

Epidemiology of malaria vivax in South East Asia and key immunological considerations for vaccine development

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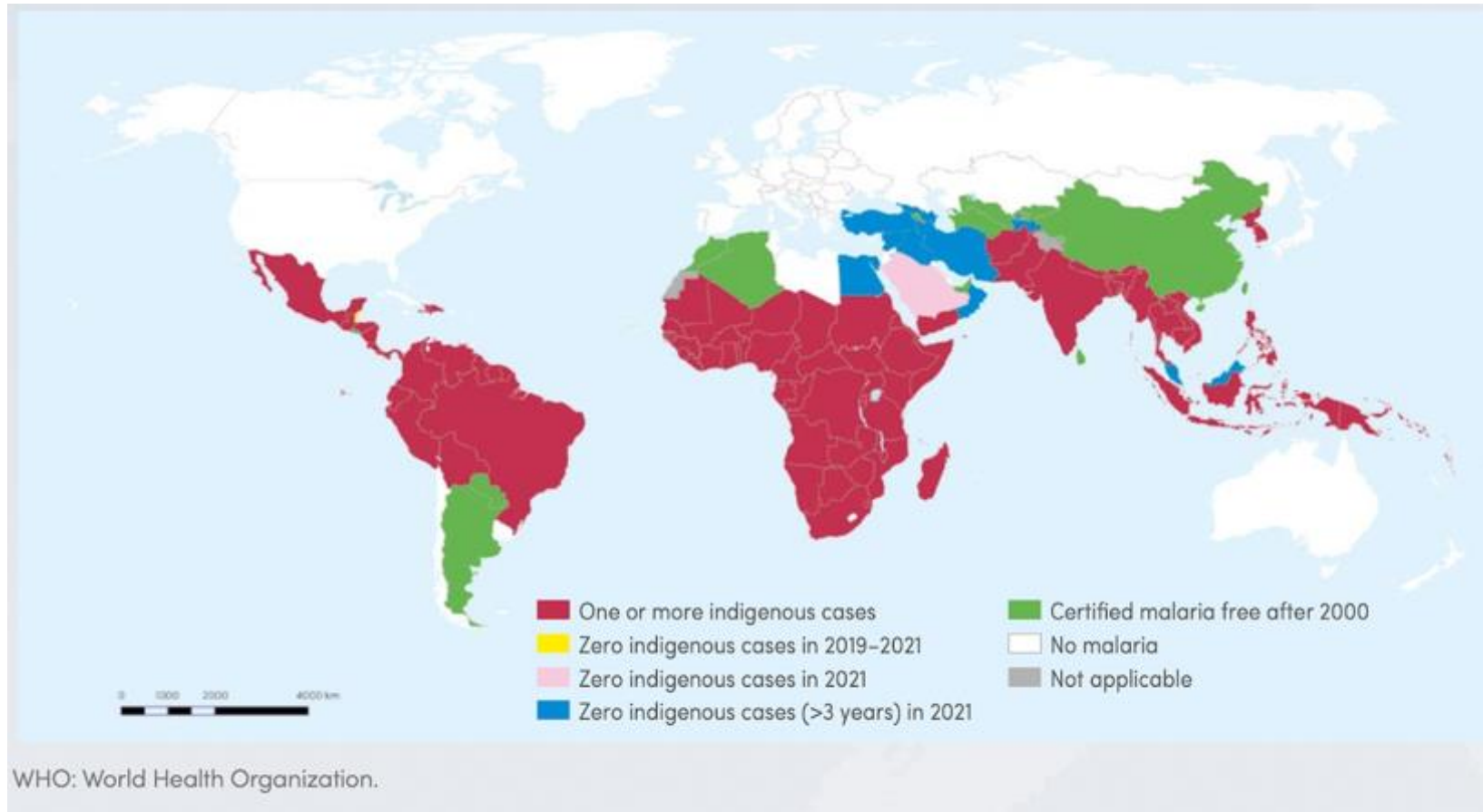
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WHO/MPP mRNA Technology Transfer Programme Regional meeting in South-East Asia

