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Evaluating the role of disease importation in the spatiotemporal transmission of indigenous dengue outbreak



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ABSTRACT

Dengue fever is one of the most widely spread mosquito-borne diseases in the world. International travelers who acquire dengue infection are important routes for virus transmission from one country to another. Previous studies have shown that imported dengue cases are able to initiate indigenous epidemics when appropriate weather conditions are present. However, the spatial-temporal associations between imported dengue cases and indigenous epidemics in areas with different social-demographic conditions remain unclear. This study investigated the determinants of spatial-temporal lags of imported dengue cases that initiated indigenous epidemics from 2003 to 2012 in Taiwan. We constructed Origin-Destination (OD) pairs of transmission from imported townships to local emergence to capture two important epidemiological characteristics: 1) the risk of diffusion and 2) the speed of transmission. We further explored the spatial-temporal associations between disease importation and socialdemographic indicators with geographic heterogeneity. Our results indicated that there were significant relationships between the time lags from imported cases to local emergence in late spring and early summer. Moreover, urbanization levels influence the speed of transmission. Our findings also showed that the risk of diffusion weighted by distance-decay characteristics increases the explanatory power of socioeconomic variables in imported townships. These findings imply that disease importation in late spring and early summer may be an early warning indicator of indigenous dengue epidemics and that the risk of transmission may be significantly influenced by the effects of inter-township travel.

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1. Introduction

Dengue virus is a vector-borne pathogen that is transmitted by contact between vectors and susceptible hosts (Galvani & May 2005). The primary vectors of dengue are the *Ae. aegypti* and *Ae. Albopictus* mosquitoes in Taiwan (CDC Taiwan, 2012), and the dengue virus is transmitted to human through the bites of infected female mosquitoes that have passed the extrinsic incubation period of 8–12 days (WHO, 2009). Since the 1970s, dengue fever has been gradually spreading throughout Southeast Asia, and its transmission involves interactions among carriers, mosquitoes, and healthy humans. As of 2010, Asia bore 70% of the global burden of disease, with 60 million infections (Bhatt et al., 2013). Over the last 30 years, the spread of dengue has been facilitated by the growing convenience and popularity of air travel (Gubler, 2011). Stoddard

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et al. (2009) claimed that human movement is a key behavioral factor in many vector-borne disease systems because it influences exposure to vectors and thus the transmission of pathogens (Stoddard et al., 2009). An abundance of vectors does not necessarily lead to high disease prevalence and epidemic stability. Human movement on different scales will influence patterns of disease diffusion. More frequent travel and more airports that experience international flights, including in dengue-endemic regions, lead to infected travelers returning to non-endemic countries with capable vectors (Aedes aegypti or Aedes albopictus) and a proper environment, initiating local dengue epidemics and increasing the public health burden (Quam et al., 2015; Semenza et al., 2014; Tatem et al., 2012). Therefore, it is important to explore how imported cases of dengue fever transmitted by returning travelers influence local epidemics or the emergence of indigenous cases.

Many studies have identified the importance of travelers in dense airline networks as an early warning of the increasing risk of local outbreaks in epidemic regions. Wilder-Smith and Gubler



proposed one important concept called "Travelers as Sentinels" (Wilder-Smith & Gubler, 2008), which was based on the Geo-Sentinel surveillance network, a clinician-based network. The concept divided regions where outbreaks occur into endemic and epidemic regions and suggested that infected returning travelers were particularly important to seasonality and annual trends of dengue fever in epidemic regions (Schwartz et al., 2008). Infected travelers have increased in number, thus increasing the risk of importing the virus and leading to severe epidemics and an increased burden to public health. Travelers can be considered sentinels, and observing travelers can help identify risk factors surrounding the local occurrence of dengue fever. Therefore, sentinels are important for epidemic regions to prevent local outbreaks. Huang et al. (2012) built the Vector-Borne Disease Airline Importation Risk Tool (VBD-AIR), a web-based GIS platform for monitoring and assessing the importation risk of vector-borne disease into countries by global air travelers (Huang et al., 2012). While VBD-AIR analyzes the global importation risk of vectorborne disease, monitoring spatial-temporal distribution of indigenous dengue cases is also crucial for the epidemic prevention and control. Delmelle, Zhu, Tang, and Casas (2014) constructed a webbased geospatial toolkit (OnTAPP) to monitor the spatial patterns of the local outbreak of dengue epidemics (Delmelle et al., 2014). Previous studies conducted statistical analysis on the spatialtemporal patterns of the local cases to explore the possible factors of the occurrence of dengue fever, including the built environment factors (Vazquez-Prokopec, Kitron, Montgomery, Horne, & Ritchie, 2010; Wen, Lin, Teng, & Chang, 2015), socio-economic factors (Hsueh, Lee, & Beltz, 2012; Machado-Machado, 2012), human movement factors (Stoddard et al., 2009; Wen, Lin, & Fang, 2012), and meteorological factors (Machado-Machado, 2012; Shang et al., 2010). The factors that influence both the importation risk and the indigenous distribution patterns were studied thoroughly in previous articles, however, the connection between the occurrence of imported cases and indigenous cases were simplified in previous literature, especially the influence of socioeconomic factors on dengue importation risk (Shang et al., 2010).

