Incidence rates of neurotropic-like and viscerotropic-like disease in three dengue-endemic countries: Mexico, Brazil, and Malaysia

Carine Cohen [a],[*], Edson D. Moreira Jr. [b], Homero Nañez [c], Jeyaseelan P. Nachiappan [d], Arvinder-Singh HS [e], Catherine Huoi [a], Joshua Nealon [f], Elsa Sarti [g], Esteban Puentes-Rosas [g], Annick Moureau [h], Alena Khromava [i], on behalf of the study team [1]

[a] Sanofi Pasteur, Lyon, France
[b] Associação Obras Sociais Irmã Dulce and Oswaldo Cruz Foundation, Brazilian Ministry of Health, Bahia, Brazil
[c] University Hospital Dr. José E. González, Faculty of Medicine Universidad Autonoma de Nuevo León, Monterrey N.L., Mexico
[d] Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia
[e] Clinical Research Centre, Malaysia
[f] Sanofi Pasteur, Asia & JPAC Region, Singapore
[g] Sanofi Pasteur LATAM, Coyoacán, CDMX, Mexico
[h] Clinical Development, Sanofi Pasteur, Marcy l'Etoile, Lyon, France
[i] Sanofi Pasteur, Toronto, Canada

ARTICLE INFO

ABSTRACT

Background: The background incidence of viscerotropic- (VLD) and neurotropic-like disease (NLD) unrelated to immunization in dengue-endemic countries is currently unknown.
Methods: This retrospective population-based analysis estimated crude and standardized incidences of VLD and NLD in twelve hospitals in Brazil (n = 3), Mexico (n = 3), and Malaysia (n = 6) over a 1-year period before the introduction of the tetravalent dengue vaccine. Catchment areas were estimated using publicly available population census information and administrative data. The denominator population for incidence rates was calculated, and sensitivity analyses assessed the impact of important assumptions.
Results: Total cases adjudicated as definite VLD were 5, 57, and 56 in Brazil, Mexico, and Malaysia, respectively. Total cases adjudicated as definite NLD were 103, 29, and 26 in Brazil, Mexico, and Malaysia, respectively. Crude incidence rates of cases adjudicated as definite VLD in Brazil, Mexico, and Malaysia were 1.17, 2.60, and 1.48 per 100,000 person-years, respectively. Crude incidence rates of cases adjudicated as definite NLD in Brazil, Mexico, and Malaysia were 4.45, 1.32, and 0.69 per 100,000 person-years, respectively.
Conclusions: Background incidence estimates of VLD and NLD obtained in Mexico, Brazil, and Malaysia could provide context for cases occurring after the introduction of the tetravalent dengue vaccine.

1. Background

Dengue has a wide geographical distribution [1]. A recombinant, live, attenuated, tetravalent dengue vaccine has been registered for the prevention of symptomatic dengue in individuals aged 9–45 years in several endemic countries such as Mexico, Brazil, and Malaysia. The vaccine was first licensed in Mexico in December 2015, and was introduced in public immunization programs in the Philippines and Parana state in Brazil in 2016 [2]. In Malaysia, the vaccine was conditionally registered in April 2017 for two years [3]. The vaccine is composed of four recombinant strains of dengue virus based on the backbone of the 17D live attenuated yellow fever (YF) vaccine (17D YF), expressing genes for dengue wild-type pre-membrane (preM) and envelope proteins for each of the four dengue serotypes.

The 17D YF vaccine has been associated with rare cases of viscerotropic (VD) and neurotropic (ND) disease meeting the Brighton

Collaboration diagnostic criteria, an international network organized to improve vaccine safety monitoring [4,5]. VD is an acute multiple organ system dysfunction with fever occurring post-vaccination when there is no alternative cause to explain it [6]. ND can manifest as several distinct clinical syndromes including meningoencephalitis, Guillain-Barre syndrome (GBS) with Fisher syndrome, acute disseminated encephalomyelitis (ADEM), and aseptic meningitis [7]. The Brighton Collaboration Viscerotropic Disease Working Group identified 60 published and unpublished reports of YF vaccine-associated VD up to March 2010 across Asia, Australia, Europe, and North and South America [6].