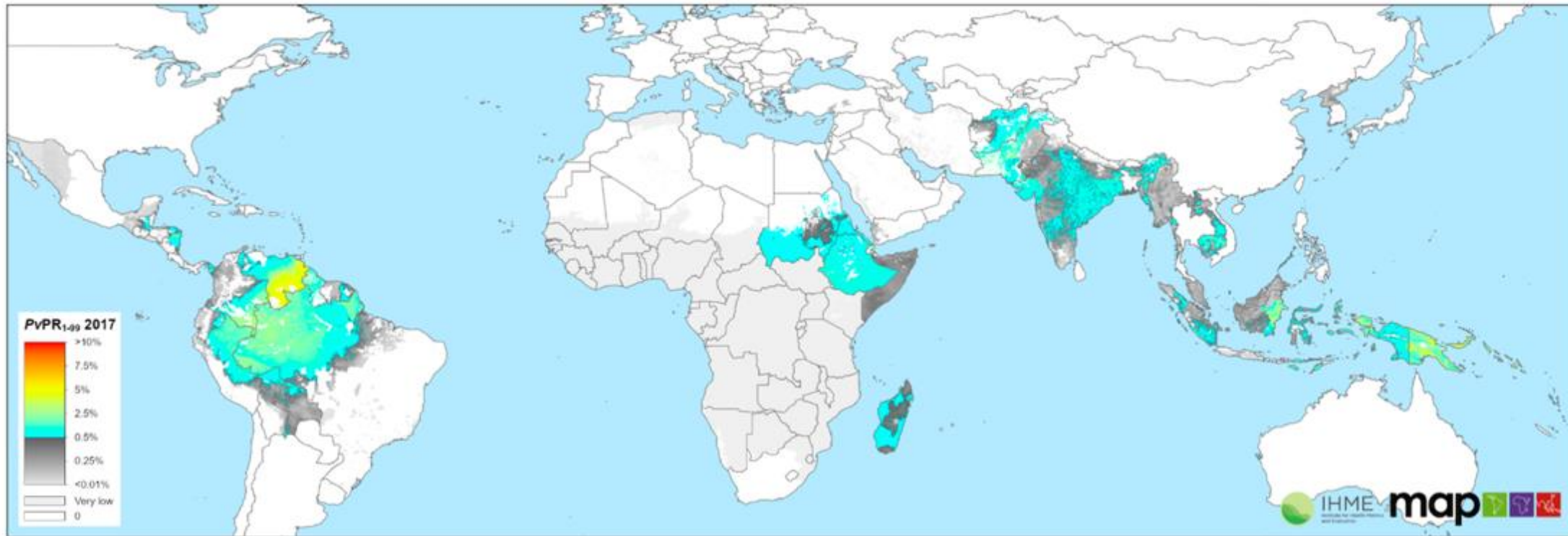
Shangri-la Hotel *Bangkok, Thailand* 31 Oct-1 Nov 2023

Global burden of malaria



- In 2020: **241 million malaria cases** in 85 malaria endemic countries (increasing from 227 million in 2019)
- **Malaria deaths** were estimated **627 000**; an estimated 47 000 (68%) of the additional 69 000 deaths were due to service disruptions during the COVID-19 pandemic.

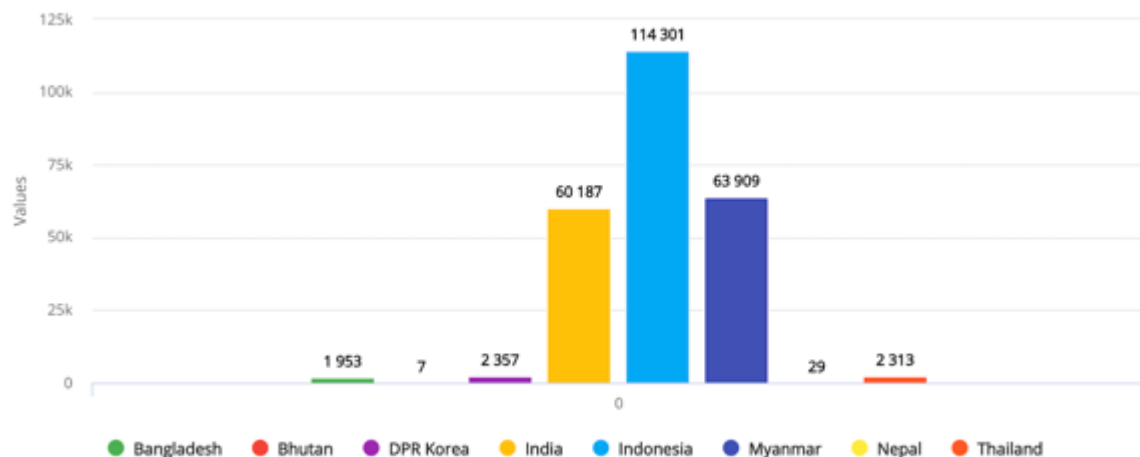
The global prevalence of patent *Plasmodium vivax* in 2017



