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Highlights

- TAK-003 a recent candidate is a significant advancement to Dengavaxia.
- Combination vaccination could have extraordinary impact on schistosomiasis control.
- New concepts on how to rationally design hookworm subunit vaccines.
- Typhoid conjugate vaccines will reduce the global burden of typhoid fever.

Next-Generation Vaccines for Tropical Infectious Diseases

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Abstract

Tropical infectious diseases inflict an unacceptable burden of disease on humans living in developing countries. While anti-pathogenic drugs have been widely used, they carry a constant threat of selecting for resistance. Vaccines offer a promising means by which to enhance the global control of tropical infectious diseases, but these have been difficult to develop, mostly due to the complex nature of the pathogen lifecycles. Here, we present recently developed vaccine candidates for five tropical infectious diseases in the form of a catalogue, that have either entered clinical trials or have been licenced for use. We deliberate on recently licensed dengue vaccines; provide evidence why combination vaccination could have a synergistic impact on schistosomiasis; critically appraise the value of typhoid conjugate vaccines; and discuss the potential of vaccines in the efforts to eliminate vivax malaria and hookworms.

Keywords: Infectious disease, Pathogen, Therapy, Vaccine, Lifecycle, Neglected

Introduction

Tropical infectious diseases impact on the quality of life across a large proportion of the global population. To meet the objectives of the World Health Organisation (WHO) Neglected Tropical Diseases and Malaria 2021-2030 roadmaps [1], the building of widespread capacity for the successful control and elimination of tropical infectious diseases over the next decade remains crucial. Ongoing advancements in the development of novel, effective and targeted vaccines play an integral role in the success of infectious diseases management worldwide [1]. This includes ongoing funding and support for research, development, production and implementation of more effective vaccines.

Vaccines have been successfully integrated into the healthcare system for decades since they have proven to be the most effective means of primary prevention for a range of conditions affecting humans. In this review, we will focus on vaccine development against five tropical infectious diseases: dengue fever, helminthiases, vivax malaria, schistosomiasis and typhoid fever. These diseases are caused by the spread of micro- or macroorganisms (see Supplementary Table 1) which can be transferred between humans, animals and environments and occur predominantly under tropical and sub-tropical climate conditions [1].

These tropical infectious diseases have received inadequate attention from global and economic research funding agendas [1]. They continue to have excessively high

disability rates, with estimated disability-adjusted life years (DALYs) being 56% and loss of life being 44% [2]. Collectively, these tropical infectious diseases represent a burden of billions of dollars annually to developing economies (Supplementary Table 1). However, this does not capture the social consequences and hardship afflicted on individuals and their families. Of concern, there is a growing problem where increased global travel and trade, combined with deforestation and climate change, have altered pathogen transmission patterns, causing geographical spread and re-emergence of tropical infectious diseases.

These five diseases have been chosen because 1) they have a high socioeconomic burden in developing countries, 2) four of these five diseases have been classified as 'neglected' by the WHO while the fifth (typhoid) continues to be difficult to eradicate, 3) clinical and commercialisation studies undertaken recently have yielded measurable outcomes, 4) author group is involved in the development of vaccines/therapeutics for tropical infectious diseases.

Dengue is a vector-borne disease caused by four serotypes (DENV1-4) of an RNA virus from the *Flaviviridae* family and transmitted by *Aedes* mosquitoes. In severe illness it can lead to death, overall costing the economy US$8.9b per year (Supplementary Table 1). Over 100 countries are endemic for dengue, with outbreaks becoming more common due to changes in vector ecology, climate change and urbanisation. In 2020, we have seen the largest dengue outbreaks in Singapore. This has resulted in substantial increased costs from $1·014 bn/ 7,645 DALYs in 2010 to $2·265bn/ 21,262 DALYs in 2020 in Singapore's management of dengue alone.