Reported incidence rates of ND and VD vary. Up to 60 days after 17D YF vaccine administration, 17 cases of ND and six cases of VD in US civilians were reported to Vaccine Adverse Event Reporting System from 2007 to 2013. A total of 2,224,790 doses had been administered, resulting in an incidence of 0.8 per 100,000 doses for ND and of 0.3 per 100,000 doses for VD [8]. In Brazil, ND was detected at a frequency of 0.084 per 100,000 doses between 1999 and 2009, while frequency of VD varied by area, being 0.31 and 0.11 per 100,000 doses administered in Sao Paulo (600,000 doses administered) and Rio Grande do Sul (3.6 million doses administered), respectively, both during the large vaccination campaigns of 2008–2009 [9]. A higher rate was reported to national agencies in Argentina during a mass vaccination campaign in 2008; 12 cases each of VD and ND were reported after >1.9 million doses were administered giving a rate of 0.6/100,000 doses for each disease [10].

As the tetravalent dengue vaccine uses the 17D YF vaccine virus backbone, there is a theoretical risk of VD and ND in dengue vaccine recipients. YF neutralizing antibodies are directed against the envelope glycoprotein E and it is assumed E proteins of flaviviruses share a common three-dimensional structure [11]. However, as the 17D YF preM and envelope genes are missing from the dengue vaccine viruses, it's unlikely it will share the same tropism as a vaccine against YF [12,13]. In addition, the YF backbone of the dengue vaccine was shown to be more attenuated than the YF vaccine through the chimerization process and any recombinant would be unlikely to cause disease [14]. This was supported in a safety overview of pooled data in 26,356 healthy participants obtained in 18 clinical trials – including trials conducted in Brazil, Mexico, and Malaysia – in which no dengue vaccine-related VD or ND events were reported during 25 months after the first injection [15]. Nevertheless, the rarity of such events was identified by the Global Advisory Committee on Vaccine Safety as a challenge in evaluating the dengue vaccine's safety profile [16].

A case-cohort study in 2017 that re-analyzed samples and data from three dengue vaccine efficacy trials reported that although the vaccine conferred protection for at least five years against the risk of hospitalized and severe dengue among participants seropositive at baseline, this risk was increased after administration of the first dose among dengue-seronegative participants [17]. This increased risk has been observed in all age groups, despite the decrease in proportion of dengue-naïve participants among the oldest age groups [18,19]. As a result of these data, the World Health Organization (WHO) recommended as a preferred option that countries considering dengue vaccination as part of their dengue control efforts should include pre-vaccination screening to ensure that only those dengue-seropositive are vaccinated [20,21].

To our knowledge, published data on the incidence rates of conditions resembling VD and ND (viscerotropic-like disease [VLD] and neurotropic-like disease [NLD], respectively) but occur in the absence of vaccination, are currently unavailable. Therefore, if cases of multi-organ failure or neurological diseases were detected in a large, vaccinated cohort, it would be difficult to compare with the frequency in an unvaccinated population and to assess vaccine safety based on expected rates of disease [22].

We undertook this retrospective population-based analysis to estimate the background incidence rate of VLD and NLD for the calendar year 2013 in Brazil, Mexico, and Malaysia prior to the introduction of the tetravalent dengue vaccine in these countries. The study was conducted as part of the dengue vaccine pharmacovigilance Risk Management Plan.

2. Methods

2.1. Study design

In this multi-national, observational, retrospective, hospital-based study, the incidence of VLD and NLD was assessed for the calendar year 2013 in Brazil and Mexico; and for a continuous 1-year period that varied by site, but started on or after January 1, 2013, in Malaysia. Assessments were based on records of hospitalized patients who were admitted, discharged or deceased, before availability of the tetravalent dengue vaccine in these countries.

This study was approved by the appropriate research ethics committees in each country. Prior to data collection in Brazil, informed consent was obtained from patients who met the study inclusion criteria (those with potential cases of VLD and NLD) or their next of kin for review of their medical records, as required by the National Ethics Committee in Brazil (CONEP). This consent was not requested from ethics committees in other countries.

