Journal of Microbiology, Immunology and Infection 57 (2024) 730—738

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Risk of severe dengue during secondary infection: A population-based cohort study in Taiwan

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Received 23 January 2024; received in revised form 9 June 2024; accepted 8 July 2024
Available online 11 July 2024

KEYWORDS
Dengue;
Severe dengue;
Dengue secondary infection

Abstract *Background:* Dengue poses a significant public health concern. Secondary dengue infections with different dengue virus (DENV) serotypes have been linked to an increased risk of severe dengue. This study aimed to assess the risk of severe dengue during secondary infection in Taiwan.
Methods: A retrospective cohort study was conducted using Taiwan's National Health Insurance Research Database to identify dengue cases with secondary dengue infection born after 1944 from 2014 to 2015. Ten matched patients with primary infection were selected as controls using propensity score matching for each secondary dengue infection case. The odds ratio (OR) for severe dengue in secondary versus primary infections was calculated using conditional logistic regression.

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https://doi.org/10.1016/j.jmii.2024.07.004

Results: This study included 357 cases with secondary dengue infection and 3570 matched controls. The risk of severe dengue was found to be 7.8% in individuals with secondary infection, compared to 3.8% in those with primary dengue infection. Secondary infection significantly increased the risk of severe dengue (OR 2.13, 95% CI: 1.40—3.25, P = 0.0004). Notably, a significant association between secondary infection and severe dengue was observed only when the interval between the first and secondary infection was greater than two years (OR 3.19, 95% CI 2.04—5.00, P < 0.0001).

Conclusion: Secondary dengue infection significantly increases the risk of severe disease in Taiwan, particularly when the interval between infections is over two years.

Healthcare professionals should maintain heightened vigilance for individuals with a history of previous dengue infection, particularly if their initial diagnosis was more than two years prior.

Introduction

Dengue is a mosquito-borne viral infection caused by any of the four identified serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4). These viruses are transmitted to humans through the bite of an infected *Aedes mosquito*, specifically *Ae. aegypti* or *Ae. albopictus*. The disease is particularly prevalent in tropical and subtropical climates. With almost half of the world's population, around four billion people, residing in areas at risk of dengue, the disease has significant global impact. The reemergence of dengue has been largely attributed to factors such as urbanization, globalization, and the absence of effective mosquito control strategies.[1—3]

Patients can experience infection with more than one serotype of DENV throughout their lifetime. Prior research indicates that patients with secondary dengue infections with heterologous serotypes are at a higher risk of developing severe dengue compared to those with primary infections, a phenomenon potentially explained by the antibody-dependent enhancement (ADE) theory.[4] In a recent meta-analysis conducted by Tsheten et al., which incorporated 29 studies, secondary dengue infection was identified as a substantial risk factor for severe dengue, with a pooled odds ratio (OR) of 3.23 (95% CI: 2.28—4.57).[5] However, the ORs derived from the 29 studies exhibited significant variability (ranging from 0.67 to 32.0). Furthermore, most of the studies included in the meta-analysis focused only on hospitalized dengue patients, restricting the generalizability of the results to patients with milder forms of the disease and potentially overestimating the risk of severe dengue following a DENV infection.

Taiwan experienced severe dengue outbreaks in 2014 and 2015, resulting in more than 58,000 indigenous cases.[6] A number of news articles and health education resources at the time stated that the case fatality rate for secondary dengue infections could increase the risk of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) and reach up to 50% without proper treatment. This alarming information raised considerable anxiety among dengue patients who had also been diagnosed previously and their families, leading some to seek medical attention at tertiary medical centers and request hospitalization. This phenomenon might partially contribute to the overwhelming workload and overcrowding in tertiary medical centers during 2015. Therefore, the aim of this study was to investigate the risk of severe dengue in patients with secondary infection compared to those with primary infection in Taiwan. Subgroup analyses were also conducted to examine the risk of severe dengue in secondary infections based on various factors, including age groups, gender, year, the time interval between primary and secondary infections, and the sequential order of dengue serotypes.

