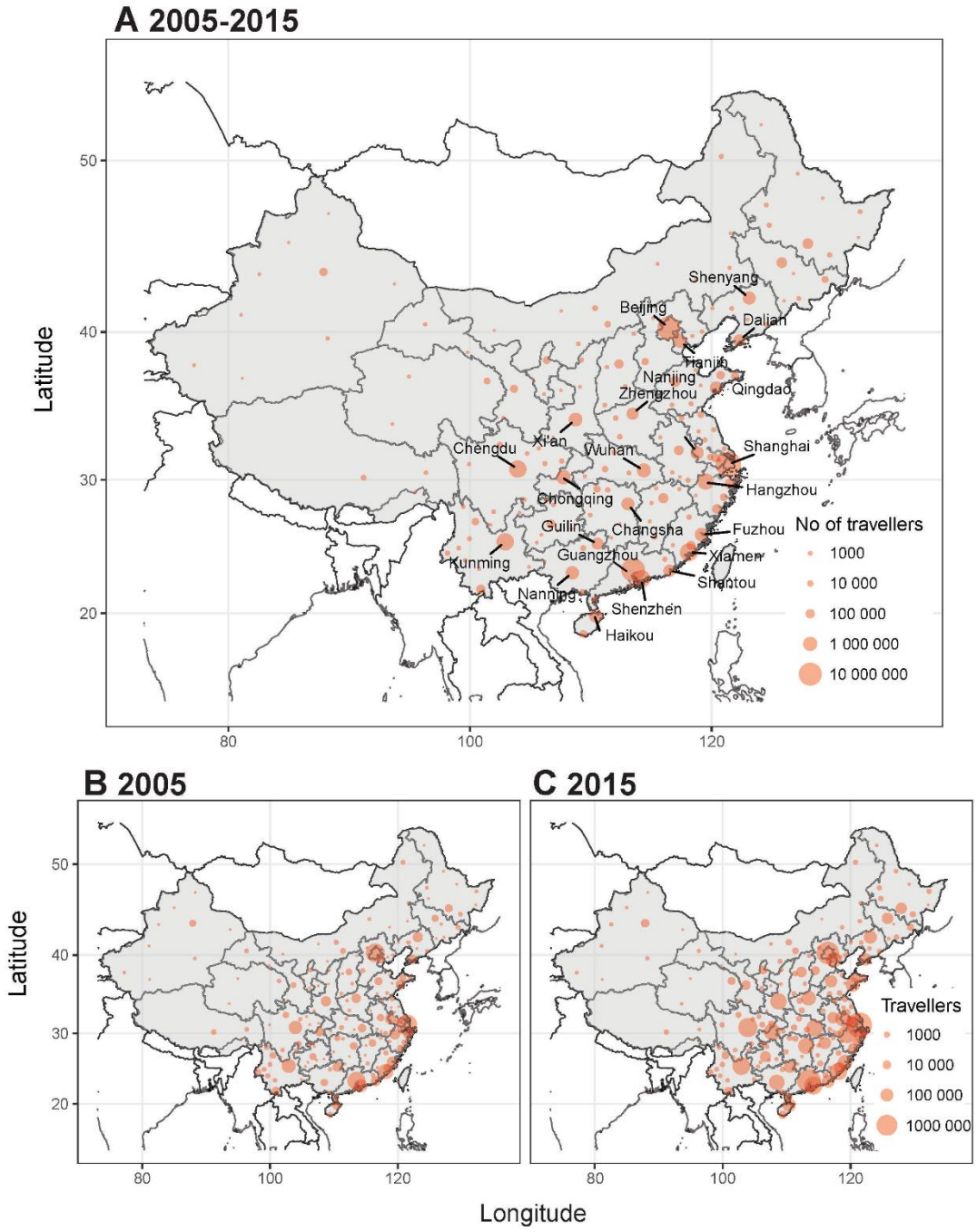


**Figure D-6. Geographic range and the volume of air travellers from nine countries of South-East Asia into cities of mainland China, 2005-2015.**

Note: (A) Total volume of travellers from 2005 to 2015. (B) Volume of travellers in 2005. (C) Volume of travellers in 2015. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