Twelve hospitals participated: three each in Brazil and Mexico, and six in Malaysia. Sites were selected after detailed assessments of study feasibility. Available hospital databases containing hospital admission or discharge records were screened to identify medical records for new potential cases of VLD and NLD that met the inclusion criteria. The charts were retrieved and screened manually by local investigators.

2.2. Screening criteria

To be included in this study, patients of any age had to meet specific criteria which included: admission to a participating hospital during the relevant assessment period and being a resident within the hospital catchment area. Medical records for potential cases of VLD and NLD were identified by International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes or discharge diagnosis as recorded in hospital administrative records.

VLD was defined as a multiple organ dysfunction syndrome with undefined cause. Patients met the screening criteria for VLD if they had ≥2 simultaneous organ system failures at any time during a stay in an intensive care unit (ICU) or an adult or pediatric high-dependency unit – or if this was considered a cause of death. Patients were included if they previously had a test conducted to seek an etiology but none was identified or confirmed, or if no previous etiological tests were conducted.

A patient met the inclusion criteria for NLD if one of the following confirmed or suspected diagnoses occurred at any point during hospitalization or were the cause of death: aseptic meningitis, encephalitis, ADEM, or GBS. Fisher syndrome was considered a subset of GBS. Patients were included regardless of underlying cause of NLD.

Each potential case of VLD and NLD was classified according to the Brighton Collaboration levels of certainty: definite (level 1), probable (level 2), and possible (level 3) [23,24]. Level 3 classification was not available for aseptic meningitis as per the Brighton Collaboration case definition. For VLD, cases of organ dysfunction were further defined using commonly used thresholds or definitions by the Brighton Collaboration. For NLD, case definitions per Brighton Collaboration definitions were assigned through a

computerized algorithm. If cases were not classified by the algorithm, manual review of medical notes was performed by a Data Review Committee (two Principal Investigators) to ascertain level of diagnosis certainty. In Malaysia, medical notes from all sites were reviewed by the Principal Investigator and their team.

2.3. Data sources

Data were collected from records of hospitalized patients who had been discharged or deceased. Records from appropriate hospital units were screened, such as neurological, pediatric, internal medicine, ICU, and high-dependency units. To further identify cases of VLD, death records were also screened. Research staff had no contact with patients. Mild cases in patients who were not hospitalized and those who died prior to hospital admission were not captured. A standard case report form was used to capture information across all countries.

Catchment areas for participating study hospitals were estimated using publicly available population census information and data on nearby hospital capacity, occupancy and likely patient flow, as provided by Principal Investigators, following local research where necessary. The type of accessible data varied in each country and the specific method of defining catchment population was country-specific and is described in **Suppl. 1.** Briefly, in Mexico, this was based on ICD-10 codes describing the proportion of neurological cases treated at the study hospital, considering only hospitals covered by the Ministry of Health. In Brazil, this was based on the total proportion of admissions within the study area at the study hospitals (except for admissions for meningitis, as one study site was a reference center for meningitis), considering only the public-sector population. In Malaysia, the estimation was based on the proportion of ICU beds in study hospitals, correcting for lower occupancy rates in private hospitals.

2.4. Outcomes

The primary outcome was an estimation of incidence rate of VLD and NLD in Brazil, Mexico, and Malaysia. Secondary outcomes included estimation of age- and sex-specific incidence rates of VLD and NLD, and description of associated diagnoses identified as possible causes of NLD.

2.5. Data analysis

2.5.1. Analysis of patient records

Anonymized data sets containing case information were transferred to RTI Health Solutions (North Carolina, USA) for data analysis and quality control. Analyses were descriptive and included a tabular description of available characteristics of the selected hospitals in Brazil and Mexico (such data were not available in Malaysia), a summary of potential cases, and adjudicated case status. Analyses were conducted using SAS version 9. 1. 4 (Cary, NC; SAS Institute Inc.).

Demographic characteristics, unit of admission, status at discharge (alive or deceased), destination to which patients were discharged e.g. home or another care facility, and study hospital by case classification were descriptive, conducted separately for VLD, NLD, and each of the four component diseases of NLD (encephalitis, ADEM, GBS, and aseptic meningitis).

