Epidemiological analysis of the Kaohsiung city strategy for dengue fever quarantine and epidemic prevention

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Research article

Abstract

Background. Dengue is endemic in over 100 countries and is an important public health problem worldwide. Dengue is not considered endemic in Taiwan however, with importation of dengue viruses from neighboring countries via close commercial links and air travel believed to be the cause of local outbreaks. Disease control efforts have therefore focused on preventing the importation of dengue into Taiwan. Here, we investigate the relationships between numbers of imported and indigenous dengue cases to test the validity of this strategy. Methods. Dengue-fever case data from between 2013 and 2018 was obtained from the surveillance systems of the Taiwan Center for Disease Control and Kaohsiung City Health department. Standard epidemiological data, including the monthly numbers of indigenous and imported dengue cases, was calculated. Potential associations between the number of indigenous and imported cases were investigated using correlation analyses. Results. We identified a possible relationship between the period of disease concealment and the number of reported imported dengue cases which resulted in indigenous dengue-fever epidemics within local communities. Further analysis of confirmed dengue cases during previous dengue-fever epidemics in Kaohsiung City found that the risk of indigenous dengue-fever may be related to the likelihood of patients suffering from imported cases of dengue-fever staying within local communities. Conclusion. Given the correlations found between imported and indigenous dengue-fever cases, as well as the relationship between disease concealment period and risk of indigenous dengue-fever, the major priorities for disease control remain prevention of disease importation and efficient identification of dengue cases within high-risk communities.

Background

Dengue is the most prevalent emerging arthropod-borne viral infection (arbovirus) in humans worldwide and is highly endemic in many Western Pacific, Southeast Asian, and South American countries [1–3]. Transmitted via bites from infective female *Aedes* mosquitoes, dengue has rapidly spread in the past few decades, and this has been driven in part by climate change and increased rates of global trade and international travel [4–7]. Approximately 2.5 billion individuals are currently at risk of contracting dengue, and approximately 100 million clinically manifesting dengue infections are estimated to occur worldwide on an annual basis [8,9]. Disease symptoms vary significantly and range from asymptomatic cases to classic dengue fever (DF), as well as more serious complications (e.g., dengue hemorrhagic fever or dengue shock syndrome) [10].

The *dengue virus* (DENV) itself is an enveloped virus with a single-stranded, positive-sense RNA genome, belonging to the genus *Flavivirus* of the family *Flaviviridae*. DENV contains 5'- and 3'-untranslated regions and a single open reading frame encoding a single polyprotein that can be cleaved into three structural proteins (capsid, premembrane/membrane, and envelope) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [11,12]. There are four genetically and antigenically distinct DENV serotypes, recognized as DENV-1, -2, -3, and -4 [13]. Since 2006, southern Taiwan has faced dengue outbreaks of varying magnitudes annually, with relatively large outbreaks occurring in 2014 and 2015; DENV-1 and -2, respectively, were identified as the major serotypes in these cases [14].

Transmission of dengue in Taiwan is driven by two species of *Aedes* mosquitoes: *Aedes albopictus* and *Aedes aegypti*. The former is found throughout Taiwan, while the latter is restricted to the south [15]. Indigenous dengue is not considered endemic in Taiwan; thus, importation of DENV (due to close commercial ties and human migration from neighboring Southeast Asian countries) is thought to be the underlying cause of DENV outbreaks. Preventing the importation of disease has therefore become the major objective of quarantine for dengue fever and the epidemic prevention network in Taiwan.

The emergence of Severe Acute Respiratory Syndrome in 2003 highlighted the role of international travel in the rapid spread of infectious diseases and prompted many countries to establish border control strategies and use noncontact infrared thermometers (NCITs) at international airports to reduce the risk of imported infections [16,17]. Taiwan expanded this noninvasive diagnostic tool to screen for various infections, including dengue, at all major entry borders.

Such strategies to reduce the risk of disease importation are particularly relevant for Kaohsiung City, a major city in the south of Taiwan, as it was the main site of the 2014 and 2015 dengue outbreaks [18,19]. Constant surveillance of dengue seroprevalence and the use of airport fever screening systems to test individuals suspected of having dengue fever have become central to the disease control program of the city.

