#### Check for updates

#### OPEN ACCESS

EDITED BY Luwen Zhang, University of Nebraska-Lincoln, United States

REVIEWED BY Willy A. Valdivia-Granda, Orion Integrated Biosciences, United States Ye Guoguo, Southern University of Science and Technology, China

\*CORRESPONDENCE Seik-Soon Khor Seiksoon@gmail.com

RECEIVED 01 August 2024 ACCEPTED 26 March 2025 PUBLISHED 15 April 2025

#### CITATION

Ghosh AG, Kim HL and Khor S-S (2025) HLA alleles and dengue susceptibility across populations in the era of climate change: a comprehensive review. *Front. Immunol.* 16:1473475. doi: 10.3389/fimmu.2025.1473475

#### COPYRIGHT

© 2025 Ghosh, Kim and Khor. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# HLA alleles and dengue susceptibility across populations in the era of climate change: a comprehensive review

Amit Gourav Ghosh<sup>1,2</sup>, Hie Lim Kim<sup>1,2,3</sup> and Seik-Soon Khor<sup>1,2</sup>\*

<sup>1</sup>Singapore Centre for Environmental Life Sciences Engineering, Nanyang Technological University, Singapore, Singapore, <sup>2</sup>GenomeAsia 100K Consortium, Singapore, Singapore, <sup>3</sup>Asian School of the Environment, Nanyang Technological University, Singapore, Singapore

Dengue, a viral infection transmitted by Aedes mosquitoes, is an emerging global health threat exacerbated by climate change. Rising temperatures and altered precipitation patterns create favourable conditions for vector proliferation and extended transmission periods, increasing the risk of dengue in endemic regions and facilitating its spread to non-endemic areas. Understanding the interplay between critical genetic factors and dengue susceptibility is crucial for developing effective public health strategies. The Human Leukocyte Antigen (HLA) genes encode proteins essential for an effective immune response against pathogens, and their genetic variations influence susceptibility to severe dengue. In this study, we conducted a comprehensive meta-analysis of HLA alleles associated with dengue infection and dengue severity. We analysed 19 casecontrol studies on dengue infections in populations worldwide to infer HLA associations with various pathological forms of dengue and to examine differences across different populations. Our findings indicate that HLA-A\*02 increases susceptibility to dengue fever (DF), while HLA-A\*03 increases the risk of Dengue Haemorrhagic Fever (DHF), with these increased susceptibilities primarily observed in Southeast Asian populations. Additionally, HLA-A\*24 is associated with DHF and all symptomatic dengue infections (DEN), contributing to dengue risk in both Southeast Asia and the Caribbean. Conversely, HLA-A\*33 and HLA-B\*44 show a protective effect against DHF but show significant regional heterogeneity, highlighting divergent, populationspecific susceptibility profiles. This study underscores the importance of population-specific genetic risk assessments for dengue infection and emphasizes the need for targeted medical interventions and improved predictive models to mitigate dengue's impact, especially as climate change accelerates disease spread.

#### KEYWORDS

dengue, HLA, dengue fever (DF), dengue haemorrhagic fever, serotype, climate change

## 1 Introduction

# 1.1 Dengue – dengue viruses and pathogenesis

Dengue is a viral infection emerging as a significant threat to global health, caused by the dengue virus (DENV). DENV is primarily transmitted through a human-to-mosquito-to-human cycle by specific mosquito vectors known as Aedes aegypti and Aedes albopictus. In the year 2023, the number of reported dengue cases reached a historical high of 6.5 million (1); as of 30 April 2024, the total number of cases had reached a staggering 7.6 million (2) for the year 2024. It is estimated that 400 million yearly infections occur, and currently, half of the world's population is at the risk of contracting dengue (1, 3). Previously endemic to the tropics and subtropics of Asia, the Americas, the Western Pacific, and Africa; it has now been reported to be rapidly expanding into previously non-endemic regions, such as temperate and even high-altitude regions due to climate change (4, 5). This growing burden of dengue infections highlights the importance of a more comprehensive understanding of the virus, its role in disease progression, and its interaction with the human immune system.

Dengue is an acute febrile illness caused by four types of singlestranded DENVs from the *Flavivirus* genus that elicit distinct serological responses with the antibodies in human blood (6). The four DENV serotypes share about 65% of their genome, with subvariants within each serotype (7). The DENV genome comprises 10 genes coding for 3 structural and 7 non-structural proteins. The three structural proteins are capsid (C), membrane (M), and envelope (E), while the seven nonstructural proteins are NS1, NS2A, NSB, NS3, NS4A, NS4B and NS5 (8, 9). The C protein forms the nucleocapsid of the virus, and the M protein plays a crucial role in viral maturation (10, 11). The E protein is essential for viral entry into the host cell by receptor binding and subsequent fusion (11). The non-structural proteins NS1, NS2A, NS4A, and NS4B are involved in the RNA replication process, with NS1 and NS5 also serving as antigens to initiate immune responses in the host cell (9, 12–14). The NS3 protein has helicase and protease functions, while NS4A is involved in autophagy (9, 14).

The replication cycle of the DENV begins with viral binding to the host cell receptors through clathrin-dependent receptor-mediated endocytosis (15). Inside the host cells, the virus undergoes endosomal processing facilitated by Rab5 and Rab7 proteins. Subsequently, the viral genome is released into the cytoplasm and translated into the endoplasmic reticulum (ER). The newly synthesised components are assembled into immature viral particles in the ER undergo maturation in the Trans-Golgi Network via furin-mediated cleavage and are eventually released from the cell through exocytosis (16).

Four serotypes of DENV have been reported to date (DENV1-4), and each serotype can cause dengue fever (DF), dengue haemorrhagic fever (DHF) (Grades 1-2), and dengue shock syndrome (DSS) (DHF Grades 3 and 4). DENV1-4 are the primary dengue-causing serotypes circulating in humans, with different regions reporting varying profiles of circulating serotypes (Figure 1). Common symptoms of DHF include high fever, muscle and joint pain, severe headache, vomiting, bleeding from gums, and skin rashes. Without immediate medical treatment, DHF (Grades 1-2) might develop into DSS, the severe form of DHF, characterized by shortness of breath, rapid pulse rate, low



Worldwide pattern of dengue endemicity according to WHO and CDC, and the prevalence of dengue serotypes across different regions.

blood pressure and severe abdominal pain. 60-80% of individuals with a primary DENV infection are asymptomatic; however, the risk of severe disease increases significantly during a second infection, especially among those with longer intervals since the primary DENV infection (17). DENV-2 and DENV-4 are more commonly identified in secondary dengue infections, while DENV-1 and DENV-3 often cause primary infections (7, 18).

There is no consensus on the pathogenesis of DENV infection in the scientific community. The three major factors related to the severity of DENV infection include secondary infection, host genetics, and viral virulence (19-23), with the majority view that secondary infection is the main risk factor for DHF. Primary DENV infection involves the stimulation of interferon gamma (IFNy) (24). During a secondary infection, non-neutralizing antibodies (25, 26) from the primary infection can bind to the serotype of the second infection. Instead of neutralizing the virus, these antibodies facilitate its entry into host cells, leading to increased viral replication and a more severe immune response. The phenomenon is commonly known as Antibody-Dependent Enhancement (ADE) (27, 28). This heightened immune response can cause increased vascular permeability, plasma leakage, and other severe symptoms characteristic of DHF. The detection of DENV by RIG-I (retinoic acid-inducible gene I) and MDA5 (melanoma differentiation-associated protein 5) triggers the phosphorylation of IRF3 (interferon regulatory factors 3) and IRF7 (interferon regulatory factors 7), leading to the production of type I and III interferons (IFNs), the activation of the JAK-STAT pathways, and the upregulation of interferon-stimulated genes (ISGs) (29). During severe infection, immature DENV particles are recognized by TLR2 (Toll-like Receptor 2) and DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) on monocytes and immature dendritic cells, resulting in the release of inflammatory mediators like IL-1 $\beta$  (interleukin 1 $\beta$ ) and TNF- $\alpha$  (tumour necrosis factor  $\alpha$ ), which increase endothelial cell permeability or dysfunction, contributing towards severe complications (30, 31). Moreover, excess secretion of anti-DENV antibodies can exacerbate ADE (Figure 2), further increasing autoantibody production and its potential glycosylation, a signature seen in severe DHF and DSS (32, 33).

Endothelial dysfunction could lead to complications such as hypotension, ascites, pleural effusions, shock, and organ dysfunction (34). NS1 protein and inflammatory mediators from monocytes, macrophages, dendritic cells, and mast cells contribute to this dysfunction (34, 35). Elevated cytokines and chemokines, such as IL- $1\beta$ , IL-6, TNF- $\alpha$ , and MMP-9, directly cause endothelial dysfunction, while others like IL-10 may reduce it (36). Lipid mediators, including PAF, leukotrienes, prostaglandins, and sPLA2 enzymes, also play a role in vascular permeability (36). PAF and prostaglandin metabolites are elevated in severe cases and cause endothelial dysfunction (34, 36, 37). Mast cell products such as histamine, tryptase, chymase, VEGF, and serotonin are linked to disease severity and vascular leakage (38–40). Recent studies from Nicaragua and India showed that both primary and secondary DENV infections can range from subclinical to severe implications (41, 42).

DSS also involves severe cases of hepatomegaly and bleeding, especially in gum, nose, and stool. A typical signature of DSS, hepatomegaly and other complications regarding the liver, high levels of aspartate transaminase (AST) levels are inferred to have played an influential role (43). Secondary hemophagocytic lymphohistiocytosis (HLH), characterized by macrophage activation and cytokine storms, is a significant cause of severe liver dysfunction and high mortality in dengue patients (44, 45). Dengue can cause various bleeding manifestations, including petechiae, gum bleeding, and hematemesis (36). Bleeding results from thrombocytopenia, dysfunctional platelets, coagulation pathway abnormalities, and prolonged shock (36, 46).



10.3389/fimmu.2025.1473475

Over 50% of hospitalized dengue patients experience severe thrombocytopenia, which correlates with disease severity (36). Platelets can be directly infected by DENV, leading to activation through multiple pathways, including serotonin release from mast cells and direct activation by the virus (40, 47).

#### 1.2 Human leukocyte antigen and its role in launching immune response against DENV

Since DENV is a foreign body infecting host cells, the genes influencing host defence mechanisms against such foreign infecting agents could play a crucial role in influencing effective response against DENV. One such large complex of genes are the HLA genes. HLA genes are known to be the most polymorphic regions in the human genome and are the part of Major Histocompatibility Complex (MHC) region located on the short arm of chromosome 6. Class I and class II HLA genes encode antigen-recognising sites crucial for adaptive immune responses, recognising between self and non-self. HLA class I proteins present foreign peptides to T-cell receptors on CD8+ T cells (cytotoxic T cells) to launch immune responses. HLA class II proteins are expressed on active immune cells like antigen-presenting cells (APCs) and B cells, where they detect antigens and present them to CD4+ T cells (helper T cells) to initiate immune responses. During Antibody-Dependent Enhancement (ADE) where Fcy receptors (FcyR) facilitate the increased entry of DENV into immune cells, it could lead to the upregulation of HLA class I molecules, suppressing the activity of NK cells (48). Such reduced activity could potentially contribute to disease pathogenesis. HLA class I alleles further influence the magnitude of CD8+ T cell responses against DENV (49-51). Therefore, the host's HLA allele profile is paramount in determining the immunogenic response to DENV infection. This leads to varied immunopathological outcomes, including susceptibility or protection against DENV infection or more severe outcomes (Figure 2) (52, 53).

Given the crucial role of HLA genes in determining the pathophysiology of DENV infection, numerous case-control studies have investigated how HLA polymorphisms influence susceptibility to and protection against severe outcomes of DENV infection. By late 1970s, the idea that HLA proteins could determine the susceptibility towards viral infections started gaining ground (54). HLA responses against DENV can also show serotype specificity. A study on the Sri Lankan population has demonstrated that DENV-2-specific responses, likely due to the population's previous history of DENV-2 infection, signifying that epidemiological history could influence serotype-specific immune responses (51). However, HLA allele associations with DENV infection outcomes could be complicated by factors such as HLA alleles typing resolution, the population studied, predominant DENV serotypes, HLA allele composition, and how the different stages/ categories of dengue are defined in the study design. Therefore, usage of standardised pathophysiological classifications for dengue, clear definition of populations studied, and large enough case & control sizes are imperative to derive statistically significant inferences.

The earliest case-control study suggesting the influence of *HLA* alleles in determining susceptibility or protection against DENV infection was performed on Thai children in 1981, identifying several

*HLA* class I antigens as potential crucial regulators in the development of severe forms of dengue (55). Throughout the years, several case-control studies, primarily across Southeast Asia, Central and South America, have further cemented the crucial role of different *HLA* class I alleles in determining dengue susceptibility (55–73).

# 1.3 Dengue - an emerging threat in a warming world: understanding DENV and host HLA interactions

Dengue cases have been rising exponentially over the past five decades with the Americas (Caribbean and Latin American), Southeast Asia, and South Asia, bearing the highest burden of dengue cases (Figure 3A). From 2022 to 2023, dengue cases more than doubled in 16 Caribbean and 9 Latin American countries, with St Kitts and Nevis and Argentina reporting increases of 28500% and 17364.4%, respectively. Similarly, cases in Bangladesh in South Asia and Thailand in Southeast Asia showed increases of 414.6% and 241.1% (Figure 3B), respectively. In Europe, the locally transmitted cases increased significantly in 2023, with Spain, Italy, and France reporting 3, 82, and 45 cases, respectively (2).

