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The dengue vaccine initiative: A bibliometric analysis of research publications

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Chapter

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Abstract

Dengue fever has become a significant public health problem in tropical and subtropical regions and affects millions of people annually. Approximately 390 million people worldwide are estimated to be infected with dengue every year, of which 96 million develop dengue fever. Recently, there has been a noticeable increase in dengue cases, primarily in areas with tropical and subtropical climates. Vaccines have been developed to prevent or reduce the severity of the disease. This study reviews the number of publications on dengue vaccines and related topics worldwide. We aimed to evaluate the research output and create a narrative on global vaccine distribution, challenges in vaccine initiatives, and the future of dengue vaccines as a strategy to combat the virus in endemic countries. We used keywords such as 'Dengue virus' AND 'Vaccines,' 'Dengue fever' AND "Vaccine initiatives" AND 'Dengue virus' AND 'Vaccine safety' to collect data from the Scopus database. We performed a descriptive analysis to determine the frequency of publications and reviewed the relevant articles for information from the Scopus database. The dengue vaccine initiative is vital in the fight against dengue through collaboration, innovation, and knowledge sharing.

Keywords: dengue vaccine, vaccine development, vaccine coverage, adverse events, vaccine administration, immune response

1. Introduction

Dengue fever has become a pressing public health problem in various tropical and subtropical areas and has a significant impact on the health of millions of people annually [1]. It is estimated to infect approximately 390 million people worldwide annually, with about 96 million cases of dengue fever [2]. The distribution of dengue cases is widespread; the disease is endemic in 100 countries, especially in Southeast Asia, the Pacific Islands, the Caribbean, and parts of Central and South America [3]. Recently, there has been a notable increase in the number of dengue fever cases, particularly in regions with tropical and subtropical climates. This surge has raised significant concerns within the global public health community about the potential for widespread impacts on affected populations and health systems [4].

Dengue fever is caused by the dengue virus, which is transmitted primarily to humans through the bite of infected Aedes mosquitoes, mainly *Aedes aegypti* [5]. Mosquitoes are more active during the day and breed in stagnant waters, making urban and suburban environments particularly susceptible to dengue transmission. Once infected, a mosquito can transmit the virus to humans for the rest of its lifespan. Aedes mosquitoes, known to carry diseases such as dengue fever, Zika virus, and chikungunya, have shown a remarkable ability to thrive in urban environments [6]. They are particularly drawn to areas with stagnant water, commonly found in residential areas and cities, making these locations hotspots for mosquito breeding. The prevalence of dengue fever in urban environments is increasing, and several factors are associated with blame. The rapid pace of urbanization has led to a higher population density, providing more breeding areas for mosquitoes that transmit the dengue virus. Additionally, substandard sanitation practices and inadequate water storage methods have exacerbated the spread of this disease. Collectively, these factors have contributed to an increase in dengue fever cases in urban settings [7]. The increasing prevalence of dengue fever in urban areas can be attributed to several factors. Rapid urbanization has caused population densities to increase and created more breeding grounds for dengue-carrying mosquitoes. Furthermore, inadequate sanitation practices and improper water storage methods have exacerbated the spread of this disease. Together, these factors have contributed to the increase in dengue cases in urban settings [8].

The dengue virus, a mosquito-borne virus, is a member of the Flaviviridae family [9] and includes other notable viruses, such as the Zika virus, the yellow fever virus, and the West Nile virus. In 2023, the World Health Organization (WHO) reported a record high of more than 6.5 million dengue cases and more than 7300 dengue-related deaths in 92 countries and territories. This increase was due to continuous transmission and an unexpected rise in cases. The Americas represent the most significant global burden, with more than 4.1 million new infections. India also recorded nearly 95,000 cases and 91 deaths by September 17, 2023. The prevalence of dengue virus is significantly higher in tropical regions because of factors such as temperature, humidity, and the presence of suitable mosquito vectors. Viral infection poses a significant public health challenge in these areas, leading to a high incidence of dengue fever and other related diseases.

Dengue epidemics often occur in cyclical patterns, with peaks typically observed every 3–5 years. Although dengue primarily affects tropical and subtropical regions, there have been instances of local transmission in non-endemic areas, mainly through infected travelers importing the virus [10]. This has led to localized outbreaks in countries with suitable mosquito vectors. Dengue infection can cause a wide range of symptoms, from mild fever and body aches to severe dengue, also known as dengue hemorrhagic fever.

The primary focus of dengue control efforts is the implementation of vector control measures in countries burdened with viral diseases. This includes comprehensive strategies, such as identifying and eliminating potential mosquito breeding sites and performing targeted insecticide spraying and repellents to minimize human-mosquito contact. These measures aim to reduce dengue fever by reducing the population of disease-carrying mosquitoes and protecting individuals from bites [11]. Furthermore, research is ongoing to develop a dengue vaccine that can potentially reduce the incidence and severity of the disease [12]. The dengue virus is a major global health problem, particularly in tropical and subtropical regions. Understanding the epidemiology of dengue is crucial for implementing effective control strategies and mitigating the impact of this viral infection [13].

