SYSTEMATIC REVIEW AND META-ANALYSIS

THE PREVALENCE OF DENGUE IN MALAYSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Dengue is a mosquito-borne viral disease and remains a significant public health burden in Malaysia, as the cases have risen substantially for the past 3 decades. This meta-analysis estimates the prevalence of dengue in Malaysia by analysing 31 studies conducted between 1981 and 2020. The prevalence trends were evaluated across time, regional variation, study design, diagnostic methods, and further explored factors contributing to variability in studies. A total of 972 records were retrieved from five electronic databases, with 31 studies meeting the inclusion criteria for qualitative and quantitative synthesis. These studies represented diverse Malaysian states and predominantly involved post-2001 data. The diagnosis methods varied, with ELISA, PCR, and serological tests commonly employed. The meta-analysis included 22,921 cases, revealing a pooled dengue prevalence of 50.22% (95% CI: 38.7–57.8) with high heterogeneity (I^2 > 99.3%, p < 0.001). Dengue prevalence increased significantly, peaking at 49.7% during 2011–2020. Dengue presents with a wide range of symptoms, of which fever is the most prevalent, accompanied by musculoskeletal symptoms, headache, retroorbital pain, and fatigue. Additional manifestations include vomiting, abdominal pain, diarrhoea, rashes, petechiae, and bleeding tendencies, which are associated with severe dengue. The findings emphasise prioritising high-risk groups alongside urban-focused dengue control strategies. Further research in rural and less populated regions is essential to address the nationwide dengue burden comprehensively.

Keywords: *febrile disease; endemic; mosquito-borne disease; dengue prevalence; systematic review; meta-analysis; Malaysia*

INTRODUCTION

Dengue is a mosquito-borne viral infection transmitted by *Aedes* mosquitoes, with an estimated 390 million infections annually, of which 96 million manifest clinically (Bhatt *et al.*, 2013). Approximately 2 million cases progress to severe dengue, including dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), leading to 21,000 deaths annually (Murugesan & Manoharan). More than 80 nations and territories throughout the world reported over five million cases of dengue fever in 2023. The surge is due to an ongoing outbreak of the disease, exacerbated by an unexpected increase in cases (Akinsulie & Idris, 2024).

Malaysia has been endemic to dengue since the early 1990s, with frequent outbreaks and rising incidence due to factors such as urbanisation, climate change, and inadequate vector control measures (Yusoff, 2008). Dengue virus (DENV) belongs to the *Flavivirus* genus and consists of four serotypes (DENV-1 to DENV-4), all of which have co-circulated in Malaysia (Mohd-Zaki *et al.*, 2014). The disease progresses through three phases: febrile, critical, and recovery. Initial symptoms include fever, myalgia, retro-orbital pain, and gastrointestinal disturbances. Severe dengue manifests with plasma leakage, haemorrhages, and organ dysfunction (Organization *et al.*, 2009).

Malaysia's tropical climate, with high temperatures and annual rainfall of approximately 2500 mm, provides ideal conditions for *Aedes* mosquito breeding and year-round dengue transmission (Barrera *et al.*, 2011; Campbell *et al.*, 2015). Studies have highlighted the link between climate conditions and dengue outbreaks, with increasing mean temperatures and rainfall intensifying mosquito proliferation (Hii *et al.*, 2016; Norli & Azmi, 2008; Rohani *et al.*, 2011) (Malaysia, 2009). Additional contributing factors include high population density, urbanisation, migration patterns, and serotype circulation (Gubler, 2011; Weaver, 2013). Accurate diagnosis is crucial for dengue surveillance, clinical management, and vaccine development. Current diagnostic

methods include NS1 antigen detection, RT-PCR, virus isolation, and serological tests (ELISA, IgM, and IgG) (Guzmán & Kourí, 2004). ELISA remains the most widely used due to its broad detection of recent and past infections, despite potential cross-reactivity with other *flaviviruses* (Azami *et al.*, 2020b).

This study aims to investigate the prevalence of dengue in Malaysia using a systematic review and meta-analysis, identifying the trends across time, regional variation, study design, and diagnostic methods. Understanding these patterns is critical for optimising clinical management and guiding public health interventions.

MATERIALS AND METHOD

Study Design & Protocol

The study protocol adhered to the updated PRISMA 2020 guidelines for systematic reviews and meta-analyses (Moher *et al.*, 2009); **Figure 1**. The study protocol was registered on PROSPERO with the registration number CRD42023494181; available at; *https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023494181*.

Search Strategy

We searched abstracts from the PROSPERO database and the database of abstracts of reviews of effects (DARE) (http://www.library.UCSF.edu) to ensure that there is no other meta-analysis on the prevalence of dengue in Malaysia that exists or is ongoing. Subsequent to that, we searched in Google Scholar and PubMed for published papers on the prevalence of dengue in Malaysia.

Additionally, titles, sources, and references from the included papers were used as a secondary search tool. The review was conducted by 5 authors to reduce bias. The searches were performed from January 2024 to February 2024, using the following databases: Cochrane Central Register, PubMed, Scopus, Web of Science (WOS), ScienceDirect, and Google Scholar. There were no search restrictions on time of publication, language, setting, or population applied. The search was carried out in English. Studies that are published in English were selected to facilitate comprehensive data extraction and synthesis.

Inclusion and Exclusion Criteria

The search results will be imported into EndNote 20 and duplicate records will be removed. The studies were independently examined by two reviewers against pretested eligibility criteria at the stages of title, abstract, and full-text study selection. We included all study designs except systematic reviews, meta-analyses, and review articles that reported the prevalence of dengue in Malaysia. Studies with inadequate information, duplication, studies on animals/mosquitoes/mosquito traps, studies on knowledge/attitude/practice (KAP), comments, case reports, and studies that did not report dengue prevalence were excluded.

Data Extraction

Studies that met our inclusion criteria were assessed based on their title, abstract, and full text. From the manuscripts, we retrieved the first author's name and the following:

- General information: Name of the study, study design, state or cities where the study was conducted, and year of publication.
- Population characteristics: Demographic details (age, gender, urban or rural area)
- Case definition and description: diagnostic method, criteria used, details on serotypes, and other clinical features or findings related to dengue.

Studies that met our exclusion criteria were recognised and excluded. Duplicate studies and those without full texts were removed. Any disagreement among the reviewers was resolved through consensus.

Study Quality Assessment

We used the Joanna Briggs Institute (JBI) critical assessment checklist to assess the quality of the included prevalence studies (Aromataris E, 2015). This assessment included nine checklists: (1) sample frame appropriate to address the target population, (2) participants sampled in an appropriate way, (3) sufficient sample size, (4) detailed study subject and setting, (5) sufficient coverage of identified sample, (6) valid methods used for the identification of the conditions, (7) standard and reliable way condition measurement for all participants, (8) applying appropriate statistical analysis, and (9) adequate response rate and low response rate management. Each checklist was rated as 'yes', 'no', 'unclear', or 'not applicable'. A 'yes' response will score 1, while 'no' and 'unclear' responses will score 0. The average score for each checklist was then analysed. Studies scoring below the mean were classified as low quality, while those above the mean were considered high quality. The study that was agreed upon by two reviewers was included in the analysis. The quality of all 31 studies featured was rated on a scale of one to nine.

Data analysis
Open Meta software was used to calculate pool prevalence and determine the random-effects model. To assess study bias, we used Comprehensive Meta-analysis Software.

RESULTS

Study selection
The process of identification and selection of this study is summarised in **Figure 1;** Summary of article search and selection process based on PRISMA 2020 guidelines for systematic review and meta-analysis. From the five electronic databases of our search, a total of 972 records were retrieved. Duplicated studies were removed, and studies that did not meet the predefined inclusion criteria were excluded and A total of 666 studies with full text were evaluated for eligibility. After evaluation of the 666 studies with full text, thirty-one studies were fully eligible and included in the qualitative and quantitative synthesis (meta-analysis).

