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Epidemiological trends and the effect of airport fever screening on prevention of domestic dengue fever outbreaks in Taiwan, 1998–2007

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SUMMARY

Objective: This study aimed to examine the epidemiological trends in dengue infection and the impact of imported cases and airport fever screening on community transmission in Taiwan, a dengue non-endemic island.
Methods: All of the dengue case data were obtained from the surveillance system of the Taiwan Center for Disease Control and were analyzed by Pearson correlations, linear regression, and geographical information system (GIS)-based mapping. The impact of implementing airport fever screening was evaluated using the Student's *t*-test and two-way analysis of variance.
Results: A total of 10 351 dengue cases, including 7.1% of imported cases were investigated between 1998 and 2007. The majority of indigenous dengue cases (98.5%) were significantly clustered in southern Taiwan; 62.9% occurred in the metropolitan areas. The seasonality of dengue cases showed a peak from September to November. Airport fever screening was successful in identifying 45% (244/542 ; 95% confidence interval 33.1–57.8%) of imported dengue cases with fever. However, no statistical difference was found regarding the impact on community transmission when comparing the presence and absence of airport fever screening.
Conclusions: Our results show that airport fever screening had a positive effect on partially blocking the local transmission of imported dengue cases, while those undetected cases due to latent or asymptomatic infection would be the source of new dengue outbreaks each year.

1. Introduction

Dengue fever is one of the most widespread viral diseases transmitted by Aedes mosquitoes, and about 2.5 billion people globally, living in more than 100 epidemic countries, are at risk of dengue infection.[1,2] The reasons for the global emergence of dengue epidemics are not fully understood, but demographic and social changes,[1–3] including the increase in population flow, population growth, rural–urban migration, inadequate basic urban infrastructure, and exponential growth in consumerism are important factors responsible for the increased transmission of dengue fever.[1–3] Since there is no vaccine or specific therapy available for dengue fever, current methods for preventing the disease involve vector control strategies and health education, which require the identification of high-risk areas and periods for control intervention.

The island of Taiwan is located in the Pacific Ocean and a Northern Tropic line crosses the middle of the island, dividing it geographically into a subtropical zone (north of 23.5°N) and a tropical zone (south of 23.5°N). These two areas have distinct ecological characteristics, including the climate, distribution of mosquito vectors, and human population density.[4–6] We used geographical information systems (GIS) to map the geographic distribution of dengue cases recorded by the Taiwan Centers for Disease Control (CDC) surveillance system and examined the epidemiological features of recorded outbreaks during the past decade.

Dengue is considered an imported disease in Taiwan. Local outbreaks usually start in the summer following the importation of dengue virus (DENV) strains, reach a peak in October and November, and then slow down and cease in the winter of each year. Therefore, dengue is listed as a quarantine agent at the international airports in Taiwan, and in 2003 active surveillance for dengue was integrated into the airport fever screening program to reduce the importation of DENV strains. An empirical investigation into the impact of this intervention has not been carried out to

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date. In this study, we evaluated the effect of this intervention on community transmission. The findings of this study will contribute towards our understanding of dengue epidemics in Taiwan and this information may be applied in other epidemic areas to develop effective control measures in the future.

2. Methods

2.1. Data sources and definition of cases

Human dengue case data were acquired through multiple sources via the surveillance systems of the Taiwan CDC. The Taiwan CDC has a standard case definition of DENV infection, which includes clinical symptoms and laboratory confirmation. The surveillance systems included a national notifiable disease surveillance system. All of the dengue cases were confirmed by a reference laboratory at the Research and Diagnostic Center of the Taiwan CDC and tested positive for DENV isolation, DENV RNA detection using real-time reverse transcriptase polymerase chain reaction (real-time RT-PCR), and/or serological diagnosis by capture IgM/IgG ELISA.[7,8] The annual incidences were calculated from the number of cases in each city or county divided by the live population in the same year for 1998–2007. The annual incidences were expressed as the number of cases per million live-population. The imported cases were defined as cases reported by local clinics or airport fever screening with a travel history in the previous 2 weeks, whereas the indigenous cases were defined as cases reported by local clinics without any travel history.