Taiwan is a dengue-epidemic region and is closely connected with Southeast Asia through air travel. For an epidemic region, imported cases are a precondition of indigenous cases (Schwartz et al., 2008). According to Shu et al. (2009) and Huang et al. (2012), molecular epidemiological data showed that Taiwan is an epidemic region for dengue fever in areas where introduced virus strains triggered local emergence events. Carriers who were infected outside of Taiwan transmitted virus strains to local residents via local mosquitoes. Imported cases are laboratoryconfirmed dengue cases with a travel history to endemic countries within 14 days before the date of dengue onset (CDC Taiwan, 2012). Because imported cases could be a precondition to trigger the local emergence of dengue fever, understanding the relationship between imported cases and indigenous cases helps us to identify the characteristics of local epidemics and to formulate prevention strategies that efficiently allocate public health resources. More importantly, exploring how such tropical diseases shift in the epidemic region and interact with local conditions is relevant to a major focus of public health research: the localization of tropical diseases in subtropical or temperate zones with global warming. Shang et al. (2010) showed that imported dengue is able to serve as an initial facilitator, or spark, for domestic epidemics. The study also discovered that the number of imported cases did not influence the number of indigenous dengue cases; imported cases only influenced the onset of a dengue epidemic, with a time lag of up to fourteen weeks (Shang et al., 2010). Local epidemics evolve independently in favorable environmental conditions with an appropriate vector population, but they must be initiated by imported cases.

However, the spatial relationship between imported and indigenous cases has not been adequately addressed. Imported cases that are located among different demographic and socioeconomic townships may have different capacities of diffusion that affect the transmitting amount, the risk of transmission, and the transmission speed. For example, the townships with higher population density would have more susceptible host exposed to the disease (Khalid & Ghaffar, 2015), and the townships with less average income (Mudrray, Quam, & Wilder-Smith, 2013) might have more suitable breeding sites for mosquitoes (Gubler, 2002). Moreover, people frequently move to the city for daily activities, and back to their residence with high population density or low income at night, thus it could increase the probability for the dengue outbreak and spreading (Adams & Kappan, 2009; Wen et al., 2012). Therefore, it is important to quantify the spatial diffusion of imported cases in terms of different socioeconomic factors and the time lag from the introduction of imported cases to local emergence under different socioeconomic conditions. The objectives of this study are to clarify the role of imported cases in initiating domestic epidemics, to examine the spatial-temporal effects between imported cases and indigenous cases, and to explore the transmission range and the transmission speed by estimating the risk of diffusion from imported cases in a township and analyzing the time lag between the occurrence of imported cases and the appearance of indigenous cases.

2. Materials

2.1. Study area

Taiwan is an island state situated in eastern Asia that experiences dengue outbreaks every year. Specifically, several severe dengue outbreaks have occurred in southern Taiwan (Chang, Huang, & Shu, 2012; Yang, Hou, Chen, & Chen, 2014) (Fig. 1). Since 2006, more than one hundred imported cases and more than five hundred indigenous cases have been identified each year (Chang et al., 2012). Indigenous epidemics mainly start in the summer and end around January or February of the following year. A township, the basic administrative unit in Taiwan, was used as the spatial unit in this study. There are a total of 359 townships in Taiwan. On average, each township had a population of 60,000 individuals and 3700–60,000 households in an area of 10–120 square kilometers with different urbanization levels. Most highly urbanized townships are concentrated in northern Taiwan.

2.2. Characteristics of the townships

The township characteristics considered in this study reflected three dimensions: socioeconomic status, urbanization levels, and whether indigenous emergence had previously been recorded. Socioeconomic status included population density and the average per capita income in each township. The population density data were obtained from the Interior Statistics in the Ministry of Interior, the per capita income data were obtained from the Market Intelligence and Consulting Institute (MIC), and the urbanization level data were obtained from a reference framework that had been adopted by the National Health Interview Survey (NHIS) in Taiwan (Liu et al., 2006). Past records of indigenous cases were compiled from the notifiable disease database, which came from the CDC Taiwan.

