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

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ABSTRACT

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 2 000 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

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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[17] 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:

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

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_i 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_i 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[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[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 isolates for indigenous cases was less than 10 (Table 1).

The results of data fitting to the Richards model are provided in Table 3, with time intervals for each wave occurring in each city during 1998-2017, along with the corresponding estimated effective reproduction number R with 95% confidence interval (*CI*). Through model fitting, there were at least one wave of dengue cases detected 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 in some locations. In 2011, waves were detected in all three southern cities/county: Kaohsiung, Tainan and Pingtung, plus the nearby island county of Penghu.

To further illustrate the possible connection between circulating serotype and transmission potential (via the effective reproduction number R), we provide in Figure 3 and 4, for each year during 1998-2015 in Tainan and Kaohsiung, the percentages of serotypes and the largest estimate of R if there is more than one wave in a city that year. In some years, there were too few serotyping results in a city (Table 2). We also note that in some years, there are no waves in either Tainan or Kaohsiung and hence no estimate for the effective reproduction number R.

Table 1

1998-2017 number of cases and serotyping in Taiwan.

Year	Location	Case No. by infection location		Serotyping	
		Indigenous	Imported	Indigenous	Imported
1998	Tainan City	141	2	41 (47.1)	1 (14.3)
	Kaohsiung City	106	4	36 (41.4)	2 (28.6)
	Taiwan	309	35	87	7
1999	Kaohsiung City	33	7	5 (55.6)	2 (28.6)
	Taiwan	42	26	9	7
2000	Tainan City	109	1	3 (75.0)	0 (0.0)
	Taiwan	113	26	4	3
2001	Kaohsiung City	208	12	79 (94.1)	3(37.5)
	Taiwan	228	53	84	8
2002	Tainan City	83	5	25 (1.1)	1 (7.7)
	Kaohsiung City	4 837	2	2 113 (90.3)	0 (0.0)
	Pingtung County	385	5	194 (8.3)	1 (7.7)
	Taiwan	5 335	52	2 341	13
2003	Kaohsiung City	72	6	16 (69.6)	0 (0.0)
	Taiwan	86	59	23	25
2004	Kaohsiung City	50	12	24 (11.4)	5 (8.5)
	Pingtung County	283	7	186 (88.6)	2 (3.4)
	Taiwan	336	91	210	59
2005	Tainan City	60	4	12 (18.8)	1 (1.6)
	Kaohsiung City	138	8	52 (81.3)	5 (8.2)
	Taiwan	202	104	64	61
2006	Kaohsiung City	953	14	409 (99.5)	10 (14.3)
	Taiwan	965	109	411	70
2007	Tainan City	1 818	33	1 103(93.7)	17 (16.0)
	Kaohsiung City	181	21	74 (6.3)	13 (12.3)
	Taiwan	2 000	179	1 177	106
2008	Kaohsiung City	426	19	183(89.3)	8 (6.7)
	Taiwan	488	226	205	120
2009	Kaohsiung City	754	25	335 (90.1)	14 (10.6)
	Pingtung County	75	5	34 (9.1)	3 (2.3)
	Taiwan	848	204	372	132
2010	Tainan City	489	18	289 (34.0)	14 (7.5)
	Kaohsiung City	1 084	31	552 (65.0)	22 (11.7)
	Taiwan	1 592	304	849	188
2011	Tainan City	96	17	56 (6.3)	13 (13.1)
	Kaohsiung City	1 178	16	716 (81.0)	11 (11.1)
	Pingtung County	145	0	38 (4.3)	0 (0.0)
	Penghu County	98	0	62 (7.0)	0 (0.0)
	Taiwan	1 545	157	884	99
2012	Tainan City	747	10	25 (27.2)	3 (2.5)
	Kaohsiung City	511	25	61 (66.3)	9 (7.6)
	Taiwan	1 271	207	92	118
2013	Tainan City	40	13	12 (31.6)	0 (0.0)
	Kaohsiung City	66	32	9 (23.7)	3 (2.6)
	Pingtung County	481	5	17 (44.7)	0 (0.0)
	Taiwan	596	264	38	117
2014	Tainan City	138	19	11 (15.7)	2 (1.6)
	Kaohsiung City	15 134	44	53 (75.7)	9 (7.3)
	Pingtung County	186	5	2 (2.9)	1 (0.8)
	Taiwan	15 492	240	70	123
2015	Tainan City	23 074	17	138 (69.0)	4 (3.0)
	Kaohsiung City	19 913	61	46 (23.0)	1 (0.7)
	Pingtung County	340	12	1(0.5)	0 (0.0)
	Taiwan	43 418	365	200	135
2016	Kaohsiung City	344	37	2(40.0)	3 (2.2)
	Taiwan	380	363	5	137
2017	Taiwan	10	333	4	134