2.2. Airport fever screening

During 1998–2002, airport screening for DENV was implemented in the form of a questionnaire filled out by all passengers. However, from 2003 to 2007, following the severe acute respiratory syndrome (SARS) outbreak, airport screening for DENV was implemented in the form of airport fever screening in combination with symptomatic passengers filling out a questionnaire.[9,10] Following thermal scanning by non-contact infrared thermometers[7] to detect those whose body temperature was $>37.5\,^{\circ}C$, blood specimens were sampled and tested by molecular and/or serological diagnosis for DENV infection.[7,8]

2.3. Statistical analysis

Analysis of annual and monthly cycles was based on the number of cases accumulated over the time period of the analysis. The association of indigenous cases and imported cases (R_{ID-IP}), as well as population density (R_{ID-PD}) and population numbers (R_{ID-PN}), were measured using the Pearson product moment correlations test ($R < 0.3$ was considered to show no statistical association) and/or the linear regression test. The effect of airport screening was analyzed by several methods including the Student's *t*-test, the positive predictive value, and two-way analysis of variance (ANOVA), assuming the number of imported cases as the independent variable, the number of indigenous cases as the dependent variable, and the implementation of airport screening during 2003–2007 and no airport screening during 1998–2002.

3. Results

3.1. Annual trends and seasonality of DENV infection

A total of 10 351 confirmed dengue cases including 9616 (92.9%) indigenous cases and 735 (7.1%) imported cases were recorded in the Taiwan CDC surveillance system from January 1998 to December 2007. There were three epidemic years in which the number of annual dengue cases reached 1000 or more, i.e., 5336 cases in 2002, 2000 cases in 2007, and 965 cases in 2006, with two additional small outbreaks in 2004 with 336 cases and 2005 with 202 cases. The yearly epidemic events showed epidemiological diversity in the site of occurrence and the DENV serotypes circulating, which differed from those of the previous or following epidemic years in 2002, 2006, and 2007 (Table 1). For example,

Table 1
The spatial heterogeneity of dengue cases and the various dominant serotypes in local outbreaks in Taiwan during the periods 1998–2002, prior to airport fever screening and 2003–2007, after implementation of airport fever screening

Year	Regions	Indigenous cases (%)	Imported cases (fever screening)	Incidence rate (cases/million)	Density (persons per km^2)	Population ($\times$100 000)	Serotype				
							I	II	III	IV	ND
1998	Taiwan	309	35	17	510	181.6	5	16	23	2	225
1999	Taiwan	42	26	2	511	182.0	2	5	4	0	46
2000	Taiwan	113	26	6	512	182.8	0	1	2	0	79
2001	Taiwan	227	54	12	514	183.0	7	85	1	2	218
2002	Taiwan	5336	52	291	514	183.0	9	2386	2	2	3371
	TP City[a]	7 (0.1)	16	27	9720	2.6	1	4	0	0	30
	TC City[a]	1 (0.02)	7	1	6098	9.9	1	1	0	1	7
	TN County[b]	18 (0.3)	2	16	549	7.5	0	5	0	0	24
	TN City[b]	66 (1.2)	3	89	4242	11.1	1	22	0	0	57
	KS County[b]	1979 (37.1)	0	1605	442	12.3	0	891	0	0	201
	KS City[b]	2832 (53.1)	2	1874	9827	15.1	1	1254	0	0	757
	PT County[b]	308 (5.8)	5	340	326	9.1	2	190	0	1	216
2003	Taiwan	86	59 (18)	5	515	184.2	11	28	4	5	138
2004	Taiwan	336	91 (57)	52	519	184.8	193	25	5	18	248
	PT County[b]	281 (83.6)	7	148	324	19	171	1	0	16	205
2005	Taiwan	202	104 (46)	11	522	185.6	6	16	43	0	198
	TN County[b]	3 (1.5)	2	3	549	7.5	0	0	0	0	8
	TN City[b]	57 (28.2)	2	75	4309	11.1	1	12	0	0	57
	KS County[b]	44 (21.8)	1	37	445	12.4	5	2	11	0	41
	KS City[b]	92 (45.5)	7	61	9835	15.1	2	5	31	0	95
2006	Taiwan	965	109 (48)	52	524	186.4	23	34	396	0	1127
	KS County[b]	185 (19.2)	4 (1)	148	446	12.5	0	1	95	0	170
	KS City[b]	757 (78.4)	10	498	9862	15.2	0	33	276	0	934
2007	Taiwan	2000	179 (75)	107	526	187.2	1095	75	0	0	1544
	TN County[b]	345 (17.3)	12 (4)	448	548	7.7	101	71	1	0	392
	TN City[b]	1459 (72.9)	21 (13)	1303	4353	11.2	916	6	0	0	937