2.3. Dengue-infected case data

Dengue fever is a notifiable disease in Taiwan, and physicians



Fig. 1. The annual average imported and indigenous dengue cases in Taiwan 2003–2012 divided by population.

are required to report all suspected cases to the CDC Taiwan. All suspected cases are confirmed as dengue fever by standard laboratory diagnosis procedures, including real-time PCR, ELISA, and antigen detection (CDC Taiwan, 2012). The data used in this study covered case numbers of each week from 2003 to 2012 and were recorded in two categories, the number of imported cases per week and the number of indigenous cases per week, in each township. Imported cases were defined as laboratory-confirmed dengue cases with travel history to endemic countries within 14 days before the onset of dengue. The average weekly number of imported cases in each township is 1.06 with standard deviation 0.27; the number of indigenous cases is 4.52 with standard deviation 7.04. Fig. 1 shows the spatial distribution of township-level average annual incidence rate of imported and indigenous dengue cases in 2003–2012 at Taiwan.

3. Methods

3.1. Space-time relationships: Origin-Destination pairs

To capture the spatial-temporal relationships of the locations where imported and indigenous cases occurred, this study constructed Origin-Destination (OD) pairs of possible transmission between a township where imported cases occurred, called an imported township, and a township where indigenous cases occurred, called a local township. An OD pair was the unit for the Poisson regression analysis for modeling the diffusion risk and

transmission speed. An OD pair is defined as a potential transmission event from an imported township to a local township (Fig. 2). The following example describes how to construct an OD pair that accounts for the influence of imported cases on the emergence of indigenous cases. Fig. 2 illustrates the process of constructing an OD pair. Assume that there were only two townships, A and B, and that each township had records of imported cases and indigenous cases week by week. A counting window, illustrated in the yellow region in Fig. 2, was defined as the effective interval between the 2nd week and the 8th week after the occurrence of imported cases. The effective interval reflects possible maximum duration between the onset weeks of an imported dengue case and the first indigenous case in a specific township. Since the extrinsic incubation period of dengue is in 8-12 days, and the intrinsic incubation period is about 4-10 days (WHO, 2009), the minimum temporal lag between the onset days of an imported case and an indigenous case is at least 12 days (8 days of extrinsic incubation in the local vector and 4 days of intrinsic incubation in the indigenous host). Therefore, the second week after the occurrence of imported cases was used as the starting week of the counting window. On the other hand, Shang et al. (2010) suggested that a significant impact of imported dengue on indigenous dengue at the low intensity of transmission phase is within 8 weeks. The indigenous case occurs after 8th weeks from an imported case might not be directly initiated by the imported case. Therefore, the maximum number of the effective interval was set to the 8th week. In sum, an OD pair is the transmission link from an imported township to a



Fig. 2. Construction of Origin-Destination (OD) pairs.

local township in the effective interval of the imported case. The attributes for each OD pair (e.g., time lag and distance) were summarized for further statistical analysis.

After constructing the OD pairs, a multivariate regression analysis was used to explore the relationships between explanatory variables and dependent variables. This study focused on two important transmission characteristics, 1) the risk of diffusion and 2) transmission speed, as dependent variables associated with possible risk factors.

3.2. Dependent variables

3.2.1. The risk of diffusion

When one occurrence in an imported township had more OD pairs in the same week, this could indicate a higher probability of successful transmission. More OD pairs in the same imported township in the same week represented a greater capacity for spreading dengue fever. This study calculated the number of OD pairs associated with every occurrence in imported townships, defined as the number of links. Therefore, the number of links for an imported township was used to capture the risk of diffusion. To capture the contagious diffusion patterns, the distance-decay characteristic was used as a weight of each link. Every link was multiplied by a weight of distance (Equation (1)). The weight was a reciprocal of the Euclidean distance between the imported and the local townships for each OD pair.

$$w(i,j) = \begin{cases} \frac{1}{d(i,j)}, & \text{if } d(i,j) > 0\\ 1, & \text{if } d(i,j) = 0 \end{cases}$$
(1)

where, w(ij) is used for the alignment of the diffusion risk, d(ij) is the Euclidean distance between the imported township and local township.