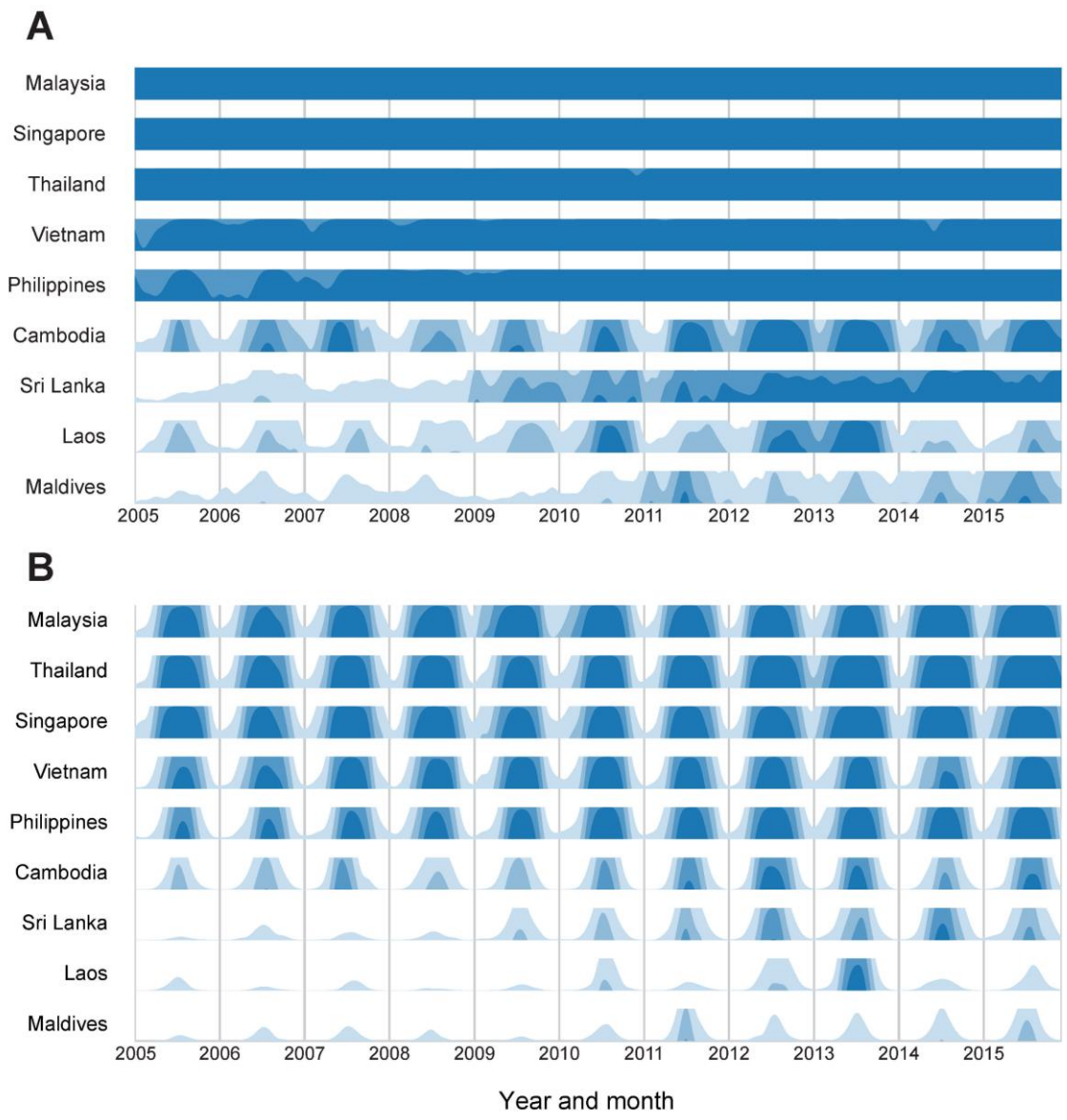


**Figure D-7. The monthly risks of dengue importation and introduced transmission from SEA into China by origin country, 2005-2015.**

Note: (A) Importation risk from SEA into China. (B) Risk of importation leading to autochthonous transmission in China. The countries are sorted by the average monthly risk of each origin country. The interpolation by basic spline was used to smooth the time series, and the risks are presented by the colour scheme from light blue (low risk) to dark blue (high risk). Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