[a] Taipei (TP) and Taichung (TC) are located in north of 23.58°N (northern and subtropical Taiwan).
[b] Kaohsiung (KS), Tainan (TN), and Pingtung (PT) are located in south of 23.58°N (southern and tropical Taiwan).

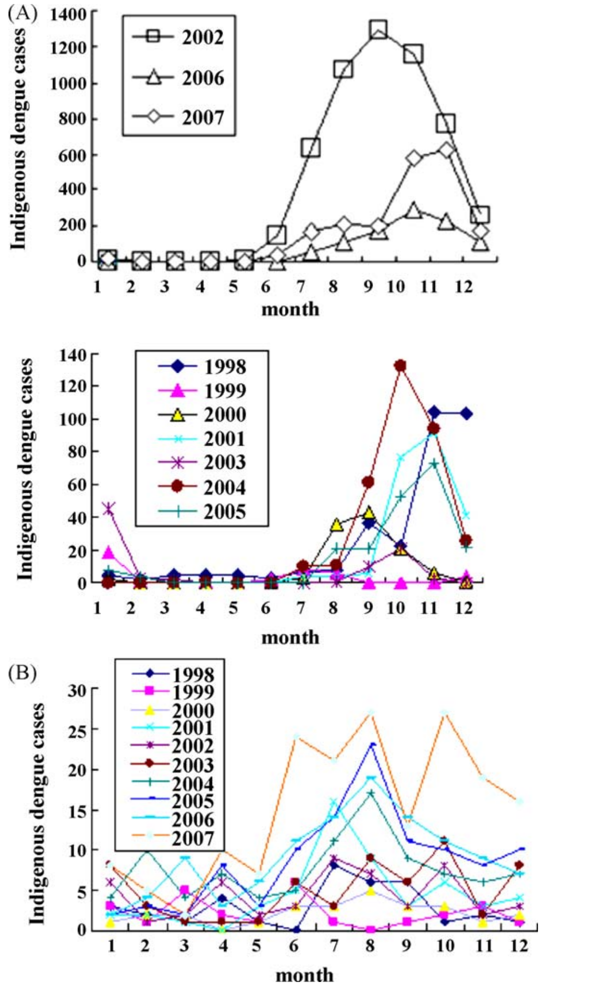

Figure 1. Fluctuations in the number of dengue cases recorded in the Taiwan CDC surveillance system during 1998–2007. Monthly data are shown to reflect the seasonality for (A) indigenous cases in epidemic years and non-epidemic years, and (B) imported cases for all years.

89.9% ((891 + 1254)/2386) of cases in 2002 in the Kaohsiung area were attributed to a circulating strain of DENV-2, 93.7% ((95 + 276)/396) of cases in 2006 in the Kaohsiung area were attributed to a circulating strain of DENV-3, and 92.9% ((101 + 916)/1095) of dengue cases in 2007 mainly in the Tainan area were attributed to a circulating strain of DENV-1 (Table 1).