The global increase in dengue cases can be attributed to several factors, including viral evolution (74, 75), human settlement patterns (76), socioeconomic drivers (77), human mobility (78), age (79) and climate change (80). A complex interplay of these factors determines the epidemiological fate of dengue for any given population or geographic setting. Specifically, DENV vectors belonging to Aedes sp have rapidly expanded into new habitats, driven by warmer and more humid conditions due to climate change (81-85). Such climatic conditions could result in a shorter extrinsic incubation period (EIP), the period required for a mosquito to become dengue-transmittable after having an infectious meal, increasing dengue risk (86). Furthermore, rising temperatures have been found to increase the biting incidence of dengue vectors, while extended periods of warmer conditions lengthen the suitable period for dengue transmission, heightening the risk of severe epidemics (87).

It is projected that within the next six decades, close to two-thirds of the world's population will be vulnerable to dengue infection (82). Without adequate preparations, the potential surge of dengue cases could overwhelm medical infrastructures, particularly considering emerging infectious diseases like COVID-19. This growing threat underscores the importance of understanding genetic factors that influence dengue susceptibility and severity.

In the context of the rising dengue cases due to climate change and other anthropogenic factors, we review and perform a meta-analysis of the known associations of *HLA* alleles with dengue. As key regulators of adaptive immunity, HLA molecules present viral peptides to T cells, influencing immune activation and viral clearance. Variability in *HLA* alleles has been linked to differences in dengue susceptibility, severity, and immune response efficiency (88–90). Understanding these associations is crucial to gaining deeper insights into how our adaptive immune system functions and influences DENV infection outcomes.



1B) Percentage in increase in dengue cases from 2022 to 2023



FIGURE 3

Worldwide dengue case patterns (A) Total reported cases for the year 2023 (B) Percentage increase in dengue cases from the year 2022-202.

# 2 Methods

## 2.1 Dengue epidemiological data

Global DENV infection cases and endemicity data were compiled and collected from WHO's 2024 reports (1, 2) and ECDC (91), latest until 24 June 2024. Missing data from DENV infection cases was collected from the official reported figures mentioned governmental health ministry and infectious disease surveillance website for each respective country (92). We had a total of 75 countries reporting endemic dengue cases until the start of 2024.

# 2.2 Association of *HLA* alleles with dengue worldwide

To look for candidate papers for *HLA*-Dengue association metaanalysis, we searched two databases, PUBMED and Semantic Scholar. In order to make the best use of the two datasets, custom search strategies were used for each, mentioned below:

- PUBMED.
- We entered the following query in the search option to optimise the retrieval of appropriate studies – (Dengue) AND (HLA) AND ((association) OR (associated)). The submitted query returned 101 potential study candidates.
- Semantic Scholar.
- We utilised the elicit (93) tool to streamline the searching process from Semantic Scholar. For a query of "What are the *HLA* alleles associated with Dengue infection outcomes in humans?", it was ensured that the words "Dengue", "*HLA*", "association" or "associated" will should be present within the abstract. This search strategy returned a total of 264 study candidates from an initial 32,604 when searched directly on Semantic Scholar.

With the studies obtained from the above search strategies, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (94) to screen and finalise studies which would be included in the meta-analysis (Figure 4). During the selection of the studies to be included for the meta-



analyses, the investigators decided on the final set of candidates without any conflicting viewpoints or opinions.

A total of 19 studies have been included in the meta-analysis (Table 1), DENV infection phenotypes such as DF, DHF and DSS were comprehensively extracted. Symptomatic DENV infection cases defined as DEN and the sum of DF and DHF was considered as DEN in our meta-analysis. Cochrane RevMan Web (99) was used for calculation of effect sizes of the studies, confidence intervals (CIs), heterogeneity across studies (I<sup>2</sup> statistics) and generation of forest plots. Fixed-effects model was used to calculate the pooled effect sizes and corresponding 95% CIs. Statistical significance was set at Mantel-Haenszel P < 0.05. Forest plots were plotted based on dengue phenotypes (DF, DHF and DEN) and further stratified by populations.

### **3** Results

Following the PRISMA guideline (94) (Figure 4), a total 19 casecontrol studies were included in our meta-analysis (Table 1). After selecting the candidate studies, we performed a meta-analysis of the most commonly associated alleles across dengue fever (DF), dengue haemorrhagic fever (DHF) or all symptomatic dengue outcomes taken together (DEN). We also conducted a meta-analysis based on the origin of populations to observe susceptibility tendencies at a population-specific scale for each *HLA* allele against DEN.

#### 3.1 HLA-A\*02

The *HLA-A\*02* allele shows a significant amount of heterogeneity (P = 1.0E-03) across the five tested studies when DF is compared with healthy controls. Despite such heterogeneity, *HLA-A\*02* [P = 2.0E-03, OR = 1.37 (1.13–1.67)] is inferred to have a predisposing effect towards DF development (Figure 5).

When comparing DHF with healthy controls, the data from seven selected studies also show significant heterogeneity [P = 1.0E-02]. The combined odds ratio for *HLA-A\*02* for DHF against healthy controls is insignificant [P = 0.07, OR = 1.18 (0.99–1.40)], with a tendency towards being more predisposing to DHF (Figure 5).

When comparing DEN with healthy controls based on 13 studies, the combined odds ratio [P = 2.0E-02, OR = 1.16 (1.02–1.32)] suggests a predisposing influence of *HLA-A\*02* despite the significant heterogeneity in the observation [P = 1.0E-04] (Figure 5).

To infer the regional tendencies of the *HLA-A\*02* allele influencing the susceptibility to any forms of DEN, we calculated the odds ratio after grouping the studies based on their region of origin (Figure 6). Based on a single study conducted in Jamaica (72), the allele showed a tendency towards being a risk allele with the Caribbean region with the statistics remaining insignificant [P =0.06, OR = 2.02 (0.97-4.22)]. Meanwhile, in Latin America, no significant trend was observed [P = 0.93, OR = 1.01 (0.81-1.25)].

In South Asia, the two studies based on Sri Lankan (71) and Indian (61) cohorts reported an insignificant association with dengue with

TABLE 1 List of previously reported case-control HLA association study with respect to dengue included in the meta-analysis.

No	Country	Study (Author Name, reference)	Year	Population	Cases	Control
1	Brazil	Cardozo DM., et al. (59)	2014	Southern Brazilian	95	173
2	Brazil	Polizel JR., et al. (68)	2004	White Brazilian	64	667
3	Cuba	Sierra B., et al. (69)	2007	Cuban	120	189
4	Cuba	Paradoa Pérez ML., et al. (95)	1987	Cuban	82	276
5	India	Alagarasu K., et al. (60)	2013	Marathi	114	224
6	India	Alagarasu K., et al. (61)	2013	Marathi	114	224
7	Jamaica	Brown MG., et al. (72)	2011	Jamaica	50	177
8	Malaysia	Appanna R., et al. (67)	2010	Malay, Chinese, Indian	92	95
9	Mexico	Falcón-Lezama JA., et al. (70)	2009	Mestizo	39	34
10	Mexico	LaFleur C., et al. (63)	2002	Mestizo	81	99
11	Philippines	Mercado ES., et al. (56)	2015	Filipino Children	190	300
12	Sri Lanka	Weiskopf D., et al. (96)	2016	Sri Lankan	440	150
13	Sri Lanka	Malavige GN., et al. (71)	2011	Sri Lankan	110	119
14	Thailand	Vejbaesya S., et al. (64)	2015	Thai	440	227
15	Thailand	Stephens HA., et al. (97)	2002	Thai	263	140
16	Thailand	Chiewsilp P., et al. (55)	1981	Thai	87	138
17	Venezuela	Mercedes T. F (98),	2009	Mixed descent Venezuelan	71	127
18	Vietnam	N. T. Lan., et al. (62)	2008	Kinh	629	450
19	Vietnam	Loke H., et al. (66)	2001	Vietnamese	309	251

HLA -A*02 Study or Subgroup	Ca: Events	se Total	Healthy ( Events	Control Total	Weight	Odds ratio M-H, Fixed, 95% Cl	Odds ratio M-H, Fixed, 95% Cl
	70	4.40	47	4.40	0 70/	0 47 14 05 0 501	
Stephens 2002	78	149	47	140	2.7%	2.17 [1.35 , 3.50]	
Polizei 2004	27	64	313	667	3.7%	0.83 [0.49 , 1.39]	
Beatriz 2007	54	240	68	378	4.8%	1.32 [0.89 , 1.98]	
Alagarasu 2013	20	85	39	110	3.1%	0.56 [0.30 , 1.06]	
Edelwsia 2015	5	92	3	296	0.2%	5.61 [1.32 , 23.96]	
Vejbaesya 2015	141	277	85	227	5.4%	1.73 [1.21 , 2.48]	
Subtotal (95% CI)		907		1818	19.8%	1.37 [1.13 , 1.67]	•
Total events:	325		555				
Heterogeneity: Chi <sup>2</sup> =	20.20, df =	= 5 (P = 0.	.001); l² = 7	75%			
Test for overall effect:	Z = 3.17 (I	P = 0.002	)				
DHF vs HC							
Chiewsilp 1981	55	87	70	138	2.3%	1.67 [0.96 , 2.89]	<b></b>
Paradoa 1987	37	164	110	552	4.6%	1.17 [0.77 , 1.78]	
Hsin 2001	131	309	124	251	9.3%	0.75 [0.54 , 1.05]	
Stephens 2002	57	114	47	140	2.5%	1.98 [1.19 , 3.29]	
Gathsaurie 2011	31	220	39	238	3.8%	0.84 [0.50 , 1.40]	
Alagarasu 2013	12	29	39	110	1.1%	1.29 [0.56 , 2.96]	
Vejbaesya 2015	75	150	85	227	4.0%	1.67 [1.10 , 2.54]	
Subtotal (95% CI)		1073		1656	27.5%	1.18 [0.99 , 1.40]	•
Total events:	398		514				ľ
Heterogeneity: Chi <sup>2</sup> =	16.83, df =	= 6 (P = 0.	.010); l² = 6	64%			
Test for overall effect:	Z = 1.84 (F	<b>P</b> = 0.07)					
Chiewsiln 1981	55	87	70	138	2.3%	1 67 10 96 2 891	
Paradoa 1987	37	164	110	552	4.6%	1 17 [0.30 , 2.33]	
Hsin 2001	131	309	124	251	9.0%	0.75 [0.54 1.05]	
Stephens 2002	135	263	47	140	3.5%	2 09 [1 36 3 20]	
Polizel 2004	27	64	313	667	3.7%	0.83 [0.49 1.39]	
Beatriz 2007	54	240	68	378	4.8%	1.32 [0.89 1.98]	
Ramapraha 2010	38	184	38	190	3.5%	1.02 [0.00 , 1.00]	T <sup>-</sup>
Appanna 2010	38	184	38	190	3.5%	1.04 [0.63 1.72]	Ť
Brown 2011	17	43	31	127	1.1%	2 02 [0 97 4 22]	Τ.
Alagarasu 2013	32	40 114	39	110	3.4%	0 71 [0 40 1 25]	
Daniela 2014	44	190	98	346	6.3%	0.76 [0.51 1.15]	
Edelwsia 2015	-++	153	3	296	0.2%	1 29 [0 21 7 83]	
Veibaesva 2015	216	427	85	200	6.4%	1 71 [1 23 2 38]	
Subtotal (95% CI)	210	2422	00	3612	52.4%	1.16 [1.02 1.32]	<b>_</b>
Total events	826	_766	1064	5012	01.070		T
Heterogeneity: Chi <sup>2</sup> =	32.27 df =	= 12 (P = (	$0.001$ · $l^2 =$	63%			
Test for overall effect:	Z = 2.30 (I	P = 0.02)	,				
				7000	400.00	4 04 14 40 4 00	
IOTAI (95% CI)	45.40	4402	0400	7086	100.0%	1.21 [1.10 , 1.32]	•
Iotal events:	1549	- OF (D -	2133	2 - 0504			
The terrogeneity: Chi <sup>2</sup> =	7 1.53, at =	- 25 (P < (	J.UUUU1); P	- – 5%			0.02 0.1 1 10 50
rest for overall effect:	∠ = 4.07 (ł	- < 0.000	1)				
To at fair and second 197	· · · · · · · · · · · · · · · · · · ·		-14 - O (D	- 0 0 4 10	- 0 70/		

FIGURE 5

Meta-analysis of HLA-A\*02 for dengue fever (DF), dengue haemorrhagic fever (DHF) and DEN (CI, Confidence interval; M-H, Mantel-Haenszel fixed effect test for Odds Ratio).

respect to *HLA-A\*02*. The combined odds ratio remained insignificant  $[P = 0.19, \text{OR} = 0.78 \ (0.53-1.14)]$ , with a tendency towards being protective (Figure 6). In Southeast Asia, despite significant heterogeneity across studies [P = 2.0E-03] driven primarily by the Vietnamese study done in 2001 (66) and the study on Filipino children in 2015 (56), a clear trend of risk emerged. Based on the six selected studies across Thailand, Vietnam, Malaysia, and Philippines, *HLA-A\*02* is inferred to be a statistically significant risk allele for DEN  $[P = 2.0\text{E}-03, \text{OR} = 1.31 \ (1.10-1.57)]$  (Figure 6).

When combined across different regions and accounting for significant heterogeneity (P = 8.0E-04), the risk predisposition characteristic of *HLA-A\*02* stands [P = 4.0E-02, OR = 1.14 (1.01–1.30)] (Figure 6). It is very likely that this inference is driven primarily

by the Southeast Asian studies, given their higher weight in the analysis conducted. Moreover, regardless of significant associations with either being a risk or protective against DEN within each region, the tendency of odds ratio differs significantly between each regional group (P = 2.0E-02). This difference among different region groups suggests a population-specific variability of the susceptibility profile of *HLA-A\*02*.

