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REVIEW

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A systematic review on malaria and dengue vaccines for the effective management of these mosquito borne diseases: Improving public health

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ABSTRACT

Insect vector-borne diseases (VBDs) pose significant global health challenges, particularly in tropical and subtropical regions. The WHO has launched the "Global Vector Control Response (GVCR) 2017–2030" to address these diseases, emphasizing a comprehensive approach to vector control. This systematic review investigates the potential of malaria and dengue vaccines in controlling mosquito-borne VBDs, aiming to alleviate disease burdens and enhance public health. Following PRISMA 2020 guidelines, the review incorporated 39 new studies out of 934 identified records. It encompasses various studies assessing malaria and dengue vaccines, emphasizing the significance of vaccination as a preventive measure. The findings indicate variations in vaccine efficacy, duration of protection, and safety considerations for each disease, influencing public health strategies. The review underscores the urgent need for vaccines to combat the increasing burden of VBDs like malaria and dengue, advocating for ongoing research and investment in vaccine development.

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Systematic review; vaccines; effective management; insect vector-borne diseases; improving public health

Introduction

Vector-borne diseases (VBD) represent a significant public health burden globally, causing substantial morbidity and mortality in human populations.[1–3] These diseases, encompassing well-known illnesses like malaria, dengue fever, chikungunya, Zika virus, yellow fever, and Lyme disease, are primarily transmitted through the bite of infected arthropod vectors such as mosquitoes, ticks, and fleas.[4] Whereas, diseases like Chagas and epidemic typhus can be transmitted through other means, such as blood transfusion or fecal contamination.[1,5] These diseases, caused by parasites, bacteria, or viruses, account for over 700,000 annual deaths, constituting more than 17% of infectious disease-related fatalities.[6] Moreover, there is a threat to more than 80% population of the world, disproportionately affecting the poorest populations living in the tropics and subtropics.[7] Globally, the complex triad of vector-pathogen-host interactions in the transmission cycle makes the prevention and control of VBD a complex challenge for healthcare systems.[8] Malaria, one of the most prevalent vector-borne diseases, is transmitted through Anopheline mosquitoes and results in approximately 219 million cases and over 400,000 deaths each year, with children under 5 years old bearing the brunt of this burden.[9,10] Similarly, dengue, primarily carried by Aedes mosquitoes, threatens over 3.9 billion people in 129 countries, resulting in an estimated 96 million symptomatic cases and around 40,000 deaths yearly.[11,12] The impact of these diseases is especially pronounced in tropical and subtropical regions, disproportionately affecting the most disadvantaged populations.[10] Nevertheless, several outbreaks of these diseases have surged among developed countries since 2014 owing to globalization, urbanization and drastic climate changes, straining healthcare systems and claiming numerous lives.[13,14]

To combat these diseases, the World Health Organization (WHO) has developed the "Global Vector Control Response (GVCR) 2017–2030," which offers guidance to nations and partners to strengthen vector control for disease prevention and outbreak response.[15] This initiative calls for program realignment, technical capacity enhancement, improved infrastructure, enhanced monitoring, and community mobilization. By taking a comprehensive approach to vector control, it aligns with national and global health goals, including Sustainable Development Goals (SDGs) and Universal Health Coverage.[16] Traditionally, vector control measures

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have primarily relied on insecticides, environmental management, and public health campaigns to reduce vector populations and prevent disease transmission.[17] While insecticide-treated bednets and indoor residual spraying have undoubtedly demonstrated success; however, their sustained efficacy is threatened by the emergence of resistance, necessitating a comprehensive approach that includes innovative strategies, such as vaccine development, to counteract the evolving landscape of vector-borne diseases.[18] The development of vaccines for malaria and dengue has been a focus of intense research efforts due to the significant global health impact of these diseases.[19] Vaccine research for Plasmodium parasites has been a central focus for almost six decades, the integration of effective vaccines into malaria control programs would signify a pivotal and revolutionary paradigm shift in combatting VBDs, offering a complementary strategy to established interventions like insecticide-treated bednets and indoor residual spraying.[20] The development of the RTS,S/AS01 vaccine, marketed as Mosquirix, represents a significant breakthrough.[21] It is the first, and currently the only, vaccine licensed for use against a parasitic disease in humans. The vaccine has shown partial protection against malaria in children in sub-Saharan Africa, highlighting a critical step forward in the fight against this disease.[22] Dengue vaccine development has also seen significant progress, notably with the creation and licensing of Dengvaxia (CYD-TDV) by Sanofi Pasteur.[23] This vaccine is recommended for individuals 9–45 years old living in dengue-endemic areas and has been approved in several countries. However, its deployment is complex due to its varying efficacy against the four different dengue virus serotypes and the need to pre-screen for prior dengue exposure to avoid the risk of severe dengue in those not previously infected.[24] By harnessing the potential of vaccines in the management of VBD, there is substantial potential for making significant strides in reducing the disease burden and improving the well-being of affected populations. This systematic review seeks to provide a comprehensive and critical analysis of the current status, challenges, and opportunities in utilizing vaccination as a key strategy for managing mosquito VBD particularly focusing on malaria and dengue, ultimately contributing to the advancement of public health initiatives worldwide. Subsequently this review aims to identify key research gaps and offer insights into future directions for vaccine development, deployment, and implementation strategies to address the challenges in combating insect VBD.

Materials and methods

Study protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[25] A comprehensive review protocol was developed before initiating the review process. The protocol outlined the review's objectives, inclusion and exclusion criteria, search strategy, data extraction methods, and the plan for assessing the quality of included studies.

Eligibility criteria

Population

Studies involving humans, both adults and children, residing in regions affected by insect VBDs. There were no restrictions based on age, gender, or comorbidities.

Intervention

Studies evaluating vaccines designed for the prevention or management of insect vector-borne diseases, including dengue fever and malaria. Both traditional and novel vaccine candidates were considered.

Comparators

Studies comparing vaccinated individuals with unvaccinated or differently vaccinated individuals were included. In cases where no comparator group was available, observational studies assessing vaccine effectiveness were considered.

Outcomes

The primary outcomes of interest included vaccine safety, immunogenicity, efficacy, and effectiveness. Secondary outcomes encompassed adverse events, duration of protection, and potential complications associated with vaccines. Additionally, studies reporting on the implications of vaccine use, including public health impact, ethical considerations, and logistical challenges, were included.

