Bio Farma Product Development Plan for Malaria Vaccine

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Research and Development PT Bio Farma

WHO/MPP mRNA Technology Transfer Programme
Regional Meeting in South-East Asia
31 October – 1 November 2023

OVERVIEW PHARMACEUTICAL SOEs HOLDING

Officially formed by the Minister of SOEs on January 31th 2020, the Pharmaceutical SOE holding currently consists of three SOEs member group: PT Bio Farma (Persero) as the holding company and PT Kimia Farma Tbk. And PT Indofarma Tbk. As a subsidiary.

biofarma

- Vaccines
- Anti sera
- Other life Science products

kimia farma

- OTC & Ethical
- Medical Services
- Retail

indofarma

- Herbal
- Medical Devices

- Export Distributions > 150 countries (polio vaccine: 2/3 global supply)
- 13 of Pharmaceutical manufacture (vaccines, drugs, herbal products, dan medical devices)
- Largest distribution channel
- Retail pharmacy network (1,262), clinic (600), dan diagnostic laboratory (62)

Distribution

Production

R&D

BIO FARMA CAPABILITIES

PQ WHO Milestones of Vaccine Products

YEAR	VACCINE
1997	OPV, measles 10 ds
2001	DTP, DT, TT (vial)
2003	TT (Uniject)
2004	Hep B (Uniject)
2006	DTP-HepB, measles 20 ds
2009	mOPV1
2010	bOPV 20 ds
2011	Td
2014	DTP/Hb/Hib (Pentabio) 5ds, 10ds
2015	bOPV 10 ds
2019	mOPV2
2020	Novel OPV2 (WHO EUL)

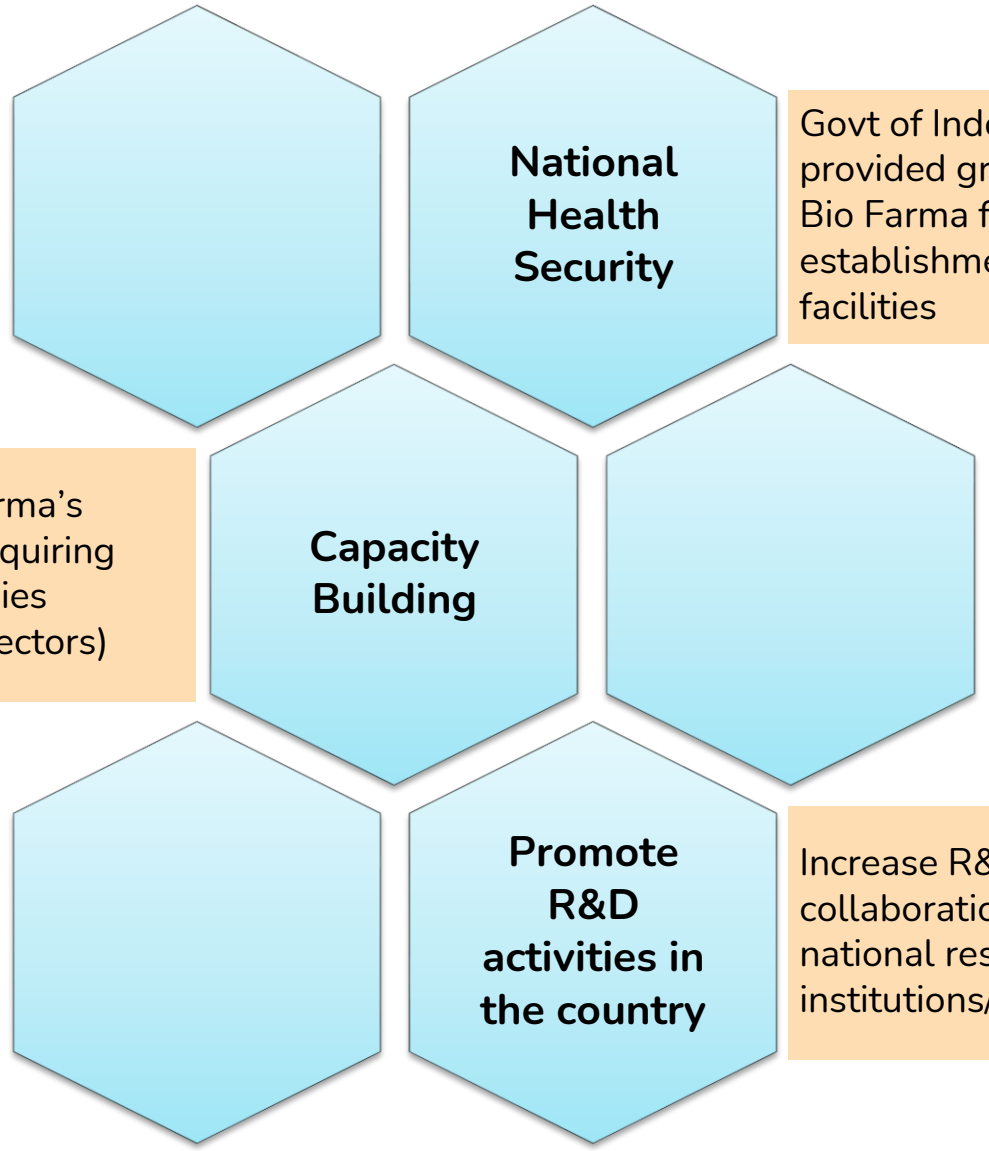
Others :

- **SEASONAL FLU Vaccine (Flubio), BCG, sIPV,**
- **Antisera : Tetanus, Diphtheria, Snake Venom**