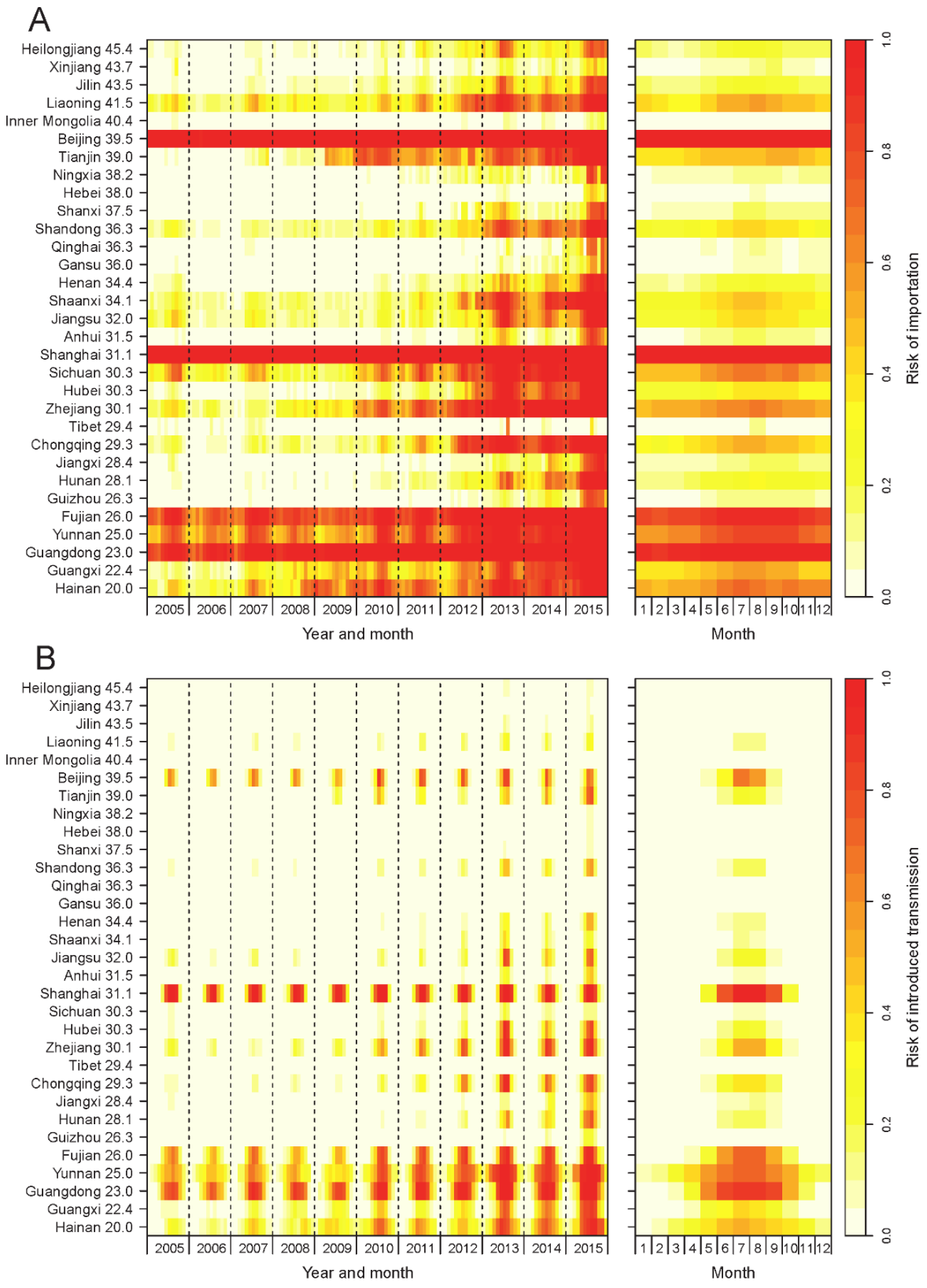


**Figure D-8. Heatmaps of monthly risks of dengue importation and introduced transmission from SEA into provinces of mainland China, 2005-2015.**

Note: (A) Heatmap of monthly DENV importation risk by province. The number behind the name of province is the latitude of the capital city of each province. (B) Heatmap of monthly risk of introduced transmission by province. The figures are sorted by the latitude of each province.