Methods

Study population

In Taiwan, dengue fever is classified as a Category 2 Notifiable Communicable Disease. Suspected cases must be reported to the Taiwan Centers for Disease Control within 24 h. Blood samples from suspected cases are required to be tested by accredited laboratories to confirm the diagnosis of dengue. The criteria for verifying dengue infection in a laboratory slightly varied over time but generally included: 1) isolation of DENV; 2) discovering viral RNA through real-time reverse transcription polymerase chain reaction; 3) a four-fold increase in IgG levels when comparing acute-phase and convalescent-phase samples; 4) detection of dengue-specific IgM and IgG antibodies in blood samples during the acute stage (before 2009); 5) identification of NS1 in blood samples.[7—9]

Dengue patients with laboratory confirmation between 1998 and 2015 were identified using the Notifiable Disease Dataset of Confirmed Cases. Individuals with missing IDs or who were not enrolled in the National Health Insurance program were excluded. If a person had two confirmed dengue infection records with disease onset dates within 30 days, these records were considered as representing the same infection and the latter record was excluded to ensure data accuracy. To minimize variations in patient care over time, we restricted our study population to laboratory-confirmed dengue cases from 2014 to 2015. Patients from these two years who also had a confirmed

diagnosis at least 6 months earlier were classified as having secondary dengue infections. Given the island-wide and severe dengue epidemic that occurred between 1942 and 1943, which is believed to have infected approximately five-sixths of Taiwan's population, we included only those patients born in 1944 or later in our analysis to avoid potential misclassification of secondary dengue infections.[10,11] For each case of secondary dengue infection in 2014 and 2015, ten matched confirmed cases without secondary infection (primary infection) were selected as controls using propensity score matching. The covariates considered for calculating propensity scores included the year of disease onset (exact matching), sex (exact matching), age (exact matching), monthly income, area of residence, corresponding urbanization level, and comorbidities. Age was categorized into four groups (0—17, 18—44, 45—64, ≥65 years old). Area of residence was classified into Tainan, Kaohsiung, Pingtung, and others.[8] Urbanization was categorized into four levels, with one representing the most urbanized and four being the least urbanized.[8,12] Comorbidities potentially affecting the dengue prognosis, such as diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401—405), coronary artery diseases (ICD-9-CM codes 411—414), chronic obstructive airway diseases/bronchial asthma (ICD-9-CM codes 490—496), stroke (ICD-9-CM codes 430—438), and chronic kidney diseases (ICD-9-CM codes 582—586), were also taken into consideration. These comorbidities were identified by any hospital admission or a minimum of three outpatient visits with corresponding ICD-9-CM codes preceding the dengue onset dates.

Study outcome and follow-up

The primary outcome of this study was severe dengue, which was obtained from the National Health Insurance Research Databases (NHIRD). The NHIRD maintains comprehensive insurance claim data from the National Health Insurance (NHI) program, providing coverage for more than 99% of Taiwan's total population exceeding 23 million individuals.[13] Severe dengue was defined as hospitalization within two weeks of disease onset dates accompanied by at least one of the following conditions: 1) admission to an intensive care unit; 2) diagnosis of dengue hemorrhagic fever (ICD-9-CM code 065.4), pleural effusion (ICD-9-CM code 511.9), ascites (ICD-9-CM code 789.59), acute respiratory failure (ICD-9-CM code 518.81), or gastrointestinal bleeding (ICD-9-CM codes 530.82, 531.0, 531.2, 532.0, 532.2, 533.0, 533.2, 534.0, 534.2, 535.01, 578); 3) use of a ventilator; 4) prescription of vasopressor drugs. Deaths recorded in the Notifiable Disease Dataset of Confirmed Cases were also considered severe dengue. This study received approval from the Institutional Review Board of National Cheng Kung University Hospital (B-ER-106-184).

