WHO Product Development Vaccine Advisory Committee, December 2024

Development of a Strategic Framework for Novel Combination Vaccines

Update on WHO/PATH/BMGF strategy/framework and plans

Bill Hausdorff, PhD
Lead, Public Health Value Propositions
and Meningococcal Vaccine Development

Center for Vaccine Introduction and Access,
Washington DC

Outline

- The need for combination vaccines
- The multiple barriers to combination vaccines: technical/scientific, policy, valuation, regulatory
- The Combination Vaccine Policy Framework Project
- Conclusions

The View from 10,000 Meters

Vaccines given to an increasingly wide range of target populations

have been successful in preventing an extraordinary number of diseases

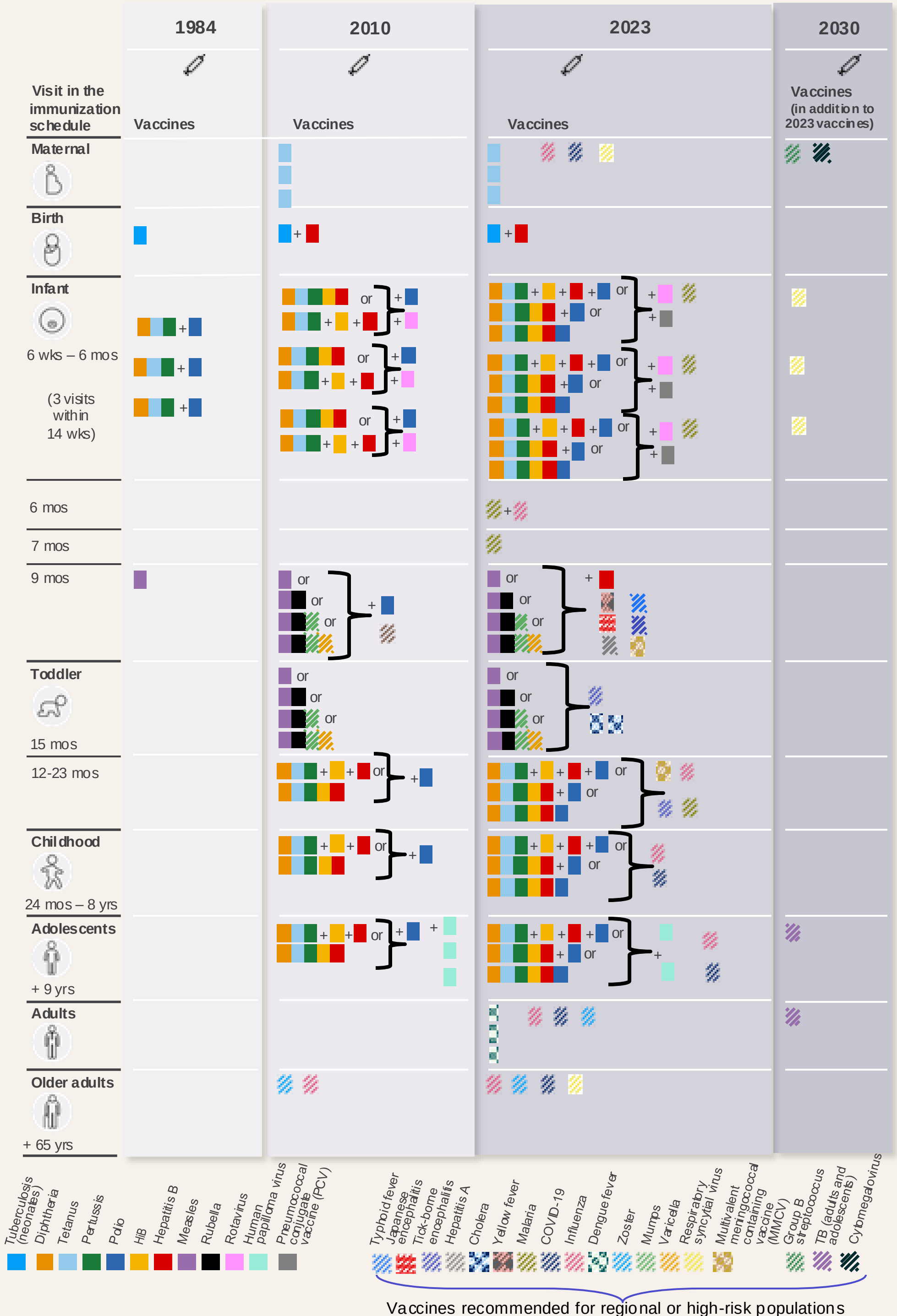
Figure 1. The increasing number of pathogens and diseases preventable by vaccination