However, the relationship between the numbers of indigenous and imported cases remains unclear [20]. This relationship is complicated in part by cases of asymptomatic disease and prolonged periods of disease latency, which can result in secondary/tertiary waves of infection many weeks after the first wave [3]. In theory, the latency period in mosquitoes is between 8 and 12 days, while the maximal latency in humans is between 3 and 8 days [10]. As such, the second wave of infections typically occurs 2–3 weeks later, and the third wave can occur 4–6 weeks after the initial bout of infections. Detailed case reports collected over prolonged periods are required to dissect the complex interactions between indigenous and imported cases of dengue fever.

In this study, we investigated the number of indigenous and imported cases of dengue fever in Kaohsiung City between 2013 and 2018, including the country of importation and status/occupation of the infected individual. We also mapped out the monthly number of cases confirmed by the Taiwan Center for Disease Control (CDC) surveillance system throughout this period. We subsequently tested for correlations between indigenous and imported cases, testing both the number of cases and the month in which they were reported. We found a significant correlation between the two types of infection after accounting for the disease latency period and delays in case reporting. Our results suggest that importation of the virus is indeed driving outbreaks of dengue fever in Taiwan, indicating that disease prevention strategies should continue to focus on human migration patterns and the efficient identification of dengue fever to reduce the incidence of disease.

Methods

Database and case definitions

We identified all cases of dengue fever reported between January 2013 and September 2018 in the public databases of the Taiwan CDC and the Kaohsiung City Health Department. We used the definitions of dengue set by the Taiwan CDC [21]. As such, according to the Diagnostic Center of the Taiwan CDC, a confirmed case of dengue fever requires positive detection of RNA using real-time reverse transcriptase polymerase chain reaction and/or serological diagnosis through an IgM/IgG enzyme-linked immunosorbent assay [22]. A standard protocol was adopted by local physicians and epidemiologists to collect individual-level information on each dengue fever case, including the onset of dengue illness, age, gender, clinical manifestations, reporting hospital, diagnosis results and travel history. Dengue case collection and surveillance involved both passive (hospital-based reporting systems) and active (fever screening at airports, self-reporting, expanded screening for contacts of confirmed cases, patients with fever of unknown origin and school-based reporting) detection.

An imported case of dengue fever is defined as a confirmed case in a patient who had traveled to another country, in which dengue fever is endemic, within 2 weeks prior to the onset of illness. Indigenous cases are defined as cases reported in infected individuals without any travel history. The total number of imported cases of dengue included inbound passengers diagnosed as dengue-positive via airport screening methods and those diagnosed in clinics or hospitals following entry into the local community.

Surveillance of dengue

The airport fever screening program was introduced in 2003 to detect travelers infected with Severe Acute Respiratory Syndrome, dengue, or other diseases. In this study, we analyzed data collected between January 2013 and September 2018 from the International Kaohsiung Airport. All airline passengers (outbound and inbound) were requested to have their body temperature measured using NCITs. Two thermal NCITs were set up at each entry gate, with each NCIT having an infrared-thermal camera. Travelers with a detected temperature >37.5°C were rechecked by quarantine officers with a symptoms survey and assessed using an ear thermometer. Travelers with a temperature >38°C, who had arrived from a dengue-affected area, were triaged for additional diagnostics. Specimens were obtained for testing with the Dengue NS1 Rapid Test (SD BIOLINE Inc., Korea; sensitivity and specificity estimated at 92% and 98%, respectively) at an airport inspection station. Duplicate specimens were sent to the central laboratory of the Taiwan CDC for simultaneous confirmation through molecular and/or serological diagnosis.

Statistical analysis

All statistical analyses were conducted using the SPSS Statistics software, version 22 (IBM Corp., Armonk, NY, USA). Overall mean scores were calculated and compared using paired t-tests. Potential correlations between the numbers of indigenous and imported cases were analyzed using Pearson's

correlation coefficient test and two-way analysis of variance. A *p*-value <0.05 was considered statistically significant.