Hookworms such as *Necator americanus*, *Ancylostoma duodenale* and *A. ceylanicum* infect about half a billion people (Supplementary Table 1), causing substantial economic cost (lost work productivity alone is estimated to be US $139 billion/ year) and health burdens (approx. US$1 billion). These parasites reside in the intestines and are particularly detrimental to the physical and cognitive growth of children. There are currently no vaccines against human hookworms, and while anthelminthic drugs are effective, there are few available and drug resistance is emerging.

Plasmodium vivax (P.vivax) is the more common human malaria parasite species in endemic countries outside of Africa [3, 4]. This species persists for longer periods than *P.falciparum (*the other common species) and is much more resistant to elimination efforts. This is largely due to its inherent biological properties, which includes dormant liver stages called hypnozoites, that contributes to its relapse potential [4]. The economic burden or *P.vivax* alone is almost US$400m per year. Therefore, more effective modalities to induce immunity, such as vaccination against *P.vivax,* is considered as an essential element in the malaria elimination toolkit. Natural immunity against vivax malaria has been well documented, both in low and high transmission settings. However, achieving effective vaccine-induced immunity continue to pose challenges.

Typhoid fever caused by the bacterium Salmonella enterica serovar typhi (S. Typhi) is prevalent in countries that lack appropriate water and sanitation infrastructure. In severe cases, intestinal perforation or life-threatening bloodstream infections such as

septicaemia can occur, costing the economy over US$1 billion (Supplementary Table 1). Antibiotic therapy is increasingly impacted by muti-drug resistant strains of S. Typhi. Hence, the development of a safe and effective vaccine against Typhoid fever has been a global health priority for several decades.

Schistosomiasis is the second most devastating parasitic disease behind malaria affecting 250 million people, with 280,000 deaths annually [5]. The adult worms inhabit blood vessels and cause abdominal pain, diarrhea and urinary tracts complications. Current MDA efforts are costly and accentuate the risk of drug resistance developing; thus, vaccines are desperately needed.

This review documents the requirements for a successful vaccine and leading candidates for next generation vaccine development trials underway for dengue (TAK-003), human hookworm, malaria (pre-erythrocytic, blood stage, transmission blocking vaccines), typhoid fever (Vi-TT) and schistosomiasis (combining Sm-TSP2 and Sm-p80).

New dengue vaccines are on the horizon: challenges and opportunities.

Given the challenges for implementing sustainable vector control measures, and the lack of dengue antivirals, the need for a vaccine is critical [6]. In recent years, several vaccine candidates have been developed, with a focus on targeting either the structural E protein or the non-structural protein NS1. A recent review has comprehensively summarised the characteristics of nine dengue vaccine candidates, each of them at different stages of development [7]. Here, we will focus on three live attenuated vaccines from which phase III results are currently available: CYD-TDV

(Dengvaxia®), TV0003/Butantan-DV and TAK-003 (Qdenga®) (Supplementary Table 2).

1) CYD-TDV. This is a tetravalent vaccine which uses the yellow fever vaccine strain (YF17D) as a backbone, with substitution of the pre-membrane (prM) and envelope (E) genes of YF17D with those of wild-type dengue viruses [8]. In 2015, hopes were raised when Mexico approved CYD-TDV as the first licensed dengue vaccine, Dengvaxia®. However, expectations were tempered when Dengvaxia was associated with increased disease severity in seronegative populations, potentially due to Antibody-Dependent Enhancement (ADE), where low levels of DENV-specific antibodies bind to the virus, enhancing host cell entry. Consequently, Dengvaxia is only recommended for individuals who had a laboratory-confirmed previous dengue infection [6].

2) Butantan-DV. This is a single-dose live-attenuated vaccine, containing all four dengue serotypes. This vaccine, manufactured by the Butantan Institute (Brazil), is analogous to TV003, a vaccine developed by the US National Institute of Allergy and Infectious Diseases [9]. Preliminary findings among volunteers 2-59 years of age from a phase III study in Brazil showed that Butantan-DV has a 79.6% overall efficacy to prevent laboratory-confirmed dengue after two years of follow-up (Butantan Institute website). Currently, no data is available regarding efficacy for all the serotypes, as the 5-year trial is expected to finalize at the end of 2024 (NCT02406729 estimated study completion November 2024). Previous data from a Phase II trial, showed that

seroconversion to the different serotypes varied between 76% (DENV-3) to 92% (DENV-2) [10].

