Dengue outbreaks in Taiwan, 1998–2017: Importation, serotype and temporal pattern

Ying-Hen Hsieh

Department of Public Health, China Medical University, Taichung Taiwan 40402

Objective: To ascertain the role of imported cases and serotypes on dengue outbreaks in Taiwan which have been sporadic yet highly volatile during the past two decades, exhibiting record-breaking magnitude in recent years. Methods: Confirmed case and serotype data from Taiwan Centers for Disease Control during 1998-2017 were fully examined, with fitting of weekly and daily case data of each city/county to a mathematical model to pinpoint the waves of cases and their locations. Moreover, we quantify the timing of turning point and transmission potential of each wave and determine its circulating serotype, to ascertain any pattern or connection between the variations in circulating serotypes and the magnitude/transmissibility of outbreak. Results: While the number of imported case increased steadily during past two decades, the yearly number of indigenous cases fluctuated wildly. Moreover, while yearly percentages of serotypes for imported cases remains steady, that of indigenous cases does not exhibit any clear pattern. There was at least one wave of reported cases somewhere in Taiwan every year from 1998 to 2015, except in 2016-2017. The effective reproduction number R for all waves in all locations ranged from 1.14 to 2.87, with the exception of two Tainan waves, in 2010 (3.95) and 2015 (6.84). Four major outbreaks of over 2000 cases reveal circulation of one dominant serotype. Conclusions: Correlation between imported cases and indigenous outbreak prove to be difficult to ascertain, even with the availability of serotype data. However, although there had been occasional co-circulation of serotypes in one location, and for some years with different serotypes circulating in different locations, all major outbreaks of over 2000 cases during the past two decades are due to circulation of mainly a single serotype, perhaps indicating greater transmission potential with one dominating serotype.

1. Introduction

Incidence of dengue has grown dramatically around the world in recent decades, when dengue is ranked among the top re-emerging diseases, posing serious public health threat[1]. In the past, the actual numbers of dengue cases were often severely underreported with many cases misclassified, mainly due to large portions of asymptomatic infections and difficulty in accurate diagnosis in early decades. Diagnosis of dengue can be challenging, highly dependent on timing of sampling, phase of infection, serotype and immune response which varies depending on whether the individual has a primary (i.e., first dengue or other flavivirus infection) or a secondary (i.e., had dengue or other flavivirus infection in past) infection. A recent study on prevalence of dengue estimates that 3.9 billion people in 128 countries are at risk for dengue infection[2]. There are four distinct but closely related serotypes of the virus...
that cause dengue, namely DENV1, DENV2, DENV3 and DENV4. Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is not only partial but also temporary. Antibody-mediated enhancement (ADE) of dengue virus infection has been known to further complicate disease severity[3]. Subsequent infections by other serotypes could actually increase the risk of developing severe dengue. Hyper-endemicity of multiple dengue virus serotypes in many countries has also contributed to the difficult challenge to predict and control dengue outbreaks.

In Taiwan, located in the tropical-subtropical region of the Northern Hemisphere, there had been many dengue fever/ dengue haemorrhagic fever outbreaks in the first half of 20th century[4-6], including a widespread outbreak island-wide in 1915-1916, when merchant ship from Southeast Asia brought the disease to Kaohsiung and subsequently spread via railroad to other cities on the island such as Keelung, Taipei and Taichung. It has been reported that several million people were infected during this outbreak[7]. Another island-wide outbreak also occurred in 1942-1943[7-9] during World War II, when Taiwan as a main transport hub for Japanese invasion in Southeast Asia which led to numerous imported dengue cases from affected regions.

However, no outbreak had occurred in the main island of Taiwan from 1944 until 1987[8,10]. From 1998, mainly initiated by imported cases[11], indigenous dengue outbreak has occurred in Taiwan mainly in the southern cities of Kaohsiung and Tainan every summer, except in 2004 and 2013 when most of cases were reported in Pingtung County in the southern tip of Taiwan. In particular, recording-breaking outbreaks occurred for two consecutive years in 2014-2015. The first of which in 2014 occurred mainly in Kaohsiung[10], while the 2015 outbreak, totaling more than 40 000 cases, struck both Tainan and Kaohsiung. Typically, Aedes albopictus mosquito is distributed throughout Taiwan while Aedes aegypti appears only in the tropical southern Taiwan, divided by the Tropic of Cancer which cuts across central Taiwan[12].