Statistical analysis

A multivariate logistic regression model was used to calculate the propensity score for secondary dengue infection based on the covariates mentioned earlier. Each secondary dengue infection case was matched with ten primary dengue infection cases using the Greedy matching algorithm and a caliper of 0.2 standard deviations of the logit-transformed propensity score.[14] The standardized mean difference (SMD) was computed to compare baseline covariates between secondary and primary infection cases, with an SMD greater than 0.1 indicating a significant imbalance between the groups.[15] Risks of developing severe dengue for both secondary and primary infection cases were calculated. Conditional logistic regression analyses were conducted to estimate the OR for severe dengue among patients with secondary infection compared to those with primary infection. Considering the short follow-up period of this matched cohort study and no loss of follow-up, a conditional Poisson regression model was also applied to estimate the relative risk (RR) for severe dengue in patients with secondary infections compared to those with primary infections for sensitivity analysis.[16,17] This adjustment was necessary as ORs could overestimate relative risks if the outcome was not rare.[18] Subgroup analyses were carried out to assess whether the ORs or RRs differed by onset year, sex, age and area.

Infection by a specific DENV serotype typically provides long-lasting protection against the same serotype. However, immunity to other dengue serotypes is transient, with heterotypic protective immunity estimated to last up to two years based on two prospective cohort studies.[19,20] Thus, we also evaluated the ORs of severe dengue by comparing secondary infection cases with primary infection cases over different time intervals between the first and second dengue infections. For this study, we assumed that the infecting serotype for each dengue patient corresponded to the predominant serotype circulating during the same year's local outbreak.[21] We also performed subgroup analyses comparing different serotype sequences in primary and secondary infections. All data processing and analysis were carried out using SAS 9.4 statistical software (SAS Institute, Cary NC). Results with a 2-tailed P-value less than 0.05 were considered statistically significant.

Results

The process of study population selection is depicted in Fig. 1. We identified a total of 357 laboratory-confirmed secondary dengue infection cases from 2014 to 2015, all born in 1944 or later. Prior to propensity score matching, significant differences in onset year, age, area of residence, and urbanization level distributions were observed between patients with secondary infection and those without, as evidenced by standardized mean differences (SMDs) greater than 0.1. Higher prevalence rates of diabetes mellitus, hypertension, and coronary artery disease were also observed in patients with secondary infection. Propensity score matching at a ratio of 1:10 yielded 3570 matched controls from a total of 51,636 newly diagnosed dengue patients. Post-matching, no substantial differences in baseline characteristics were detected between patients with and without secondary dengue infection (Table 1).

The risk of severe dengue was found to be 7.8% in individuals with secondary dengue infection, compared to 3.8% in those with primary dengue infection. Conditional