Vector control measures without specific antiviral treatments or vaccines are insufficient to prevent the spread of DENV. Therefore, developing a safe and effective vaccine is a priority in countries with the highest burden of dengue fever. In 2014, a Dengue Vaccine Initiative (DVI) was launched as a global collaborative effort to accelerate the creation and introduction of dengue vaccines through a Bill and Melinda Gates-funded project [14]. We thoroughly examined the relevant literature from the Scopus database to improve our understanding of the dengue virus and vaccine efforts. Our selection of this database was primarily based on the abundance of articles from Scientific, Technical, and Medical (STM) journals equipped with easily accessible references. This facilitated our ability to review the literature, which allowed us to understand the current knowledge of dengue vaccines. This review analyses the number of publications on dengue vaccines and related topics worldwide. The purpose was to gain insight into the ongoing discussion and evaluate the research output related to dengue vaccine initiatives worldwide. To collect data, we used keywords such as 'dengue virus' OR 'dengue fever' AND 'Vaccines,' OR 'Vaccine initiatives,' 'dengue virus' AND 'Vaccine safety' to extract information from the Scopus database, which we then downloaded as a MS Excel CSV file. We meticulously cleaned the data and conducted descriptive analysis to determine the frequency of publications. Furthermore, we scanned relevant articles to create a narrative on the global distribution of vaccines, challenges in vaccine initiatives, and the future of the dengue vaccine as a strategy to combat the dengue virus in endemic countries.

2. Pathogenic mechanism of dengue virus hemorrhagic fever

An understanding of the pathogenic mechanism of dengue virus hemorrhagic fever is vital to selecting an appropriate vaccine [15]. It is imperative to dive into the intricate genetic variability of the virus genotypes, as this diversity directly impacts the efficacy of potential vaccines. Moreover, recognizing specific genetic variations is crucial to tailor vaccine development and deployment strategies to combat the virus effectively [16, 17].

The development of dengue hemorrhagic fever (DHF) is a complex process that involves several factors. Viral factors, such as the virulence of the dengue virus, its ability to spread, and the presence of nonstructural protein 1 (NS1) viral antigen, all influence the pathogenesis of DHF [13]. Meanwhile, host factors, including the immune system, genetic characteristics, and immunological conditions, also play a crucial role [15, 18]. The immune system is intricately combating the virus through innate and adaptive responses. Innate responses encompass the action of the complement system and interferons, while adaptive responses involve the activation of cytotoxic T-cells and the production of immunoglobulins [19, 20].

The leading theory explaining the development of severe dengue is known as antibody-dependent enhancement (ADE). This occurs when the dengue virus (DENV) enters a more considerable number of mononuclear lineage cells by forming complexes with non-neutralizing antibodies, leading to increased virus production [21, 22]. Another significant factor in developing dengue hemorrhagic fever (DHF) is the uncontrolled generation of inflammatory cytokines. This excessive cytokine production can trigger a cytokine storm, potentially resulting in a life-threatening condition [23, 24].

3. Global distribution of dengue vaccine

The dengue virus vaccine, also known as Dengvaxia, is a live vaccine for weakened dengue viruses. Its mechanism of action involves triggering an immune response against all four types of dengue viruses. This vaccine has been commercially released in 19 countries, including Mexico, Indonesia, and Singapore. However, only Brazil and the Philippines have incorporated Dengvaxia into their public immunization programs. Sanofi Pasteur is responsible for producing this vaccine [25]. It should also be mentioned that there have been safety concerns regarding its use, which has led some countries to impose restrictions or recommendations. Currently, dengue vaccines are being developed and evaluated in clinical trials in several countries, including Brazil, Malaysia, Thailand, Vietnam, Indonesia, Mexico, Colombia, and Singapore [26].

Dengue fever (DF) is a mosquito-borne viral disease affecting millions worldwide. Researchers have been working to develop a vaccine to prevent the spread of the dengue virus for several years. The development of a dengue vaccine is a complex process that involves extensive research and clinical trials to ensure its safety and effectiveness [27, 28]. Scientists are working to create a vaccine that can protect against the four strains of dengue virus. The vaccine development process involves testing vaccine candidates in animal models and conducting human clinical trials to determine their safety and efficacy [29, 30]. Despite these challenges, developing a dengue vaccine is crucial to reduce the incidence of this disease and prevent its spread.

Currently, multiple vaccine candidates are being evaluated in clinical trials to determine their effectiveness in preventing the spread of infectious diseases. Large-scale clinical trials are being conducted to ensure the safety and efficacy of vaccine candidates [31, 32]. Dengue vaccine candidates are currently in various stages of testing to determine their immunogenicity and side effects. Regulatory authorities will approve them only after they have met strict safety standards. Current vaccine candidates in clinical trials include mRNA, viral vector, protein subunit, and inactivated or weakened viral vaccines [33–35]. Various pharmaceutical companies and research institutions around the world have developed these vaccines. Public health organizations and governments closely monitor their progress.

The dengue vaccine is a preventive measure designed to protect people from contracting the dengue virus. It is available in various countries, including Mexico, Brazil, and the Philippines. The vaccine is administered in multiple doses and is recommended for people who live or plan to travel to areas where dengue fever is prevalent [36]. It is important to note that although the vaccine is considered adequate; it does not provide complete protection against all strains of the virus and people should still take precautions to avoid mosquito bites [37, 38].