3) TAK-003. A new attenuated tetravalent candidate (TAK-003) is currently looking favourable based on results from a Phase III study involving 20,000 children in Asia and Latin America (NCT02747927 estimated study completion August 2024) [11]. On October 2023, WHO's Strategic Advisory Group of Experts (SAGE) endorsed the use of this vaccine in children 6-16 years of age from high-endemic settings. TAK-003 consists of a DENV-2 strain with a mutation in non-structural 3 protein, which attenuates the virus in the original vaccine DENV-2-PDK-53. In addition, it contains three chimeric viruses with pre-membrane and envelope genes of DENV-1, -3 and -4 cloned into the attenuated DENV-2 'backbone' (Figure 1). TAK-003 displayed efficacy against virologically-confirmed dengue of 64·2% in seropositive individuals and of 53·5% in seronegative individuals after 54 months [12]. However, the effectiveness of TAK-003 was not equivalent across serotypes, with higher efficacy for DENV-2 and DENV-1, compared to DENV-3 and DENV-4. Although the potential for ADE is a concern, so far, the TAK-003 vaccine does not have any major safety risks.

Time will tell if Butantan-DV or TAK-003 would be the 'silver bullet' vaccine for protecting the most vulnerable from this potentially deadly disease. Besides vaccine efficacy, equitable vaccine distribution must be considered, particularly in light of global childhood vaccination coverage which is currently at a 30-year low [13]. Finally, any dengue vaccine must be considered as part of a holistic approach to

dengue fever management including vector control, vector and disease surveillance, community engagement, research and innovation [13].

Hookworms: vaccine updates

There are several hookworm vaccines that have been tested in animal and human trials, primarily live attenuated or subunit parasite protein vaccines. X-irradiated and attenuated *A. caninum* L3 larval vaccines were efficacious in dogs with induction of IgG, IL-4 and strong PBMC proliferation to crude L3 [14]. Building from these early studies, the first ever trial in humans of a live ultraviolet-C-attenuated larval vaccine was recently shown in *N. americanus*-challenged humans to be safe, immunogenic and potentially protective (Supplementary Figure 1) [15]. Interestingly, similar safety and potential efficacy profiles were observed in a more recent study using short-term exposure to live un-attenuated larvae with repeated drug cure [16]. The live vaccines induced hookworm-specific higher serum IgG titres, IFNγ, TNFα, IL-2, IL-4 and IL-5 concentration, and blood eosinophilia without any serious adverse events. These human studies provide proof-of-principle that protective immunity to hookworms can be achieved through vaccination which may arrest larval development to the adult helminth inside the host. Consequently, the live larval, or attenuated hookworm vaccines, could be used as a benchmark for new vaccine candidates (Supplementary Table 2). However, there are logistical challenges (production, storage, transportation methods) regarding whether live or attenuated vaccines could be employed for use in hookworm endemic areas.

Operating concurrently with attenuated vaccine approaches has been the development of subunit recombinant hookworm protein vaccines that could mitigate

such logistical challenges. Ancylostoma Secreted Protein-(ASP)-2 was once the lead vaccine candidate for human hookworm, but elicited immunoglobulin (Ig)-E mediated allergic reactions in people from hookworm-endemic areas and consequently that vaccine, and any hookworm vaccine that elicits IgE responses, had to be shelved as a candidate for safety reasons (Supplementary Figure 1) [17]. Currently, the lead protein vaccine candidates are *N. americanus* aspartic protease-1 (*Na*-APR-1) and glutathione S-transferase-1 (*Na*-GST-1), which are essential for haemoglobin digestion and detoxification by the adult hookworm, are safe and immunogenic when delivered independently or co-administered (Supplementary Figure 1) [18]. In Phase I clinical trials, these proteins induced high, persistent serum IgG levels. Sera from endemic population were tested for anti-N*a*-APR-1 and anti-*Na*-GST-1 IgE and found barely detectable (<0.6%) or below the clinical threshold of 0.1 kU/L (0.24 ng/dL), indicating less likely to develop anaphylaxis following immunisations. The *Na*-GST-1 vaccine has been designed to eliminate adult hookworm by starvation and is currently in Phase II clinical testing with results becoming available soon (NCT03172975).