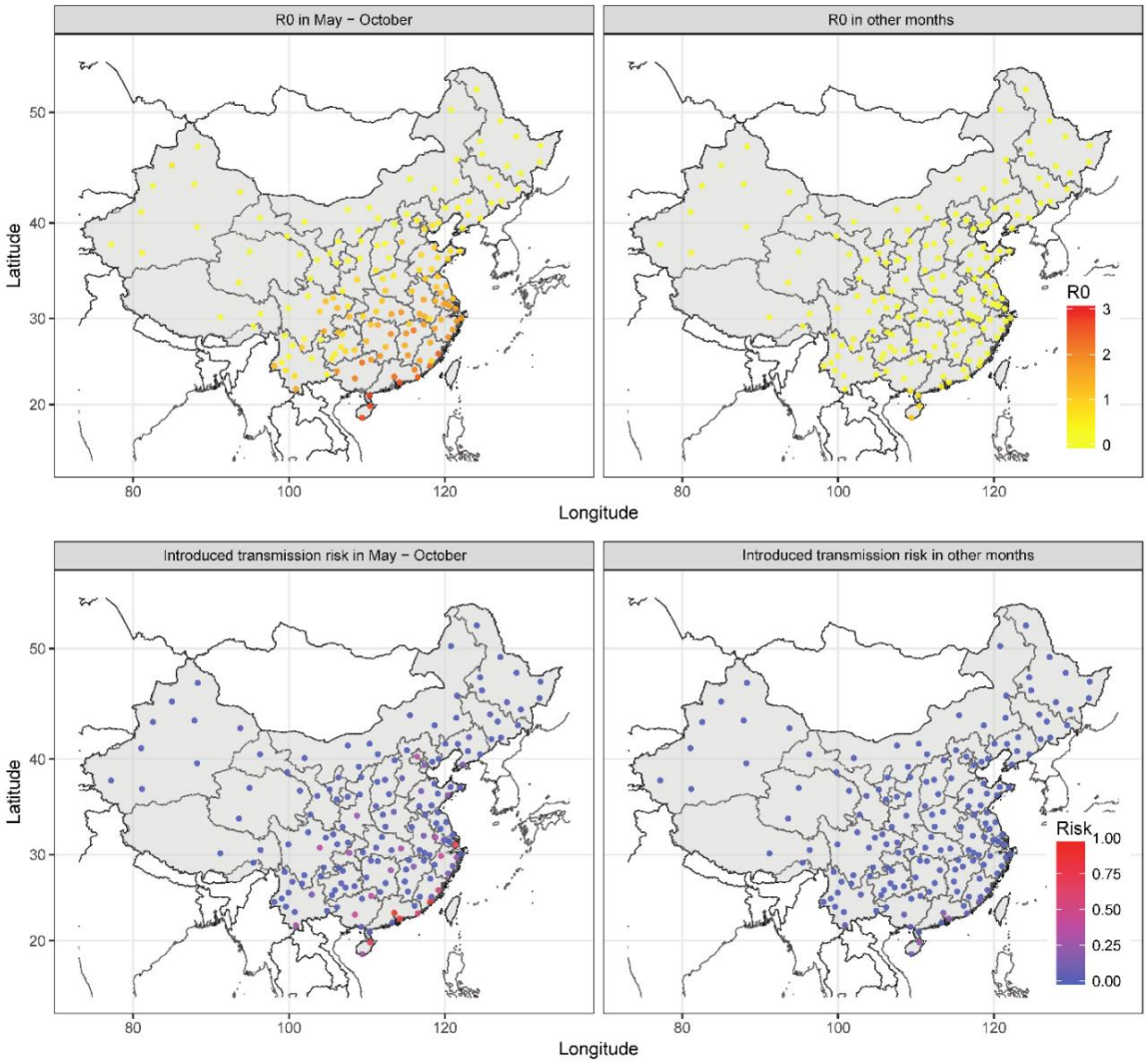


**Figure D-9. Geographic range and seasonal risk of DENV introduced transmission from SEA into cities of mainland China, 2005-2015.**

Note: (A) Average basic reproduction number (R0) between May and October. (B) Average R0 in other months. (C) Risk of introduced transmission between May and October. (D) Risk of introduced transmission in other months. Nine countries (Cambodia, Laos, Malaysia, Maldives, Philippines, Singapore, Sri Lanka, Thailand, Vietnam) with available data of monthly DENV incidence were included here.

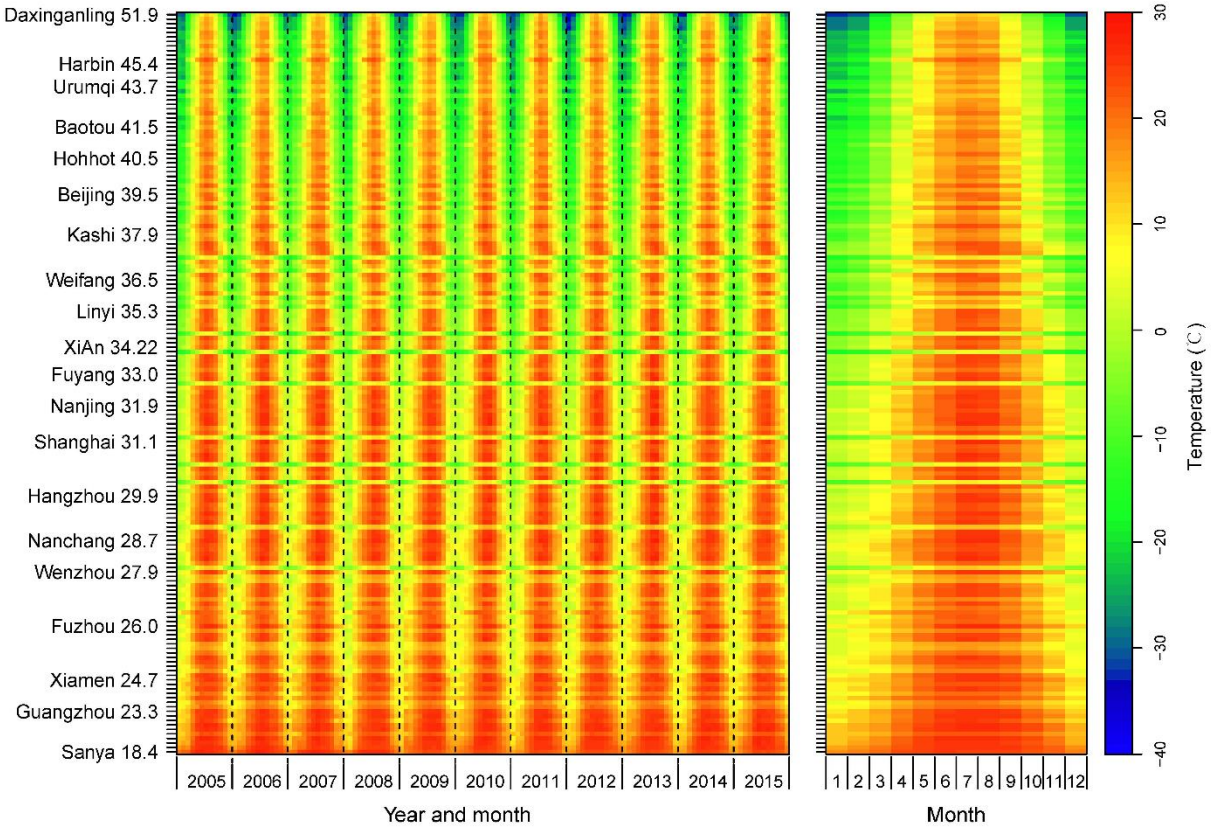


**Figure D-10. Heatmap of monthly average value of minimum temperature by city, 2005-2015.**

Note: The figure is sorted by the latitude of each city with the number of latitude behind the name of each city.