Incidence rates of NLD, VLD, and each of the four component diseases of NLD were estimated by collating information on new events (the first eligible event recorded per patient during the 1-year observation period). Incidence rates were calculated for the following: definite cases only; definite and probable cases; and definite, probable, and possible cases. Incidence rates (expressed per 100,000 person-years) and 95% confidence intervals (CIs) were

estimated with the Poisson exact method [25] overall, and for each of the age and sex categories for each outcome.

An overall standardized incidence rate and 95% CI using Gamma distribution [26] were estimated for each condition, weighted by age and sex distribution of the 2010 population of Malaysia [27], the 2010 population of Brazil [28], and the 2015 population of Mexico [29].

2.5.2. Sensitivity analyses

Due to potential uncertainty in the accuracy of denominator counts and the above proxy, country-specific sensitivity analyses were conducted to explore the impact on these incidence rates and 95% CIs of varying the size of the denominator (**Suppl. 2**).

3. Results

3.1. Study cases

The total cases of VLD and components of NLD identified in the study hospitals in Brazil, Mexico, and Malaysia are summarized in Table 1.

3.2. Incidence rates

3.2.1. VLD

Crude and standardized incidence rates of VLD are presented in Table 2. In Brazil, the crude incidence rate of VLD was somewhat higher in females than males. The incidence based on definite and probable cases was also similar in both sexes in Mexico and Malaysia. In Brazil and Mexico, the highest incidence was amongst patients aged 45–64 years, but in Malaysia, the highest incidence was in the 0–4 year age group.

Results of sensitivity analyses (**Suppl. 2**) indicate the standardized incidence estimate of VLD could be as low as 0.86 per 100,000 person-years in Brazil, and range from 2.37 per 100,000 person-years to 3.73 per 100,000 person-years in Mexico, and 1.37 per 100,000 person-years to 1.66 per 100,000 person-years in Malaysia.

3.2.2. NLD

Crude and standardized incidence rates of NLD are presented in Table 3. The crude incidence of NLD tended to be higher in males than females, irrespective of country. In Brazil, the highest incidence rates of encephalitis were in those aged 1–9 years and in adults aged ≥65 years based on 23 cases adjudicated as definite, probable, or possible (data not shown). In Mexico, based on 12 cases adjudicated as definite, probable, or possible, adults aged ≥45 years had the highest incidence. In Malaysia, based on 59 definite, probable, or possible adjudicated cases, the incidence was highest in the youngest (0–4 years) and oldest age groups (≥65 years).

Results of sensitivity analyses (**Suppl. 2**) indicate the standardized incidence estimate of NLD could be as low as 12.78 per 100,000 person-years in Brazil, and range from 3.44 per 100,000 person-years to 5.41 per 100,000 person-years in Mexico, and from 3.32 per 100,000 person-years to 4.02 per 100,000 person-years in Malaysia.

The standardized incidence of definite cases of ADEM was 0.05 (95% CI 0.00–0.26) per 100,000 person-years and 0.10 (95% CI 0.03–0.27) per 100,000 person-years in Mexico and Malaysia, respectively. ADEM events were not observed in Brazil. There were only two events in Mexico (one definite, and one definite or probable), both of which occurred in females who were aged 0–14 years. In Malaysia, there were five events adjudicated as definite, probable, or possible.

Table 1
Incident cases of VLD and NLD in the study hospitals in Brazil, Mexico, and Malaysia.

