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Trends and insights in dengue virus research globally: a bibliometric analysis (1995–2023)

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Abstract

Background Dengue virus (DENV) is the most widespread arbovirus. The World Health Organization (WHO) declared dengue one of the top 10 global health threats in 2019. However, it has been underrepresented in bibliometric analyses. This study employs bibliometric analysis to identify research hotspots and trends, offering a comprehensive overview of the current research dynamics in this field.

Results We present a report spanning from 1995 to 2023 that provides a unique longitudinal analysis of Dengue virus (DENV) research, revealing significant trends and shifts not extensively covered in previous literature. A total of 10,767 DENV-related documents were considered, with a notable increase in publications, peaking at 747 articles in 2021. ***Plos Neglected Tropical Diseases*** has become the leading journal in Dengue virus research, publishing 791 articles in this field—the highest number recorded. Our bibliometric analysis provides a comprehensive mapping of DENV research across multiple dimensions, including vector ecology, virology, and emerging therapies. The study delineates a complex network of immune response genes, including IFNA1, DDX58, IFNB1, STAT1, IRF3, and NFKB1, highlighting significant trends and emerging themes, particularly the impacts of climate change and new outbreaks on disease transmission. Our findings detail the progress and current status of key vaccine candidates, including the licensed Dengvaxia, newer vaccines such as Qdenga and TV003, and updated clinical trials. The study underscores significant advancements in antiviral therapies and vector control strategies for dengue, highlighting innovative drug candidates such as AT-752 and JNJ-1802, and the potential of drug repurposing with agents like Ribavirin, Remdesivir, and Lopinavir. Additionally, it discusses biological control methods, including the introduction of Wolbachia-infected mosquitoes and gene-editing technologies.

Conclusion This bibliometric study underscores the critical role of interdisciplinary collaboration in advancing DENV research, identifying key trends and areas needing further exploration, including host-virus dynamics, the

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development and application of antiviral drugs and vaccines, and the use of artificial intelligence. It advocates for strengthened partnerships across various disciplines to effectively tackle the challenges posed by DENV.

Keywords Dengue Virus (DENV), Global Research Trends, Bibliometric Analysis, Vaccine Development, Antiviral therapies, Vector Control Strategies

Background

The Dengue virus (DENV) is a global public health threat transmitted primarily by mosquitoes [1]. Dengue fever manifests with symptoms including fever, headache, eye pain, muscle and joint pain, and skin rash [2, 3]. Dengue fever is prevalent in tropical and subtropical regions, resulting in millions of infections and thousands of deaths annually. It has expanded to non-traditional areas, including the United States and Europe, with significant case surges in the Americas in 2015 and 2019 and a notable outbreak in the Western Pacific in 2013. For a comprehensive overview of global dengue cases and related deaths since 1995, see Table S1 in the supplementary materials, which includes World Health Organization data, although some information may be incomplete due to COVID-19-related disruptions [3]. Recent epidemiological trends show a concerning expansion in Dengue's geographic and demographic scope, exacerbated by climate change and urbanization that facilitate vector breeding and shorten the viral incubation period. Studies predict an increase in the global population at risk from 53% in 2015 to 63% by 2080 [4]. First identified in Myanmar in 1943 by American virologists Albert Sabin and Robert Phillips, DENV was isolated from a patient's blood sample, laying the foundation for subsequent research on the virus [5]. The Dengue virus, a single-stranded RNA virus of the Flavivirus genus, comprises four serotypes (DENV-1, DENV-2, DENV-3, DENV-4). Each confers lifelong immunity against itself but leaves individuals susceptible to the other serotypes, complicating prevention efforts and contributing to the severity of outbreaks [6].

Many commonly used vector control strategies, such as insecticide spraying, have failed to curb disease incidence but continue to be employed in the absence of robust evidence for their effectiveness or optimal implementation. However, advancements in understanding dengue epidemiology, immune response, and innovative control measures, including effective management, vaccines, and novel mosquito control methods, could significantly enhance dengue control efforts.

To tackle the complex challenges posed by the Dengue virus (DENV), this study employs bibliometric analysis to assess the breadth and impact of DENV-related research across various disciplines. Integrating existing studies is crucial to encapsulate the comprehensive scope of DENV research, covering aspects such as transmission dynamics, clinical manifestations, treatment options, and preventive measures. This approach is vital to identify critical research gaps and new potential areas of study, which are essential for advancing our understanding of the virus.

Methods

Data source

Data for this bibliometric analysis were retrieved from two primary databases: Web of Science (WOS) Science Citation Index Expanded (SCI-EXPANDED) and Scopus. These databases are widely recognized and extensively utilized in academic research, providing access to a broad array of high-quality academic journals. The selection of these databases enhances the comprehensiveness and credibility of our findings. The SCI-EXPANDED offers extensive coverage of scientific literature, particularly within the natural sciences, and includes high-impact journals, thereby ensuring the quality and reliability of the data. Scopus, as a multidisciplinary database, spans a wide range of subjects including science, technology, medicine, social sciences, arts, and humanities. Its broad coverage and high-quality data make it an indispensable resource for academic research. However, it is important to note that both SCI-EXPANDED and Scopus have a higher representation of English-language literature and high-impact journals, which may result in the underrepresentation of non-English literature and research published in lower-impact journals. Additionally, despite their extensive coverage, literature from certain specific fields may be underrepresented in these databases.

These databases are particularly well-suited for research on the Dengue virus (DENV) due to their reliable indexing in disciplines such as virology and public health. This study, covering the period from 1995 to 2023, focuses on the increase in Dengue-related publications and advancements in scientific databases, with an emphasis on research articles and reviews.

Research methods

In this study, we employed a variety of software tools to conduct comprehensive bibliometric analyses. VOSviewer (versions 1.6.18 and 1.6.20) and Pajek were utilized to analyze countries, institutions, journals, co-cited journals, authors, co-cited authors, and keyword co-occurrence, facilitating the construction of collaboration, co-citation, and co-occurrence networks. The visualization maps produced by VOSviewer and Scimago Graphica provided insightful visual representations of

these networks. Pajek offered additional network analysis capabilities, particularly effective for handling large networks with its advanced features for detailed analysis and visualization. CiteSpace (version 6.1.R1) was employed to generate dual-map overlays of journals and to analyze references with Citation Bursts. The R package "bibliometrix" (version 3.2.1) was used to analyze thematic evolution and identify the 15 most active authors in DENV research. Microsoft Office Excel 2019 facilitated the quantitative analysis of publications. Gene visualization analysis was conducted using VOSviewer, while keyword visualization was performed using the R packages ComplexHeatmap (version 2.16.0) and circlize (version 0.4.16). Gene information was sourced from the Citexs Big Data Analysis Platform (https://www.citexs.com), which generated relevant visualizations to delineate the current research landscape, identify key research areas, and discern trends. The document selection and analysis process is illustrated in Fig. 1.

