Novel Combination Vaccines for Endemic Pathogens for Children Under 5 Years of Age

PDVAC, 6 October 2025

Mateusz Hasso-Agopsowicz, WHO

The authors include staff members of the World Health Organization. The authors alone are responsible for the views expressed in these materials and they do not necessarily represent the decisions, policy or views of the World Health Organization. The mention of specific manufacturers and vaccine products in this analysis is for explanatory purposes only and does not imply any endorsement or recommendation by the World Health Organization. All information presented is based on publicly available sources, unless otherwise indicated.

PATH

World Health Organization

Session Goal and Agenda

Goal: To obtain PDVACs guidance on the analysis, prioritization and value assessment for novel combination vaccines

Agenda:

1. Combination vaccine challenges and recommendations from PDVAC, Bill Hausdorff (PATH), 5 min
2. A framework to identify and analyse and prioritise combination vaccines, Mateusz Hasso-Agopsowicz (WHO), 25 min
3. A case study: Shigella vaccine combinations, Bill Hausdorff (PATH), 5 min
4. A case study: a hookworm and malaria combination,

    Rationale for hookworm malaria combination, Peter Jay Hotez and Maria Elena Bottazzi, 10 min

    Stakeholder preferences study, Bill Hausdorff, 5 min

4. Discussion, 40 min

Questions for discussion

1. Framework: Do you consider the proposed framework appropriate for identifying novel combination vaccines?

2. Results: How can we best structure future engagements with NITAGs and RITAGs to advance the prioritization of the 27 combinations?

3. Case studies:

3.1. Do you agree with how we are addressing the age for vaccination against Shigella and its impact on Shigella-containing combinations?

3.2. What would be your advice to vaccine manufacturers or funders investing in combination vaccines that are not being evaluated within our framework?

Combination vaccine challenges and recommendations from PDVAC

Bill Hausdorff, PATH

Combination vaccine challenges: they could help broaden and strengthen immunization programs, but few are in development

Challenges

The potential for new vaccines to address major public health challenges, including AMR, **has never been greater.**

But immunization schedules are already **saturated** with multiple vaccines often administered at the same visit.

Potential solutions

Combination vaccines could **simplify immunization schedules, increase coverage**, allow **introduction of new vaccines, and enhance efficiency** of immunization programs.

However – they will likely **cost more**.

Opportunities

REGULATORY: Evaluate simplifying licensure pathways, focusing on the benefit/risk of a combination as a whole

POLICY: **Articulate public health impact** of combinations relative to stand-alone components

ECONOMIC: Assess full health impact and economic value of combinations

COMMERCIAL: **De-risk investment** by providing clarity on priorities, approval and policy pathways

Build on the successful experience with DTP-Hib-HepB-(IPV) and MR combinations

Advisory Group reflections about the project

TAG on Combination Vaccines

- **Credible and compelling** project
- Consider highlighting some combinations that are not priorities
- Understand **end-user feasibility**
- Review priorities in a context of a dynamic environment
- Highlight the need **for immuno/ safety** studies
- Identify **low-hanging fruit** to assess value
- Noted challenges in identifying additional populations for combination prioritization

SAGE

- Combinations help countries deliver vaccines
- **Support for the framework** and value assessment
- **Important to engage NITAGs and RITAGs to further prioritize**

IVIR-AC

- New value drivers and possibly metrics are needed to assess the value of combinations
- Consider risk of combinations
- Develop a **priority list of value metrics and drivers**
- **Engage with RITAGs, NITAGS and EPI** managers to inform implementation
- Suggested special issue in a journal

PDVAC recommendations from December 2024 meeting

Articulate priority problem statement and align on the type of vaccines:
"To identify and prioritize novel vaccine combinations for children under 5 that do not increase the number of injections"

Derive some 'rules' for inclusion of vaccines and candidates:
Essentially pair-wise combinations of 2 licensed vaccines, or 1 licensed plus a candidate in phase 2/3 in target population; endemic disease

Weight criteria and parameters; prioritize those with certainty, e.g,, target ages; existing recommendations
Done

Public health and socio-economic benefit should be well characterized and compelling to drive demand
Comprises current, final stage of prioritization framework analysis: public health and market opportunity

Engage with manufacturers and policy makers at country and regional levels
Iterative process involving various virtual consultations for key feedback, including with all RITAGs

Develop template of parameters and populated data, that developers could use to inform investment decisions
Developed checklist of consensus benefits, value drivers & metrics analysts should consider when evaluating combinations