	Total potential cases	Adjudicated result				
		Definite, n (%)	Probable, n (%)	Possible, n (%)	Cannot be ruled out, n (%)	Can be ruled out, n (%)
VLD[a]						
Brazil	5	5 (100)	0 (0)	NA	0 (0)	0 (0)
Mexico	65	57 (88)	8 (12)	NA	0 (0)	0 (0)
Malaysia	59	56 (95)	3 (5)	NA	0 (0)	0 (0)
NLD						
Brazil						
NLD total[b]	297	103 (35)	156 (53)	10 (3)	23 (8)	5 (2)
Encephalitis	29	0 (0)	12 (41)	11 (38)	4 (14)	2 (7)
ADEM	0	0	0	0	0	0
GBS[c]	12	2 (17)	5 (42)	0 (0)	5 (42)	0 (0)
Aseptic meningitis	257	101 (39)	139 (54)	NA	14 (5)	3 (1)
Mexico						
NLD total[b]	106	29 (27)	57 (54)	7 (7)	12 (11)	1 (1)
Encephalitis	12	0 (0)	7 (58)	5 (42)	0 (0)	0 (0)
ADEM	2	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)
GBS[c]	57	15 (26)	35 (61)	2 (4)	5 (9)	0 (0)
Aseptic meningitis	36	13 (36)	15 (42)	NA	7 (19)	1 (3)
Malaysia						
NLD total[b]	177	26 (15)	96 (54)	20 (11)	33 (19)	2 (1)
Encephalitis	63	2 (3)	41 (65)	16 (25)	4 (6)	0 (0)
ADEM	5	4 (80)	1 (20)	0 (0)	0 (0)	0 (0)
GBS[c]	30	8 (27)	10 (33)	4 (13)	7 (23)	1 (3)
Aseptic meningitis	79	12 (15)	44 (56)	NA	22 (28)	1 (1)

ADEM, acute disseminated encephalomyelitis; GBS, Guillain-Barré syndrome; NA, not applicable; NLD, neurotropic-like disease; VLD, viscerotropic-like disease.
Percentages in the table are row percentages and may not total 100 due to rounding. Study periods were January 1, 2013, through December 31, 2013 (Brazil and Mexico), and any 1-year period (selected by the sites) starting on or after January 1, 2013 (Malaysia).
[a] Defined as any multiple organ dysfunction syndrome of unknown origin following vaccination.
[b] For patients with more than one of the four component diseases of NLD, total NLD cases is the highest-level result of any of the four component diseases of NLD.
[c] Cases of Fisher syndrome are included in this category.

GBS with Fisher syndrome had a standardized incidence rate of 0.50 (95% CI 0.06–1.86) per 100,000 person-years, 0.68 (95% CI 0.38–1.13) per 100,000 person-years, and 0.23 (95% CI 0.10–0.45) per 100,000 person-years in Brazil, Mexico, and Malaysia, respectively. There were two events adjudicated as definite and seven as definite or probable in Brazil. In Mexico, there were 15 events adjudicated as definite and 50 as definite or probable. In Malaysia, eight events were adjudicated as definite and 18 as definite or probable.

Aseptic meningitis had a standardized incidence rate of 4.42 (95% CI 3.59–5.38) per 100,000 person-years, 0.59 (95% CI 0.32–1.02) per 100,000 person-years, and 0.31 (95% CI 0.16–0.55) per 100,000 person-years in Brazil, Mexico, and Malaysia, respectively. In Brazil, there were 101 events adjudicated as definite and 240 as definite or probable, with more in the 20–44 years age group. In Mexico, 13 events were adjudicated as definite and 28 as definite or probable. In Malaysia, 12 events were adjudicated as definite and 56 as definite or probable, with more in the 0–4-year age group.

3.3. Possible causes of NLD

The most common possible cause of NLD recorded for definite cases was infection (99% in Brazil, 48% in Mexico, and 23% in Malaysia), or unknown. Infection was the possible cause of the 5/12 potential cases of GBS in Brazil, 21/57 potential cases in Mexico, and 3/30 in Malaysia.

The most common NLD diagnosis was aseptic meningitis in Brazil (87%) and Malaysia (45%), and GBS in Mexico (54%). The least common diagnosis was ADEM, with no cases in Brazil, two in Mexico, and five in Malaysia. Infection was the possible cause of one case of ADEM in Mexico, with one listed as "other" causes. The cause of all ADEM cases in Malaysia was unknown.

4. Discussion

This retrospective epidemiological study estimated the population-based background incidence of VLD and NLD across three dengue-endemic countries, with an extensive catchment area for each. As there are no published population-based incidence rates of VLD and NLD in these countries, these data could aid with interpretation of the reported AEs following introduction of the tetravalent dengue vaccine.