Despite their powerful capabilities, tools like VOSviewer, Pajek, CiteSpace, and various R packages have limitations such as steep learning curves, complexity in data integration, and challenges in interpretation. These tools may also face performance issues with large datasets and might not fully capture the qualitative aspects of research trends. Therefore, a combination of multiple tools and methodologies is often necessary to achieve a comprehensive and accurate bibliometric analysis.

Results

Global trends and collaborative dynamics in dengue virus research

Over the past 30 years, Dengue virus research has shown a significant upward trend, peaking at 747 articles in 2021. This growth can be divided into three phases: slow (1991–2002, under 120 publications annually), fast (2003–2013, 120–600 publications annually), and rapid (2014–2023, over 640 publications annually), likely influenced by global infectious disease outbreaks (Fig. 2a). From 2021 to 2023, 45.5% of these publications were in high-impact, Q1 journals (Fig. 2b).

Geographical analysis reveals significant disparities in research quality across continents. Europe leads with 59.36% of its publications in the top quartile, followed by Central America and the Caribbean (57.14%), and North America (51.17%) (Fig. 2c). Geographical disparities in research output and quality are notable across different regions, and are influenced by a range of factors. Addressing these factors and proposing solutions is crucial for promoting global academic equality and enhancing research quality.

Analysis of the top 20 corresponding authors' countries shows variations in self-citation percentage (SCP) and most cited paper (MCP) metrics. The United States leads with the highest SCP (1281) and MCP (885), highlighting its significant contribution to the field. China and India also emerge as key players, supported by robust research infrastructures and extensive funding (Fig. 3a). Visual maps from VOSviewer and Scimago Graphic illustrate the collaborative landscape, with the United States, China, and India leading in publications and collaborations (Fig. 3b). This global network underscores the

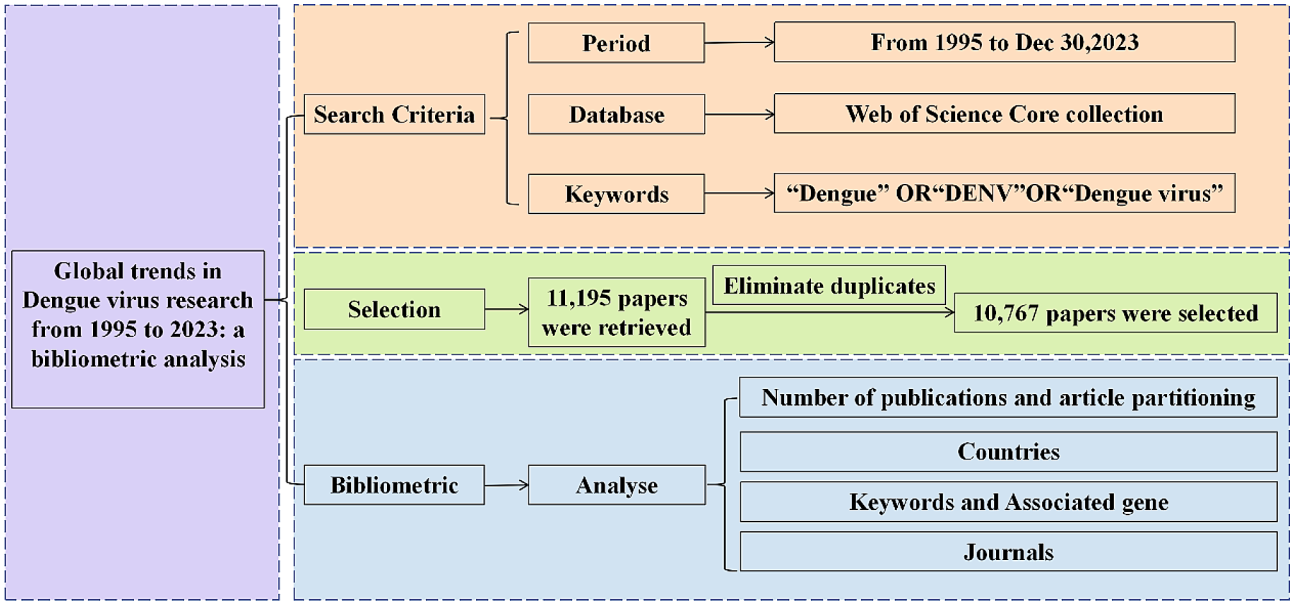
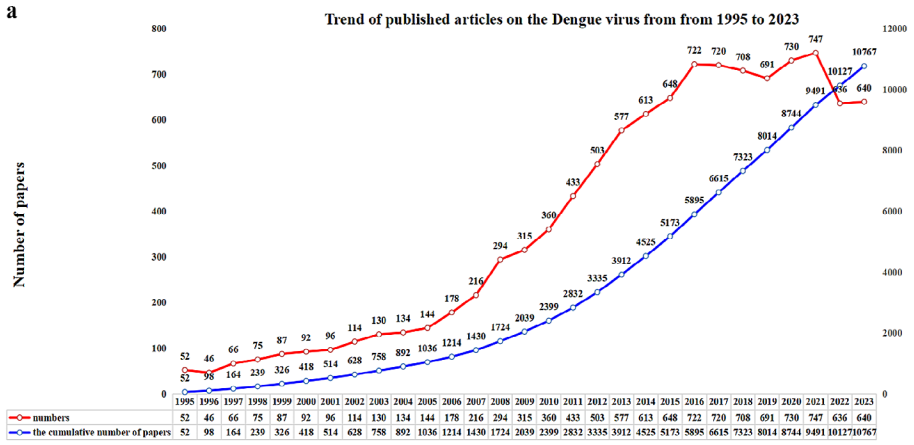
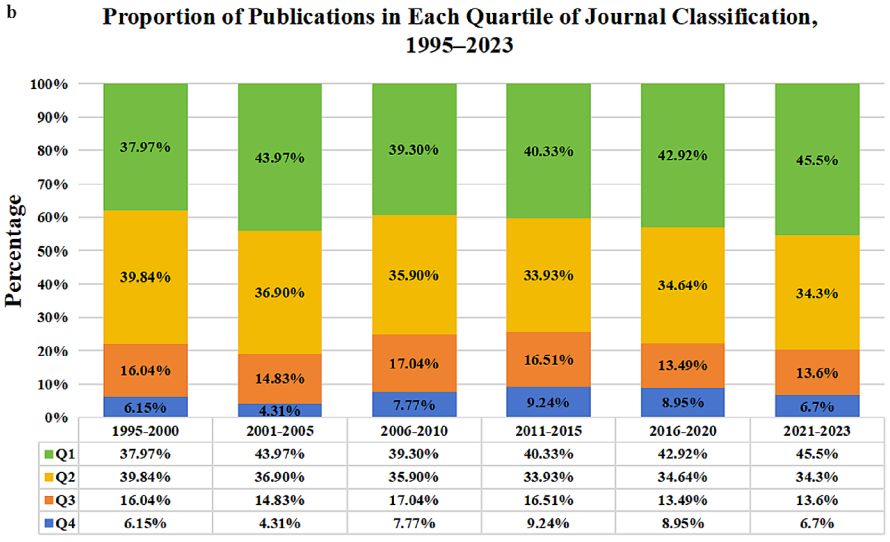