3.2.2. Transmission speed

We used the length of the time lag from an imported township to a local township to capture the transmission speed. When one dengue case in an imported township was introduced from abroad, the time to emergence in local townships could be used as a reference for allocating public health resources in a timely fashion. For each OD pair, a time lag was considered to represent the transmission speed between an imported township and a local township. This study excluded time lags shorter than two weeks because the estimated minimum time for physical transmission was approximately two weeks from a carrier being capable to infect others via mosquitoes (Aldstadt et al., 2012). This study also excluded time lags longer than 8 weeks because numbers of imported cases are better correlated with numbers of indigenous cases after a lag of 1–2 months (Kuan & Chang, 2012).

3.3. Independent variables

To quantify the relationships between imported townships and local townships, the following categories of independent variables could be divided into characteristics of imported and local townships in OD pairs.

3.3.1. Socio-demographic indicators

During transmission, local socioeconomic indicators were used to estimate which area would be easily infected (Schmidt et al., 2011). In previous studies, the socioeconomic conditions in each area were estimated by using population density (Hsueh et al., 2012; Khalid & Ghaffar, 2015) and the average income (Mudrray et al., 2013; Mulligan, Dixon, Sinn, & Elliott, 2015) as the surrogate variables for the susceptible population and social-economic conditions, respectively. Therefore, we used the population density and the average income of each township as the explanatory variables for measuring the effect of socio-demographic factors on dengue importation. That is, there were two socioeconomic variables associated with the risk of diffusion in imported townships. Because an OD pair could include two dimensions in transmitting (imported) and transmitted (local) townships, there were four independent variables associated with the transmission rate.

3.3.2. Presence of indigenous records

A township with a past record of indigenous emergence represented a township in which the population carried antibodies that might allow them to resist similar virus strains, decreasing the rate of infection. In Taiwan, however, the virus strains often differed each year; thus, the antibodies would not necessarily allow an effective immune response. Therefore, a history of the indigenous emergence of dengue fever was considered to indicate a township in which the environment was suitable for vectors to transmit dengue virus, promoting the occurrence of indigenous cases. In this study, this variable was considered to have one variable associated with the risk of diffusion and two variables (imported vs. local) associated with the transmission speed.

3.3.3. The urbanization levels of Taiwan townships

Because degrees of urban development are closely related to the spread of dengue fever (Gubler, 2011), this study selected urbanization levels as an explanatory variable. To better represent the urbanization levels of Taiwan townships, Liu et al. (2006) modified the established principle of stratified sampling and designed stratified sampling for the 2005 National Health Interview Survey (NHIS) in Taiwan. They clustered 359 townships in Taiwan into seven clusters: highly urbanized, modernly urbanized, new, ordinary, aging, agro-township, and remote. The principle of clustering had three dimensions: demographic characteristics, industrialization, and medical resources. The western district and the central district of Tainan were merged into the center-west district in 2004, and this study adopted characteristics of the center district to represent the center-west district. Their seven clusters were simplified into three types of urbanization that were used in this study as township characteristics and as an explanatory variable. Urbanized townships included highly urbanized and modernly urbanized townships; ordinary townships included new and ordinary townships; and under-urbanized townships included aging, agro-townships, and remote townships. To capture the characteristics of imported townships, we used categorical independent variables associated with the risk of diffusion and the transmission speed for each OD pair.

3.4. Statistical analysis

Since the diffusion risk (number of links) with distance alignment, and transmission speed (time-lag) of dengue importation are count variables, and the variances of these variables are equal to their mean values, indicating that these variables can be regarded as Poisson-distributed random numbers (Fig. 3). Therefore, this study constructed Poisson regression models for analyzing the risk of diffusion and the transmission speed. In the global model, this study examined the time-lag effects and statistical significance of risk factors. We also grouped OD pairs by each month to reflect temporal (monthly) variations for identifying specific periods which are sensitive to diffusion risk or transmission speed of dengue importation.

4. Results

4.1. Descriptive statistics

Descriptive statistics associated with the risk of diffusion and the transmission speed are shown in Tables 1 and 2, respectively. The mean number of links (townships that an imported township can influence) for the risk of diffusion was 15, representing 4.2% of the townships of Taiwan. Generally, imported townships have a greater than average population density and a greater than average income of Taiwan. Additionally, approximately 40% of imported townships have past records of local cases, and imported townships are mostly urbanized. The data show that the transmission speed is approximately one month. Moreover, imported and local townships have a greater than average population density and a greater than average income of Taiwan, local townships (85%) are more likely to have past records of local cases than imported townships (42%), and more imported townships than local townships are urbanized.