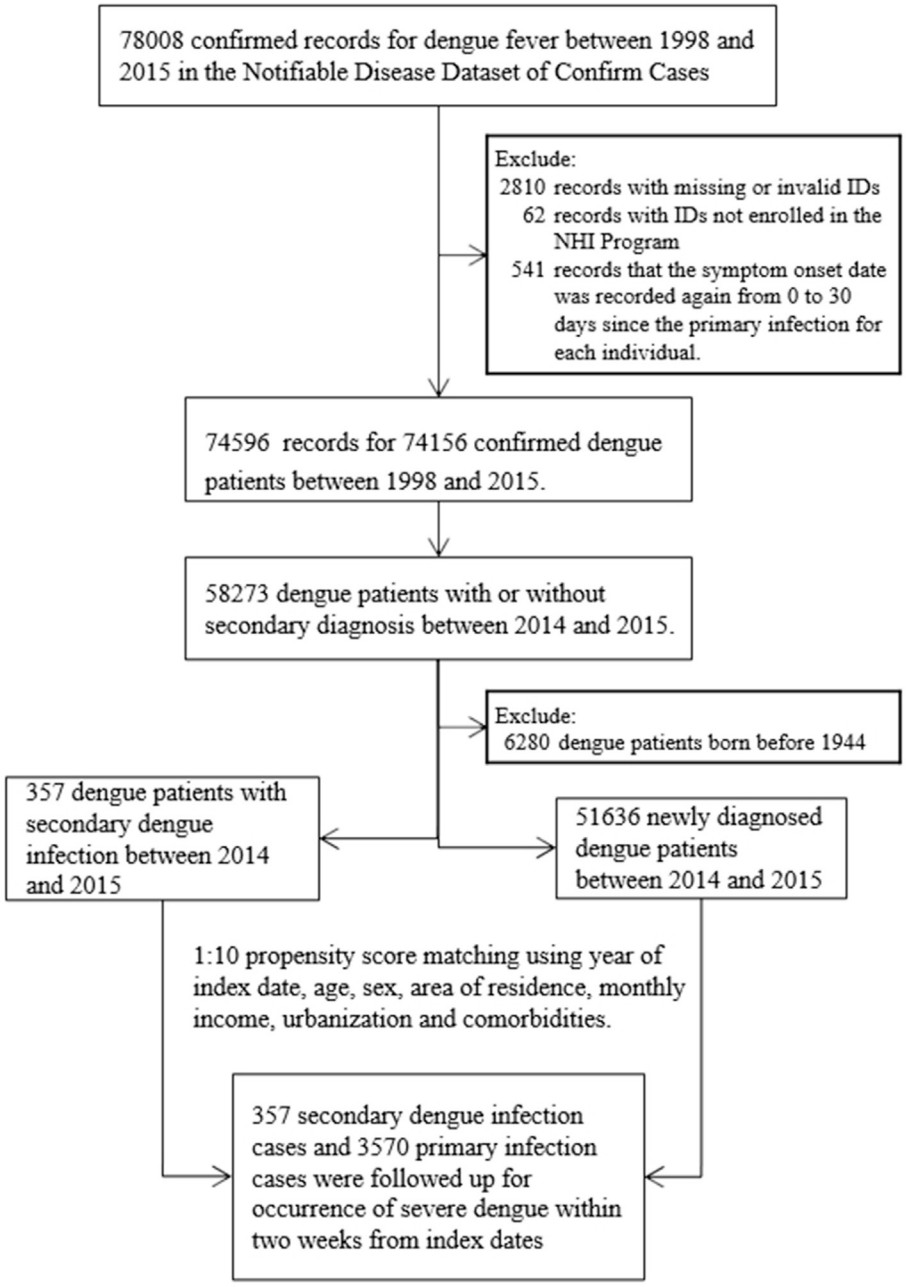

Fig. 1. Flow diagram of the selection of the study population.

logistic regression analysis revealed that the OR for severe dengue, comparing individuals with secondary dengue infection to those with primary infection, was 2.13 (95% confidence interval [CI]: 1.40—3.25, P = 0.0004, Table 2). Stratified analyses indicated that the association remained statistically significant across different onset years and sexes. However, when stratified by age, the association was only statistically significant among individuals aged between 45 and 64 years (OR 2.24, 95% CI 1.25—4.00, P = 0.006). When stratified by geographic area, the association was significant only in Tainan (OR 3.49, 95% CI 1.82—6.66, P = 0.0002), but not in Kaohsiung (OR 1.54, 95% CI 0.89—2.69, P = 0.121). RRs derived from conditional Poisson regression models were found to be highly similar to ORs obtained from conditional logistic regression analyses, probably because severe dengue in both primary and secondary infection groups was relatively rare (<10%).

We further investigated whether the association between secondary dengue infection and severe dengue varied across different time intervals and serotype sequences between the first and second dengue infections. A significant association between secondary infection and severe dengue was observed only when the interval between the first and secondary infection was greater than two years (OR 3.19, 95% CI 2.04—5.00, P < 0.0001). There was no such association when the interval was less than 2 years (Table

Table 1 Demographic and clinical characteristics in patient with secondary or primary dengue infection.