Fig. 1 Flowchart Illustrating the Document Selection and Analysis Process for Dengue Virus Research



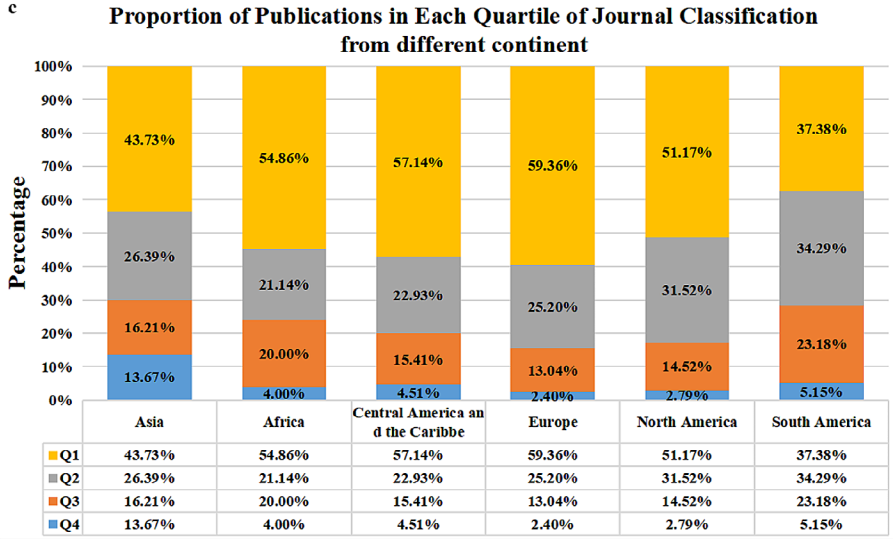
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
numbers	52	46	66	75	87	92	96	114	130	134	144	178	216	294	315	360	433	503	577	613	648	722	720	708	691	730	747	636	640
the cumulative number of papers	52	98	164	239	326	418	514	628	758	892	1036	1214	1430	1724	2039	2399	2832	3335	3912	4525	5173	5895	6615	7323	8014	8744	9491	10127	10767

b



	1995-2000	2001-2005	2006-2010	2011-2015	2016-2020	2021-2023
Q1	37.97%	43.97%	39.30%	40.33%	42.92%	45.5%
Q2	39.84%	36.90%	35.90%	33.93%	34.64%	34.3%
Q3	16.04%	14.83%	17.04%	16.51%	13.49%	13.6%
Q4	6.15%	4.31%	7.77%	9.24%	8.95%	6.7%

c



	Asia	Africa	Central America an d the Caribbe	Europe	North America	South America
Q1	43.73%	54.86%	57.14%	59.36%	51.17%	37.38%
Q2	26.39%	21.14%	22.93%	25.20%	31.52%	34.29%
Q3	16.21%	20.00%	15.41%	13.04%	14.52%	23.18%
Q4	13.67%	4.00%	4.51%	2.40%	2.79%	5.15%

Fig. 2 Overview of Dengue Virus (DENV) Research Publication Trends and Distributions. (**a**) Temporal trends in publications from 1980 to 2020; (**b**) classification of these publications into journal quartiles from 1995 to 2023, using Journal Citation Reports (JCR) rankings; (**c**) geographical distribution of these publications by continent, categorized by the same journal quartiles. Quartiles are determined by the journal's rank within its category, divided by the total number of journals in that category, and expressed as a percentile: Q1 (top 25%), Q2 (25–50%), Q3 (50–75%), and Q4 (bottom 25%). For journals spanning multiple WOS categories, the harmonic mean of Category Expected Citations is used to determine quality

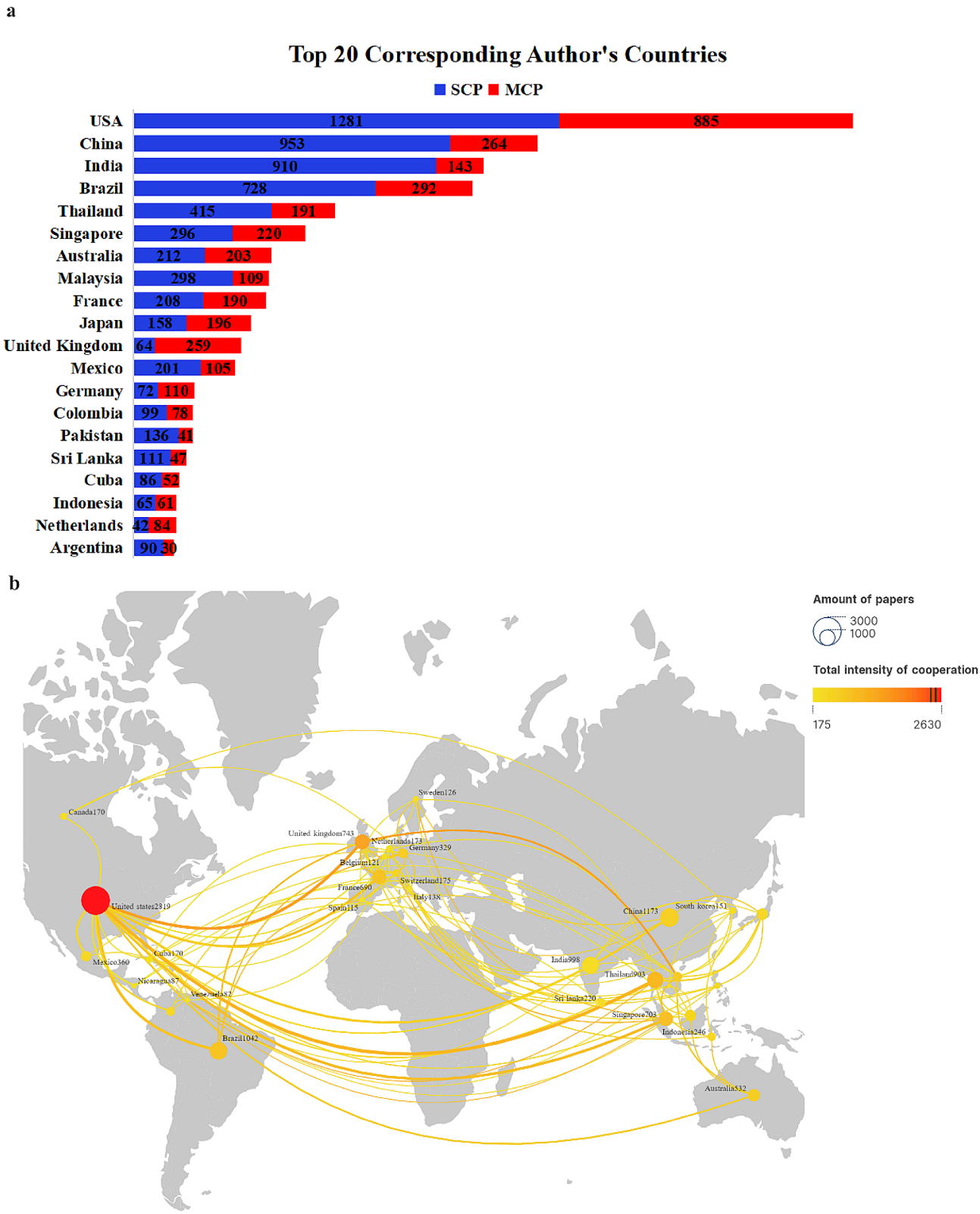


Fig. 3 Global Collaboration in Dengue Virus (DENV) Research from 1995 to 2023. (**a**) Displays the top 20 countries ranked by the number of corresponding authors in DENV research. (**b**) Showcases a VOSviewer network visualization of international co-authorship among these countries, where each country is represented as a node. The size of each node indicates the quantity of publications or the centrality in the collaborative network—larger nodes suggest higher publication outputs or more extensive collaboration. Links between nodes illustrate collaborative relationships, and node colors denote clusters of countries with frequent research collaborations in DENV

importance of international partnerships in advancing Dengue virus research.