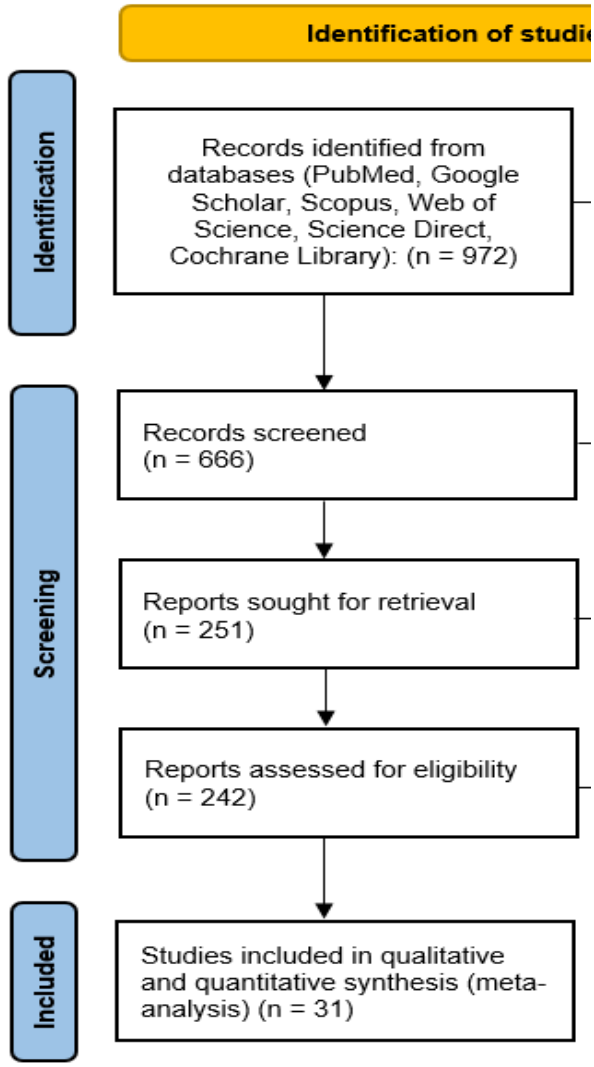

Figure 1: Summary of article search and selection process based on PRISMA 2020 guidelines for systematic review and meta-analysis.

Features of the included studies
The studies included in this systematic review were conducted across different regions in Malaysia, with nearly all the states in Malaysia represented. However, the majority of the reports were from Selangor and Kuala Lumpur. Besides that, more than 50% of the studies were conducted after 2001 and onwards. Furthermore, the sample type used for dengue diagnosis was a blood sample. The diagnostic methods were varied, with ELISA, PCR, and serological tests being the most commonly used. Features of the included studies are presented in **Table 1a,1b and 1c;** a major description of the included studies.

Table 1a: Major description of the included studies.

Study ID	Study period	States/cities	Study design	Method	Dengue positive cases	Study Reference
Azami et al., 2020	2006-2012	Multiple cities (Johor Bahru, Malacca City, Seremban, Kuala Lumpur, Shah Alam, Ipoh, George Town, Alor Setar, Kota Bahru, Kuala Terengganu, and Kuantan)	Retrospective	ELISA	2196	(Azami *et al.*, 2020a)
Abd-Jamil et al., 2020	2007-2010	Multiple cities of OA (Sungai Perah village, the Sungai Bumbun village, the Gurney village, the Pos Iskandar village, the Hulu Langat village, the Kuala Betis village, the Pos Betau village, and the Sungai Layau village)	Cross-sectional	ELISA	83	(Abd-Jamil *et al.*, 2020)
MG et al., 2012	2010	Multiple cities in Negeri Sembilan (Jelebu, Jempol, Kuala Pilah, Port Dickson, Rembau, Seremban, and Tampin)	Retrospective	ELISA	1121	(MG *et al.*, 2012)
Capeding et al., 2013	2010-2011	Multiple cities (Kuala Lumpur, Jinjang, Putrajaya, and Pulau Pinang)	Cohort	ELISA	2	(Capeding *et al.*, 2013)
Chang and Jute 1986	1983	Sarawak	Epidemiological	Serology	74	(Chang & Jute, 1986)
Chong et al., 2020	2017-2018	Selangor	Cross-sectional	ELISA, RT-PCR	227	(Chong *et al.*, 2020a)
Chong et al., 2021	2018	Selangor	Cross-sectional	ELISA	363	(Chong *et al.*, 2021)
Dhanoa et al., 2022	2019	Multiple cities (Southern cities)	Passive surveillance	ELISA, RT-PCR	96	(Dhanoa *et al.*, 2022)
Dhanoa et al., 2018	2015	Multiple cities (Southern cities)	Cross-sectional	ELISA	240	(Amreeta Dhanoa *et al.*, 2018)

HI: Haemagglutination Inhibition. NR: Not reported. OA: Orang Asal.

Table 1b: Major description of the included studies.

Ding et al., 2016	2015	Kuala Lumpur	Cross-sectional	HI assay	1153	(Ding *et al.*, 2016)
Fang et al., 1992	1990	Kuala Lumpur	NR	Serology	1880	(Fang *et al.*, 1992)
Gintarong et al., 2018	2016	Sabah	Cross-sectional	RT-PCR	31	(Gintarong *et al.*, 2018)
Harif et al., 2014	2009-2010	Multiple cities (Northern cities)	NR	ELISA	166	(Harif *et al.*, 2014)
Juni et al., 2015	2005-2006	Multiple cities (Multiple cities in Negeri Sembilan)	Cross-sectional	Serology	39	(Juni *et al.*, 2015)
Loong et al., 2022	2016-2018	Kuala Lumpur	Cohort	ELISA	16	(Loong *et al.*, 2022)
Ismail et al., 2014	2014	Kuala Lumpur	Cross-sectional	ELISA	128	(Ismail *et al.*, 2019)
Azami et al., 2011	2008	Multiple cities (NR)	Cohort	ELISA	916	(Azami *et al.*, 2011)
Ng et al., 2022	2018	Kuala Lumpur	Cross-sectional	ELISA	395	(Ng *et al.*, 2022)
Ngim et al., 2020	2018	Johor Bharu	Cross-sectional	ELISA, RT-PCR, RDT	167	(Ngim *et al.*, 2021b)

HI: Haemagglutination Inhibition. NR: Not reported. OA: Orang Asal.

Table 1c: Major description of included studies.

Ooi et al., 2008	2004	Multiple cities (Kuala Lumpur, Jinjang, Putrajaya, and Pulau Pinang)	Retrospective	ELISA	201	(Ooi *et al.*, 2008)
Poh et al., 2020	2017-2018	Kuala Lumpur	Cohort	Serology	38	(Poh *et al.*, 2020)
Rathakrishnan et al., 2014	2010-2011	Kuala Lumpur	Surveillance Study	ELISA, RT-PCR, HI assay	311	(Rathakrishnan *et al.*, 2014)
Rosenberger et al., 2023	2011-2016	Multiple cities (NR)	Observational	ELISA, RT-PCR	259	(Rosenberger *et al.*, 2023)
Sharifah et al., 2020	NR	Selangor	Cohort	ELISA	494	(Sharifah *et al.*, 2020)
Sulaiman et al., 2010	2010	Kelantan	Case-control	ELISA	162	(Sulaiman *et al.*, 2016)
Tan et al., 2020	2018-2019	Selangor	Cross-sectional	ELISA, RT-PCR	94	(Tan *et al.*, 2020b)
Tiong et al., 2014	2008-2009	Multiple cities (NR)	NR	ELISA	156	(Tiong *et al.*, 2015)
Tong SF et al., 2006	2003	Selangor	Cross-sectional	ELISA	24	(Tong *et al.*, 2006)
Vinomarlini et al., 2011	2005-2009	Multiple cities (NR)	NR	RT-PCR	134	(Vinomarlini *et al.*, 2011)
Chen et at., 2003	2000-2001	Multiple cities (NR)	Cross-sectional	ELISA	65	(Chen *et al.*, 2003)
Zakaria et al., 2014	2008-2012	Multiple cities (Selangor and Kelantan)	Retrospective	ELISA	281	(Zakaria *et al.*, 2014)

Pooled Prevalence

Dengue prevalence data were available in all of these 31 studies included in this meta-analysis, with the total number of tested cases being 22,921. Using the random-effect model, the pooled prevalence estimate for dengue was 50.22% (95% CI: 38.7-57.8) (**Figure 2**, **Table 2a and 2b**). High heterogeneity was observed for all the estimates (I^2>99.3%, p<0.001).

