RESEARCH PAPER

Specific Severity Patterns In Dengue Virus Infection: A Systematic Review And Meta-Analysis

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ABSTRACT

Dengue is caused by four distinct serotypes of the dengue virus 1-4 (DENV-1-4), which are the Flaviviridae family and genus Flavivirus members. Finding severity indicators is challenging due to the wide range of reactions to DENV infection among individuals. Understanding how each serotype correlates with disease severity is critical for effective surveillance and targeted intervention strategies. The main aim of the study was to evaluate the association between DENV serotypes and severity of dengue illness using a systematic review and meta-analysis of global studies from 2010 to 2022. We systematically searched PubMed, Google Scholar, Science Direct, and Springer for studies reporting laboratory-confirmed dengue infections stratified by serotype and clinical severity. Included studies were assessed using the Newcastle-Ottawa Scale. Meta-analysis was conducted using a random-effects model, and heterogeneity was assessed using I^2 statistics. DENV-2 showed the highest proportion of association with severe dengue cases (64.52%) compared to DENV-1, DENV-3, and DENV-4. Subgroup estimates were analyzed, highlighting that DENV-2 has a higher association with severe cases of dengue fever compared to other serotypes. The dengue burden is rising worldwide, even though its prevalence varies remarkably. These findings suggest that DENV-2 may pose a higher risk for severe dengue, which can guide targeted public health interventions.

Keywords: Dengue Virus; Meta-analysis; Flavivirus serotypes, DENV-2

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INTRODUCTION

The viral infection of dengue is brought on by the dengue virus (DENV), which is carried by mosquitoes that bite humans. Around half of the world's population is now at risk from dengue, estimated to cause 100–400 million illnesses yearly. Dengue is a tropical and subtropical disease that affects urban and semi-urban settings [1]. Dengue is caused by one of the four distinct serotypes of the dengue virus (DENV-1-4), which are the Flaviviridae family and genus Flavivirus members. The most common Aedes mosquito species that transmit dengue to humans are *Aedes aegypti* and *Aedes albopictus* [2].

Dengue fever (DF), an acute but moderate illness, is one of the symptoms of DENV infection. On the other hand, severe dengue is a term used to describe dengue's aftereffects. Potentially lethal infections such as dengue shock syndrome (DSS) or dengue hemorrhagic fever (DHF) are among the severe dengue sequelae. DF is the most typical dengue symptom. Typical clinical manifestations include headaches, rash, joint and muscle discomfort, nausea, and vomiting. Most DF infections are self-limited but occasionally DF can progress to severe dengue which can be fatal. Over 128 nations have reported DENV infections and dengue occurrences worldwide, which have substantially increased in recent decades [3]. *Aedes aegypti* population potential, along with the survival of adult and immature stages, is an important factor in the transmission of the dengue virus. A high rate of morbidity and mortality is experienced during DF/DHF outbreaks, and the public may get alarmed and expect the government to take immediate action [4].

The mosquito species that carry *Aedes aegypti* and *Aedes albopictus* bite susceptible people to transmit the four virus serotypes that cause dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Lifelong immunity against one serotype is provided by recovery from infection

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**Author for Correspondence: Telugu Seetharam Deepak* with that serotype, but only temporary and incomplete protection is offered against recurrent infection with the other three. It was first identified in the 1950s and it is now a significant contributor to child mortality in various Asian and South American nations. Between 1950 and 1959, there were 908 DF/DHF cases on average reported to WHO annually. Between 1990 and 1999, 514,139 cases were reported. The actual number is thought to be closer to 50 million instances per year with 24,000 fatalities. According to WHO approximately 5% of the estimated 500,000 cases of DHF/DSS that require hospitalization each year pass away [5].