	Maternal	Birth	Infants and toddlers	Childhood and adolescents	Adults and older adults
1984: 6 global diseases		• Tuberculosis	• Pertussis • Tetanus • Polio • Measles • Diphtheria		
2010: 11 global +5 regional diseases	• Tetanus	• Hepatitis B • Tuberculosis	• Diphtheria • Tetanus • Pertussis • Hepatitis B • Polio • Measles • Rubella • *H. influenzae* b • Rotavirus • Pneumococcus • Meningococcus • Mumps	• Diphtheria • Tetanus • Pertussis • Hepatitis B • Polio • *H. influenzae* b • HPV • Meningococcus	• Zoster (Shingles) • Yellow Fever • Varicella • Influenza • Meningococcus
2023: 12 global +16 regional diseases	• Tetanus • COVID-19 • Pertussis • Influenza • RSV	• Hepatitis B • TB	• Diphtheria • Tetanus • Pertussis • Hepatitis B • Polio • Measles • Rubella • *H. influenzae* b • Rotavirus • Pneumococcus • Mumps • Cholera • Tick Borne Enceph • Varicella • Hepatitis A • Jap. Encephalitis • Typhoid • Meningococcus • Yellow Fever • Malaria	• Diphtheria • Tetanus • Pertussis • Hepatitis B • *H. influenzae* b • HPV • COVID-19 • Influenza • Meningococcus	• Pneumococcal • Zoster (Shingles) • RSV • Dengue • COVID-19 • Influenza • Meningococcus
2030: Up to 30 diseases	• GBS • Tetanus • COVID-19 • Pertussis • RSV • Influenza • CMV	• Hepatitis B • TB	• Diphtheria • Tetanus • Pertussis • Hepatitis B • Polio • Measles • Rubella • *H. influenzae* b • Rotavirus • Pneumococcus • RSV • Mumps • Cholera • Tick Borne Enceph • Varicella • Hepatitis A • Jap. Encephalitis • Typhoid • Meningococcus • Yellow Fever • Malaria • Shigella	• Diphtheria • Tetanus • Pertussis • Hepatitis B • *H. influenzae* b • HPV • COVID-19 • Influenza • Meningococcus • Tuberculosis*	• Pneumococcal • Zoster (Shingles) • RSV • Dengue • COVID-19 • Influenza • Meningococcus • Tuberculosis*

Recommended schedule

Maternal
Birth
Infants and toddlers
Childhood and adolescents
Adults and older adults

Which means the immunization calendar is quite crowded



Translating into increasing…

- Numbers of separate administrations and injections at a single visit
- Logistical complexities of storing and delivering so many vaccines
- Costs
- Reduced acceptability