API

1. **Polio bulk**
2. **Measles bulk**
3. **Diphtheria bulk**
4. **Tetanus bulk**
5. **Pertussis bulk**
6. **Hib bulk**

National Strategy in mRNA base Vaccine development



Govt of Indonesia provided grant funds to Bio Farma for establishment of mRNA facilities

- Pandemic preparedness
- Utilization for other mRNA base products

Expand Bio Farma's capability in acquiring new technologies (mRNA, viral vectors)

Increase R&D collaboration with national research institutions/Universities

World Health Organization

medicines patent pool

Afrigen

Afrigen, South Africa, TT mRNA Hub

Product pipeline :

- COVID-19 Vaccine

Collaboration Scheme:

Bio Farma is WHO/MPP Technology Transfer recipients, and the Afrigen as mRNA Hub TT

Progress :

- 6 BF researchers trained in Afrigen on April 2022 for introductory mRNA tech
- Agreement between MPP and BF for TT program (Package 1,2,3) has been signed
- TT package 1a has been delivered to BF

CEPI

Production facility establishment and capacity building for pandemic/outbreak preparedness

Progress :

- Partnering Agreement 10 years (25 August 2023)
- Kickoff meeting 25 Sept 23
- Start 6 mo. Program (1 Oct 2023)

biofarma

Bio Farma mRNA vaccine development programme

Quantoom Biosciences

Development of new generation of mRNA vaccine (low COGS)

Progress :

- Early discussion as part of WHO/MPP TT Program
- MoU with Bio Farma signed
- Co-development of mRNA-based Rabies vaccine as POC

MANCHESTER 1824

Manchester University, UK

Product pipeline :

- COVID-19 Vaccine
- mRNA Vaccine

Collaboration Scheme:

Research collaboration for mRNA seed preparation

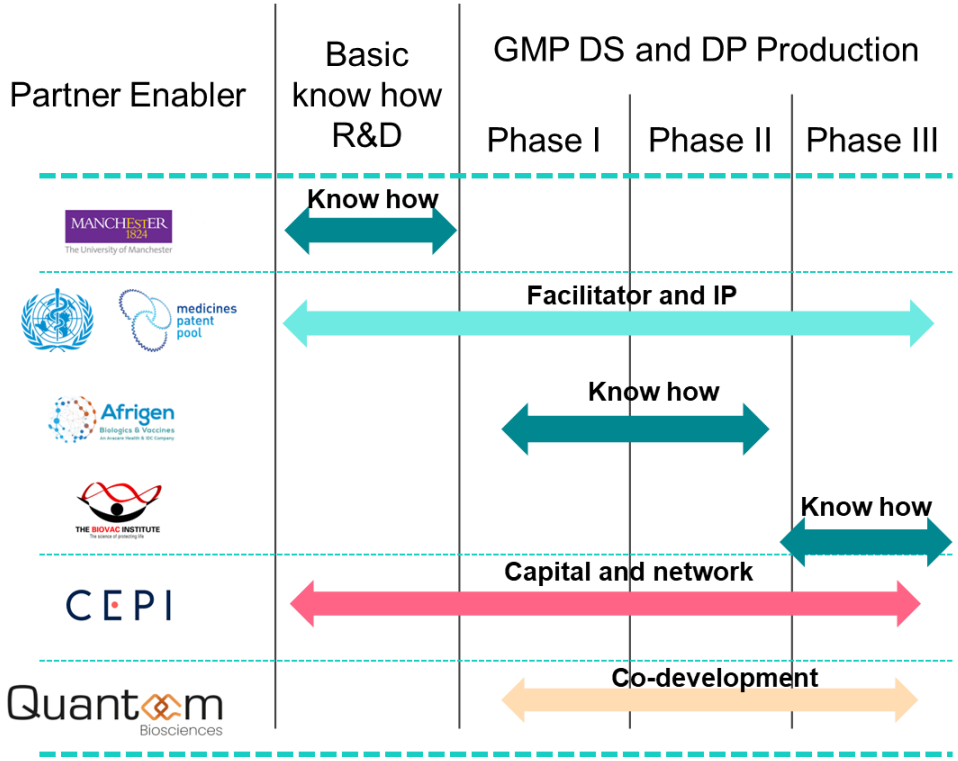
Progress :

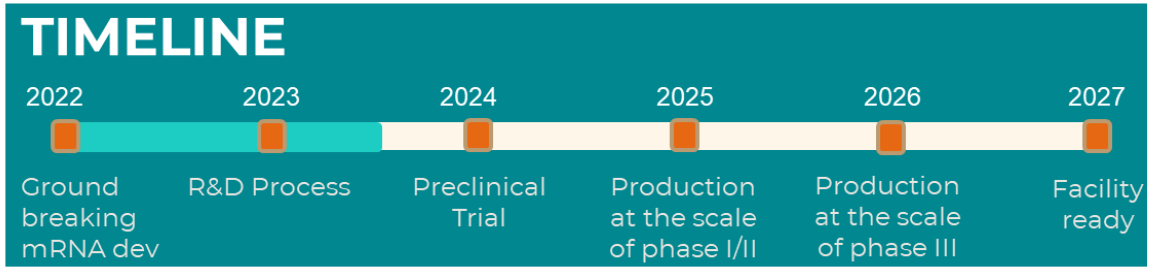
- MTA & Agreement already signed
- On-going PoC (in vitro and in vivo of mRNA seed of COVID-19)