Complementing these protein vaccine approaches has been the development of analogous *Na*-APR-1 peptide-based vaccines that can be produced cheaply and delivered orally. A lipopeptide formulated p3 epitope of the *Na*-APR-1 vaccine was able to elicit high serum anti-p3 and anti-APR-1 IgG antibodies and reduce worm burden by 99% in immunised mice (6), and if developed further could become practical for hookworm-endemic areas. Concerningly, there is a limited pipeline of other hookworm vaccine candidates. Future efforts could employ immunomics-based

approaches to discover novel vaccines, which have been used for other parasite [19] and helminth species [20].

A vaccine against *P. vivax*: a reality or a dream?

Progress of vaccine studies in *P.vivax* have been persistently slow due to multiple reasons, including major gaps in knowledge of its biology. Despite such setbacks, the revised Malaria Vaccine Technology Roadmap to 2030 [21] calls for a next-generation vaccine to achieve 75% efficacy against *P. falciparum* and *P. vivax*. Modelling-based predictions indicate that mass administration of even partially effective vaccines for *P. vivax* with a half-life of 3 years could help drive *P.vivax* transmission to elimination [22]. In this backdrop the developments during the past 2 decades [23] are encouraging and add more hope for such potential achievements (NCT01082341) (Supplementary Table 2).

Pre-erythrocytic vaccines:

An effective pre-erythrocytic vaccine would interrupt the parasite life cycle at an early stage, preventing the parasites from getting established in the liver enabling protection from primary infections. The most advanced malaria vaccines developed against *P.falciparum* so far, RTS,S/AS01 [24] and R21/Matrix-M [25] target the pre-erythrocytic stages. In *P.vivax* such a vaccine will have the added benefit of preventing the establishment of hypnozoites and thus relapses of infections that act as reservoirs of infection during subsequent years increasing the risk of transmission. The recent recommendation of a pre-erythrocytic vaccine for use against *P.falciparum* by the WHO may have given impetus for more active pursuance of already known and novel vaccine candidates for *P.vivax*. A

randomized, double-blind, controlled clinical trial recently tested the protective efficacy of a *P.vivax* circumsporozoite synthetic vaccine that was given in 3 doses over 6 months to healthy malaria naïve (phase IIa) and semi-immune (phase IIb) individuals. Although more work should follow, the initial results have been encouraging with notable protection of both naïve and semi-immune study participants against challenge infection after 3 months of vaccination [26]. Clinical trials using irradiated sporozoites of *P.vivax* also have been completed and results are awaited.

Blood stage vaccines:

These vaccines will prevent or arrest parasite growth in the blood stream and therefore, prevent disease, reduce the parasitemia and gametocytemia minimizing the likelihood of transmission. However, a blood stage vaccine alone will not prevent liver stage infections, which in turn may release merozoites that will infect red cells triggering disease, hence the importance of combining pre-erythrocytic and a blood stage component in a malaria vaccine to prevent disease. There have been many attempts to pursue vaccine candidates that target *P.vivax* merozoite proteins and those which prevent merozoite entry into red cells that include members of *P.vivax* erythrocyte binding protein family (PvEBP) [27]. Within this family the Duffy Binding Protein (DBP) II is likely to be the most studied. A few merozoite surface protein candidates (PvMSP1, MSP3 and MSP9) and apical merozoite antigens (PvAMA1) also have been explored for immunogenicity and protection. However, only a few have reached up to phase IIa clinical trials [28].