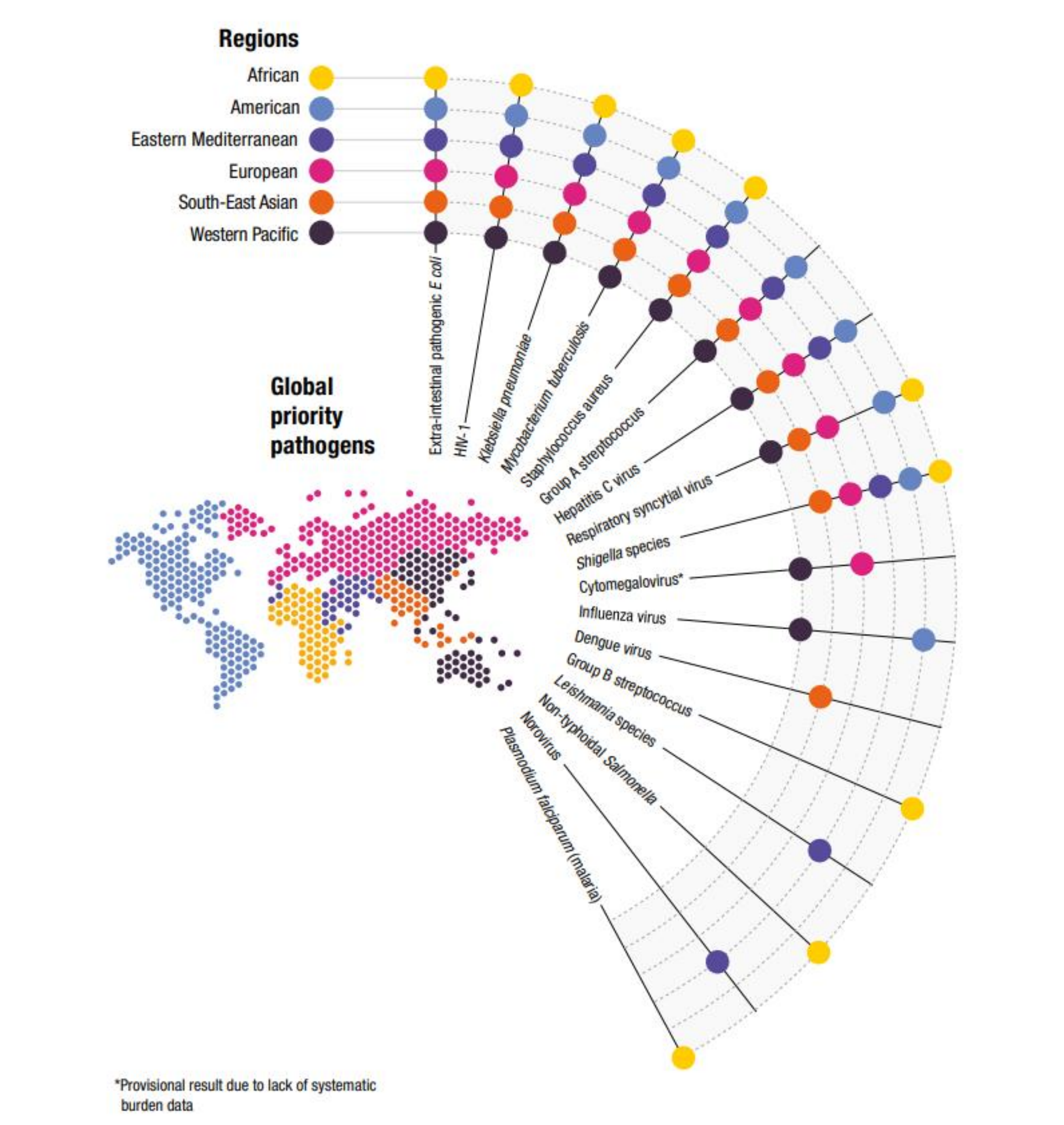
In addition, there are multiple competing priorities for new vaccine development (and introduction)

Identifying WHO global priority endemic pathogens for vaccine research and development (R&D) using multi-criteria decision analysis (MCDA): an objective of the Immunization Agenda 2030

Mateusz Hasso-Agopsowicz,[a,*] Angela Hwang,[b,c] Maria-Graciela Hollm-Delgado,[a] Isis Umbelino-Walker,[b] Ruth A. Karron,[d] Raman Rao,[e] Kwaku Poku Asante,[f] Meru Sheel,[g] Erin Sparrow,[a] and Birgitte Giersing[a]

oa

eBioMedicine 2024;■: 105424
Published Online XXX
https://doi.org/10.1016/j.ebiom.2024.105424



And yet many priority pathogens don't have robust vaccine candidate pipelines in clinical development

Vaccines in development for AMR priority pathogens

Number of candidates in phase 1, 2 and 3 studies

Vaccine Value Profiles, *Vaccines*
https://www.who.int/publications/i/item/9789240052451

Because vaccine developers suspect that standalone vaccines against most of these pathogens would not be prioritized for adoption and introduction by NITAGs and ministries of health

An obvious part of the solution: Combination Vaccines

	Potential Advantages
Vaccine Delivery	Improved timeliness of vaccination Greater acceptability Higher, more equitable vaccination coverage
Health impact	Greater, more equitable impact Facilitate targeting less prevalent but still important pathogens* Syndromic combinations
Vaccine Administration Efficiency and Cost	Fewer syringes Fewer packaging disposal needs Less cold chain storage/transportation space Shorter administration time & errors Fewer needlestick injuries
Vaccine Supply & Demand	Potentially greater demand for combination than individual components, leading to economies of scale and reduced cost of goods

Hausdorff et al Lancet Global Health 2024

*Based on recent qualitative research, *Shigella* and improved, parenteral rotavirus vaccine candidates are likely prominent examples; iNTS also?