To effectively address the growing demand for dengue vaccines, it is crucial to establish strong collaborative partnerships with pharmaceutical manufacturers. These partnerships are vital for ensuring consistent and reliable production and distribution of vaccines. They should be built on mutual trust and a shared commitment to public health through regular communication and collaboration to ensure efficient and effective vaccine production and distribution [39].

Therefore, building solid partnerships and implementing strict quality control measures is crucial to ensure vaccine safety and effectiveness. This involves rigorous testing and monitoring at each stage of the production process. Surveillance and evaluation of vaccine safety and efficacy should be conducted once it is on the market. These quality control measures must be scientifically rigorous and transparent and involve close collaboration between regulatory agencies, public health officials, and pharmaceutical manufacturers [40].

Expanding the production capacity is essential to meet the growing demand for dengue vaccines. This requires investment in new manufacturing facilities, technologies, and processes to increase vaccine production's speed, efficiency, and scalability. This also means developing innovative distribution models to reach the most remote and underserved communities. Additionally, it is crucial to ensure that the vaccine is affordable and accessible to all people in need [41, 42].

In summary, addressing the growing demand for the dengue vaccine requires a comprehensive approach that involves building strong partnerships with pharmaceutical manufacturers, implementing rigorous quality control measures, and expanding production capacity to ensure the widespread availability of the vaccine. Through collaborative efforts, we can help prevent the spread of dengue fever and protect the health and well-being of people worldwide.

4. Challenges for dengue vaccination initiatives

In 2015, the Philippines introduced a dengue vaccine to reduce the incidence of dengue fever [43]. The safety of the dengue vaccine has been a topic of concern because of its severe adverse effects on some individuals who have received it. Adverse effects included fever, headache, and muscle and joint pain. This vaccine effectively prevents dengue in some individuals; however, the associated risks have decreased its use in some areas. Further research is needed to determine the effectiveness and safety of the dengue vaccine to ensure that it can be administered and used to prevent dengue fever [44–46].

In 2019, the United States Food and Drug Administration granted restricted approval to Sanofi Pasteur's Dengvaxia, a live attenuated vaccine (LAV) designed to prevent dengue fever. The approval was restricted because of concerns that the vaccine sensitized some recipients with no previous exposure to dengue, leading to an increased risk of severe dengue fever. This restriction was put in place to ensure the safe and effective use of the vaccine while further research and monitoring are conducted to understand its impacts better.

4.1 Dengue vaccine efficacy and safety

The long-term efficacy of dengue vaccines has been questioned because of a lack of long-term efficacy data. Studies have shown that the vaccine offers short-term protection against all four strains of dengue virus. Nevertheless, additional research is necessary to determine their long-term efficacy. This is mainly because the efficacy may decrease with time, and the duration of immunity remains unclear. Furthermore, there is the possibility that the vaccine may increase the risk of more severe dengue infection in people who have not previously been infected with the dengue virus. Therefore, further research is essential to determine their long-term efficacy and safety [44, 47, 48].

Because of these challenges, the Philippine government had to stop the spread of the vaccine and conduct further investigations into its safety and efficacy [49]. This setback has also led to the intensification of research efforts to develop safer and better vaccines that can effectively prevent dengue fever without causing adverse effects. Research efforts have yielded promising results, and several potential vaccines are currently at various stages of testing. With the development of safer and more effective vaccines, it is hoped that the fight against dengue fever will be more successful, and the incidence of this deadly disease will be significantly reduced in the Philippines and beyond [50–52].

However, the effectiveness of dengue vaccines remains a significant challenge. To combat the disease, the vaccine aims to protect against all four serotypes of the dengue virus, which is crucial [37]. Studies have shown that its effectiveness varies for different serotypes because the vaccine generates an immune response that targets the specific serotype for which it is designed. This could result in lower efficacy rates for some viral strains, thus reducing the protection.

Age, previous dengue infections, and timing of vaccine doses can affect vaccine effectiveness. Therefore, it is essential to continue researching and developing vaccines to protect against this deadly disease. Concerns have been raised about the dengue fever vaccine because of its potential risks [53, 54]. According to previous studies, people who have not been exposed to the virus and have received the vaccine may be at increased risk of developing severe dengue infection. These concerns have been discussed by health experts and the public, highlighting the importance of addressing the potential harm caused by vaccines. Although the vaccine effectively reduces the incidence of dengue fever in areas where the virus is prevalent, it is crucial to prioritize safety and take the necessary measures to ensure the well-being of those who receive it [54, 55].

Dengue fever (DF) is a viral disease caused by the Aedes mosquito. It is a significant public health problem in numerous tropical and subtropical countries. A dengue vaccine has been developed to prevent dengue infection and is currently approved for people aged 9–45 years [56]. However, this age restriction poses a significant limitation, as it leaves a broader population that could benefit from the vaccine, including younger children and older adults, who are also at risk of dengue infection. Although the vaccine has shown efficacy in preventing dengue infection in clinical trials, broadening its approval to include all age groups is crucial to reducing the overall burden of the disease [57, 58]. Therefore, further research is needed to assess the safety and efficacy of the vaccine in younger and older age groups. This would help expand the vaccine's age limit and make it more accessible to larger populations [59].