Figure 1 shows the monthly distribution of dengue cases during the study period. There was significant seasonal fluctuation of indigenous cases among epidemic and non-epidemic years (Figure 1A). A slight increase in the number of cases was seen in June, this peaked from September to November and then subsided gradually in December, and new cases ceased between January and April. Regarding the four seasons, i.e., winter (December–February), spring (March–May), summer (June–August), and autumn (September–November), the highest prevalence of DENV infection was seen between summer and autumn annually. By comparing the seasonality of imported cases to indigenous cases, the pattern appeared to be slightly shifted to the left, except in 2002 (Figure 1B).

3.2. Geographical distribution

Figure 2 shows the heterogeneous distribution of the total number of 9616 indigenous and imported cases recorded in the GIS surveillance system from 1998 to 2007. The majority (98.5%; 9475/9616) of indigenous dengue cases were significantly clustered in southern Taiwan, which has a tropical climate, especially in metropolitan areas (62.9%; 6051/9616), whereas only sporadic cases occurred in northern Taiwan, which has a subtropical climate. Further analysis of the indigenous cases in the hot spot regions of southern (tropical) Taiwan showed a higher prevalence of dengue in the urbanized cities than in the neighboring urban areas (Table 1, Figure 2A). For example, a higher number (43.8%;

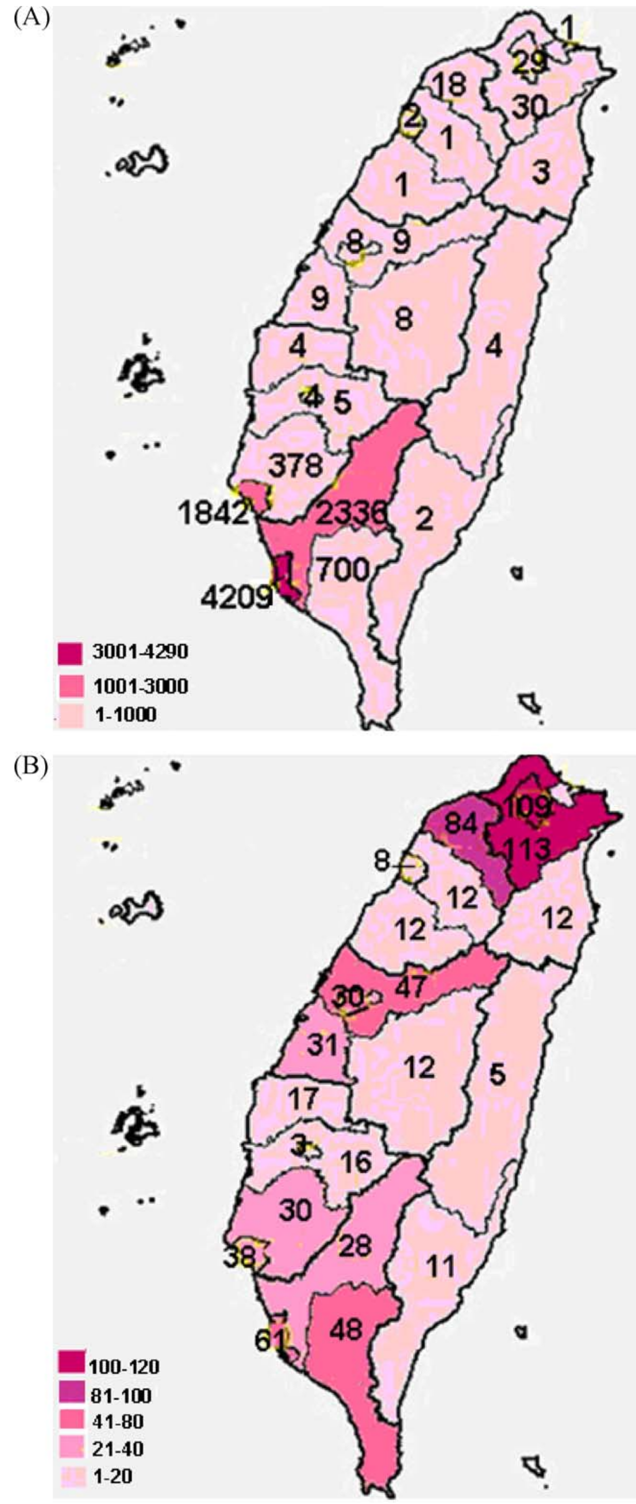

Figure 2. The heterogeneous geographical distribution of the cumulative number of (A) indigenous dengue cases, mainly clustered in outbreaks in southern Taiwan and heavily clustered in the metropolitan areas, and (B) imported dengue cases, which appeared more in northern Taiwan, during 1998–2007.

4209/9616) of dengue cases occurred in Kaohsiung City with a higher population density (9862–9872 persons per km^2), than in Kaohsiung County (24.3%; 2336/9616) with a lower population density (442–446 persons per km^2) during the 10-year period. Similarly, a higher number (19.2%; 1842/9616) of dengue cases occurred in Tainan City with a higher population density (4242–4353 persons per km^2) than in Tainan County (3.9%; 378/9616) with a lower population density (548–549 persons per km^2) during the 10-year period (Figure 2).

Moreover, we observed that, under similar climatic conditions, the number of dengue cases appeared to be positively associated with population density (R_{ID-PD} = 0.4–0.6) and population number (R_{ID-PN} = 0.5–0.7) in the epidemic years of 2002, 2006, and 2007. In the epidemic year 2002, the incidence rate of DENV infection was 53.1% (1874 per million) in the urbanized Kaohsiung City, compared with 37.1% (1605 per million) in the less urbanized Kaohsiung County. In the epidemic year 2006, the incidence rate of DENV infection was 78.4% (498 per million) in Kaohsiung City, compared with 19.2% (149 per million) in Kaohsiung County. In the epidemic year 2007, the incidence rate of DENV infection was 72.9% (1303 per million) in Tainan City, compared with 17.3% (448 per million) in Tainan County (Table 1, Figure 2A).