Appendix D

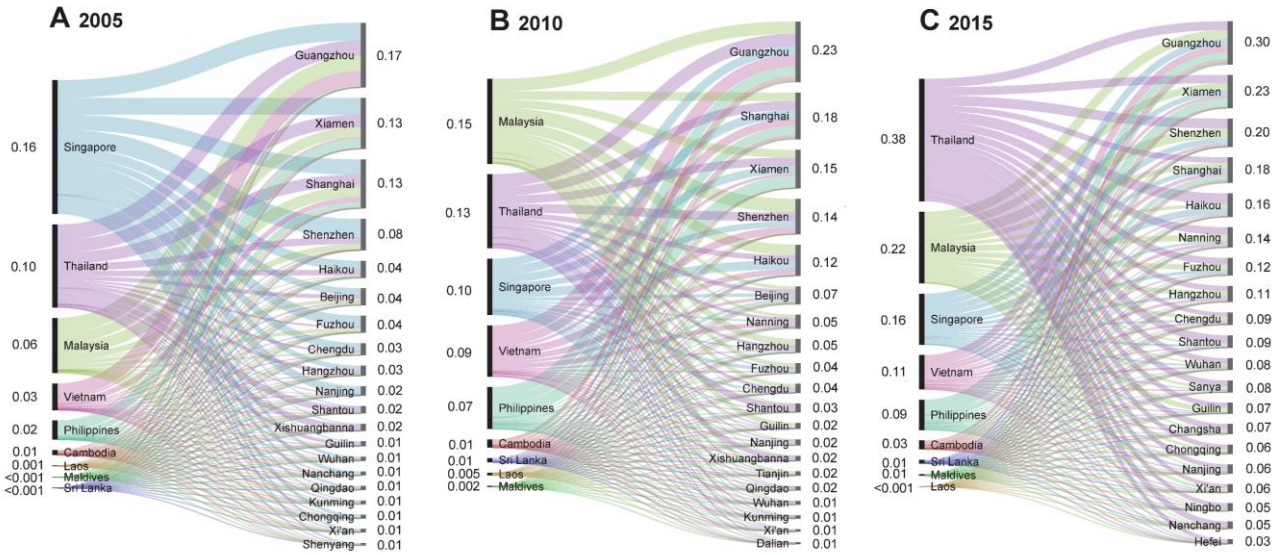


**Figure D-11. Origin-destination routes of dengue introduced transmission from SEA into top 20 high-risk cities of China in 2005, 2010 and 2015.**

Note: (A) Introduced transmission risk in 2005. (B) Introduced transmission risk in 2010. (C) Introduced transmission risk in 2015. The numbers in the figures are the average risk of all routes from/into each origin/destination. The thickness of line for each route is scaled to the risk from the lowest value (thinnest) to the highest value (thickest) within each figure.