Comprehensive gene and keyword analysis in dengue virus research

Using VOSviewer 1.6.18 for gene visualization and keyword co-occurrence analysis has revealed a complex landscape in Dengue virus research, covering six main clusters: vector ecology, clinical manifestations, virology, vaccine development, immune response, diagnostic methods, and disease epidemiology (Fig. 4a and b). This extensive range highlights the breadth of research, from molecular interactions to epidemiological patterns. Specific attention is focused on the virus's basic properties, including replication mechanisms and immune responses, as well as disease transmission and epidemic trends, emphasizing crucial aspects such as viral transmission routes and genetic diversity.

The heatmap analysis from 1995 to 2023 shows an increased focus on keywords like "Aedes" (the primary vector), "antibody", "ADE" (antibody-dependent enhancement), "dengue vaccine", and "antiviral agents", indicating heightened research activity in developing prevention and treatment methods (Fig. 4c). Emerging keywords such as "covid-19" and "zika" indicate a shift towards research on new infectious diseases, with significant regional research activity in Brazil, Thailand, and Indonesia.

The co-occurrence clustering analysis of genes including IFNA1, DDX58, IFNB1, STAT1, IRF3, and NFKB1

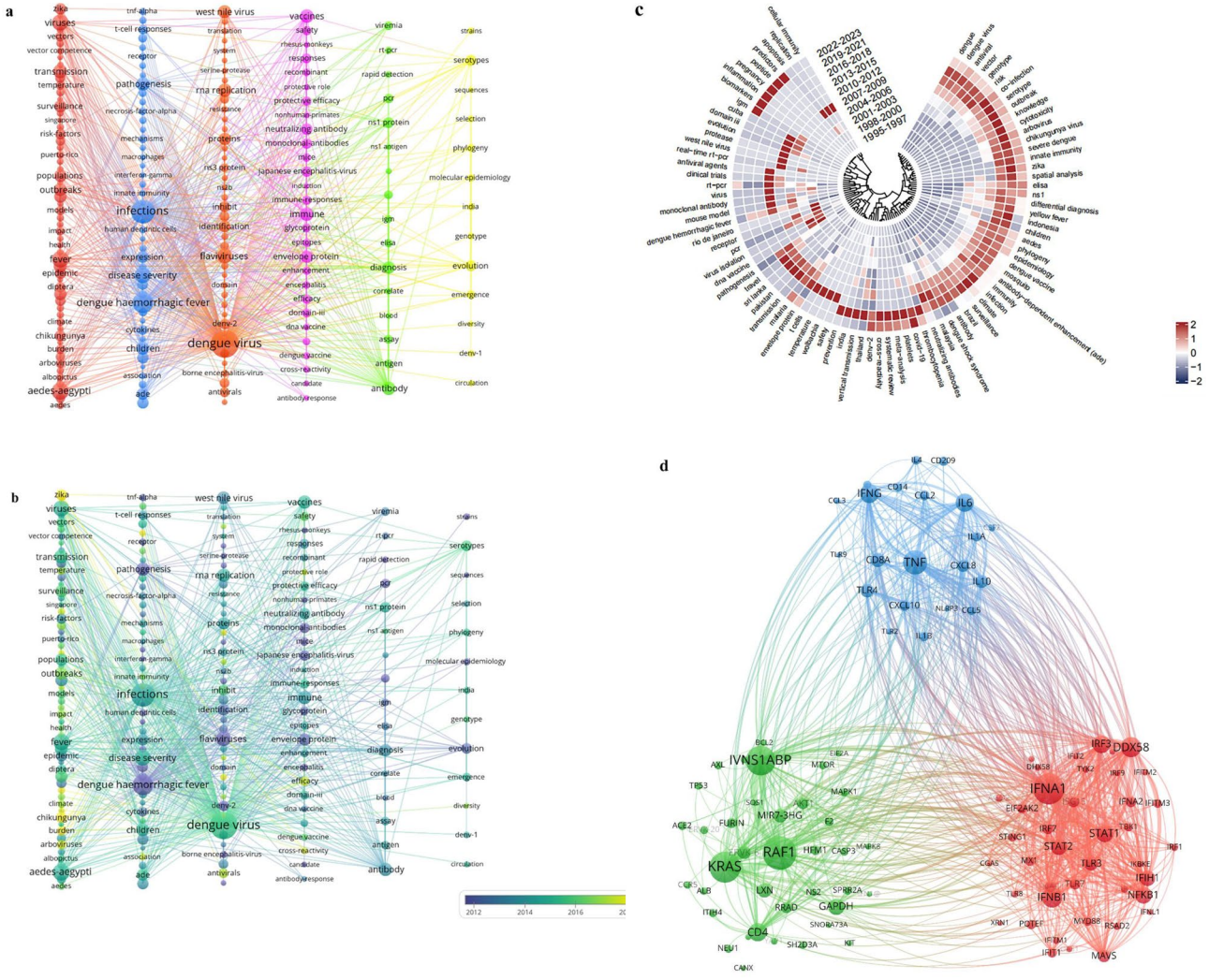


Fig. 4 Keyword Analyses in Dengue Virus-Related Publications from 1995 to 2023. (**a**) A co-occurrence network of 16,833 unique keywords with 58 keywords occurring more than 200 times, organized into six color-coded clusters. (**b**) An overlay visualization showing the temporal progression of keywords, with early keywords in blue and more recent ones in yellow. (**c**) A heatmap detailing the trends of keyword usage over the study period. (**d**) A co-occurrence cluster analysis focusing on genes associated with the Dengue virus

has identified key molecular players in the immune response to Dengue infection. This analysis reveals complex networks of gene interactions via pathways such as Toll-like and RIG-I-like receptors, essential for recognizing viral components and initiating antiviral defenses (Fig. 4d). Genes such as IFITM3, TBK1, and STAT2 have been identified as potential therapeutic targets for their roles in modulating the host's immune response and controlling viral load.

