Prioritizing New Malaria Vaccine Candidates for Further Development

The current state of affairs in the field of malaria vaccinology: Thoughts on how vaccine candidates should be prioritized for further development

David C. Kaslow, MD
Director, PATH Malaria Vaccine Initiative
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Thoughts on how vaccine candidates should be prioritized for further development

• Why prioritize?

• What to prioritize?

• How to approach prioritization?
Why prioritize?

• No need to prioritize if:
  • Resources are unlimited
  • Only one choice / no trade-offs between or within goals / projects

• What is the current state of affairs in the global malaria vaccine pipeline?
Tables of malaria vaccine projects globally: "The Rainbow Tables"

UPDATED NOVEMBER 2012

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<thead>
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<tbody>
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<td>RTS,S/AS01E</td>
<td>World Health Organization (WHO/IVR/TDR)</td>
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Pre-erythrocytic Projects

# Global malaria vaccine pipeline

<table>
<thead>
<tr>
<th>Phase 1a</th>
<th>TRANSLATIONAL PROJECTS</th>
<th>Phase 1b</th>
<th>VACCINE CANDIDATES</th>
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<tbody>
<tr>
<td></td>
<td><strong>Phase 2a</strong></td>
<td><strong>Phase 2b</strong></td>
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<td><strong>Phase 3</strong></td>
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<td><strong>P. falciparum vaccines:</strong></td>
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<td><strong>Pre-erythrocytic</strong></td>
<td><strong>Blood-stage</strong></td>
<td><strong>Transmission-blocking</strong></td>
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<td><strong>P. vivax vaccines:</strong></td>
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</tbody>
</table>

- **ChAd63/MVA ME-TRAP + Matrix M™ (Oxford U)**
- **PsSPZ (Sanaria)**
- **Polyepitope DNA EP 1300 (NIAID)**
- **PfCelTOS FMP012 (USAMRMC)**
- **CSVAC (Oxford U)**
- **ChAd63.AMA/MVA. AMA1 +AI/CGP7909 (Oxford U)**
- **SR11.1 (Institut Pasteur)**
- **Pfs25-EPA (NIAID)**

- **Ad35.CS/RTS,S-AS01 (GSK/Crucell/WRAIR)**
- **Ad35.CS/Ad26.CS (Cruell/Seattle BioMed)**
- **ChAd63/MVA MSP 1 (Oxford U)**
- **ChAd63/MVA (Oxford U)**
- **ChAd63/MVA (CS; ME-TRAP) (Oxford U)**
- **ChAd63.AMA1/ MVA.AMA1 (Oxford U)**
- **FMP2.1-AS01B (AMA1 3D7 (USAMRMC)**
- **FMP2.1-AS01B (AMA1 3D7 (USAMRMC)**
- **NMRC.M3V.Ad.PfCA (USAMRMC)**
- **NMRC.M3V.D/ Ad.PfCA (USAMRMC)**
- **SE36 (Osaka U)**

Thoughts on how vaccine candidates should be prioritized for further development

- Why prioritize?
- What to prioritize?
- How to approach prioritization?
What to prioritize?

• Strategic goals?
  • Specific approaches or targets?
  • Preferred product characteristics
    • Which species?
    • Which age groups?
    • What geographies?
    • With what other malaria interventions?

• Early versus late-stage development?

• Specific projects?
• The Malaria Vaccine Technology Roadmap was launched in 2006 at the WHO Global Vaccine Research Forum and established a shared Vision, Strategic Goal (2025), and Landmark (2015) for development of malaria vaccines. The Roadmap also identified 11 Priority Areas in four categories: research, vaccine development, key capacities, policy, and commercialization.


http://www.malariavaccine.org/files/Malaria_Vaccine_TRM_Final_000.pdf
The Malaria Vaccine Technology Roadmap circa 2006

Vision

The malaria vaccine community will develop an effective vaccine that prevents severe disease and death caused by Plasmodium falciparum malaria in children under five in sub-Saharan Africa and other highly endemic regions. Efficient global coordination and collaboration will stimulate the malaria vaccine pipeline and accelerate progress towards this achievement.