One of the significant hurdles in the distribution of dengue vaccines is their affordability and availability. This challenge ensures that these vaccines reach the populations that need them the most. However, the vaccine cost is significantly high, making it unaffordable to low-income countries and individuals. This pricing creates a significant obstacle to accessing the vaccine, limiting its availability to those who need it most [60].

Vaccines require adequate storage and transportation infrastructure, which may not be available in remote or resource-limited areas. The vaccine must be stored at a specific temperature, and if the infrastructure is not in place, spoilage and waste can occur [61, 62]. This could further exacerbate the challenges of vaccine distribution and access, particularly in areas with limited access to electricity or refrigeration. The distribution of vaccines requires a robust logistical framework that can ensure that the vaccine reaches all those in need, regardless of location and economic status.

The long-term efficacy of the dengue vaccine remains uncertain, as studies have shown that its protection decreases with time. As a result, there has been a gradual increase in the number of cases of dengue among vaccinated individuals [63]. This has raised concerns about the long-term efficacy of the vaccine and the need for booster doses to maintain immunity. The dengue vaccine was developed to reduce the incidence of the disease and is effective in clinical trials. Research has also revealed that vaccine protection decreases with time, affecting people vaccinated against the disease. This has led to calls for booster doses of the vaccine to be administered to maintain immunity. The optimal timing and frequency of booster doses are still being studied, and there is no consensus on the best approach [64, 65]. Meanwhile, vaccinated people must continue to take other measures to prevent dengue, such as using mosquito repellents, wearing protective clothing, and avoiding mosquito breeding sites [51, 66].

4.2 Dengue vaccine uptake and coverage

The successful implementation of vaccination programs is highly dependent on the development of public awareness and trust in dengue vaccines [67]. It is essential to provide accurate and transparent information on vaccines to combat misinformation and hesitancy [68, 69]. Distrust in vaccines can result in low vaccine coverage and pave the way for further outbreaks. To ensure effective vaccination programs, it is necessary to educate the public about the benefits and safety of dengue vaccines [70]. This involves engaging communities, healthcare professionals, and other stakeholders to address their concerns and answer questions about the vaccine [71]. Furthermore, it is crucial to ensure that the vaccine is accessible and affordable for all people in need. By building public trust and awareness, we can prevent the spread of dengue and protect individuals and communities from the harmful effects of the disease [72].

Acquiring high uptake and coverage rates for dengue vaccines is a complex challenge, particularly in regions where dengue is highly prevalent [73]. Several factors can contribute to the difficulty in achieving high vaccination coverage rates. A significant challenge is limited access to healthcare facilities, which can allow people to access vaccines. Sometimes, people may not have the economic means to access health services. Furthermore, low acceptance among some communities can affect the overall coverage rates. This may be because of concerns about vaccine safety and efficacy or a lack of awareness [68, 73].

Although current clinical trials employ prolonged prime-boost schedules, there is concern that imbalanced immunity could temporarily leave some vaccine recipients unprotected or with increased susceptibility to increased disease [65]. To address this problem, we developed a DNA vaccine for DENV serotype 1 (DENV-1) that removes immunodominant cross-reactive B-cell epitopes associated with immune enhancement. We compared wild type (WT) with this cross-reactivity reduction (CRR) and discovered that both vaccines were equally effective in protecting against the lethal homologous DENV-1 challenge [35, 74]. In mice that received the WT vaccine under conditions that mimicked natural exposure before acquiring protective immunity, we observed an improvement in a normally sublethal heterologous DENV-2 infection, which resulted in disease and 95% mortality [75]. However, mice vaccinated with the CRR vaccine exhibited redirected serotype-specific and protective immunity and significantly reduced morbidity and mortality, indistinguishable from those of naive mice. Our findings illustrate that non-protective vaccine-induced immunity can predispose individuals to enhanced DHF-like disease and that CRR DNA immunization significantly reduces this potential vaccine safety concern. The modified vaccine sculpts immune memory and redirects humoral immunity, providing valuable information on immune responses induced by the DENV vaccine in an *in vivo* model of DENV disease [76, 77].

For more than 50 years, extensive research has been conducted using various technologies, including live attenuated viruses, purified inactivated viruses, recombinant

	Publication	%
Institution		
National Institute of Allergy and Infectious Diseases	81	13
National Institutes of Health	69	11.4
Sanofi Pasteur	41	6.8
National Institute of General Medical Sciences	17	2.8
The National Natural Science Foundation of China	17	2.8
Conselho Nacional de Desenvolvimento Científico e Tecnológico	15	2.5
Bill and Melinda Gates Foundation	13	2.1
U.S. Department of Health and Human Services	11	1.8
Medical Research Council	10	1.6
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior	8	1.3
Type of publication		
Article	492	64.6
Review	135	17.7
Note	47	6.2
Letter	25	3.3
Erratum	18	2.4
Editorial	15	2.0
Conference Paper	12	1.6
Short Survey	11	1.4
Book Chapter	7	0.9

Table 1.
Institutions that support the dengue vaccine and types of research publications.

subunits, virus-like particles, and plasmids or viral vectors [78, 79]. Each approach has strengths and weaknesses with varying progress, as detailed in **Table 1**. Clinical trials have been conducted for the most attenuated, inactivated, and chimeric live vaccines. The first chimeric vaccine, CYD, was developed by Pasteur et al. [80]. To effectively combat dengue, vaccine developers must prioritize the development of tetravalent vaccines. However, the development of vaccines against this virus is hampered by significant scientific obstacles. These include the absence of a suitable and inadequate understanding of the factors that contribute to effective human immunity against the virus compared to the latter [81].