It has been proposed that the July 31, 2014 gas explosion in Kaohsiung had contributed significantly to the recording-breaking outbreak in Kaohsiung that year[10,11,13]. Moreover, the Kaohsiung Rapid Transit System also played a role in spreading the disease within the metropolitan area[14]. However, no certain explanation can be given for the 2015 explosive outbreak in Taiwan. Moreover, since the end of that outbreak there has been an extremely drastic drop in subsequent reported indigenous case number in 2016-2017 from a few hundred cases in 2016, down to only 10 reported indigenous cases in all of Taiwan in 2017[15]. The sudden explosion of indigenous cases in 2014-2015 and its subsequent disappearance in 2016-2017 in Taiwan mirrors the unpredictability of dengue outbreaks in many countries in Asia and Latin America, albeit sometimes in a less dramatic fashion, which has left scientists with many theories yet no clear explanation for this unusual phenomenon. Dengue outbreaks in Taiwan has been typically initiated by imported cases in early summer, continuing through summer and spreading locally being boosted by summer international travels, peaking in late summer and early fall, and finally ending in winter as the temperature drops[16]. The pattern repeats almost yearly, albeit with decidedly different magnitude from year to year.

In this work, we attempt to explore the relationship between dengue outbreak and local/imported serotype evolution, by using a mathematical model to pinpoint each wave of infections in Tainan and Kaohsiung during 1998-2017. We further quantify the transmission potential of each wave via its effective reproduction number R, to ascertain its temporal changes in relation to the circulating serotype(s) during this wave as well as the circulating serotypes(s) and transmission potential of the preceding waves. The focus is whether our results can offer some clues to the perplexing puzzle of emergence and magnitude of dengue outbreaks, for the purpose of predicting future outbreaks.

2. Methods and materials

2.1. Data

We make use of the Taiwan daily dengue confirmed case statistics and dengue serotyping data on the city/county level during the period of 1998-2017, respectively available from Taiwan Centers for Disease Control[15] and Government Open Data Platform[16] websites to generate weekly data, and to fit the Richards model, in order to determine the exact number of waves that had occurred for each year in each city/county in Taiwan.

2.2. Mathematical model

The Richards model, first proposed by ecologists to study biological growth[18], has been found to be useful in modeling the increase in cumulative case number in infectious diseases in recent years and has become a useful choice of modeling among modelers in the world[19-22]. It has also been found to be useful in modeling dengue outbreaks[10,23-26].

The Richards model, with C(t) denoting the cumulative number of reported dengue cases at time t, is given by the analytic formula:

$$C(t) = K \left[ 1 + e^{r t - (1/a) (1 + a)^{r t} - 1/a} \right]$$

where K is the total cumulative case number of a wave of cases, r is the per capita growth rate of cumulative case number, a is the exponent of deviation of cumulative case curve, and t is time at which a turning point (or the peak) occurs, which signifies the exact moment of an upturn or downturn in the rate of increase for the cumulative case number of a wave of cases.

The Richards model is a phenomenological model which models the growth of cumulative case number. Since dengue outbreak is known to occur in waves, the model is most suitable to study temporal progression of dengue infections. Three model parameters of epidemiological importance are K, r, and the turning point t, of one single wave of the outbreak, which can be estimated by fitting
the Richards model to the cumulative case curve of the outbreak, using any standard software with nonlinear least-squares (NLS) approximation subroutine, e.g., SAS (which is used in this work) or MATLAB.

We can subsequently compute the well-known basic reproduction number $R_0$, the mean number of secondary human infections produced by an infective individual in a totally susceptible population in the absence of intervention measures. It is given by

$$R_0 = \exp(rT),$$

where $r$ is the per capita growth rate estimated for a given wave and $T$ is the serial interval, or the mean time interval from onset of one infected individual to the onset of his/her infectees. It has been shown mathematically\cite{27} that, given $r$, the expression $\exp(rT)$ provides an upper bound for basic reproduction number over any estimates of $T$ obtained from all assumed distributions. However, in countries with sustained dengue outbreaks such as Taiwan, some level of herd immunity is present in the community, hence the estimate we obtain in this study is not the basic reproduction number, but rather the effective reproduction number $R$. See Hsieh and Chen\cite{24} for related discussions.