The barriers to combination vaccine design and development

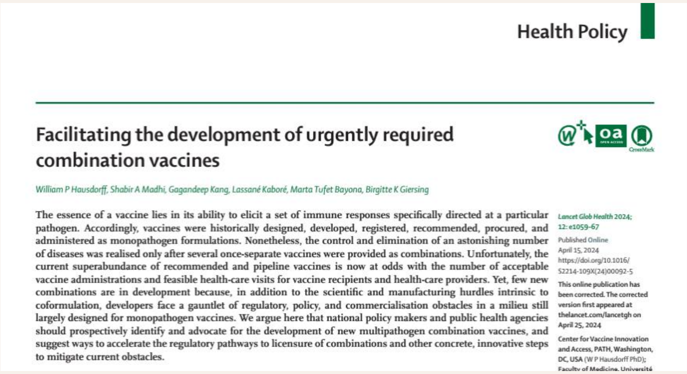
- **Greater risk of technical failure** due to physical incompatibility, immunological interference, unacceptable reactogenicity, and/or manufacturing complexity

- **Complex, lengthy and expensive clinical development and regulatory pathways**
  - Including need to develop and validate additional assays

- **Little policy guidance/recommendations from public health community** regarding combination priorities
  - In fact, combinations often not explicitly preferred to administration of multiple standalones
  - Not clear how to value, much less prioritize, combinations

Leading to uncertain demand and return on investment

And very few combination vaccines in development


Health Policy

Facilitating the development of urgently required combination vaccines

William P Hausdorff, Shabir A Madhi, Gagandeep Kang, Lassané Kaboré, Marta Tufet Bayona, Birgitte K Giersing

The essence of a vaccine lies in its ability to elicit a set of immune responses specifically directed at a particular pathogen. Accordingly, vaccines were historically designed, developed, registered, recommended, procured, and administered as monopathogen formulations. Nonetheless, the control and elimination of an astonishing number of diseases was realised only after several once-separate vaccines were provided as combinations. Unfortunately, the current superabundance of recommended and pipeline vaccines is now at odds with the number of acceptable vaccine administrations and feasible health-care visits for vaccine recipients and health-care providers. Yet, few new combinations are in development because, in addition to the scientific and manufacturing hurdles intrinsic to coformulation, developers face a gauntlet of regulatory, policy, and commercialisation obstacles in a milieu still largely designed for monopathogen vaccines. We argue here that national policy makers and public health agencies should prospectively identify and advocate for the development of new multipathogen combination vaccines, and suggest ways to accelerate the regulatory pathways to licensure of combinations and other concrete, innovative steps to mitigate current obstacles.

Lancet Glob Health 2024; 12: e1059-67
Published Online April 15, 2024
https://doi.org/10.1016/S2214-109X(24)00092-5
This online publication has been corrected. The corrected version first appeared at thelancet.com/lancetgh on April 25, 2024
Center for Vaccine Innovation and Access, PATH, Washington, DC, USA (W P Hausdorff PhD);
Faculty of Medicine, Université

Adapted from Hausdorff et al
Lancet Global Health 2024

The Policy Barriers

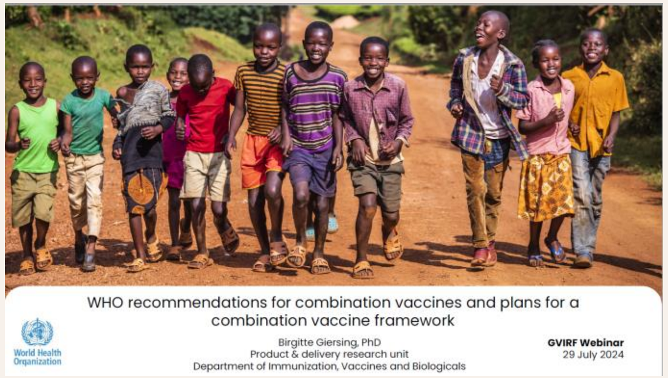
- There is a need for a robust and transparent dialogue and process for evaluation and prioritization of novel combination vaccine candidates

- It could serve as a platform for continued partnership with country and regional level stakeholders

- It could help RITAGs, WHO SAGE etc to come up with short lists of priority combinations that are based on country and regional programmatic priorities

- **Prioritization could guide, de-risk and encourage future vaccine development efforts and investments**

- WHO/IVB is working with PATH to elaborate this process, with 2-year support from BMGF



PATH

Some Considerations in Developing a Policy Framework on Combinations

- Not too abstract or high level: focus on real world examples
- Doable: not entire universe of vaccines and vaccine candidates
- Need to simultaneously develop a set of health impact and economic metrics relevant to LMIC settings to evaluate and help prioritize combination vaccines.