Transmission blocking vaccines:

A potent transmission blocking vaccine (TBV) would arrest or prevent growth of parasites within the mosquito vector and thus prevent transmission of infection to others. Such a vaccine would have value even in settings where malaria has been eliminated to sustain the elimination status since it will prevent re-introduction of malaria to such localities where the environment remains conducive for malaria transmission. However, only a limited number of antigens have been recognized as *P.vivax* TBV targets viz. Pvs25, Pvs28, Pvs47, PVS48/45, Pvs230 and PvHAP2, which are orthologs of *P.falciparum* candidates [29]. Though some candidates have been studied more than others, none have gone beyond stage I clinical trials [28].

Going forward, the use of innovative approaches such as high-throughput immuno-profiling for genome-wide discovery of 'new' *P.vivax* vaccine candidates, novel delivery platforms that boost immune responses, including mRNA vaccine technology, virus-like particles, nano particle delivery and improved functional assays or correlates of immunity may enhance the outcome of future vaccine design and testing. Therefore, although *P.vivax* vaccine development continues to be an uphill task technological advancements and innovative approaches combined with improved investments will accelerate research and development in the field paving the way for success.

Typhoid Fever: the dawn of universal typhoid fever prevention by typhoid conjugate vaccines

First generation typhoid vaccines were inactivated S. Typhi bacteria prepared by chemical or physical inactivation of S. Typhi in 1896 (Figure 2). Efficacy studies

performed in 1960 confirmed that such vaccines provide 65-80% protection for up to 7 years. However, side effects, such as fever and systemic reactions, have prevented this vaccine from being approved as a routinely used public health intervention and it was mainly given to military personnel. A subsequently developed chemically mutagenized live-attenuated vaccine (Vivotif Oral) emerged in the 1980s. Because of its repeat dose scheduling, need for a cold chain, and recommendation for use in people ≥6 years, this vaccine is mainly given to travellers but is not WHO-prequalified.

To overcome the side effects and limited immunogenicity of live attenuated vaccines, a subunit vaccine that utilises the Vi homopolymer capsular polysaccharide from S. Typhi (Typhim Vi) was developed [30]. Although Typhim Vi can induce anti-Vi antibodies, the relatively low efficacy (64-72%) and shorter protection period (~3 years) remains an ongoing problem. Furthermore, younger vaccinates only generate a mild immune response and there is no robust boost response on subsequent immunisation.

While Typhim Vi solved the problem of significant side effects induced by the inactivated typhoid vaccine, the increase in efficacy was relatively modest. More recently, research on different ‘carrier’ proteins confirmed that physical mixture or a chemically covalent bond of Vi with a bacterial toxoid could significantly improve the immunogenicity of the antigen. Hence, to enhance its immunity, carrier proteins such as exotoxin A from Pseudomonas aeruginosa (rEPA), a nontoxic mutant of diphtheria toxin (CRM197), diphtheria toxoid (DT) and tetanus toxoid (TT) were coupled to Vi in 3rd generation vaccines [31]. These so-called typhoid conjugate vaccines (TCVs) induce T cell dependent immunity, protect individuals for more than

3 years, and are immunogenic in children with only one dose (Supplementary Table 2).

Currently, Vi-TT appears to be an emerging TCV candidate to be routinely used and is well advanced in the clinical trial pipeline. PedaTyph was licensed in India in 2008 and Typbar TCV was pre-qualified by the WHO in 2017 and licensed in India, Nepal, Cambodia and Nigeria in 2018. TYPHIBEV (Vi-CRM197) was also pre-qualified by the WHO in 2020, but there is no evidence that other TCVs demonstrate better performance than Vi-TT. Several studies (CTRI/2018/11/016419; NCT02645032) confirmed that the safety and efficacy of Vi-rEPA, Vi-CRM197 and Vi-DT are either slightly lower or comparable to Vi-TT [32]. Studies performed in the last 5 years also confirmed that a single dose of Vi-TT is safe, induces persistent antibody responses for up to 7 years without long-term side effects, and confers robust protection against typhoid fever in all age ranges [33].