Inclusion and exclusion criteria

Inclusion criteria encompassed peer-reviewed articles and clinical trials published in English, focusing on vaccines or vaccination strategies for malaria or dengue. The selected studies comprised studies emphasizing outcomes related to vaccine efficacy, safety, immunogenicity, and adverse events. Conversely, exclusion criteria involved non-peer-reviewed articles, editorials, letters, and conference abstracts, along with studies in languages other than English, those unrelated to vaccines or vaccination strategies for the specified diseases, animal studies, in vitro studies, and modeling studies lacking empirical data. Studies devoid of relevant data on vaccine efficacy, safety, or immunogenicity were also excluded.

Study designs

Randomized controlled trials (RCTs) and observational studies (cohort studies, case-control studies) were considered for inclusion.

Search strategy

A comprehensive search strategy was developed to identify relevant studies. The following electronic databases were systematically searched from inception to August 2023: PubMed, Embase, Google Scholar, Web of Science, and the Cochrane Library. The search strategy combined Medical Subject Headings (MeSH) terms, keywords, and tailored to each database's syntax. The search strategy was piloted and refined iteratively to ensure sensitivity and comprehensiveness. The search terms employed a combination of keywords related to

insect vector-borne diseases (VBDs), vaccination, and disease management. The search string included but was not limited to the following keywords: "vector-borne diseases," "mosquito-borne diseases," "malaria," "dengue," "vaccine," "vaccination," "immunization," "preventive measures," and "public health." Boolean operators (AND, OR) were employed to refine the search and capture relevant articles pertaining to the intersection of vaccines and insect VBD.

Study selection

Two independent reviewers conducted the initial title and abstract screening using predefined inclusion and exclusion criteria. Full-text articles of potentially eligible studies were then assessed independently by the same reviewers. Discrepancies were resolved through discussion, and a third reviewer was consulted if consensus could not be reached.

Data extraction

A standardized data extraction form was developed and used to collect relevant information from the included studies. Data extraction included study characteristics (e.g., author, publication year, country, study design, study duration), participant demographics (vector-borne disease, sample size for both vaccinated and control/placebo group), vaccine details, outcomes of interest, and any additional relevant information (follow-up and findings). Data extraction was performed independently by two reviewers, with a third reviewer available to resolve discrepancies. A narrative synthesis of the findings from the included studies was performed, structured around the outcomes of interest. Qualitative synthesis was supplemented by tabulation of relevant study characteristics, vaccine details, and outcomes.

Quality assessment

The quality and risk of bias assessment for included studies were conducted using appropriate tools tailored to the study design. For RCTs, the Cochrane Risk of Bias tool 2.0 was used, while the Newcastle-Ottawa Scale (NOS) was employed for observational studies. The GRADE approach was utilized to assess the overall quality of evidence for each outcome. Visualization of Risk of Bias assessment is generated by Robvis Tool.

Ethical considerations

Ethical approval was not required for this systematic review as it involved the analysis of publicly available data from previously published studies.

Results

In this systematic review, the PRISMA flow diagram illustrates the comprehensive process of study selection. Initially, 934 records were identified from various databases. After eliminating 411 duplicate records, the researchers screened 523 unique records. During the screening phase, 249 records were excluded based on criteria like not pertaining to VBD vaccines. This left the researchers with 274 records for which they sought full-text articles. Following a thorough assessment of these articles for eligibility, 107 reports were excluded due to factors such as being unrelated to VBD vaccines, not in English, or other reasons. Ultimately, the systematic review included 39 new studies, reflecting a meticulous and rigorous process in the selection of relevant research for the review (Figure 1).

Dengue vaccines

While the studies in Table 1 collectively highlight the potential of Dengue vaccines, they vary in terms of study designs, target populations, vaccine types, and follow-up durations. Some studies, like those by Rivera et al. and Kallas et al., focus on vaccine efficacy over several years. Others, such as Sridhar et al. and Vannice et al., emphasize the protection of individuals with prior Dengue exposure. The studies provide a valuable foundation for understanding the safety, immunogenicity, and efficacy of Dengue vaccines across diverse populations and regions. Notably, CYD-TDV demonstrated good tolerability over three years in Dengue-endemic regions among individuals aged 1.5–45 years. TAK-003 displayed efficacy against symptomatic Dengue in pediatric populations across various countries over three years. Dengvaxia post-licensure studies, spanning four years among pediatric populations, emphasized robust surveillance and risk management. Butantan-DV and TV003 vaccines induced balanced neutralizing antibody responses across all four DENV serotypes in adults, whether naïve or exposed. CYD-TDV exhibited efficacy with a satisfactory safety profile, meeting WHO standards but maintained Dengue mortality rates at 50%. These diverse results underscore promising avenues for Dengue vaccine development but highlight the need for enhanced efficacy and mortality rate reduction. Moreover, the TV003 trial in the USA observed a significant antibody response in 90% of flavivirus-naive subjects within a six-month follow-up.

Malaria vaccines

The Table 2 presents a compilation of studies on malaria vaccines conducted across various countries and populations. These studies collectively demonstrate significant progress in the development of malaria vaccines, with varying levels of efficacy, safety, and immunogenicity. RTS, S/AS01 exhibits promise in safeguarding against clinical and severe malaria, with efficacy spanning 12 to 19 months. Conversely, GMZ2 displays limited efficacy despite reducing malaria incidence within a six-month follow-up. R21/Matrix-M booster doses maintain high efficacy against multiple episodes of clinical malaria. R21/MM, while safe and immunogenic, demonstrates high-level efficacy for 12 months. RTS, S/AS01's greater activity against malaria parasites in children aged 5–17 months is evident in Kenya and across seven countries. Additionally, in different African sites, RTS, S/AS01 showcases potential in combination with other control measures. DNA/MVA heterologous prime-boost vaccination proves safe and highly immunogenic for effector T cell induction. Notably, two RTS, S/