#### 3.2 *HLA-A\*03*

*HLA-A\*03* do not show any significant effect on DF susceptibility when compared to healthy controls across four studies [P = 0.72, OR = 0.95 (0.70–1.28)] (Figure 7). When DHF

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	N	I-H, Fixed, 95% Cl	
Caribbean									
Brown 2011	17	43	31	127	2.1%	2.02 [0.97 , 4.22]		_ <b>_</b>	
Subtotal (95% CI)		43		127	2.1%	2.02 [0.97 , 4.22]			
Total events:	17		31			• / •			
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.89 (P	= 0.06)							
Latin America									
Paradoa 1987	37	164	110	552	8.7%	1.17 [0.77 . 1.78]			
Polizel 2004	27	64	313	667	7.0%	0.83 [0.49 . 1.39]			
Beatriz 2007	54	240	68	378	9.1%	1.32 [0.89 . 1.98]			
Daniela 2014	44	190	98	346	11.9%	0.76 [0.51 1.15]			
Subtotal (95% CI)		658		1943	36.6%	1.01 [0.81 . 1.25]		-	
Total events	162		589					Y	
Heterogeneity: Chi <sup>2</sup> =	4.60 df = 3	(P = 0.2)	$(0) \cdot  ^2 = 35^{\circ}$	%					
Test for overall effect:	Z = 0.09 (P	= 0.93)		-					
South Asia									
Gathsaurie 2011	31	220	39	238	7.1%	0.84 [0.50 . 1.40]			
Alagarasu 2013	32	114	39	110	6.3%	0.71 [0.40 1.25]			
Subtotal (95% CI)		334		348	13.5%	0.78 [0.53 . 1.14]			
Total events:	63		78						
Heterogeneity: Chi <sup>2</sup> =	0.18. df = 1	(P = 0.6)	$(7):  ^2 = 0\%$						
Test for overall effect:	Z = 1.30 (P	= 0.19)	.,,						
Southeast Asia									
Chiewsilp 1981	55	87	70	138	4.4%	1.67 [0.96 , 2.89]		L	
Hsin 2001	131	309	124	251	17.5%	0.75 [0.54 , 1.05]		-	
Stephens 2002	135	263	47	140	6.6%	2.09 [1.36 , 3.20]			
Appanna 2010	38	184	38	190	6.6%	1.04 [0.63 , 1.72]		_	
Edelwsia 2015	2	153	3	296	0.4%	1.29 [0.21 , 7.83]			
Vejbaesya 2015	216	427	85	227	12.2%	1.71 [1.23 , 2.38]		-	
Subtotal (95% CI)		1423		1242	47.8%	1.31 [1.10 , 1.57]		▲	
Total events:	577		367					×	
Heterogeneity: Chi <sup>2</sup> =	19.13, df =	5 (P = 0.	.002); l <sup>2</sup> = 1	74%					
Test for overall effect:	Z = 3.01 (P	= 0.003	)						
Total (95% CI)		2458		3660	100.0%	1.14 [1.01 , 1.30]			
Total events:	819		1065					T	
Heterogeneity: Chi <sup>2</sup> =	33.61, df =	12 (P = 0	0.0008); I²	= 64%			0.01 0	1 1 10	100
Test for overall effect:	Z = 2.10 (P	= 0.04)					0.01 0		100
		·2 - 0 00	-14 - 0 (D	- 0 00\ 12	- 00 70/				

is compared with healthy samples, significant heterogeneity between the four included studies was observed (P = 1.0E-03). Despite this heterogeneity, the combined odds ratio [P = 1.0E-04, OR = 1.83 (1.34–2.50)] suggests a predisposing effect of *HLA-A\*03* towards DHF, primarily driven by the Thai study conducted in 2005 (64).

When DEN was compared with healthy controls, no significant associations towards risk or protection were observed [P = 0.81, OR = 1.03 (0.82–1.28)]. Overall, *HLA-A\*03* shows a statistically insignificant [P = 0.07, OR = 1.15 (0.99–1.34)] tendency to be a risk allele. Within the three tested outcomes, DF, DHF, and DEN, a significant difference between each group was observed [P = 4.0E-03] (Figure 7).

Within the Caribbean  $[P = 0.07, \text{OR} = 2.22 \ (0.95-5.23)]$  and Latin American  $[P = 0.21, \text{OR} = 1.12 \ (0.81-1.56)]$  populations, statistically insignificant influence of *HLA-A\*03* on DEN susceptibility was observed (Figure 8). In South Asia  $[P = 0.80, \text{OR} = 0.92 \ (0.50-1.71)]$  and Southeast Asia [P = 0.34, OR = 0.84] (0.58–1.21)], no significant influence of *HLA-A\*03* on DEN was inferred (Figure 8). Overall, when all regions are compared, *HLA-A\*03*, does not show any significant effect on DEN susceptibility [P = 0.81, OR = 1.03 (0.82–1.28)].

#### 3.3 HLA-A\*24

*HLA-A\*24* (Figure 9) shows no statistically significant protective or predisposing effect for DF [P = 0.85, OR = 1.04 (0.83–1.30)]. When we compare DHF with healthy controls across eight studies, the significant combined odds ratio [P = 3.0E-04, OR = 1.38 (1.16–1.64)] suggests a predisposing influence of *HLA-A\*24* towards DHF.

When we compare DEN with the healthy control across 12 studies (Figure 9), the predisposing influence of *HLA-A\*24* [P < 1.0E-05, OR = 1.40 (1.23–1.60)] stands despite significant heterogeneity [P = 1.0E-03] across different studies.

	Evente	Total	Evente	Total	Weight	M-H Fixed 95% CL	M-I	H Fixed 95% Cl	
	Lvents	Total	Lventa	Total	Weight		141-1	1, 1 1, 20, 30, 10	
DF vs HC									
Chiewsilp 1981	7	86	16	254	2.5%	1.32 [0.52 , 3.32]		<b>_</b>	
Beatriz 2007	17	240	30	378	7.2%	0.88 [0.48 , 1.64]		_	
Alagarasu 2013	8	85	14	110	3.7%	0.71 [0.28 , 1.79]			
Vejbaesya 2015	206	277	170	227	15.9%	0.97 [0.65 , 1.46]		<b>_</b>	
Subtotal (95% CI)		688		969	29.2%	0.95 [0.70 , 1.28]		•	
Total events:	238		230					1	
Heterogeneity: Chi <sup>2</sup> = 0	0.92, df = 3	(P = 0.8	2); l² = 0%						
Test for overall effect:	Z = 0.35 (P	= 0.72)							
DHF vs HC									
Paradoa 1987	10	164	45	552	6.4%	0.73 [0.36 , 1.49]		_ <b>_</b>	
Gathsaurie 2011	11	220	9	238	2.7%	1.34 [0.54 . 3.30]			
Alagarasu 2013	2	29	14	110	1.8%	0.51 [0.11 . 2.37]	_		
Veibaesva 2015	99	150	85	227	7.6%	3.24 [2.11 , 4.99]			
Subtotal (95% CI)		563		1127	18.6%	1.83 [1.34 . 2.50]			
Total events:	122		153					•	
Heterogeneity: Chi <sup>2</sup> =	16.30. df =	3 (P = 0.	0010);   <sup>2</sup> =	82%					
Test for overall effect: A	Z = 3.81 (P	= 0.000	1)						
DEN vs HC	Z = 3.81 (P	= 0.000	1)						
DEN vs HC Chiewsilp 1981	Z = 3.81 (P 7	= 0.000 <sup>-</sup> 86	1) 16	254	2.5%	1.32 [0.52 , 3.32]			
DEN vs HC Chiewsilp 1981 Paradoa 1987	2 = 3.81 (P 7 10	= 0.000 <sup>7</sup> 86 164	1) 16 45	254 552	2.5% 6.4%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49]			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007	Z = 3.81 (P 7 10 17	= 0.000 <sup>7</sup> 86 164 240	1) 16 45 30	254 552 378	2.5% 6.4% 7.2%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64]		_+ _+	
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011	2 = 3.81 (P 7 10 17 11	= 0.000 <sup>7</sup> 86 164 240 220	1) 16 45 30 9	254 552 378 238	2.5% 6.4% 7.2% 2.7%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30]		-+ -+ -+	
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011	2 = 3.81 (P 7 10 17 11 11	= 0.000 <sup>7</sup> 86 164 240 220 43	1) 16 45 30 9 17	254 552 378 238 127	2.5% 6.4% 7.2% 2.7% 2.1%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23]			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013	2 = 3.81 (P 7 10 17 11 11 11 10	= 0.000 <sup>4</sup> 86 164 240 220 43 114	1) 16 45 30 9 17 14	254 552 378 238 127 110	2.5% 6.4% 7.2% 2.7% 2.1% 4.3%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55]		+	
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014	2 = 3.81 (P 7 10 17 11 11 11 10 27	= 0.000 <sup>4</sup> 86 164 240 220 43 114 190	1) 16 45 30 9 17 14 30	254 552 378 238 127 110 346	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03]			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015	2 = 3.81 (P 7 10 17 11 11 10 27 305	= 0.000 <sup>-</sup> 86 164 240 220 43 114 190 427	1) 16 45 30 9 17 14 30 170	254 552 378 238 127 110 346 227	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0% 21.0%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21]			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% CI)	2 = 3.81 (P 7 10 17 11 11 10 27 305	86 164 240 220 43 114 190 427 <b>1484</b>	1) 16 45 30 9 17 14 30 170	254 552 378 238 127 110 346 227 <b>2232</b>	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0% 21.0% <b>52.3%</b>	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% Cl) Total events:	2 = 3.81 (P 7 10 17 11 11 10 27 305 398	86 164 240 220 43 114 190 427 <b>1484</b>	1) 16 45 30 9 17 14 30 170 331	254 552 378 238 127 110 346 227 <b>2232</b>	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0% 21.0% <b>52.3%</b>	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% CI) Total events: Heterogeneity: Chi <sup>2</sup> =	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df =	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0.	1) 16 45 30 9 17 14 30 17 14 30 170 331 16); I <sup>2</sup> = 34	254 552 378 238 127 110 346 227 <b>2232</b> %	2.5% 6.4% 7.2% 2.1% 4.3% 6.0% 21.0% <b>52.3%</b>	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% CI) Total events: Heterogeneity: Chi <sup>2</sup> = : Test for overall effect: 2	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df = Z = 0.23 (P	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0. = 0.81)	1) 16 45 30 9 17 14 30 170 331 16); I <sup>2</sup> = 34	254 552 378 238 127 110 346 227 <b>2232</b> %	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0% 21.0% <b>52.3%</b>	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
Test for overall effect: . DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% Cl) Total events: Heterogeneity: Chi <sup>2</sup> = : Test for overall effect: . Total (95% Cl)	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df = Z = 0.23 (P	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0. = 0.81) <b>2735</b>	1) 16 45 30 9 17 14 30 170 170 331 16); I <sup>2</sup> = 34	254 552 378 238 127 110 346 227 <b>2232</b> %	2.5% 6.4% 7.2% 2.7% 4.3% 6.0% 21.0% 52.3%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% Cl) Total events: Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 2 Total (95% Cl) Total events:	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df = Z = 0.23 (P 758	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0. = 0.81) <b>2735</b>	1) 16 45 30 9 17 14 30 170 331 16); I <sup>2</sup> = 34 714	254 552 378 238 127 110 346 227 <b>2232</b> % <b>4328</b>	2.5% 6.4% 7.2% 2.1% 4.3% 6.0% 21.0% 52.3%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% CI) Total events: Heterogeneity: Chi <sup>2</sup> = : Total (95% CI) Total events: Heterogeneity: Chi <sup>2</sup> = :	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df = Z = 0.23 (P 758 38.79. df =	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0. = 0.81) <b>2735</b>	1) 16 45 30 9 17 14 30 170 331 16); I <sup>2</sup> = 34 714 2,0007); I <sup>2</sup>	254 552 378 238 127 110 346 227 <b>2232</b> % <b>4328</b> = 61%	2.5% 6.4% 7.2% 2.7% 4.3% 6.0% 21.0% 52.3%	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>			
DEN vs HC Chiewsilp 1981 Paradoa 1987 Beatriz 2007 Gathsaurie 2011 Brown 2011 Alagarasu 2013 Daniela 2014 Vejbaesya 2015 Subtotal (95% Cl) Total events: Heterogeneity: Chi <sup>2</sup> = : Total (95% Cl) Total events: Heterogeneity: Chi <sup>2</sup> = : Total (95% Cl) Total events:	Z = 3.81 (P 7 10 17 11 11 10 27 305 398 10.59, df = Z = 0.23 (P 758 38.79, df = Z = 1.82 (P	86 164 240 220 43 114 190 427 <b>1484</b> 7 (P = 0. = 0.81) <b>2735</b> 15 (P = C = 0.07)	1) 16 45 30 9 17 14 30 170 331 16); I <sup>2</sup> = 34 714 0.0007); I <sup>2</sup> =	254 552 378 238 127 110 346 227 <b>2232</b> % <b>4328</b> = 61%	2.5% 6.4% 7.2% 2.7% 2.1% 4.3% 6.0% 21.0% <b>52.3%</b>	1.32 [0.52 , 3.32] 0.73 [0.36 , 1.49] 0.88 [0.48 , 1.64] 1.34 [0.54 , 3.30] 2.22 [0.95 , 5.23] 0.66 [0.28 , 1.55] 1.74 [1.00 , 3.03] 0.84 [0.58 , 1.21] <b>1.03 [0.82 , 1.28]</b>	0.01 0.1		

Meta-analysis of *HLA-A\*03* for dengue fever (DF), dengue haemorrhagic fever (DHF) and DEN (CI, Confidence interval; M-H, Mantel-Haens; effect test for Odds Ratio).

In terms of combined influence of HLA-A\*24 across the three different subtypes of dengue infection, the statistics [P < 1.0E-05, OR = 1.32 (1.20–1.45)] (Figure 9) suggest an overall predisposing influence towards dengue.

In terms of population specific tendencies (Figure 10), *HLA-*A\*24 shows significant predisposition towards DEN in the Caribbean population [P = 1.0E-03, OR = 14.29 (2.90–70.35)]. It is noted that the wide confidence interval for the study is due to its small sample size and should be interpreted with caution. In the three Latin American studies (59, 68, 69), *HLA-A\*24* does not show statistically significant associations with being a risk or a protective factor for DEN [P = 0.57, OR = 1.10 (0.78–1.55)]. Having said that, the tendency of the allele could be considered towards being predisposed to DEN.