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	Indig	Imp	Indig	Imp
1998	Tainan City(3)	1 (2.4)	1 (100.0)	0 (0.0)	0 (0.0)	40 (97.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Kaohsiung City(2)	3 (8.3)	2 (100.0)	28 (77.8)	0 (0.0)	4 (11.1)	0 (0.0)	1 (2.8)	0 (0.0)
	Taiwan(2,3*)	6 (6.9)	4 (57.1)	31 (35.6)	2 (28.6)	49 (56.3)	1 (14.3)	1 (1.2)	0 (0.0)
1999	Kaohsiung City(-)	2 (40.0)	1 (50.0)	3 (60.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
	Taiwan(-)	2 (22.2)	3 (42.9)	3 (33.3)	2 (28.6)	4 (44.4)	2 (28.6)	0 (0.0)	0 (0.0)
2000	Tainan City(-)	0 (0.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)	0 (-)	3 (100.0)	0 (-)
	Taiwan(-)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (25.0)	2 (66.7)	3 (75.0)	0 (0.0)
2001	Kaohsiung City(2)	0 (0.0)	2 (66.7)	79 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Taiwan(2)	0 (0.0)	6 (75.0)	82 (97.6)	2 (25.0)	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
2002	Tainan City(2)	1 (4.0)	0 (0.0)	24 (96.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Kaohsiung City(2)	1 (0.1)	0 (0.0)	2 112 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pingtung County(2)	2 (1.0)	0 (0.0)	192 (99.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
	Taiwan(2)	4 (0.2)	5 (38.5)	2 337 (99.8)	4 (30.8)	0 (0.0)	2 (15.4)	0 (0.0)	2 (15.4)
2003	Kaohsiung City(2)	0 (0.0)	0 (0.0)	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Taiwan(2)	2 (8.7)	9 (36.0)	20 (87.0)	8 (32.0)	0 (0.0)	4 (16.0)	1 (4.4)	4 (16.0)
2004	Kaohsiung City(1)	22 (91.7)	1 (20.0)	0 (0.0)	4 (80.0)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)
	Pingtung County(1)	170 (91.4)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	16 (8.6)	0 (0.0)
	Taiwan(1)	192 (91.4)	16 (27.1)	0 (0.0)	24 (40.7)	0 (0.0)	6 (10.2)	18 (8.6)	13 (22)
2005	Tainan City(2)	0 (0.0)	1 (100.0)	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Kaohsiung City(3)	6 (11.5)	1 (20.0)	4 (7.7)	3 (60.0)	42 (80.8)	1 (20.0)	0 (0.0)	0 (0.0)
	Taiwan(3)	6 (9.4)	13 (21.3)	16 (25.0)	19 (31.2)	42 (65.6)	17 (27.9)	0 (0.0)	12 (20.0)
2006	Kaohsiung City(3)	0 (0.0)	3 (30.0)	34 (8.3)	4 (40.0)	375 (91.7)	2 (20.0)	0 (0.0)	1 (10.0)
	Taiwan(3)	1 (0.2)	22 (31.4)	34 (8.3)	24 (34.3)	376 (91.5)	19 (27.1)	0 (0.0)	5 (7.1)
2007	Tainan City(1)	1 027 (93.1)	12 (70.6)	76 (6.9)	3 (17.7)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)
	Kaohsiung City(1)	74 (100.0)	7 (53.9)	0 (0.0)	5 (38.5)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
	Taiwan(1)	1 101 (93.5)	45 (42.5)	76 (6.5)	33 (31.1)	0 (0.0)	22 (20.8)	0 (0.0)	6 (5.7)
2008	Kaohsiung City(1)	152 (83.1)	4 (50)	30 (16.4)	3 (37.5)	0 (0)	1 (12.5)	1 (0.6)	0 (0.0)
	Taiwan(1)	174 (84.9)	63 (52.5)	30 (14.6)	24 (20)	0 (0)	23 (19.2)	1 (0.5)	10 (8.3)
2009	Kaohsiung City(3)	0 (0.0)	6 (42.9)	2 (0.6)	4 (28.6)	333 (99.4)	4 (28.6)	0 (0.0)	0 (0.0)
	Pingtung County(2)	0 (0.0)	1 (33.3)	30 (88.2)	1 (33.3)	4 (11.8)	0 (0.0)	0 (0.0)	1 (33.3)
	Taiwan (3)	1 (0.3)	52 (39.4)	33 (8.9)	41 (31.1)	338 (90.9)	24 (18.2)	0 (0.0)	15 (11.4)
2010	Tainan City(4)	45 (15.6)	6 (42.9)	0 (0.0)	2 (14.3)	4 (1.4)	1 (7.1)	240 (83.0)	5 (35.7)
	Kaohsiung City(2,3*)	4 (0.7)	8 (36.4)	201 (36.4)	9 (40.9)	341 (61.8)	4 (18.2)	6 (1.1)	1 (4.6)
	Taiwan(3)	53 (6.2)	71 (37.8)	204 (24.0)	62 (33.0)	346 (40.8)	35 (18.6)	246 (29.0)	20 (10.6)
2011	Tainan City(1)	52 (92.9)	1 (7.7)	3 (5.4)	6 (46.2)	0 (0.0)	2 (15.4)	1 (1.8)	4 (30.8)
	Kaohsiung City(2)	2 (0.3)	4 (36.4)	666 (93.0)	6 (54.6)	48 (6.7)	1 (9.1)	0 (0.0)	0 (0.0)
	Pingtung County(3)	0 (0.0)	0 (-)	3 (7.9)	0 (-)	35 (92.1)	0 (-)	0 (0.0)	0 (-)
	Penghu County(2)	0 (0.0)	0 (-)	62 (100.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)	0 (-)
	Taiwan(2)	64 (7.2)	34 (34.3)	735 (83.1)	37 (37.4)	84 (9.5)	15 (15.2)	1 (0.1)	13 (13.1)
2012	Tainan City(1)	24 (96.0)	0 (0.0)	1 (4.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
	Kaohsiung City(2)	2 (3.3)	3 (33.3)	52 (85.3)	2 (22.2)	1 (1.6)	2 (22.2)	6 (9.8)	2 (22.2)
	Taiwan(2)	31 (33.7)	44 (37.3)	54 (58.7)	35 (29.7)	1 (1.1)	17 (14.4)	6 (6.5)	22 (18.6)
2013	Tainan City(2)	0 (0.0)	0 (-)	12 (100.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)	0 (-)
	Kaohsiung City(-)	0 (0.0)	1 (33.3)	9 (100.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pingtung County(2)	6 (35.3)	0 (-)	10 (58.8)	0 (-)	1 (5.9)	0 (-)	0 (0.0)	0 (-)
	Taiwan(2)	6 (15.8)	50 (42.7)	31 (81.6)	33 (28.2)	1 (2.6)	18 (15.4)	0 (0.0)	16 (13.7)
2014	Tainan City(1)	10 (90.9)	0 (0.0)	1 (9.1)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
	Kaohsiung City(1)	52 (98.1)	4 (44.4)	1 (1.9)	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
	Pingtung County(-)	2 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Taiwan(1)	68 (97.1)	52 (42.3)	2 (2.9)	40 (32.5)	0 (0.0)	22 (17.9)	0 (0.0)	9 (7.3)
2015	Tainan City(2)	0 (0.0)	1 (25.0)	138 (100.0)	2 (50.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
	Kaohsiung City(2)	2 (4.4)	1 (100.0)	44 (95.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pingtung County(-)	0 (0.0)	0 (-)	1 (100.0)	0 (-)	0 (0.0)	0 (-)	0 (0.0)	0 (-)
	Taiwan(2)	6 (3.0)	46 (34.1)	194 (97.0)	50 (37.0)	0 (0.0)	21 (15.6)	0 (0.0)	18 (13.3)
2016	Kaohsiung City(-)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
	Taiwan(-)	2 (40.0)	52 (38.0)	3 (60.0)	33 (24.1)	0 (0.0)	37 (27.0)	0 (0.0)	15 (11.0)
2017	Taiwan(-)	3 (75.0)	51 (38.0)	0 (0.0)	41 (30.6)	1 (25.0)	22 (16.4)	0 (0.0)	20 (14.9)