3. Results

A summary of dengue cases and serotype data during 1998-2017 are given in Table 1 & 2, and Figure 1 and 2. Here we also provide the circulating serotype(s) in every city/county for each year between 1998-2017, using the definition that a serotype is “circulating” in a location in a given year if: (1) there are 10 or more indigenous cases with isolates of this serotype in this location during the year; and (2) this particular serotype also constitutes 35% or more of all indigenous serotype isolates obtained in this location during this year. Furthermore, the serotype is “dominant” in that year if it constitutes more than 50% of all isolates. There is at least one serotype circulating somewhere in Taiwan every year except in 1999-2000 and 2016-2017, when the respective yearly number of serotype circulating somewhere in Taiwan every year during 1998 to 2015. Interestingly, there is no wave pinpointed anywhere in Taiwan in 2016 or 2017. In some years, namely 1998 and 2013-2015, there were multiple waves somewhere in Taiwan every year during 1998 to 2015. In some years, there are no waves in either Tainan or Kaohsiung and hence no estimate for the effective reproduction number $R$.

We can subsequently compute the well-known basic reproduction number $R_0$, the mean number of secondary human infections produced by an infective individual in a totally susceptible population in the absence of intervention measures. It is given by

$$R_0 = \exp(rT),$$

where $r$ is the per capita growth rate estimated for a given wave and $T$ is the serial interval, or the mean time interval from onset of one infected individual to the onset of his/her infectees. It has been shown mathematically\cite{27} that, given $r$, the expression $\exp(rT)$ provides an upper bound for basic reproduction number over any estimates of $T$ obtained from all assumed distributions. However, in countries with sustained dengue outbreaks such as Taiwan, some level of herd immunity is present in the community, hence the estimate we obtain in this study is not the basic reproduction number, but rather the effective reproduction number $R$. See Hsieh and Chen\cite{24} for related discussions.

| Year | Location | Case No. by infection location | Serotyping |
|------|----------|-----------------------------|------------|
|      |          | Indigenous                  | Imported   |
| 1998 | Tainan City | 141                          | 2          |
|      | Kaohsiung City | 106                        | 4          |
|      | Taiwan     | 309                          | 35         |
| 1999 | Kaohsiung City | 33                          | 7          |
|      | Taiwan     | 42                          | 26         |
| 2000 | Tainan City | 109                          | 1          |
|      | Taiwan     | 113                          | 26         |
| 2001 | Kaohsiung City | 208                        | 12         |
|      | Taiwan     | 228                          | 53         |
| 2002 | Tainan City | 83                           | 5          |
|      | Kaohsiung City | 4837                        | 2          |
|      | Pingtung County | 385                        | 5          |
|      | Taiwan     | 5355                         | 52         |
| 2003 | Kaohsiung City | 72                          | 6          |
|      | Taiwan     | 86                           | 59         |
| 2004 | Kaohsiung City | 50                          | 12         |
|      | Pingtung County | 283                        | 7          |
|      | Taiwan     | 336                          | 91         |
| 2005 | Tainan City | 60                           | 4          |
|      | Kaohsiung City | 138                        | 8          |
|      | Taiwan     | 202                          | 104        |
| 2006 | Kaohsiung City | 953                        | 14         |
|      | Taiwan     | 965                          | 109        |
| 2007 | Tainan City | 1818                         | 33         |
|      | Kaohsiung City | 181                        | 21         |
|      | Taiwan     | 20000                        | 179        |
| 2008 | Kaohsiung City | 426                        | 19         |
|      | Taiwan     | 488                          | 226        |
| 2009 | Kaohsiung City | 754                        | 25         |
|      | Pingtung County | 75                         | 5          |
|      | Taiwan     | 848                          | 204        |
| 2010 | Tainan City | 489                          | 18         |
|      | Kaohsiung City | 1084                       | 31         |
|      | Taiwan     | 1592                         | 304        |
| 2011 | Tainan City | 96                           | 17         |
|      | Kaohsiung City | 1178                       | 16         |
|      | Pingtung County | 145                        | 0          |
|      | Penghu County | 98                          | 0          |
|      | Taiwan     | 1545                         | 157        |
| 2012 | Tainan City | 747                          | 10         |
|      | Kaohsiung City | 511                        | 25         |
|      | Taiwan     | 1271                         | 207        |
| 2013 | Tainan City | 40                           | 13         |
|      | Kaohsiung City | 66                          | 32         |
|      | Pingtung County | 481                        | 5          |
|      | Taiwan     | 596                          | 264        |
| 2014 | Tainan City | 138                          | 19         |
|      | Kaohsiung City | 15134                      | 44         |
|      | Pingtung County | 186                        | 5          |
|      | Taiwan     | 15492                        | 240        |
| 2015 | Tainan City | 23074                        | 17         |
|      | Kaohsiung City | 19931                       | 61         |
|      | Pingtung County | 340                        | 12         |
|      | Taiwan     | 43418                        | 365        |
| 2016 | Kaohsiung City | 344                        | 37         |
|      | Taiwan     | 380                          | 363        |
| 2017 | Taiwan     | 10                           | 333        |