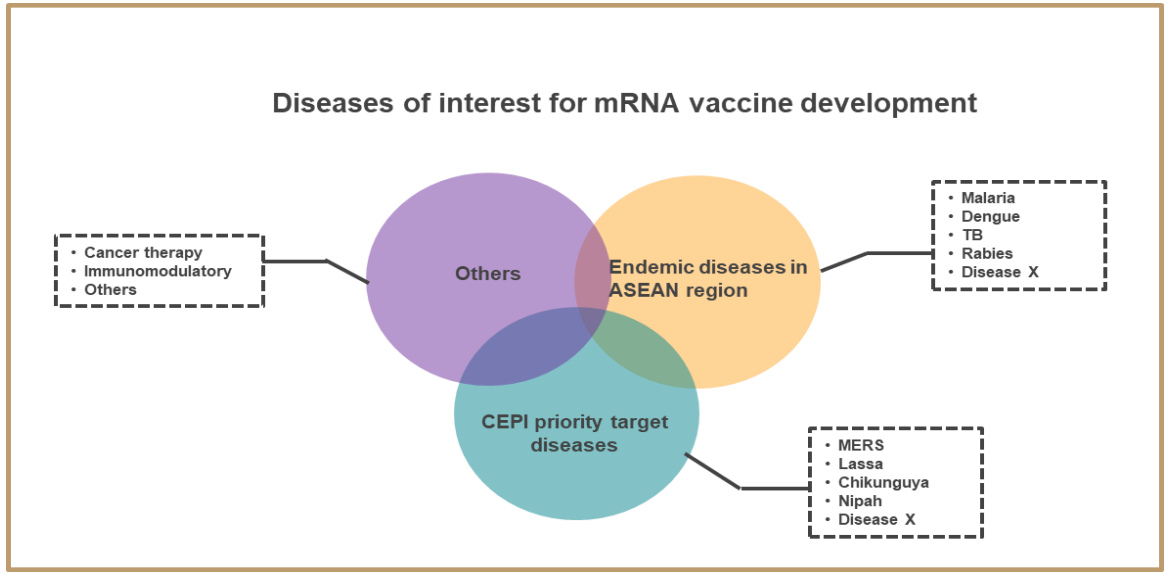
Other potential partner

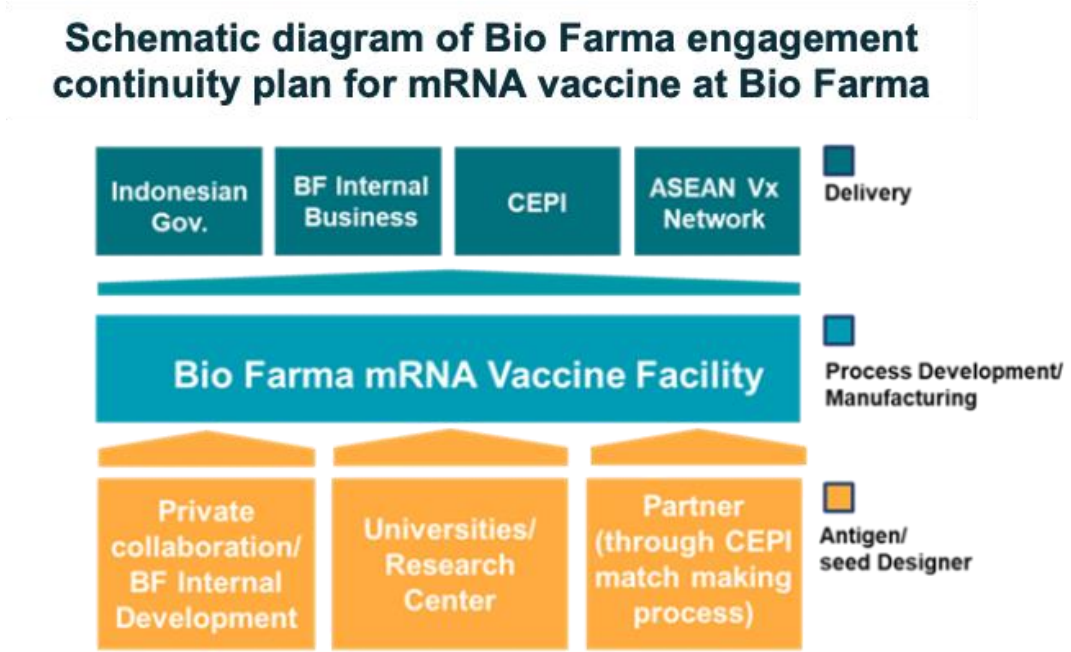
Biofarma GROUP

mRNA vaccine programmes at Bio Farma and development timeline







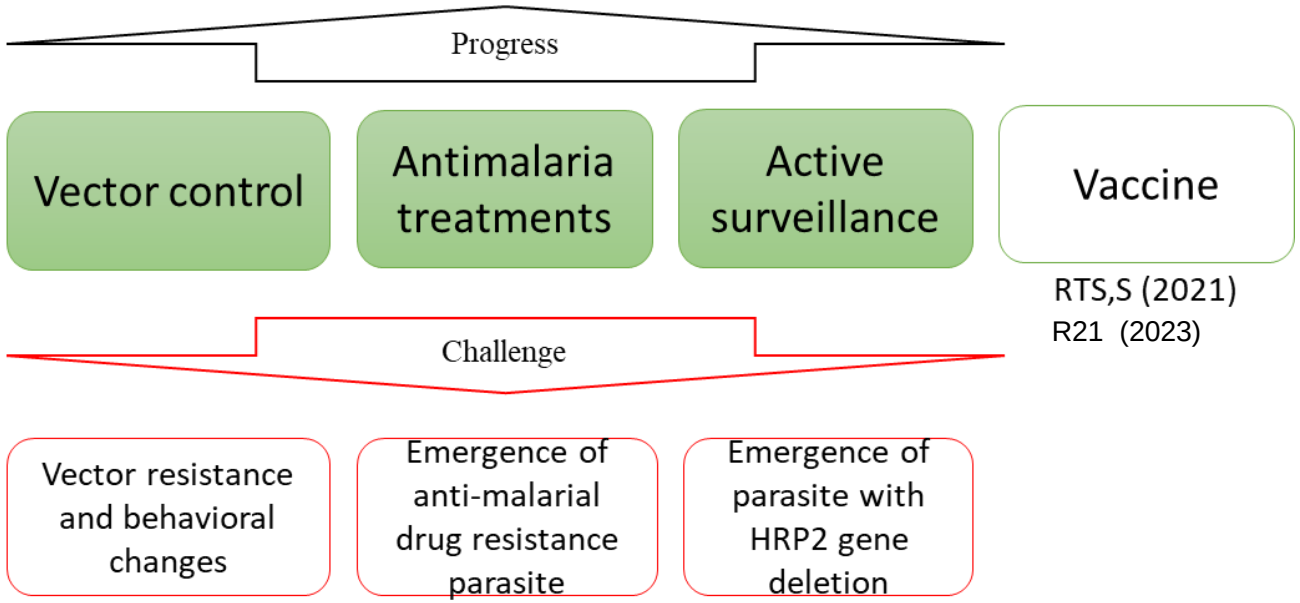


Malaria disease: current status, control and prevention

Global Malaria Burden

- **214M** Global malaria cases
- **619K** Global malaria death
- **95%** Global malaria cases and death occurred in WHO African region
- **80%** Children under 5 accounted for 80% of malaria death in WHO African region

Malaria control progress



Malaria vaccine is needed to further reduce and control malaria cases