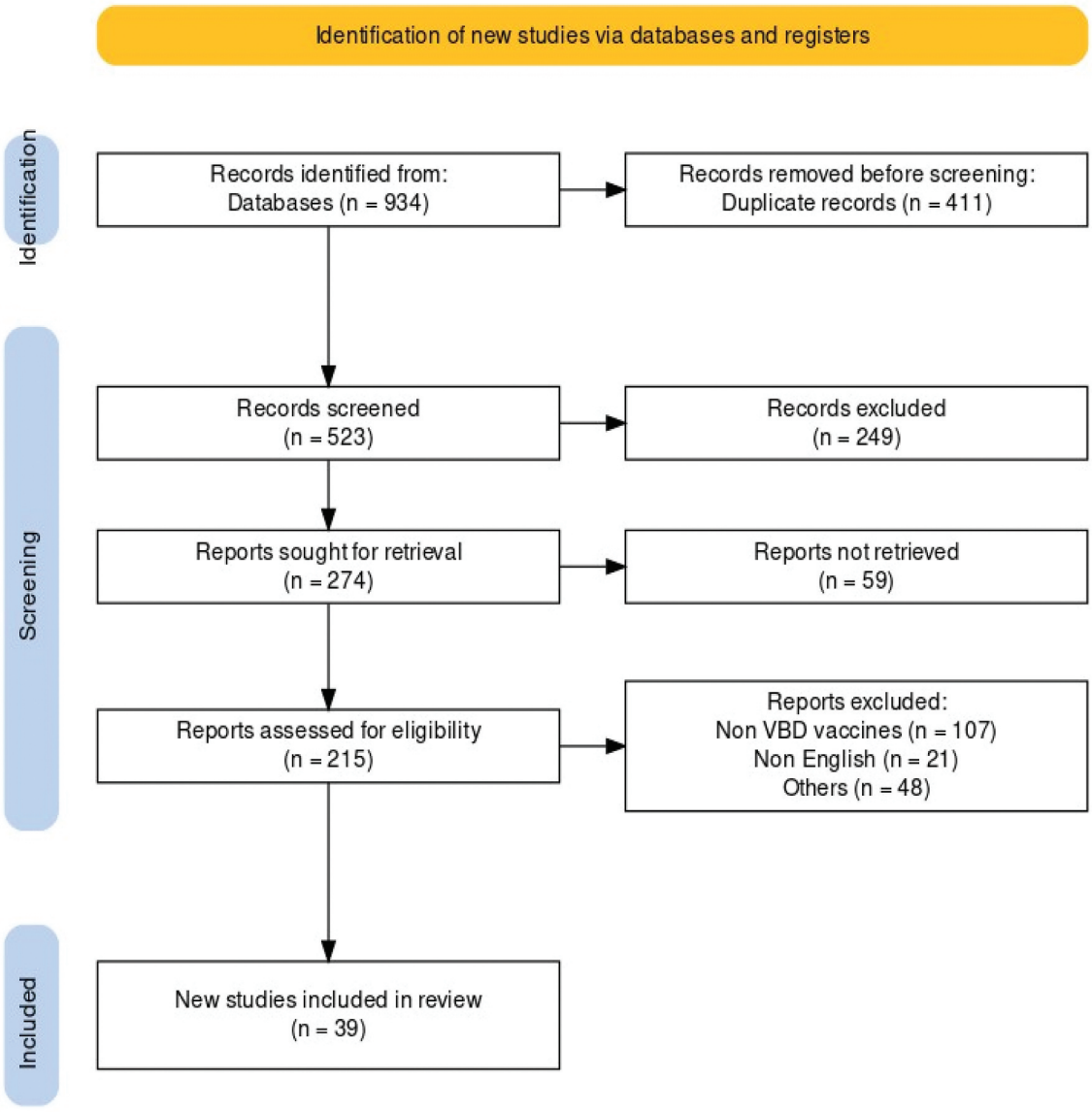

Figure 1. Prisma flow diagram.

AS01E formulations exhibit equal safety and immunogenicity, providing modest protection against malaria when co-administered with EPI vaccines.

Risk of assessment

The quality assessment of the included studies reveals variations in the risk of bias across different domains as described in Table 3 and Figure 2. Risk of assessment was carried out for the randomized controlled trials (RCTs) in this systematic review to validate the results and ensure that the design, conduct, and reporting of RCTs are of high quality, helping the reviewers and readers to determine the degree to which the study results can be attributed to the intervention rather than methodological flaws as well as minimizing the systematic errors as it is crucial for drawing accurate conclusion about the effectiveness of interventions.[66] A rigorous risk of bias assessment in this systematic review of RCTs was carried out to ensure the reliability and acceptability of the synthesized evidence putting a step forward in contributing to evidence based decision-making in healthcare, informing both clinical practice and future research endeavors. Cochrane Collaboration introduced a risk of bias tool to assess the internal validity of randomized controlled trials in February 2008. The risk of bias tool comprises six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other sources of bias." Distinct evaluations of the risk of bias (categorized as high, low, or unclear) are conducted for each individual domain. The ultimate comprehensive evaluation, either within a single study or across multiple studies, is determined by the collective assessments of individual domains.[67]

Figure 1 represents the traffic light visualization of risk of bias assessment of RCTs in this systematic review. This color coded system is user friendly, allowing researchers, clinicians and readers to quickly gasp the overall risk of bias in different domains of a study. Green color indicates Low risk, suggesting high level of methodological rigor and reliability. Yellow color

Table 1. Key attributes of published research on dengue vaccination.