4.2. Modeling the risk of diffusion

Table 3 illustrates two comparisons: the first comparison is of model A, without alignment by distance effect, versus model B1, with alignment by distance effect; the second comparison is of models B1 and B2, showing the influence of urbanization. The results show both models B1 and B2 have lower AIC values than A, indicating that an imported township had some contagious properties in diffusion when links were aligned with distance. After the urbanization level types were added to model B2, the influence of population density was reduced and replaced in part by that of urbanization. The regression coefficients in Table 3 revealed two important phenomena: (1) urbanization increases the risk of diffusion; and (2) a higher population density or urbanization with a lower income increases the risk of diffusion.

Table 4 shows the risk factors associated with the risk of diffusion in the monthly models. Significant differences were reported in the coefficients and the significance of log-likelihood ratio test for each month, reflecting monthly variations. The socio-



Fig. 3. Histogram of the dependent variables in the diffusion risk and transmission speed models: (a) diffusion risk (the number of links with alignment by distance decay effect) and (b) transmission speed (time-lag in weeks).

Table 1

Descriptive statistics in measuring the risk of diffusion.

Variable		Mean	Std. dev.	Min	Max
A number of links imported township	Density of population (1000 person/km ²) Average income (1000 NT\$/person) Presence of previous indigenous records Type of urbanization	15.03 8.740 601.202 41.89%	12.54 9.748 237.404	0 0.012 235.96 0	44 41.408 1365.29 1
	An urbanized township An ordinary township An under-urbanized township	60.31% 32.68% 7.00%		0 0 0	1 1 1

Note. 1. A sample is a number of OD pairs in each imported township. 2. Sample size, n = 1542.3. In Taiwan, Average density of population is 2.835 (1000person/Km2) and Average of average income is 435.463(1000TWD/person).

Table 2

Descriptive statistics in measuring the speed of transmission.

Variable		Mean	Std. dev.	Min	Max
Time lags (week)		4.285	2.023	2	8
Distance (km)		177.484	106.572	0	341.908
imported township	Density of population (1000 person/km ²)	8.871	9.710	0.012	41.408
	Average income (1000 NT\$/person)	598.986	234.317	235.96	1365.29
	Presence of previous indigenous records	46.80%		0	1
	Type of urbanization				
	An urbanized township	61.10%		0	1
	An ordinary township	33.16%		0	1
	An under-urbanized township	5.74%		0	1
local township	Density of population (1000person/km ²)	7.941	8.296	0.014	41.408
-	Average income (1000TWD/person)	520.724	152.308	233.53	1365.29
	Presence of previous indigenous records	85.33%		0	1
	Type of urbanization				
	An urbanized township	52.80%		0	1
	An ordinary township	38.74%		0	1
	An under-urbanized township	8.46%		0	1

Note. 1. A sample is an OD pair. 2. Sample size, n = 23,175.3. In Taiwan, Average density of population is 2.835 (1000person/Km2) and Average of average income is 435.463(1000TWD/person).

Table 3

Model results for the risk of diffusion: A without alignment of distance, B with alignment of distance.

	Model	А	B1	B2
	Variables	Risk	Risk	Risk
Imported township	Population density Average income Previous indigenous records Type of urbanization ref. ordinary - Urbanized - Under-urbanized Constant Observations Log-likelihood ratio test AIC pseudo-R2 (McFadden's)	2.58e-4 -5.59e-05 0.199* 2.65* 1542 -11978* 23,963 0.0095	0.0174* -1.05e-3* 1.52* -1.33* 1542 -1161* 2331 0.1399	9.50e-3* -1.39e-3* 1.47* 0.403* -0.188 -1.29* 1542 -1153* 2319 0.1459

Note. Conducted using Poisson regression. *p < 0.05.

demographic variables became significant from July to December. The presence of previous indigenous records is a significant indicator to the risk of transmission within these months.