Natural acquired immunity (NAI) against malaria

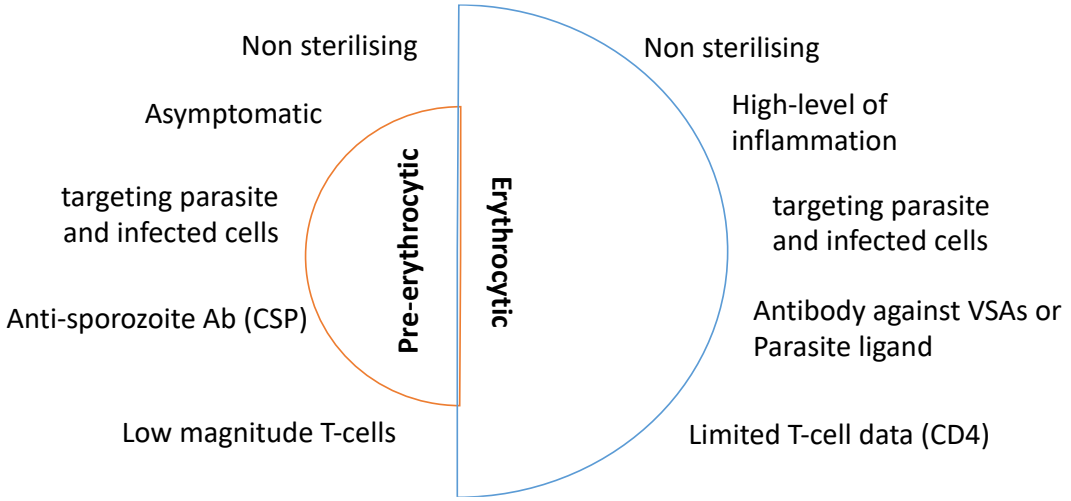
- NAI developed as a result of **prolonged and continuous exposure** to malaria infection.
  - This immunity not sterilizing and wanes rapidly after malaria exposure ceases.

- **High parasitemia** associate with **inflammation** and can lead to **immuno-pathology.**

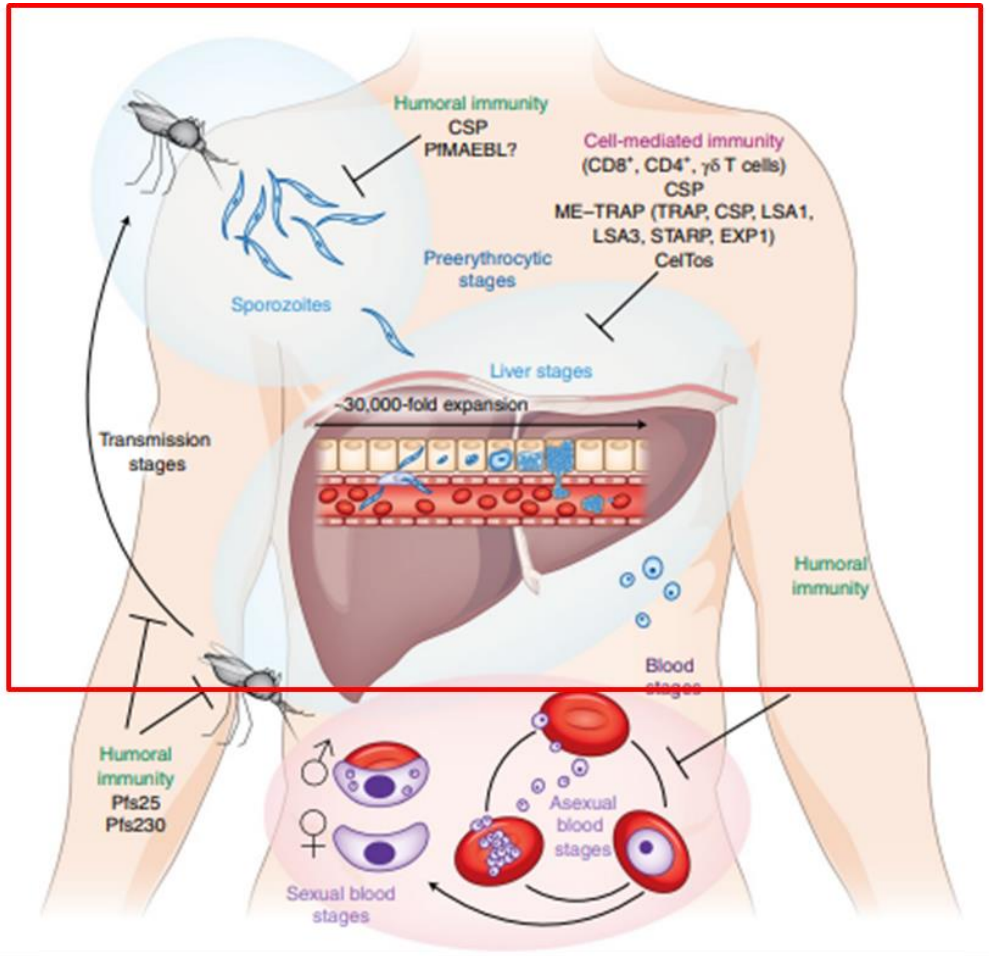
- NAI can directly neutralise the parasite to decrease the parasite density **(anti-parasitic)** or diminish excessive proinflammatory cytokines to reduce severity of diseases **(anti-disease immunity)**.