Results

Statistical analysis of indigenous and imported cases of dengue fever in Kaohsiung City between 2013 and September 2018

Statistics for the total number of imported cases of dengue fever in Kaohsiung City

A total of 239 imported cases of dengue (32, 44, 61, 37, 34, and 31 cases in 2013, 2014, 2015, 2016, 2017, and 2018, respectively) were identified in Kaohsiung City during the examination period (Table 1), including 80 women (33.5%) and 159 men (66.5%). The majority of cases involved individuals arriving from Southeast Asian countries: 48 from the Philippines (20.0%), 47 from Indonesia (19.6%), 33 from Vietnam (13.8%), 30 from Malaysia (12.6%), 24 from Thailand (10.0%), and 13 from Singapore (5.4%). Additional cases were also imported from the Indian subcontinent (i.e., India, Bangladesh, Sri Lanka, and the Maldives) and the South Pacific region (Tuvalu). Supplementary Figure 1 shows the top and bottom 5 countries from which dengue was imported, and the distance from these countries to Kaohsiung.

Further analyses of the 239 imported cases of dengue revealed that 142 of the infected individuals (59.4%) were Taiwanese nationals who had traveled abroad. However, foreign workers and tourists entering the country accounted for a further 15.5% and 8.8% of cases, respectively (Table 2). Analysis of patient occupation is presented in Table 3, with home management, business, and studying being the most commonly cited occupations (together accounting for 46.4% of cases). Figure 1 shows fluctuations in the monthly reporting rates of imported cases of dengue in Kaohsiung City (Figure 1).

Predominant serotypes of annual indigenous cases of dengue fever in Kaohsiung City

Between 2013 and September 2018, there were 35,148 indigenous cases of dengue fever in Kaohsiung City, with 70, 14,999, 19,723, 342, 3, and 11 cases reported in 2013, 2014, 2015, 2016, 2017, and 2018 (up to the end of September), respectively. Primary cases of dengue fever were concentrated in the 24 consecutive months between May 2014 and April 2016 (Figure 2). During this period, there were 35,062 indigenous cases of dengue fever in Kaohsiung City (99.8%). The major epidemic serotype of dengue fever in 2014 was serotype 1, while that from 2015 to April 2016 was serotype 2.

Concealment of cases for more than 3 days

Further analysis of the 239 confirmed imported cases revealed that 37 infected individuals did not stay within local communities after contracting dengue. This included 5/32 cases that occurred in 2013

(15.6%); 3/44 cases in 2014 (6.8%); 1/61 cases in 2015 (1.7%); 10/37 cases in 2016 (27.0%); 12/34 cases in 2017 (35.3%); and 6/31 cases in 2018 (19.4%) (Table 4).

We also identified a significant number of cases whose concealment period was >3 days (139/239, 58.16%). Of these, we found 24 such cases in 2013 (75.0% of cases that year), 32 in 2014 (72.7%), 39 in 2015 (63.9%), 22 in 2016 (59.5%), 14 in 2017 (41.2%), and 8 in 2018 (19.4%) (Figure 3).

Statistical analysis of the number of indigenous and imported cases of dengue fever in Kaohsiung City between 2013 and September 2018

The 35,148 confirmed cases of indigenous dengue fever reported in Kaohsiung City between 2013 and September of 2018, along with the 239 imported cases, were sorted according to the month of identification (n = 69). A significant positive correlation (paired sample correlation coefficient, r = 0.407, p = 0.001) was found between the numbers of imported and indigenous cases reported each month (Table 5).

However, actual clinical surveillance reports were delayed by approximately 1–2 months during local epidemics of dengue fever; furthermore, a concealment period ≥2 days was common. Therefore, instead of investigating correlations between reported cases in the same month, we tested for relationships between the number of imported cases in a single month and the number of indigenous cases reported 2 months later, also accounting for differences in the concealment period. When accounting for concealment periods >2 days, we found significant positive correlations between the number of imported cases and the number of indigenous cases reported 2 months later (Pearson's correlation coefficient, r = 0.459, p = 0.0001), >3 days (r = 0.394, p = 0.001), and >4 days (r = 0.387, p = 0.001) (Table 6).

Discussion

Dengue fever spreads via "virus-mosquito-human" transmission. Current preventive strategies focus on the mosquito itself, with a particular focus on environmental rectification and maintenance (e.g., targeting sites of mosquito breeding) [23,24]. The large-scale outbreaks of dengue fever that occurred in Kaohsiung City between 2014 and 2015, which were likely the result of imported cases of dengue, showed the limitations of this vector-focused approach.