The four flavivirus serotypes are DENV-1, DENV-2, DENV-3, and DENV-4*Aedes aegypti* and *Aedes albopictus* mosquitoes, which are the carriers of the virus, disseminate it from human to human. Given the variability in severity among different DENV serotypes, understanding their specific roles is critical for improving treatment strategies and developing effective vaccines. It is currently uncertain what exact pathophysiology causes severe dengue infections, such as dengue hemorrhagic fever and dengue shock syndrome. Furthermore, except for precautionary fluid therapy and supportive measures, there is no treatment for dengue. Over the past 50 years, clinical studies have evaluated various therapy options with varying degrees of success. The "critical period" or risk window for dengue during which the patient may suddenly deteriorate is only between 48 and 72 hours long. A fatal outcome is unlikely if the patient is adequately handled throughout this stage. Still, this necessitates constant observation and flexible management evaluation [6].

Finding severity indicators is challenging due to the wide range in reactions to DENV infection among individuals. Analyzing changes in metabolite levels shows that DENV affects lipid metabolism in host cells throughout its life cycle. To enable virus assembly, replication, and immune response evasion, DENV generates replication complexes (RCs) in the endoplasmic reticulum. These RCs require fatty acids, cholesterol, and phospholipids. The formation of triacylglycerol and the absorption of cholesterol are enhanced by the sequestration of enzymes such as fatty acid synthase (FASN) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) by viral proteins, especially NS3. Furthermore, DENV regulates host lipid droplet disintegration via the viral protein NS4A, which takes advantage of AUP1's acyltransferase activity on the lipid droplet. Since receptors like the low-density lipoprotein receptor (LDLR) are known to influence lipid metabolism during DENV infection, understanding these changes could result in the development of new biomarkers for determining the severity of the illness. [7]. This study aimed to determine the association between individual DENV serotypes (DENV-1 to DENV-4) and disease severity, as categorized by standard clinical classifications. This analysis seeks to inform public health strategies based on serotype-specific risks.

MATERIALS AND METHODS

This systematic review and meta-analysis were carried out in accordance with the Cochrane Handbook's recommendations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was adhered throughout the whole search, selection, extraction of pertinent data, analysis, and result interpretation[7].

2.1. Search Strategies

A comprehensive search was conducted on human studies from the beginning, using Google Scholar, PubMed, Springer, and Science Direct. A total of 1463 publications published between January 2010 and December 2022 were found. A search was conducted using the terms Dengue, Severe Dengue, Dengue virus, severity of illness index, Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS**).**

The total number of dengue cases recorded from 2010 to 2022 is shown in **Figure 1**. The number of articles determines the height of the bars. The number of articles collected in 2010 is 5.3% (78), the least amount is 4% (59) in 2011, followed by 4.3% (63) in 2012, 6.6% (97) in 2013, 6.5% (96) in 2014, 7.1% (104) in 2015, 10.1% (148) in 2016, 8.6% (127) in 2017, 8.7% (128) in 2018 and 9.6% (141) in 2019, the highest amount is 10.4% (153) in 2020, followed by 10.3% (151) in 2021, and 8% (118) in 2022.

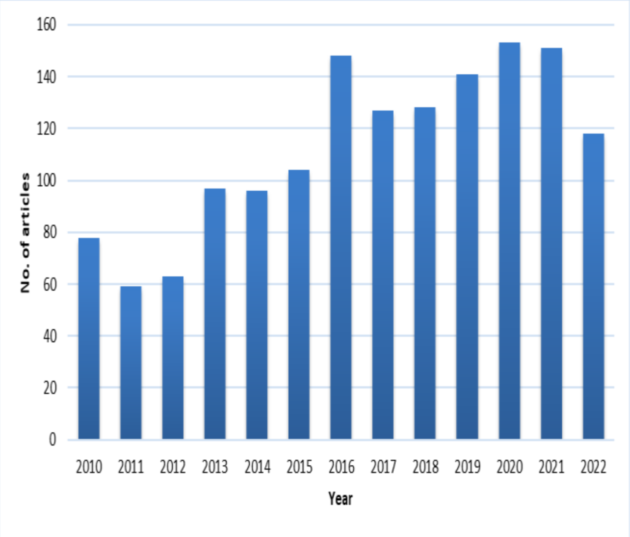


Figure 1. Distribution of number of articles collected per year from 2010 to 2022.