Global burden under-estimates the latent and sub-patent reservoirs of infections

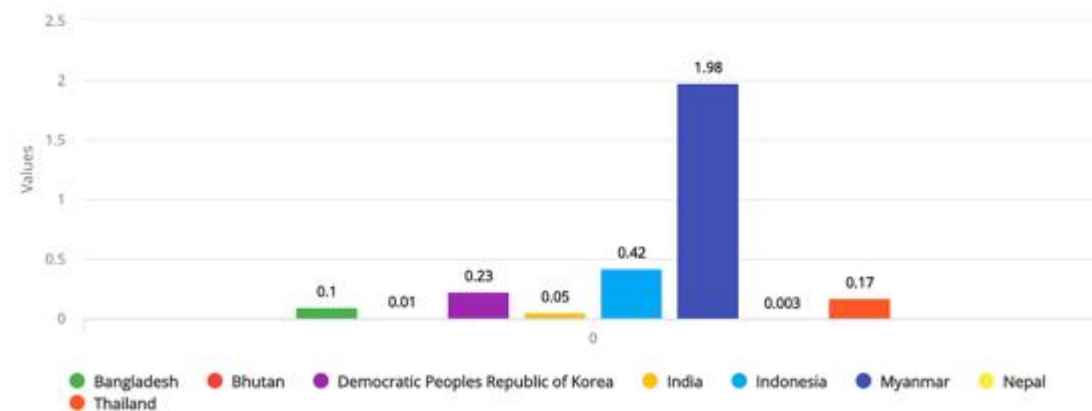
Battle and Baird, 2021

South East Asia: Number of *P. vivax* reported cases per country 2021



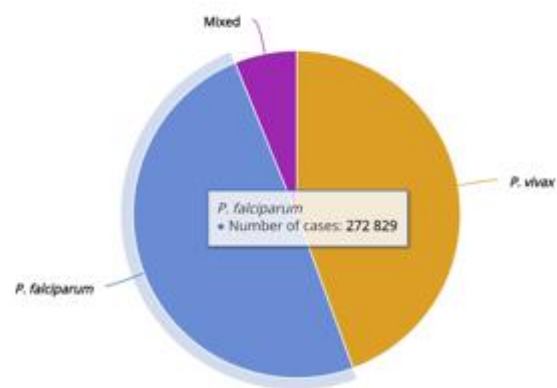
Source: World Malaria Report 2022

South East Asia: Incidence of *P. vivax* reported cases per 1000 population at risk 2021



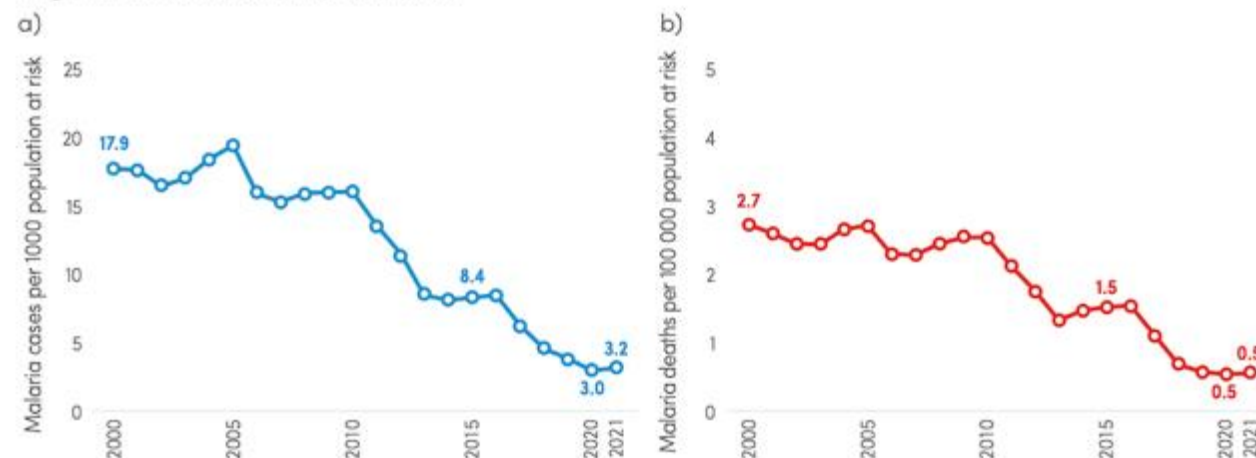
Source: World Malaria Report 2022

South East Asia: Reported malaria cases (thousands) 2021



Source: World Malaria Report 2022

Trends in a) malaria case incidence (cases per 1000 population at risk) and b) mortality rate (deaths per 100 000 population at risk), 2000–2021; and c) malaria cases by country in the WHO South-East Asia Region, 2021 Source: WHO estimates.