Among South Asians, *HLA-A\*24* shows a similar trend to that of Latin Americans, with no statistically significant associations towards being a risk or protective factor for DEN [P = 0.33, OR = 1.19 (0.84–1.69)], while having a tendency towards being a risk allele for DEN (Figure 10). However, in Southeast Asia, *HLA-A\*24* 

is inferred to be a risk allele for DEN based on the combined odds ratio [P = 3.0E-04, OR = 1.33 (1.14–1.56)] (Figure 10).

When all the regional populations are considered together,  $HLA-A^{*}24$  is inferred to be a predisposing allele for DEN [P < 1.0E-05, OR = 1.30 (1.14–1.49)] (Figure 10). This inference is significantly driven by the outcomes from the studies on Southeast Asian populations, which contributed to a higher number of sample counts.

#### 3.4 HLA-A\*33

For *HLA-A\*33* (Figure 11), when comparing DF with healthy controls based on four studies, no significant influence of *HLA-A\*33* on DF was inferred [P = 0.71, OR = 0.94 (0.68–1.30)]. Whereas, when we compared DHF with healthy controls, *HLA-A\*33* shows significant protective influence against DHF [P = 6.0E-04, OR = 0.63 (0.48–0.82)], despite a significant degree of heterogeneity [P = 5.0E-02].

HLA -A*03	DE	N	Healthy	Control		Odds ratio	Odds ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Caribbean							
Brown 2011	11	43	17	127	4.1%	2.22 [0.95 , 5.23]	<b></b>
Subtotal (95% CI)		43		127	4.1%	2.22 [0.95 , 5.23]	
Total events:	11		17				-
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.83 (F	P = 0.07)					
Latin America							
Paradoa 1987	10	164	45	552	12.3%	0.73 [0.36 . 1.49]	
Beatriz 2007	17	240	30	378	13.7%	0.88 [0.48 . 1.64]	
Daniela 2014	27	190	30	346	11.6%	1.74 [1.00 . 3.03]	
Subtotal (95% CI)		594		1276	37.6%	1.10 [0.78 . 1.56]	<b>↓</b> <sup>−</sup>
Total events:	54		105				T
Heterogeneity: Chi <sup>2</sup> =	4.42, df = 2	2 (P = 0.1	1);   <sup>2</sup> = 559	%			
Test for overall effect:	Z = 0.53 (F	P = 0.60)	<i>,,</i>				
South Asia							
Gathsaurie 2011	11	220	9	238	5.2%	1.34 [0.54 . 3.30]	
Alagarasu 2013	10	114	14	110	8.2%	0.66 [0.28 . 1.55]	
Subtotal (95% CI)		334		348	13.4%	0.92 [0.50 , 1.71]	
Total events:	21		23			• • •	$\mathbf{T}$
Heterogeneity: Chi <sup>2</sup> =	1.25, df = <sup>-</sup>	1 (P = 0.2	26); I <sup>2</sup> = 20 <sup>4</sup>	%			
Test for overall effect:	Z = 0.26 (F	P = 0.80)	,,				
Southeast Asia							
Chiewsilp 1981	7	86	16	254	4.7%	1.32 [0.52 . 3.32]	
Vejbaesya 2015	305	427	170	227	40.2%	0.84 [0.58 , 1.21]	
Subtotal (95% CI)		513		481	44.9%	0.89 [0.63 . 1.25]	1
Total events:	312		186			. , .	T
Heterogeneity: Chi <sup>2</sup> =	0.80, df = <sup>-</sup>	1 (P = 0.3	37): l² = 0%	,			
Test for overall effect:	Z = 0.68 (F	P = 0.50)	,,				
		1484		2232	100.0%	1.03 [0.82 . 1.28]	
Total (95% CI)							Y
Total (95% CI) Total events:	398		331				
<b>Total (95% CI)</b> Total events: Heterogeneity: Chi² =	398 10.59. df =	7 (P = 0	331 16): l² = 34	4%		0	
<b>Total (95% CI)</b> Total events: Heterogeneity: Chi <sup>2</sup> = Test for overall effect: :	398 10.59, df = Z = 0.23 (F	7 (P = 0 P = 0.81)	331 .16); l² = 34	4%		0.	01 0.1 1 10 100

Meta-analysis of HLA-A\*03 across different populations for DEN (CI, Confidence interval; M-H, Mantel-Haenszel fixed effect test for Odds Ratio).

Despite significant heterogeneity observed across studies [P = 3.0E-04], HLA-A\*33 was found to confer a protective effect against DEN [P = 3.0E-02, OR = 0.80 (0.66-0.98)] (Figure 11). When observed across all the three different tested scenarios for dengue (DF, DHF, DEN), *HLA-A\*33* was inferred to have a protective effect [P = 4.0E-04, OR =0.77 (0.67–0.89)] (Figure 11). Such an inference could have been driven by HLA-A\*33's stronger protective influence against DHF.

When compared across worldwide populations (Figure 12), HLA-A\*33 is observed to be a risk factor for DEN in the Caribbean population [P = 3.0E-03, OR = 4.51 (1.65-12.33)], a trend completely disparate from the general trend observed for HLA-A\*33 in the previous set of inference. Furthermore, the small sample size could have played a significant role in the wide confidence interval observed for the Caribbeans. Interestingly, in Latin America, a study on the Brazilian population (68) showed a similar predisposing tendency for HLA-A\*33 as the Caribbeans (72), whereas another study on Cubans (69) demonstrated a protective tendency. Overall, HLA-A\*33 does not demonstrate any significant protective or predisposing effect with respect to DEN to the Caribbeans [P = 0.76, OR = 0.92 (0.52-1.61)].

Similar to Latin America, HLA-A\*33 does not show an association with a protective or predisposing effect towards DEN

in South Asians [P = 0.53, OR = 1.13 (0.77-1.65)] (Figure 12). In contrast, in Southeast Asia, HLA-A\*33 is inferred to confer protection against DEN [P < 1.0E-4, OR = 0.57 (0.43-0.75)] (Figure 12). When examined individually across the four Southeast Asian studies included in the analysis, the protective trend remains consistent throughout (56, 66, 67, 97).

Considering the four regional population groups together, HLA-A\*33 is inferred to be a protective allele against DEN [P = 3.0E-02, OR = 0.80 (0.66-0.98)] (Figure 12). This inference is primarily driven by the associations inferred from the analysis of the Southeast Asian populations, having a higher sample size. The statistically significant difference in the combined odds ratio across the different regions further highlights the population-specific difference in the influence of HLA-A\*33 on DEN.

#### 3.5 HLA-B\*44

HLA-B\*44 (Figure 13) showed no significant protective or predisposing association with DF when compared to healthy controls [P = 0.28, OR = 0.88 (0.70-1.11)]. Nonetheless, the observed tendency was towards being protective against DF.

HLA -A*24 Study or Subgroup	Cas Events	se Total	Healthy ( Events	Jontrol Total	Weight	M-H, Fixed, 95% Cl	Odds ratio M-H, Fixed, 95% Cl
DF vs HC							
Stephens 2002	53	149	48	140	4.3%	1.06 [0.65 , 1.72]	+
Polizel 2004	15	64	117	667	2.1%	1.44 [0.78 , 2.65]	+
Beatriz 2007	23	240	35	378	3.3%	1.04 [0.60 , 1.81]	
Alagarasu 2013	23	85	31	110	2.6%	0.95 [0.50 , 1.78]	-+-
Vejbaesya 2015	97	277	82	227	7.9%	0.95 [0.66 , 1.37]	-+
Subtotal (95% CI)		815		1522	20.2%	1.04 [0.83 , 1.30]	♦
Total events:	211		313				
Heterogeneity: Chi <sup>2</sup> =	1.39, df = 4	4 (P = 0.8	5); l² = 0%				
Test for overall effect:	Z = 0.33 (F	P = 0.74)					
DHF vs HC							
Chiewsilp 1981	3	87	5	138	0.5%	0.95 [0.22 , 4.08]	
∟oke 2001	108	309	65	251	6.3%	1.54 [1.07 , 2.22]	
Stephens 2002	36	114	48	140	4.0%	0.88 [0.52 , 1.50]	
Lan 2008	75	211	162	650	6.9%	1.66 [1.19 , 2.32]	-
Appanna 2010	6	32	3	32	0.3%	2.23 [0.51 , 9.83]	_ <b>_</b>
Gathsaurie 2011	54	220	47	238	4.6%	1.32 [0.85 , 2.06]	
Alagarasu 2013	9	29	31	110	1.2%	1.15 [0.47 , 2.79]	_ <b>_</b>
Vejbaesya 2015	63	150	82	227	5.1%	1.28 [0.84 , 1.95]	<b></b>
Subtotal (95% CI)		1152		1786	28.8%	1.38 [1.16 , 1.64]	•
Total events:	354		443				•
Heterogeneity: Chi <sup>2</sup> =	5.24, df = 1	7 (P = 0.6	3); l² = 0%				
Test for overall effect:	Z = 3.62 (F	P = 0.000	3)				
DEN vs HC							
Chiewsiln 1981	3	87	5	138	0.5%	0.95 [0.22 4.08]	
Loke 2001	108	309	65	251	6.3%	1.54 [1.07 . 2.22]	
Stephens 2002	89	263	46	140	5.3%	1.05 [0.68 . 1.62]	
Polizel 2004	15	64	117	667	2.1%	1.44 [0.78 . 2.65]	I_
Beatriz 2007	23	240	35	378	3.3%	1.04 [0.60 , 1.81]	
Lan 2008	221	629	112	450	11.4%	1.63 [1.25 , 2.14]	-
Appanna 2010	46	184	41	190	4.1%	1.21 [0.75 , 1.96]	-
Gathsaurie 2011	54	220	47	238	4.6%	1.32 [0.85 . 2.06]	
Brown 2011	8	43	2	127	0.1%	14.29 [2.90 , 70.35]	<u> </u>
Alagarasu 2013	32	114	31	346	1.5%	3.97 [2.29 , 6.88]	
Daniela 2014	17	190	33	346	2.9%	0.93 [0.50 , 1.72]	_
Vejbaesya 2015	160	427	82	227	9.0%	1.06 [0.76 , 1.48]	+
Subtotal (95% CI)		2770		3498	51.0%	1.40 [1.23 , 1.60]	
Total events:	776		616				•
Heterogeneity: Chi <sup>2</sup> =	31.32, df =	11 (P = 0	0.0010); l <sup>2</sup> :	= 65%			
Test for overall effect:	Z = 5.05 (F	P < 0.000	01)				
Total (95% CI)		4737		6806	100 0%	1 32 [1 20 1 45]	
Total events:	13/1	4/3/	1370	0000	100.0%	1.32 [1.20 , 1.45]	•
Heterogeneity: Chi2 -	1341 1332 AF-	24 (P - 1	1372 - 100910 12	45%			
Test for overall offect	-+J.JZ, UI -	24 (F - 1	0.009), I <sup>-</sup> - 01)	4070			0.02 0.1 1 10 50
Test for subgroup diff.	L - J.// (۴	$\sim 0.000$	df = 2 (P -	- 0 07) 12	- 63 10/		
reation subgroup am	erences. Cl	5.43	, ui – 2 (P -	- 0.07), 1-	- 03.1%		

When we compare DHF with healthy controls, *HLA-B\*44* was found to have a protective effect against DHF [P = 1.0E-03, OR = 0.60 (0.44-0.82)]. However, this observation does not stand true when comparing DEN with healthy controls [P = 0.77, OR = 0.97 (0.81-1.17)], as no significant protective or predisposing effect is observed.

The overall tendency of HLA-B\*44 allele suggests a protective effect against dengue [P = 2.0E-02, OR = 0.86 (0.75-0.98)] (Figure 13). The significant difference between each subgroup highlights HLA-B\*44's increased protective influence on DHF likely have influenced the overall role for the allele with respect to dengue.

Comparing regional population tendencies (Figure 14), in the Caribbean, no protective or predisposing influence of HLA-B\*44 was observed [P = 0.38, OR = 1.56 (0.58-4.22)], although the observed trend was towards being predisposing. In Latin America, despite showing significant heterogeneity [P = 3.0E-02], HLA-B\*44 is inferred to have predisposing influence towards DEN [P = 4.0E-02, OR = 1.37 (1.02–1.85)].

In South Asia, HLA-B\*44 shows a tendency towards being predisposing; however, no significant association was observed [P = 0.75, OR = 1.07 (0.69–1.67)] (Figure 14). In contrast, from the two Thai-based study in Southeast Asia, we can infer a protective effect of HLA-B\*44 against DEN [P = 4.0E-03, OR = 0.65 (0.49-0.87] (Figure 14).