The percentage of each sector represents the total number of articles gathered from all search engines. The total number of publications retrieved from Springer is 65% which is maximum, followed by PubMed (16%), Google Scholar (12%), and Science Direct (7%) is the minimum, which are illustrated through pie chart (**Figure 2**).

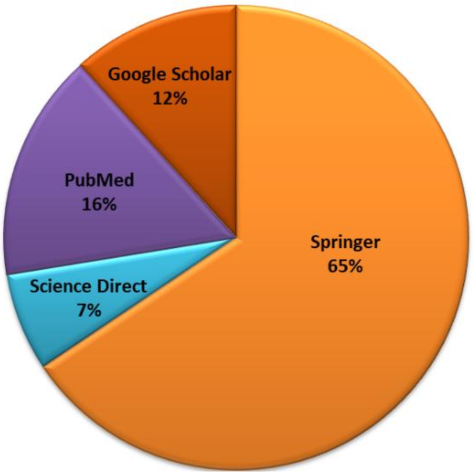


Figure 2. Percentage of downloaded articles in different search engines

2.2. Criteria for Eligibility and Quality Assessment.

Two separate reviewers originally scanned primary titles and abstracts to identify eligible full-text publications for additional examination in accordance with the inclusion and exclusion criteria. Studies including dengue patients from all age groups and geographical areas from all publication years were selected. Only English-language articles were examined. We assessed the quality of the studies using the Newcastle-Ottawa Scale, which evaluates selection, comparability, and outcome. Articles that compare dengue infection in patients with shock to DHF and present the epidemiology, clinical symptoms, and laboratory results. Studies describing dengue consequences, serotype information on the virus, and dengue seroprevalence were also included. The significance of each one was assessed by analysing the article's types, objectives, and methodologies. We did not include genetic markers in this investigation since genetic markers for DSS groups are not frequently published. Reviews lacking original re-search data and proceedings not compliant with peer review were also disregarded. Studies on people who had the dengue virus colonized but were not infected as well as studies examining the impact of recombinant proteins from different serotypes of dengue on responders. Based on discussion and agreement between the two reviewers, each study was either included or omitted. After consulting with a third reviewer in cases of disagreement, a consensus choice was made. The high heterogeneity observed may stem from differences in diagnostic criteria, geographic variations in serotype prevalence, and the quality of included studies. [7-9].

To evaluate disease severity across serotypes, we extracted classification details reported in each study. Severity was categorized based on the WHO 1997 or 2009 guidelines, typically into: Dengue Fever, Dengue Hemorrghagic Fever, Dengue Shock Syndrome. In cases where studies only reported severity by serotype without specific clinical classification, we noted this limitation and included them in the serotype-stratified prevalence analysis only. Misclassification risk was minimized by cross-checking diagnostic approaches and reviewing study methodology.

2.3. Data Extraction

For studies involving humans, we gathered information on the year, country/city of patient recruitment (the study's time period), total dengue cases, data collection (prospective or retrospective), study design, diagnosis methods, dengue classification criteria, baseline characteristics, patient population characteristics and clinical manifestation (**Figure 3**).