Development of Combo Vaccine Policy Framework

WHO and PATH staff, along with external consultants, **in collaboration with RITAGs**, will

1) Prioritize a short list of potential combination vaccines for further assessment

- Based on programmatic compatibility of potential components

2) Further refine based on the technical feasibility and commercial aspects of possible combinations

3) Assess selected combination vaccine candidates

- Using evaluation metrics specifically devised and chosen for relevance to combinations

---

Goal: provide the tools to allow immunization advisory committees (RITAGs, WHO SAGE, NITAGs) to prioritize potential vaccine combinations

- Technical advice to be provided by a *Combination Vaccine Technical Advisory Group* that includes NITAG, RITAG, IVIRAC and SAGE members

- With periodic WHO advisory committee and RITAG awareness and endorsement, if appropriate and feasible

WHO Advisory Group on Combination vaccines

- To **advise** WHO on the **scientific, technical, and strategic aspects of combination vaccines**, focusing on their potential public health impact, technical feasibility, and alignment with global immunization priorities.

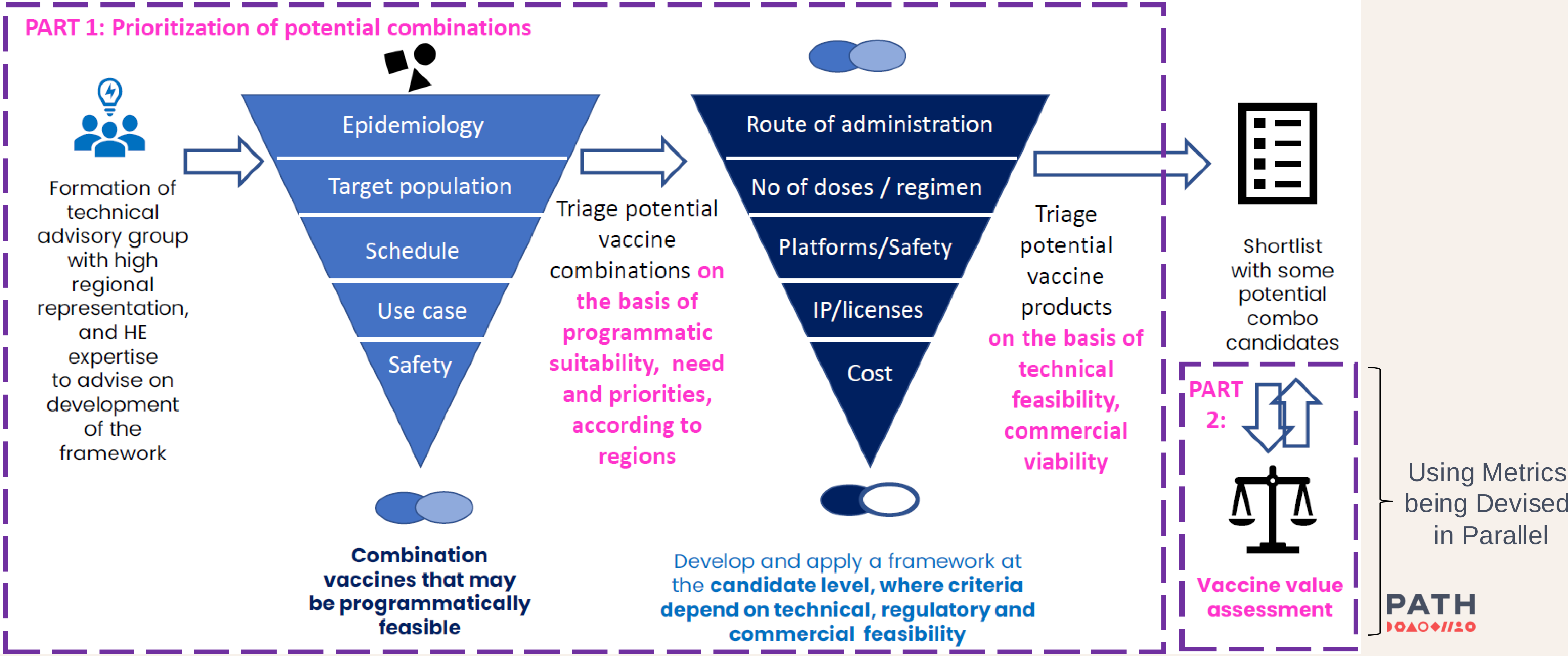
- To **advise** WHO on the **development of a framework for evaluating and identifying priority combination vaccines**, including the establishment of metrics and criteria for assessing their public health and economic value, particularly in LMICs.