- NAI against severe malaria and death rapidly developed. Meanwhile, anti-parasitic immunity slowly acquired

- Since NAI did not induce sterile immunity against malaria infection, therefore, vaccine should be able to induce immune response beyond NAI –e.g high antibody and T-cell responses.



Malaria vaccine development



*Cockburn, I.A. and R.A. Seder. Nat Immunol, 2018. **19**(11): p. 1199-1211.*

- Infection of hepatocyte during pre-erythrocytic stage is asymptomatic. Vaccine targeting pre-erythrocytic stage can **induce sterile immunity**.

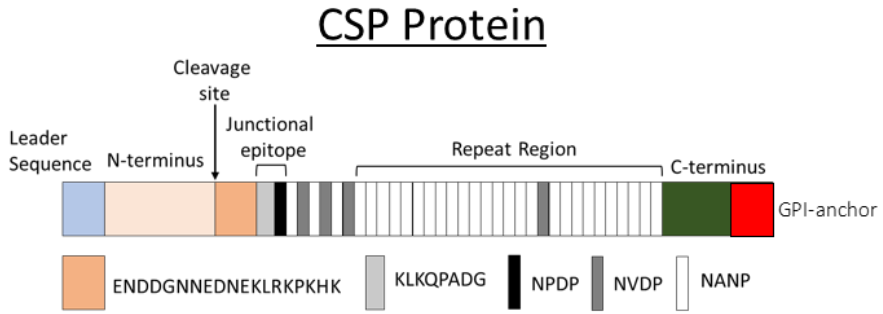
- Blood-stage infection associate with clinical pathology.
  - Symptoms: fever, chills, sweats, headaches, body aches, malaise, nausea and vomiting.
  - Outcomes: broad range from mild to severe and death.
  - Vaccine targeting blood stage can **reduce diseases severity**

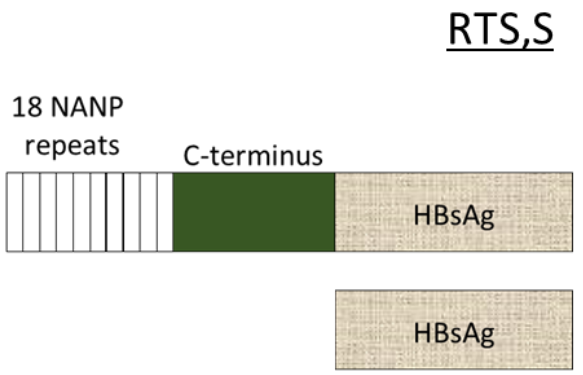
- Malaria vaccines are developed based on parasite's life cycle:

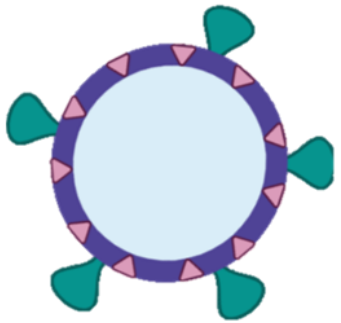
  - **Pre-erythrocytic stage (PEV): extracellular (sporozoite stage) and intracellular (liver-stage) phase.**
  - Erythrocytic stage: Merozoite ligand and VSAs
  - Sexual stage: de-novo antigen express during parasite development in mosquito

Current progress on subunit PEV

- **RTS,S/AS01E** (Mosquirix) is **a subunit PEV** based on truncated of circumsporozoite protein (**CSP) antigen.**
- The vaccine induce high-level of **anti-NANP antibodies** that target the **extracellular sporozoites**.
- RTS,S **protect 25-50%** children and infant against malaria infection in endemic setting; indicating CSP is a protective antigen
- RTS,S were **received authorisation** from WHO in 2021 to be used in children living in areas of moderate to high malaria transmission.
- R21/Matrix M is second malaria vaccine that received authorization from WHO in 2023
- Malaria Vaccine Technology Roadmap 2013 indicated that an ideal malaria vaccine **require to provide at least 75% protective efficacy** against clinical malaria and reduce transmission.
- **More research are still needed** to developed high-efficacious malaria vaccine.



