"Immunization Agenda 2030" Towards a Vision and Strategy for Vaccines and Immunization for the Decade Ahead

2021-2030

IPAC June 2019

Immunization Agenda 2030

Developing together the vision and strategy for immunization - 2021-2030

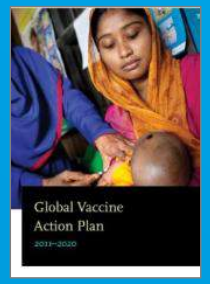
Immunization Agenda 2030

A Global Strategy To Leave No One Behind

Draft One for Co-creation by 5 August 2019

Immunizationagenda2030@who.int

Draft one for the vision and strategic framework will be shared for consultation on 1 July 2019



With GVAP coming to an end in 2020

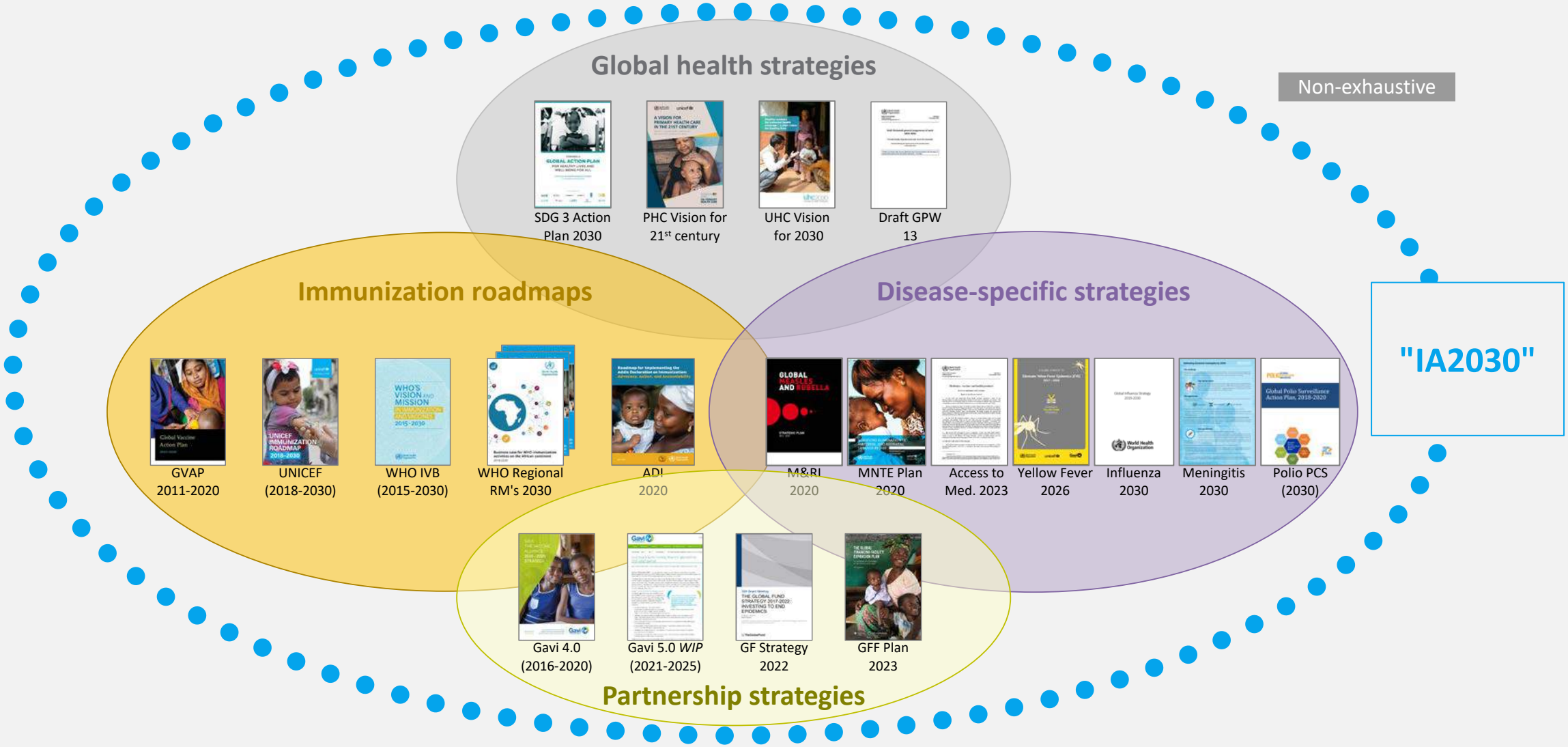
New vision and strategy for vaccines and immunization is needed