South East Asia: Number of *P. vivax* reported cases per country 2021

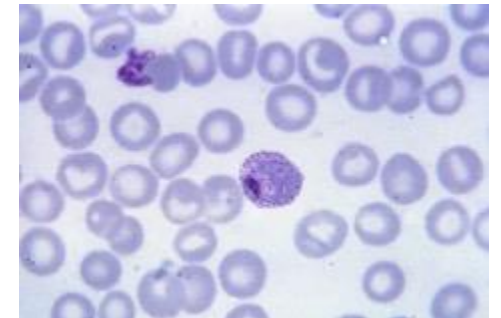
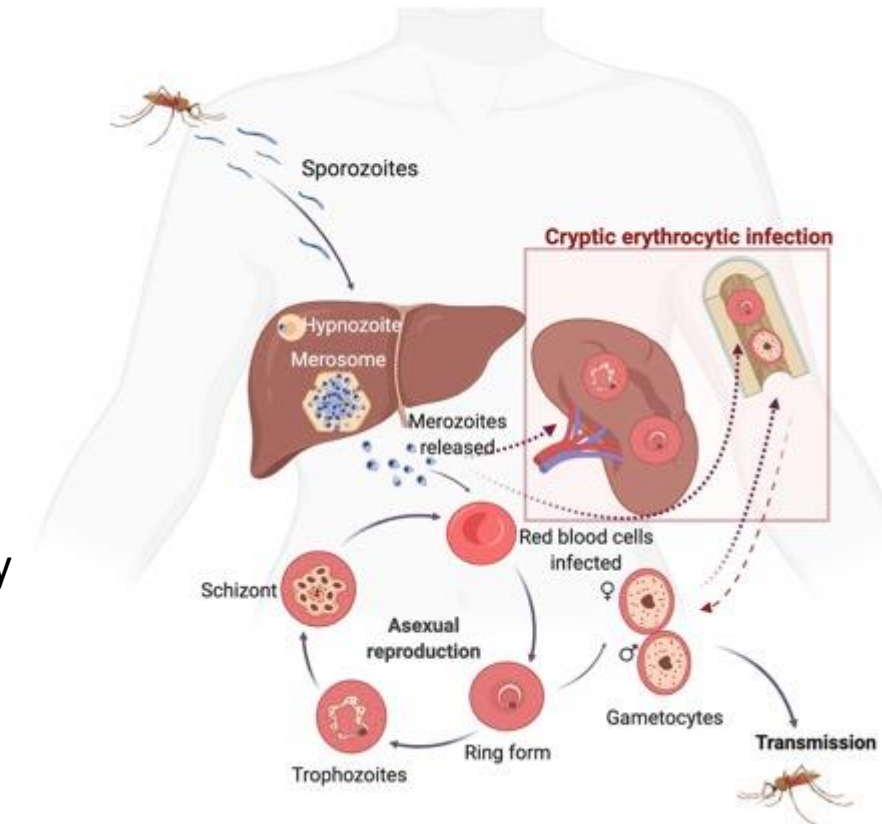
Malaria vaccine is required to add to the current interventions (drug and bednets) to control and eliminate malaria