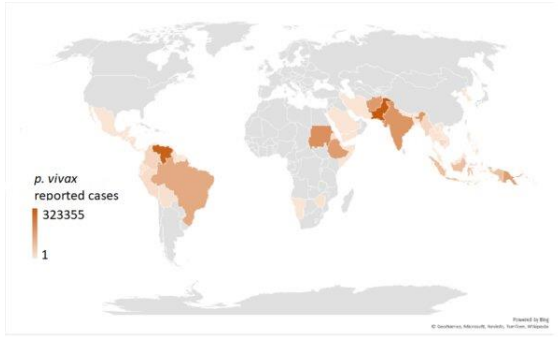




Opportunity for malaria vaccine development in South-East Asia Region: Using rapid-scalable and low-cost Quantoom technology to produce mRNA vaccine targeting *P. falciparum and P. vivax*

Introduction

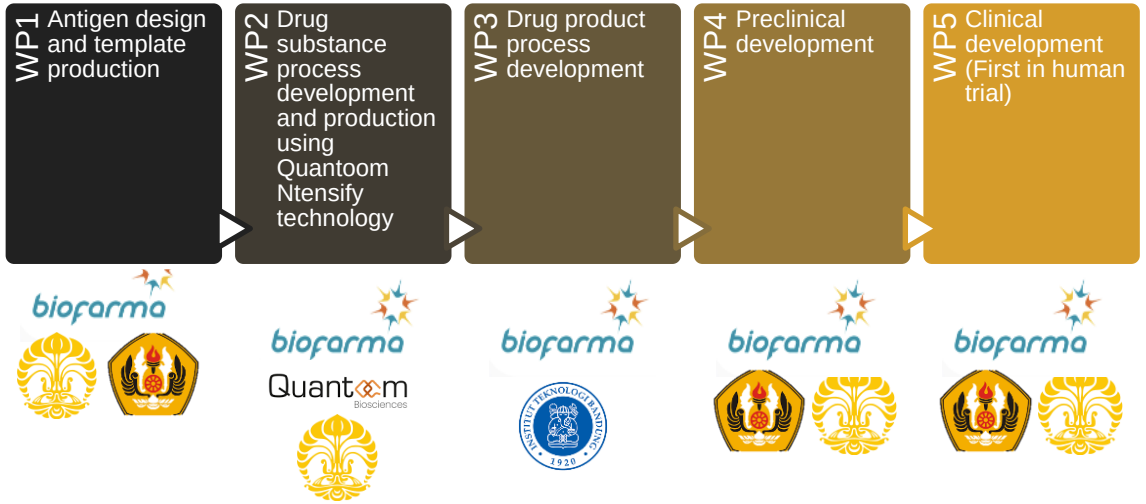
- While *P. falciparum* is the most common cause of malaria worldwide, other Plasmodium species, such as *P. vivax*, play a significant role in the number of malaria cases outside of Sub-Saharan Africa.
- *Plasmodium vivax* is the second major caused of malaria cases globally with estimates around 7.1 million cases in 2019.



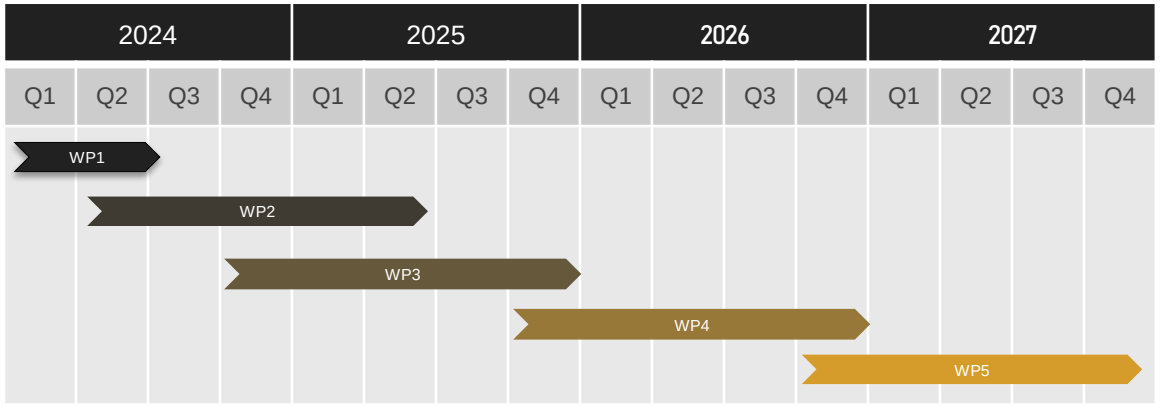
Global prevalence of P. vivax (sources: vivaxmalaria.org)

- Currently, there is no available vaccine targeting *P. vivax*.
  - Development of vaccine targeting *P. vivax* is pivotal to support parasite control and prevent malaria diseases caused by *P. vivax*.
- mRNA technology is a versatile vaccine platform that capable to induce robust humoral and cellular immune response.
  - These types of immunity are required to provide protection against malaria.
- Bio Farma aim to develop mRNA vaccine targeting pre-erythrocytic stage of *P. falciparum & P. vivax* using strain that **commonly circulated in South-East Asia Region**