4.3 Antibody-dependent enhancement (ADE) in dengue vaccine immune response

Antibody-dependent enhancement (ADE) is a phenomenon that occurs when antibodies generated in response to the dengue virus (DENV) cannot prevent infection (**Figure 1**) effectively. Instead, these antibodies can facilitate the entry into cells and exacerbate the immune response [83]. This mechanism is also seen in the immunological response of the dengue vaccine, which has led to more severe illness than

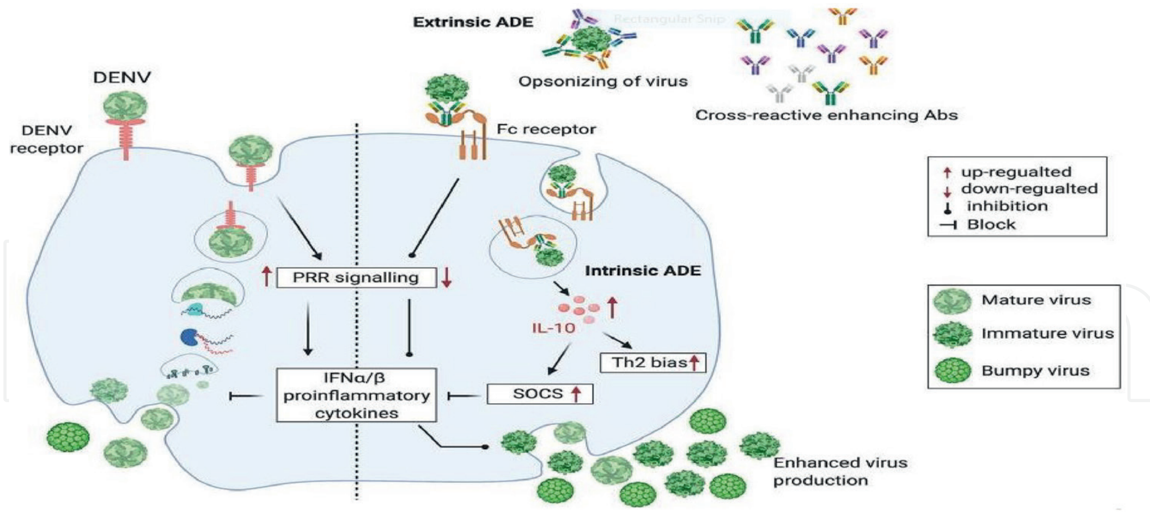

Figure 1.
Diagrammatic illustration of the ADE mechanism to dengue virus adopted from Shukla et al. [82].

if the person had not been vaccinated. ADE happens when the antibodies produced by the vaccine bind to the virus, helping it infect more cells than it would typically be able to. This increased viral replication can lead to pro-inflammatory responses and vascular hyperpermeability, which is a common cause of severe dengue [84].

Antibody-dependent enhancement is believed to play an essential role in the increased severity of secondary DENV infections, leading to severe conditions such as dengue hemorrhagic fever and dengue shock syndrome [85]. DENV-specific antibody levels are insufficient to cover all the virus-binding sites necessary for preventing cell entry. Virus-antibody complexes bind to Fc receptors on the surface of immune cells, such as B lymphocytes, natural killer cells, macrophages, neutrophils, and mast cells. These complexes are then internalized into cells *via* FcγRs, potentially leading to infection of more target cells and increased viral production [86]. ADE promotes viral entry into immune cells, resulting in increased viremia and pro-inflammatory responses, which can contribute to disease pathologies such as vascular hyperpermeability, a common feature of severe dengue [87, 88].

4.4 Genotype of dengue virus and dengue vaccine development

Dengue virus is classified into four serotypes, including DENV serotype 1 (DENV1), DENV2, DENV3, and DENV4 [82]. Initial infections in humans with any of the DENV serotypes rarely show symptoms. However, where symptoms occur, they may include high fevers, severe joint and muscle pain, and rash. The four dengue serotypes exhibit well-documented variations, but there is also a suggestion that intraserotypic antigenic diversity may contribute to viral evolution and the fluctuation of epidemics. This implies that, within each serotype there maybe additional variations in antigenic properties, potentially influencing the behavior and spread of the virus within a population.

Recently, the World Health Organization (WHO) and the US Foods and Drug Administration (FDA) have approved the use of Dengvaxia, a live attenuated tetravalent DENV vaccine developed by Sanofi Pasteur. This approval is specifically for individuals with preexisting immunity acquired through natural infections [89]. The vaccine has been authorized for administration to individuals who have previous exposure to the virus (seropositive) because of its demonstrated high effectiveness in this demographic. Conversely, the vaccine's overall effectiveness was low in children who have not been previously exposed to the virus (seronegative). Additionally, vaccination was associated with an increased likelihood of developing severe illness following infection with the wild-type DENV [90]. The Dengvaxia vaccine demonstrates varying levels of efficacy for the four DENV serotypes. It is 74% effective against DENV4, 75% effective against DENV3, and 63% effective against DENV1. However, its effectiveness sharply drops in DENV2, with an overall efficacy of only 39% [91], and in select populations, less than 10% efficacy, as shown in Thai children [92]. The reasons behind Dengvaxia's ineffectiveness against DENV2, which is because of immunological or virological factors, have not been established. One explanation is the inadequate replication of the DENV2 vaccine component, as mentioned previously [31] as well as genetic and antigenic differences between the DENV2 vaccine component and the circulating DENV2 strains.