P. falciparum: PfRTS,S, Pf R21/M-Matrix, and PfSPz

P. vivax: PvDBP, Rv21, and mRNA-based vaccine

P. vivax malaria and challenges in vaccine developments

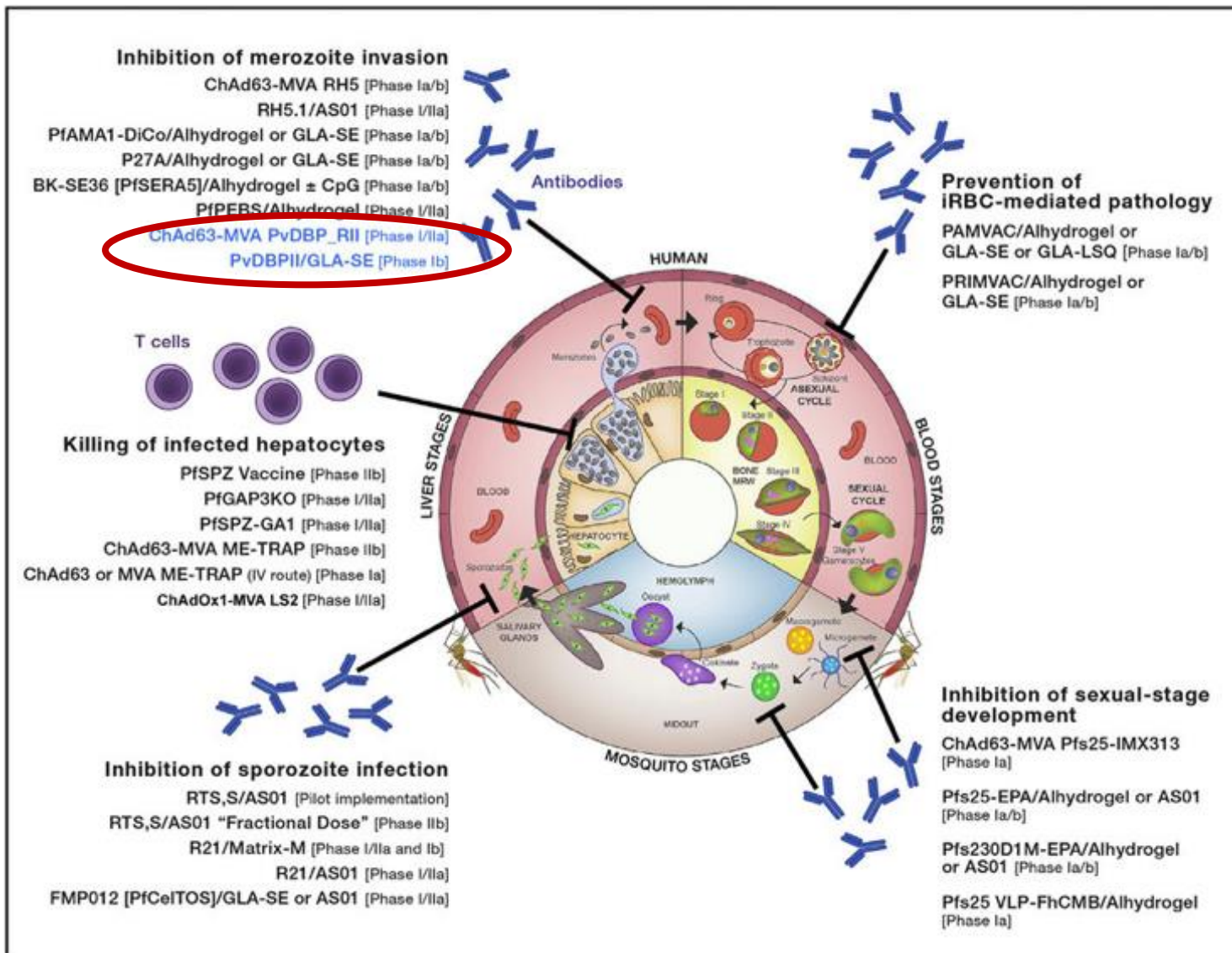
- The second most common cause of malaria
- Widely distributed species
- Complex life cycle: present as a latent form - hypnozoites
- Mostly present as asymptomatic individuals
- Hard to grow in *in vitro* culture
- Limited availability of good animal model for testing *P. vivax* vaccine efficacy
- Require transgenic parasites (ie. *P. berghei* sporozoites expressing PvCSP)
- The need of highly potent adjuvants



Key immunological considerations for vaccine development

- Include the multiple-stage proteins involved in parasite development (ie. against sporozoites, liver-stage, sexual and asexual stages)
- Induce protective immune response (humoral and cellular)
- Overcome antigenic diversity or consisting relatively conserved parasite epitopes (several epitopes that are represented by various MHC)

Malaria Vaccine: *P. falciparum* and *P. vivax* - updates



Other potential Pv vaccine candidate:

1. *PvRMC-1*, a Multistage Chimeric Protein (Matos *et al.* 2023): *PvCelTOS*, *PvCyRPA*, *Pvs25*
2. *Rv21* (Salman *et al.* 2017): *PvCSP*
3. Combination of *Rv21*, *PvCSP-VLP*, and *PvTRAP* viral vectors (Atcheson *et al.* 2018)

TABLE 1 *Plasmodium vivax* vaccines in clinical trials.