Table 1
1998-2017 number of cases and serotyping in Taiwan.
Table 2

1998-2017 dengue serotyping results and circulating serotypes (defined by the serotype with 10 serotyping results and ≥35% of all results in that year) in each location for indigenous and imported cases (n%).

| Year          | Location (circulating serotype) | DENV1 | DENV2 | DENV3 | DENV4 |
|---------------|---------------------------------|-------|-------|-------|-------|
|               |                                 | Indig | Imp   | Indig | Imp   |
| 1998          | Taiwan(3)                       | 1 (2.4) | 1 (100) | 0 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 3 (8.3) | 2 (100) | 28.778 | 0 (0.0) |
|               | 1999                             | 6 (6.9) | 4 (57.1) | 31.556 | 2 (28.6) |
|               | Kaohsiung(2)                    | 2 (40.0) | 1 (50.0) | 3.000 | 0 (0.0) |
|               | Taiwan(2,3*)                    | 3 (22.2) | 0 (0.0) | 3 (33.3) | 2 (28.6) |
|               | Tainan City(-)                  | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
|               | 2000                             | 6 (6.9) | 4 (57.1) | 31.556 | 2 (28.6) |
|               | Kaohsiung(2)                    | 2 (40.0) | 1 (50.0) | 3.000 | 0 (0.0) |
|               | Taiwan(-)                       | 3 (22.2) | 0 (0.0) | 3 (33.3) | 2 (28.6) |
|               | Tainan City(-)                  | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 2001          | Kaohsiung(2)                    | 0 (0.0) | 2 (66.7) | 79.100 | 1 (33.3) |
|               | Taiwan(-)                       | 0 (0.0) | 6 (75.0) | 82.976 | 2 (25.0) |
|               | Tainan City(-)                  | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
|               | Kaohsiung(2)                    | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 2002          | Kaohsiung(2)                    | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
|               | Kaohsiung(2)                    | 1 (0.1) | 0 (0.0) | 21 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 2 (1.0) | 0 (0.0) | 19.920 | 0 (0.0) |
| 2003          | Kaohsiung(2)                    | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 2 (87.7) | 3 (36.0) | 20.970 | 8 (22.0) |
|               | Kaohsiung(2)                    | 1 (21.0) | 0 (0.0) | 4.000 | 0 (0.0) |
|               | Kaohsiung(2)                    | 2 (87.7) | 3 (36.0) | 20.970 | 8 (22.0) |
| 2004          | Kaohsiung(2)                    | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
|               | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
| 2005          | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
|               | Kaohsiung(2)                    | 6 (9.4) | 13 (25.3) | 16 (25.0) | 19 (31.2) |
| 2006          | Kaohsiung(2)                    | 0 (0.0) | 3 (30.0) | 34.830 | 4 (40.0) |
|               | Kaohsiung(2)                    | 1 (8.3) | 0 (0.0) | 24.966 | 1 (100.0) |
| 2007          | Kaohsiung(2)                    | 0 (0.0) | 6 (42.9) | 2 (26.6) | 4 (8.3) |
|               | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
| 2008          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
| 2009          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
| 2010          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
| 2011          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
| 2012          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
| 2013          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 1 (4.0) | 0 (0.0) | 24.966 | 1 (100.0) |
| 2014          | Kaohsiung(2)                    | 0 (0.0) | 1 (33.3) | 30.064 | 3 (37.5) |
|               | Kaohsiung(2)                    | 6 (35.3) | 0 (0.0) | 10.588 | 0 (0.0) |
| 2015          | Kaohsiung(2)                    | 6 (35.3) | 0 (0.0) | 10.588 | 0 (0.0) |
|               | Kaohsiung(2)                    | 6 (35.3) | 0 (0.0) | 10.588 | 0 (0.0) |
|               | Kaohsiung(2)                    | 6 (35.3) | 0 (0.0) | 10.588 | 0 (0.0) |
| 2016          | Kaohsiung(2)                    | 0 (0.0) | 1 (25.0) | 138.000 | 2 (28.6) |
|               | Kaohsiung(2)                    | 0 (0.0) | 1 (25.0) | 138.000 | 2 (28.6) |
| 2017          | Kaohsiung(2)                    | 0 (0.0) | 1 (25.0) | 138.000 | 2 (28.6) |