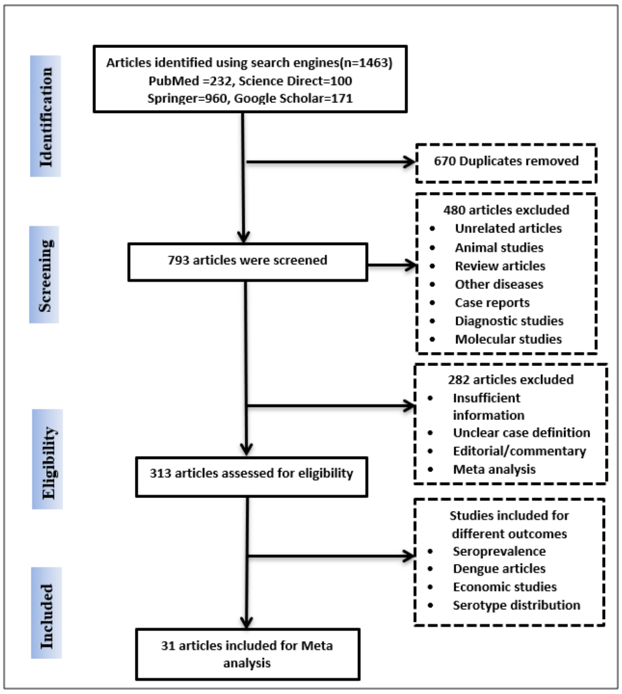


Figure 3. Prisma flow diagram of the study selection process

We collected different kinds of data input pertaining to the relevant factors when it was available. We evaluated the possibility of duplicate data in research publications from the same group and including the same variables, accounting for the year of patient recruitment and the hospital that recruited the patients. When a meta-analysis revealed a strong correlation between a factor and DSS and other data sources or methods were offered, we gave priority to the information that showed the least significant correlation.

2.4. Statistical Analysis

To determine meta-estimates of primary and secondary outcomes that would characterize the frequency of laboratory-confirmed dengue among clinically suspected patients, we carried out a quantitative and qualitative synthesis. The frequency of acute infection was summed up as a proportion for each trial, and the 95% confidence intervals were calculated. For variance stabilization of proportions, the logit and in-verse logit transformations were computed. If considerable heterogeneity in the mediators' levels was discovered, a random effects model was employed to determine the overall mean effect of positive dengue case prevalence among the population across 31 investigations. We used the Cochrane Q and I^2 statistics to test for heterogeneity. We considered $I^2 > 50\%$

and P-value is less than 0 .10 as criteria for substantial heterogeneity. The publication bias was examined by Regression Test and Funnel plots, where the x-axis represents the logit prevalence and standard errors on y-axis [9 ,10]. Comprehensive Meta-Analysis (CMA) V3.3.070 software (USA) was used for the analysis.

RESULTS

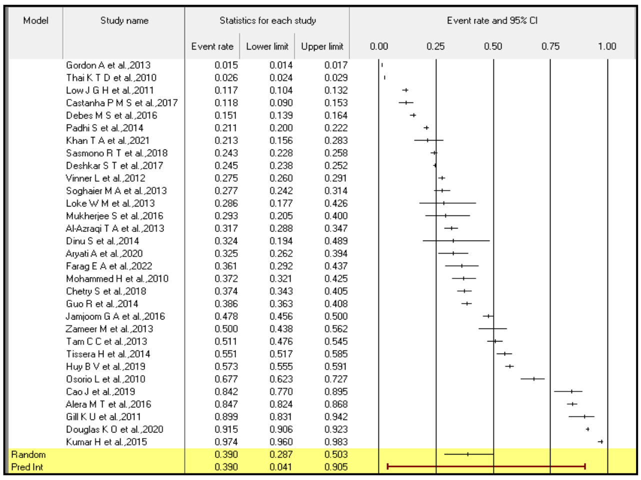
The key features of each study are summarized in **Table 1**. A total 31 articles are included in the studies, nine were retrospective studies (29%), seven were cross-sectional studies (22.6%), six were prospective studies (19.4%), cohort and observational studies were two each (2/31, 6.5%), one case study and one case control study each (1/31, 3.2%). All of the included research were carried out from 2010 to 2022 in the areas of Asia (India(seven studies), China(two studies), Pakistan(two), Sri Lanka(two), Saudi Arabia(three)), America (Barbodas(one), Brazil(one)), Europe (Denmark(one)), Africa (Sudan(one)). The detection of IgG or IgM antibodies by viral isolation, reverse transcriptase polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), and nonstructural (NS1) antigen detection were among the diagnostic techniques used. Six studies classified the severity of dengue as DF, DHF, and DSS primarily using WHO 1997 criteria, whereas the other twenty-five studies classified it by DENV-1, 2, 3, 4 serotypes of dengue. There were 19507 positive dengue cases out of 89030 tested patients