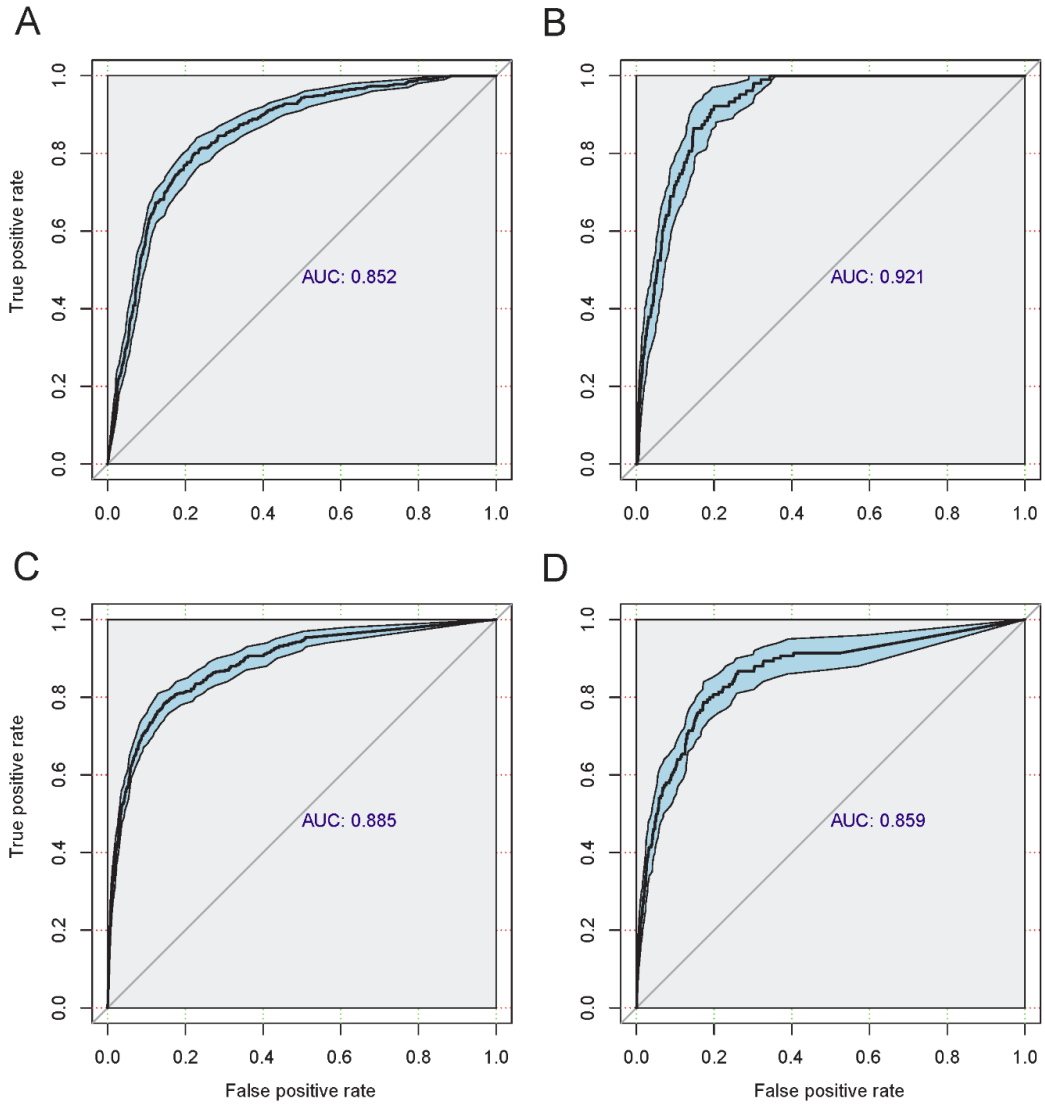


**Figure D-12. ROC curve with 95% CI to evaluate the performance of estimated risk by comparing with the reported occurrence of imported and locally transmitted DENV cases in China.**

Note: (A) ROC for importation risk at provincial level. (B) ROC for introduced transmission risk at provincial level. (C) ROC for importation risk at city level. (D) ROC for introduced transmission risk at city level. The risk is the DENV importation and onward transmission risk from nine countries of South-East Asia into 165 cities in mainland China, 2005-2015. ROC curves provide a comprehensive and visually attractive way to summarize the accuracy of predictions of risk. Each point on the curve represents the true-positive rate and false-positive rate associated with a particular value of risk. The 95% CI of ROC curve were generated by 10,000 stratified bootstrap replicates. The value of AUC close to 1 indicates an excellent diagnostic/predict model, a curve that lies close to the diagonal (AUC = 0.5) has no information content and therefore no diagnostic utility.

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Zhou, Z. J. (1981). The malaria situation in the People's Republic of China. *Bull World Health Organ* 59(6), 931-6.

# List of Publications

During my PhD study since January 2015, a total of 41 papers and five chapters of book have been published with 12 papers of malaria and dengue directly related to my thesis.

## Journal Publications (*contributed equally)

***Malaria***

1. **Lai S**, Li Z, Wardrop N A, Sun J, Head M G, Huang Z, Zhou S, Yu J, Zhang Z, Z SS, Xia Z, Wang R, Zheng B, Ruan Y, Zhang L, Zhou XN, Tatem A J, Yu H (2017). Malaria in China, 2011-2015: an observational study. ***Bulletin of the WHO*** 95(8):564-573. DOI:10.2471/BLT.17.191668

2. **Lai S**, Wardrop NA, Huang Z, Bosco C, Sun J, Bird T, Wesolowski A, Zhou S, Zhang Q, Zheng C, Li Z, Tatem AJ, Yu H (2016). Plasmodium falciparum malaria importation from Africa to China and its mortality: an analysis of driving factors. ***Scientific Reports*** 6:39524. DOI:10.1038/srep39524

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4. Li Z, Yang Y, Xiao N, Zhou S, Lin K, Wang D, Zhang Q, Jiang W, Li M, Feng X, Yu J, Ren X, **Lai S**, Sun J, Fang Z, Hu W, Clements AC, Zhou X, Yu H, Yang W (2015). Malaria imported from Ghana by returning gold miners, China, 2013. ***Emerging Infectious Diseases*** 21(5):864-867. DOI:10.3201/2105.141712

5. Zhang Q, Sun J, Zhang Z, Geng Q, **Lai S**, Hu W, Clements AC, Li Z (2016). Risk assessment of malaria in land border regions of China in the context of malaria elimination. ***Malaria Journal*** 15(11):546. DOI:10.1186/s12936-016-1590-1

6. Sun J, Zhou S, Geng Q, Zhang Q, Zhang Z, Zheng C, Hu W, Clements ACA, **Lai S**, Li Z (2016). Comparative evaluation of the diagnosis, reporting and investigation of malaria cases in China, 2005–2014: transition from control to elimination for the national malaria programme. ***Infectious Diseases of Poverty*** 5(1):1-10. DOI:10.1186/s40249-016-0163-4

7. Sun J*, **Lai S***, Zhang Z, Geng Q, Zhou S, Zhang Q, Li Z (2016). Comparison of demographical characteristics of malaria cases from malaria control to elimination in China. ***Chinese***