*denoting the dominant serotype (>50%) among two circulating serotypes in 1998; (-) denotes no circulating serotype.
Table 3
Summary table for waves of weekly dengue cases with the Richards model fit during 1998-2008 in Taiwan.

| Year | Location (serotype) | Time interval | Turning point Ti | Case number | Reproduction number R | 95% CI for R |
|------|---------------------|---------------|------------------|-------------|----------------------|-------------|
| 1998 | Tainan* (3)         | 11/8-11/30    | 11/25 (W47)      | 112         | 1.57                 | (1.46, 1.66) |
|      |                     | 11/30-12/15   |                  | 69          | 1.21                 | (1.15, 1.25) |
|      | Kaohsiung (2)       | 5/7/1998-8/3/1999 | W50       | 124         | 1.29                 | (1.25, 1.34) |
| 1999 | Kaohsiung* (-)      | 7/8/24        | 8/5              | 18          | 1.99                 | (1.69, 2.29) |
| 2000 | Tainan W37-W52      | W42           | 109              | 1.14        | (1.12, 1.16)         |             |
| 2001 | Kaohsiung (2)       | W40-W52       | W45              | 229         | 2.36                 | (2.28, 2.44) |
| 2002 | Tainan (2)          | W35-W51       | W45              | 59          | 1.39                 | (1.32, 1.47) |
|      | Kaohsiung (2)       | W28-W52       | W37              | 5167        | 2.87                 | (1.75, 4.00) |
|      | Pingtung (2)        | W32-W52       | W46              | 384         | 1.60                 | (1.49, 1.70) |
| 2003 | Kaohsiung (2)       | 9/30-11/17    | W42              | 33          | 1.92                 | (1.48, 2.37) |
| 2004 | Kaohsiung (1)       | 5/6/2004-10/5/2005 | W46       | 73          | 1.49                 | (1.25, 1.73) |
|      | Pingtung (1)        | W34-W52       | W42              | 291         | 1.97                 | (1.78, 2.16) |
| 2005 | Tainan (2)          | W37-W52       | W45              | 70          | 2.80                 | (1.34, 4.26) |
|      | Kaohsiung (3)       | W32-W52       | W46              | 146         | 1.37                 | (1.31, 1.43) |
| 2006 | Kaohsiung (3)       | W34-W52       | W44              | 1002        | 1.91                 | (1.39, 1.58) |
|      | Tainan (1)          | W28-W52       | W45              | 85          | 1.35                 | (1.24, 1.46) |
| 2007 | Kaohsiung (1)       | W24-W53       | W46              | 444         | 1.35                 | (1.29, 1.41) |
| 2008 | Kaohsiung (3)       | 5/26/2009-8/20/2010 | W47       | 815         | 1.59                 | (1.47, 1.71) |
|      | Pingtung (2)        | W35-W49       | W45              | 74          | 2.38                 | (1.82, 2.93) |
| 2010 | Taiwan (4)          | W31-W52       | W41              | 510         | 3.95                 | (2.99, 4.91) |
|      | Kaohsiung (2)       | W2/3/2100-10/8/2011 | W43       | 1131        | 1.60                 | (1.55, 1.83) |
| 2011 | Tainan (1)          | W31-W52       | W47              | 118         | 1.52                 | (1.41, 1.64) |
|      | Kaohsiung (2)       | W34-W52       | W47              | 1200        | 1.46                 | (1.38, 1.54) |
|      | Pingtung* (3)       | 9/11-12/26    | W44              | 146         | 1.91                 | (1.82, 2.21) |
|      | Penghu* (2)         | 10/11-12/15   | W42              | 99          | 1.73                 | (1.32, 1.96) |
| 2012 | Tainan (1)          | W41-W52       | W39              | 754         | 2.50                 | (1.62, 3.38) |
|      | Kaohsiung (2)       | W20-W52       | W45              | 533         | 1.44                 | (1.38, 1.5)  |
| 2014 | Tainan (4)          | W28-53        | W47              | 134         | 1.74                 | (1.60, 1.88) |
|      | Kaohsiung* (3)      | 9/5-8/28      | 8/20 (W34)       | 904         | 2.05                 | (1.8, 2.29)  |
|      |                     | 10/22-12/31   | 11/1 (W45)       | 8287        | 1.76                 | (1.61, 1.9)  |
| 2015 | Tainan (2)          | W35-53        | W45              | 191         | 1.83                 | (1.58, 2.08) |
|      | Kaohsiung (2)       | W26-52        | W45              | 22704       | 1.89                 | (1.74, 2.05) |
|      | Pingtung* (-)       | W32-41        | W38              | 77          | 2.21                 | (1.69, 2.72) |
|      |                    | W41-52        | W47              | 258         | 1.74                 | (1.58, 1.89) |