Each dengue virus (DENV) serotype is characterized by significant genetic and antigenic diversity, leading to multiple distinct genotypes within each serotype [93, 94]. The text discusses the understanding of immune responses to different strains of dengue virus (DENV) and the potential impact on vaccine effectiveness. It explains that previously; it was believed that genetic and antigenic differences between DENV strains within the same serotype would not significantly affect long-term immunity. Vaccines were designed based on the assumption that a single strain envelope (E) protein would generate broadly protective antibody responses against all genotypes within a serotype. However, recent studies have questioned this assumption. The text highlights that natural variations in the E protein of DENV strains within serotypes 1, 3, and 4 can substantially impact the ability of monoclonal antibodies and immune sera from individuals exposed to DENV infections or vaccines to neutralize the virus [95]. There have been instances where individuals have been infected more than once with the same serotypes [96]. Examining samples and data from DENV vaccine trials indicates that the variation in antigens within the same serotype (intraserotype) influences the vaccine's performance [28, 97].

In clinical trials of Dengvaxia, scientists conducted a genetic sieve analysis of viral sequences from both the vaccine and placebo arms. The study revealed that the vaccine demonstrated higher effectiveness against a specific strain of DENV4 compared to another strain [91]. These observations emphasize the importance of conducting additional research to understand better the influence of intraserotype E protein on antibody neutralization and its role in enhancing protective immunity.

5. Research publications on dengue virus and vaccine initiatives

Between January 2020 and April 2024, researchers published 1407 studies to examine the effectiveness and safety of the dengue vaccine. These studies aimed to provide an evidence-based understanding of the efficacy and safety profile, and the results are expected to inform clinical practice and public health policy worldwide. We evaluated the global impact of these efforts using a bibliometric analysis of related publications. This analysis aimed to identify the countries that contributed the most to the body of knowledge on dengue vaccines.

Figure 2 provides detailed information on the level of participation in vaccinations. The United States has the highest number of publications, indicating a strong interest in this area of research. Other regions that showed significant involvement included South America and South Asia, where the disease burden of dengue is high. Based on the data

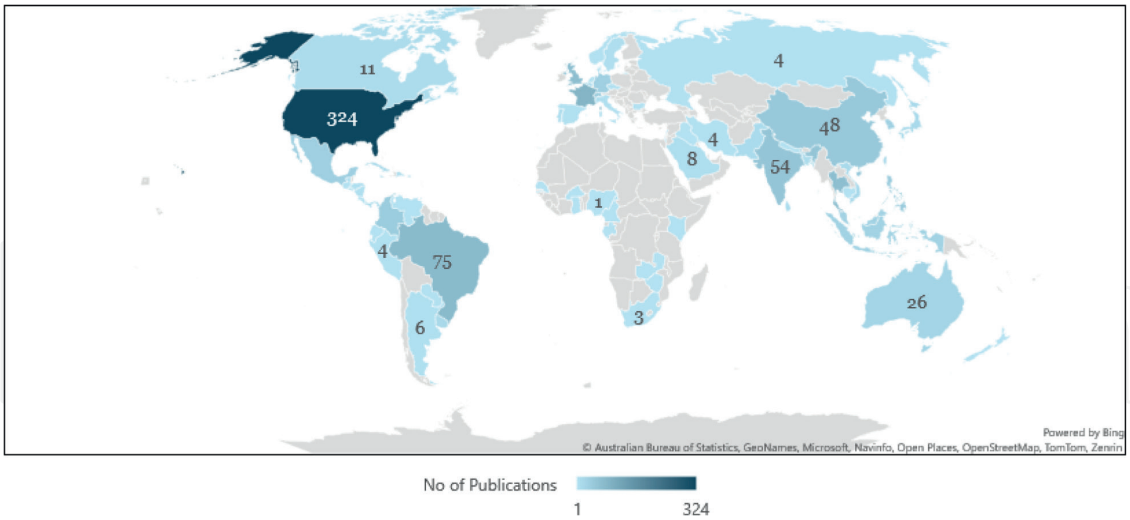

Figure 2.
Scientific publications on dengue vaccine in various regions of the world. The highest numbers of publications are reported in northern and Southern American regions with the least publications in Africa.

in **Table 1**, the National Institute of Allergy and Infectious Diseases reported the highest number of cases, with 246 cases representing 13.3%. This institution is actively conducting research, developing treatments, and disseminating information to the public. The National Institutes of Health came second with 69 cases, representing 11.4% of the total cases. This organization has also been actively involved in conducting research, developing vaccines, and providing health services to patients. Sanofi Pasteur was third in 41 cases, accounting for 6.8%. Pharmaceutical companies are actively involved in the development of vaccines and the treatment of infectious diseases. These institutions have played a critical role in addressing the current situation and have contributed significantly to global efforts to combat the spread of contagious diseases.