Address regulatory considerations
Next slide

PATH/WHO Regulatory Convening on Combination Vaccines

One day in-person meeting in Rio de Janeiro, March 2025 with ~40 regulators, vaccine developers, plus representatives from funding and policy agencies

Goal: *Identify innovative clinical regulatory pathways to facilitate combination vaccine licensure without lowering safety or efficacy "bar".*

Clinical Trial Design Elements
Greater acceptance of Controlled Human Infection Models (CHIM)
Possibility of using clinical disease (syndromic) endpoint as primary objective of pivotal study

Clinical Trial Parameters
Flexibility in required threshold of vaccine efficacy (VE)
Flexibility in acceptable lower limit of 95% CI for VE point estimate
Flexibility in acceptable non-inferiority margins used as basis for comparisons between vaccines
Using multiple immunological endpoints to establish non-inferiority

Clinical study elements and design should help evaluate benefit-risk of the combination as a whole, and NOT solely focus on the individual components

Regulators open to scientifically well-grounded proposals

Manuscript submitted
Preprint: https://verixiv.org/articles/2-309/v1

A framework to identify, analyse, and prioritise combination vaccines

Mateusz Hasso-Agopsowicz

Project goal

2025	2026

Identify and prioritize novel vaccine combinations for children under 5 that do not increase the number of injections

Goal

To develop a combination vaccine priority-setting framework that identifies **novel vaccine combinations** likely to be:

- Programmatically compatible
- Technically feasible
- Impactful in the long term

To inform

2-5 years	5-10 years	beyond

Vaccine developers

Regulators and policy makers

Country decision makers

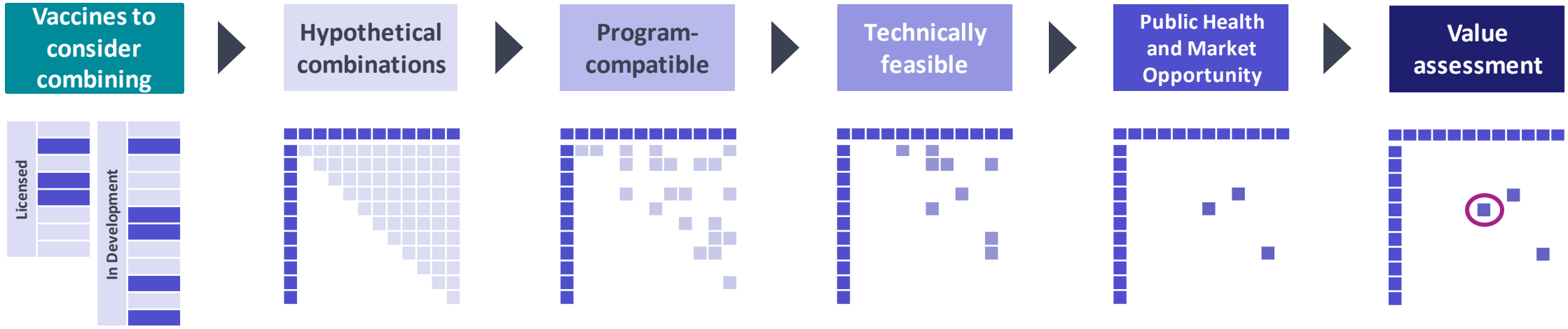
Combination vaccine R&D

Clinical trials to ensure safety and efficacy

Regulatory and policy considerations for use and introduction

Market shaping to enable access to novel combination vaccines and sustain access to essential standalone vaccines

Staged approach to prioritize combinations



1. Identify vaccines to consider combining and apply entry criteria to focus on the most relevant vaccines

2. Combine vaccines pairwise for analysis

3. Identify programmatically compatible combinations

4. Identify technically feasible combinations

5. Identify the combinations with greatest potential impact and sustainability

6. Health economics value assessment and priorities

Question to PDVAC: Do you consider the proposed framework appropriate for identifying novel combination vaccines?