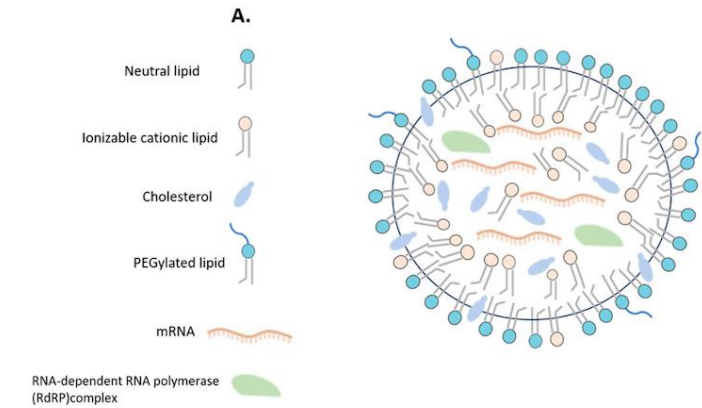
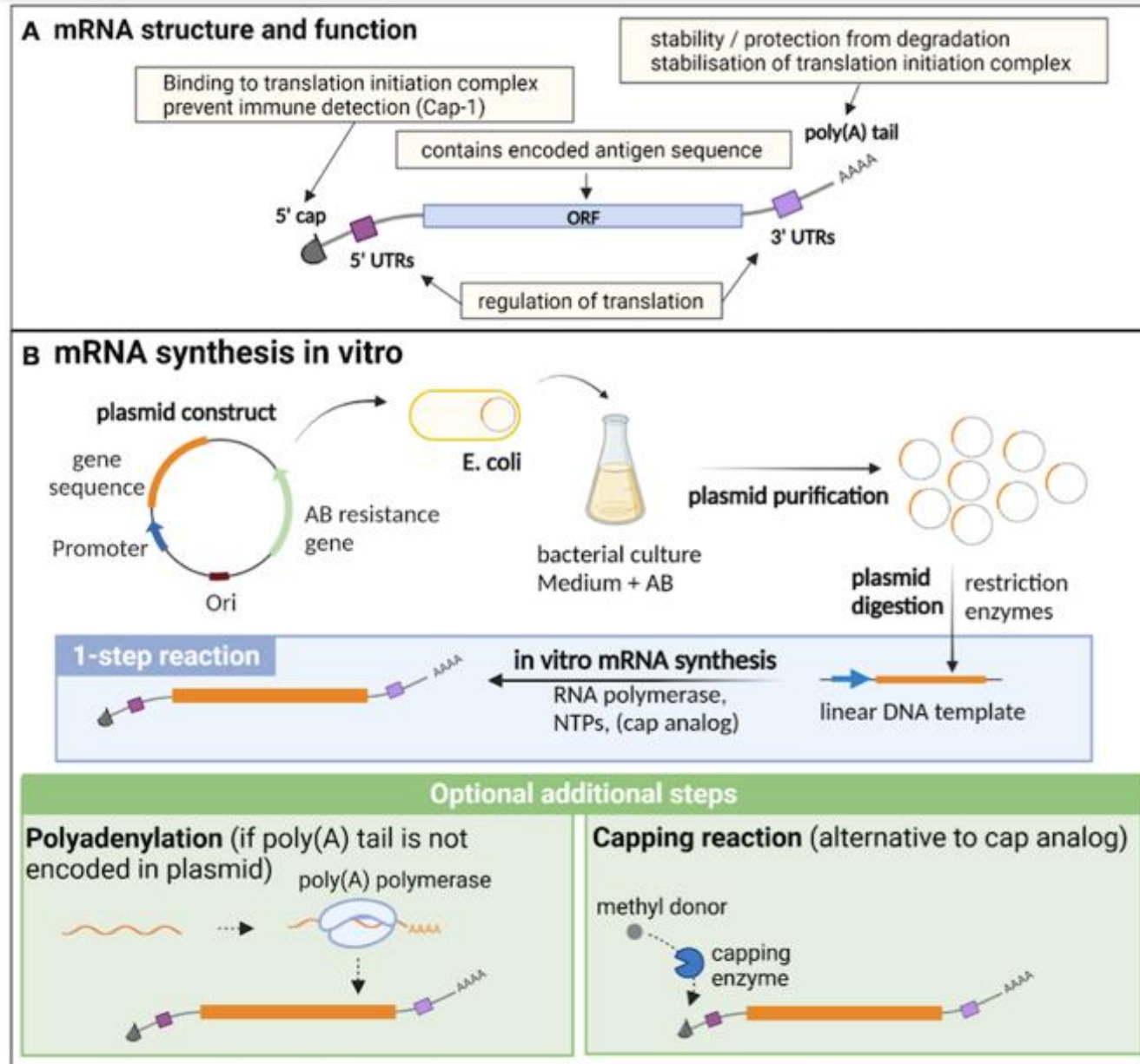
| Candidate | Phase | Key findings | Clinical Trial Number | References |
|--------------------------------|-------|---|-----------------------|------------|
| Preerythrocytic stage vaccines | | | | |
| VMP001 | 1/2a | Recombinant PvCSP with adjuvant AS01B. Reduction of parasitemia, but low efficacy. | NCT01157897 | (21) |
| Peptides N R&C | 1b/2 | PvCSP derived from long synthetic peptides (LSP) with Montanide ISA 720 and 51. Long-lasting antibody response, with 36.6% efficacy in naive volunteers. | NCT0108184 | (22, 23) |
| PvRAS | 1/2a | <i>P. vivax</i> irradiated sporozoite. Poor cellular response and 42% efficacy. | NCT01082341 | (24) |
| Blood-stage vaccines | | | | |
| ChAd63-MVA-PvDBPII | 1a/2a | Heterologous <i>prime-boost</i> regimen with recombinant viral vectors ChAd63-MVA-PvDBPII. Induction of antibodies that inhibit interaction with reticulocytes, humoral and cellular response, 50% of strain-transcendent immunity. | NCT01816113 | (25) |
| PvDBPII-GLA-SE | 1 | Recombinant PvDPBII with GLA-SE adjuvant. High production of specific antibodies can inhibit interaction with reticulocytes and strain-transcendent response. | CTRI/2016/09/007289 | (26) |
| Transmission-blocking vaccines | | | | |
| Pvs25 | 1 | Recombinant Pvs25 with Montanide ISA 51 adjuvants. Good induction of antibodies and 30% reduction in infected mosquitoes. High reactogenicity. | NCT00295581 | (27) |