Journal impact and citation dynamics in dengue virus research

Over 29.76% of Dengue virus-related publications have appeared in the top 10 journals, underscoring the significant concentration of research output in high-impact periodicals. For more information on these leading journals, refer to Table S2 in the supplementary materials, which lists the top 10 global journals in the field of Dengue. Notably, ***Plos Neglected Tropical Diseases*** leads with 791 articles, followed by the ***American Journal of Tropical Medicine and Hygiene*** with 579 articles, ***Journal of Virology*** with 322 articles, and ***BMC Infectious Diseases*** with 207 articles. Predominantly classified within the Q1 and Q2 quartiles, these journals have a profound impact on the scientific community, covering areas such as virology, immunology, epidemiology, and public health. These leading journals contribute significantly to various research domains within the field. For instance, ***Plos Neglected Tropical Diseases*** and the ***American Journal of Tropical Medicine and Hygiene*** are instrumental in advancing basic research and epidemiological research. The ***Journal of Virology*** plays a critical role in disseminating virological and immunological research, while ***BMC Infectious Diseases*** provides extensive coverage of clinical studies and the public health implications of research. This interdisciplinary approach is essential for addressing the multifaceted challenges of Dengue research.

A dual-map overlay analysis provides further insights by visualizing the diversity of research topics covered in these journals and the co-citation relationships among articles in the Dengue virus research field (Fig. 5). This analysis highlights the interconnectedness of research activities, with molecular biology, immunology, and clinical medicine prominently featured. It also reveals extensive collaboration across research domains, underscoring the pivotal role of molecular biogenetics as a frequently cited area in Dengue virus research. This network illustrates the depth of collaborative efforts and showcases the journals' roles in fostering a comprehensive understanding of and response to global Dengue fever challenges.

Discussion

Summary

The inaugural bibliometric analysis of the global research landscape on the dengue virus reveals a field predominantly characterized by descriptive and observational studies. From 1995 to 2023, the number of published papers peaked in 2021, with 747 articles. This surge suggests a rapid advancement and increased interest in Dengue virus research, potentially driven by emerging challenges and advancements in the field. These pivotal moments have often been marked by disease outbreaks, policy changes, or scientific breakthroughs. For instance,

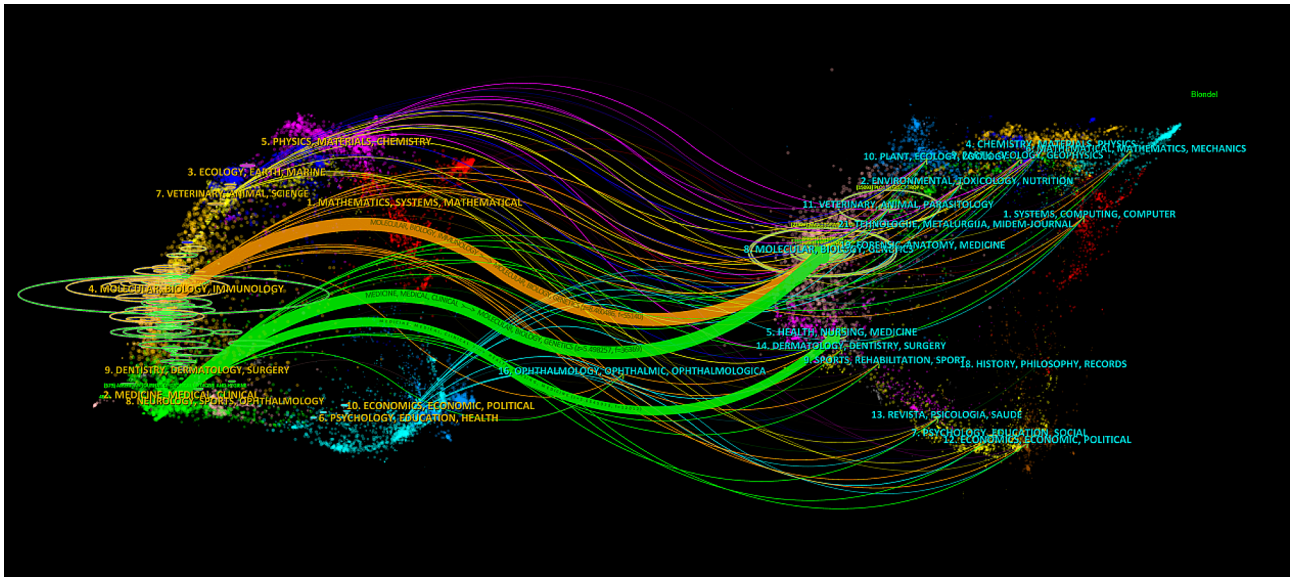


Fig. 5 Dual Map Overlay of Journals in Dengue Virus Research. This visualization illustrates the thematic distribution and citation flows among disciplines involved in Dengue studies. It highlights key citation trajectories between journals in Molecular Biology, Genetics, and other related fields, showcasing the interconnectivity of medical, clinical, and biological research in advancing our understanding of Dengue

severe outbreaks in the Philippines and Brazil during 2019–2021 led to an increased focus on studying transmission patterns and developing effective prevention strategies [7, 8]. Global health organizations and national governments have implemented new policies to combat the rising threat of Dengue. The World Health Organization's comprehensive Dengue control strategy, launched in 2020, emphasized the need for enhanced surveillance, improved diagnostics, and vaccine development. These policies spurred increased funding and research initiatives, contributing to the surge in publications. Advances in genomics, proteomics, and bioinformatics have provided new tools and methodologies for studying the Dengue virus. Breakthroughs in vaccine development, such as the approval and rollout of the Dengvaxia vaccine, and innovative diagnostic methods have accelerated research efforts to evaluate efficacy and safety, understand virus-host interactions, and explore novel therapeutic targets. These pivotal events have directed research towards specific aspects of Dengue virus biology, immunology, and epidemiology, guiding the evolution of the field [9]. Initially dominated by basic research on viral properties, replication mechanisms, and vaccine development, the field has progressively expanded to encompass broader areas such as vector ecology [10], clinical manifestations [11], diagnostic methods [12], and disease epidemiology [13, 14].

Geographical analysis reveals significant disparities in research quality across continents. Europe leads with 59.36% of its publications in the top quartile, followed by Central America and the Caribbean (57.14%), and North America (51.17%). These disparities are influenced by several factors. Research output is disproportionately lower in regions such as Sub-Saharan Africa, parts of the Middle East, and smaller island nations in the Pacific. Despite the presence of Dengue in these areas, they contribute relatively few research publications compared to regions like Southeast Asia and Latin America. Many underrepresented regions lack the necessary infrastructure, funding, and trained personnel to conduct extensive research. Limited access to advanced technologies and laboratories hampers local research efforts. In regions burdened by multiple infectious diseases (e.g., malaria, HIV/AIDS), public health resources and research funding are often directed towards more immediate health threats, sidelining Dengue research. Variations in Dengue virus transmission dynamics and environmental conditions might influence the intensity and focus of research activities. Regions with sporadic outbreaks may not prioritize Dengue research as highly as those with continuous high transmission rates. These disparities impact global Dengue virus research and control efforts by creating gaps in knowledge and hindering the development of universally effective interventions. Underrepresentation in research limits the understanding of region-specific transmission patterns, vector behavior, and population immunity, which are crucial for designing targeted control measures.