In conclusion, with nearly 100% seroconversion rate, cost-effectiveness (~$1/dose), up to 87.1% efficacy, 7 years protection and the ability to be co-administered with other vaccines, Vi-TT appears to a TCV candidate for potential mass administration [34]. Inclusion of Vi-TT in childhood immunisation programs would particularly benefit developing countries by reducing the burden of typhoid fever. It is tempting to speculate that a global roll-out of TCVs could lead to widespread herd immunity and potentially even mark the end of the ever-present threat worldwide.

Schistosomiasis: heterologous prime-boost immunisation may promote antibody onslaught against schistosome tegument

While progress has been made in the past 30 years, including discovery of two potential vaccines Sm-TSP-2 [35] and Sm-p80 [36] for the prevention of schistosomiasis, the parasite's ability to evade the host's defences has hindered development of a single target-based vaccine for public use. Here we look at the rationale for and prospective outcomes of combining multiple lead vaccine candidates to synergistically boost the immune system and improve vaccine efficacy.

The ideal approach to create a schistosomiasis vaccine is to target the schistosomula, the parasite's juvenile stage and to overwhelm it with synergistic antibodies that target adjacent antigens [37]. There are currently separate clinical trials that are being conducted on two vaccines that target critical structures on the parasite's tegument: The Sabin Vaccine Institute's Sm-TSP-2/Alhydrogel® (NCT03910972) and Texas Tech University's Sm-p80/SchistoShield® (NCT05292391) (Supplementary Table 2). It has taken approx. 30 years to advance to clinical trials. While developing these lead vaccines separately is challenging, a unified combination approach that improves the persistence of antibody titres elicited by single Sm-TSP-2 vaccination would be more effective, save resources and expediate development [38]. Mix-and-match booster vaccination approaches such as the combination of AstraZeneca and Pfizer-BioNTech vaccines were 88% effective in preventing SARS-CoV-2.

The effectiveness of the Sm-TSP-2 vaccine could similarly benefit from a synergistic vaccine candidate that also targets the tegument, such as Sm-p80. While Sm-TSP-2 is readily recognised by IgG1 and IgG3 antibodies, Sm-p80, the large calpain subunit that mediates the tegument's biogenesis, induces complement- and antibody-

dependent cytotoxicity, making it an excellent choice for use in combination with Sm-TSP-2 [39]. In support of this view, a previous study found that antibody responses to Sm-TSP-2 were only significantly higher in sera from people who were putatively resistant to *S. mansoni*. This is corroborated by a second immunomics study that evaluated antibody responses to multiple schistosomiasis vaccine candidates using sera from endemic countries.

An unresolved question is whether anti-Sm-TSP-2 antibodies generated by vaccination could access Sm-TSP-2 antigens from intact parasites to the level sufficient to trigger a lethal immune response. It seems unlikely, especially in light of the recent results of underwhelming worm burden reduction. Hence, the notion of using vaccine-linked chemotherapy to increase Sm-TSP-2 induced immunity was proposed instead. It is conceivable that targeting Sm-p80 of both 3- and 5-day-old schistosomula might lead to changes in the tegument that would expose more tetraspanins, including Sm-TSP-2. Since both antigens are independently immunogenic to stimulate distinct B-cell clones, it is possible that heterologous boosting or a combination of Sm-TSP-2 and Sm-p80 would efficiently activate various B-cell compartments (Supplementary Figure 2), however this requires additional testing in animal models. Ultimately, this could lead to a more efficient or long-lasting germinal centre response, allowing for a longer cycle of somatic hypermutations and the possible emergence of several B cell clones producing high affinity IgGs. Moreover, the proposed strategy is a simple logistical undertaking that does not need the creation of a new product; instead, existing knowledge gained via development and clinical testing may be put to good use.[5, 35, 36, 38]