	Secondary dengue infection (n = 357)	All primary dengue infection (n = 51636)	SMD (unmatched)	Matched primary infection (n = 3570)	SMD (matched)
Onset year					
2015	278 (77.9)	37513 (72.7)	0.117	2780 (77.9)	0.000
2014	79 (22.1)	14123 (27.4)	—	790 (22.1)	—
Sex					
Female	189 (52.9)	25599 (49.6.)	0.067	1890 (52.9)	0.000
Male	168 (47.1)	26037 (50.4)	—	1680 (47.1)	—
Age	50.5 (16.2)	41.3 (18.3)	0.503	50.1 (16.3)	0.021
0-17	17 (4.8)	6472 (12.5)	0.235	170 (4.8)	0.000
18-44	83 (23.3)	20635 (40.0)	0.341	830 (23.3)	0.000
45-64	190 (53.2)	19515(37.8)	0.318	1900 (53.2)	0.000
≥ 65	67 (18.8)	5014 (9.7)	0.304	670 (18.8)	0.000
Area of residence					
Tainan	136 (38.1)	19597 (38.0)	0.003	1391 (39.0)	0.018
Kaohsiung	219 (61.3)	30608 (59.3)	0.042	2157 (60.4)	0.019
Pingtung	1 (0.3)	572 (1.1)	0.079	6 (0.2)	0.014
Others	1 (0.3)	859 (1.7)	0.108	16 (0.5)	0.017
Monthly insured income					
≤ 15840	59 (16.5)	9839 (19.1)	0.064	620 (17.4)	0.022
15841-25000	152 (42.6)	21450 (41.5)	0.021	1518 (42.5)	0.001
≥ 25001	146 (40.9)	20347 (39.4)	0.031	1432 (40.1)	0.016
Level of urbanization					
1	159 (44.5)	18593 (36.0)	0.178	1548 (43.4)	0.024
2	141 (39.5)	20251 (39.2)	0.006	1444 (40.5)	0.019
3	54 (15.1)	11103 (21.5)	0.155	556 (15.6)	0.012
4-7	3 (0.8)	1689 (3.3)	0.137	22 (0.6)	0.028
Comorbidity					
Diabetes mellitus	73 (20.5)	5495 (10.6)	0.317	661 (18.5)	0.049
Hypertension	127 (35.6)	10716 (20.8)	0.365	1251 (35.0)	0.011
Coronary artery disease	57 (16.0)	4071 (7.9)	0.298	533 (14.9)	0.029
Chronic obstructive airway disease	70 (19.6)	8680 (16.8)	0.075	641 (18.0)	0.043
Stroke	19 (5.3)	2206 (4.3)	0.052	129 (3.6)	0.089
Chronic kidney disease	16 (4.5)	1985 (3.8)	0.033	88 (2.5)	0.094

Data are number (%) or mean (standard deviation), unless otherwise stated. SMD = standardized mean difference.

3). Regarding the sequence of infection, a larger number of cases involved a sequence of DENV-1 to DENV-2. Therefore, these cases were further stratified by interval (≤2 years and >2 years). This analysis revealed that secondary infection was associated with severe dengue only when the interval was greater than two years (OR 3.62, 95% CI 1.82—7.17, P = 0.0002). For other sequences of infection, while secondary infection appeared to be positively associated with severe dengue, only the sequence of DENV-2 to DENV-1 was statistically significant (OR 3.91, 95% CI 1.34—11.44, P = 0.013), probably likely due to smaller sample sizes for the other sequences of infection.

Discussion

In this study, we found that the risk of severe dengue was considerably higher among patients who had a previous diagnosis of the disease (7.8%) compared to those diagnosed for the first time (3.8%). This risk associated with secondary dengue infection in our study is significantly lower than that reported in many previous studies. For instance, a meta-analysis by Tsheten et al. showed that 9 out of the 29 included studies reported the risk of severe dengue in secondary infection to be higher than 50%.[5] It's important to note, however, that these studies primarily encompassed hospitalized cases and therefore might have overestimated the risk associated with secondary infection. In our study, individuals with secondary dengue infections were found to have more than twice the risk of developing severe dengue compared to those with primary infections. This is less than the pooled odds ratio (OR) of 3.23 reported in the aforementioned meta-analysis.[5] Our study also highlights that the occurrence of severe dengue in patients with secondary infections was particularly pronounced when the interval between the first and second infection exceeded two years.

Table 2 Odds ratios and risk ratios for severe dengue in secondary dengue infection compared to primary dengue infection in different groups.