Steps 1 and 2: Scope and Hypothetical combinations

1. Scope

Include	Exclude
• Licensed for children under 5 *OR* • **Vaccines in development for which Phase 2+ trials that include children under 5 have been started** *AND* which are: • For routine use • For endemic diseases	• Post-exposure vaccines (e.g. rabies) • Relevant **only** to High-income countries • Where higher-order combinations that are more relevant to low- and middle-income countries are already licensed • Example: because we are including Hexa, exclude Penta and IPV

Future projects may consider other populations

2. Hypothetical combinations

For included vaccines:

1. Conduct pairwise analyses; each pair must include a licensed vaccine
2. Do not combine two vaccines delivered through different routes: oral, intranasal, and injectable vaccines

Steps 3 and 4: Programmatic compatibility and technical feasibility

3. Programmatic compatibility criteria

1. **Geography:** do both diseases occur in the same regions?
2. **Number and timing of doses:** are the schedules similar?
3. **Ages to protect:** can vaccination begin early enough to meet WHO recommendations?
4. **Programmatic effects:** does the combination create complications for delivery?

Use a scoring rubric to score compatibility as **Very high**, High, Medium, Low, or **Very low**

Combinations with Very high and High programmatic compatibility are being evaluated for technical feasibility

4. Technical feasibility criteria

1. **Vaccine platforms and manufacturing:** are there similarities? Do we anticipate manufacturing challenges?
2. **Adjuvants:** are they similar or compatible?
3. **Physical and biochemical properties:** are presentation and ingredients similar?
4. **Routes of administration:** can they be delivered by the same route?
5. **Stability and storage:** can they be stored under the same conditions?

Use a scoring rubric to score compatibility as **Very likely combinable within two years**, five years, or **Not likely combinable within five years**

Timeframes refer to when Phase 1 trials of the novel combinations could plausibly begin

Preliminary results: Programmatically compatible, technically feasible combinations (licensed + in development)

REDACTED

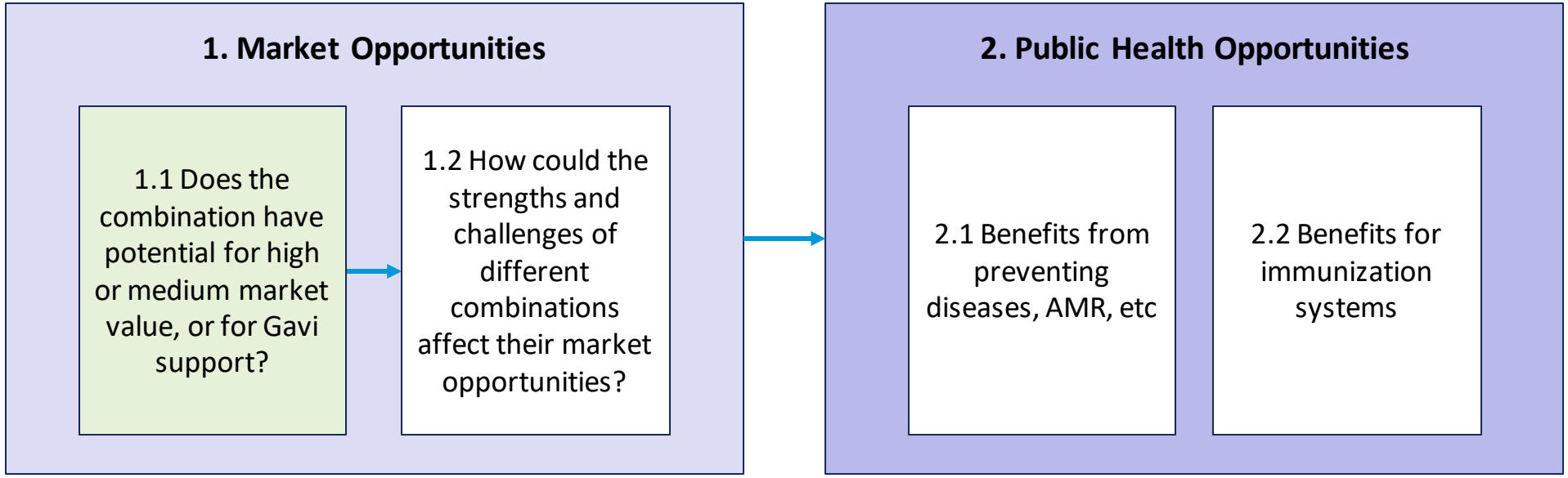
Analysis is in progress

Preliminary results: Programmatically compatible, technically feasible combinations (licensed + licensed)

REDACTED

Analysis is in progress

Step 5: Public health and market opportunities (in progress)



Analysis and results on next two slides

In progress: currently defining which factors to assess

Abbreviations: AMR – Antimicrobial resistance

Market potential

1.1 Does the combination have potential for high or medium market value, or for Gavi support?

Goal: to understand the market potential of the novel combination vaccines

Approach:

1. Consider the potential market value and potential for Gavi interest in individual vaccines, drawing on the 2024 MI4A Public Vaccine Purchase Dataset, current Gavi policies, and Gavi Vaccine Investment Strategy decisions
2. Score each combination according to this rubric:

Low Potential	Medium Potential		High Potential
Both vaccines have Low value and at least 1 is unlikely to receive Gavi support	Both vaccines have Low value and potential for Gavi support	At least 1 vaccine has Medium value	At least 1 vaccine has High value

3. Drop Low Potential combinations from further analysis

Market potential results: Emerging opportunities

REDACTED

Analysis is in progress

Emerging opportunities, cluster view

REDACTED

Analysis is in progress

Value analysis of combination vaccines

- The value of combination vaccines is not fully captured in health economic analyses;
- Project team reviewed literature to identify benefits and risks of combination vaccines and translated them into metrics;
- With input from stakeholders, metrics were categorized:

	High Feasibility	Low Feasibility
High resonance	***Strongly recommend*** • Coverage of focal vaccine • Changes in cases, hospitalizations...due to focal vaccine • Commodity costs	***Measurement or data innovation needed*** • Coverage of another vaccine/intervention • Changes in cases, hospitalizations...due to broader health system impacts of combination vaccine • Population views of immunization
Low resonance	***Optional*** • Household wages lost due to time spent ill or obtaining vaccines	***Low priority*** • Population views of health system

Engagement to identify priorities and inform R&D and manufacturing strategies

"**IVIR-AC** recommends continued engagement with **RITAGs, NITAGs, and EPI managers** to examine data availability to inform framework implementation and additionally communicate findings"

"**SAGE** highlighted the importance of **engaging with national and regional immunization technical advisory groups** to identify regional priorities for combination vaccines."

Engagement with country and regional stakeholders is a recurring theme.

For what purpose?

- To identify priorities out of the 27 shortlisted combinations
- To implement metrics and value drivers to evaluate combination vaccines
- To inform R&D and manufacturing regional priorities

How?

- Engagement with NITAGs at the Global NITAG Network meeting (Nov 2025)
- Pilot engagement with selected RITAGs
- Engagement with DCVMN and IFPMA

Question to PDVAC: How can we best structure future engagements with NITAGs and RITAGs to advance the prioritization of the 27 combinations?

Acknowledgments

Technical Advisory Group on Combination Vaccines

Ali Turab
Benjamin Lopman
Betzana Zambrano
Dagna Constenla
Deliana Permatasari
Frederick Were
Jane Soepardi
Jonathan Hare
Kawsar Talaat
Laura Cornelissen
Michelle Giles
Michelle Groome
Mina Adel
Nhamo Gonah
Paul Stéphane
Rakesh Aggarwal
Raman Rao
Robbert van der Most

Funders

BMGF

Other groups

RITAGs
SP7
IVIR-AC
IFPMA
DCVMN
Gavi
Wellcome

A case study: Shigella vaccine combinations

Bill Hausdorff

A case study: *Shigella* combinations

Challenge	Possible Approaches	Considerations	Way Forward
Current WHO PPC: primary series given by 12 months; first dose as early as 6 mo. Four *Shigella* candidates are currently being tested in 2-dose regimens beginning only at 6 or 9 months. Yet recent epi data and analyses suggest protection **by 6 months** could prevent the most severe outcomes. Will be reviewed by *Shigella* vaccine TAG	Using our programmatic criteria, we should adhere to current WHO PPC and/or schedules actually being evaluated. This would lead to: • A combination with TCV at 6 or 9 months, or YF at 9 or 12 mo However, based on recent data, one could imagine combinations with: • Malaria at 5, 6 and/or 7 mo • JE, Hexa, PCV, MenACWY or MenB at 6, 10, and 14 weeks **Do we stray from our methodology and "invent" infant *Shigella* vaccine schedules for the purpose of combinations?**	TCV and YF vaccines require only 1 shot. And TCV schedule is evolving. Some of these or infant combinations would be more regional than others	Based on Combo TAG discussion, team decided NOT establish an exception in order to "invent" new schedules for *Shigella* vaccines. Instead, we're planning to highlight this complexity in the discussion of our final analyses and within the manuscript.

Question to PDVAC: Do you agree with how we are addressing the age for vaccination against Shigella and its impact on Shigella-containing combinations?