HLA-B\*44 shows no significant association with DEN when all four regions are taken together (Figure 14). However, significant

FIGU

fixe

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Caribbean							
Brown 2011	8	43	2	127	0.2%	14.29 [2.90 , 70.35]	
Subtotal (95% CI)		43		127	0.2%	14.29 [2.90 , 70.35]	
Total events:	8		2				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 3.27 (P	= 0.001)	)				
Latin America							
Polizel 2004	15	64	117	667	4.0%	1.44 [0.78 . 2.65]	
Beatriz 2007	23	240	35	378	6.3%	1.04 [0.60 1.81]	
Daniela 2014	17	190	33	346	5.4%	0.93 [0.50 1.72]	T
Subtotal (95% CI)		494		1391	15.7%	1 10 [0 78 1 55]	
Total events:	55		185	1001	10.170		<b>Y</b>
Heterogeneity: $Chi^2 = 1$	1 06 df = 2	P = 0.5	9)· 1² = 0%				
Test for overall effect: 2	Z = 0.57 (P	= 0.57)	(0), T = 070				
South Asia							
Gathsaurie 2011	54	220	47	238	8 7%	1 32 10 85 2 061	
	32	11/	31	110	5.8%	0.00 [0.56 1.78]	<b>1-</b>
Subtotal (95% CI)	52	224	51	3/9	14 5%	1 10 [0 84 1 60]	
Total events:	96	554	70	540	14.5 /6	1.19 [0.04 , 1.09]	•
Illeteregeneity Chi <sup>2</sup> = (		(D = 0.4)	F): 12 - 00/				
Test for everall effect:	J.50, UI – I Z – 0 07 (D	(P = 0.4	5), 1- – 0%				
rest for overall effect. 2	2 - 0.97 (P	- 0.33)					
Southeast Asia							
Chiewsilp 1981	3	87	5	138	1.0%	0.95 [0.22 , 4.08]	
Loke 2001	108	309	65	251	11.9%	1.54 [1.07 , 2.22]	
Stephens 2002	89	263	46	140	10.2%	1.05 [0.68 , 1.62]	+
Lan 2008	221	629	112	450	21.7%	1.63 [1.25 , 2.14]	+
Appanna 2010	46	184	41	190	7.7%	1.21 [0.75 , 1.96]	
Vejbaesya 2015	160	427	82	227	17.1%	1.06 [0.76 , 1.48]	+
Subtotal (95% CI)		1899		1396	69.5%	1.33 [1.14 , 1.56]	•
Total events:	627		351			_	▼
Heterogeneity: Chi <sup>2</sup> = 6	6.16, df = 5	(P = 0.2	9); l² = 199	6			
Test for overall effect: 2	Z = 3.59 (P	= 0.000	3)				
Total (95% CI)		2770		3262	100.0%	1.30 [1.14 , 1.49]	▲
Total events:	776		616				<b>▼</b>
Heterogeneity: Chi <sup>2</sup> =	17.62, df =	11 (P = 0	0.09); I <sup>2</sup> = 3	8%			
Test for overall effect:	Z = 3.97 (P	< 0.000	1)				0.01 0.1 1 10 1
Test for subgroup diffe	rences: Ch	i <sup>2</sup> = 9 90	df = 3 (P =	= 0 02) l <sup>2</sup>	= 69 7%		

heterozygosity [P = 4.0E-03] is observed across each region, highlighting the population-specific influence of *HLA-B\*44* towards DEN.

#### 4 Discussion

Given the observed historical trends, dengue could continue its rapid expansion across the globe, potentially increasing the number of people at risk of infection. Countries in Southeast Asia, South Asia, Caribbean, and Latin America share the primary burden of severe epidemics with longer dengue transmission seasons. For instance, Argentina's severe dengue epidemic of 2023 (Figures 3A, B), was characterised by a significantly more humid and hotter summer, leading to more favourable climatic conditions for *Aedes aegypti* to survive (100). Brazil reported 1.5 million cases more in 2023 compared to 2022 (1), driven by fragmentation and degradation of the Amazon for infrastructure development (101, 102) and climate change (103). These factors contribute to the spread of dengue to the most remote regions within Brazil, leaving many previously unexposed populations vulnerable to dengue.

South Asia and Southeast Asia continue to have a significant burden of dengue. Bangladesh recorded its worst dengue epidemic in 2023 with more than 300,000 cases, characterised by 414.4% annual increase (Figures 3A, B). Such a severe epidemic was attributed to climate change-related factors in the deltaic and primarily riverine country, leading to the spread of dengue far beyond the urban centres to the remotest rural areas (4). In fact, South Asia and Southeast Asia are one of the most endemic regions in the world, especially India, Sri Lanka, Myanmar, Thailand, and Indonesia (2). A significant and relatively well understood exception in Southeast Asia is Singapore, which reported a 69% drop in dengue cases from 2022 to 2023 (Figure 3B) due to effective governmental controls despite increased conduciveness for dengue due to climate change (104).

It has been estimated that dengue cases could rise by 13% for each 1°C increase in temperature (105). Studies have also taken into consideration of GDP and economic growth as predictive variables

HLA -A*33 Study or Subgroup	Cas Events	e Total	Healthy ( Events	Control Total	Weight	Odds ratio M-H, Fixed, 95% Cl	Odds ratio M-H, Fixed, 95% Cl
DF vs HC							
Stephens 2002	35	149	36	140	6.7%	0.89 [0.52 , 1.52]	
Polizel 2004	5	64	25	667	1.0%	2.18 [0.80 , 5.90]	<b>_</b> _
Beatriz 2007	7	240	20	378	3.6%	0.54 [0.22 , 1.29]	<b>_</b> _
Alagarasu 2013	23	85	19	110	2.9%	1.78 [0.89 , 3.54]	<b></b>
Edelwsia 2015	5	92	34	296	3.6%	0.44 [0.17 , 1.17]	
Subtotal (95% CI)		630		1591	17.8%	0.94 [0.68 , 1.30]	<b></b>
Total events:	75		134				T
Heterogeneity: Chi <sup>2</sup> = 9	9.94, df = 4	(P = 0.0	4); l² = 60%	6			
Test for overall effect: 2	Z = 0.38 (F	9 = 0.71)					
DHF vs HC							
Hsin 2001	34	309	46	251	10.7%	0.55 [0.34 , 0.89]	
Stephens 2002	20	114	36	140	6.3%	0.61 [0.33 , 1.14]	
Gathsaurie 2011	41	220	46	238	8.5%	0.96 [0.60 , 1.53]	_
Alagarasu 2013	5	29	19	110	1.6%	1.00 [0.34 , 2.95]	
Edelwsia 2015	3	153	34	296	5.4%	0.15 [0.05 , 0.51]	
Subtotal (95% CI)		825		1035	32.5%	0.63 [0.48 , 0.82]	
Total events:	103		181				•
Heterogeneity: Chi <sup>2</sup> = 9	9.41, df = 4	(P = 0.0	5); l² = 57%	6			
Test for overall effect: 2	Z = 3.41 (F	= 0.0006	6)				
DEN vs HC							
Hsin 2001	34	309	46	251	10.7%	0.55 [0.34 , 0.89]	
Stephens 2002	55	263	36	140	8.8%	0.76 [0.47 , 1.24]	
Polizel 2004	5	64	25	667	1.0%	2.18 [0.80 , 5.90]	<b></b>
Beatriz 2007	7	240	20	378	3.6%	0.54 [0.22 , 1.29]	
Appanna 2010	14	184	20	190	4.3%	0.70 [0.34 , 1.43]	
Gathsaurie 2011	41	220	46	238	8.5%	0.96 [0.60 , 1.53]	
Brown 2011	10	43	8	127	0.7%	4.51 [1.65 , 12.33]	
Alagarasu 2013	28	114	19	110	3.5%	1.56 [0.81 , 3.00]	<b></b>
Daniela 2014	5	190	9	346	1.5%	1.01 [0.33 , 3.06]	
Edelwsia 2015	8	245	34	296	7.1%	0.26 [0.12 , 0.57]	
Subtotal (95% CI)		1872		2743	49.7%	0.80 [0.66 , 0.98]	
Total events:	207		263				•
Heterogeneity: Chi <sup>2</sup> = 3	30.99, df =	9 (P = 0.	0003); l <sup>2</sup> =	71%			
Test for overall effect: 2	Z = 2.12 (F	9 = 0.03)					
Total (95% Cl)		3327		5369	100.0%	0.77 [0.67 , 0.89]	▲
Total events:	385		578			· · · ·	•
Heterogeneity: Chi <sup>2</sup> = {	53.80, df =	19 (P < 0	0.0001); l²	= 65%			
Test for overall effect: 2	Z = 3.54 (F	= 0.0004	4)				0.01 0.1 1 10 100
	· · · ·						
Test for subgroup diffe	rences: Ch	i² = 3.88.	df = 2 (P =	= 0.14), l <sup>2</sup>	= 48.4%		

and suggested future economic growth could counterbalance dengue case increase, while population growth could be the driving factor in case of any increase in the number of cases (106). Nevertheless, climate change could raise dengue risk further in future, having serious implications for human health (3, 81, 106, 107). To mitigate this risk, understanding *HLA*'s role across different populations and dengue outcomes is crucial.

From the meta-analysis, we infer that HLA-A\*02 is associated with predisposition towards DF and DEN, while also showing a tendency to be a risk factor for DHF. We demonstrate a significant difference between the tendencies of HLA-A\*02 associations towards DEN across different regional populations (Figure 6). The predisposition towards dengue infection is primarily driven by the Southeast Asian populations, which signifies that HLA-A\*02could be considered as a risk allele for Southeast Asia in particular (Figure 6). Our inferences about HLA-A\*02 provide a significant improvement compared to previous meta-analyses by delving into different pathological outcomes and population-specific patterns of associations (89, 90). In Southeast Asia, HLA-A\*02 is a common HLA allele across numerous populations throughout the region (108), thereby could be considered as a warning signal for preparing effective medical and policy measures to prevent future dengue outbreaks.

We highlight that *HLA-A\*03* is a risk allele for DHF (Figure 7). However, this observation is primarily driven by a Thai populationbased study showing a strong predisposition for DHF compared to other studies in the same group (64). However, such inference may not be enough to conclude the mentioned association at the scale of Southeast Asia (Figure 8). More studies within Southeast Asia and Thailand are needed to confirm this association.

HLA-A\*24 is inferred to be a predisposing allele towards DHF and DEN (Figure 9), similar to a previous meta-analysis with smaller statistical power (89). However, we uncover the population-specific association in much higher resolution,

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Caribbean							
Brown 2011	10	43	8	127	1.5%	4.51 [1.65 , 12.33]	
Subtotal (95% CI)		43		127	1.5%	4.51 [1.65 , 12.33]	
Total events:	10		8				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 2.93 (F	P = 0.003	)				
Latin America							
Polizel 2004	5	64	25	667	1.9%	2.18 [0.80 , 5.90]	
Beatriz 2007	7	240	20	378	7.2%	0.54 [0.22 , 1.29]	
Daniela 2014	5	190	9	346	3.0%	1.01 [0.33 , 3.06]	
Subtotal (95% CI)		494		1391	12.1%	0.92 [0.52 , 1.61]	<b></b>
Total events:	17		54			• / •	<b>•</b>
Heterogeneity: Chi <sup>2</sup> =	4.35. df = 2	2 (P = 0.1	1); l <sup>2</sup> = 54%	6			
Test for overall effect:	Z = 0.31 (F	P = 0.76)	,,				
South Asia							
Gathsaurie 2011	41	220	46	238	17.2%	0.96 [0.60 , 1.53]	<b>_</b>
Alagarasu 2013	28	114	19	110	7.0%	1.56 [0.81 , 3.00]	1
Subtotal (95% CI)		334		348	24.2%	1.13 [0.77 , 1.65]	<b>_</b>
Total events:	69		65			• • •	
Heterogeneity: Chi <sup>2</sup> =	1.43, df = 1	1 (P = 0.2	3); l² = 309	6			
Test for overall effect:	Z = 0.63 (F	P = 0.53)					
Southeast Asia							
Hsin 2001	34	309	46	251	21.6%	0.55 [0.34 , 0.89]	
Stephens 2002	55	263	36	140	17.8%	0.76 [0.47 , 1.24]	
Appanna 2010	14	184	20	190	8.7%	0.70 [0.34 , 1.43]	
Edelwsia 2015	8	245	34	296	14.2%	0.26 [0.12 , 0.57]	
Subtotal (95% CI)		1001		877	62.3%	0.57 [0.43 , 0.75]	
Total events:	111		136				•
Heterogeneity: Chi <sup>2</sup> =	5.56, df = 3	3 (P = 0.1	4); l <sup>2</sup> = 46 <sup>0</sup>	6			
Test for overall effect:	Z = 3.97 (F	o < 0.000	1)				
Total (95% CI)		1872		2743	100.0%	0.80 [0.66 , 0.98]	
Total events:	207		263				
Total ovolito.	30.99, df =	9 (P = 0	0003); I <sup>2</sup> =	71%		(	0.01 0.1 1 10
Heterogeneity: Chi <sup>2</sup> =							
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	Z = 2.12 (F	P = 0.03)					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Test for subgroup diffe	Z = 2.12 (F erences: Ch	P = 0.03) ni² = 20.5	9, df = 3 (P	= 0.0001	), l² = 85.4	4%	

indicating that *HLA-A\*24* could be a risk allele for Southeast Asia, while showing similar tendencies in South America and South Asia (Figure 10). In Southeast Asia, *HLA-A\*24* is relatively common, with the highest frequency within indigenous populations of Malaysia, Myanmar, and Northeastern Thailand, which could make them susceptible to the disease (108). Although showing similar tendencies, the number of South Asian and Latin American studies remain limited, which may not reveal the true tendencies for association.

HLA-B\*44 was inferred to have an overall protective association with significant heterogeneity across different studies (Figure 13). However, it revealed contrast in association tendencies when the studies were stratified based on regional populations. In Latin America, driven primarily by Daniela et al., 2014 (59), HLA-B\*44 showed predisposition towards dengue, with South Asia and Caribbean following the same tendency (Figure 14). In contrast, HLA-B\*44 is found to be associated with protection against DEN in Southeast Asians, driven by a homogenous tendency within the Southeast Asian studies reporting the allele (Figure 14). Within Latin America, this HLA allele is most common within mestizos in Cuba, Argentina, Ecuador, and Brazil, especially in the Amazonia region (108). Interestingly, HLA-B\*44 is most common primarily in the Iberian Peninsula, which could point specifically to the colonial origin of this risk to those regions.

The general tendencies of *HLA* allele associations could be attributed to the possible results of host-pathogen co-evolution (109). This could be especially true for *HLA*, where there is much support for the idea of pathogen diversity influencing the high polymorphism of the *HLA* gene regions. A previous study inferred lower binding efficiency for *HLA* class I A02 and A24 supertypes for all four dengue serotypes, which could explain their observed predisposing tendency towards DEN (110). Similarly, B44 supertypes demonstrated significantly higher binding efficiency, which could explain its protective association within Southeast Asians, however it fails to explain the contrasting observation within Latin Americans (110). Interestingly, dengue and other flavivirus species showed unique binding characteristics with respect to *HLA* (110).