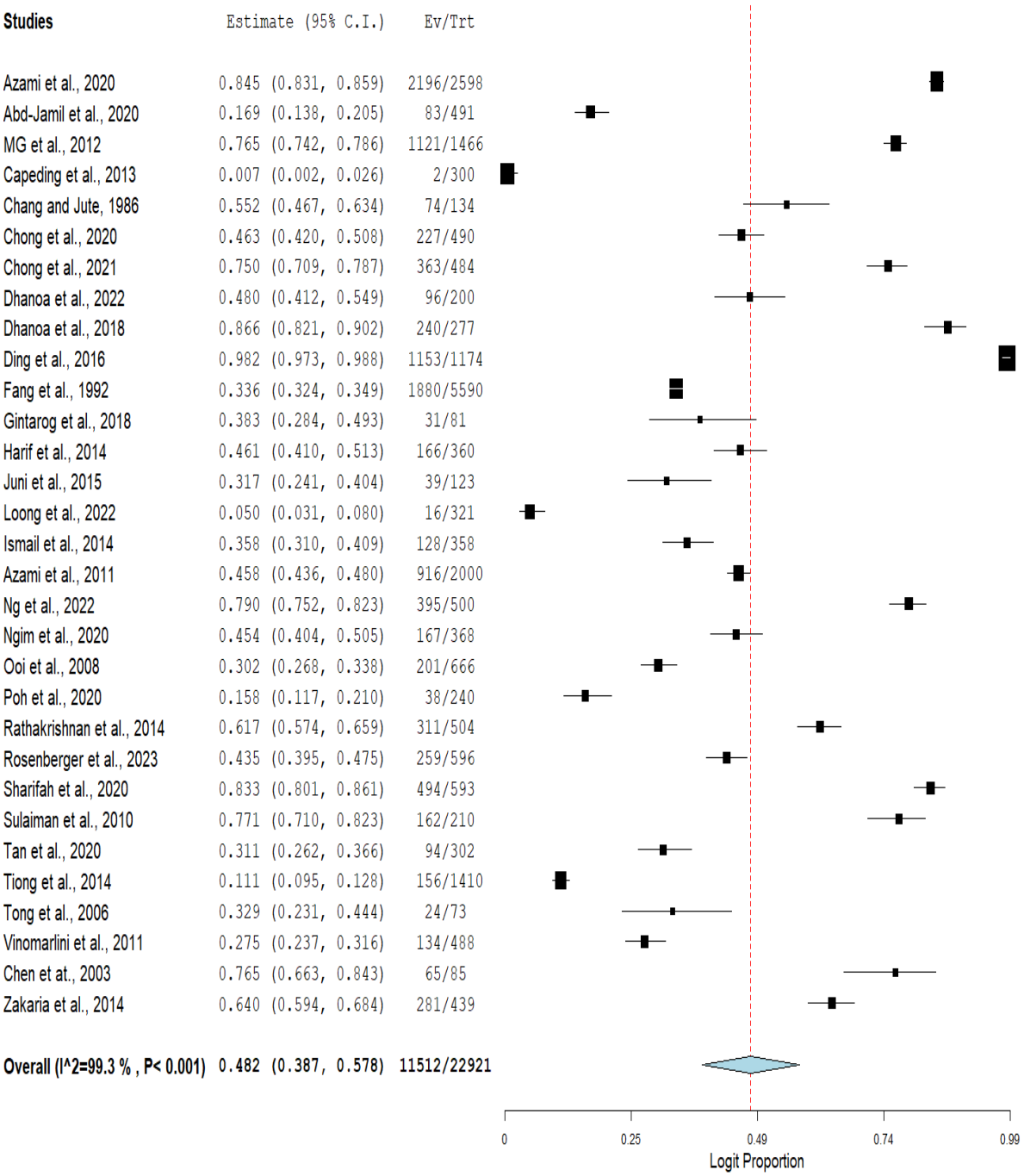

Figure 2: Forest plot of the pool prevalence of Dengue in Malaysia.

Table 2a: Demographical characteristics, overall dengue prevalence, dengue serotypes and reported symptoms among studied cases.

Study ID	Gender		Age groups (Years)	Prevalence of Dengue		Dengue serotype	Symptoms	Study Reference
	Male	Female		Total studied cases	Dengue positive cases			
Azami et al., 2020	1089	1509	35-74	2598	2196	NR	NR	(Azami *et al.*, 2020a)
Abd-Jamil et al., 2020	282	209	NS	491	83	NR	NR	(Abd-Jamil *et al.*, 2020)
MG et al., 2012	860	606	0.8-89	1466	1121	DEN 1: 79 DEN 2: 36 DEN 3: 56 DEN 4: 9	fever, headache, myalgia, arthralgia, vomiting/ nausea, rash, petechiae, bleeding tendencies, and/or neurological deficits	(MG *et al.*, 2012)
Capeding et al., 2013	156	144	2-14	300	2	NR	fever	(Capeding *et al.*, 2013)
Chang and Jute, 1986	70	64	NS	134	74	NR	NR	(Chang & Jute, 1986)
Chong et al., 2020	NR	NR	NS	490	227	DEN 1: 31 DEN 2: 29 DEN 3: 30 DEN 4: 1	NR	(Chong *et al.*, 2020a)
Chong et al., 2021	250	234	1-84	484	363	NR	NR	(Chong *et al.*, 2021)
Dhanoa et al., 2022	114	86	24-36	200	96	DEN 1: 7 DEN 2: 45 DEN 3: 37 DEN 4: 7	fever, fatigue, chills/rigors, headache, and/or anorexia	(Dhanoa *et al.*, 2022)
Dhanoa et al., 2018	116	161	NS	277	240	NR	NR	(Amreeta Dhanoa *et al.*, 2018)
Ding et al., 2016	NR	NR	NR	1174	1153	NR	acute febrile disease	(Ding *et al.*, 2016)
Fang et al., 1992	NR	NR	NR	5590	1880	NR	NR	(Fang *et al.*, 1992)
Gintarong et al., 2018	NR	NR	11-70	81	31	DEN 1: 17 DEN 2: 5 DEN 3: 9 DEN 4: 12	NR	(Gintarong *et al.*, 2018)
Harif et al., 2014	NR	NR	NR	360	166	NR	NR	(Harif *et al.*, 2014)
Juni et al., 2015	53	70	NS	123	39	NR	NR	(Juni *et al.*, 2015)
Loong et al., 2022	156	165	5-71	321	16	NR	fever	(Loong *et al.*, 2022)

NR: Not reported. NS: Not specified.

Table 2b: Demographical characteristics, overall dengue prevalence, dengue serotypes and reported symptoms among studied cases.

Ismail et al., 2014	0	358	19-41	358	128	NR	fever, headache and/or myalgia	(Ismail *et al.*, 2019)
Azami et al., 2011	400	600	35-74	2000	916	NR	NR	(Azami *et al.*, 2011)
Ng et al., 2022	260	240	NS	500	395	NR	NR	(Ng *et al.*, 2022)
Ngim et al., 2020	227	141	NS	368	167	DEN 1: 32 DEN 2: 64 DEN 3: 17 DEN 4: 1	fever, fatigue, myalgia and/or headache	(Ngim *et al.*, 2021b)
Ooi et al., 2008	433	233	12-72	666	201	NR	vomiting/nausea, abdominal pain, diarrhoea, and/or GI bleeding	(Ooi *et al.*, 2008)
Poh et al., 2020	124	114	14-90	240	38	NR	NR	(Poh *et al.*, 2020)
Rathakrishnan et al., 2014	381	123	12-81	504	311	DEN 1: 34 DEN 3: 15	vomiting/nausea, myalgia, arthralgia, diarrhoea, headache, retro-orbital pain, rashes and/or petechia	(Rathakrishnan *et al.*, 2014)
Rosenberger et al., 2023	NR	NR	NS	596	259	NR	NR	(Rosenberger *et al.*, 2023)
Sharifah et al., 2020	NR	NR	NR	593	494	NR	NR	(Sharifah *et al.*, 2020)
Sulaiman et al., 2010	251	214	NS	210	162	NR	fever, myalgia, headache, vomiting and/or arthralgia	(Sulaiman *et al.*, 2016)
Tan et al., 2020	NR	NR	18-76	302	94	NR	NR	(Tan *et al.*, 2020b)
Tiong et al., 2014	NR	NR	7-18	1410	156	NR	NR	(Tiong *et al.*, 2015)
Tong et al., 2006	49	24	NR	73	24	NR	NR	(Tong *et al.*, 2006)
Vinomarlini et al., 2011	NR	NR	NS	488	134	DEN 1: 34 DEN 2: 32 DEN 3: 46 DEN 4: 12	NR	(Vinomarlini *et al.*, 2011)
Chen et at., 2003	46	39	5-71	85	65	NR	NR	(Chen *et al.*, 2003)
Zakaria et al., 2014	168	113	NS	439	281	NR	NR	(Zakaria *et al.*, 2014)

NR: Not reported. NS: Not specified

Prevalence of dengue in different subgroups
Dengue prevalence was further evaluated based on variables such as the study period, study region, method of diagnosis, and study design. This provided a robust overview of the prevalence rate and probed the heterogeneity observed. **Table 3;** summarises the prevalence of dengue according to the analysed variables.