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8. Q Zhang, Q Geng, J Sun, Z Zhang, **S Lai**, S Zhou, Z Li (2016). Epidemiological analysis of the deaths of malaria in China, 2005-2014. ***Chinese Journal of Preventive Medicine*** 50(4): 302-305. (In Chinese) DOI:10.3760/cma.j.issn.0253-9624.2016.04.004

***Dengue***

9. **Lai S**[*], Huang Z[*], Zhou H[*], Anders KL, Perkins TA, Yin W, Li Y, Mu D, Chen Q, Zhang Z, Qiu Y, Wang L, Zhang H, Zeng L, Ren X, Geng M, Li Z, Tatem AJ, Hany SI, Yu H (2015). The Changing Epidemiology of Dengue in China, 1990-2014: a descriptive analysis of 25 years of Nationwide Surveillance Data. ***BMC Medicine*** 13:100. (**Editorial Commentary**: Ooi EE. The re-emergence of dengue in China. BMC Medicine 2015;13:99) DOI:10.1186/s12916-015-0336-1

10. Guo Y[*], **Lai S**[*], Liu X, Li G, Yu H, Liu Q (2016). Governmental supervision and rapid detection on dengue vectors: an important role for dengue control in China. ***Acta Tropica*** 156:17–21. DOI:10.1016/j.actatropica.2015.12.011

11. Guo Y[*], **Lai S**[*], Huang Q[*], Ren D, Zou J, Liu Q, Zhang H (2016). Coexistence of *Aedes aegypti* and *Aedes albopictus* in Jinghong City, Yunnan province: a survey of *Aedes aegypti* invasion***.*** ***Journal of tropical disease & public health*** 4(5):227. DOI:10.4172/2329-891X.1000227

12. Mu D, He Y, Chen Q, Li Y, Wang Q, Yin W, **Lai S**[#], Yu H (2017). Comparison of epidemiological features between imported and indigenous dengue cases in China. ***Disease Surveillance*** 32(3):176-181. (In Chinese, [#] corresponding author) DOI:10.3784/j.issn.1003-9961.2017.03.004http://eprints.soton.ac.uk/376728/

***Avian Influenza***

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***Environmental Research and Risk Assessment*** 31(2):392-402. DOI:10.1007/s00477-016-1362-z

15. Wang X, Jiang H, Wu P, Uyeki TM, Feng L, **Lai S**, Wang L, Huo X, Xu K, Chen E, Wang X, He J, Kang M, Zhang R, Zhang J, Wu J, Hu S, Zhang H, Liu X, Fu W, Ou J, Wu S, Qin Y, Zhang Z, Shi Y, Zhang J, Artois J, Fang V, Zhu H, Guan Y, Gilbert M, Horby PW, Leung GM, Gao GF, Cowling BJ, and Yu H (2017). Epidemiology of avian influenza A H7N9 virus in human beings across five epidemics in mainland China, 2013-17: an epidemiological study of laboratory-confirmed case series. ***Lancet Infectious Diseases*** 17: pii: S1473-3099(17)30323-7. DOI:10.1016/S1473-3099(17)30323-7

16. Jiang H, **Lai S**, Qin Y, Zhang Z, Feng L, Yu H (2017). A review of global human infection with avian influenza and epidemiological characteristics. ***Chinese Science Bulletin*** 62(19):2104-2115. (In Chinese) DOI:10.1360/N972017-00267

***Brucellosis***

17. **Lai S***, Zhou H*, Xiong W*, Gilbert M, Huang Z, Yu J, Yin W, Wang L, Chen Q, Li Y, Mu D, Zeng L, Ren X, Geng M, Zhang Z, Cui B, Li T, Wang D, Li Z, Wardrop N A, Tatem A J, Yu H (2017). Changing Epidemiology of Human Brucellosis, China, 1955-2014. ***Emerging Infectious Diseases*** 23 (2):184-194. DOI:10.3201/eid2302.151710

18. Chen Q, **Lai S**, Yin W, Zhou H, Li Y, Mu D, Li Z, Yu H, Yang W (2016). Epidemic characteristics, high-risk townships and space-time clusters of human brucellosis in Shanxi Province of China, 2005-2014. ***BMC Infectious Diseases*** 16:760. DOI:10.1186/s12879-016-2086-x

19. Shi Y*, **Lai S***, Chen Q, Mu D, Li Y, Li X, Yin W, Yu H (2017). Analysis on the epidemiological features of human brucellosis in northern and southern areas of China, 2015-2016. ***Chinese Journal of Epidemiology*** 38(4):435-440. (In Chinese). DOI:10.3760/cma.j.issn.0254-6450.2017.04.005

***Enterovirus infections***

20. Yu J*, Ye C*, **Lai S***, Zhu W, Zhang Z, Geng Q, Xue C, Yang W, Wu S, Hall AJ, Sun Q, Li Z (2017). Incidence of norovirus-associated diarrhea in Shanghai, China, 2012-2013. ***Emerging Infectious Diseases*** 23 (2): 312-315. DOI:10.3201/eid2302.161153

21. Yu J*, Jing H*, **Lai S***, Xu W, Li M, Wu J, Liu W, Yuan Z, Chen Y, Zhao S, Wang X, Zhao Z, Ran L, Wu S, Klena J D, Feng L, Li F, Ye X, Qiu Y, Wang X, Yu H, Li Z, Yang W (2015). Etiology of