*denoting fitting with daily case data (Hsieh 2017); (-) denotes no circulating serotype.

4. Discussion

4.1. Role of importation

While the number of indigenous cases in Taiwan has fluctuated greatly with large swings since it was first recorded in 1998, the number of imported cases exhibits a slow but steady increasing trend (Table 1), partly attributable to a similar pattern of increases in the number of international tourists to and from Taiwan during the past two decades[28], and also in the number of migrant workers in Taiwan from the Association of Southeast Asian Nations (ASEAN) countries with historically frequent dengue outbreaks[29].
It has been long conjectured that dengue outbreaks in Taiwan is related to outbreaks in neighboring Association of Southeast Asian Nations countries, especially after 1987 with the end of martial law which commenced an era of unrestricted tourism. King et al.[30] show that three major dengue fever/dengue haemorrhagic fever outbreaks in Taiwan between 1981 and 1998 had statistically significant association with the increasing numbers of dengue cases in several Asian countries before or during these outbreaks in Taiwan, suggesting imported cases played an important role in indigenous outbreaks in Taiwan. Shang et al.[31] conclude that imported dengue cases could initiate indigenous outbreaks in Taiwan, albeit only under suitable climate conditions. However, our results indicate that, while such relationship is likely to exist, it is by no means simply quantifiable, nor can it be easily introduced in an early warning system with a set of quantities that are widely different, such as vector indices and climatologic factors.

4.2. Role of serotype

Serotyping results of indigenous cases reveal that all four serotypes had been reported in Taiwan since 1998, with each serotype taking the role of a circulating serotype during at least some years, although DENV2 and DENV1 are clearly the most frequently circulating serotypes. In every year except 2010, the circulating serotype is also the dominant serotype (>50% of the total results) of that year. In 2010, Tainan had an outbreak of DENV4 while Kaohsiung had an outbreak of both DENV2 and DENV3. Subsequently as all three serotypes coexisted more or less evenly with no one dominant serotype.

Except in 1999-2010, 2016-2017 (mainly due to a scarcity of positive isolates), as well as in 2010 (when both DENV2 and DENV3 were circulating in Kaohsiung), there was typically one highly dominant (>95%) serotype every year, including all four major outbreaks with more than 2000 cases - 2002 (DENV2 in Tainan), 2014 (DENV1 In Kaohsiung) and 2015 (DENV2 in Tainan and Kaohsiung), perhaps indicating the greater transmission potential of one dominating serotype.

Coincidentally, in 2002 the last serotype to emerge in Taiwan, DENV4, was first found in one imported case in Pingtung County. Furthermore, Figure 2 reveals that since 2002 a clear and consistent pattern in the serotypes of imported cases in Taiwan emerges, with frequency of serotypes in the order of mostly DENV1 and DENV2, followed by DENV3, with DENV4 the least but being present every year. Subsequently, there seems to be no noticeable correlation between the serotypes of imported cases and circulating serotypes of indigenous cases in Taiwan. However, how the four serotypes interact in antibody-mediated immunity and enhancement remains a mystery. One might speculate that this lack of knowledge has played a significant role in our difficulty in predicting dengue outbreak.