3.3. Impact of imported cases and the effect of airport fever screening

During 1998–2007, a high proportion of imported cases (65.0%; 478/735) occurred annually in northern and central Taiwan metropolitan areas, yet the resulting epidemics were relatively small. In contrast, a lower proportion of imported cases (34.9%; 257/735) appeared in southern Taiwan metropolitan areas, yet the resulting epidemics were more significant (Figure 2; Table 1).

In 2003, Taiwan introduced airport fever screening using non-contact infrared thermometers (NCIT) at international airports. This surveillance system successfully identified 45% (244/542; 95% confidence interval 33.1–57.8%) of imported dengue cases during 1998–2007 (Table 1). The efficacy of airport thermal screening for detecting DENV infection was tested and the derived positive predictive value (PPV) varied from 30.5% to 62.6% (Table 1). However, results from two-way ANOVA indicated that there was no significant difference between the fluctuating numbers of imported cases and indigenous cases ($F = 0.15 < 4.49$, $p = 0.71$; $F = 2.64 < 4.49$, $p = 0.12$), or the interaction effect ($F = 0.26$, $p = 0.62$) between them, i.e., the impact of imported cases on the annual trends of indigenous cases with or without airport fever screening. Throughout the island of Taiwan, the number of indigenous dengue cases and imported dengue cases also exhibited very little association ($-0.2 < R_{ID-IP} < 0.3$), even in the epidemic years of 2002, 2006, and 2007 (R_{ID-IP} = −0.035, 0.002, and 0.2, respectively). Nevertheless, in view of the geographical heterogeneity, the association of imported cases with indigenous cases (R_{ID-IP} = 0.08–0.95 by Pearson) was relatively higher in 2003–2007 in southern Taiwan after airport fever screening had been implemented, than in 1998–2001 (R_{ID-IP} = −0.54–0.89) prior to airport fever screening (Figure 3). Furthermore, the imported dengue cases detected by airport fever screening may provide a guide to the total number of imported dengue cases; during 2003–2007, the total number of imported cases = 3.459 + 0.418 × num- number of imported cases detected by fever screening ($n = 5$, $R = 0.90$, $R^2 = 0.80$, $p < 0.05$). Considering the geographical heterogeneity, the number of imported dengue cases was positively associated with indigenous cases in a linear regression manner; during 2003–2007, in which airport fever screening had been implemented, the number of indigenous cases = −169.283 + 53.398 × number of imported cases ($n = 25$, $R = 0.78$, $R^2 = 0.61$, $y = 53.40x - 169.28$). This association was lower ($n = 25$, $R = 0.13$, $R^2 = 0.02$) during 1998–2002, prior to the implementation of airport fever screening in southern Taiwan (Figure 3).