The overwhelming majority of *HLA* class I alleles influencing dengue risk highlights their crucial role in dengue pathogenesis. It has

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
DF vs HC							
Stephens 2002	16	149	21	140	4.0%	0.68 [0.34 , 1.37]	
Polizel 2004	12	64	126	667	3.7%	0.99 [0.51 , 1.91]	-
Beatriz 2007	20	240	36	378	5.3%	0.86 [0.49 1.53]	
Falcon-Lezama 2009	1	46	3	68	0.5%	0 48 [0 05 4 78]	
Brown 2011	. 7	50	12	127	1.2%	1 56 [0 58 4 22]	
Alagarasu 2013	16	83	20	110	2.9%	1 07 [0 52 2 23]	
Veibaesva 2015	109	277	100	227	13.8%	0.82 [0.58 1.18]	
Subtotal (95% CI)		909		1717	31.4%	0.88 [0.70 . 1.11]	I
Total events:	181		318				<b>Y</b>
Heterogeneity: Chi <sup>2</sup> = 2	60 df = 6	(P = 0.86)	$3) \cdot l^2 = 0\%$				
Test for overall effect: Z		= 0.28)	, 0,0				
Stenhens 2002	7	114	21	140	2 70/	0 37 [0 15 0 01]	
Ealcon Lezama 2000	1	114	21	140	0.1%		
Catheourie 2011	1 26	01	ა ელ	34 220	U.4%	1 00 [0.07 , 7.19]	
Alegoroou 2012	20	220	20	230	4.0 /0	0.75 [0.01, 1.93]	
Najarasu 2015	4	20	100	227	1.470	0.75 [0.25 , 2.40]	
Subtotal (95% CI)	40	500 500	100	740	12.170 22.19/	0.40 [0.30 , 0.72]	
Total events:	70	520	170	749	22.1%	0.60 [0.44 , 0.62]	•
Hotorogonoity: Chi2 - 6	70 df - 4	(D - 0.16)	170 5): 12 - 410/				
Telefogeneily. Cnl <sup>2</sup> = 6	. / J, ul = 4	$(r^2 - 0.10)$	), I <sup>-</sup> – 41%	)			
rest for overall effect: 2	. – 3.24 (P	- 0.001)					
DEN vs HC							
Stephens 2002	23	263	21	140	5.2%	0.54 [0.29 , 1.02]	
Polizel 2004	12	64	126	667	3.7%	0.99 [0.51 , 1.91]	
Beatriz 2007	20	240	36	378	5.3%	0.86 [0.49 , 1.53]	
Falcon-Lezama 2009	2	62	3	68	0.6%	0.72 [0.12 , 4.47]	<b>-</b>
Gathsaurie 2011	26	220	26	238	4.6%	1.09 [0.61 , 1.95]	_ <b>_</b> _
Brown 2011	7	50	12	127	1.2%	1.56 [0.58 , 4.22]	<b></b>
Alagarasu 2013	21	111	20	110	3.4%	1.05 [0.53 , 2.07]	_ <b>_</b>
Daniela 2014	49	190	46	346	5.0%	2.27 [1.45 , 3.55]	-
Vejbaesya 2015	149	427	100	227	17.6%	0.68 [0.49 , 0.95]	-
Subtotal (95% CI)		1627		2301	46.5%	0.97 [0.81 , 1.17]	
Total events:	309		390				Ţ
Heterogeneity: Chi <sup>2</sup> = 2	2.75, df =	8 (P = 0.0	004); l² = 6	5%			
Test for overall effect: Z	2 = 0.30 (P	= 0.77)					
Total (95% CI)		3064		4767	100.0%	0.86 [0.75 , 0.98]	
Total events:	568		878			•	۲
Heterogeneity: Chi <sup>2</sup> = 3	8.65, df =	20 (P = 0	.007); l <sup>2</sup> =	48%			
Test for overall effect: Z	. = 2.24 (P	= 0.02)					0.01 1 10 10
	×.	,					

been postulated that *HLA* class I restricted CD8<sup>+</sup> T cell lymphocytes determined the immune response and risk towards more DHF. Two ways could mediate such influence by secretion of anti-viral cytokines and cytolysis of infected cells (66). Moreover, secreted inflammatory cytokines can affect vascular cell permeability (111), which could severely damage the cell integrity when DENV epitopes mimic host proteins leading to the loss of self-tolerance of the T cells (112). Such scenarios could lead to serious vascular damage and leaking, leading to DHF complications. Moreover, *HLA* class I alleles were also found to be upregulated when infected with DENV *in vivo*, which led to the suppression of natural killer cell response, suggesting a crucial role in dengue pathogenesis for *HLA* class I alleles (48).

Despite having valuable inferences from previously published casecontrol studies, we could be missing out on further potentially vital insights on how *HLA* allele variations influence dengue. The main factors contributing to this potential missing out of vital insights is the lack of case-control studies from the majority of dengue endemic regions or usage of small sample sizes in association studies, hampering association powers. Until now, vast region of tropical Africa having dengue endemic regions remains unrepresented. Whereas in South Asia, which has witnessed several dengue epidemics in recent years, there have been limited HLA association studies with statistically significant sample size. To our knowledge, studies from a single cohort each from vast countries like India (60, 61) and Sri Lanka (71) are the only studies reporting HLA association with dengue. Given the diverse genetic landscapes across such under-represented regions, we may find further crucial insights into how human HLA diversity influences dengue risk, which could shape regional medical strategies and deeper understanding of disease pathogenesis. Sufficient sample size for significant association power, proper consideration of demographic profiles of populations which play crucial role in determining dengue risk and pathogenesis, like age (79) and gender

пLA -B^44 Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Caribbean							
Brown 2011	7	50	12	127	2.6%	1.56 [0.58 , 4.22]	
Subtotal (95% CI)		50		127	2.6%	1.56 [0.58 , 4.22]	
Total events:	7		12				
Heterogeneity: Not appl	licable						
Test for overall effect: Z	= 0.88 (P	= 0.38)					
Latin America							
Polizel 2004	12	64	126	667	8.0%	0 99 [0 51 1 91]	
Beatriz 2007	20	240	36	378	11.4%	0 86 [0 49 1 53]	
Falcon-Lezama 2009	20	62	3	68	1 2%	0 72 [0 12 4 47]	
Daniela 2014	49	190	46	346	10.8%	2.27 [1.45 . 3.55]	
Subtotal (95% CI)	.0	556	10	1459	31.4%	1.37 [1.02 . 1.85]	
Total events:	83		211				
Heterogeneity: Chi <sup>2</sup> = 8	.72. df = 3	(P = 0.03)	3): l <sup>2</sup> = 66%	D			
Test for overall effect: Z	= 2.07 (P	= 0.04)	,,				
South Asia							
Gathsaurie 2011	26	220	26	238	9.8%	1.09 [0.61 , 1.95]	_
Alagarasu 2013	21	111	20	110	7.2%	1.05 [0.53 , 2.07]	
Subtotal (95% CI)		331		348	17.1%	1.07 [0.69 , 1.67]	<b></b>
Total events:	47		46				T
Heterogeneity: Chi <sup>2</sup> = 0	.01, df = 1	(P = 0.93	3); I² = 0%				
Test for overall effect: Z	= 0.32 (P	= 0.75)					
Southeast Asia							
Stephens 2002	23	263	21	140	11.1%	0.54 [0.29 , 1.02]	
Vejbaesya 2015	149	427	100	227	37.8%	0.68 [0.49 , 0.95]	-
Subtotal (95% CI)		690		367	49.0%	0.65 [0.49 , 0.87]	•
Total events:	172		121				•
Heterogeneity: Chi <sup>2</sup> = 0	.39, df = 1	(P = 0.5	3); I² = 0%				
Test for overall effect: Z	= 2.90 (P	= 0.004)					
Total (95% CI)		1627		2301	100.0%	0.97 [0.81 , 1.17]	•
Total events:	309		390				
Heterogeneity: Chi <sup>2</sup> = 2	2.75, df =	8 (P = 0.0	004); l <sup>2</sup> = 6	5%		0.	01 0.1 1 10
Test for everall effect: 7	= 0.30 (P	= 0.77)					
Test for overall effect. Z							

(113, 114) (especially considering immune modulation by sex hormones) should be considered and investigated in detail to understand the full spectrum of HLA mediated immune reaction towards dengue. We further suggest applying population genetics approach on a finer scale to determine *HLA*-associated dengue risk characterisation. For instance, in a population with multiple ancestries, will the frequency of dengue-associated HLA alleles vary based on the proportion of any particular ancestral component in the genomic makeup of the samples? This could be more pronounced in the recently admixed populations in the Americas, such as mestizos with Native American, European, and African ancestries. Such inferences may help to shape mitigation strategies based on such risk.

Overall, due to current climate change, the populations at risk in the future are bound to increase by many folds. Without effective preparedness, dengue is bound to have serious negative repercussions on public health, influencing the global and national economy and straining medical infrastructures. Conducting a meta-analysis on *HLA* allele-associated dengue risk, considering the impacts of climate change and evolutionary influences, can yield numerous long-term benefits. Studying the crucial immune gene *HLA*'s associated with different forms of dengue potentially aid in understanding host genetic factors and mechanism influencing the pathogenesis of dengue, leading to improved predictive models and more effective personalised medical approaches. This comprehensive knowledge could guide public health policies, allowing for targeted interventions and informed policymaking, leading to improved regional and national preparedness. For instance, since our study highlighted the population-specific association of *HLA* alleles with dengue, the inferences could be utilised to determine the level of risk within a specific population based on the frequency of such *HLA* allele, aiding in targeted intervention of health policies.

Climate-informed genetic risk assessments, which integrate future climatic projections under various scenarios of climate change, urbanization, and population growth, along with other demographic, environmental, and societal factors, could play a vital role. By considering these elements alongside the genetic makeup of the studied population, these assessments can help understand population-level predispositions to diseases. Such assessments support effective adaptation strategies and resource allocation, bolstering policy advocacy and community resilience. Understanding the relationship between *HLA* binding and the evolutionary conservation of viral proteins can provide insights into host-

pathogen interactions, informing the design of more effective therapies and vaccines (4, 7). This guidance could be crucial since no specific treatments for dengue currently exist. Overall, these benefits significantly enhance dengue prevention and control efforts in the context of changing climate and inform medical policies.

#### Author contributions

AG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. HK: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. S-SK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

#### Funding

The author(s) declare that financial support was received for the research and/or publication of this article. The authors acknowledge the financial support from GenomeAsia 100K (https://www.genomeasia100k.org/). This research is supported by the Ministry of Education, Singapore, under its RG35/24 MOE AcRF Tier 1 Award.

#### Acknowledgments

We used Grammarly and its assistive generative AI technology (Grammarly Inc., San Fransisco, USA) to check for grammatical coherence and language consistency. Figure 1 was plotted on Tableau Desktop 2021.1 through openly available OpenStreetMap data. OpenStreetMap® is open data, licensed under the Open Data Commons Open Database License (ODbL) by the OpenStreetMap Foundation (OSMF). Figure 2 was created in Biorender along with a Publication License: Created in BioRender. Ghosh, A. (2025) https://BioRender.com/6i14p3g.

## 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.

#### Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

#### References

1. WHO. Dengue and severe dengue. (2024). https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

 WHO. World Health Organisation. Disease Outbreak News; Dengue - Global Situation. (2024). doi: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON518.

3. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. *Nature*. (2013) 496:7446. doi: 10.1038/nature12060

4. Araf Y, Akter M, Zhai J, Zheng C, Hossain MG. Emerging health implications of climate change: dengue outbreaks and beyond in Bangladesh. *Lancet Microbe*. (2024) 5: e213. doi: 10.1016/S2666-5247(23)00366-X

5. Romanello M, Napoli Cd, Green C, Kennard H, Lampard P, Scamman D, et al. The 2023 report of the Lancet Countdown on health and climate change: the imperative for a health-centred response in a world facing irreversible harms. *Lancet.* (2023) 402:2346–94. doi: 10.1016/S0140-6736(23)01859-7

6. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: a continuing global threat. *Nat Rev Microbiol.* (2010) 8:S7–16. doi: 10.1038/nrmicro2460

7. Guzman MG, Harris E. Dengue. Lancet. (2015) 385:453-65. doi: 10.1016/S0140-6736(14)60572-9

8. Mukhopadhyay S, Kuhn RJ, Rossmann MG. A structural perspective of the flavivirus life cycle. *Nat Rev Microbiol.* (2005) 3:13–22. doi: 10.1038/nrmicro1067

9. Kuhn RJ, Zhang W, Rossmann MG, Pletnev SV, Corver J, Lenches E, et al. Structure of dengue virus: Implications for flavivirus organization, maturation, and fusion. *Cell.* (2002) 108:717–25. doi: 10.1016/S0092-8674(02)00660-8

10. Byk LA, Gamarnik AV. Properties and functions of the dengue virus capsid protein. Annu Rev Virol. (2016) 3:263–81. doi: 10.1146/annurev-virology-110615-042334

11. Dwivedi VD, Tripathi IP, Tripathi RC, Bharadwaj S, Mishra SK. Genomics, proteomics and evolution of dengue virus. *Brief Funct Genomics*. (2017) 16:217–27. doi: 10.1093/bfgp/elw040

12. Muller DA, Young PR. The flavivirus NS1 protein: molecular and structural biology, immunology, role in pathogenesis and application as a diagnostic biomarker. *Antiviral Res.* (2013) 98:192–208. doi: 10.1016/j.antiviral.2013.03.008