Conclusion

Here, we have attempted to summarise recent progress made in the control or elimination of five important tropical infectious diseases. Backed by funding agencies, research efforts have focussed on the exploration and identification of new targets, like never before. Novel approaches have uncovered host-parasite interactions at various tissue levels, not only during transmission and infection but long after infection clearance. Some of the emerging candidates have already been tested in clinical trials. It is important to keep this momentum because these candidates could not only help in prevention and treatment, but also have follow-on effects on diagnosis, prognosis, transmission and provision of appropriate medical care using adjunct therapies, in a cost-effective and timely manner. Given potential challenges in effective coverage, vaccine administration may remain just one tool in the suite of management strategies to break the cycle of infection and prevent disease in those most at risk. As outlined by the Immunisation Agenda (IA 2030), vaccines could be integrated into other prevention and control programmes of primary health care services. During rollout, due consideration must be given to cultural sensitivities to overcome vaccine hesitancy, and equitable distribution amongst developing countries. Exciting times lie ahead, and we are on the cusp of translating new lessons learnt into therapeutic options that will decrease the socioeconomic burden of these diseases.

Footnote

*Contributed equally to literature searches, writing, editing, revisions, figures, table, and intellectual input. Author order was determined alphabetically and by discussion.

#Conceptualised and designed the paper and managed author contributions.

Author Contribution

SP conceptualised and designed the paper and managed author contributions. TA, MCR, PG, NK, AK, JCL, DS, SS, BT, LVE, DV, GZ, SP contributed equally to literature searches, writing, editing, revisions, figures, table, and intellectual input. Author order was determined alphabetically and by discussion.

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Conflict of Interest

Authors have no competing interests to declare.