Table 3: Prevalence of dengue infection in Malaysia according to the different subgroups.

Subgroup	Number of studies	Prevalence (%)	95% CI	Heterogeneity test	
				I^2 (%)	*p-value*
Year					
2011-2020	15	49.7	33.7 – 65.8	99.47	<0.001
2001-2010	13	44.4	30.8 – 58.8	98.79	<0.001
1981-1990	2	43.7	24.6 – 65.0	96.08	<0.001
Overall	30	46.8	37.4 – 56.4	99.29	<0.001
Region					
Multiple cities	15	42.9	28.8 – 58.2	99.45	<0.001
Sarawak	1	55.2	46.7 – 63.4	NA	NA
Selangor	5	55.4	33.1 – 75.8	98.72	<0.001
Kuala Lumpur	7	49.8	27.8 – 71.9	99.39	<0.001
Sabah	1	38.3	28.4 – 49.3	NA	NA
Johor Bharu	1	45.4	40.4 – 50.5	NA	NA
Kelantan	1	77.1	71.0 – 82.3	NA	NA
Overall	31	48.2	38.7 – 57.8	99.3	<0.001
Method					
ELISA	18	48.4	34.3 – 62.8	99.42	<0.001
Serology	4	32.6	21.5 – 46.1	94.81	<0.001
Multiple assays	7	60.1	43.4 – 74.7	98.55	<0.001
RT-PCR	2	31.7	22.4 – 42.8	74.31	0.048
Overall	31	48.2	38.7 – 57.8	99.3	<0.001
Study design					
Retrospective	4	65.8	40.5 – 84.5	99.55	<0.001
Cross-sectional	12	54.7	38.0 – 70.4	98.76	<0.001
Cohort	5	18.2	0.5 – 45.7	99.19	<0.001
Epidemiological	1	55.2	46.7 – 63.4	NA	NA
Passive surveillance	1	48.0	41.2 – 54.9	NA	NA
Pilot	1	86.6	82.1 – 90.2	NA	NA
Descriptive	1	61.7	57.4 – 65.9	NA	NA
Observational	1	43.5	39.5 – 47.5	NA	NA
Case control	1	77.1	71.0 – 82.3	NA	NA
Overall	27	51.6	41.5 – 61.6	99.05	<0.001

The forest plot (**Figure 3**) clearly illustrates the temporal trend over time, showing an increasing prevalence rate observed over the 3 decades. The period of 1981–1990 subgroup exhibited the lowest prevalence rate (43.7%, 95% CI: 24.6–65.6). The majority of the studies (n=15) were conducted during the period of 2001-2010, with the pooled prevalence (44.4%, 95% CI: 30.8-58.8) showing an increasing in trend of dengue prevalence. Finally, the period of 2011–2020 showed the highest prevalence rate (49.7%, 95% CI: 33.7–65.8) with significant heterogeneity (I^2 = 99.47%, p < 0.001).

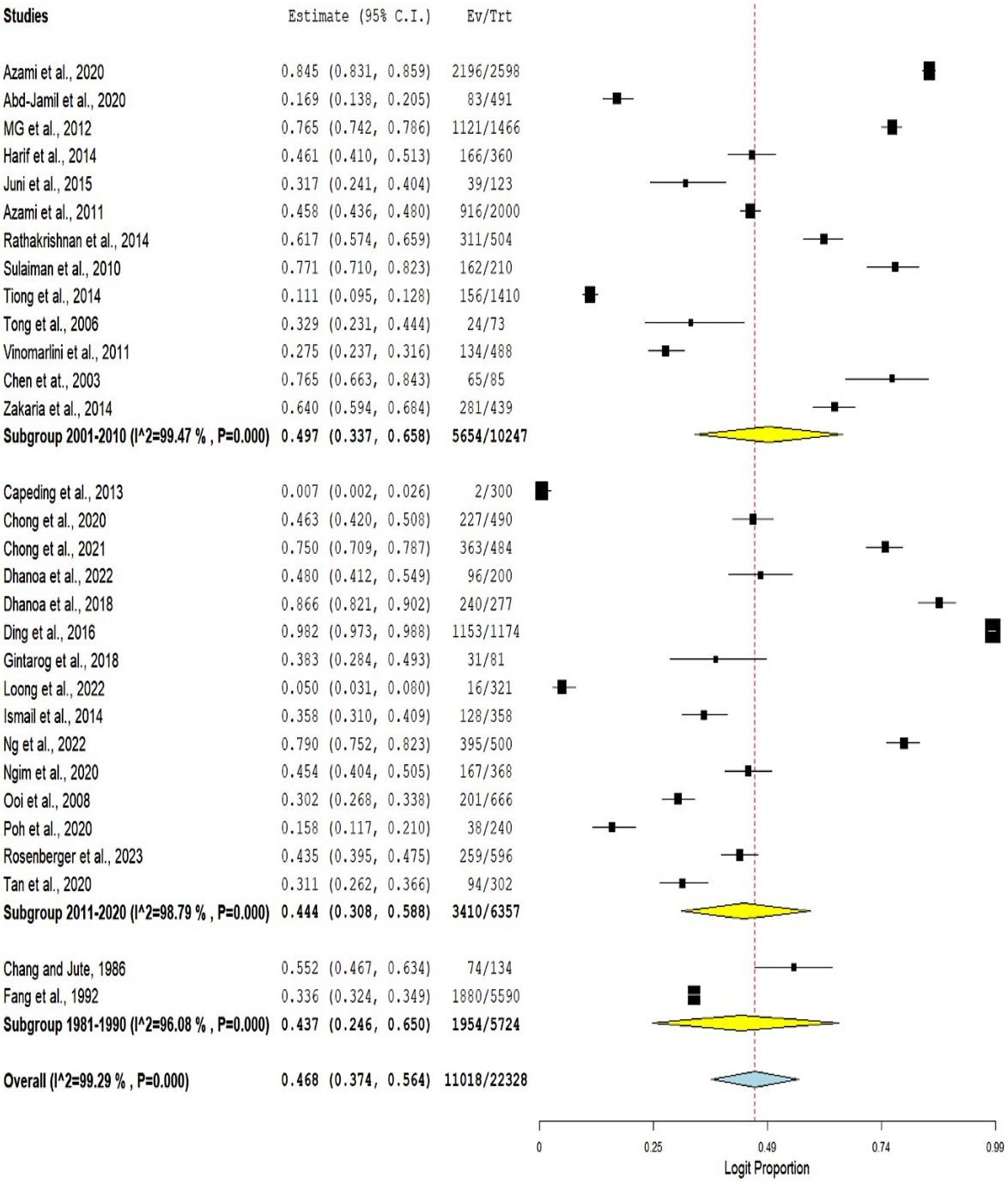

Figure 3: Forest plot of the pool prevalence of Dengue in Malaysia (Study period).

In the forest plot for the study region (**Figure 4**), the prevalence rate varied. The studies contributing to subgroup analysis were from multiple states, with Kuala Lumpur being the most represented (n=7). The highest prevalence (77.7%, CI: 71.0-82.3) was observed in Kelantan, followed by Selangor (55.4%, 98.72% CI: 33.1-75.8) and Sarawak (55.2%, CI: 46.7-63.4). The lowest prevalence rate was in Sabah (38.3%, 95% CI: 28.4-49.3).