Table 1. Characteristic features of the included studies for Meta Analysis

Author	Country	Year	Study Design	Sample Size	Dengue Cases	Serotype	Diagnostic Test
Mohammed H et al.,2010 [10]	US Virgin Island	2010	Case Control	331	123	DENV-2	RT-PCR
Osorio L et al.,2010 [11]	Venezuela, Vietnam	2010	Cross Sectional	310	210	DENV-1,2,3,4	NS1
Thai K T D et al.,2010 [12]	Vietnam	2010	Prospective	14595	382	DENV-1,2,3,4	IgG-ELISA,IgM-capture-ELISA
Gill K U et al.,2011 [13]	India (Lahore)	2011	Prospective	119	107	DF	IgM
Low J G H et al.,2011 [14]	Singapore	2011	Longitudinal	2129	250	DENV-1,2,3,4	RT-PCR
Vinner L et al.,2012 [15]	Denmark	2012	Observational	3181	875	DENV-1,2,3,4	RT-PCR, IgM, IgG
Al-Azraqi T A et al.,2013 [16]	Saudi Arabia	2013	Retrospective	965	306	DENV-1,2,3,4	IgG
Gordon A et al.,2013 [17]	America	2013	Cohort	22826	351	DENV-1,2,3,4	ELISA
Loke W M et al.,2013 [18]	Singapore	2013	Retrospective	49	14	DENV-2	RT-PCR
Soghaier M A et al.,2013 [19]	Sudan	2013	Cross-Sectional	600	166	DF	IgG
Tam C C et al.,2013 [20]	Sri Lanka	2013	Prospective	797	407	DENV-2	IgG, ELISA
Zameer M et al.,2013 [21]	Pakistan	2013	Prospective	250	125	DENV-1,2,3,4	IgG, IgM
Dinu S et al.,2014 [22]	Romania	2014	Prospective	37	12	DENV-1,2,3	IgG, IgM
Guo R et al.,2014 [23]	China	2014	Retrospective	1779	686	DENV-1,2,3,4	RT_PCR
Padhi S et al.,2014 [24]	India	2014	Retrospective	5102	1074	DENV-1,2,3,4	IgM
Tissera H et al.,2014 [25]	Sri Lanka	2014	Cohort	800	441	DENV-1,2,3,4	IgG
Kumar H et al.,2015 [26]	India	2015	Observational	766	746	DENV-1,2,3,4	NS1, IgG, IgM

Alera M T et al.,2016 [27]	Philippines	2016	Prospective Longitudinal Cohort	1008	854	DENV-1,2,3	RT-PCR,IgG ELISA,IgM
Debes M S et al.,2016 [28]	Saudi Arabia	2016	Retrospective	3277	496	DENV-1,2,3,4	NS1, IgM
Jamjoom G A et al.,2016 [29]	Saudi Arabia	2016	Cross-Sectional	1939	927	DENV-1,2,3,4	IgG, ELISA
Mukherjee S et al.,2016 [30]	India	2016	Retrospective	82	24	DF, DHF, DS	NS1, IgM
Castanha P M S et al.,2017 [31]	Brazil	2017	Prospective Cohort	415	49	DENV-1,2,3,4	IgG,IgM,ELISA,RT-PCR
Deshkar S T et al.,2017 [32]	India	2017	Cross-Sectional	15606	3822	DF, DHF, DS	IgM, ELISA
Chetry S et al.,2018 [33]	India	2018	Retrospective	918	343	DENV-1,2,3,4	IgG, IgM-ELISA, NS1
Sasmono R T et al.,2018 [34]	Indonesia	2018	Cross-Sectional	3210	780	DENV-1,2,3,4	IgG, ELISA
Cao J et al.,2019 [35]	China	2019	Case Study	133	112	DENV-1,2	NS1, RT-PCR, IgG, IgM
Huy B V et al.,2019 [36]	Vietnam	2019	Cross Sectional	2922	1675	DF	NS1, RT-PCR
Aryati A et al.,2020 [37]	Indonesia	2020	Cross Sectional	191	62	DENV-1,2,3	IgG,IgM
Douglas K O et al.,2020 [38]	Barbados	2020	Retrospective	4367	3994	DENV-1,2,3,4	RT-PCR,IgM-ELISA,NS1
Khan T A et al.,2021 [39]	Pakistan	2021	Prospective	160	34	DF	NS1, IgG, IgM
Farag E A et al.,2022 [40]	Qatar	2022	Retrospective	166	60	DENV-1,2,3,4	RT-PCR