Priorities circa 2006

• Prevent severe disease and death
• *P. falciparum*
• Children under five
• Sub-Saharan Africa and other highly endemic countries
• In conjunction with other malaria interventions?

http://www.malaria vaccine.org/files/Malaria_Vaccine_TRM_Final_000.pdf
Reasons to update the Roadmap

• “The need to update the Roadmap Vision and 2025 Strategic Goal in response to a number of changes since 2006, including changes in the strategic role of malaria vaccines and changes in malaria epidemiology and control status.”

• “Further reviews of the vision and strategic goals will occur at least every 5 years in light of the epidemiological and control situation at that time and progress with other tools and technologies. Changes will be made only if necessary. Should projects aimed at either of the 2 strategic vaccine goals reach major milestone performance indicators, such as proof of concept of efficacy, this will trigger a WHO-led consultative process to develop new Landmark goals for late stage development of these vaccines.”

2 http://www.who.int/vaccine_research/diseases/malaria/Roadmap_update_for_second_public_consultation.pdf
Vision after first public consultation in October 2012

The malaria vaccine community will develop safe and effective vaccines that prevent disease and death caused by *Plasmodium falciparum* and *Plasmodium vivax* in malaria-endemic regions. Vaccines that interrupt malaria transmission will contribute to ensuring that malaria is no longer a significant public health problem, and, in conjunction with other tools, will enable malaria elimination. Efficient global coordination and collaboration will stimulate the malaria vaccine pipeline and accelerate progress towards these achievements.

Expanded vision

- Includes *P. vivax*
- Not restricted to children under five
- Includes all malaria-endemic regions
- Includes vaccines that interrupt transmission
- In conjunction with other malaria interventions, contemplates elimination

Updated the Malaria Vaccine Technology Roadmap

Expanded Strategic Goals – Part 1 (draft)

**Strategic Goals** after first public consultation in Oct 2012

In the 2025 to 2050 timeframe, license safe vaccines targeting malaria species with significant global disease burden and encompassing the following two objectives, for use by the international public health community:

1) Malaria vaccines with a protective efficacy of more than 80% against clinical malaria, suitable for administration to both children and adults in malaria-endemic areas. The efficacy measure will be an 80% absolute reduction in incidence of all episodes of clinical malaria over at least 2 years.

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**New strategic goal for disease prevention**

- Protective efficacy of more than 80%
- Clinical malaria
- Over at least 2 years
- Children and adults
- Includes all malaria-endemic areas

Strategic Goals after first public consultation in Oct 2012

In the 2025 to 2050 timeframe, license safe vaccines targeting malaria species with significant global disease burden and encompassing the following two objectives, for use by the international public health community:

2) Malaria vaccines that inhibit transmission of the parasite and thereby substantially reduce the incidence of human malaria infection to achieve elimination in multiple settings, in conjunction with other malaria control tools. The vaccines should be suitable for administration to people of all ages in mass campaigns.

Additional new strategic goal

- Inhibit transmission*
- Reduce incidence of malaria infections
- Achieve elimination in multiple settings
- All ages
- Mass campaigns

*Not restricted to any one life-cycle stage or vaccine approach

Strategic goals, outcomes, and vaccine targets

Goal/impact

Control & elimination

Saving lives & preventing disease
Strategic goals, outcomes, and vaccine targets

Goal/impact

Control & elimination

Transmission interrupted

Infections prevented

Cases averted*

Saving lives & preventing disease

*Impact on asymptomatic reservoir?
Strategic goals, outcomes, and vaccine targets

Goal/impact

Control & elimination

Outcome

Transmission interrupted

Infections prevented

Cases averted*

Vaccine target

Sexual/sporogonic/mosquito (SSM)

Pre-erythrocytic (PE)

Blood-stage (BS)

Saving lives & preventing disease

*Cases averted refers to the number of infections prevented.
Another level of prioritization

Projects

Stage of development

*P. falciparum* vaccines:
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking

*P. vivax* vaccines:
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking
Thoughts on how vaccine candidates should be prioritized for further development

• Why prioritize?
• What to prioritize?
• How to approach prioritization?
How to approach prioritization?