4.3. Modeling the transmission speed

Table 5 shows that the properties of a local township have significant influence on the transmission speed. Compared to Model A, Model B1 dealt with distance as a linear variable, and Model B2 handled distance as a non-linear variable by adding the squared distance. The linear form of distance variable was not significant in Model B1. The results in Model B2 show that distance had a significant non-linear (quadratic) relationship to time lag. The negative sign of the coefficient for the squared variable suggests that the influence of distance on time lags has a ceiling. Distance may not unlimitedly extend time lag because people change their capacity for movement through transportation, permitting longdistance connections in a short time. The results of Model B2 also indicated that the time to local emergence from an imported township may be explained by the average income and the underurbanization variables of the imported townships. The positive coefficients of which suggest that these factors may delay local emergence after transmission. In the properties of local township (Model B2), higher population density had a negative coefficient, indicating rapid local emergence, and higher income had a positive coefficient, indicating delayed local emergence. That is, if diffusion

Table 4

Model results for the risk of diffusion: monthly mod
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	Model	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Imported township	Population density	0.0323	-0.0344	-0.0357	-7.03e- 3	-0.0136	-0.0109	0.021*	0.0129	0.0171	0.0113	-8.81e-3	-0.0142
x	Average income	-5.21e- 3	-1.97e- 3	-3.54e- 4	-4.92e- 3	-4.42e- 3	-7.23e- 4	-1.07e- 3	-3.79.e-3	— 1.56e- 3*	—2.36e- 3*	-4.09e- 3*	-2.35e- 3
	Previous records Type of urbanization	0.939	2.08	1.90	1.10	2.28	1.21*	1.28*	1.28*	1.39*	1.52*	2.20*	2.35*
	- urbanized - under-urbanized	1.77 0.263	0.833 1.25	0.569 -0.903	1.02 -9.85	1.06 -0.0499	0.644 0.3	0.363 -0.0271	0.435 * 0.0479	0.207 3.25e-3	0.442 -0.613	0.931* -0.913	0.693 -0.244
	Constant Observations LLR test AIC pseudo-R2 (McFadden's)	-2.01 91 -18 47 0.1505	-4.51 78 -5 22 0.1046	-4.36 54 -7 27 0.1120	-1.81 77 -8 28 0.1377	-2.22 88 -18 48 0.2172	- 1.97 * 122 - 67 * 145 0.0935	- 1.24 * 183 - 146 * 305 0.1435	- 1.35 * 305 - 267 * 545 0.1598	-0.592 159 - 152 * 316 0.1542	-0.374 161 - 145 * 302 0.2052	-0.312 107 - 93 * 198 0.2844	- 2.41 * 117 - 46 * 104 0.1840

Note. Conducted using Poisson regression. *p \leq 0.05.

Table 5

Model results for the speed of transmission: Model A excludes a distance variable and Models B1 and B2 include distance variables.

	Month	A	B1	B2
	Variables	Lag	Lag	Lag
Proximity	Distance Squared distance		-3.26e-5	3.99e-4* —1.39e-6*
Imported township	Population density Average income Previous indigenous records Type of urbanization	1.30e-4 2.87e-5 -0.0101	1.52e-4 3.27e-5 -0.0123	2.65e-4 3.87e-5 * -9.09e-3
	- urbanized - under-urbanized	2.26e-3 0.0423 *	2.20e-3 0.0404 *	5.28e-3 0.0387 *
Local township	Population density Average income Previous indigenous records Type of urbanization - urbanized - under-urbanized	-1.18e-3* 8.29e-5* -0.163* -0.0571* 0.0832*	-1.16e-3* 8.15e-5* -0.161* -0.0571* 0.0836*	-1.04e-3 8.66e-5* -0.159* -0.0573* 0.0832*
	Constant Observations Log-likelihood ratio test AIC pseudo-R2 (McFadden's)	1.56 * 23,175 48004 * 96,029 0.0070	1.57 * 23,175 48003 * 96,030 0.0071	1.54 * 23,175 47999 * 96,023 0.0071

Note. Conducted using Poisson regression. *p \leq 0.05.

is successful, a local township with a higher density and lower income will be more likely to experience a more rapid spread of disease.

Table 6 shows the significant risk factors associated with the transmission speed in the monthly models. The models in April and May have higher pseudo- R^2 , it indicates that the modes in these months have better fitting performance than other months. It suggests that intensively monitoring dengue importation in late spring and early summer (April and May) may identify early warning signs of indigenous dengue epidemics.

5. Discussions

Previous studies focused on the disease prevalence, incidence rate, and mortality rate as regression outcome variables for identifying spatial risk factors (Hu, Clements, Williams, Tong, & Mengersen, 2012; Naish et al. 2014). However, these models ignored the spatial and temporal interactions among areas. This study constructed OD pairs as the unit of analysis, instead of using administration units, to explore the spatial and temporal relationships of epidemic processes. We investigated two important epidemic characteristics of dengue fever: the risk of diffusion and the transmission speed. Our significant results indicated that (1) the risk of diffusion is correlated with the socioeconomic status of townships where imported dengue cases emerge, and the risk of diffusion to geographically neighboring townships is higher than to remote townships; (2) temporal variability may influence the speed of transmission from imported townships to local townships, and there is a significant relationship between the time lags from imported cases to local emergence in late spring; and (3) the urbanization levels also influence the transmission speed from imported townships to local townships, showing that shorter time lags were concentrated in highly urbanized townships.