*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 K	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	12/6 (W49)	69	1.21	(1.15,1.25)
	Kaohsiung (2)	W31/1998-W8/1999	W50	124	1.29	(1.25,1.34)
1999	Kaohsiung* (-)	7/8-8/24	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	(1.28,3.44)
2002	Tainan (2)	W37-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)	W36/2004-W10/2005	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	1.49	(1.39,1.58)
2007	Tainan (1)	W28-W52	W45	1850	1.41	(1.34,1.47)
	Kaohsiung (1)	W44-W52	W46	200	1.35	(1.24,1.46)
2008	Kaohsiung (1)	W24-W53	W46	444	1.35	(1.29,1.41)
2009	Kaohsiung (3)	W26/2009-W7/2010	W47	815	1.59	(1.47,1.71)
	Pingtung (2)	W35-W49	W45	74	2.38	(1.83,2.93)
2010	Tainan (4)	W31-W52	W41	510	3.95	(2.99,4.91)
	Kaohsiung (2,3)	W23/2010-W8/2011	W43	1131	1.69	(1.55,1.83)
2011	Tainan (1)	W31-W52	W47	118	1.52	(1.4,1.64)
	Kaohsiung (2)	W34-W52	W47	1200	1.46	(1.38,1.54)
	Pingtung* (3)	9/11-12/26	11/3 (W44)	146	1.91	(1.18,2.21)
	Penghu* (2)	9/11-12/15	10/16 (W42)	99	1.73	(1.32,1.96)
2012	Tainan (1)	W14-W52	W39	754	2.50	(1.62,3.38)
	Kaohsiung (2)	W20-W52	W45	533	1.44	(1.38,1.5)
2014	Tainan (1)	W28-53	W47	134	1.74	(1.60,1.88)
	Kaohsiung* (1)	8/5~8/28	8/20 (W34)	904	2.05	(1.8, 2.29)
		10/22~12/31	11/1 (W45)	8287	1.76	(1.61,1.9)
	Pingtung (1)	W35-53	W45	191	1.83	(1.58,2.08)
2015	Tainan (2)	W21-52	W37	22704	6.84	(4.77,8.91)
	Kaohsiung (2)	W26-52	W45	19837	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.
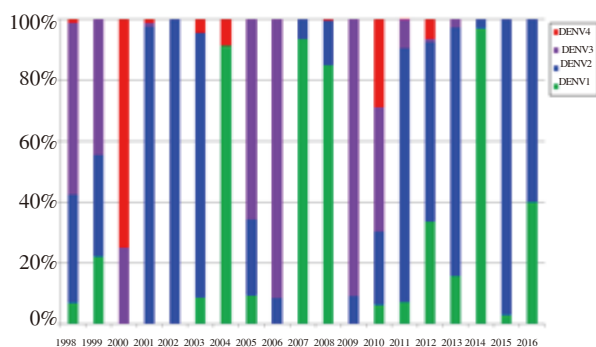