Author and Year	Country	Study Design	Study Duration	Vector-Borne Disease	Study Population	Sample Size		Vaccine	Follow-up	Findings
						Vaccinated	Control/ Placebo			
Rivera et al.[26]	8 countries	RCT	September 2016 – March 2017	Dengue	Pediatrics	13 380	6687	TAK-003	4–4.5x years	TAK-003 was efficacious against symptomatic dengue over 3 years.
Kallas et al.[27]	Brazil	RCT	Nov 5, 2013, – Sept 21, 2015	Dengue	Adults	DENV-naive 114 DENV-exposed 116	41 29	Butantan-DV and TV003	5 years	Butantan-DV and TV003 were safe and induced robust, balanced neutralizing antibody responses against the four DENV serotypes.
Sridhar et al.[28]	3 countries	Case-Cohort Study	N/A	Dengue	Pediatrics	2384	1194	CYD-TDV administered subcutaneously.	6 years	CYD-TDV protected against severe VCD and hospitalization for VCD for 5 years' in persons who had exposure to dengue before vaccination
Vannice et al.[29]	Multiple countries of Asia and Latin America	Prospective Cohort and Case control studies	N/A	Dengue	Pediatrics	20,762	10,382	Dengvaxia	4 years	Manufacturers' risk management plans (RMPs) and post-licensure monitoring with strong surveillance.
Barranco-Santana et al.[30]	4 countries	RCT	16 November 2011– 2 August 2013	Dengue	Adults & Pediatrics	498	222	CYD-TDV administered subcutaneously.	3 years	TDV is generally well tolerated in people aged 1.5–45 years who live in dengue-endemic countries.
B. Guy et al.[31]	5 countries	RCT	NA	Dengue	Pediatrics	2669	1333	CYD-TDV administered subcutaneously.	25 months	CYD-TDV is efficacious with a satisfactory safety profile meeting the WHO standards in maintaining the dengue mortality rates by 50%.
Villar, Dayan et al.[32]	5 countries	RCT	June 2011 – March 2012	Dengue	Pediatrics	13,920	6949	CYD-TDV administered subcutaneously.	25 months	The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD
Capeging et al.[33]	5 countries	RCT	June 3, 2011–Dec 01, 2011	Dengue	Pediatrics	6710	3350	CYD-TDV administered subcutaneously.	25 month	Our findings show that CYD-TDV was safe and efficacious when given as a three-dose schedule to 2–14 year-olds.
Dayan et al.[34]	Brazil	RCT	Aug 19 – Oct 20, 2010	Dengue	Children & Adolescent	89	46	CYD-TDV administered subcutaneously.	13 months	CYD-TDV vaccination elicited a neutralizing antibody response against all four dengue virus serotypes and was well-tolerated in children and adolescents
Durbin et al.[35]	USA	RCT	July 2010 – Feb 2011	Dengue	Adults	80	32	TV001, TV002, TV003, TV004 administered subcutaneously.	6 months	TV003 induced greater antibody response in 90% of flavivirus-naive vaccines.
Villar et al.[36]	Latin America	RCT	October 2009 – February 2010	Dengue	Pediatrics	401	199	CYD-TDV administered subcutaneously.	28 days	CYD-TDV had a favorable safety profile and antibody responses against all 4 dengue virus serotypes.
Hss, Koh et al.[37]	Malaysia	RCT	December 2010 – August 2012	Dengue	Pediatrics	199	55	CYD-TDV administered subcutaneously.	6 months	Satisfactory safety profile and a balanced humoral immune response against all four DENV serotypes for CYD-TDV
Lanata et al.[38]	USA	RCT	September 2008 – February 2009	Dengue	Pediatrics	199	99	CYD-TDV administered subcutaneously.	12 months	A 3-dose regimen of CYD-TDV had a good safety profile and elicited a robust antibody response.
Sabchareon et al.[39]	Thailand	RCT	Feb 5, 2009 – Feb 5, 2010	Dengue	Pediatrics	2666	1331	CYD-TDV administered subcutaneously.	13 months	Safe dengue vaccine is possible.
Luong et al.[40]	Vietnam	RCT	March - July 2009	Dengue	Adults & Pediatrics	120	60	CYD-TDV administered subcutaneously.	6 months	Safety and reactogenicity of CYD-TDV were satisfactory and consistent with results from phase I and other phase II studies.
Osorio et al.[41]	Laboratory	RCT	N/A	Dengue	6–8-week-old AG129 mice	72 subjects		DENVax	68 days	It is shown to be safe and immunogenic in humans.

Table 2. Key attributes of published research on malaria vaccination.

Author and Year	Country	Study Design	Study Duration	Vector-Borne Disease	Study Population	Sample Size		Vaccine	Follow-up	Findings
						Vaccinated	Control/ Placebo			
Datoo et al.[42]	Africa	RCT	June 2020 – July 2020	Malaria	Pediatrics	300	150	R21 in Matrix-M administered intramuscularly	12 months	A booster dose of R21/Matrix-M at 1 year following the primary three-dose regimen maintained high efficacy against first and multiple episodes of clinical malaria.
Datoo et al.[43]	Africa	RCT	May 2019 – June 2019	Malaria	Pediatrics	300	150	R21 in Matrix-M administered intramuscularly	12 months	R21/MM appears safe and very immunogenic in African children, and shows promising high-level efficacy.
Sirima et al.[44]	Africa	RCT	November 2010 – September 2011	Malaria	Pediatrics	926	923	GMZ2 vaccine administered intramuscularly.	6 months	GMZ2 was well tolerated and immunogenic, and reduced the incidence of malaria, but efficacy would need to be substantially improved.
Neafsey et al.[45]	Kenya	RCT	March 2007 – November 2014	Malaria	Pediatrics	223	224	RTS, S/AS01 Vaccine administered intramuscularly.	7 years	The RTS, S/AS01 vaccine has greater activity against malaria parasites in pediatrics of age 5 to 17 months.
Rts SC[46]	7 countries	RCT	March 2009 – January 2011	Malaria	Pediatrics	5948	2974	RTS, S/AS01 Vaccine administered intramuscularly.	18 months	The vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures
RTS et al.[47]	11 African sites	RCT	March 2009 – January 2011	Malaria	Pediatrics	5949	2974	RTS, S/AS01 vaccines administered intramuscularly	12 months	RTS,S/AS01 could be an important addition to current malaria control in Africa
Moorthy et al.[48]	Africa	RCT	July 2002 – December 2002	Malaria	Adults	186	186	DNA ME-TRAP vaccine administered intramuscularly and intradermally.	6 months	DNA/MVA heterologous prime-boost vaccination is safe and highly immunogenic for effector T cell induction in a malaria-endemic area.
Olotu et al.[49]	2 countries	RCT	-	Malaria	Pediatrics	223	224	RTS, S/AS01E vaccines administered intramuscularly	4 years	The two formulations of RTS,S were equally safe and immunogenic, and the lyophilized formulation showed similar levels of efficacy
RTS et al.[50]	Africa	RCT	December 2009 – January 2011	Malaria	Pediatrics	1462	738	RTS,S/AS01 vaccine administered intramuscularly	12 months3	The RTS,S/AS01 vaccine co-administered with EPI vaccines provided modest protection against both clinical and severe malaria in young infants.
Olotu et al.[51]	2 countries	RCT	March 2007 – October 2008	Malaria	Pediatrics	447	447	RTS, S/AS01E vaccines administered intramuscularly	15 months	RTS,S/AS01E confers sustained efficacy for at least 15 months and shows promise as a potential public health intervention against childhood malaria in malaria endemic countries
Asante et al.[52]	3 countries	RCT	April 2007 – October 2009	Malaria	Pediatrics	340	171	RTS, S/AS01E vaccines administered intramuscularly	19 months	Vaccine efficacy was consistent with the target put forward by the WHO-sponsored malaria vaccine technology roadmap for a first-generation malaria vaccine.
Leach et al.[53]	Africa	RCT	May 2009 – February 2011	Malaria	Pediatrics	8000	4000	RTS, S/AS01 vaccines administered intramuscularly	32 months	The study will provide efficacy and safety data to fulfill regulatory requirements, together with data on a broad range of endpoints that will facilitate the evaluation of the public health impact of the vaccine and will aid policy and implementation decisions.
Agnandji, Lell et al.[54]	Africa	RCT	March 2009 – January 2011	Malaria	Pediatrics	3997	2003	RTS,S/AS01 vaccine administered intramuscularly	12 months	The RTS,S/AS01 vaccine provided protection against both clinical and severe malaria in African children.
Guinovart et al.[55]	Africa	RCT	August – September 2008	Malaria	Pediatrics	209	208	RTS,S/AS02A vaccine administered intramuscularly	12 months	Contrary to observations in cohort 1, where efficacy against clinical malaria did not wane over time, in cohort 2 the efficacy decreases with time.
Sacarlal et la.[56]	Africa	RCT	April 2003 – May 2007	Malaria	Pediatrics	803	802	RTS, S/AS02A vaccines administered intramuscularly	45 months	These results show evidence that RTS, S/AS02A maintained protection during the 45-month surveillance period, and they highlight the feasibility of developing an effective vaccine against malaria.
Kester et al.[57]	Bangkok	RCT	-	Malaria	Adults	02	361	RTS, S/AS01B and RTS, S/AS02A vaccines	5 months	RTS, S/A01IB and RTS.S/AS02A were well tolerated and were safe.