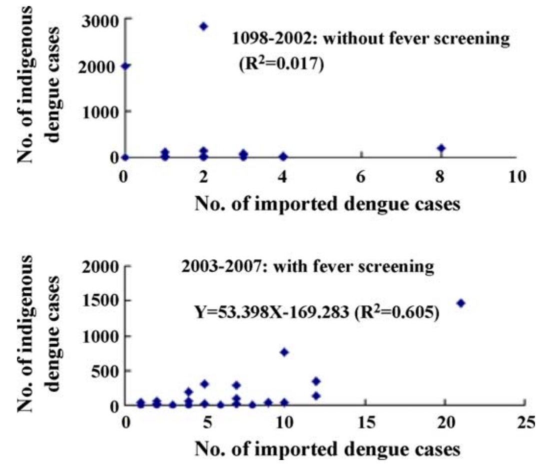

Figure 3. The epidemiological trends of dengue infection in dengue epidemic regions of southern Taiwan with regard to the number of imported cases vs. indigenous cases during: (A) 1998–2002, prior to implementation of airport fever screening (no significant association was found ($n = 25$, $R = 0.13$, $R^2 = 0.02$)); (B) 2003–2007, after implementation of airport fever screening (a significant linear regression was found between the imported dengue cases and the indigenous cases ($n = 25$, $R = 0.78$, $R^2 = 0.61$, $y = 53.40x - 169.28$)).

4. Discussion

By analyzing the dengue case database recorded by the Taiwan CDC surveillance system, trends in seasonality and geographical distribution were clearly exhibited. Dengue outbreaks were mainly clustered in southern (tropical) Taiwan, especially in the metropolitan areas. The heterogeneity of dengue incidence in time and geography might be attributed to the complexity of risk factors involved in the disease in Taiwan, including the interaction of ecological factors, such as mosquito vectors, human density, and climate. The mosquito vectors *Aedes albopictus* and *Aedes aegypti* coexist in tropical southern Taiwan. The multi-meal feeding vector, *A. aegypti*, is the main vector, often found among humans in urban dwellings.[5,6] For example, the distribution of *A. aegypti* in densely populated Kaohsiung City was found to be wider than *A. albopictus* and appeared to be increasing, whereas this was not found in the nearby counties.[11] Also, a significant correlation was found between the number of dengue cases per week and the adult *A. aegypti* index obtained 5 weeks before the disease occurred, whereas no correlation was found between the number of cases and the adult *A. albopictus* index in the Kaohsiung and Pingtung areas during 2004–2008.[11] In subtropical northern Taiwan, however, only *A. albopictus* has been found and only sporadic dengue cases have been recorded during the past decade. The weather in tropical Taiwan, with heavy rain, lasting high temperatures averaging 28 °C, and a moist environment (50–55% relative humidity), has been considered optimal for mosquitoes seeking their hosts,[12,15] leading to DENV replication.[12–14] However, in winter, dry conditions, relatively low temperatures averaging 20 °C, and occasional drops in temperature to 10–18 °C, could be a bottleneck for virus survival, amplification, and transmission.[16,17] In northern Taiwan with a subtropical climate, the rainfall is moderate and temperatures are relatively mild.[4,5] We observed that the dominant DENV abated each winter (December to February) even in tropical Taiwan, with diverse serotypes causing subsequent epidemics in following years (Table 1). This annual diversity in the dominant serotype and data from phylogenetic studies[7,9,10] indicate that dengue is not endemic in Taiwan.