The spread and control of infectious diseases are key aspects in promptly preventing the occurrence of disease. Kaohsiung City experienced a severe epidemic outbreak of dengue fever from 2014 to 2015, in part due to a lack of real-time reporting of cases, which allowed the virus to spread in the community. Following this, the Kaohsiung City Government refocused its disease prevention efforts on border quarantine to prevent importation of disease, which should consequently reduce the number of indigenous cases resulting from secondary infections. The Kaohsiung City Government devised the following action plans to improve the anti-epidemic capacity of Kaohsiung City to prevent dengue fever.

These efforts included the establishment of a quarantine referral station, a quarantine period for foreign workers and fishermen, return of new residents and foreign students to their home country for health care measures, and increased incentives for the local or returning citizens related to the prevention of epidemics.

During the 2014 and 2015 outbreaks, there were 14,999 and 19,723 cases of indigenous dengue fever, respectively. Case reports from early 2016 showed signs of a continuation of the 2015 epidemic, with 340 indigenous cases reported before April. However, there were only two cases of native dengue fever throughout the remainder of 2016. In 2017 and 2018, Kaohsiung City achieved the two lowest numbers of indigenous cases on record (3 and 11 cases, respectively) [19]. This significant reduction in the number of dengue cases was in part due to a complete reorganization of the dengue quarantine and epidemic preventive network in Kaohsiung in April 2016, though other factors (such as the emergence of cross-protection between heterologous Dengue serotypes following disease outbreaks) may have also contributed to the extent of this reduction.

A new project focusing on imported cases was initiated in July 2016 to cover both border quarantine and epidemic prevention work. In October 2016, the only "Quarantine referral station" in Taiwan was established at the Kaohsiung International Airport to identify infected travelers. Thus, the airport and seaport of Kaohsiung City constitute the front line of the border quarantine network in South Taiwan for the prevention of dengue fever epidemics.

Kaohsiung City possesses large native populations of *Aedes aegypti* and *Aedes albopictus*, resulting in a high risk of secondary dengue infection after importation of an initial case from abroad. Although the ongoing collection and testing of thousands of human and mosquito specimens suggest that the DENV has not yet localized in Kaohsiung, it is vital that control programs targeting mosquitoes continue to reduce the likelihood of future localization and minimize the risk of secondary outbreaks following the initial wave of infections [25]. Efforts for the control of dengue, whether focused on vector control or prevention of disease importation, are costly both in terms of resources and workload. Constant innovation is required to maintain the low number of dengue cases reported in Kaohsiung City, while reducing unnecessary expenditure. This includes improved, efficient targeting of high-risk individuals to reduce the likelihood of transmission throughout local communities. For example, foreign workers and fishermen from countries in which dengue is endemic could be screened for dengue (NS1) within the first 3 days of entering Taiwan [26]. Those identified as being dengue-positive would then receive hospital inpatient care. This approach will assist in isolating the DENV carrier from the vector mosquitoes in the community, effectively blocking DENV from spreading into the community from foreign sources. Furthermore, the use of mathematical modelling, both to predict patterns of future disease outbreaks and to test the origin of disease cases, has becoming increasingly widespread in recent years [27,28]. The wealth of data available as a result of the dengue outbreaks in Kaohsiung could be utilized to develop such models and thus assist in disease control efforts.

Based on the above findings, the lowest record of local confirmed cases of dengue fever in Kaohsiung City in the past few years was the result of its unique geographical location used to strengthen the efficiency of quarantine outside the battle zone, optimize medical network resources against dengue, construct specific quarantine and epidemic prevention networks, and effectively shorten the incubation period of cases. In other words, the dengue protection network has successfully utilized the natural advantages of Taiwan for disease control to adopt an effective quarantine strategy. In spite of this, the threat posed by dengue (as well as other communicable diseases) is likely to increase in line with increases in international exchange and trade. Local networks must be able to constantly innovate and adopt an international focus to effectively combat dengue and prevent future outbreaks of dengue in Taiwan.

Conclusions

Though there may be several factors influencing disease transmission (including vector migration), dengue fever outbreaks in Kaohsiung are the likely the result of imported cases of the disease, in which dengue virus is transported to Kaohsiung via infected individuals and then spread within the community. Therefore, it is vital that strategies, including modern quarantine methodologies and high-efficiency health care, are utilized to reduce the likelihood of dengue fever becoming endemic in Kaohsiung City.