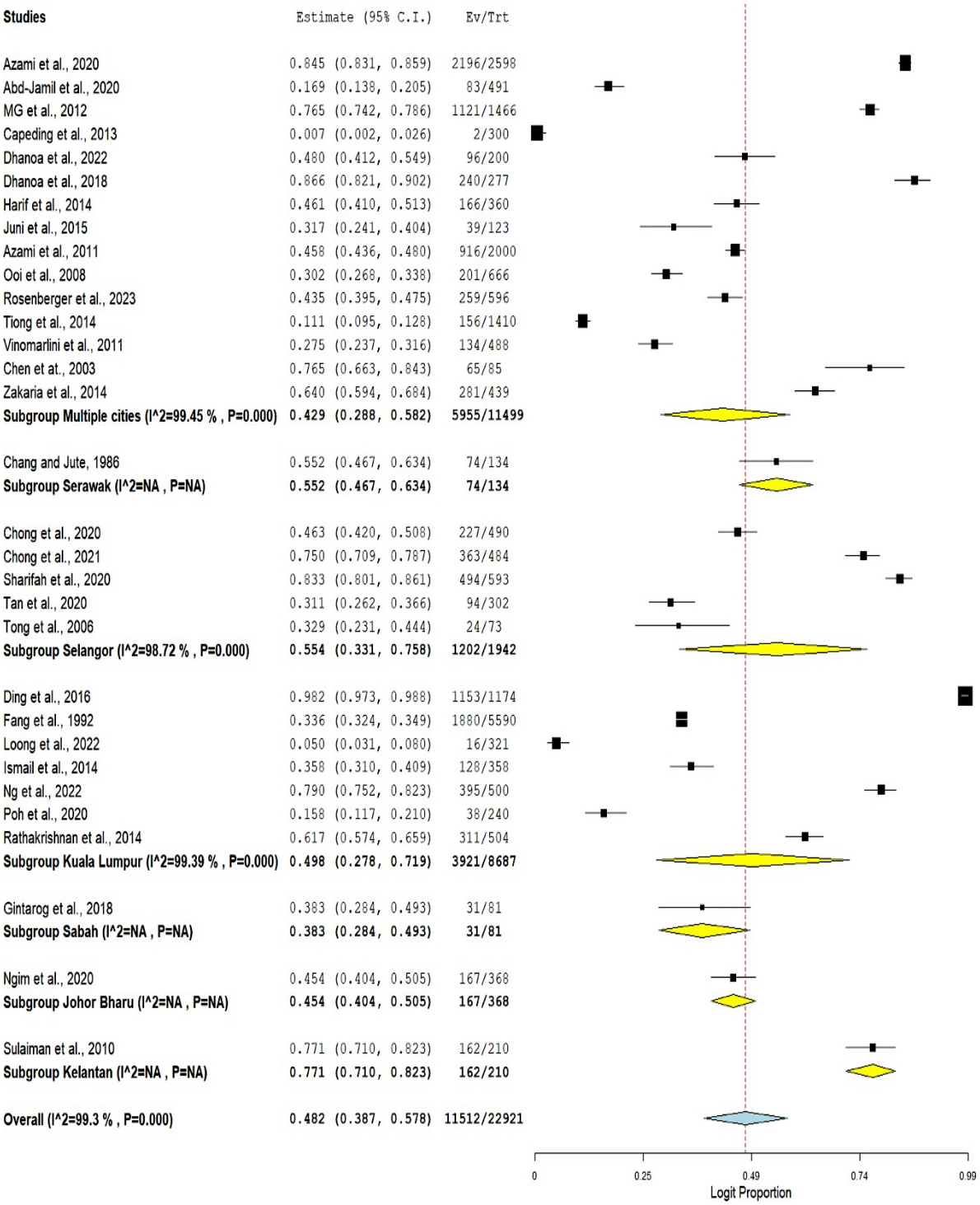

Figure 4: Forest plot of the pool prevalence of Dengue in Malaysia (Study region).

The methods of diagnosis significantly contributed to the variance of the reported prevalence. Based on the method of diagnosis (**Figure 5**), ELISA was the most commonly used (n=18), with a pooled prevalence rate of 48.4% (95% CI: 34.3-62.8) in this group.

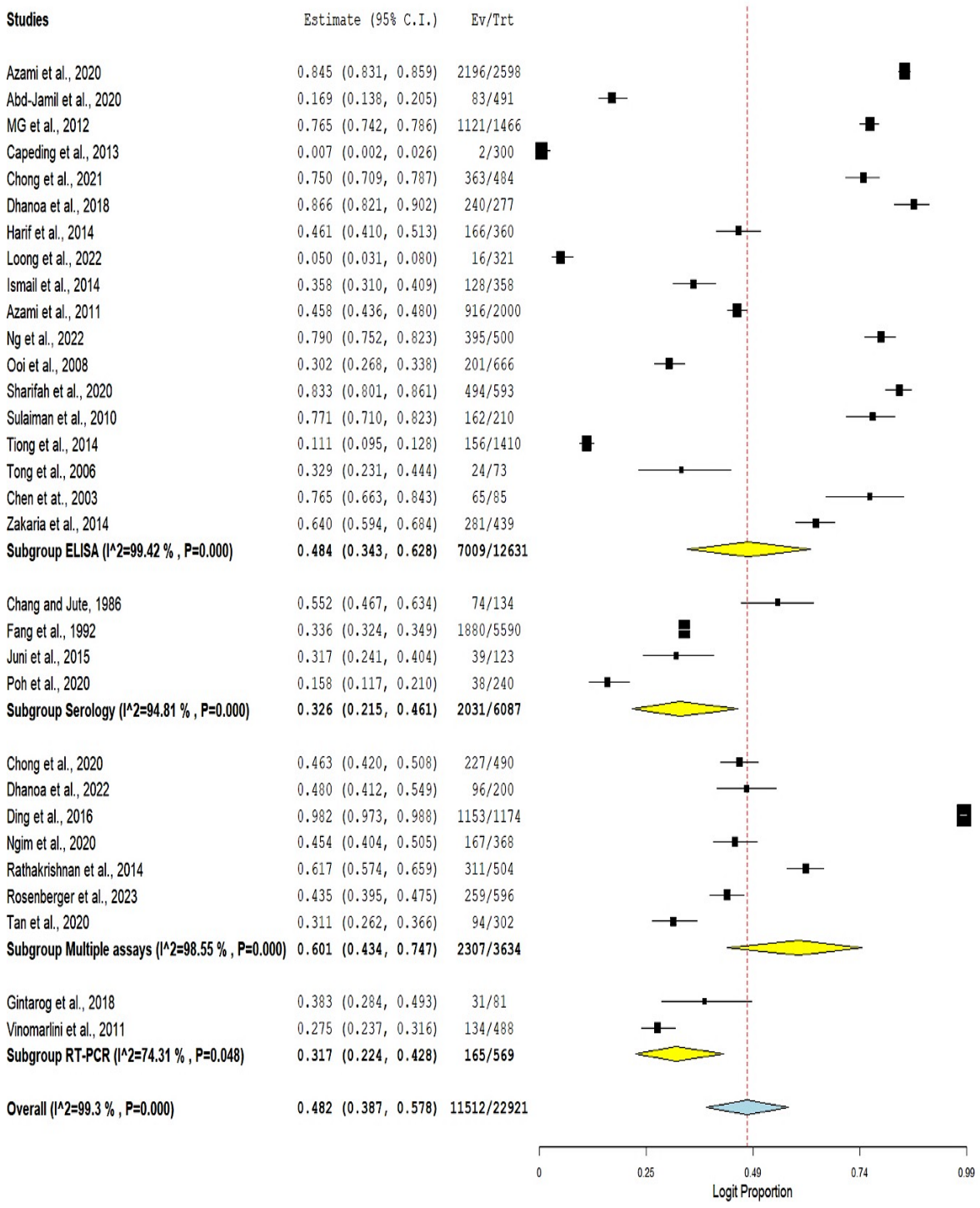

Figure 5: Forest plot of the pool prevalence of Dengue in Malaysia (Method of diagnosis).