In tropical southern Taiwan, the heterogeneity in distribution of dengue cases in the same epidemic years under a similar climate is further explained by the varied level of urbanization. The urbanized Kaohsiung City was found to be the highest risk area, followed by nearby Kaohsiung County, Tainan City, Tainan County, and then Pingtung County (Figure 2, Table 1). Wu et al.[5] proposed that the utilization of incidence rates to assess the occurrence of dengue infections gave limited results. In this study, we assessed the dengue incidence rate based on the number of cases divided by the stratified population of each separate region, instead of dividing by the total population. This provided meaningful differences between subtropical and tropical zone regions in epidemic years, but the results were rather meaningless in non-epidemic years or other areas (Table 1).

The reappearance of dengue epidemics in tropical Taiwan has previously been suggested to be complicated by demographic and social diversity,[1–3] however we observed an alternative phenomenon. In the metropolitan areas of tropical Taiwan, despite the living conditions (including housing and public facilities) improving each year, the magnitude of dengue epidemics did not decline (Table 1, Figure 1A). The dengue outbreak in Tainan in 2007 may instead have been due to decreasing herd immunity in the local population[3] and failed control measures.

The overall number of indigenous cases was not proportional to the number of imported cases, and airport fever screening barely affected the epidemiological trends when two different intervention periods (1998–2002 and 2003–2007) were compared. However, airport fever screening followed by laboratory confirmation by real-time RT-PCR[8] successfully identified approximately half, 45% (244/542), of imported dengue cases in the viremic stages on days 1–5 after onset of illness. Our results also indirectly demonstrate that about 55.0% (298/542) of imported cases were temporary, non-febrile, i.e., latent cases, undetected by airport fever screening, entering Taiwan with some risk of community transmission. We agree with the findings of a previous report[17] that 50–90% of dengue infection cases are asymptomatic, and therefore transmission of DENV into Taiwan via incoming travelers may be inevitable. Nevertheless, our findings that the total number of imported cases = 3.459 + 0.418 $\times$ number of imported cases detected by fever screening (R^2 = 0.80, $p < 0.05$), and that the geographical heterogeneity was the number of indigenous cases $-$169.283 + 53.398 $\times$ number of imported cases (R^2 = 0.61) during 2003–2007 when airport fever screening had been implemented, indicate that border screening might provide a guide to the total number of dengue imported cases and indirectly alert authorities of possible domestic outbreaks in southern Taiwan. The immediate quarantine of infectious cases could also help to block partial domestic transmission, reducing the risk to the population and the need for subsequent intervention, including vector control and medical care for patients. The efficacy of screening symptomatic passengers passing through Taiwan airports by NCIT was found to have a PPV = 30.5–62.6% when fever prevalence among passengers was $<$1%; this is similar to a previous report.[8,18] However, the effect on mitigating community transmission in dengue epidemics was not significantly different between pre-2003 border control methods (filling out questionnaires) and post-2003 methods (fever screening). This limitation was attributed to latent dengue cases, resulting from asymptomatic infection and possibly other factors, such as passengers hiding their symptoms.[8,18] All of these factors that could impair airport screening strategies should be considered when setting up border control measures to delay the pandemic progression of DENV.

Conflict of interest

This study had no conflict of interest, no sponsors, and no involvement of ethical issues.

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