The available data reveal that research on dengue vaccines has been conducted for a considerable period, spanning several years. The studies were conducted over two different periods, with 92 studies in 2016 and 87 between 2019 and 2020. After introducing the dengue vaccine, 28 studies were published as of April 2024 (**Figure 3**). Most of these studies [78] were published in vaccine, as shown in **Figure 4**. Furthermore,

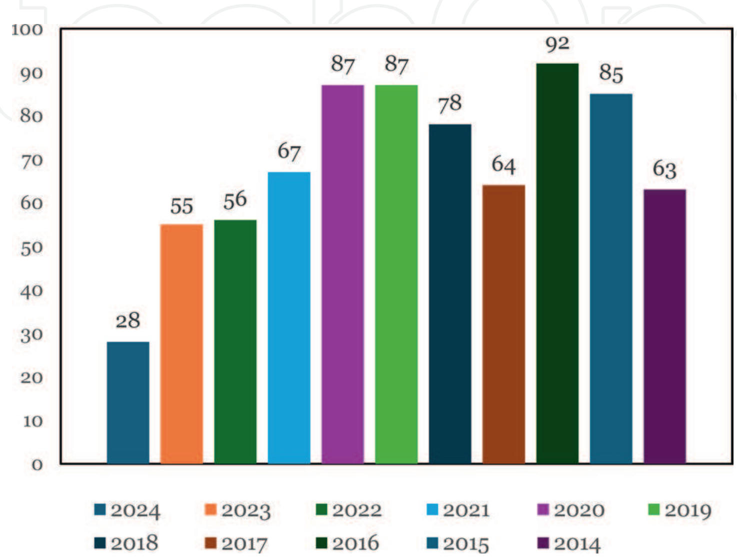

Figure 3.
Distribution of research publications on dengue vaccines from January 2014 to April 2024.

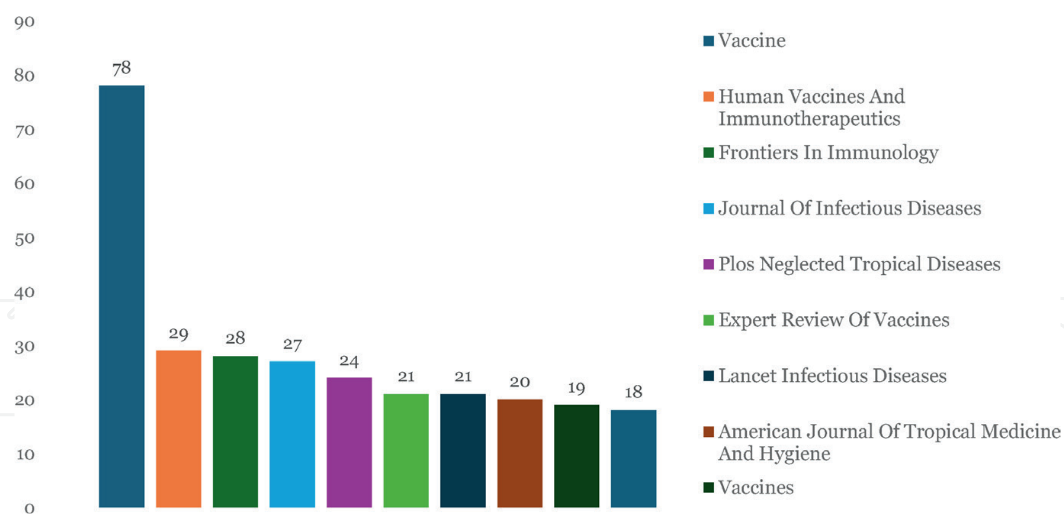

Figure 4.
Scientific journals with the highest number of publications on dengue vaccines.

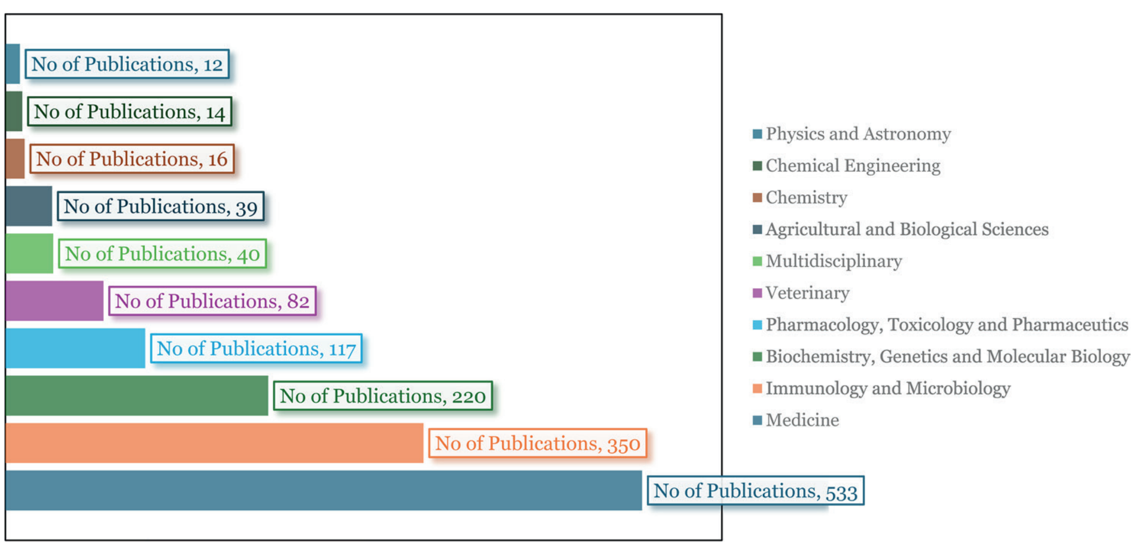

Figure 5.
Research areas with the highest number of publications on studies related to dengue vaccine.