A particular strength of this study was that case definitions of NLD from the standardized and globally-implemented Brighton Collaboration criteria were utilized, and were adapted for VLD [6,23,30]. As this is considered a good model for case definitions and guidelines for AEs following immunization, the definitions in this study were aligned to determine background incidence rates. A further strength was the detailed method used to estimate catchment populations, which served as denominators for incidence rate calculations.

The incidence of VLD in Mexico, Brazil, and Malaysia varied when stratified by age and sex. The highest incidence of VLD was amongst patients aged 45–64 years in Brazil and Mexico. Age may influence incidence rates as an increased risk of YF vaccine-associated VD was observed in older compared with younger populations [31]. In addition, gender may also impact incidence rates as young women were identified as a risk group for YF vaccine-associated VD [31]. In this study, the crude incidence rate of VLD was higher in females than males.

Similarly, the incidence of NLD in these countries differed when stratified by age and gender. The incidence of GBS in our study was higher in males and older age groups, irrespective of country. This was consistent with previous observations, since a background estimate of the incidence of GBS in North America and Europe showed a 20% increase for every 10-year increment in age, and with a higher risk in males than females [32]. The point estimate

Table 2
Estimated Incidence per 100,000 Person-years of VLD in Brazil, Mexico, and Malaysia – Crude, Standardized, and Stratified by Age and Sex.

Stratum	Total person-years	Definite cases			Definite or probable cases		
		Events	IR*	95% CI	Events	IR*	95% CI
Brazil							
Crude incidence	428,082	5	1.17	0.38–2.73	5	1.17	0.38–2.73
Standardized incidence*	–	–	1.21	0.39–2.87	–	1.21	0.39–2.87
Sex							
Female	225,639	3	1.33	0.27–3.89	3	1.33	0.27–3.89
Male	202,443	2	0.99	0.12–3.57	2	0.99	0.12–3.57
Age							
<1	5631	0	0.00	0.00–65.51	0	0.00	0.00–65.51
1–4	22,692	0	0.00	0.00–16.26	0	0.00	0.00–16.26
5–9	30,309	0	0.00	0.00–12.17	0	0.00	0.00–12.17
10–14	35,155	1	2.84	0.07–15.85	1	2.84	0.07–15.85
15–19	35,627	1	2.81	0.07–15.64	1	2.81	0.07–15.64
20–44	193,688	0	0.00	0.00–1.90	0	0.00	0.00–1.90
45–64	80,489	3	3.73	0.77–10.89	3	3.73	0.77–10.89
≥65	24,491	0	0.00	0.00–15.06	0	0.00	0.00–15.06
Mexico							
Crude incidence	2,193,798	57	2.60	1.97–3.37	65	2.96	2.29–3.78
Standardized incidence*	–	–	2.59	1.96–3.35	–	2.94	2.27–3.75
Sex							
Female	1,114,134	27	2.42	1.60–3.53	33	2.96	2.04–4.16
Male	1,079,664	30	2.78	1.87–3.97	32	2.96	2.03–4.18
Age, years							
0–14	607,446	0	0.00	0.00–0.61	1	0.16	0.00–0.92
15–29	578,055	17	2.94	1.71–4.71	18	3.11	1.85–4.92
30–44	500,329	18	3.60	2.13–5.69	23	4.60	2.91–6.90
45–64	379,752	21	5.53	3.42–8.45	22	5.79	3.63–8.77
≥65	128,216	1	0.78	0.02–4.35	1	0.78	0.02–4.35
Malaysia							
Crude incidence	3,781,655	56	1.48	1.12–1.92	59	1.56	1.19–2.01
Standardized incidence*	–	–	1.45	1.09–1.88	–	1.53	1.16–1.97
Sex							
Female	1,840,683	26	1.41	0.92–2.07	29	1.58	1.06–2.26
Male	1,940,972	30	1.55	1.04–2.21	30	1.55	1.04–2.21
Age, years							
0–4	353,402	28	7.92	5.26–11.45	30	8.49	5.73–12.12
5–9	386,603	3	0.78	0.16–2.27	3	0.78	0.16–2.27
10–14	389,802	4	1.03	0.28–2.63	4	1.03	0.28–2.63
15–19	424,528	1	0.24	0.01–1.31	1	0.24	0.01–1.31
20–44	1,482,234	8	0.54	0.23–1.06	8	0.54	0.23–1.06
45–64	574,672	9	1.57	0.72–2.97	10	1.74	0.83–3.20
≥65	170,415	3	1.76	0.36–5.14	3	1.76	0.36–5.14