- To **review** and **make recommendations** to WHO on the **programmatic and technical feasibility of specific vaccine combinations**, ensuring that the proposed combinations are viable from both a technical and regulatory perspective and can be integrated into existing immunization schedules.

- To **advise** WHO in **strengthening links with regional immunization stakeholders**, ensuring that regional input is integrated into the development of combination vaccines.

- To **support** WHO in **developing communication strategies** that highlight the importance and benefits of combination vaccines, helping to build consensus among policymakers, donors, and other stakeholders.

IVB's approach to developing guidance on combo vaccines in collaboration with PATH



Some Considerations in Developing a Policy Framework on Combinations

- Not too abstract or high level, focus on real world examples
- Doable: not entire universe of vaccines and vaccine candidates
- Need to simultaneously develop a set of health impact and economic metrics relevant to LMIC settings to evaluate and help prioritize combination vaccines.

PATH

How Best to Circumscribe the Universe of Potential Combination Vaccine Components to Consider?

Include:

a) Pediatric vaccines
b) Maternal vaccines
c) Vaccine component candidates in phase II+

Exclude

a) Vaccines against emerging diseases
b) Primarily adult or adolescent formulations
c) Vaccine component candidates in phase I, maybe early Phase II

PDVAC Comments?

PATH

How to Refine and Validate Assessments of Technical Feasibility

Analyses by and consultation with vaccine development and CMC experts,

- especially on platform compatibility, formulation issues, IP barriers, forbidding COGs

Assumption is that developers will talk to us

Will request feedback from IFPMA, DCVMN representatives

PATH

Some Considerations in Developing a Policy Framework on Combinations

- Not too abstract or high level, focus on real world examples
- Doable: not entire universe of vaccines and vaccine candidates
- Need to simultaneously develop a set of health impact and economic metrics relevant to LMIC settings to evaluate and help prioritize combination vaccines.

Some Potential Metrics of Combination Vaccine Value

- Value of improved immunization coverage and/or timing and/or more equitable impact
- Decreases in procurement, supply chain, delivery and administration costs, and/or health worker time and errors
- The synergistic impact on antimicrobial use and resistance of combining vaccines against pathogens causing same clinical syndrome
- Societal value of a combination that targets pathogen of moderate importance for which a standalone vaccine would generally not be considered viable (in terms of financing and uptake)
- Societal value of combining two or more pathogens currently delivered as separate vaccines to “make room” for introduction of another, high impact, vaccine
- End-user acceptability studies and comparative demand assessments

PATH

Development of Combo Vaccine Metrics and Application

- Establish Baseline understanding of how combination vaccines have been valued to date (lit review)
- Develop an extensive list of potential metrics
- Prioritize metrics based on perceived “added value,” *feasibility of quantifying value*, and resonance of metrics *in consultation with WHO TAG and with key stakeholders*.
- Develop two new models allowing quantitation of combination vaccine value using novel metrics
- Gather feedback from vaccine developers, international agencies, IVIRAC, national governments, donors, health economists and modelers of proposed high value metrics
- Apply findings to potential future vaccine combinations triaged in Framework

Conclusions

The current public health immunization paradigm is centered around vaccines targeting single pathogens

It needs to change if we want combinations

Other initiatives, such as on Regulatory Barriers to Combinations, would also benefit from focused efforts

- March 2025 convening

Key PATH and WHO personnel (to date):

Bill Hausdorff, Clint Pecenka, Fred Debellut (PATH)

Birgitte Giersing, Mateusz Hasso-Agopsowicz (WHO/IVB)

Many other collaborators, internal and external, en route…

Question to PDVAC

Does PDVAC support the high-level approach to develop a framework to identify priority combination vaccines?