For study design (**Figure 6**), Cross-sectional studies were the most predominant (n=12). Retrospective studies showed the highest prevalence rate at 65.8% (95% CI: 40.5-84.5). While other parameters indicated high heterogeneity, moderate heterogeneity (I^2=74.31%) was observed in studies using RT-PCR as a diagnostic method, and no heterogeneity (I^2=0%) was observed for those conducted in Sarawak, Sabah, Johor Bharu, and Kelantan.

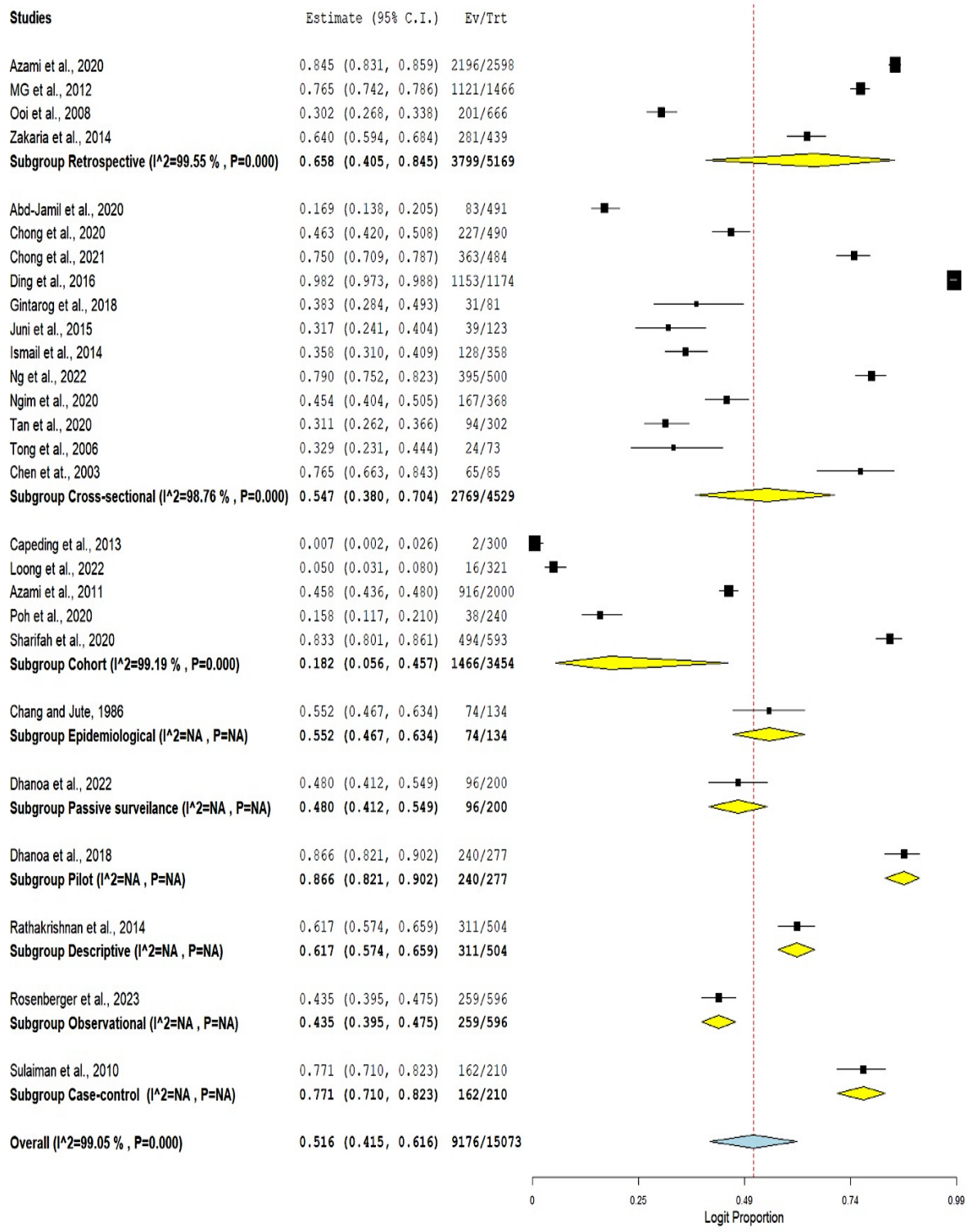

Figure 6: Forest plot of the pool prevalence of Dengue in Malaysia (study design).

Study quality and publication bias assessment

Thirty-one studies that were included were assessed for methodological quality using the JBI tools checklist, which illustrated that the included studies were good quality prevalence studies (**Figure 7**). A funnel plot was generated to assess for possible publication bias. The plot was asymmetrical (**Figure 8**), thus revealing the possibility of publication bias. Then, the asymmetry funnel plot was further probed using Egger's regression test, which revealed a

non-significant *p-value* for studies contributing to the prevalence of dengue (p=0.0756).

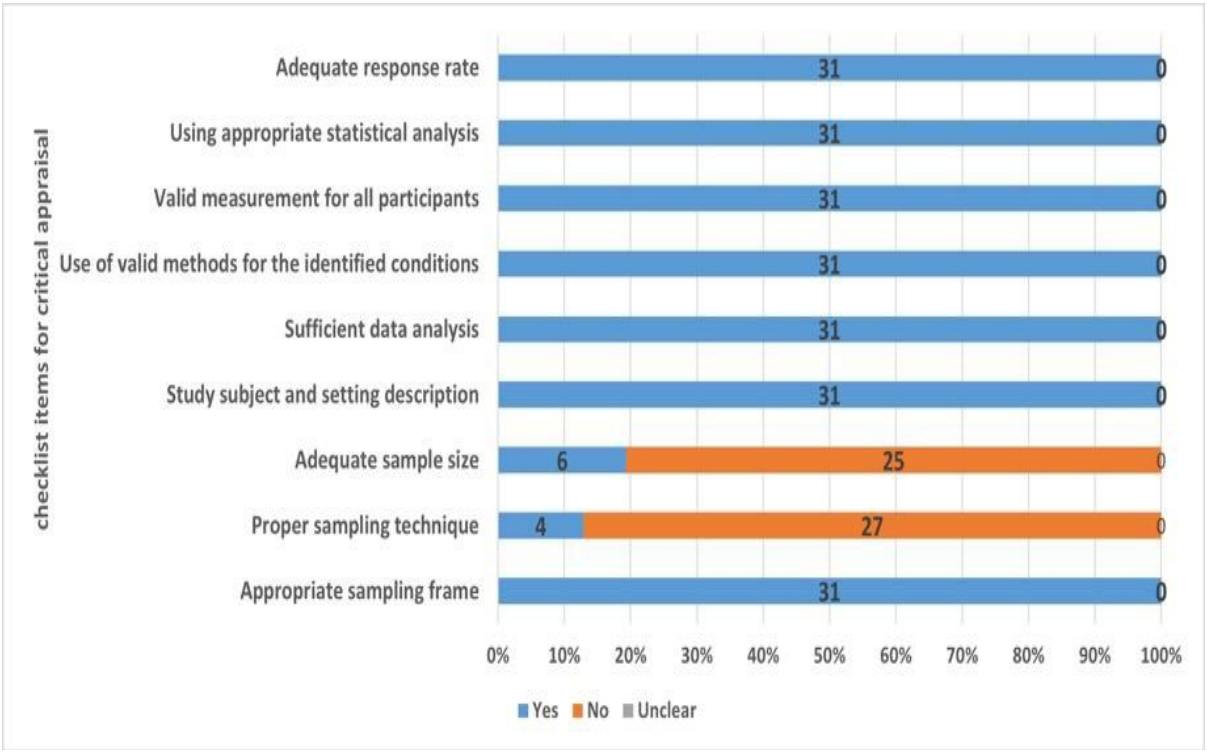

Figure 7: Quality assessment of included studies using the JBI tool.