Some other *P. vivax* vaccine candidates

TABLE 1 | *Plasmodium vivax* blood stage vaccine candidates.

| Description/delivery system | | Development phase | Antigen | Reference |
|---|--|-------------------|----------------|--|
| <i>Pv</i> DBPII/GLA-SE | Recombinant <i>Pv</i> DBPII with Glucopyranosyl Lipid Adjuvant-Stable Emulsion | Phase I b | <i>Pv</i> DBP | Bharadwaj et al., 2017; Singh et al., 2018 |
| ChAd63-MVA <i>Pv</i> DBP RII | Prime boost, viral vectors (Chimpanzee Adenovirus 63/Modified Vaccinia Ankara) | Phase I a | <i>Pv</i> DBP | de Cassan et al., 2015; Payne et al., 2017 |
| <i>Pv</i> DBPII-DEK ^{null} | Recombinant protein | Pre-clinical | <i>Pv</i> DBP | Ntumngia and Adams, 2012 |
| <i>Pv</i> MSP1 ₁₉ | Recombinant protein-Montanide ISA720 | Pre-clinical | <i>Pv</i> MSP1 | Fonseca et al., 2016 |
| ChAd63- <i>Pv</i> AMA1/MVA- <i>Pv</i> AMA1 | Chimpanzee Adenovirus 63/Modified Vaccinia Ankara | Pre-clinical | <i>Pv</i> AMA1 | Bouillet et al., 2011 |
| <i>Pv</i> AMA1 | Recombinant protein-adjuvant | Pre-clinical | <i>Pv</i> AMA1 | Vicentin et al., 2014; Arévalo-Pinzón et al., 2017 |
| <i>Pv</i> RBP2b | Recombinant protein | Pre-clinical | <i>Pv</i> RBP | Gruszczyk et al., 2018a, Gruszczyk et al., 2018b |

In vitro synthesis of mRNA vaccine



Things to consider to increase the immunogenicity of mRNA vaccines

- Addition of adjuvants to stimulate the innate and adaptive immune response (humoral and cellular and generation of memory cells)
- The adjuvant effect is essential to the recruitment and activation of APCs and priming of T cells to induce adaptive responses.