	Secondary dengue infection			Primary dengue infection						
	N	Severe	%	N	Severe	%	OR (95% CI)	p-value	RR (95% CI)	p-value
All	357	28	7.8	3570	137	3.8	2.13 (1.40—3.25)	0.0004	2.13 (1.40—3.25)	0.0004
Onset year										
2015	278	21	7.6	2780	114	4.1	1.91 (1.18—3.10)	0.009	1.91 (1.17—3.11)	0.009
2014	79	7	8.9	790	23	2.9	3.24 (1.35—7.82)	0.009	3.24 (1.43—7.34)	0.005
Sex										
Female	189	13	6.9	1890	65	3.4	2.07 (1.12—3.84)	0.020	2.07 (1.15—3.74)	0.015
Male	168	15	8.9	1680	72	4.3	2.19 (1.23—3.91)	0.008	2.19 (1.20—4.00)	0.011
Age										
0—44[a]	100	4	4.0	1000	15	1.5	2.74 (0.89—8.41)	0.079	2.74 (0.86—8.71)	0.089
45-64	190	15	7.9	1900	70	3.7	2.24 (1.26—4.00)	0.006	2.24 (1.25—4.00)	0.006
≥ 65	67	9	13.4	670	52	7.8	1.84 (0.87—3.93)	0.113	1.84 (0.87—3.92)	0.112
Area										
Tainan	136	13	9.6	1391	40	2.9	3.57 (1.86—6.85)	0.0001	3.49 (1.82—6.66)	0.0002
Kaohsiung	219	15	6.8	2157	97	4.5	1.56 (0.89—2.74)	0.120	1.54 (0.89—2.69)	0.121

[a] The two age strata (0—17 and 18—44) were combined because the number of severe dengue cases was too small.

DENV comprises four serotypes, all of which share a significant degree of structural antigens. Previous studies show that DENV infection elicits both type-specific and cross-reactive antibodies.[4,22] Primary DENV infection induces a type-specific neutralizing antibody response, providing long-term protection against the primary infecting serotype but only transient protection against other DENV serotypes.[23,24] Cross-serotype protection against symptomatic infection has been observed for up to two years post-primary infection in two prospective cohort studies,[19,20] after which individuals are at increased risk of symptomatic infection and severe dengue upon subsequent heterologous infection.[20,25] Repeated reexposure maintains sufficient cross-reactive neutralizing antibodies in endemic regions. Neutralizing antibody titers are essential for preventing symptomatic DENV infection, with higher pre-infection cross-reactive neutralizing antibody titers correlating with a lower probability of symptomatic infection in children in a longitudinal cohort study in Nicaragua.[26] Nevertheless, the risk of severe dengue escalates if secondary exposure to a heterologous DENV serotype occurs after this two-year period, likely mediated via ADE.[27,28] ADE occurs when antibodies bind to the virus particle but fail to neutralize it effectively. This may result from the non-neutralizing nature of the antibody (binding to viral epitopes other than those involved in cell attachment and entry) or from sub-neutralizing concentrations of antibodies (binding to viral epitopes below the threshold

Table 3 Odds ratios and risk ratios for severe dengue in secondary dengue infection compared to primary dengue infection across different time intervals and serotype sequences between the first and second dengue infections.

	Secondary dengue infection			Primary dengue infection						
	N	Severe	%	N	Severe	%	OR (95% CI)	p-value	RR (95% CI)	p-value
Interval										
≤2 years	92	—	—	920	—	—	0.21 (0.03—1.53)	0.123	0.21 (0.03—1.58)	0.129
>2 years	265	27	10.2	2650	91	3.4	3.19 (2.04—5.00)	<0.0001	3.19 (2.06—4.95)	<0.0001
Sequence										
≤2 years										
DENV-1 ⇒ DENV-2	92	—	—	920	—	—	0.21 (0.03—1.53)	0.123	0.21 (0.03—1.58)	0.129
>2 years										
DENV-1 ⇒ DENV-2	111	12	10.8	1110	36	3.2	3.62 (1.82—7.17)	0.0002	3.62 (1.83—7.13)	0.0002
DENV-2 ⇒ DENV-1	43	5	11.6	430	14	3.3	3.91 (1.34—11.44)	0.013	3.91 (1.43—10.72)	0.008
DENV-3 ⇒ DENV-1	27	—	—	270	—	—	3.52 (0.68—18.37)	0.135	3.52 (0.80—15.53)	0.097
DENV-3 ⇒ DENV-2	33	4	12.1	330	17	5.2	2.54 (0.80—8.05)	0.113	2.54 (0.82—7.88)	0.107
DENV-4 ⇒ DENV-2	17	—	—	170	—	—	4.40 (0.79—24.65)	0.092	4.40 (0.85—22.82)	0.078