A case study: Hookworm and malaria combination

Bill Hausdorff
Maria Elena Bottazzi
Peter Jay Hotez

Question to PDVAC: What would be your advice to vaccine manufacturers or funders investing in combination vaccines that are not being evaluated within our framework?

Case Study: Hookworm Malaria Combo Vaccine

Overview for PDVAC

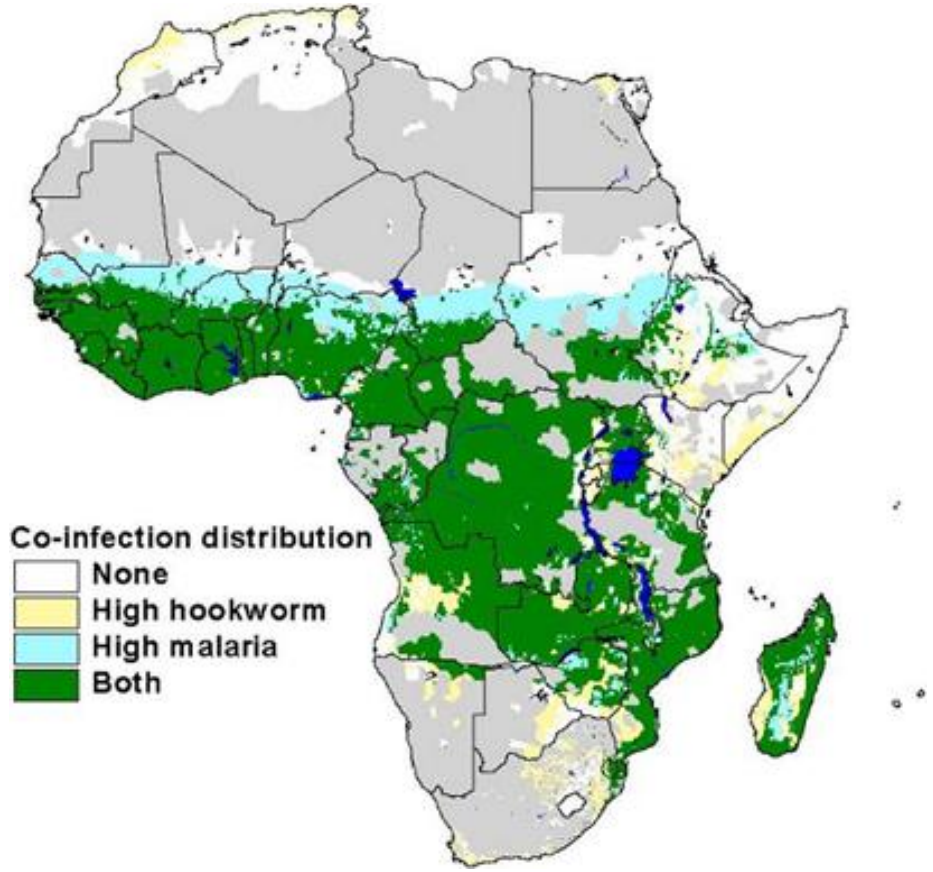
Maria Elena Bottazzi

Non-Confidential Summary

October 2025

Hookworm drives significant global disease burden, and together with malaria are leading causes of anemia

HOOKWORM DISEASE BURDEN & MALARIA CO-INFECTION



- Hookworms are widespread **soil-transmitted helminths** that can reside in the small intestine and feed on a host's blood
- Hookworm infections affect **~500 million people worldwide** and contribute to **>4 million disability-adjusted life-years (DALYs)** lost annually, especially in low-socioeconomic regions
- Hookworm and malaria are **leading causes of anemia** (~1.9B cases globally), posing serious risks to maternal and child health
- High degree of hookworm **co-infection with malaria, predominantly in sub-Saharan Africa**

Source: Loukas et al. (2016) *Nature Review Disease Primers;* Bartsch et al. (2016) *PLoS Negl Trop Dis;* Gardner et al. (2023) *The Lancet Haematology;* Hotez et al (2008) *PLoS Trop Dis*