Abbreviations

Dengue fever: DF

Dengue virus: DENV

Dengue hemorrhagic fever: DHF

Dengue shock syndrome: DSS

Severe Acute Respiratory Syndrome: SARS

Noncontact infrared thermometer: NCIT

Centers for Disease Control: CDC

Declarations

Ethics approval and consent to participate

The need for ethics approval was deemed unnecessary according to "Communicable Disease Control Act" of Taiwan. Data sets were extracted without personal identifiers and organized into literature by this study, institutional research guidelines were adhered, to ensure scientific soundness.

Consent for publication

All authors have read the manuscript and approve the manuscript to be published.

Availability of data and material

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request. A person who wants to access the raw data should contact with the corresponding author.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

CYP, JJH, LJL, PYS and CHC contributed to research conception and design. CYP, HPH, LJL and CHC analyzed the data. CYP, WLL, TPC and CHC performed experiments. CYP, WLL, MPS, LJL and CHC wrote the original manuscript. CYP, WLL, MPS, PYS and CHC wrote the review and editing. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, the tables have been placed in the Supplementary Files section.

Supplementary Figure Legend

Supplementary Figure 1. Map showing the distance between the top/ bottom 5 countries from which Dengue was imported and Kaohsiung city between 2013 and 2018.
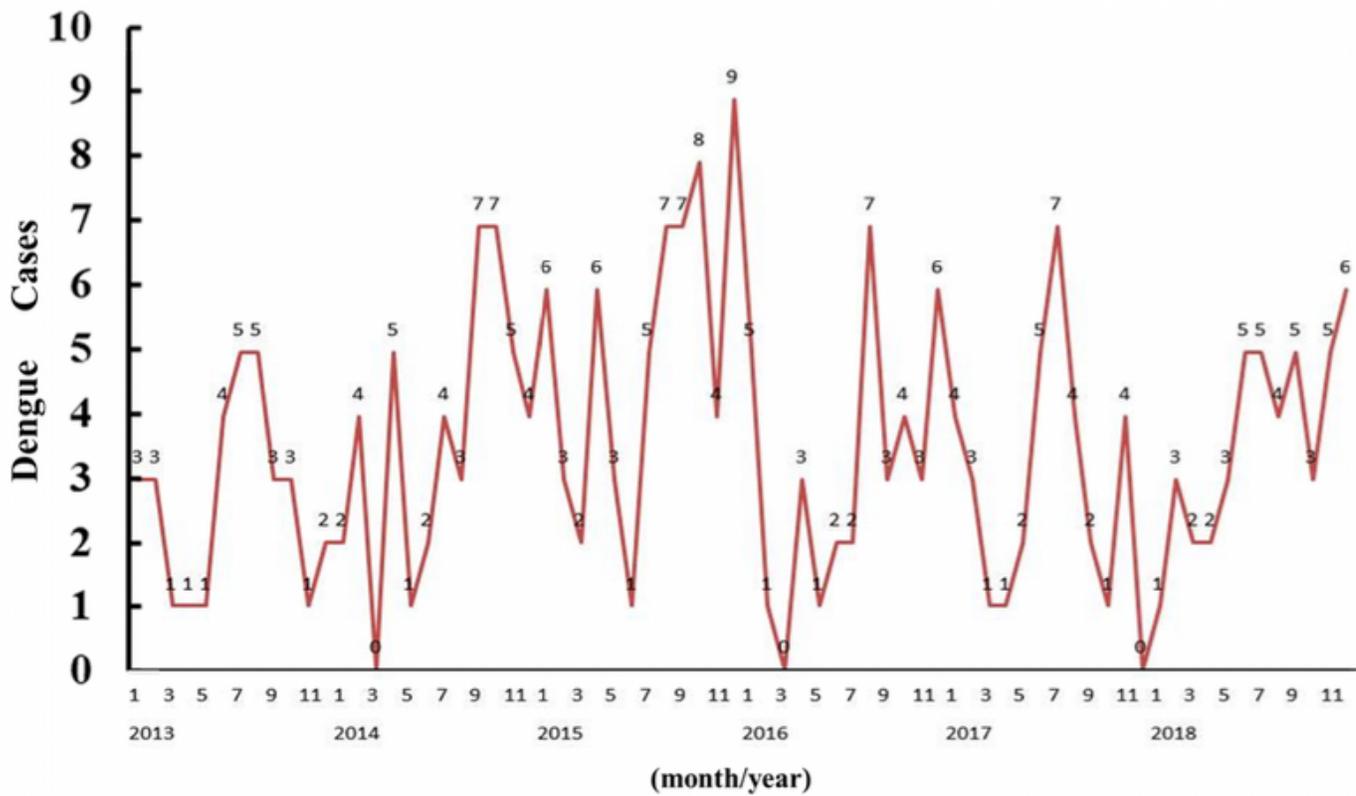
Figures