Comparison with existing literature

Spanning from 1995 to 2023, this study provides a unique longitudinal analysis of Dengue virus research, revealing significant trends and shifts using advanced bibliometric and statistical techniques like network and trend analyses. Our findings are consistent with and build upon prior bibliometric studies on Dengue virus and related arboviruses. By integrating disciplines like epidemiology, biology, and environmental science, the study provides an in-depth view of the field's evolution and the challenges posed by the Dengue virus. It particularly highlights the impact of global climate change on disease transmission, offering insights not extensively covered in previous literature. For instance, the study titled "Dengue," published in ***The Lancet*** in February 2024, includes data only up until October 10, 2022 [15]. In contrast, our research incorporates updated data, extending our analysis from 1995 to 2023. This expansion enables a more comprehensive analysis and deeper insights into long-term trends that elucidate the development and impact of Dengue fever.

Hotspots and frontiers

The analysis of keywords and gene clustering patterns highlights emerging trends and research priorities in DENV research. Key research focuses include vaccine development [16, 17], novel antiviral therapies, virus transmission and control strategies, climate change and disease distribution, epidemiology and model predictions [18–20], and immune responses and pathogenic mechanisms [21–23]. The dynamic nature of DENV research is evident, with a recent pivot toward issues such as climate change and the emergence of viruses like Zika and chikungunya [24–27]. Since 2019, the focus has notably shifted toward antiviral activities [28, 29] and the exploration of neutralizing antibodies [30–34] as critical areas of investigation. Effective antiviral strategies are essential to control the rising prevalence of Dengue virus infection and reduce mortality. The identified trends indicate a growing reliance on interdisciplinary approaches in DENV research. To comprehensively understand the transmission mechanisms and pathological processes of the dengue virus, future studies should continue to foster collaborations across fields such as epidemiology, molecular biology, climate science, and public health. Additionally, the hotspots reveal the rapid development of new diagnostic and therapeutic technologies. Future research should further promote innovation in areas such as nanotechnology, gene editing, and vaccine development to

discover more effective prevention and treatment methods. Moreover, enhancing global data sharing and applying big data analytics can enable researchers to more accurately predict dengue outbreaks and develop more effective interventions. The analysis of research trends and hotspots can also provide evidence-based support for policy-making. Understanding regional patterns of virus transmission and high-risk factors can help formulate targeted control strategies. Furthermore, public health strategies can be significantly improved by integrating community involvement and education, environmental management, and continuous monitoring. Environmental factors play a significant role in virus transmission, as indicated by hotspot analyses. Public health strategies should establish and refine monitoring systems and emergency plans to ensure swift and effective action during outbreaks.

Vaccine development

The development of an effective dengue vaccine has been hindered by the immunological complexities of its four serotypes, requiring uniform protection to prevent antibody-dependent enhancement (ADE), a significant challenge for vaccine efficacy [35, 36]. Several vaccine candidates have emerged, targeting either the structural E protein or the non-structural protein NS1, with various stages of development currently underway [37–39]. Currently, three primary vaccines are in use: Sanofi Pasteur's Dengvaxia (CYD-TDV), the first licensed vaccine; this vaccine has shown an efficacy rate of approximately 60% but has been associated with an increased risk of severe dengue in seronegative individuals. This risk led to its restricted use to those who have had a previous dengue infection. Recent studies have continued to monitor its long-term efficacy and safety, providing critical data on its performance in diverse populations. Takeda's Qdenga (TAK-003), approved in the EU in December 2022 and in Brazil in March 2023; Qdenga has demonstrated a higher efficacy rate, with recent studies showing an 80% reduction in hospitalizations and a 90% reduction in severe dengue cases among vaccinated individuals. where the vaccine was approved for ages 4–60, corroborate these findings, showing substantial decreases in dengue-related hospitalizations and severe cases. and the NIH's TV003 has shown promise, with phase II trials indicating strong immunogenicity and a balanced response against all four serotypes. Phase III trials are ongoing, and preliminary data suggest high efficacy across different age groups and regions [40]. This vaccine's simpler dosing schedule and robust immune response make it a strong candidate for broad use. For a comparison of the efficacy of licensed and Phase 3 live attenuated tetravalent Dengue vaccines across targeted populations, refer to Table 1. Additional candidates, such as attenuated live, inactivated, recombinant, and DNA vaccines, are currently under clinical or preclinical evaluation. For a comprehensive overview of these vaccine candidates, refer to Table S3 in the supplementary materials.

Novel antiviral therapies

The urgent need for effective antiviral agents against the Dengue virus is underscored by the limited efficacy of currently available treatments [41, 42]. Substantial efforts have been invested in identifying potent antivirals, with a notable shift toward repurposing existing drugs as a viable strategy [43]. However, drugs such as balapiravir, chloroquine, lovastatin, and celgosivir have shown limited success in clinical trials, highlighting the need for a targeted approach in developing novel therapies. Many repurposed drugs were originally designed to target different pathogens or disease mechanisms, which do not align well with the unique biology of the Dengue virus. For instance, chloroquine, primarily an anti-malarial drug, failed to exhibit significant antiviral activity against Dengue in clinical settings [44]. The pharmacokinetic profiles of some repurposed drugs are not suitable for achieving effective concentrations in tissues affected by Dengue. Additionally, toxicity at the required doses for antiviral efficacy can limit their use. Balapiravir, for instance, showed hepatotoxicity in clinical trials, making it unsuitable for Dengue treatment [45]. The potential for the development of viral resistance is another concern. Drugs like lovastatin, initially considered for their antiviral properties, may induce resistance mechanisms in the virus, reducing their long-term efficacy [46]. Lessons learned for future drug development include the importance of tailoring drug design to the specific viral and host mechanisms involved in Dengue pathogenesis. Additionally, a better understanding of the pharmacokinetic and pharmacodynamic requirements for effective antiviral activity is crucial. Future efforts should focus on identifying compounds that specifically target Dengue virus replication and its interaction with host cells.

Detailed information on the most promising candidates(see Table 2), such as AT-752 and JNJ-1802, can shed light on the potential breakthroughs in antiviral treatments for Dengue. AT-752-This candidate has shown potent in vitro activity against all four DENV serotypes. Phase I trials have indicated favorable pharmacokinetics and safety profiles, making it a promising candidate for further development. AT-752 targets the viral RNA polymerase, inhibiting viral replication. Early clinical data suggest that AT-752 can achieve therapeutic concentrations in the blood with minimal side effects, paving the way for phase II trials to assess its efficacy in Dengue patients. JNJ-1802-An inhibitor of the DENV NS4B protein, JNJ-1802 has demonstrated robust antiviral activity in preclinical models. It disrupts the viral replication

Table 1 Compares the efficacy of licensed and phase 3 live attenuated tetravalent dengue vaccines for targeted use populations. (the table includes findings from research by Saranya Sridhar, M.B. and colleagues, published in the Lancet in 2024 [15]. It has been further updated and expanded based on a 2024 article by Lise Alves, also in the Lancet, titled "Brazil to start widespread dengue Vaccinations" [63]." Updates and expansions are highlighted to clearly distinguish them from the original data.)