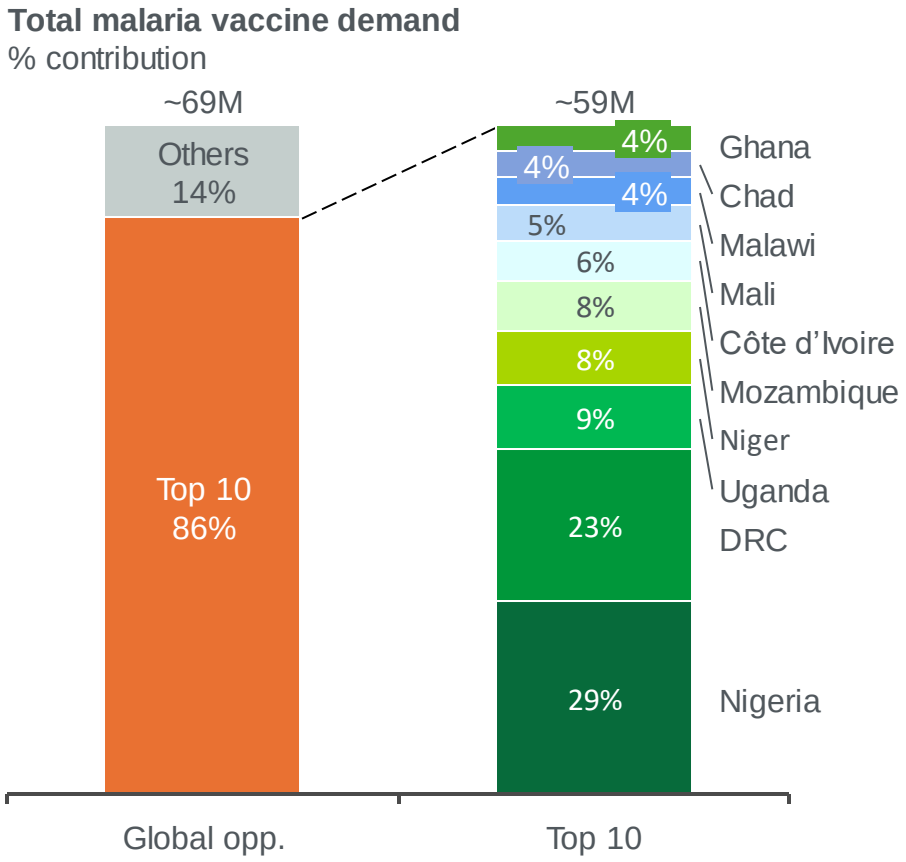
Combining hookworm with a malaria vaccine addresses co-endemicity and syndromic overlap, and represents a market opportunity for 20 countries in Africa

RATIONALE FOR COMBINING WITH MALARIA VACCINE

Combining hookworm and malaria vaccines is an attractive opportunity

- Malaria and hookworm have extensive **co-endemicity and syndromic overlap** (i.e., anemia), particularly in sub-Saharan Africa
- Opportunity to **align hookworm with malaria TPP**
- Malaria is on **WHO's list of priority endemic pathogens** where improved vaccines need to be further developed
- Developing a combination vaccine is more attractive commercially given **existing funding and public-private commitment to malaria R&D**

TOP COUNTRIES WITH HIGH CO-ENDEMICITY



Source: PATH demand forecast (April 2025); External KOL interviews

Our plan is to combine the recombinant protein *Na*-GST-1 vaccine against hookworm with a licensed malaria vaccine and align to the malaria TPP

KEY DEVELOPMENT ASSUMPTIONS

1

DIFFERENT ADJUVANT

- Combo development will require a switch from current hookworm vaccine adjuvant (alum/CpG) to one in a **licensed malaria adjuvant**

2

BRIDGE TO TARGET POPULATION

- Hookworm infection burden in highest in school age children (SAC); however, combo vaccine will be administered to infants (malaria target pop.)
- Hookworm efficacy signal will be easier to establish in SAC vs. infants given higher incidence rates

PROPOSED PLAN

- Establish efficacy of **standalone hookworm vaccine in SAC using a licensed malaria adjuvant**, and establish a **correlate of protection (CoP)**
- Use CoP from standalone hookworm trial to run a **bridging study for the combination vaccine in infants**, and aligned with the malaria schedule (4-dose series)

Additional preclinical and clinical studies needed with the stand-alone hookworm vaccine to support derisking of the combination vaccine approval pathway

Source: External KOL interviews; BCM External Advisory Board

Challenges to advance a stand-alone hookworm vaccine led to prioritization of a malaria combo, but combo development feasibility requires additional data and technical input

STAND-ALONE HOOKWORM VACCINE

Pros

- Ph 2 POC in CHIM model with significant protection with alum/CpG adjuvant
- Simple GMP manufacturing process (recombinant protein in yeast), tech transfer ready program
- Access to commercial scale alum and CpG adjuvant
- Shorter development timeline