Large-scale inter-township transmission of a dengue epidemic may occur in three pathways: (1) mosquitoes infected in an imported township fly to a local township and infect people; (2) infected humans move to a local township and infect mosquitoes that can cause a local emergence; and (3) both infected humans and infected mosquitoes move to a local township. However, the migration distance of a mosquito is hundreds of meters (Liew & Curtis, 2004), therefore human mobility may be an important risk factor of inter-township dengue transmission (WHO, 2009; Wen

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Model results for the speed of transmission: monthly models.

	Month	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Proximity	Distance	-3.21e- 4	-2.93e- 4	3.15e-3	-4.80e-4	-1.64e- 3	-7.77e-4	1.80e-4	-2.04e-4	3.46e-4	3.53e-4	3.72e-4	1.96e-3
	Squared distance	1.03e-6	-2.41e- 6	-7.71e- 6	1.66e-6	5.37e-6	2.49e-6	-1.97e- 7	3.62e-7	-1.38e-6	-1.04e- 6	-9.67e-7	-4.82e-6
Imported township	Population density	-2.42e- 3	-7.49e- 3	-0.0125	-0.0183	-3.16e- 3	5.39e-3*	-5.64e- 4	4.75e-4	1.53e-3	2.03e-3	6.82e-4	-3.54e-3
-	Average income	3.74e-4	1.34e-4	-1.60e- 7	5.44e-4	3.34e-5	9.78e-6	1.51e-5	2.48e-5	2.69e-5	-1.66e- 5	-1.18e-4	-8.75e-5
	Previous records Urbanization	0.104	0.0774	-0.0904	-0.186	-0.116	-8.44e-3	0.0268	-0.0143	-0.0183	8.69e-3	-0.0219	0.0298
	- urbanized - under-urbanized	-0.183 0.162	0.0503 -0.332	0.268 0.0121	0.132 1.45e- 16 *	0.0216 0.0946	- 0.0887 * -0.0238	8.99e-3 -0.0214	-2.92e-3 0.0632*	-0.0212 -0.0506	0.0284 0.0613	-0.0142 -0.0963	0.131* 0.0187
Local township	Population density	-0.0128	0.0347*	-0.0225	-0.0998*	0.0123*	8.06e-3*	4.12e-3*	-5.20e- 3*	-5.84e- 3*	8.56e-4	8.47e-4	1.34e-3
	Average income	1.08e-3	3.06e-3	-1.92e- 3	-1.06e-3	-4.74e- 4	2.26e-4*	-1.90e- 5	2.03e-4*	-9.00e-5	-6.90e- 5	—3.07e- 4*	-1.19e-4
	Previous records Urbanization	0.713*	-0.0235	-0.61	-0.931	-0.339*	-0.155*	0.0664*	-0.173*	-0.153*	-0.212*	-0.0166	0.065
	- urbanized - under-urbanized	-0.134 0.46	- 1.36 * -	0.0232 -	0.283 -	0.232 * 0.0967	- 0.152 * 0.0411	-0.0277 0.0806 *	- 0.149 * -3.62e-3	-5.16e-3 0.24 5*	-0.0303 0.0643 *	0.133* 0.276*	-0.156* -0.256*
	Constant Observations Log-likelihood ratio test	0.145 201 397 *	0.413 66 - 116 *	3.21 * 67 - 125 *	3.31 * 101 - 177 *	2.14 * 283 - 588 *	1.74 * 1103 2344 *	1.49 * 2866 - 6104 *	1.68 * 7045 - 14614 *	1.59 * 4313 - 8673 *	1.53 * 4285 - 8531 *	1.3 * 2066 - 3678 *	1.04 * 779 – 1353 *
	AIC pseudo-R2 (McFadden's)	820 0.0283	255 0.1081	274 0.0887	376 0.1766	1201 0.0305	4714 0.0152	12,235 0.0024	29,255 0.0153	17,372 0.0198	17,089 0.0087	7381 0.0078	2732 0.0090

Note. Conducted using Poisson regression. *p \leq 0.05.

et al., 2012). Our study shows that the risk of diffusion weighted by distance-decay characteristics increases the explanatory power of socioeconomic variables in imported townships, indicating that the risk of transmission may be significantly influenced by the effect of distances. On the other hand, the transmission speed model also showed the significant distance-decayed effect, which means the further distance between townships cause longer transmission time-lag. These findings suggested the meso- or micro-scale movement could be attributable to the influence of socioeconomic status and human behavioral factors rather than to vector density or abundance (Stoddard et al., 2009; Wesolowski et al., 2012).