(*Continued*)

Table 2. (Continued).

Author and Year	Country	Study Design	Study Duration	Vector-Borne Disease	Study Population	Sample Size		Vaccine	Follow-up	Findings
						Vaccinated	Control/ Placebo			
Bejon et al.[58]	Tanzania	RCT	March 2007 – August 2007	Malaria	Pediatrics	447	447	RTS, S/AS01E vaccines administered intramuscularly	10.5 months	RTS,S/AS01E shows promise as a candidate malaria vaccine.
Abdulla et al.[59]	Tanzania	RCT	July 2006 – February 2008	Malaria	Pediatrics	170	170	RTS, S/AS02D vaccines administered intramuscularly	7 months	The use of the RTS,S/AS02D vaccine in infants had a promising safety profile, did not interfere with the immunologic responses to co-administered EPI antigens, and reduced the incidence of malaria infection
Kester et al.[60]	South Africa	RCT	-	Malaria	Adults	34	6	RTS, S/AS02A vaccine	10 weeks	The two formulations of RTS,S were equally safe and immunogenic, and the lyophilized formulation showed similar levels of efficacy.
Aponte et al.[61]	Africa	RCT	June 1005 – March 2007	Malaria	Infants	107	107	RTS,S/AS02D vaccine administered intramuscularly	3 months	The RTS,S/AS02D malaria vaccine was safe, well tolerated, and immunogenic in young infants.
Bojang et al.[62]	The Gambia	RCT	February 1998 – December 1998	Malaria	Adults	131	119	RTS, S/AS02A vaccines administered intramuscularly	15 weeks	RTS,S/AS02 is safe, immunogenic, and is the first pre-erythrocytic vaccine to show significant protection against natural *P falciparum* infection.

Table 3. Risk of bias assessment for randomized controlled trials.

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Rivera et al.[26]	Low Risk	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Low Risk
Kallas et al.[27]	Unclear	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Barranco-Santana et al.[30]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
B. Guy et al.[31]	Unclear	Low Risk	High Risk	Low Risk	Unclear	High Risk	High Risk
Villar, Dayan et al.[32]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Capeging et al.[33]	Low Risk	Unclear	Low Risk	Low Risk	Low Risk	Unclear	Unclear
Dayan et al.[34]	Low Risk	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Durbin et al.[35]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Villar et al.[36]	Low Risk	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk
Hss, Koh et al.[37]	Low Risk	Unclear	Low Risk	Unclear	High Risk	Low Risk	Low Risk
Lanata et al.[38]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear	Low Risk
Sabchareon et al.[39]	Low Risk	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Luong et al.[40]	Low Risk	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Unclear
Osorio et al.[41]	Low Risk	Unclear	Low Risk	Low Risk	Low Risk	Unclear	Unclear
Camacho et al.[63]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Monath et al.[64]	High Risk	Unclear	Low Risk	High Risk	High Risk	Low Risk	High Risk
Datoo et al.[42]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Datoo et al.[43]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Sirima et al.[44]	Low Risk	Low Risk	Low Risk	Unclear	High Risk	Low Risk	Low Risk
Neafsey et al.[45]	Low Risk	High Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Rts SC[46]	Low Risk	Unclear	High Risk	High Risk	Low Risk	Low Risk	Unclear
RTS et al.4[47]	Low Risk	Low Risk	Low Risk	Unclear	High Risk	Low Risk	High Risk
Moorthy et al.[48]	Low Risk	Unclear	High Risk	Unclear	High Risk	High Risk	High Risk
Olotu et al.[49]	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk	Low Risk
RTS et al.[50]	Low Risk	Unclear	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Olotu et al.[51]	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk
Asante et al.[52]	Low Risk	High Risk	High Risk	High Risk	High Risk	Unclear	High Risk
Leach et al.[53]	Low Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Agnandji, Lell et al.[54]	Low Risk	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Low Risk
Guinovart et al.[55]	Low Risk	Unclear	Low Risk	High Risk	Low Risk	Low Risk	Low Risk
Sacarlal et la.[56]	Low Risk	Low Risk	Low Risk	High Risk	High Risk	Low Risk	High Risk
Kester et al.[57]	Low Risk	Unclear	Low Risk	Unclear	Low Risk	Low Risk	Unclear
Bejon et al.[58]	Low Risk	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk
Abdulla et al.[59]	Low Risk	Unclear	Low Risk	Unclear	High Risk	Low Risk	Low Risk
Kester et al.[60]	Low Risk	High Risk	High Risk	High Risk	Low Risk	Unclear	High Risk
Aponte et al.[61]	Low Risk	Unclear	Unclear	Unclear	Low Risk	Unclear	High Risk
Bojang et al.[62]	Low Risk	Unclear	High Risk	Unclear	High Risk	Low Risk	Unclear