Cons

- Lack of WHO policy prioritization or LMIC demand
- Infection burden highest in SAC – challenges with vaccination schedule timing/feasibility in population
- Bridge from pilot to commercial CpG adjuvant required; limited CpG safety data to age de-escalate to SAC in endemic populations

HOOKWORM/MALARIA COMBO VACCINE

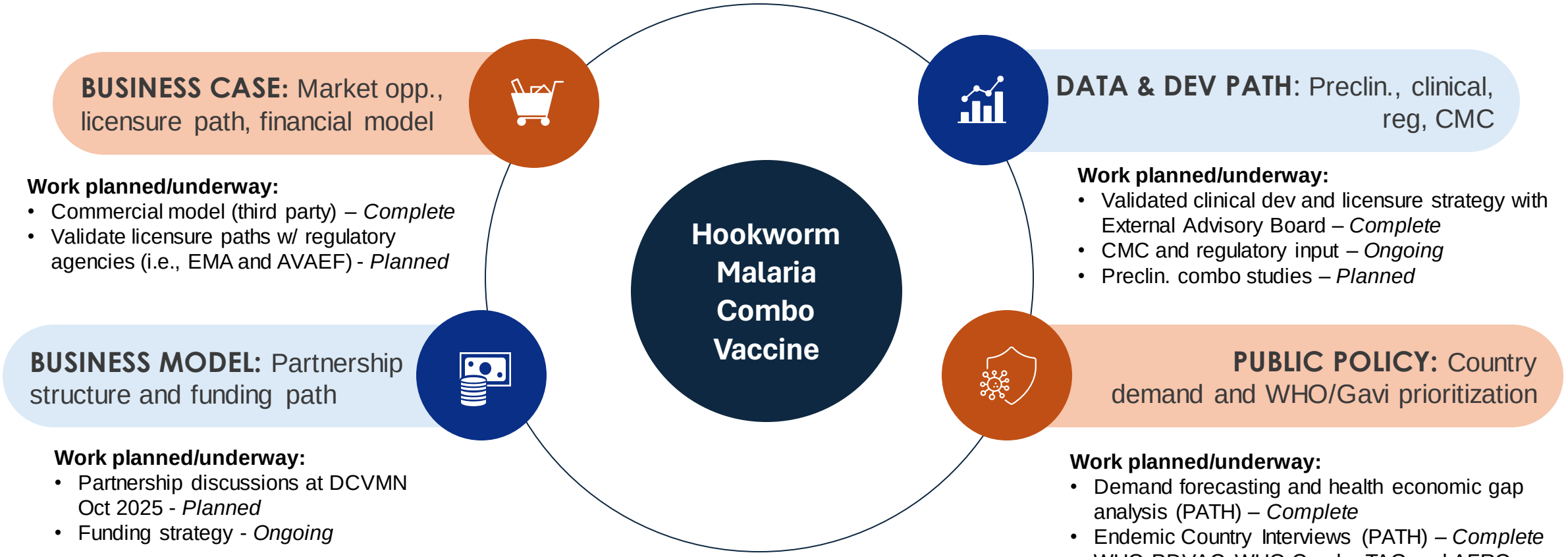
Pros

- Co-endemic populations in Africa - addressing leading causes of anemia
- Low COGs projected for the addition to commercial vaccines (additional ~$0.50/dose)
- Market opportunity/differentiator, LMIC demand and stronger policy prioritization
    - Meets most of WHO criteria for combo vaccine development

Cons

- Requires formulation switch to a licensed malaria adjuvant – necessitates restarting development and clinical studies
    - Don't yet have adjuvant access or supporting data
    - Potential target population mismatch (infants: malaria vs SAC: hookworm)
    - Need to demonstrate efficacy in SAC in stand-alone, before bridging to infants with the combo
- Longer development timeline

WHO technical input and guidance is needed to help a secure partnership with a malaria manufacturer to advance combo vaccine for licensure



BUSINESS CASE: Market opp., licensure path, financial model

Work planned/underway:
- Commercial model (third party) – *Complete*
- Validate licensure paths w/ regulatory agencies (i.e., EMA and AVAEF) - *Planned*

DATA & DEV PATH: Preclin., clinical, reg, CMC

Work planned/underway:
- Validated clinical dev and licensure strategy with External Advisory Board – *Complete*
- CMC and regulatory input – *Ongoing*
- Preclin. combo studies – *Planned*