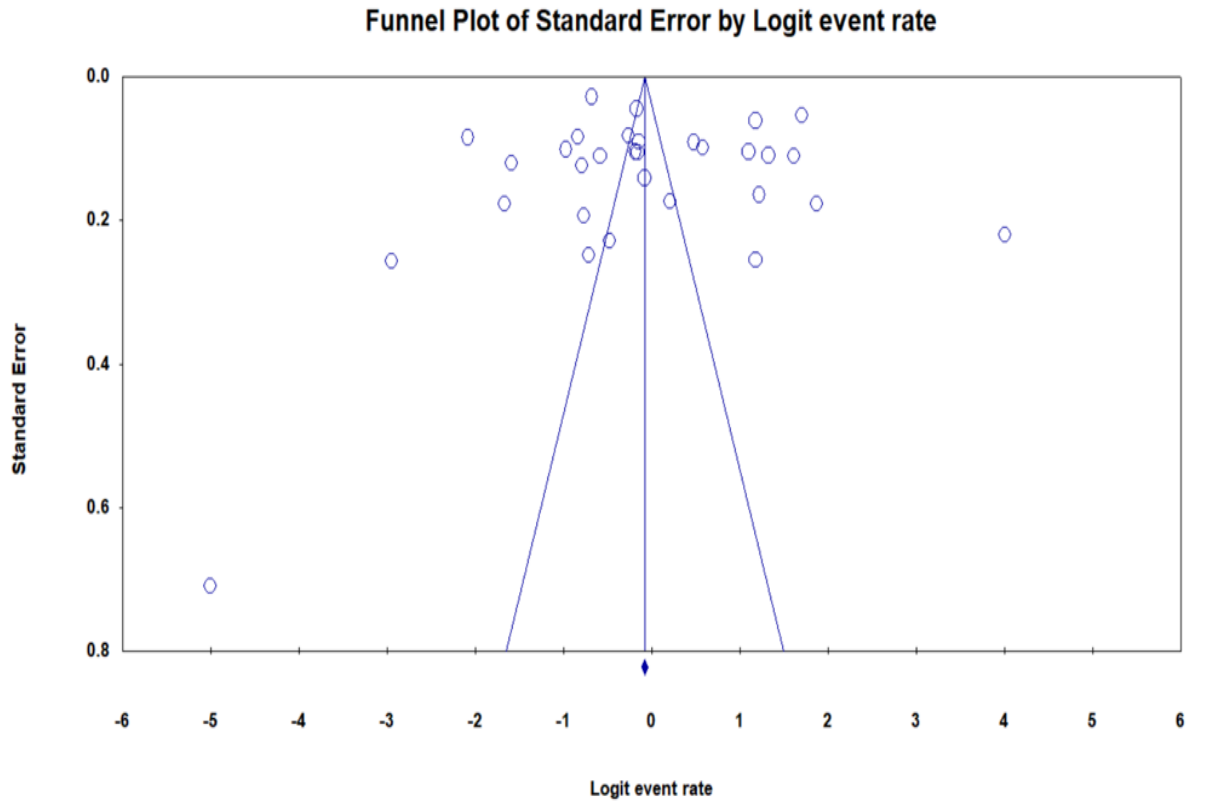

Figure 8: Funnel plot showing there is no significant publication bias for dengue [Egger's test, p=0.3943] estimates.

DISCUSSION

In this study, we presented the first systematic review and meta-analysis of dengue prevalence in Malaysia. We reported 22,921 dengue cases from 1981 until 2020 in Malaysia. There are several risk factors that contributed to the rise of dengue prevalence in Malaysia.
From 1980 to 2022, the forest plot revealed a temporal trend over time showing a substantial increase in dengue prevalence from 2011 to 2020, with the highest prevalence at 49.7% (95% CI: 33.7% – 65.8%) and significant heterogeneity I^2 = 99.47%, p < 0.001. The increased prevalence during 2011-2020 compared to earlier decades aligns with 15 studies conducted during this period, where all studies were conducted in highly urbanised and densely populated regions such as Kuala Lumpur, Selangor, Johor Bharu, and Sandakan, Sabah. The growing, uncontrolled urbanisation with densely populated regions associated with high mosquito profusion contributed to the higher transmission of dengue, as highlighted in the studies by; (Azami *et al.*, 2020b; MG *et al.*, 2012) and the forest plot further supports this temporal increase of dengue prevalence compared to the earlier decades.

In addition to that, the forest plot subgroup analysis by region, Selangor and Kuala Lumpur, showed a high prevalence rate of 55.4% (CI: 33.1 – 75.8) and 49.8% (CI:27.8-71.9) with significant heterogeneity (I^2): 98.72% and 99.39% (p < 0.001). The urbanised districts in this region, Selangor, such as Petaling Jaya, Shah Alam, and Subang Jaya, increase human-mosquito contact, facilitating transmission of dengue, as highlighted in the studies by (Sharifah *et al.*, 2020; Tong *et al.*, 2006). While the other two studies in this region by (Chong *et al.*, 2021; Tong *et al.*, 2006) mentioned that stagnant water from construction sites and improper waste disposal provide breeding grounds for *Aedes aegypti* and *Aedes albopictus* mosquitoes. These factors combine with insufficient preventive measures due to the rapidly growing urban environment in Selangor and infrastructure challenges, making it difficult to effectively control the dengue epidemic, as highlighted in the studies by (Chong *et al.*, 2021; Tong *et al.*, 2006).

Additionally, the forest plot subgroup analysis study design revealed four retrospective studies with a high prevalence rate; 65.8 (CI: 40.5 – 84.5) with significant heterogeneity (I^2): 99.55% (p < 0.001). These studies again mentioned that urbanised regions with high population density and infrastructure favour the breeding of *Aedes* mosquitoes (Zakaria *et al.*, 2014) (MG *et al.*, 2012). Besides that, a surveillance study done by (Rathakrishnan *et al.*, 2014) shows a high prevalence of dengue from the forest plot study design conducted in the Klang Valley, which is another highly urbanised and densely populated district in Selangor, where dengue is endemic. Again, as mentioned earlier, all these studies found that urban areas, particularly those with high population density, have a greater potential for the transmission of *Aedes* mosquitoes.

Besides urbanisation and population densities, dengue cases are strongly linked with the tropical climate in Malaysia. Several studies found that Malaysia's tropical climate creates ideal conditions for the breeding of *Aedes* mosquitoes and causes non-ending transmission of dengue throughout the year. For the years 2011-2020, with the highest dengue prevalence estimate, the study by (Zakaria *et al.*, 2014) mentioned that climate conditions such as frequent rainfall create favourable conditions for *Aedes* mosquito breeding, further escalating dengue outbreaks during that period, which show the highest prevalence rate and significant heterogeneity.

In addition to that, the forest plot subgroup analysis by regions shows a wide variation of dengue in Malaysia, such as in Kelantan, which shows the highest prevalence rate among all the other regions (77.7%, 95% CI: 71.0-82.3). This case-control study showed the second-highest prevalence rate among the other study designs. A study, (Sulaiman *et al.*, 2016) highlighted that the tropical climate in Kelantan, with frequent rainfall during the monsoon season (November to February), creates an environment that favours mosquito breeding. Moreover, rubber plantations in the area were identified as significant risk zones because rubber taps and other containers could accumulate rainwater, thus further facilitating mosquito breeding. This revealed that environmental factors, poor waste disposal (particularly the presence of discarded containers that serve as mosquito breeding grounds), behavioural risks, and insufficient use of protective measures all contributed to the highest prevalence of dengue in Kelantan by the forest plot subgroup analysis by region.

Furthermore, the forest plot subgroup analysis from 2011-2020 illustrates that rising dengue cases have a strong link between population density and migration patterns. These factors could influence disease transmission, resulting in a higher number of cases detected in more recent years, as highlighted in the studies by (Cao *et al.*, 2017; Norli & Azmi, 2008; Seng *et*

al., 2005). Besides that, another study by (Juni *et al.*, 2015) mentioned increased migration or mobility in and out of epidemic locality is an important explanation for the recent increased in dengue cases during this period. Furthermore, the study of the outbreak in Sarawak by (Chang & Jute, 1986) which show a high prevalence rate (55.2%) reported that the epidemic spread rapidly through migration, particularly during festive periods when people returned to rural areas from urban areas.