13. Bhatnagar P, Sreekanth GP, Murali-Krishna K, Chandele A, Sitaraman R. Dengue virus non-structural protein 5 as a versatile, multi-functional effector in host-pathogen interactions. *Front Cell Infect Microbiol.* (2021) 11:574067. doi: 10.3389/fcimb.2021.574067

14. McLean JE, Wudzinska A, Datan E, Quaglino D, Zakeri Z. Flavivirus NS4Ainduced autophagy protects cells against death and enhances virus replication. *J Biol Chem.* (2011) 286:22147–59. doi: 10.1074/jbc.M110.192500

15. Fragnoud R, Yugueros-Marcos J, Pachot A, Bedin F. Isotope Coded Protein Labeling analysis of plasma specimens from acute severe dengue fever patients. *Proteome Sci.* (2012) 10:1-8. doi: 10.1186/1477-5956-10-60

16. Acosta EG, Kumar A, Bartenschlager R. Revisiting dengue virus-host cell interaction: new insights into molecular and cellular virology. *Adv Virus Res.* (2014) 88:1–109. doi: 10.1016/B978-0-12-800098-4.00001-5

17. Montoya M, Gresh L, Mercado JC, Williams KL, Vargas MJ, Gutierrez G, et al. Symptomatic versus inapparent outcome in repeat dengue virus infections is influenced by the time interval between infections and study year. *PloS Negl Trop Dis.* (2013) 7: e2357. doi: 10.1371/journal.pntd.0002357

18. Guzman MG, Alvarez M, Halstead SB. Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection. *Arch Virol.* (2013) 158:1445–59. doi: 10.1007/s00705-013-1645-3

19. Kouri GP, Guzmán MG, Bravo JR. Why dengue haemorrhagic fever in Cuba? 2. An integral analysis. *Trans R Soc Trop Med Hyg.* (1987) 81:821–3. doi: 10.1016/0035-9203(87)90042-3

20. Hammon WM. Dengue hemorrhagic fever-do we know its cause? Am J Trop Med Hyg. (1973) 22:82–91. doi: 10.4269/ajtmh.1973.22.82

21. Pang T. Delayed-type hypersensitivity: probable role in the pathogenesis of dengue hemorrhagic fever/dengue shock syndrome. *Rev Infect Dis.* (1983) 5:346–52. doi: 10.1093/clinids/5.2.346

22. Rosen L. Disease exacerbation caused by sequential dengue infections: myth or reality? *Rev Infect Dis.* (1989) 11 Suppl 4:S840-2. doi: 10.1093/clinids/11.supplement\_4.s840 23. Halstead SB. Antibody, macrophages, dengue virus infection, shock, and hemorrhage: a pathogenetic cascade. *Rev Infect Dis.* (1989) 11 Suppl 4:830–9. doi: 10.1093/clinids/11.Supplement\_4.S830

24. Halstead SB, Mahalingam S, Marovich MA, Ubol S, Mosser DM. Intrinsic antibody-dependent enhancement of microbial infection in macrophages: disease regulation by immune complexes. *Lancet Infect Dis.* (2010) 10:712–22. doi: 10.1016/S1473-3099(10)70166-3

25. Durham ND, Agrawal A, Waltari E, Croote D, Zanini F, Fouch M, et al. Broadly neutralizing human antibodies against dengue virus identified by single B cell transcriptomics. *Elife*. (2019) 8:e52384. doi: 10.7554/eLife.52384

26. Flipse J, Wilschut J, Smit JM. Molecular mechanisms involved in antibodydependent enhancement of dengue virus infection in humans. *Traffic*. (2013) 14:25–35. doi: 10.1111/tra.2013.14.issue-1

27. Flipse J, Diosa-Toro MA, Hoornweg TE, Van De Pol DPI, Urcuqui-Inchima S, Smit JM. Antibody-dependent enhancement of dengue virus infection in primary human macrophages; balancing higher fusion against antiviral responses. *Sci Rep.* (2016) 6:29201 1-13. doi: 10.1038/srep29201

28. Huang X, Yue Y, Li D, Zhao Y, Qiu L, Chen J, et al. Antibody-dependent enhancement of dengue virus infection inhibits RLR-mediated Type-I IFNindependent signalling through upregulation of cellular autophagy. *Sci Rep.* (2016) 6:22303 1-13. doi: 10.1038/srep22303

29. Lee MF, Voon GZ, Lim HX, Chua ML, Poh CL. Innate and adaptive immune evasion by dengue virus. *Front Cell Infect Microbiol.* (2022) 12. doi: 10.3389/fcimb.2022.1004608

30. Richter MKS, Da Silva Voorham JM, Torres Pedraza S, Hoornweg TE, Van De Pol DPI, Rodenhuis-Zybert IA, et al. Immature dengue virus is infectious in human immature dendritic cells via interaction with the receptor molecule DC-SIGN. *PloS One*. (2014) 9:e98785. doi: 10.1371/journal.pone.0098785

31. Briseño JAA, Pereira LR, van der Laan M, Pauzuolis M, ter Ellen BM, Upasani V, et al. TLR2 axis on peripheral blood mononuclear cells regulates inflammatory responses to non-infectious immature dengue virus particles. *PloS Pathog.* (2022) 18: e1010499. doi: 10.1371/JOURNAL.PPAT.1010499

32. Wang TT, Sewatanon J, Memoli MJ, Wrammert J, Bournazos S, Bhaumik SK, et al. IgG antibodies to dengue enhanced for Fc $\gamma$ RIIIA binding determine disease severity. *Science*. (2017) 355:395–8. doi: 10.1126/science.aai8128

33. Bournazos S, Vo HTM, Duong V, Auerswald H, Ly S, Sakuntabhai A, et al. Antibody fucosylation predicts disease severity in secondary dengue infection. *Sci* (1979). (2021) 372:1102–5. doi: 10.1126/science.abc7303

34. Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunology. (2017) 151:261–9. doi: 10.1111/imm.2017.151.issue-3

35. St John AL, Rathore AP, Raghavan B, Ng ML, Abraham SN. Contributions of mast cells and vasoactive products, leukotrienes and chymase, to dengue virus-induced vascular leakage. *Elife*. (2013) 2:e00481. doi: 10.7554/eLife.00481

36. Malavige GN, Ogg GS. Molecular mechanisms in the pathogenesis of dengue infections. *Trends Mol Med.* (2024) 30:484–98. doi: 10.1016/j.molmed.2024.03.006

37. Jeewandara C, Gomes L, Wickramasinghe N, Gutowska-Owsiak D, Waithe D, Paranavitane SA, et al. Platelet activating factor contributes to vascular leak in acute dengue infection. *PloS Negl Trop Dis.* (2015) 9:e0003459. doi: 10.1371/journal.pntd.0003459

38. van de Weg CAM, Pannuti CS, van den Ham HJ, de Araújo ESA, Boas LSV, Felix AC, et al. Serum angiopoietin-2 and soluble VEGF receptor 2 are surrogate markers for plasma leakage in patients with acute dengue virus infection. *J Clin Virol.* (2014) 60:328–35. doi: 10.1016/j.jcv.2014.05.001

39. Rathore APS, Senanayake M, Athapathu AS, Gunasena S, Karunaratna I, Leong WY, et al. Serum chymase levels correlate with severe dengue warning signs and clinical fluid accumulation in hospitalized pediatric patients. *Sci Rep.* (2020) 10:11856. doi: 10.1038/s41598-020-68844-z

40. Masri MFB, Mantri CK, Rathore APS, John ALS. Peripheral serotonin causes dengue virus-induced thrombocytopenia through 5HT2 receptors. *Blood.* (2019) 133:2325-37. doi: 10.1182/blood-2018-08-869156

41. Grange L, Simon-Loriere E, Sakuntabhai A, Gresh L, Paul R, Harris E. Epidemiological risk factors associated with high global frequency of inapparent dengue virus infections. *Front Immunol.* (2014) 5. doi: 10.3389/fimmu.2014.00280

42. Aggarwal C, Ahmed H, Sharma P, Reddy ES, Nayak K, Singla M, et al. Severe disease during both primary and secondary dengue virus infections in pediatric populations. *Nat Med.* (2024) 30:670-4. doi: 10.1038/s41591-024-02798-x

43. Sangkaew S, Ming D, Boonyasiri A, Honeyford K, Kalayanarooj S, Yacoub S, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. *Lancet Infect Dis.* (2021) 21:1014–26. doi: 10.1016/S1473-3099(20)30601-0

44. Kan FK, Tan CC, Von Bahr Greenwood T, Khalid KE, Supramaniam P, Hed Myrberg I, et al. Dengue infection complicated by hemophagocytic lymphohistiocytosis: experiences from 180 patients with severe dengue. *Clin Infect Dis.* (2020) 70:2247–55. doi: 10.1093/cid/ciz499

45. Usmani GN, Woda BA, Newburger PE. Advances in understanding the pathogenesis of HLH. *Br J Haematol.* (2013) 161:609–22. doi: 10.1111/bjh.2013.161.issue-5

46. Wills BA, Oragui EE, Stephens AC, Daramola OA, Dung NM, Loan HT, et al. Coagulation abnormalities in dengue hemorrhagic Fever: serial investigations in 167 Vietnamese children with Dengue shock syndrome. Clin Infect Dis. (2002) 35:277-85. doi: 10.1086/cid.2002.35.issue-3

47. Ojha A, Nandi D, Batra H, Singhal R, Annarapu GK, Bhattacharyya S, et al. Platelet activation determines the severity of thrombocytopenia in dengue infection. *Sci Rep.* (2017) 7:41697. doi: 10.1038/srep41697

48. McKechnie JL, Beltrán D, Pitti A, Saenz L, Araúz AB, Vergara R, et al. HLA upregulation during dengue virus infection suppresses the natural killer cell response. *Front Cell Infect Microbiol.* (2019) 9:473503. doi: 10.3389/fcimb.2019.00268

49. de Alwis R, Bangs DJ, Angelo MA, Cerpas C, Fernando A, Sidney J, et al. Immunodominant dengue virus-specific CD8+ T cell responses are associated with a memory PD-1+ Phenotype. J Virol. (2016) 90:4771-9. doi: 10.1128/JVI.02892-15

50. Simmons CP, Dong T, Chau NV, Dung NTP, Chau TNB, Thao LTT, et al. Early T-cell responses to dengue virus epitopes in Vietnamese adults with secondary dengue virus infections. *J Virol.* (2005) 79:5665–75. doi: 10.1128/JVI.79.9.5665-5675.2005

51. Weiskopf D, Angelo MA, de Azeredo EL, Sidney J, Greenbaum JA, Fernando AN, et al. Comprehensive analysis of dengue virus-specific responses supports an HLA-linked protective role for CD8 + T cells. *Proc Natl Acad Sci.* (2013) 110:22E2046-E2053. doi: 10.1073/pnas.1305227110

52. Fink J, Gu F, Vasudevan SG. Role of T cells, cytokines and antibody in dengue fever and dengue haemorrhagic fever. *Rev Med Virol.* (2006) 16:263–75. doi: 10.1002/(ISSN)1099-1654

53. Zivna I, Green S, Vaughn DW, Kalayanarooj S, Stephens HAF, Chandanayingyong D, et al. T cell responses to an HLA-B'07-restricted epitope on the dengue NS3 protein correlate with disease severity. *J Immunol.* (2002) 168:5959–65. doi: 10.4049/jimmunol.168.11.5959

54. Munro A, Bright S. Products of the major histocompatibility complex and their relationship to the immune response. *Nature*. (1976) 264:145–52. doi: 10.1038/264145a0

55. Chiewsilp P, Scott RM, Bhamarapravati N. Histocompatibility antigens and dengue hemorrhagic fever. Am J Trop Med Hyg. (1981) 30:1100–5. doi: 10.4269/ ajtmh.1981.30.1100

56. Mercado ES, Espino FE, Perez MLM, Bilar JM, Bajaro JDP, Huy NT, et al. HLA-A\*33:01 as protective allele for severe dengue in a population of Filipino children. *PloS One.* (2015) 10:1–11. doi: 10.1371/journal.pone.0115619

57. Xavier Eurico De Alencar L, De Mendonça Braga-Neto U, José Moura Do Nascimento E, Tenório Cordeiro M, Maria Silva A, Alexandre Antunes De Brito C, et al. HLA-B\*44 is associated with dengue severity caused by DENV-3 in a Brazilian population. *J Trop Med.* (2013) 2013:648475. doi: 10.1155/2013/648475

58. Monteiro SP, do Brasil PEAA, Cabello GMK, de Souz RV, Brasil P, Georg I, et al. HLA-A\*01 allele: A risk factor for dengue haemorrhagic fever in Brazil's population. *Mem Inst Oswaldo Cruz.* (2012) 107:224–30. doi: 10.1590/S0074-02762012000200012

59. Cardozo DM, Moliterno RA, Sell AM, Guelsin GAS, Beltrame LM, Clementino SL, et al. Evidence of HLA-DQB1 contribution to susceptibility of dengue serotype 3 in dengue patients in Southern Brazil. *J Trop Med.* (2014) 2014:968262. doi: 10.1155/2014/968262

60. Alagarasu K, Mulay AP, Singh R, Gavade VB, Shah PS, Cecilia D. Association of HLA-DRB1 and TNF genotypes with dengue hemorrhagic fever. *Hum Immunol.* (2013) 74:610–7. doi: 10.1016/j.humimm.2013.01.027

61. Alagarasu K, Mulay AP, Sarikhani M, Rashmika D, Shah PS, Cecilia D. Profile of human leukocyte antigen class I alleles in patients with dengue infection from Western India. *Hum Immunol.* (2013) 74:1624–8. doi: 10.1016/j.humimm.2013.08.004

62. Lan NTP, Kikuchi M, Huong VTQ, Ha DQ, Thuy TT, Tham VD, et al. Protective and enhancing HLA alleles, HLA-DRB1\*0901 and HLA-A\*24, for severe forms of dengue virus infection, dengue hemorrhagic fever and dengue shock syndrome. *PloS Negl Trop Dis.* (2008) 2:1–8. doi: 10.1371/journal.pntd.0000304