The mean effect size is 0.390 with a 95% confidence interval of 0.287 to 0.503 (**Figure 4**). From the results, 39% of the individuals with clinically suspected dengue fever had laboratory-confirmed dengue infection. Studies conducted out in various contexts revealed varying dengue burdens. The prevalence of dengue disease is estimated based on event rate. An event rate less than 5% is considered rare, indicating a lower occurrence of the disease. The highest prevalence was found in Kumar H studies i. e 0.974 with a 95% CI: 0.960 – 0.983. The maximum number of studies is under the prevalence rate of 21% to 57%. A subgroup analysis by geographic location revealed that DENV-2's association with severe dengue was strongest in Southeast Asia, suggesting regional variations in serotype virulence



Model	Study name	Statistics for each study		
		Event rate	Lower limit	Upper limit
	Gordon A et al.,2013	0.015	0.014	0.017
	Thai K T D et al.,2010	0.026	0.024	0.029
	Low J G H et al.,2011	0.117	0.104	0.132
	Castanha P M S et al.,2017	0.118	0.090	0.153
	Debes M S et al.,2016	0.151	0.139	0.164
	Padhi S et al.,2014	0.211	0.200	0.222
	Khan T A et al.,2021	0.213	0.156	0.283
	Sasmono R T et al.,2018	0.243	0.228	0.258
	Deshkar S T et al.,2017	0.245	0.238	0.252
	Vinner L et al.,2012	0.275	0.260	0.291
	Soghaier M A et al.,2013	0.277	0.242	0.314
	Loke W M et al.,2013	0.286	0.177	0.426
	Mukherjee S et al.,2016	0.293	0.205	0.400
	Al-Azraqi T A et al.,2013	0.317	0.288	0.347
	Dinu S et al.,2014	0.324	0.194	0.489
	Aryati A et al.,2020	0.325	0.262	0.394
	Farag E A et al.,2022	0.361	0.292	0.437
	Mohammed H et al.,2010	0.372	0.321	0.425
	Chetry S et al.,2018	0.374	0.343	0.405
	Guo R et al.,2014	0.386	0.363	0.408
	Jamjoom G A et al.,2016	0.478	0.456	0.500
	Zameer M et al.,2013	0.500	0.438	0.562
	Tam C C et al.,2013	0.511	0.476	0.545
	Tissera H et al.,2014	0.551	0.517	0.585
	Huy B V et al.,2019	0.573	0.555	0.591
	Osorio L et al.,2010	0.677	0.623	0.727
	Cao J et al.,2019	0.842	0.770	0.895
	Alera M T et al.,2016	0.847	0.824	0.868
	Gill K U et al.,2011	0.899	0.831	0.942
	Douglas K O et al.,2020	0.915	0.906	0.923
	Kumar H et al.,2015	0.974	0.960	0.983
Random		0.390	0.287	0.503
Pred Int		0.390	0.041	0.905

Figure 4. A forest plot was created based on the prevalence of laboratory-confirmed dengue in individuals with clinical suspicions

The null hypothesis that every study in the analysis has the same effect size is tested using the Q-statistic. The predicted value of Q would be equal to the degrees of freedom (the total number of studies minus 1) if every study had the same genuine effect size. With 30 degrees of freedom and $p < 0.001$, the Q-value is 14648.21 (**Table 2**). We can rule out the null hypothesis that the true effect size is the same in each of these studies by using a criteria alpha of 0.100. The 99.8% I-squared statistic indicates that sampling error does not account for 100% of the variance in reported effects. Instead, it represents variance in genuine effects. The variation of the genuine effect size, or tau-squared, is 1.697 logit units. In logit units, tau, the standard deviation of real effect sizes, is 1.303. We can calculate the prediction interval to be between 0.041 and 0.905 if we assume that the genuine effects are normally distributed (in logit units). In ninety-five percent of all comparable populations, the true effect size lies within this range. High heterogeneity with an inconclusive difference in VEGF levels was seen in the DF and DHF data ($I^2 = 99.8\%$, $P < .01$) from the Random-Effects Model when compared directly to healthy controls

Table 2. Heterogeneity Statistics of the association between significant factors.