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29. Yu J, Zhu W, Ye C, Xue C, **Lai S**, Zhang H, Zhang Z, Geng Q, Yang W, Sun Q, Li Z (2017). A cross-sectional study of acute diarrhea in Pudong, Shanghai, China: Prevalence, risk factors, and healthcare-seeking practices. ***Epidemiology and Infection*** *145*(13):2735-2744. DOI:10.1017/S0950268817001844

***Respiratory infections***

30. Cui D, Feng L, Chen Y, **Lai S**, Zhang Z, Yu F, Zheng S, Li Z, Yu H (2016). Clinical and epidemiologic characteristics of hospitalized patients with laboratory-confirmed respiratory syncytial virus infection in eastern China between 2009 and 2013: a retrospective study. ***PLoS One*** 11(11):e0165437. DOI:10.1371/journal.pone.0165437

31. Ye C, Zhu W, Yu J, Li Z, Fu Y, Lan Y, **Lai S**, Wang Y, Pan L, Sun Q, Zhao G (2016). Viral pathogens among elderly people with acute respiratory infections in Shanghai, China: Preliminary results from a laboratory-based surveillance, 2012-2015. ***Journal of Medical Virology***. 2016 Dec 12. DOI:10.1002/jmv.24751

32. Jiang X, **Lai S**, Liu X (2015). Study on viral etiology of 942 cases of lower respiratory tract infections in Gansu Province during 2010-2013. ***Chinese Journal of Disease Control & Prevention*** 19(7): 659-662. (In Chinese) DOI:10.16462/j.cnki.zhjbkz.2015.07.004

***Disease surveillance and early warning***

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34. Zhang H, Wang L, **Lai S**, Li Z, Sun Q, and Zhang P (2017). Surveillance and early warning systems of infectious disease in China: From 2012 to 2014. ***International Journal of Health Planning and Management*** 32(2):1–11. DOI:10.1002/hpm.2434

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36. Zhou D, Yang W, Sun Q, **Lai S**, Zhang H, Li Z, Lyu W, Lan Y (2016). Application and evaluation of signal strength indictor in communicable disease automatic early warning system. ***Chinese Journal of Preventive Medicine*** 50(2):184-187. (In Chinese) DOI:10.3760/cma.j.issn.0253-9624.2016.02.016

***Disease and population mapping***

37. Chen W*, **Lai S***, Yang Y, Liu K, Li X, Yao H, Li Y, Zhou H, Wang L, Mu D, Yin W, Fang L, Yu H, Cao W (2016). Mapping the distribution of anthrax in mainland China, 2005-2013. ***PLoS Neglected Tropical Diseases*** 10(4): e0004637. DOI:10.1371/journal.pntd.0004637

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40. Gaughan AE, Stevens FR, Huang Z, Nieves J, Sorichetta A, **Lai S**, Ye X, Linard C, Hornby G, Hay SI, Yu H, Tatem AJ (2016). Spatiotemporal Patterns of Population in Mainland China, 1990 to 2010. ***Scientific Data*** 3:160005. DOI:10.1038/sdata.2016.5

41. Geng M, Khan K, Ren X, German M, Creatore M, Wang L, Li Z, Gao GF, **Lai S**[#], Yu H[#] (2016). Assessing the Risk of MERS Importation from South Korea into Cities of China: A Retrospective Study. ***Chinese Science Bulletin*** 61(9): 1016-1024. (In Chinese, [#] corresponding author) DOI:10.1360/N972015-01174

## Book Chapters

**Lai S**, Li X, Zhang H. *Early Detection for Hand, Foot, and Mouth Disease Outbreaks*. Early Warning for Infectious Disease Outbreak, 04/2017: pages 283-294; Elsevier, ISBN: 9780128123430, DOI:10.1016/B978-0-12-812343-0.00015-1

JinNL, Ma J, Lv W, **Lai S**, Hong Z. *Development of Early Warning Information Systems*. Early Warning for Infectious Disease Outbreak, 04/2017: pages 99-112; Elsevier, ISBN: 9780128123430, DOI:10.1016/B978-0-12-812343-0.00005-9

Lan Y, Li Z, Zhou D, **Lai S**. *Evaluation of Early Warning Systems*. Early Warning for Infectious Disease Outbreak, 04/2017: pages 113-130; Elsevier, ISBN: 9780128123430, DOI:10.1016/B978-0-12-812343-0.00006-0

Lan Y, Zhou D, Zhang H, **Lai S**. *Development of Early Warning Models*. Early Warning for Infectious Disease Outbreak, 04/2017: pages 35-74; Elsevier, ISBN: 9780128123430, DOI:10.1016/B978-0-12-812343-0.00003-5

Yang W, Li Z, Lan Y, Ma J, Jin L, **Lai S**, Liao Y, Lv W, Sun Q, Wang J. *China Infectious Diseases Automated-Alert and Response System (CIDARS)*. Early Warning for Infectious Disease Outbreak, 04/2017: pages 133-161; Elsevier, ISBN: 9780128123430, DOI:10.1016/B978-0-12-812343-0.00007-2