Figure 1. Yearly percentages of serotype isolate results in Taiwan among indigenous dengue cases during 1998-2016.
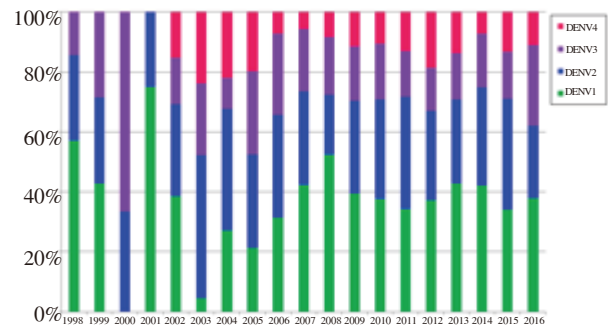

Figure 2. Percentages of serotype isolate results in Taiwan among imported dengue cases during 1998-2016.
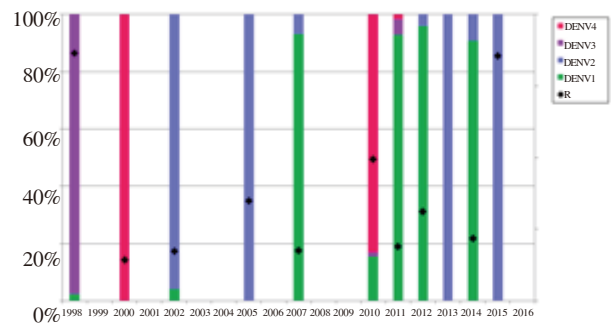

Figure 3. Yearly percentages of indigenous serotype isolate results in Taiwan during 1998-2016, with black diamond denoting largest effective reproduction number R of that year.
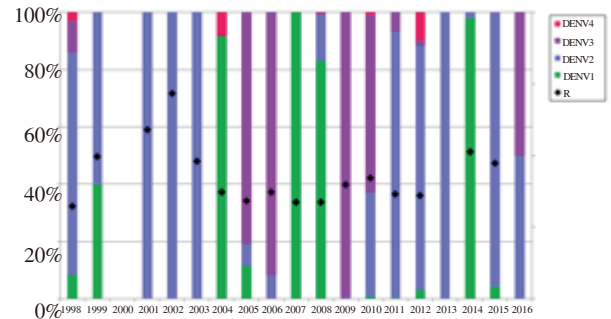

Figure 4. Yearly percentages of indigenous serotype isolate results in Kaohsiung during 1998-2016, with black diamond denoting largest effective reproduction number R of that year.

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 DENV 4 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.

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