BUSINESS MODEL: Partnership structure and funding path

Work planned/underway:
- Partnership discussions at DCVMN Oct 2025 - *Planned*
- Funding strategy - *Ongoing*

PUBLIC POLICY: Country demand and WHO/Gavi prioritization

Work planned/underway:
- Demand forecasting and health economic gap analysis (PATH) – *Complete*
- Endemic Country Interviews (PATH) – *Complete*
- WHO PDVAC, WHO Combo TAG and AFRO RITAG input – *Requested/planned*
- Combo health econ modeling - *Planned*

We seek PDVAC/WHO in-depth technical review and input on the combo vaccine strategy – Manufacturers and funders follow WHO leadership

Stakeholder preference study: hookworm/malaria vaccine

Study lead: Manjari Quintanar-Solares, MD, MPH (PATH)

Objective: Understand LMIC stakeholder perspectives on potential use case and target populations for a hookworm vaccine

Study design: Qualitative research (May – August 2025) utilizing in-depth interviews of 16 national level stakeholders in Ghana, DRC, Uganda, & Malawi

Stakeholder type (one per country)	No.
National EPI manager (MOH*)	4
NITAG member	4
National NTD manager (MOH)	4
Malaria vaccine implementation (MOH and non-profit)	4

Results:

- Only 38% (6/16) of stakeholders considered hookworm a serious public health problem; 63% (10/16) considered it a small or moderate problem
- After seeing potential vaccine profiles (next slide):
  - **The majority of stakeholders (10/16) considered a hookworm standalone vaccine to be fairly valuable, with 2 considering it highly valuable.**
  - **In contrast, almost all (13/16) thought a hookworm/malaria combination vaccine would be highly valuable.**

Hookworm vaccine profile considered for routine immunization

Attribute	Hookworm Standalone Vaccine Targets	Malaria Vaccine	Hookworm/Malaria Combination Vaccine Targets
Presentation	2 dose vial		
Route of administration	Intramuscular		
Dosing schedule	Total: 4 doses Dose 1–3: given at 4-week intervals (min) starting ~5 months. Dose 4: booster dose, given 6–18 months after dose 3		
Efficacy	30-75%* (both)		
Storage	2-8 °C		
Duration of protection	5 years (protection from moderate/severe infections)	Varies	5 years (hookworm target)
Price per dose	$1–$2 / dose (target)	$3.90 (R21) $10.42 (RTS,S)*	Additional $0.50–$1 per dose**

*On 6/25/25 Bharat Biotech announced it "will be reducing the price of RTS,S...by more than half, to less than $5 progressively by 2028."

Strong preference for a hookworm/malaria combination vaccine and principal benefits, per stakeholders

After considering the modeled data for hookworm anemia specific to their country…

Preference	n (N=16)
Strongly prefer a standalone	0
Prefer a standalone	0
Neutral	0
Prefer a combination	**2**
Strongly prefer a combination	**14**

Stakeholders' perceptions of the **principal benefits** of a hookworm/malaria combination vs. a hookworm standalone vaccine:

FINANCIAL

- Value for money
- Cost-savings (low add-on cost to existing malaria vaccine, no additional administration and waste management costs)
- Cost-effective when compared to hookworm standalone vaccine

PROGRAMMATIC

- Easy to integrate into existing malaria vaccination platform
- One less painful injection leading to greater acceptability by population, compared to a hookworm standalone vaccine
- Decreased missed vaccination opportunities (i.e., when caregivers reject multiple injections for child in same day)
- No impact on cold chain capacity
- Reduced vaccinator workload
- Hookworm protection even if caregiver only coming for malaria component

In addition...

Stakeholders considered that, to prioritize a hookworm vaccine, NITAGs would need

- local hookworm burden of disease data
- safety/efficacy data from phase 2/3 trials conducted in a similar African country,
- cost-effectiveness analyses that consider existing hookworm interventions.

Questions for discussion

1. Framework: Do you consider the proposed framework appropriate for identifying novel combination vaccines?

2. Results: How can we best structure future engagements with NITAGs and RITAGs to advance the prioritization of the 27 combinations?

3. Case studies:

3.1. Do you agree with how we are addressing the age for vaccination against Shigella and its impact on Shigella-containing combinations?

3.2. What would be your advice to vaccine manufacturers or funders investing in combination vaccines that are not being evaluated within our framework?