Figure 1

Fluctuations in the number of dengue cases from 2013 to September 2018. The recorded by the Taiwan CDC surveillance system in Kaohsiung City from 2013 to September 2018. Monthly data are shown to reflect imported cases for all years.
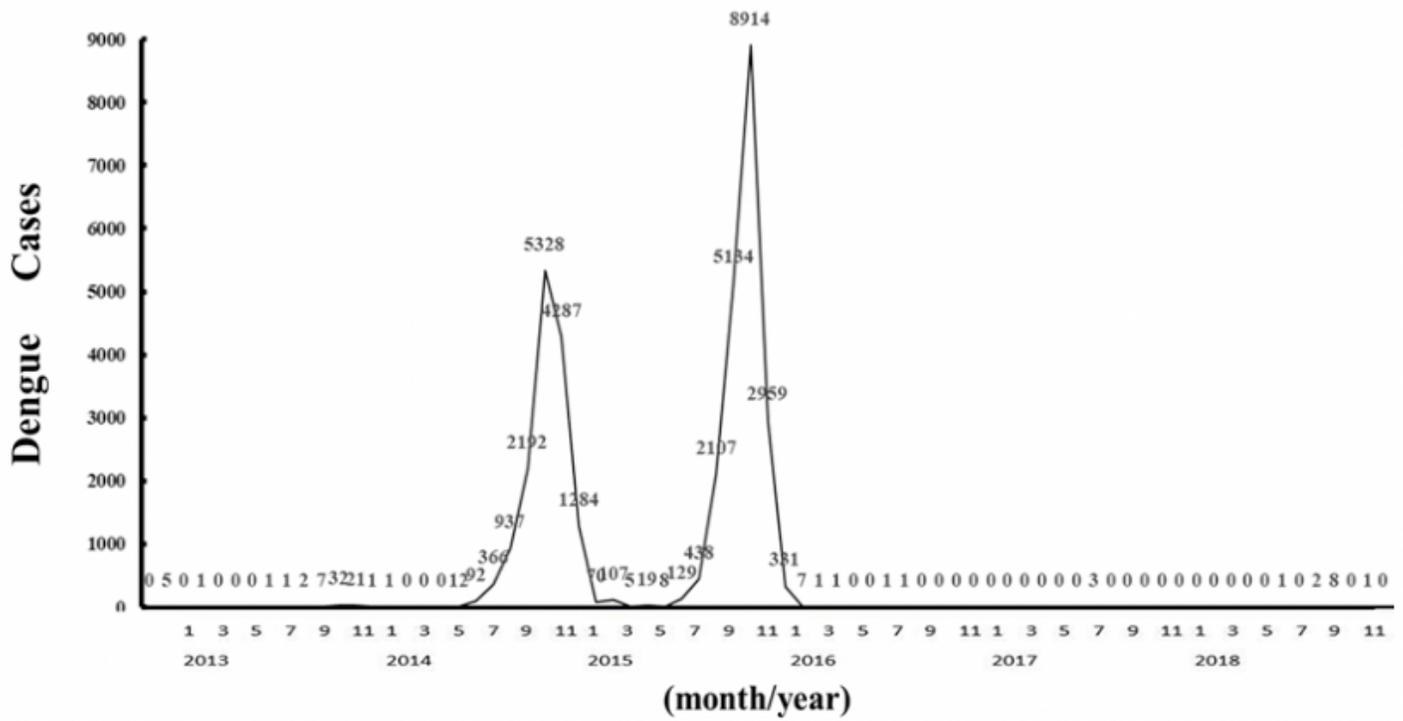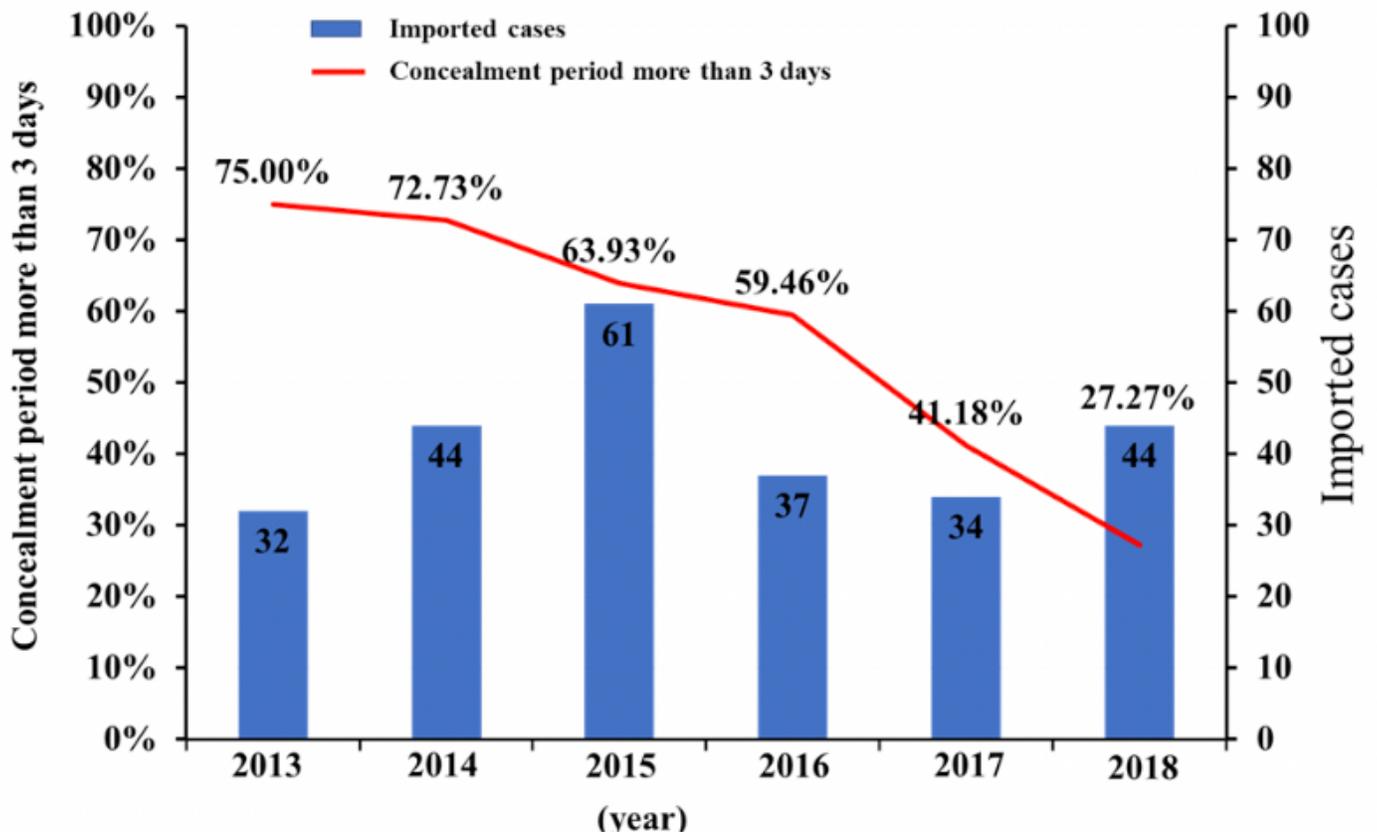
Figure 2

The number of indigenous cases of dengue in Kaohsiung city from 2013 to September 2018.

Figure 3

Analysis and correlations between the imported dengue cases and concealment period. The number of imported dengue cases and the percentage of cases with a concealment period of more than 3 days in Kaohsiung city from 2013 to September 2018.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Supplementaryfigure1.docx
- Table3.docx
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