Bio Farma Product Development Plan for Malaria Vaccine

Neni Nurainy
Research and Development PT Bio Farma

WHO/MPP mRNA Technology Transfer Programme
Regional Meeting in South-East Asia
31 October – 1 November 2023
Officially formed by the Minister of SOEs on January 31st 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.

- Vaccines
- Anti sera
- Other life Science products

▪ Vaccines ▪ Anti sera ▪ Other life Science products

▪ OTC & Ethical ▪ Medical Services ▪ Retail

▪ 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)
BIO FARMA CAPABILITIES

PQ WHO Milestones of Vaccine Products

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

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

- Pandemic preparedness
- Utilization for other mRNA base products

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

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

Increase R&D collaboration with national research institutions/Universities

Promote R&D activities in the country

Capacity Building

National Health Security
Bio Farma mRNA vaccine development programme

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)

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

Product pipeline:
- COVID-19 Vaccine

Other potential partner
mRNA vaccine programmes at Bio Farma and development timeline

<table>
<thead>
<tr>
<th>Partner Enabler</th>
<th>Basic know how R&amp;D</th>
<th>GMP DS and DP Production</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Know how</td>
<td>Facilitator and IP</td>
<td>Know how</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital and network</td>
<td>Know how</td>
<td>Co-development</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diseases of interest for mRNA vaccine development

- Others
- Endemic diseases in ASEAN region
- CEPI priority target diseases

Schematic diagram of Bio Farma engagement continuity plan for mRNA vaccine at Bio Farma

TIMELINE

- 2022: Ground breaking mRNA dev
- 2023: R&D Process
- 2024: Preclinical Trial
- 2025: Production at the scale of phase I/II
- 2026: Production at the scale of phase III
- 2027: Facility ready
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

82.3 in 2000 Cases per 1000 population at risk

60.1 in 2015

Progress

Vector control

Antimalaria treatments

Active surveillance

Vaccine

RTS,S (2021)

R21 (2023)

Challenge

Vector resistance and behavioral changes

Emergence of anti-malarial drug resistance parasite

Emergence of parasite with HRP2 gene deletion

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

- 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.
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 cause of malaria cases globally with estimates around 7.1 million cases in 2019.

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

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*

### Project plan

- **WP1**: Antigen design and template production
- **WP2**: Drug substance process development and production using Quantoom Ntensify technology
- **WP3**: Drug product process development
- **WP4**: Preclinical development
- **WP5**: Clinical development (First in human trial)

### Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>2024</th>
<th>2025</th>
<th>2026</th>
<th>2027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Biofarma Group*
WP.1 Workflow of mRNA design and template production


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

- 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

mRNA encapsulation, filtration, packaging

- mRNA
- Lipids
- Nanoprecipitation
- Lipid nanoparticle
- mRNA vaccine
- Filtration

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

Bio Farma & ITB
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.
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

Bio Farma:
Adriansjah Azhari
Indra Rudiansyah
Anna Sanawati
Trilokita Tanjung Sari
Shinta Kusumawardani
Elgiani Yassifa Yulia Nurinsani

Universitas Padjajaran:
Toto Subroto
Muhammad Yusuf
Wahyu
Arie Hardianto

University of Indonesia:
Budiman Bela
Febrina Meutia Wati
Cla Shinta Ayu
Ayu Nur Sasangka
Tania SW

Institute Teknologi Bandung:
Diky Mudhakir

National Research and Innovation Agency/BRIN:
Rintis Noviyanti