signals an unclear risk of bias i.e., there might be some concerns or uncertainties regarding the evaluation of risk of bias in selected domain as the information provided in those RCTs is insufficient to clearly categorize it either low or high risk. Red color signifies high risk of bias depicting a potential impact on the validity of the study results. This visualization is generated by Robvis Tool (a web app designed for visualizing risk of bias assessments performed as a part of systematic review). Quality assessment of cohort studies was done using Newcastle-Ottawa scale (NOS) to ensure the reliability and validity of results. Higher quality score indicates that it has met the quality standards.

Discussion

In this systematic review, our exploration into the realm of insect VBDs and their management through vaccination revealed significant insights into the efficacy, challenges, and future prospects of vaccination strategies. Our synthesis of the literature highlighted several key findings: the efficacy of existing vaccines, challenges in deployment and accessibility, the role of adjuvants, and promising avenues for future research and vaccine development. This discussion aims to delve deeper into these key facets, shedding light on the implications of these findings in the broader context of public health and disease management.

Dengue poses a significant public health threat, with potentially severe outcomes, including hospitalizations and mortality. As such, the development of effective vaccines has been a critical endeavor in reducing the burden of this disease.[68] Studies are being carried out in the context of the global Strategy for Dengue Prevention and Control, 2012–2020 by WHO which aims to address this need and at least reduce the mortality and morbidity rates by 50% and 25% respectively by the end of 2020.[39,69] A critical literature review shows that the dengue vaccine TAK-003 demonstrated a high efficacy over 3 years against symptomatic dengue. A clinical trial in the pediatric population, conducted across 8 dengue-endemic countries showed that Takeda's dengue vaccine is efficacious against symptomatic dengue over 3 years. The efficacy may decline over time but its robustness remained intact in hospitalized dengue.[26,70] Among the 4 different serotypes of dengue, TAK-003 shows a high level of dengue serotype 2 neutralizing antibodies while the other serotypes 1, 3, and 4 responses are lower.[71] TAK-003 has a sustained long-term efficacy overall dengue in hospitalized individuals without any increased risk

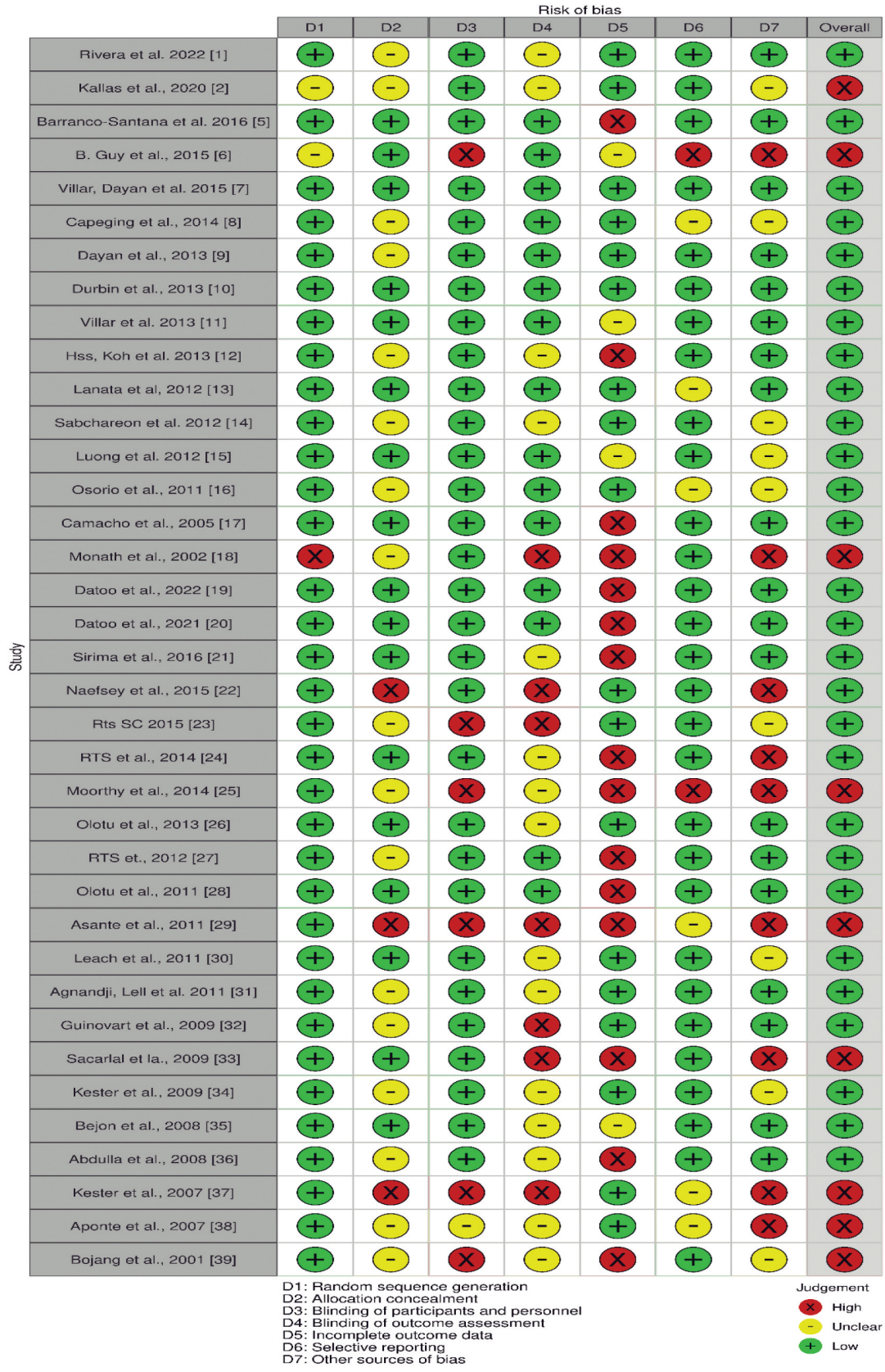

Figure 2. Visualization of risk of bias assessment is generated by robvis tool.[65]