Some mRNA-based malaria vaccines to date

nature immunology

Article


<https://doi.org/10.1038/s41590-023-01562-6>

mRNA vaccine against malaria tailored for liver-resident memory T cells

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 Check for updates

Mitch Ganley^{1,2,13}, Lauren E. Holz^{3,13}, Jordan J. Minnell⁴, Maria N. de Menezes³, Olivia K. Burn⁴, Kean Chan Yew Poa⁵, Sarah L. Draper¹, Kieran English⁶, Susanna T. S. Chan¹, Regan J. Anderson¹, Benjamin J. Compton¹, Andrew J. Marshall¹, Anton Cozijnsen⁷, Yu Cheng Chua³, Zhengyu Ge³, Kathryn J. Farrand⁴, John C. Mamum⁴, Calvin Xu³, Ian A. Cockburn⁸, Katsuyuki Yui⁹, Patrick Bertolino⁶,

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Exploring *in vitro* expression and immune potency in mice using mRNA encoding the *Plasmodium falciparum* malaria antigen, CelTOS

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npj | vaccines

www.nature.com/npjvaccines

ARTICLE OPEN

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mRNA-LNP expressing PfCSP and Pfs25 vaccine candidates targeting infection and transmission of *Plasmodium falciparum*

Ifford T. H. Hayashi^{1,6}, Yi Cao^{1,6}, Leor C. Clark¹, Abhai K. Tripathi^{1,2}, Fidel Zavala^{1,2}, Garima Dwivedi³, James Knox⁴, Ohamad-Gabriel Alameh³, Paulo J. C. Lin⁵, Ying K. Tam⁵, Drew Weissman³ and Nirbhay Kumar^{1,2,3}

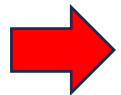
Malaria is a deadly disease responsible for between 550,000 and 627,000 deaths annually. There is a pressing need to develop vaccines focused on malaria elimination. The complex lifecycle of *Plasmodium falciparum* provides opportunities not only to target the infectious sporozoite stage, introduced by anopheline mosquitoes, but also the sexual stages, which are ingested by mosquitoes during blood feeding, leading to parasite transmission. It is widely recognized that a vaccine targeting multiple stages would induce efficacious transmission reducing immunity. Technological advancements offer new vaccine platforms, such as mRNA-LNPs, which can be used to develop highly effective malarial vaccines. We evaluated the immunogenicity of two leading *P. falciparum* vaccine candidates, Pfs25 and PfCSP, delivered as mRNA-LNP vaccines. Both vaccines induced extremely potent immune responses when administered alone or in combination, which were superior to Pfs25 and PfCSP DNA vaccine formulations. Purified IgGs from Pfs25 mRNA-LNPs immunized mice were highly potent in reducing malaria transmission to mosquitoes. Additionally, mice after three and four immunizations with PfCSP mRNA-LNP provided evidence for varying degrees of protection against sporozoite challenge. The comparison of immune responses and stage-specific functional activity induced by each mRNA-LNP vaccine, administered alone or in combination, also supports the development of an effective combination vaccine without any risk of immune interference for targeting malaria parasites at various life cycle stages. A combination of vaccines targeting both the infective stage and sexual/midgut stages is expected to interrupt malaria transmission, which is critical for achieving elimination goals.

npj Vaccines (2022)7:155; <https://doi.org/10.1038/s41541-022-00577-8>

Issue for achieving higher vaccine efficacy

- (i) generation of highly potent functional immunity - this requires **a strong knowledge of mechanisms and mediators of protective responses**;
- (ii) choosing the right antigens and epitopes (or combinations) that mediate protective immunity
(*multiple antigen components, the type of adjuvants, may be required to increase higher vaccine efficacy*);
- (iii) developing strategies to overcome immune evasion and prevent vaccine escape

Notes: malaria exposed populations showed lower vaccine efficacy than seen in malaria naïve populations raising the prospect of considerable immune dysregulation in malaria exposed populations



affects the ability to generate and maintain potent protective responses

A deeper understanding of mechanisms and key targets of immunity is needed to underpin this, and research to reveal new strategies for the induction of a higher level of protective functional immunity.

THANK YOU