Category			TV003/TV005 [64, 65]	Dengvaxia (CYD-TDV) [66, 67]	Qdenga (TAK-003 or DENVax) [68–72]
Manufacturer			National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)	Sanofi Pasteur	Takeda
Current Stage			Phase 3 in progress or planning stages	Licensed for use in individuals 9–45 years old in endemic areas, licensed in 20 countries as of December 2015	Approved for use in the European Union as of December 5, 2022. Brazil's Health Ministry has approved vaccination the authorisation of Qdenga in March, 2023.
Vaccine Platform			Live Attenuated Tetravalent Dengue Vaccine (LATV). Each component has a 30-nucleotide deletion in the 3' untranslated region of the viral genome, with variations in the DENV-2 component concentration between TV003 and TV005.	Live recombinant tetravalent dengue vaccine developed using a yellow fever 17D vaccine backbone.	Live-attenuated dengue vaccine based on a dengue serotype 2 virus backbone, designed to protect against all four dengue virus serotypes.
Ages of Trial Participants			Adults and children aged 4–16 years in various studies, with a focus on flavivirus-seronegative individuals for initial efficacy.	Trials included participants aged 2 to 16 years. However, the vaccine is recommended for individuals 9–45 years old due to an increased risk of hospitalization in younger children, particularly those aged 2–5 years in the CYD14 trial in Asia.	Healthy children and adolescents aged 4 to 16 years living in dengue-endemic areas
Doses			1-dose; a second booster tested 6 months after the first in some trials	3-dose series administered on a 0/6/12-month schedule	2-doses, administered subcutaneously on Months 0 and 3
Prevaccination Antibody Screening Recommended?			Not explicitly mentioned, but trials included both flavivirus-seronegative and seropositive participants	Yes, to identify individuals seropositive for prior dengue infection	Not explicitly stated but efficacy evaluated based on serostatus
Timeframe for Efficacy Endpoint			Varied; in one study, overall efficacy observed over 17 months post-vaccination	Evaluated 25 months post-first dose, with an ongoing follow-up period of four additional years	Primary endpoint analysis through 12 months after the second dose, with continued evaluation up to three years
Efficacy among seropositive people	VCD: overall		76% (64–84%)	64% (58–69%)	61.2% (56.0–65.8%) [73]
	VCD: by serotype	DENV-1	67% (46–80%)	56% (45–65%)	56.1% (44.6–65.2%)
		DENV-2	67% (47 to 80%)	80% (73–86%)	80.4% (73.1–85.7%)
		DENV-3	80% (67–88%)	52% (37–64%)	52.3% (36.7–64.0%)
		DENV-4	89% (80–94%)	71% (40–86%	70.6% (39.9–85.6%))
	Hospitalisation: overall		79%(46–80%)	86% (79–91%	84.1%(77.8-88.6%)
	Hospitalisation: by serotype	DENV-1	78%(55–90%)	67% (37%to 82%)	66.8% (37.4–82.3%)
		DENV-2	82%(66–90%)	96%(90%to 98%)	95.8% (89.6%to 98.3%)
		DENV-3	63%(18–83%)	74%(39–89%)	74.0% (38.6%to 89.0%)
		DENV-4	89%(62–99%)	100%(NE)	100.0% (NE)
Efficacy among seronegative people	VCD: overall		39% (–1–63%)	54% (42–63%)	53.5% (41.6–62.9%)
	VCD: by serotype	DENV-1	41%(-7–67%)	45% (26–60%)	45.4% (26.1%to 59.7%)
		DENV-2	-21%(-136%to 38%)	88%(79–93%)	88.1% (78.6–93.3%)
		DENV-3	52%(-6% to78%)	-16% (-108–36%)	–15.5% (–108.2–35.9%)
		DENV-4	65%(24–84%)	-106%(-629–42%)	–105.6% (–628.7–42.0%)
	Hospitalisation: overall		−41%(-168–93%)	79%(64–88%)	79.3% (63.5–88.2%)
	Hospitalisation: by serotype	DENV-1	−37%(-219–41%)	78%(44–92%)	78.4% (43.9–91.7%)
		DENV-2	−141%(-795%to 35%)	100%(NE)	100.0% (NE)
		DENV-3	15%(-225–78%)	−88%(-573–48%)	–87.9% (–573.4–47.6%)
		DENV-4	7%(-712–89%)	100%(NE)	100.0% (NE)
DHF	Seropositive		NR	NR	80.9% (46.3–93.2%)
	Seronegative		NR	NR	–3.4% (–464.7–81.1%)

Table 1 (continued)

Category		TV003/TV005 [64, 65]	Dengvaxia (CYD-TDV) [66, 67]	Qdenga (TAK-003 or DENVax) [68–72]
SD	Seropositive	NR	48.0%(20.0–66.0)	90.1% (15.3–98.8%)
	Seronegative	NR	NR	NE
DHF or SD	Seropositive	NR	NR	85.4% (60.3–94.6%)
	Seronegative	NR	NR	–29.2% (–566.1–74.9%)

Ranges in parentheses are 95% CIs. DENV = dengue virus. NE = not possible to estimate due to a zero cell in one of the groups. NR = not reported. VCD = virologically confirmed dengue. DHF = Dengue Hemorrhagic Fever. SD = Severe dengue

Table 2 Lists the Dengue drug candidates currently being evaluated in clinical trials

Drug	Target(s)	Mechanism(s) of Action	Clinical Trials	References
AT-752	the viral replication process across all dengue serotypes	inhibiting the virus polymerase	Phase I	[74]
JNJ-1802	inhibiting the interaction between two viral proteins, NS3 and NS4B	inhibit the virus's ability to infect and replicate within the host	Phase II	[75]

complex, effectively reducing viral load. Early-phase clinical trials have shown promising results, with significant reductions in viral RNA levels in treated individuals. The safety profile has also been favorable, with no serious adverse events reported. Ongoing trials aim to determine the optimal dosing regimen and confirm its efficacy in larger patient cohorts. Additionally, research into host-targeted therapies, such as those modulating the immune response or viral entry pathways, is ongoing, with several candidates showing promise in preclinical studies. These approaches aim to enhance the host's ability to combat the virus or prevent the virus from entering and replicating within host cells. Continued interdisciplinary research and innovative methodologies are crucial in addressing the challenges of treating DENV infections. For detailed information on recent advances, refer to Table S4 in the supplementary materials, which outlines the development of new antiviral drugs for Dengue. The integration of novel therapeutic approaches, combined with a deeper understanding of the virus-host interactions, holds the potential for significant breakthroughs in managing Dengue virus infections.