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Figure legends

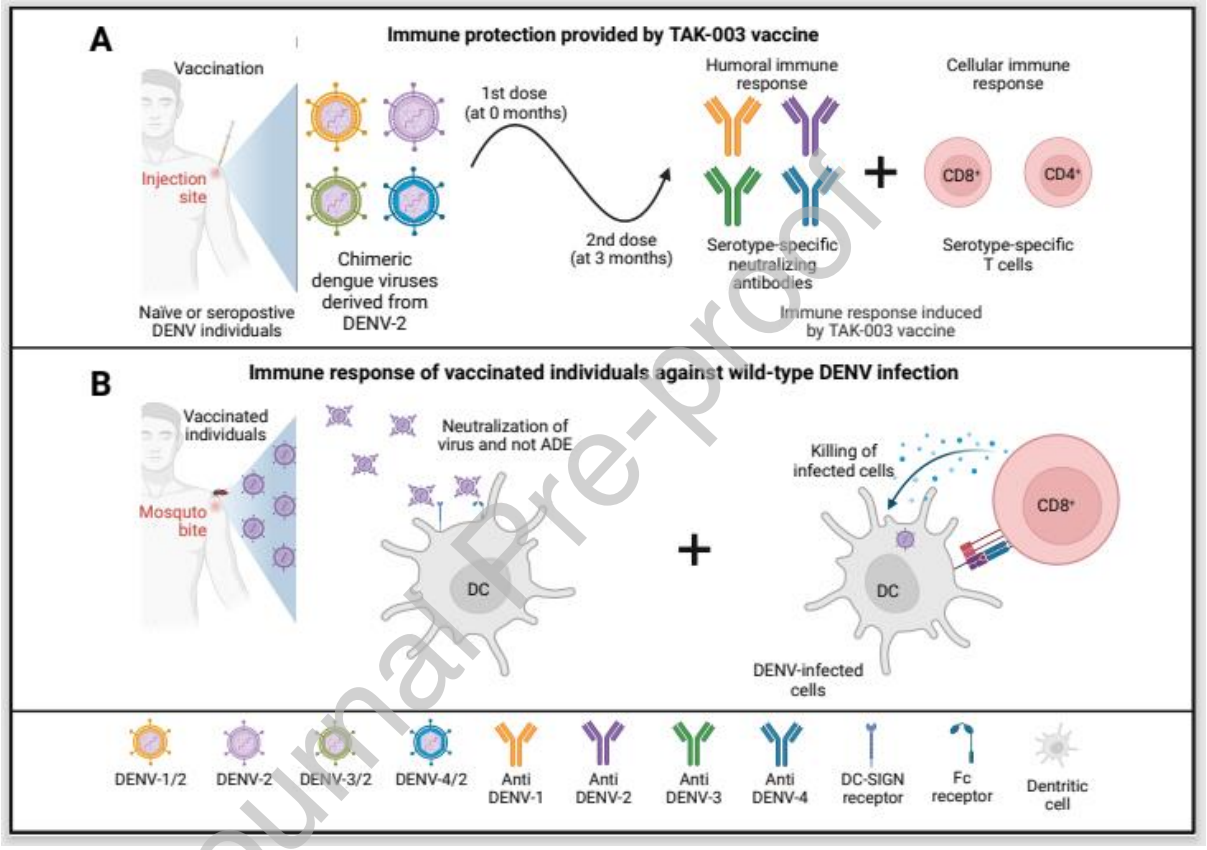

Figure 1. Illustration of hypothetical immunity protection provided by TAK-003. **A)** Panel shows the immune protection in naïve or seropositive DENV individuals provided by two doses of the TAK-003 vaccine (chimeric dengue viruses for each serotype derived from DENV-2), which includes the humoral (serotype-specific neutralizing antibodies) and cellular immunity (serotype-specific T cells). **B)** Panel shows the immune response of vaccinated individuals against wild-type DENV infections, which is mediated by neutralizing antibodies before the virus interacts with

dendritic cells (DC), not resulting in antibody-dependent enhancement but killing of infected cells via cytotoxic cells. Created with BioRender.com.

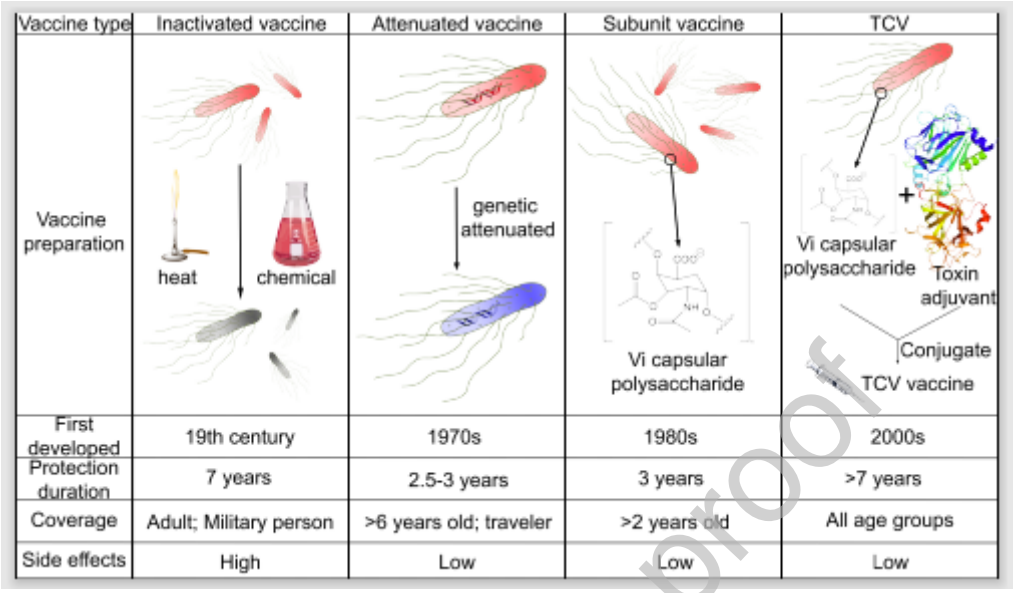

Figure 2. Comparison of typhoid vaccines. Method of preparation, protective efficacy, coverage and side effects of different typhoid fever vaccines over time.

Conflict of Interest:

Authors have no competing interests to declare.