Effect size and 95% interval			**Prediction Interval**		**Between-study**		**Heterogeneity Statistics**			
Point estimate	Lowest limit	Upper limit	Lower limit	Upper limit	Tau	Tau^2	Q	df	I^2	p- value
0.39	0.287	0.503	0.041	0.905	1.303	1.697	14648.21	30	99.8	0.0001

The average impact size is 0.39, with a 95% confidence interval spanning from 0.29 to 0.50. In 95% of all comparable populations, the actual impact size lies between 0.04 and 0.91 (**Figure 5**).

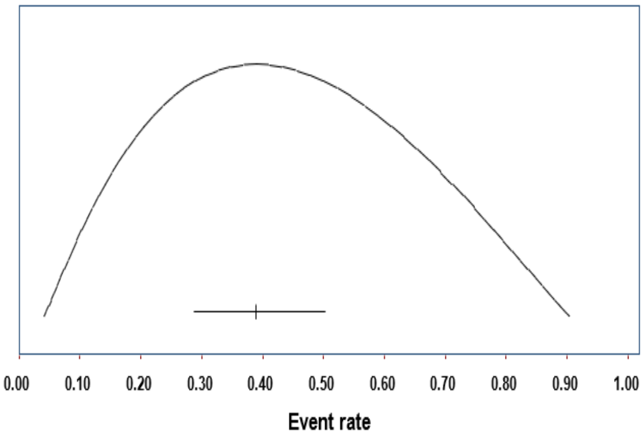


Figure 5. Distribution of True Effects

Under the null hypothesis that there is no Publication bias, we obtained from the funnel plot (**Figure 6**) based on Regression Test with z = 0.173 and p-value is 0.863 at 5 %level of significance (**Table 3**). From the results, we accept the null hypothesis and conclude that the estimates of dengue prevalence in hospital-based surveillance studies showed no evidence of publication bias.

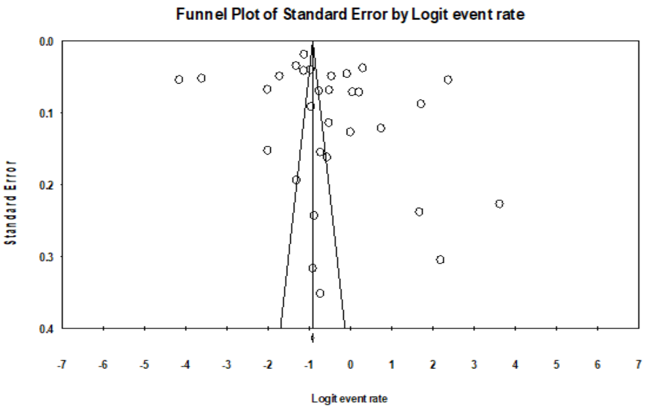


Figure 6. Funnel plot of the logit event rate v/s standard error.

Table 3. Regression Test for Funnel Plot Asymmetry.

Regression Test for Funnel Plot Asymmetry	
Z	P
0.173	0.863

DISCUSSION

Dengue virus infection remains the most prevalent mosquito-borne viral disease globally. This meta-analysis evaluated serotype-specific trends in dengue severity to understand how different DENV serotypes contribute to disease burden. Our analysis showed that DENV-2 was associated with the highest proportion of severe dengue cases, consistent with findings from Southeast Asia and previous literature. These results highlight the clinical and epidemiological importance of distinguishing dengue infections by serotype.