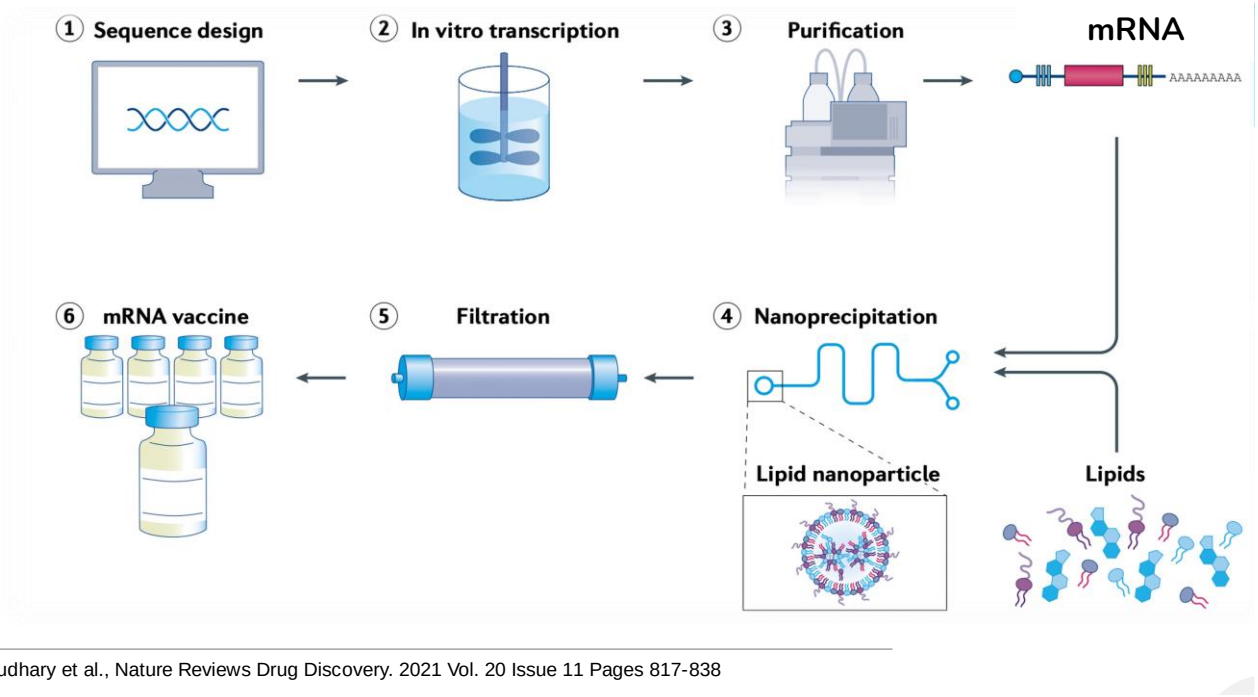
Project plan



Timeline



WP.1 Workflow of mRNA design and template production



Chaudhary et al., Nature Reviews Drug Discovery. 2021 Vol. 20 Issue 11 Pages 817-838

Sequence design

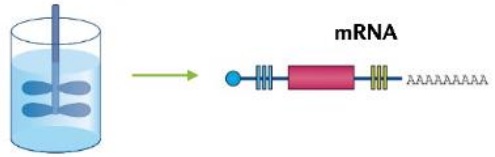
UI, Bio Farma, Unpad

- Pre-erythrocyte stage
- *Plasmodium falciparum* and *Plasmodium vivax*, Southeast Asia Strain
- Target protein: PfCSP and PvCSP
- Optimization of 5; and 3'-UTR
- Codon optimization for full-length protein
  Bioinformatic analysis for the elimination of toxicity, allergenic region, and adjustment with HLA recognition from (Indonesia/SEA)

WP2. Drug substance process development and production using Quantoom Ntensify technology

mRNA production

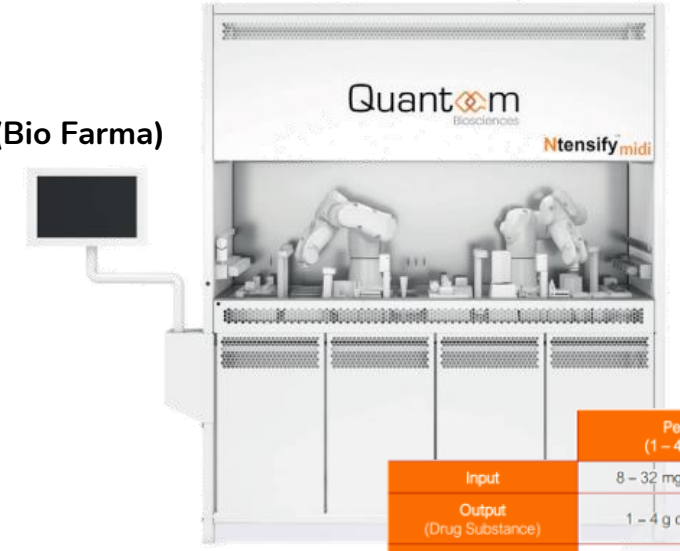
In vitro transcription



UI & Bio Farma

- Ntensify Mini (UI)
- Ntensify Midi (Bio Farma)

	Drug Discovery (up to 192 different RNAs)	Pre-clinical use (1 RNA sequence)
Input	4 µg of linear DNA	768 µg of linear DNA
Output (Drug Substance)	0.5 mg of RNA x 192 wells	100 mg of RNA pooled
Batch duration	< 1 day	< 1 day