Figure 5 provides detailed information on the distribution of dengue vaccine research in various subject areas, including medicine (533), immunology and microbiology (350), biochemistry, genetics, and Molecular Biology (220), being the top three.

6. Future perspectives for dengue vaccine

The dengue vaccine is a crucial weapon in the fight against the dengue virus, which is transmitted by mosquitoes and can cause potentially fatal mild and severe hemorrhagic fever. Although they have been available for several years, experts have continued to strive to improve their efficacy and availability. Researchers are researching innovative vaccine formulations, investigating the immune response to the vaccine, and extending its dissemination to areas where dengue is particularly prevalent. These efforts have boded well for dengue vaccines, instilling optimism for a safer and healthier future for those susceptible to the virus [98, 99].

The DVI strategic plan focuses on advancing next-generation dengue vaccines, which will feature tetravalent formulations that are safer, more effective, and more affordable than the current alternatives. Additionally, the DVI is committed to improving national immunization programs and promoting community participation to ensure the successful implementation of vaccination. Continued research on dengue epidemiology, immunology, and vector control strategies will play a crucial role in future vaccine development and implementation [11, 89].

The current dengue vaccine is administered in multiple doses over a specific period. However, researchers are currently developing a single-shot vaccine that can provide long-term protection against the four types of dengue virus [100]. This new vaccine can enhance the immune response to the virus, thus preventing infection. This is expected to provide greater convenience to patients and reduce the cost and complexity of vaccination programs. Developing a single-shot vaccine for dengue is a significant step forward in the fight against this disease, which affects millions of people worldwide annually. With continued research and development, this new vaccine will soon become publicly available [73, 101].

Scientists and healthcare professionals are exploring possibly developing combination vaccines to protect against diseases such as dengue fever. This innovative vaccine approach has the potential to offer several benefits, including greater convenience and cost-effectiveness. When multiple vaccines are administered in a single-shot, patients can receive protection against numerous diseases during a visit to the doctor, thereby reducing the need for various appointments and vaccinations. Furthermore, combination vaccines are less expensive to produce and distribute, making them more accessible to people in low-resource settings. This could be a significant step forward in the fight against infectious diseases [70, 102].

Continuous steps are being taken to improve the availability and reach of dengue vaccines, particularly in regions where the disease is widespread. Experts and researchers are seeking an innovative means of vaccine production that could potentially minimize production and dissemination costs, making it more accessible to underprivileged communities. These efforts include exploring novel techniques to increase vaccine efficacy and safety and adopting measures to simplify the vaccine supply chain and distribution mechanism. Considerable progress has been made in mitigating the impact of dengue on afflicted societies by expanding the scope of access to dengue vaccines [103, 104].

Ongoing research is being conducted to address the potential safety concerns that have arisen with the use of dengue vaccines. One of the main concerns is the risk of severe dengue in individuals not previously exposed to the virus. This is a significant issue, as it can cause serious health complications and can even be fatal in some cases. Research has focused on identifying the causes of this risk and developing strategies to mitigate it. The findings of this study will be crucial to determining the safety and effectiveness of dengue vaccines and will inform future vaccination policies and practices [11, 105].

With the increasing availability of dengue vaccines, they can now be effectively integrated into existing dengue control strategies. Besides traditional measures such as vector control and public awareness campaigns, vaccination can now be included as an essential part of a comprehensive approach to combating the disease. By combining the dengue vaccine with other measures, such as vector control and public awareness campaigns, a comprehensive approach can be established to significantly reduce the global burden of dengue fever. This approach helps prevent the spread of the disease and ensures that those who contract dengue fever receive appropriate treatment and care [106, 107].

The future of dengue vaccines appears promising with ongoing efforts to improve their effectiveness, accessibility, and safety. Scientists are exploring innovative approaches, such as developing multi-serotype vaccines and their efficacy against different virus strains. Heat-stable formulations and alternative delivery methods are also being investigated to make vaccines more accessible, particularly in low-resource areas. Safety measures are paramount, with rigorous testing and surveillance to monitor possible adverse effects [27]. Collaborative partnerships among researchers, governments, and global health organizations are crucial to promoting vaccine development and deployment. Therefore, addressing the unique needs of diverse regions and populations is essential.

7. Conclusions

Through its development and implementation, the Dengue Vaccine Initiative (DVI) has played an essential role in global efforts to combat dengue fever. Despite various challenges and setbacks, DVI promotes collaboration, innovation, and knowledge sharing to pave the way for developing effective dengue vaccines. Continuous and unwavering efforts supported by comprehensive research, surveillance, and community participation are indispensable for the long-term success of dengue control worldwide.

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