Set a new direction for the next decade that engages and aligns stakeholders – immunization and beyond – at all levels

Address emerging issues, and harness new solutions for impact

Re-iterate the importance of vaccinations in contributing to the broader health & development agendas

New vision and strategy will build on/ live within ecosystem of recent strategies, responding to changing context



Immunization linked to …

14 of 17 SDGs

… broad set of compelling arguments for value of vaccines

2021-2030 Innovation

1 Healthy children & families = INCREASED PROSPERITY

2 Immunization + nutrition = HEALTHIER FAMILIES

3 Immunization = HEALTHY LIVES & WELL-BEING

4 Vaccines support cognitive development through better health = IMPROVED LEARNING

5 Immunization = EMPOWERED WOMEN & GIRLS

6 Clean water, sanitation & hygiene (WASH) + vaccines = LESS DISEASE

7 Efficient supply chain equipment = CLEANER ENVIRONMENT

8 Healthy population = MORE PRODUCTIVE WORKFORCE

9 Healthy vaccine market = INNOVATION

10 Better health = INCREASED EQUALITY

11 Protected urban public health = HEALTHIER CITIES

13 Vaccines = MITIGATION OF CLIMATE CHANGE IMPACT

16 Strong health systems = LONG-TERM STABILITY

17 Innovative partnership = UNPRECEDENTED PROGRESS

Source: UN; Gavi analysis

… Bringing broad representation of organizations & geographies

Non-exhaustive

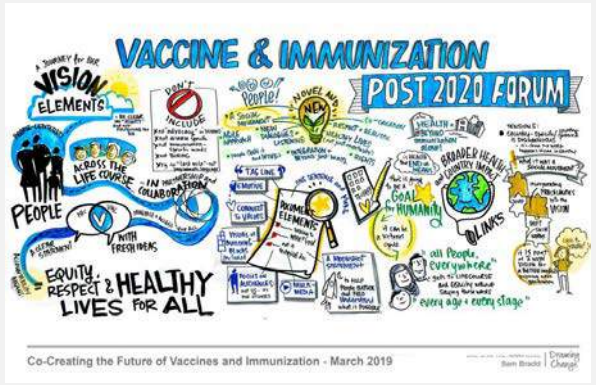
50+ organizations

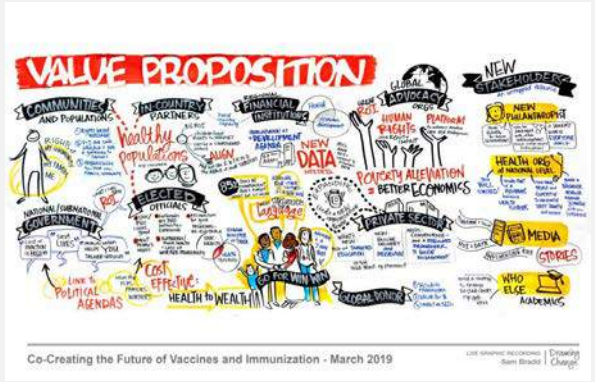
30+ countries across all regions

Survey of participants to Forum sent on Thursday 3/14/2019; n= 66 respondents as of Sunday 3/17/2019

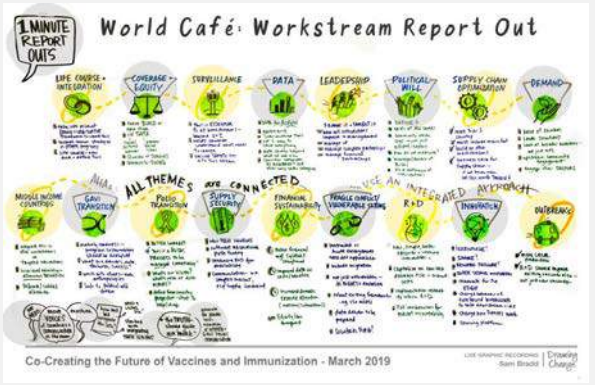
Participants created ideas and provided direction for all key components of "IA2030"