* The cells left blank indicated that the numbers of events in some cells was too small and were therefore not allowed to be exported under the regulations of the Health and Welfare Data Science Center of Taiwan to prevent re-identification.

for neutralization). These virus—antibody complexes can bind to the Fc region of cellular Fc receptors (FcRs) on the surface of mononuclear phagocytes enhancing viral entry and facilitating viral replication.[29,30] The ADE theory has been proposed as a principal mechanism behind the increased severity of secondary dengue infections past this two-year interval.[4,31—41] A study from Cuba notably reported a considerable increase in disease severity among patients who experienced a prolonged interval (20 years) between their initial and secondary dengue infections.[42] This finding underscores the critical role of re-exposure timing to DENV in the risk assessment of severe dengue. In alignment with previous studies, our data also suggest that individuals with secondary dengue infections have a risk of severe dengue approximately two to three times higher than those with primary infections, particularly when the interval between infections exceeds two years. Consequently, healthcare professionals should exercise heightened vigilance towards individuals with a history of dengue infection, especially if their initial diagnosis was more than two years ago.

Previous research indicates that DENV-2, DENV-3, and DENV-4 from the Southeast Asia region and DENV-2 and DENV-3 from regions outside of Southeast Asia account for the highest percentage of severe cases in dengue infections.[43] In Taiwan, phylogenetic analyses suggest that most of the DENV isolates are DENV-1 and DENV-2 strains that are common in Southeast Asia.[44—47] Notably, our study implies that a primary infection with DENV-2 followed by a secondary dengue infection with DENV-1 poses a higher risk of progressing to severe dengue, especially when the interval between infections exceeds two years. While it is possible that other strains may also present a higher risk of severe dengue in secondary infections, this was not significantly demonstrated in our study, probably due to limited case numbers involving those strains.

Throughout the first half of the 20th century, Taiwan experienced three island-wide dengue fever outbreaks; the largest and most severe outbreak transpired in the years 1942—43, with an estimated five-sixths of the island's inhabitants contracting the disease. It is postulated that this extensive rate of infection was primarily due to the substantial population movement during the World War II era.[10,11,48] Following nearly four decades of dormancy, a DENV-2 outbreak occurred in Pingtung in 1981. Since then, more dengue fever outbreaks have occurred in Southern Taiwan, especially in Kaohsiung, Tainan, and Pingtung. Particularly noteworthy were the years 2014 and 2015, when Southern Taiwan faced the most severe dengue outbreaks in its history, resulting in over 58,000 dengue cases and 228 fatalities. Compared to the frequent dengue outbreaks in Kaohsiung, Tainan has had fewer large-scale dengue outbreaks prior to 2015.[49] One recent serosurvey showed that the overall age-standardized seroprevalence of DENV-IgG was 25.77% in Kaohsiung and 11.40% in Tainan.[50] Interestingly, our study revealed an elevated risk of severe dengue in secondary infection cases specifically in Tainan, but not in Kaohsiung. This discrepancy could be because a higher proportion of cases in Kaohsiung classified as primary infections might have previously experienced asymptomatic or unreported DENV infections. This potentially higher rate of misclassification may lead to an underestimation of the impact of secondary dengue infections on the development of severe dengue in Kaohsiung. Additionally, the 2014 outbreak occurred mainly in Kaohsiung, while the 2015 outbreaks occurred in both Kaohsiung and Tainan. Therefore, people in Kaohsiung had a higher chance of contracting repeated dengue infections within two years, during which secondary infection is not a significant risk factor for severe dengue. Furthermore, stratified analyses by age revealed that the association between severe dengue and secondary infection was only statistically significant among individuals aged between 45 and 64 years. For those aged 0—44, the small number of severe dengue cases (4 out of 100) likely contributed to the lack of statistical significance. For those aged $\geq$65, the limited sample size (67 cases) and higher variability in health status may explain the lack of significance, despite a higher percentage (13.4%) of severe cases. However, the odds ratios for both age groups were consistently above one, indicating an elevated risk of severe dengue with secondary dengue infection.