4.3. Transmission potential

Data fitting with the Richards model results in at least one wave somewhere in Taiwan each year from 1998 to 2015 (Table 3), but there had been very few indigenous cases reported in Taiwan after January of 2016[15]. The mean estimate of the effective reproduction number $R$ for all waves ranges consistently between 1.21 and 2.87, except in Tainan in 2010 ($R=3.95$) and in 2015 ($R=6.84$). We note the exceptionally high estimate in 2015, when a historically large number of cases were reported, and the wave of cases fitted was unusual in both its early start in May (week 21) and its length (over 30 weeks). We speculate that the early starting point might contribute to a high initial growth rate and subsequently a high estimate for $R$.

4.4. Conclusion

Many studies have shown a significant correlation between dengue outbreak and many factors, including climate, serotype, imported cases, timing, geographic location, human mobility, etc. Subsequently, there are ample studies endeavoring to predict future dengue outbreak[32]. However, a scientifically reliable prediction or early warning system of dengue outbreak still very much eludes us. The reason is that dengue outbreak often occurs due a combination of the factors mentioned above, not the least of which is the interaction of serotypes in hosts. As technology advances that enable the collection of data pertaining to these factors, the primary challenge becomes that of consolidation of these different datasets in a multi-layered model constructed in a suitable platform to make the result explicitly understandable to policy makers. Multi-layered information on infectious diseases pertaining to its epidemiology, etiology, immunology, and related climatology/geography/sociology, must be consolidated into one single model incorporating different types of data, in order to truly ascertain its potential threat to humans.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

Yu-Han Li contributed to the data analysis of 2013-2016 dengue outbreaks. YHH is supported by funding from grants from Taiwan Ministry of Science and Technology (MOST 103-2314-B-039-010-MY3) and China Medical University-Taiwan (CMU106-S-02).

References

[1] Braga IA., Valle D. Aedes aegypti: histórico do controle no Brasil. [Aedes aegypti: history of control in Brazil]. Epidemiologia e Serviços de Saúde 2007; 16(2): 113-118.
[2] Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG, et al. Refining the global spatial limits of dengue virus transmission by
[3] Filipje D, Diosa-Toro MA, Hoornweg TE, van de Pol DPI, Urcuqui-Inchima S, Smit JM. Antibody-dependent enhancement of dengue virus infection in primary human macrophages: balancing higher fusion against antiviral responses. Sci Rep 2016; 6:29201.

[4] Akashi K. Tainan dengue epidemic study. *Taiwan J Med* 1952; 31(7): 767-777. (In Japanese).

[5] Clarke EJ Jr, Suitor EC Jr, Jenkin HM. A serologic survey for arbovirus antibodies in inhabitants of a southwest Taiwan village. *Trop Geogr Med* 1967; 19(4): 326-332.

[6] Kuno G. Research on dengue and dengue-like illness in East Asia and the Western Pacific during the first half of the 20th century. *Rev Med Virol* 2007; 17(5): 327-341.

[7] Ooi T. Dengue epidemic in Taiwan: Epidemiology and clinical symptoms in Kaohsiung. *Taiwan J Med* 1943; 4: 734-741. (In Japanese).

[8] Ko YC. Epidemiology of dengue fever in Taiwan. *Gaoxiong Yi Xue Ke Xue Za Zhi* 1989; 5: 1–11. (In Chinese).

[9] Tung TTH, Tsai KH, King CP, Huang SYJ, King CC. The relationships among socio-political/environmental changes, prevention and control strategies, and epidemics of dengue fever in Taiwan—future prospects. *Taiwan Med J* 2011; 30(6): 517-532.

[10] Hsieh, YH. Ascertaining the impact of catastrophic events on dengue outbreak: The 2014 gas explosions in Kaohsiung, Taiwan. *PLoS one* 2017; 12(5):e0177422.

[11] Wang SF, Chang K, Lu RW, Wang WH, Chen YH, Chen M, et al. Large dengue virus type 1 outbreak in Taiwan. *Emerg Microbes & Infect* 2015a; 4(8):e46.

[12] Yang CF, Hou JN, Chen TH, Chen WJ. Discriminable roles of *Aedes aegypti* and *Aedes albopictus* in establishment of dengue outbreaks in Taiwan. *Acta Tropica* 2014; 130: 17-23.