of hospitalization and important safety risks.[72] Butantan-DV and TV003 are analogous to each other and effective and well-tolerated against DENV-naive and DENV-exposed participants. Seroconversion is achieved for all DENV serotypes.[27,73] The rash is a common systemic adverse effect and it is associated with a tetravalent immune response.[74] The immunogenicity of Butantan-DV is elucidated by its plasmablast expansion in the blood and its ability to induce B-cell activation.[75] Dengvaxia hereafter referred to as CYP-TDV is a live, attenuated, recombinant, tetravalent dengue vaccine that is the first vaccine approved for the prevention of symptomatic dengue in individuals aged 9–60 years by any of the 4 DENV serotypes in many endemic areas.[31,76-78] Studies are conducted for the safety and efficacy of CYD-TDV after thoroughly assessing the potential risks and a risk-minimization action plan was defined subsequent review of data generated thereafter was followed by the World Health Organization (WHO), Pan American Health Organization, Centers for Disease Control and Prevention, key opinion leaders, and regulatory agencies.[31] A phase 3 clinical trial conducted in Latin America shows the desired efficacy of CYD-TDV in symptomatic VCD, hospitalization for dengue, and severe dengue in children aged 9–16 years after three-dose vaccination schedule[32] that lines with findings of similarly designed Asian trials.[33] In a Phase III trial of CYD-TDV efficacy after 1 or 2 doses in dengue endemic areas showed that CYD-TDV efficacy was null to modest in the seronegative participants of any age group after any dose.[79] The decreased effectiveness of the CYD-TDV vaccine against DENV2, a notably severe strain associated with dengue outbreaks, raises significant concerns about its ability to provide adequate protection.[80] The risk of severe dengue (DHF/DSS) is recognized to be greater during a secondary infection compared to primary infection,[81,82] thus there is a theoretical proposition suggesting that administering CYD-TDV vaccination to an individual lacking prior dengue exposure may mimic a primary infection, potentially heightening the susceptibility to severe dengue following a subsequent natural infection post-vaccination.[83]

Phase II clinical studies in Singapore and Vietnam showed persistent anti-dengue antibodies over 5 years with no safety concerns and suggested the use of a three-dose schedule at 0-, 6-, and 12 months in those with prior dengue exposure.[84] Ongoing safety and efficacy assessment of live attenuated vaccine by manufacturer's risk management plan (RMP) and post-licensure monitoring played an integral role and the countries that introduce the vaccine are encouraged to conduct their post-licensure monitoring and evaluation which in turn requires planning and strengthening of vaccine surveillance.[29] Currently, CYD-TDV is licensed and available in 20 countries for the population age 9–45 years old. According to Sanofi Pasteur's official guidelines, the World Health Organization (WHO) recommends the administration of CYD-TDV specifically to individuals with documented prior dengue virus infections. This strategic approach aims to mitigate the potential risk of severe dengue should these individuals encounter the virus after vaccination. The data analyzed from three efficacy trials elucidated this concern and showed that CYD-TDV has a protective effect for 5 years in seropositive persons against VCD and hospitalization for VCD but there is evidence of a higher risk of VCD and hospitalization for VCD in persons who are not exposed to dengue.[28]

Malaria stands as a prominent global health burden within the spectrum of VBDs, exerting a substantial impact on public health by contributing significantly to both morbidity and mortality. It is estimated that nearly half of the world's population resides in regions where the risk of malaria transmission prevails.[16] In the World Malaria Report 2019 issued by the WHO, it was reported that in 2018, there were an estimated 228 million cases of malaria and 405,000 malaria-induced fatalities documented on a worldwide scale. Malaria can be attributed to any of the 8 Plasmodium species, with the majority of malaria cases being attributed to P. falciparum and P. vivax. However, fatalities primarily result from falciparum malaria.[85–87] Malaria is endemic in over 90 countries, impacting an estimated 40% of the global population.[88] A recombinant protein malaria vaccine GMZ2 is prepared, containing the conserved fragments of two blood-stage antigens of *Plasmodium falciparum*, glutamate-rich protein (GLURP) and merozoite surface protein 3 (MSP3)[89] both of these proteins have been recognized as subjects of naturally acquired immunity to malaria[90,91] and stimulates the production of specific and functional antibodies capable of controlling parasite replication at high levels.[92,93] GMZ2 demonstrated good tolerability and immunogenicity, leading to a reduction in malaria incidence.[93–95] However, to fulfill a potential public health role, the vaccine's efficacy would require significant improvement through the development of a more immunogenic formulation.[44]

The development of an efficacious malaria vaccine has posed a formidable challenge within the realm of medical science. Nevertheless, remarkable progress has been achieved on a global scale in the endeavor to combat malaria. In light of this concerning trend necessitating the emergence of innovative tools to address the disease, the RTS, S vaccine has been introduced at a pivotal moment. In 1987 by the collaboration of GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR), the RTS, S vaccine was created.[96] In the journey of testing multiple adjuvants of this vaccine AS01 adjuvant system which comprises liposomes MPL, and QS-21, provided an opportunity to improve RTS, S immunogenicity.[97–99] Comparative field trials between RTS, S/AS01B, and RTS, S/AS02A formulations demonstrated a more advantageous immunogenicity profile of RTS, S/AS01B as compared to RTS, S/AS02A while both vaccines have favorable tolerability during a 12-month surveillance period.[100,101] The phase 3 trial of the RTS, S/AS01 malaria vaccine elicited a safe and efficacious response against clinical and severe malaria in all age groups, reducing the burden of overall disease and improving the health outcomes in the areas endemic to malaria caused by P. falciparum.[46–47-49–54-102–103] On October 6, 2021, WHO approved RTS, S AS01 for widespread use. The vaccine demonstrates a significant reduction in both the overall incidence of malaria cases and the incidence of severe, life-threatening malaria among young children.