Our study has several strengths. Firstly, it includes a broad patient cohort consisting of both adults and children diagnosed with dengue in Taiwan, and encompasses both hospitalized and outpatient patients. This diverse sample provides better generalizability than studies that only include hospital-based patients or with smaller sample sizes. Secondly, the outcomes were retrieved from Taiwan's NHIRD, which boasts a coverage rate of over 99%. This high coverage significantly reduces the likelihood of selection bias due to loss to follow-up. Thirdly, our study conducted a stratified analysis by age, area of residence, and the interval and sequence of primary and secondary infections, offering more comprehensive insights. Lastly, potential confounding variables such as demographics and comorbidities were controlled for using propensity score matching, ensuring a balanced representation of baseline characteristics across groups.

Several limitations need to be addressed. Firstly, the National Health Insurance Research Database (NHIRD) used in this study, which is primarily an insurance claims database, incorporates records of diagnoses, drugs, and procedures received by all beneficiaries of Taiwan's National Health Insurance. However, it lacks detailed medical records such as test results and clinical symptoms. Consequently, we were unable to classify the severity of dengue according to the 1997 or 2009 World Health Organization (WHO) classification criteria. Secondly, some cases identified as primary infection in this study may have been wrongly classified due to the possibility of subclinical and underreported DENV infections. This misclassification bias may be more pronounced in Kaohsiung, given the higher frequency and severity of dengue outbreaks in that region.[50] Thirdly, the NHIRD does not encompass certain potential confounders such as body weight and smoking habits, potentially leading to residual confounding. Lastly, we must note that some stratified analyses related to specific serotypes and intervals between primary and secondary infections were not performed. This limitation arises from the privacy regulations of the Health and Welfare Data Science Center in Taiwan, which prohibits reporting results from less than three persons to prevent reidentification.

In conclusion, our study found that in Taiwan, the risk of severe dengue in patients with a previous diagnosis of dengue infection was 7.8%, which is more than double the risk faced by those without a previous diagnosis. Notably, the occurrence of severe dengue in patients with secondary dengue infection was particularly evident when the interval between the first and secondary infection exceeded two years. As a result, healthcare professionals should maintain heightened vigilance for individuals with a history of previous dengue infection, particularly if their initial diagnosis was more than two years prior.

Funding

This study was partially supported by grants from the National Science and Technology Council (MOST-111-2625-M-006-016-[HIS]), National Health Research Institute (MR-112-GP-05[CYC]), the Higher Education Sprout Project, the Ministry of Education to the Headquarters of University Advancement at National Cheng Kung University (NCKU), and the National Cheng Kung University Hospital (NCKUH-11203040, NCKUH-11303018 [HIS]). The funders had no role in the study's design, data collection and analysis, decision to publish, or manuscript preparation.

Data availability

This study used national databases obtained from the Health and Welfare Data Science Center (HWDC) of the Ministry of Health and Welfare in Taiwan (https://dep.mohw.gov.tw/dos/cp-5119-59201-113.html). All data were anonymized and deidentified by the HWDC. The data used in this study can only be accessed and analyzed in the HWDC after an application is completed according to the relevant regulations and thus cannot be shared. Permission was required to access data in the NHIRD, and our study group obtained the necessary permission. Contact information for data application, analysis and inquiry was obtained (https://dep.mohw.gov.tw/dos/cp-2516-59203-113.html).

Medical writing/Editorial assistance

The authors would like to acknowledge the use of ChatGPT, an AI language model developed by OpenAI, for providing editorial assistance in improving the English language of this manuscript. It is important to note that the assistance provided by ChatGPT was limited to language editing, while all the original content, ideas, data analysis, results, and discussion were solely generated by the authors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Hsin-I Shih: Conceptualization, Funding acquisition, Writing — original draft, Writing — review & editing. **Yu-Ching Wang:** Data curation, Writing — original draft. **Yu-Ping Wang:** Data curation, Formal analysis, Software, Validation. **Chia-Yu Chi:** Funding acquisition, Project administration, Resources, Writing — original draft. **Yu-Wen Chien:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing — original draft, Writing — review & editing.

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