Advances in diagnostic method technologies have improved the sensitivity and specificity of dengue detection throughout the year. The forest plot also examined the role of diagnostic methods in the dengue prevalence rate, and we found that ELISA has a high prevalence rate; 48.4% (95% CI: 34.3 – 62.8), with significant heterogeneity (I^2 = 99.42%, p < 0.001). Multiple tests (ELISA + RT PCR or ELISA + HI) with the highest prevalence rate of 60.1% (95% CI: 43.4 – 74.7), again with significant heterogeneity (I^2 = 98.55%, p < 0.001). This is due to the majority of the dengue studies using ELISA for dengue detection due to its high sensitivity and broad detection abilities, which can identify both recent and past infections, contributing to a relatively high prevalence rate in dengue studies, as mentioned by (Mohamed Ismail *et al.*, 2014a), (Dhanoa *et al.*, 2021) and (Ooi *et al.*, 2008).

Besides that, ELISA is commonly used in both large-scale epidemiological studies and smaller clinical research projects, making it more likely to capture a wide range of cases. In addition to that, ELISA can detect antibodies even in individuals with asymptomatic or mild dengue infections, unlike more specific methods such as RT-PCR that focus on active cases, as found in the study by (Dhanoa *et al.*, 2021). Related to that, the forest plot subgroup analysis by study design, the cross-sectional study by (A. Dhanoa *et al.*, 2018) reported the highest prevalence rate at 86.6%. This study used ELISA for confirmation of dengue and thus found out that previous exposure to the dengue virus causes a higher prevalence rate of dengue, which is explained by the fact that the area where the study was conducted is actually a dengue hotspot, with high seroprevalence despite few clinically reported dengue cases in the Segamat district in Selangor.

Another study contributed to the highest prevalence rate during the study period of 2011-2020; the study by (Tan *et al.*, 2020a); reported that among residents living in a dengue hotspot, the overall dengue seroprevalence was found to be more than 70% of the population showing IgG positivity, indicating previous exposure to the virus. This concluded that many participants had been exposed to the virus even without symptoms, and some had subclinical infections contributing to the high seroprevalence but low reported incidence. However, one limitation of ELISA is the potential for cross-reactivity with other *flaviviruses*, such as *Zika* or *West Nile virus*, which could exaggerate dengue prevalence in areas where multiple *flaviviruses* are endemic, as highlighted in the studies by (Azami *et al.*, 2020b) and (Capeding *et al.*, 2013).

Another significant factor is the co-circulation of multiple dengue serotypes that contributed to the rise of dengue prevalence during the recent decade. The forest plot subgroup analysis by year, the period of 2011-2020, revealed the cocirculation of multiple dengue serotypes, with DEN-1 being the most prevalent serotype, followed by DEN-2, highlighted in the studies by (MG *et al.*, 2012) (Chong *et al.*, 2020b; Gintarong *et al.*, 2018) and (Rathakrishnan *et al.*, 2014). While the other study by (Vinomarlini *et al.*, 2011) highlights the different dengue virus serotypes circulating in the country from 2005 to 2009 from serum and blood samples collected from hospitalised patients suspected of dengue infection on the East Coast of Malaysia. The study showed that all four dengue virus serotypes were circulating, with DENV-1 and DENV-3 being predominant by 2005-2006, while DENV-3 was the most common serotype by 2008-2009. Related to that, Selangor had the second-highest prevalence rate from the forest plot subgroup analysis by region, according to a study by (Chong *et al.*, 2021) mentioned that dengue transmission in Selangor is complicated by the presence of cocirculation of multiple dengue virus serotypes (DENV-1 to DENV-4), leading to possible reinfection with multiple dengue virus serotypes and leading to the high prevalence observed in this region. Moreover, the forest plot subgroup analysis by study design, the surveillance study done by (Rathakrishnan *et al.*, 2014) which shows high prevalence rate 61.7% (CI: 57.4-65.9); was conducted in the Klang Valley district in Selangor, which is described as a hyperendemic region where regular outbreaks of dengue occur due to the cocirculation of multiple dengue serotypes, leading to a continuous transmission cycle and thus increasing the chances of dengue infection and reinfection in the population. These studies indicated that the cocirculation of multiple dengue serotypes contributed to the ongoing transmission and high dengue

prevalence in the regions and during the mentioned period.

The heterogeneity of the forest plot is contributed by the variety of dengue clinical manifestations, where across the studies reported, fever is the most prevalent sign and is often associated with musculoskeletal symptoms (arthralgia and myalgia), headache, retroorbital pain, and rashes (Dhanoa *et al.*, 2022; MG *et al.*, 2012) (Mohamed Ismail *et al.*, 2014b; Ngim *et al.*, 2021a). This highlights the importance of suspecting dengue in all patients who present with acute febrile disease, especially in the dengue outbreak region. In addition, gastrointestinal manifestations like persistent vomiting and abdominal pain usually progress to severe dengue in the dengue endemic region, as highlighted in the studies by (Rathakrishnan *et al.*, 2014), which show a high prevalence, 61.7% and (Ooi *et al.*, 2008). Community-based studies show a lower prevalence rate in the forest plot, as tests were done on asymptomatic or mildly symptomatic participants. While the regions with a high prevalence of severe dengue and a majority of hospital-based studies, like Selangor and Kuala Lumpur, influenced the higher prevalence estimate in the forest plot.

Furthermore, it is important to identify the high-risk group in order to implement targeted interventions for public health intervention. The forest plot demonstrated the impact of dengue on certain occupations and demographic groups. In Kelantan, a region with the highest prevalence rate, a study by (Sulaiman *et al.*, 2016) shows that many of the affected individuals were students and rubber tappers. These groups spent considerable time outdoors, particularly during peak mosquito activity times (morning and evening), thus increasing their exposure to mosquito bites and contributing to higher transmission rates. The second group is the immunocompromised individuals. This is supported by the forest plot subgroup study design with a significant prevalence (61.7%) by (Rathakrishnan *et al.*, 2014); highlighted that people with weakened immune systems are more susceptible to severe dengue symptoms, especially if they are exposed to multiple dengue virus serotypes; (Zakaria *et al.*, 2014). The third group is the older population. The majority of the studies found that the seroprevalence of dengue increased with age. Related to that, the forest plot subgroup study design, a Cross-sectional study with the highest dengue prevalence (86.6%) by (A. Dhanoa *et al.*, 2018) and (Chen *et al.*, 2003) found that seropositivity increased with age, indicating that the older participants are more likely to have previous exposure to the virus, and reinfection with a different serotype will put this vulnerable group at high risk of developing severe dengue. Thus, it is important to identify high-risk groups in order to implement targeted public health interventions and to be extra vigilant when this group presents to the emergency department with acute febrile disease. Clinicians, particularly emergency physicians, play a crucial role in the early recognition, diagnosis, and management of dengue, especially in acute settings where timely intervention can prevent severe disease outcomes. Enhanced clinical vigilance and rapid diagnostic capabilities in emergency departments are vital to reducing complications and mortality.

LIMITATION OF THE STUDY

There is insufficient regional data, such as in Kelantan and Sarawak, which shows insufficient numbers of studies, causing an inability to proceed with the heterogeneity tests. Furthermore, the geographic distribution of studies may not be representative of all regions in Malaysia, particularly in the rural and less populated areas, as most of the studies were conducted in the urbanised and highly populated areas. Besides that, cross-reactivity in serological tests like ELISA could exaggerate dengue prevalence in areas where multiple *flaviviruses* are endemic.

CONCLUSION

The systematic review and meta-analysis provides critical insights into dengue prevalence in Malaysia from 1981 to 2020. The findings demonstrate a significant increase in prevalence, with the highest recorded between 2011 to 2020 at 49.7%. The rising trend is influenced by multiple factors, including environmental risk factors, socioeconomic factors, behavioural and preventive measures, dengue transmission dynamics, and diagnostic advances. Despite decades of research and surveillance, dengue remains endemic in Malaysia as of 2024, continuing to burden the healthcare system while often being overlooked in national health priorities. This highlights the urgent need for continuous and integrated public health strategies by targeting high-risk groups such as outdoor workers, students, immunocompromised individuals, and the elderly in future public health interventions. The results also highlight the need for effective dengue control strategies in urban areas and improved public health measures to prevent recurrent outbreaks. Further

research, particularly in rural and less populated areas, is needed to fully understand the scope of the dengue burden across the country. As a diagnostic method, RT-PCR is recommended in regions with high dengue prevalence where there is a risk of cross-reactivity when using the ELISA test with other *flaviviruses* that are endemic.

Conflict of interest

The authors declare that they have no conflicts of interest

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