- A wide range of tools
- Most efficient and effective, when done as a portfolio rather than on a project-by-project basis
  - Incents better resource stewardship
  - Allows richer strategic trade-offs analyses

Probability of Success (%) vs. Cost vs. NPV

Development costs (x$10M)
(Bubble area is proportional to NPV)
A commercial-sector model for prioritization: *Portfolio management*

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Metrics</th>
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<tbody>
<tr>
<td><strong>POS</strong> (risk)</td>
<td>Probability of technical &amp; regulatory success (PTRS)</td>
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<tr>
<td></td>
<td>Commercialization risk</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>Development costs</td>
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</tr>
<tr>
<td></td>
<td>“Strategic value”</td>
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</tbody>
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- **Probability of success (POS)** (Bubble area is proportional to NPV)
- **Cost**
- **Value**

Portfolio management

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## Adaptation of portfolio management model for prioritization

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<tr>
<td>POS</td>
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<tr>
<td></td>
<td>Financing and country-level uptake</td>
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<tr>
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<tr>
<td></td>
<td>Implementation, including cost of goods sold (COGs)</td>
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<tr>
<td>Value</td>
<td>Public health impact (metric?)</td>
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<tr>
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<td>“Strategic value”</td>
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**Saving lives & preventing disease**

**Public health impact:** Cases or deaths averted

**Control & elimination**

**Strategic value:** Metric???
A commercial-sector model for prioritization: *Portfolio management*

**Inputs**
- Probability of Technical & Regulatory Success (PTRS)
- Commercialization Risk
- Development costs

**Costs**
- Commercialization, including cost of goods sold (COGs)

**Value**
- Net Present Value (Discounted Cash Flow)
  - “Strategic Value”

**Highly sensitive to assumptions**
- **Assumptions** = Risk + Uncertainty

*Bubble Area is proportional to NPV*
Probability of technical & regulatory success (PTRS)
Sources and management of uncertainty and risk in vaccine development (PTRS + commercial opportunity)

### Sources of uncertainty and risk in vaccine development

<table>
<thead>
<tr>
<th>Biological</th>
<th>Technical (R&amp;D)</th>
<th>Commercial</th>
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<tbody>
<tr>
<td>Immunity</td>
<td>Safety/ Tolerability</td>
<td>CMC</td>
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<tr>
<td>Pathogen</td>
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<tr>
<td>Vaccine</td>
<td>Uncertainty</td>
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- = Mainly uncertainty
- = Mainly risk
- = Both uncertainty and risk

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### Malaria vaccines

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Sources and management of uncertainty and risk in vaccine development (PTRS)

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Prioritizing through defining/managing uncertainty
Prioritizing through defining/managing uncertainty: controlled human malaria infections

- In human volunteer

- Challenge

- Liver (pre-erythrocytic) stage
  - Blood (erythrocytic) stage
  - Thick blood smear

- Infected mosquitoes
  - Aseptic sporozoites
  - Blood-stage parasites

- Time after challenge
  - Control
  - Vaccine 1
  - Vaccine 2

Experimental medicine
Translational research

Challenge model(s)

Product development
Translational development

Challenge model(s)

Phase 1
Translational research → product development
learn-confirm* (+ apply) paradigm

*Sheiner, 1997

Translational research

Experimental medicine

Translational research

Challenge model(s)

Translational development

Phase 1

Late-stage development

Phase 2

Phase 3

Post approval

File

Phase 4/5

Learn*

Confirm*

Apply

Product development
Summary

- There is an ongoing need to prioritize the global malaria vaccine pipeline.

- Updating the Malaria Vaccine Technology Roadmap (T-2013) serves to maintain a shared Vision, Strategic Goals, and Landmarks for development of malaria vaccines.

- A portfolio management approach is likely the most efficient and effective way to deploy limited resources.

- Leveraging the Controlled Human Malaria Infection models in Translational Research and Translational Development in a Learn-Confirm-Apply paradigm enables defining and managing the uncertainty in the high-risk endeavor of developing malaria vaccines.
Thank you

For more information:
www.malariaavaccine.org
www.path.org