[13] Wang SF, Wang WH, Chang K, Chen YH, Tseng SP, Yen CH, et al. Severe dengue fever outbreak in Taiwan. *Am J Trop Med Hyg* 2015b; 94(1): 193-197.

[14] Sanna M, Hsieh YH. Ascertaining the impact of public rapid transit system on spread of dengue in urban settings. *Sci Total Environ* 2017; 598: 1151-1159.

[15] Taiwan Centers for Prevention and Control. TCDC: Dengue surveillance data; Taiwan CDC Notifiable Diseases Surveillance System (NDSS) [Online]. Available from: http://ndss.cdc.gov.tw/ch [Accessed on 1st July 2018].

[16] Lin CC, Huang YH, Shu PY, Wu HS, Lin YS, Yeh TM, et al. Characteristic of dengue disease in Taiwan: 2002–2007. *Am J Trop Med Hyg* 2010; 82(4): 731-739.

[17] Taiwan Open Data. Daily confirmed dengue case data; Taiwan Government Open Database [Online]. Available from: https://data.gov.tw/dataset/21025 [Accessed on 1st July 2018].

[18] Richards FJ. A flexible growth function for empirical use. *J Exp Bot* 1959; 10: 290-300.

[19] Hsieh YH, Lee JY, Chang HL. SARS epidemiology modeling. *Emerg Infect Dis* 2004; 10: 1165–1167.

[20] Hsieh YH, Cheng YS. Real-time forecast of multiphase outbreak. *Emerg Infect Dis* 2006; 12: 122–127.

[21] Mostaço-Guidolin LC, Greer A, Sander B, Wu J, Moghadas SM. Variability in transmissibility of the 2009 H1N1 pandemic in Canadian communities. *BMC Res Notes* 2011; 4: 537.

[22] Chan CH, Tuite AR, Fisman DN. Historical epidemiology of the second cholera pandemic: relevance to present day disease dynamics. *PLoS One* 2013; 8(8):e72498.

[23] Hsieh YH, Ma S. Intervention measures, turning point, and reproduction number for dengue, Singapore, 2005. *Am J Trop Med Hyg* 2009; 80(1): 66–71.

[24] Hsieh YH, Chen CWS. Turning points, reproduction number, and impact of climatological factors for multi-wave dengue outbreaks. *Trop Med & Int Health* 2009; 14: 628-638.

[25] Hsieh YH, de Araozoa H, Lounes R. Temporal trends and regional variability of 2001–2002 Multi-wave DENV-3 epidemic in Havana City: Did hurricane michelle contribute to its severity? *Trop Med Internat Health* 2013; 18(7): 830-838.

[26] Sanna M, Wu J, Zhu Y, Yang Z, Lu J, Hsieh YH. Spatial and temporal characteristics of 2014 dengue outbreak in Guangdong, China. *Sci Rep* 2018; 8(1): 2344.

[27] Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc Royal Socie London B: Biol Sci* 2007; 274(1609): 599-604.

[28] Taiwan Ministry of Transportation and Communication. MOTC: Tourism statistics database; tourism bureau. [Online]. Available from: http://stat.taiwan.net.tw/system/index.html [Accessed on 1st July 2018].

[29] Taiwan Ministry of Labor. MOL: Labor Statistics Information; Bureau of Statistics Labor Statistics Database [Online]. Available from: http://statdb.mol.gov.tw/statis/sjspProxy.aspx?sys=210&kind=21&type=1&func=130903&parm1=c0de1xx3D0xx20code2xx3D0&different=pejBiYe [Accessed on 1st July 2018].

[30] King CC, Wu YC, Chao DY, Lin TH, Chow L, Wang H T, et. al. Major epidemics of dengue in Taiwan in 1981–2000: related to intensive virus activities in Asia. *Dengue Bulletin* 2000; 24: 1-10.

[31] Shang CS, Fang CT, Liu CM, Wen TH, Tsai KH, King CC. The role of imported cases and favorable meteorological conditions in the onset of dengue epidemics. *PLoS Negl Trop Dis* 2010; 4(8):e775.

[32] Chang FS, Tseng YT, Hsu PS, Chen CD, Lian IB, Chao DY. Re-assess vector indices threshold as an early warning tool for predicting dengue epidemic in a dengue non-endemic country. *PLoS Negl Trop Dis* 2015; 9(9): e0004043.