Virus transmission and control strategies

Recent advances in biological control methods have significantly shaped strategies to mitigate dengue fever transmission via vector mosquitoes. One notable approach is infecting Aedes mosquitoes with Wolbachia, an endosymbiotic bacterium that effectively reduces the mosquitoes' ability to transmit the dengue virus [47]. Another method is the release of sterile mosquitoes through radiation or genetic modification, which controls population numbers by preventing offspring production after mating with wild mosquitoes [48]. Additionally, the use of CRISPR-Cas9 gene editing technology is emerging as a revolutionary approach to engineer mosquitoes that either cannot survive or transmit the dengue virus, although this remains experimental [48]. The application of nanotechnology in insecticides shows promise, enhancing the delivery and effectiveness of chemical controls with minimal environmental impact by targeting specific biological pathways in mosquitoes [49]. Furthermore, smart surveillance systems utilizing IoT (Internet of Things), AI (Artificial Intelligence), and big data are improving the monitoring and predictive analysis of vector populations and dengue transmission patterns, leading to more targeted and efficient control measures [50].

Epidemiology and model predictions

Recent advancements in epidemiological modeling have significantly enhanced our understanding of disease transmission in the context of climate change. Machine learning and AI models have become essential for processing large datasets and predicting disease spread patterns with high accuracy, leveraging complex nonlinear data to forecast trends and potential outbreaks [51]. Spatial statistical models, another critical tool, use geographic and environmental data to map the potential distribution of vectors like Aedes mosquitoes and predict regions at increased risk for dengue outbreaks [51]. Dynamic simulation models, such as the Susceptible-Exposed-Infectious-Recovered (SEIR) model, simulate transmission dynamics within populations using differential equations to describe interactions between hosts, pathogens, and the environment, providing a detailed predictive framework [52]. Additionally, regression analysis identifies key factors influencing transmission, while Geographic Information Systems (GIS) assess how environmental factors, exacerbated by climate variability, affect disease patterns. Integrating GIS with epidemiological data helps guide targeted interventions and resource allocation [53].

Immune responses and pathogenic mechanisms

Gene co-occurrence analysis has highlighted critical molecular mechanisms in Dengue virus infection, pinpointing key genes such as IFNA1, DDX58, and STAT1

that play significant roles in the host immune response. IFNA1 enhances antiviral gene expression and adaptive immunity [54]. DDX58 activates innate immune signaling upon viral RNA recognition [55], and STAT1 is crucial for cytokine production and immune cell activation [56, 57]. Dysregulation of these genes can lead to severe outcomes in Dengue fever. Other important genes in the Toll-like and RIG-I-like receptor pathways, such as TLR3, TLR7, TLR9, IFNAR1, and MAVS, have been linked to virus recognition and response mechanisms [58]. The dynamic host immune response to Dengue virus involves innate immune sensor activation, cytokine production, and adaptive immune response induction. The virus employs evasion strategies that can lead to dysregulated immune responses and severe disease manifestations such as cytokine storm and tissue damage [30, 59–61]. This understanding opens avenues for targeted therapies, such as viral RNA-sensor inhibitors or cytokine blockers, which could mitigate immune-mediated damage and improve outcomes in severe Dengue cases. Insights from gene co-occurrence studies suggest potential therapeutic targets in immune signaling, viral replication, and inflammation pathways, crucial for developing novel treatments to control viral replication and modulate immune responses in Dengue virus infection [62].

Strategic initiatives for global dengue research collaboration

Future research on Dengue virus (DENV) should prioritize international collaboration and interdisciplinary cooperation to effectively address global challenges. Establishing international research consortia and networks is essential, aiming to foster partnerships among countries, institutions, and disciplines to facilitate knowledge exchange, resource sharing, and collaborative research efforts. Initiatives like joint funding programs, collaborative research projects, and researcher exchange programs are crucial for promoting cross-cultural collaborations and interdisciplinary approaches. Leveraging the strengths of diverse stakeholders, such as researchers, policymakers, public health agencies, and community organizations, is key to driving innovation and accelerating progress in understanding and combating DENV globally. Future studies should explore Dengue virus dynamics, leveraging advanced technologies and data analysis methods to predict outbreaks and identify key environmental, social, and biological factors. Collaborative efforts among epidemiologists, virologists, entomologists, climatologists, and public health experts can provide a holistic understanding of transmission mechanisms and accelerate the development of targeted interventions. Integrating real-time surveillance systems, geographic information systems (GIS), and mathematical modeling can enhance the accuracy and timeliness of outbreak predictions, optimizing resource allocation for prevention and control. Community-based interventions, such as vector control programs and health education campaigns, are crucial in reducing transmission and mitigating the impact of outbreaks. Despite advancements, challenges in rapid diagnostics, effective antiviral treatments, and developing vaccines that are efficacious across all DENV serotypes remain. Addressing these challenges through innovative diagnostic technologies, novel vaccine platforms, and interdisciplinary collaboration is vital for progress. Moreover, emerging technologies like gene editing and biotechnology hold promise for new therapeutic interventions, underscoring the importance of international and interdisciplinary efforts in advancing DENV research and developing sustainable solutions for its control and prevention.

Conclusions

This bibliometric analysis reveals key trends and research gaps in DENV studies from 1995 to 2023, highlighting the importance of interdisciplinary approaches in understanding virus behavior, vaccine development, and prevention strategies. Although notable progress has been made, our analysis identifies several underexplored areas, including the interactions between DENV and its host, the socio-economic impacts of public health interventions, and the application of advanced technologies like artificial intelligence in epidemic prediction and management. Future research requires strengthened interdisciplinary collaboration, uniting experts from molecular biology, epidemiology, data science, and other fields to address comprehensively the challenges posed by DENV. By fostering such cooperation, we can bridge existing research gaps and pioneer new directions, ultimately achieving effective control and prevention of DENV.

Supplemental materials

To further enrich the understanding of our research, we have provided detailed Supplemental Materials. These include Table S1, which presents data on global dengue cases and related deaths since 1995; Table S2, which lists the top 10 global journals in the field of dengue; Table S3, which details current dengue vaccine candidates under evaluation; and Table S4, which summarizes recent advances in dengue antiviral drug development. These materials offer additional insights and broader context to the discussions presented in this paper.

Abbreviations

DENV	Dengue virus
WHO	The World Health Organization
WOS	The Web of Science
SCI-EXPANDED	Science Citation Index Expanded
SCP	Self-citation percentage (SCP)
MCP	Most cited paper (MCP)
COVID-19	Corona Virus Disease 2019

ADE	Antibody-dependent enhancement
IFNA1	Interferon Alpha 1
DDX58	DEAD (Asp-Glu-Ala-Asp) Box Polypeptide 58
IFNB1	Interferon Beta 1
STAT1	Signal Transducer and Activator of Transcription 1
IRF3	Interferon Regulatory Factor 3
NFKB1	Nuclear Factor Kappa B Subunit 1
TLR	Toll-like Receptors
RLR	RIG-I-like Receptors
IFITM3	Interferon-Induced Transmembrane Protein 3
TBK1	TANK-Binding Kinase 1
STAT2	Signal Transducer and Activator of Transcription 2
NIH	National Institutes of Health
IoT	Internet of Things
AI	Artificial Intelligence
SEIR	Susceptible-Exposed-Infectious-Recovered (a compartmental model in epidemiology)
GIS	Geographic Information System

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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