CI, confidence interval; IR, incidence rate.
* Standardized IR is the incidence rate per 100,000 person-years standardized to the age and sex distribution of the 2010 populations of Brazil and Malaysia and the 2015 population of Mexico.

of the standardized incidence rate of GBS observed in the present study for definite or probable cases was similar to the overall incidence of 1.1–1.8 cases per 100,000 person-years observed in a systematic literature review [33]. In addition, the observed point estimate of the incidence rate for definite cases was 0.50 per 100,000 person-years, which is near to an estimate from one study in a review of cases in São Paulo, Brazil, with an annual incidence estimated at 0.60 per 100,000 people [34]. However, the catchment areas for hospitals in Brazil differed in this study to those selected by Rocha *et al.*, so these data may not be generalizable and representative of the whole country.

In Brazil, the estimated frequency of NLD and VLD cases were slightly higher in this study than those of ND and VD previously detected (1.17 per 100,000 person-years vs. 0.08 per 100,000 doses) [9]. This difference was anticipated due to the active population-based nature of this study compared with the passive surveillance system applied in the literature.

The most common component of NLD detected in this study was aseptic meningitis in Brazil, which was the major driver of the overall standardized incidence rate in this country, most likely due to one center being a referral center for meningitis. The rates in this study were similar to the standardized rate of 10.9 cases per 100,000 person-years in a study in Olmsted County, Minnesota over a 32-year period [35]. However, the populations and defined study periods of these studies were different so the rates should be interpreted with caution.

This study has some limitations. Due to the nature of the study outcomes and defined period, a retrospective analysis was preferred over a prospective approach. However, retrospective studies are liable to under-estimate incidence rates because misclassified cases cannot be captured. For example, the overall incidence rate of GBS worldwide was higher in prospective studies (1.11–1.66 per 100,000 per year) than for retrospective and database studies with record review [33]. The variation in incidence rates of VLD could be due to the low number of events observed in subgroups of age and sex. The assessment of incidence rates could be affected by possible errors in estimating denominators in the catchment areas based on proxy measures. Estimating denominators in

Table 3
Estimated Incidence per 100,000 Person-years of NLD Overall in Brazil, Mexico, and Malaysia – Crude, Standardized, and Stratified by Age and Sex.