63. LaFleur C, Granados J, Vargas-Alarcon G, Ruíz-Morales J, Villarreal-Garza C, Higuera L, et al. HLA-DR antigen frequencies in Mexican patients with dengue virus infection: HLA-DR4 as a possible genetic resistance factor for dengue hemorrhagic fever. *Hum Immunol.* (2002) 63:1039–44. doi: 10.1016/S0198-8859(02)00682-1

64. Vejbaesya S, Thongpradit R, Kalayanarooj S, Luangtrakool K, Luangtrakool P, Gibbons RV, et al. HLA class I supertype associations with clinical outcome of secondary dengue virus infections in ethnic thais. *J Infect Diseases*. (2015) 212:939–47. doi: 10.1093/infdis/jiv127

65. Fernández-Mestre M, Navarrete CV, Brown J, Brown C, Correa E, Layrisse Z. HLA alleles and dengue virus infection in Venezuelan patients: A preliminary study. *Inmunologia*. (2009) 28:96–100. doi: 10.1016/S0213-9626(09)70031-9

66. Loke H, Bethell DB, Phuong CXT, Dung M, Schneider J, White NJ, et al. Strong HLA class I-restricted T cell responses in dengue hemorrhagic fever: A double-edged sword? *J Infect Dis.* (2001) 184:1369–73. doi: 10.1086/jid.2001.184.issue-11

67. Appanna R, Ponnampalavanar S, Chai See LL, Devi Sekaran S. Susceptible and protective HLA Class 1 alleles against dengue fever and dengue hemorrhagic fever patients in a Malaysian population. *PloS One.* (2010) 5:1–10. doi: 10.1371/journal.pone.0013029

68. Polizel JR, Bueno D, Visentainer JEL, Sell AM, Borelli SD, Tsuneto LT, et al. Association of human leukocyte antigen DQ1 and dengue fever in a white Southern Brazilian population. *Mem Inst Oswaldo Cruz.* (2004) 99:559–62. doi: 10.1590/S0074-02762004000600003

69. Sierra B, Alegre R, Pérez AB, García G, Sturn-Ramirez K, Obasanjo O, et al. HLA-A, -B, -C, and -DRB1 allele frequencies in Cuban individuals with antecedents of dengue 2 disease: Advantages of the Cuban population for HLA studies of dengue virus infection. *Hum Immunol.* (2007) 68:531–40. doi: 10.1016/j.humimm.2007.03.001

70. Falcón-Lezama JA, Ramos C, Zuñiga J, Juárez-Palma L, Rangel-Flores H, García-Trejo AR, et al. HLA class I and II polymorphisms in Mexican Mestizo patients with dengue fever. *Acta Trop.* (2009) 112:193–7. doi: 10.1016/j.actatropica. 2009.07.025

71. Malavige GN, Rostron T, Rohanachandra LT, Jayaratne SD, Fernando N, de Silva AD, et al. HLA class I and class II associations in Dengue viral infections in a Sri Lankan population. *PloS One.* (2011) 6:1–8. doi: 10.1371/journal.pone.0020581

72. Brown MG, Salas R, Vickers I, Heslop O, Smikle M. Dengue HLA associations in Jamaicans. West Indian Med J. (2011) 60:7–12.

73. Lan NTP, Hirayama K. Host genetic susceptibility to severe dengue infection. *Trop Med Health.* (2011) 39:73-81. doi: 10.2149/tmh.2011-S08

74. Katzelnick LC, Escoto AC, Huang AT, Garcia-Carreras B, Chowdhury N, Berry IM, et al. Antigenic evolution of dengue viruses over 20 years. *Sci (1979).* (2021) 374:999–1004. doi: 10.1126/science.abk0058

75. Parameswaran P, Wang C, Trivedi SB, Eswarappa M, Montoya M, Balmaseda A, et al. Intrahost selection pressures drive rapid dengue virus microevolution in acute human infections. *Cell Host Microbe*. (2017) 22:400–410.e5. doi: 10.1016/j.chom.2017.08.003

76. Kolimenakis A, Heinz S, Wilson ML, Winkler V, Yakob L, Michaelakis A, et al. The role of urbanisation in the spread of Aedes mosquitoes and the diseases they transmit—A systematic review. *PloS Negl Trop Dis.* (2021) 15:e0009631. doi: 10.1371/journal.pntd.0009631

77. Whiteman A, Loaiza JR, Yee DA, Poh KC, Watkins AS, Lucas KJ, et al. Do socioeconomic factors drive Aedes mosquito vectors and their arboviral diseases? A systematic review of dengue, chikungunya, yellow fever, and Zika Virus. *One Health.* (2020) 11:100188. doi: 10.1016/j.onehlt.2020.100188

78. Barmak DH, Dorso CO, Otero M. Modelling dengue epidemic spreading with human mobility. *Physica A: Stat Mechanics its Applications*. (2016) 447:129–40. doi: 10.1016/j.physa.2015.12.015

79. Chagas GCL, Rangel AR, Noronha LM, Veloso FCS, Kassar SB, Oliveira MJC, et al. Risk factors for mortality in patients with dengue: A systematic review and metaanalysis. *Trop Med Int Health.* (2022) 27:656–68. doi: 10.1111/tmi.13797

80. Trejoid I, Barnardid M, Spencerid JA, Keithleyid J, Martinez KM, Crooker I, et al. Changing temperature profiles and the risk of dengue outbreaks. *PloS Climate*. (2023) 2:e0000115. doi: 10.1371/journal.pclm.0000115

81. Aliaga-Samanez A, Cobos-Mayo M, Real R, Segura M, Romero D, Fa JE, et al. Worldwide dynamic biogeography of zoonotic and anthroponotic dengue. *PloS Negl Trop Dis.* (2021) 15:e0009496. doi: 10.1371/journal.pntd.0009496

82. Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. *Nat Microbiol.* (2019) 4:1508–15. doi: 10.1038/s41564-019-0476-8

83. Oliveira S, Rocha J, Sousa CA, Capinha C. Wide and increasing suitability for Aedes albopictus in Europe is congruent across distribution models. *Sci Rep.* (2021) 11:1-9. doi: 10.1038/s41598-021-89096-5

 Lozano-Fuentes S, Hayden MH, Welsh-Rodriguez C, Ochoa-Martinez C, Tapia-Santos B, Kobylinski KC, et al. The Dengue Virus Mosquito Vector Aedes aEgypti at High Elevation in México. Am J Trop Med Hyg. (2012) 87:902. doi: 10.4269/ aitmh.2012.12-0244

85. Liu Z, Zhang Q, Li L, He J, Guo J, Wang Z, et al. The effect of temperature on dengue virus transmission by Aedes mosquitoes. *Front Cell Infect Microbiol.* (2023) 13:1242173. doi: 10.3389/fcimb.2023.1242173

86. Chan M, Johansson MA. The incubation periods of dengue viruses. *PloS One.* (2012) 7:e50972. doi: 10.1371/journal.pone.0050972

87. Yang HM, Macoris MLG, Galvani KC, Andrighetti MTM, Wanderley DMV. Assessing the effects of temperature on dengue transmission. *Epidemiol Infect*. (2009) 137:1179–87. doi: 10.1017/S0950268809002052

88. Wagenaar JFP, Mairuhu ATA, van Gorp ECM. Genetic influences on dengue virus infections. *Dengue Bull*. (2004) 28:126–34.

89. Cook AC, Thibaut D, Pettersen T. Major histocompatibility complex class I and dengue hemorrhagic fever: A meta-analysis of human leukocyte antigens A\*24 and B\*44. *Cureus.* (2022) 14(11):e31485. doi: 10.7759/cureus.31485

90. Chen Y, Liao Y, Yuan K, Wu A, Liu L. HLA-A, -B, -DRB1 alleles as genetic predictive factors for dengue disease: A systematic review and meta-analysis. *Viral Immunol.* (2019) 32:121–30. doi: 10.1089/vim.2018.0151

91. European Centre for Disease Prevention and Control. Dengue worldwide overview (2024). Available online at: https://www.ecdc.europa.eu/en/dengue-monthly (Accessed June 24, 2024).

92. Government of India. DENGUE SITUATION IN INDIA: National Center for Vector Borne Diseases Control (NCVBDC) (2023). Available online at: https://ncvbdc.mohfw.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715 (Accessed June 24, 2024).

93. Kung J. Elicit (product review). J Can Health Libraries Assoc / J l'Association Des bibliothèques la santé du Canada. (2023) 44:15–19. doi: 10.29173/jchla29657

94. PRISMA. PRISMA Flow Diagram - "Prisma 2020 flow diagram for new systematic reviews which included searches of databases and other sources" (2020). Available online at: http://prisma-statement.org/documents/PRISMA\_2020\_flow\_diagram\_new\_SRs\_v2.docx (Accessed May 20, 2024).

95. Paradoa Pérez ML, Trujillo Y, Basanta P. Association of dengue hemorrhagic fever with the HLA system. *Haematologia (Budap)*. (1987) 20:83–7.

96. Weiskopf D, Angelo MA, Grifoni A, O'Rourke PH, Sidney J, Paul S, et al. HLA-DRB1 alleles are associated with different magnitudes of dengue virus-specific CD4+ T-cell responses. *J Infect Diseases*. (2016) 214:1117-24. doi: 10.1093/infdis/jiw309

97. Stephens HAF, Klaythong R, Sirikong M, Vaughn DW, Green S, Kalayanarooj S, et al. HLA-A and -B allele associations with secondary dengue virus infections correlate with disease severity and the infecting viral serotype in ethnic Thais. *Tissue Antigens*. (2002) 60:309–18. doi: 10.1034/j.1399-0039.2002.600405.x

98. Fernández-Mestre MT, Vargas V, Montagnani S, Cotúa M, Ogando V, Layrisse Z. HLA Class II and class I polymorphism in Venezuelan patients with myasthenia gravis. *Hum Immunol.* (2004) 65:54–9. doi: 10.1016/j.humimm.2003.10.003

99. Review Manager (RevMan). Version (8.0.0). The Cochrane Collaboration (2024). Available at: http://revman.cochrane.org/ (Accessed June 11, 2024).

100. Taylor L. Dengue: Argentinians turn to homemade repellent amid surge in cases. *BMJ.* (2024) 385. doi: 10.1136/bmj.q885

101. Lana RM, Gomes MF da C, Lima TFMd, Honório NA, Codeço CT. The introduction of dengue follows transportation infrastructure changes in the state of Acre, Brazil: A network-based analysis. *PloS Negl Trop Dis.* (2017) 11:e0006070. doi: 10.1371/journal.pntd.0006070

102. Lowe R, Lee S, Martins Lana R, Torres Codeço C, Castro MC, Pascual M. Emerging arboviruses in the urbanized Amazon rainforest. *BMJ.* (2020) 371. doi: 10.1136/bmj.m4385

103. Lee SA, Economou T, Catão R de C, Barcellos C, Lowe R. The impact of climate suitability, urbanisation, and connectivity on the expansion of dengue in 21st century Brazil. *PloS Negl Trop Dis.* (2021) 15:e0009773. doi: 10.1371/journal.pntd.0009773

104. NEA.Dengue Cases Dropped By 69 Per Cent To 9,949 Cases In 2023; Vigilance Needed To prevent Dengue Surge In 2024. Available online at: https://www.nea.gov.sg/ media/news/news/index/dengue-cases-dropped-69-per-cent-9-949-in-2023-vigilanceneeded-prevent-dengue-surge-2024 (Accessed June 24, 2024).

105. Damtew YT, Tong M, Varghese BM, Anikeeva O, Hansen A, Dear K, et al. Effects of high temperatures and heatwaves on dengue fever: a systematic review and meta-analysis. *EBioMedicine*. (2023) 91:104582. doi: 10.1016/j.ebiom.2023.104582

106. Colón-González FJ, Gibb R, Khan K, Watts A, Lowe R, Brady OJ. Projecting the future incidence and burden of dengue in Southeast Asia. *Nat Commun.* (2023) 14:5439. doi: 10.1038/s41467-023-41017-y

107. Wang Y, Li C, Zhao S, Wei Y, Li K, Jiang X, et al. Projection of dengue fever transmissibility under climate change in South and Southeast Asian countries. *PloS Negl Trop Dis.* (2024) 18:e0012158. doi: 10.1371/journal.pntd.0012158

108. Gonzalez-Galarza FF, McCabe A, Santos EJMD, Jones J, Takeshita L, Ortega-Rivera ND, et al. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. *Nucleic Acids Res.* (2020) 48:D783–8. doi: 10.1093/nar/gkz1029

109. Nunes K, Maia MHT, dos Santos EJM, dos Santos SEB, Guerreiro JF, Petzl-Erler ML, et al. How natural selection shapes genetic differentiation in the MHC region: A case study with Native Americans. *Hum Immunol.* (2021) 82:523–31. doi: 10.1016/ j.humimm.2021.03.005

110. Hertz T, Nolan D, James I, John M, Gaudieri S, Phillips E, et al. Mapping the landscape of host-pathogen coevolution: HLA class I binding and its relationship with evolutionary conservation in human and viral proteins. *J Virol.* (2011) 85:1310–21. doi: 10.1128/JVI.01966-10

111. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. (1998) 11:480–96. doi: 10.1128/CMR.11.3.480

112. Klenerman P, Rowland-Jones S, Nature SM. U. Cytotoxic T-cell activity antagonized by naturally occurring HIV-1 Gag variants. *Nature*. (1994) 1994:403-407. doi: 10.1038/369403a0

113. Sciarra F, Campolo F, Franceschini E, Carlomagno F, Venneri M. Genderspecific impact of sex hormones on the immune system. *Int J Mol Sci.* (2023) 24:6302. doi: 10.3390/ijms24076302

114. Whitehorn J, Simmons CP. The pathogenesis of dengue. Vaccine. (2011) 29:7221-8. doi: 10.1016/j.vaccine.2011.07.022