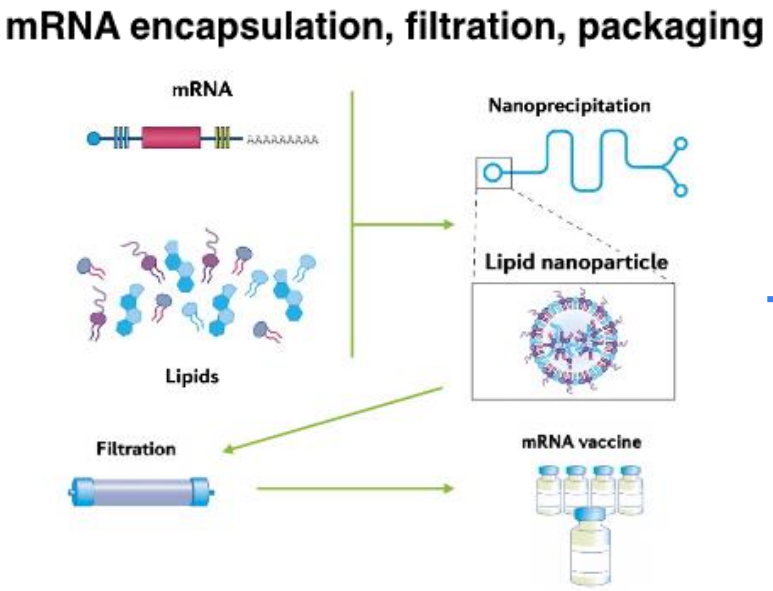


	Per batch (1 – 4 reactors)	Per year (4 reactors)
Input	8 – 32 mg of linear DNA	4.8 g of linear DNA
Output (Drug Substance)	1 – 4 g of naked RNA	612 g of naked RNA
Nbr Batch	Max 1 per day	150 per year

Ntensify system by Quantoom Bioscience

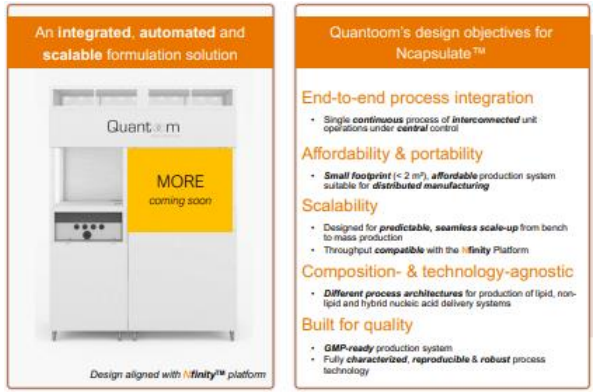
- Provide an integrated, seamless production system for mRNA vaccine.
  - From IVT to mRNA purification
- Small footprint area with scalability from pre-clinical development to GMP manufacturing.
- Reduce COGS, resulting in affordable mRNA vaccine.

WP.3 Drug Product Process Development



Bio Farma & ITB

- NCapsulate



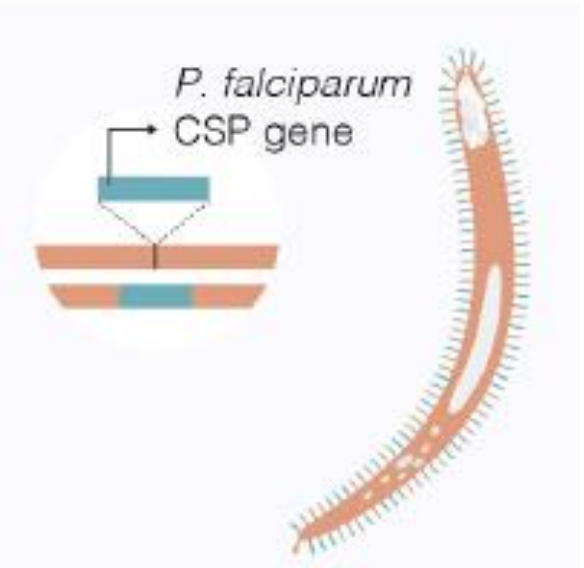
- LNP formulation based on Pfizer-BioNTech LNP
- LNP formulation based on Moderna LNP
- LNP formulation from Pharmacy of ITB/UI
- LNP formulation based on alternative lipid (Indonesian palm oil)
- Polymer-based or Peptide-based vehicle

WP.4 Preclinical Development

- Both antibody and T-cells against *Plasmodium* Ag (such as CSP) has been proven important for immunity against malaria.
  - It has been demonstrated that not only titre of Antibody, but certain subclass and quality of Ab (Avidity) were associate with protection status against malaria infection.
  - High Ag-specific CD8 T-cell responses were found correlate with protection against malaria infection.
  - Therefore, it is important to evaluate antibody and T-cell response against malaria Ag during preclinical trial

- Since *P. falciparum* is restricted human pathogen, transgenic *P. berghei* expressing *P. falciparum* protein can be used to evaluate malaria vaccine candidate in mice.

Transgenic
P. berghei sporozoites



Lead candidate	Process Development	Immunogenicity	Toxicity
High expression and CSP formation	Quality of mRNA Stable, high potency Low reactogenicity	Titer and Quality of Ab, T cell response	Acute and sub chronic toxicity in rodent and non rodent animal model

Summary

- Malaria is a serious and persistent threat to public health in many parts of Asia. The South-East Asia Region is the region with the second highest estimated malaria burden globally. An effective vaccine against *P.falciparum* and *P.vivax* is needed.
- Bio Farma project plan is to develop second-generation of PfCSP and PvCSP vaccine using mRNA technology that increase the overall affinity and longevity of the B cell response against the protective antibody epitopes and high Ag-specific T-cell response.
- The mRNA design is targeted to more effective vaccine candidate, rapid scalable, low-cost production. Development of novel UTRs and alternate lipids to ensure the freedom to operate.
- Global partnership and build innovation capacity within the country will speedy malaria vaccine development in Indonesia.

Thank You

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