Moreover, our findings showed that imported townships with high levels of urbanization may have a higher risk of transmission. One of the mechanisms for this phenomenon could be that dense populations indicate larger susceptible populations and thus more infected people who move to other townships and initiate local emergence events (Keeling & Rohani, 2008). Another mechanism may be that highly urbanized areas have relatively abundant medical resources; thus, even mild symptoms of dengue fever are easily diagnosed, increasing the rate of detection (Bhatt et al., 2013). Additionally, townships with dense populations but low average incomes usually located on the periphery of a city center, are likely to see a higher rate of human behaviors that increase the risk of intense transmission. These behaviors may include storage of water (Schmidt et al., 2011) by people who cannot afford tap water, thus creating mosquito habitats, and not using air-conditioning, which shelters people in houses from exposure to mosquitoes (Reiter et al., 2003).

If transmission from imported to local townships is successful, we further determine the time to the emergence of local cases. This study found the temporal relationship between imported cases and local cases to be significant in late spring, specifically March to April. The characteristics of a local township dominate the emergence of dengue epidemics during this period. Local townships with higher population density and income displayed a quicker emergence of indigenous dengue cases. This may be related to the higher vector-host ratio in cities, where more susceptible hosts promote short emergence times (Cummings et al., 2004).

Recently, scientific communities have confirmed that the ranges and transmission periods of insect-borne diseases, such as dengue fever and Zika virus, will expand, which will possibly localize infectious diseases from Southeast Asia, African or South America, because of rising temperatures (Smith et al., 2014). Under the threat of global warming, it is important to understand the relationship between imported cases and indigenous cases with the potential risk of localization, particularly in subtropical or temperate regions, where vectors also exist. This study explores a possible transmission link from cross-state introduction to local emergence events, which may generate local outbreaks in favorable environments shaped by socio-demographic factors. We proposed the concept of OD pairs to capture the risk of diffusion and transmission speed to measure the influence of imported dengue risk. The results show that interactions between contagious diffusion and socioeconomic status are significant in the latter half of the year. Time lags showed a significant relationship between rapid transmission and high urbanization in early spring. Our findings suggest that an introduced tropical disease may show intense diffusion in suitable meteorological and socioeconomic environments and may become gradually localized under possible scenarios of global warming.

Our study shows that the areas with high population, low income, and high urbanization level, would have higher risk of transmission to the nearby townships while imported case occurs. On the other hand, the areas where located nearby imported townships with high urbanization level, and the presence of previous indigenous records, might be immediate targets of the local dengue outbreak. These findings provide spatial-temporal insights into dengue importation. Meanwhile, the significant sociodemographic characteristics and sensitive periods identified in this study can also beneficial for early warning of indigenous dengue outbreak, healthcare resources allocation, and the public's risk perceptions of epidemics.

This study has several limitations. First, no meteorological data were incorporated in this study. We used monthly models to reflect the ability of model explanation in each month for exploring monthly variations in dengue importation. But we did not take meteorological variables into consideration in our models. Some meteorological variables in different time scales, such as daily, weekly or monthly average temperature and rainfall showed inconsistent effects on dengue risk (Jury, 2008; Pinto, Coelho, Oliver, & Massad, 2011). The duration of time-lag of the meteorological conditions on dengue outbreak also varied in different studies (Depradine & Lovell, 2004; Gu et al., 2016; Horta, Bruniera, Ker, Catita, & Ferreira, 2014). Therefore, our study focused on the socio-demographic characteristics in imported and local townships on dengue importation. Second, at the meso- or micro-scale, there were no data on human population mobility or the mosquito vector distribution, which may ignore the interactions between hostvector contacts and human behaviors. Therefore, we used the concept of fixed counting window to capture the possible transmission from imported to indigenous cases. Also, distance-decayed weights in our model implied the geographic pattern of human mobility. Third, methodologically, in the stage of constructing OD pairs, we simplified the transmission process from imported to local townships. We assumed that the length of the window was fixed based on previously published findings in the literature. The effects of heterogeneity on host susceptibility and host-vector contact frequency were ignored for measuring disease transmission.

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