Based on the published research from some of the countries spanning more than a decade, the current study has approximated the burden of dengue fever. The majority of the published works used in the research were reports of dengue outbreak investigations or hospital- or laboratory-based surveillance studies [39]. This meta-analysis evaluated the percentage of severe dengue virus infections among various serotypes. Data from earlier investigations were gathered and merged to get a big enough sample of each dengue serotype. Serotype DENV-1,3 had a severity rate of 54.84% for severe cases. DENV-4 has been discovered to be 45.16%, whereas DENV-2 is 64.52%. DENV-2 was shown to be 6.45% more prevalent than the other serotypes, DF, DH, and DHF.

Our meta-analysis found that DENV-2 had a higher proportion of severe dengue cases compared to other serotypes, which may be due to its unique immunopathological mechanisms. The clinical signs of infections caused by the various serotypes were comparable, but symptoms were more frequently seen. Between 2010 and 2022, DENV-2 was the most common serotype, followed by DENV-1, DENV-3 and DENV-4 [11]. Between 2010 and 2022, patients were identified as having dengue serotypes DF, DHF, DENV-1, DENV-2, DENV-3, and DENV-4 using RT-PCR, IgM, ELISA, IgG, and NS-1. Throughout the years, 19507 out of 89030 people tested positive for dengue with different serotypes. In 2020, the Barbodos region's patients who sought medical attention were tracked and tested. All the serotypes were found in 91.45% of the patients [36]. Comparatively speaking, Romania's serotype DENV-1, DENV-2 and DENV-3 positive case rates were excessively low.

Future research should also be done to show whether the consequences of severe dengue are similar to those of other arboviruses that are significant to medicine, like Chikungunya, Zika, Yellow fever. Given DENV-2's association with severe dengue, public health efforts should prioritize vaccination campaigns and enhanced surveillance in regions where this serotype is predominant. The prevalence of dengue cases has been assessed in the current study using available literature from throughout the globe. The prevalence of dengue cases was observed from 31 studies that revealed significant statistical heterogeneity. This meta-analysis evaluated the percentage of severe cases of various serotypes of DENV in primary and secondary infections, and it demonstrated that patients with dengue were diagnosed [7]. Data from earlier research were gathered and pooled to reach a suitable sample size from both primary and secondary infections caused by each dengue serotype [9,10]. The association between serotypes and severe cases of dengue was also found to be impacted by the use of various WHO classifications. Before any judgements can be drawn, more research must be done. Additionally, including retrospective studies provide less evidence than prospective studies. The issue must be considered when determining the clinical severity of dengue patients because it has been discovered that the dengue serotype involved and the time between the primary and secondary infections have an impact on the severity of the infection. Dengue serotypes have been demonstrated to impact the severity of dengue infection. Furthermore, since DENV-2 serotypes have a higher percentage of severe cases than other serotypes, they need appropriate clinical care. Additionally, DENV-4 was discovered to be the least common cause among the sample size [37]. The specifics are important because they could act as confounding variables in a study looking at the relationship among serotypes, infection types, and the percentage of dengue cases. Despite these findings, several limitations must be noted. Most included studies did not stratify outcomes by primary vs. secondary infections—an important determinant of severity. Furthermore, inconsistent application of WHO severity classifications and retrospective study designs limited comparability. Future studies should include standardized severity metrics and account for immunological history to strengthen serotype-specific risk models. Nonetheless, our findings suggest that public health surveillance and vaccine strategies should prioritize regions with high DENV-2 circulation. Future research must take these perplexing variables into account [38,39].

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, T.S.D., C.N. and A.J.; methodology, C.N., R.N.N and U.K. ; software, C.N.; validation, C.S., B.S., A.J. and T.S.D.; formal analysis, C.S., C.S., C.D., S.S.P., and G.S.M.; investigation, C.S. and S.S.P.; resources, C.S., and C.N.; data curation, C.N., A.J., and S.S.P.; writing—original draft preparation, C.N., T.S.D., C.D., B.S. and A.J.; writing—review and editing, C.S., C.S., G.S.M., and S.S.P.; project administration, T.S.D., C.S., C.D., C.S. All authors have read and agreed to the published version of the manuscript

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