Plasmodium falciparum circumsporozoite (CS) and hepatitis B surface (HBs) antigens when assessed and cell-mediated immune responses, the anti-CS antibody response was

predominantly higher with RTS, S/AS01 than with RTS, S/AS02,[101–104–109] notably, both vaccines have acceptable safety profile and higher reactogenicity as compared to the non-adjuvanted RTS, S.[110,111] RTS, S/AS01 induced strong humoral immunity and cell-mediated immunity in all pre-clinical and clinical trials when tested with various antigens and it has been considered safe to use in adults as well as pediatrics.[57] In the context of vaccine adjuvants, it's important to note that inflammation plays a pivotal role in initiating immune responses. This inflammation can result from the activation of specific receptors or nonspecific activation, and it represents the primary mechanism by which adjuvants stimulate antigen-specific cellular immunity.[16]

A next-generation RTS, S-like vaccine/improved version of RTS, S, the R21 was developed by Jenner Institute in Oxford, UK. After conducting preclinical studies with R21 plus various adjuvants, Matrix-M (R21/MM) was chosen for clinical development due to its notable immunogenicity.[112] In phase 1/2a clinical trials, R21/MM showed a favorable safety profile and strong antibody responses.[43,43,113] In Nanoro, Burkina Faso, one of the 11 trial sites for the RTS, S/AS01 phase 3 trial, the R21 vaccine combined with a higher dose of adjuvant MM demonstrated a superior efficacy of 77%. This outperformed the 44% efficacy observed with RTS, S/AS01 at the same site over a 12-month follow-up, without any planned seasonal administration.[114] The adverse events profile of the R21 vaccine shows fewer events than RTS, S AS01.[43] Over 2 years of follow-up after the primary series of vaccination, high efficacy of R21/Matrix-M malaria vaccine is reported which reached the WHO efficacy goal of 75% or greater in the target population of African children over 24 months. The R21/Matrix-M vaccine maintains a satisfactory safety profile during the second year of follow-up, even after the administration of a fourth dose.[42] Following RTS, S AS01, R21/Matrix-M vaccine is the second malaria vaccine that is recommended by WHO for malaria prevention in its updated advice on immunization published on October 2, 2023, due to its high efficacy when administered before the high transmission season, good efficacy in an aged-based schedule, high impact, cost-effectiveness similarity with RTS, S vaccine and safety.[115]

Viral vectors hold substantial promise in vaccine development as they facilitate intracellular antigen expression, enhancing the capacity to elicit potent cytotoxic T-lymphocyte responses and pro-inflammatory interferon and cytokine production without any adjuvants.[116] Multiple epitopes (ME)-thrombospondin-related adhesion protein (TRAP) candidate vaccines against *Plasmodium falciparum* are engineered to effectively stimulate effector T cells.[48] In a Phase IIb trial conducted in malaria-endemic areas in Kenya, both ChAd63 ME-TRAP and MVA ME-TRAP vaccines demonstrated some protective efficacy.[117] The prime-boost vaccination regimen involving ChAd63 and MVA ME-TRAP has exhibited a satisfactory safety profile across four cohorts of children with progressively younger ages in The Gambia and Burkina Faso, MVA ME-TRAP being more reactogenic than ChAd63 and indicated greater AE incidence.[118] The immunogenicity is reduced in the participants who are previously exposed to malaria[119] thus in this context DNA/MVA heterologous prime-boost vaccination resulted in a significant decrease in liver-stage parasites during challenge studies involving nonimmune volunteers but this initial T cell-inducing vaccine demonstrated ineffectiveness in reducing the natural infection rate among semi-immune African adults.[48]

While the systematic review on vaccines for the effective management of insect VBD provides valuable insights, it also has few limitations. The quality of the studies included in the review varies. Some studies may have a higher risk of bias, impacting the overall reliability of the findings. The review might also be subjected to publication bias including language bias, as it mainly relies on published literature, potentially excluding unpublished studies or reports, leading to an incomplete representation of available data. The review doesn't account for the real-world availability and implementation of these vaccines, which can significantly impact their public health impact. The review covers studies conducted over various timeframes. Changes in disease prevalence, vector behavior, and healthcare practices over time may affect the relevance of the findings. VBD and the effectiveness of vaccines can vary by region. The review doesn't always distinguish between these regional variations, potentially oversimplifying the findings. Some studies have relatively short follow-up periods, which might not capture the long-term safety and efficacy of vaccines. Nevertheless, our manuscript offers a consolidated and critical analysis that synthesizes current knowledge, identifies gaps, and emphasizes the importance of sustained efforts in vaccine development and deployment to combat insect VBD effectively. Globally, physicians and pharmacies play a pivotal role in educating, advocating, and providing access to vaccines against VBD. Their expertise, advocacy, and accessibility significantly impact the public's perception, acceptance, and access to these preventive measures, ultimately contributing to effective disease management and public health improvement on a global scale.

Conclusions

In conclusion, VBDs, notably dengue and malaria, pose significant global health threats, especially in tropical regions. Vaccines like TAK-003 and Butantan-DV exhibit potential against dengue, with TAK-003 showing efficacy over three years and Butantan-DV effective against various DENV serotypes. GMZ2 demonstrates promise in reducing malaria incidence, while RTS, S/AS01 marks a milestone, providing protection against clinical and severe malaria, especially in children. R21/Matrix-M enhances effectiveness and safety, earning WHO recommendation. Viral vector-based vaccines show potential against *Plasmodium falciparum*, but challenges persist in heavily affected regions. The review consolidates advancements in dengue and malaria vaccines, highlighting TAK-003, Butantan-DV, RTS, S/AS01, and R21/Matrix-M. It underscores the importance of viral vector-based vaccines and the 17D-derived vaccine in preventing yellow fever outbreaks. Further research is crucial to tackle the complex challenges posed by these diseases globally.

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