Stratum	Definite cases		Definite or probable cases		Definite, probable, or possible cases	
	IR	95% CI	IR	95% CI	IR	95% CI
Brazil[**]						
Crude incidence	4.45	3.25–5.65	13.90	11.53–16.27	16.24	13.46–19.02
Standardized incidence[*]	4.92	1.17–8.67	15.19	11.14–19.25	17.89	13.59–22.19
Sex						
Female	2.98	1.25–4.71	9.98	7.15–12.81	11.31	8.10–14.52
Male	6.07	3.93–8.21	18.26	14.24–22.28	21.72	16.96–26.48
Age						
<1	23.97	0.00–86.50	65.92	0.00–132.20	65.92	0.00–132.20
1–4	14.13	0.00–30.38	40.03	20.34–59.72	53.25	28.52–77.98
5–9	14.99	2.72–27.26	38.84	23.70–53.98	42.14	25.68–58.60
10–14	5.28	0.00–15.43	12.96	2.14–23.78	18.65	6.48–30.82
15–19	6.16	0.00–16.26	16.50	4.63–28.37	16.50	4.63–28.37
20–44	2.61	0.67–4.55	7.99	5.17–10.81	8.50	5.50–11.50
45–64	1.05	0.00–5.37	9.76	3.17–16.35	11.00	3.98–18.02
≥65	0.00	0.00–13.93	4.77	0.00–18.70	12.94	0.00–30.89
Mexico						
Crude incidence	1.32	0.89–1.90	3.92	3.14–4.84	4.24	3.42–5.19
Standardized incidence[*]	1.32	0.88–1.90	3.94	3.15–4.87	4.27	3.44–5.23
Sex						
Female	1.08	0.56–1.88	3.14	2.19–4.37	3.32	2.34–4.58
Male	1.57	0.92–2.52	4.72	3.52–6.21	5.19	3.92–6.74
Age, years						
0–14	1.65	0.79–3.03	3.79	2.40–5.68	4.28	2.80–6.27
15–29	0.52	0.11–1.52	2.59	1.45–4.28	2.94	1.71–4.71
30–44	1.20	0.44–2.61	3.00	1.68–4.94	3.00	1.68–4.94
45–64	2.37	1.08–4.50	7.11	4.69–10.34	7.37	4.90–10.66
≥65	0.78	0.02–4.35	4.68	1.72–10.19	5.46	2.20–11.25
Malaysia						
Crude incidence	0.69	0.45–1.01	3.23	2.68–3.85	3.75	3.16–4.43
Standardized incidence[*]	0.71	0.46–1.03	3.16	2.62–3.77	3.69	3.11–4.36
Sex						
Female	0.38	0.15–0.78	2.61	1.92–3.46	2.99	2.25–3.89
Male	0.98	0.59–1.53	3.81	2.99–4.79	4.48	3.59–5.53
Age, years						
0–4	0.57	0.07–2.04	13.58	10.01–18.01	14.71	10.99–19.30
5–9	0.78	0.16–2.27	2.59	1.24–4.76	3.10	1.60–5.42
10–14	0.77	0.16–2.25	2.57	1.23–4.72	2.82	1.41–5.05
15–19	0.00	0.00–0.87	1.18	0.38–2.75	1.41	0.52–3.08
20–44	0.54	0.23–1.06	1.69	1.09–2.49	2.02	1.37–2.89
45–64	1.04	0.38–2.27	2.61	1.46–4.31	3.48	2.13–5.37
≥65	1.76	0.36–5.14	3.52	1.29–7.66	4.69	2.03–9.25

CI, confidence interval; IR, incidence rate.

[*] Standardized IR is the incidence rate per 100,000 person-years standardized to the age and sex distribution of the 2010 populations of Brazil and Malaysia and the 2015 population of Mexico.

[**] For Brazil, the rates for NLD overall were calculated by summing the rates for the four conditions that made up NLD because a different denominator was used for aseptic meningitis than for the other conditions. Therefore, the person-year totals are not displayed in this table.

surveillance studies can be challenging even in a defined geographic and administrative region due to the mobility of individuals and the unpredictability of their health-seeking behavior. This challenge was addressed by performing sensitivity analyses to provide estimates for different assumptions of the size of the denominator. With differences in the population sizes, data availability in the three countries, and variation in the structure of their healthcare systems, direct comparison of results among countries was likely inappropriate.

Despite these challenges, this hospital-based surveillance captured estimates of the frequency of cases of VLD and NLD. Ultimately, this analysis could be used for comparison with the rates in these dengue-endemic regions following vaccination (during the risk period) for post-marketing safety monitoring of tetravalent dengue vaccine and interpretation of potential early safety signals.

5. Conclusion

These background incidence estimates of VLD and NLD obtained in Mexico, Brazil, and Malaysia could provide context for the surveillance of cases occurring after the introduction of the tetravalent dengue vaccine, or other vaccines.

Conflicts of interest

Funding

Ethical approval

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

Author contributions

CC was involved in data analysis/interpretation; EM, HN, NJ, HSA, and ERP were involved in the data acquisition, data analysis/interpretation. CH, JN, ES, AM, and KA were responsible for concept design, data analysis/interpretation. EM, NH, NJ, and HAS were lead investigators in this study. All authors contributed to this publication and approved the final manuscript for submission. All authors had access to the study data and are responsible for the veracity and completeness of the data reported.

Role of funding source

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.087.

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