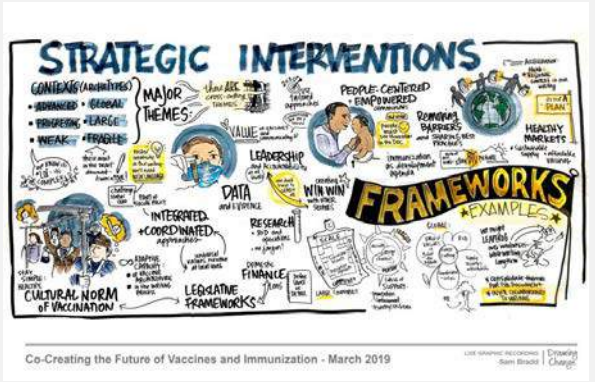
Vision



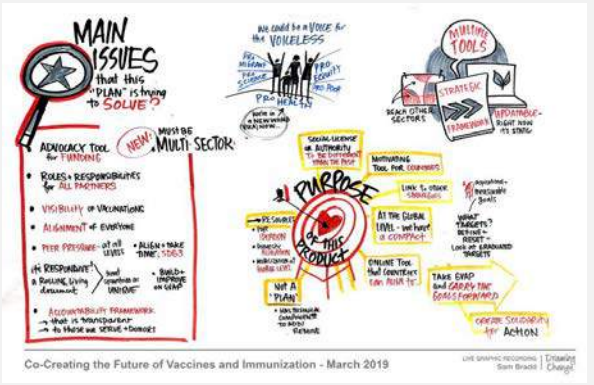


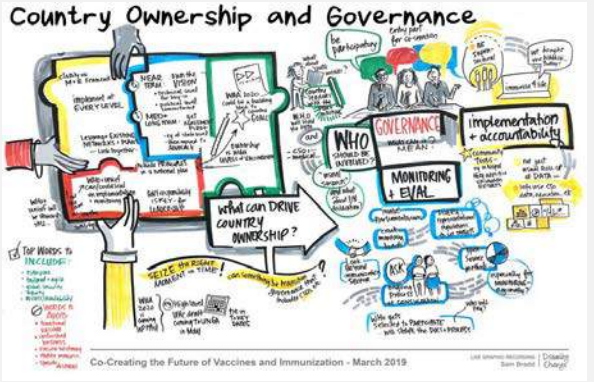
Strategic Priorities





Operationalization





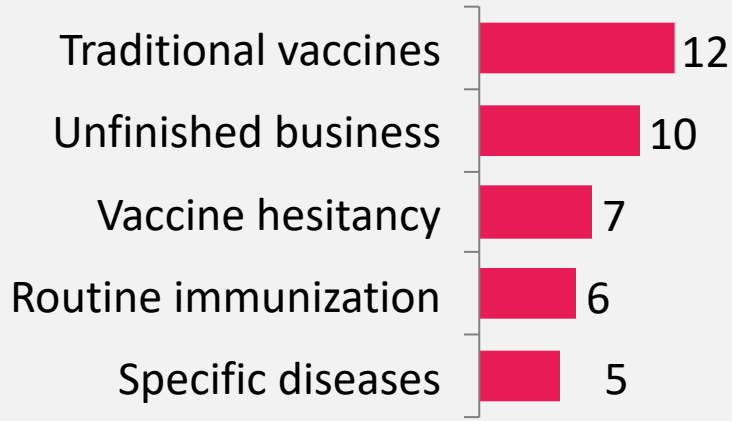
Draft 2030 Vision

A world where everyone, everywhere, fully benefits from vaccines to improve health and wellbeing

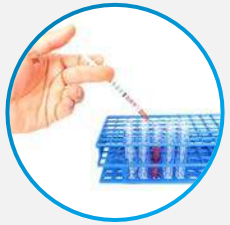
Feedback from co-creation forum

5 top concepts to include

5 'phrases' to avoid



"IA 2030" will be responsive to changes in global context…



Delivering vaccines along the life-course

Including gender-specific interventions to vaccination services

Addressing wide subnational variation in coverage

Responding to changing demographics

Implementing services during and following fragility & emergencies

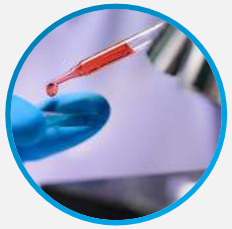
Responding to outbreaks and antimicrobial resistance

Ensuring access to vaccines, and optimal use of vaccines

Harnessing innovations to improve programme function and coverage

Responding to the decreasing awareness of the value of immunization

Addressing vaccine hesitancy and anti-vaccination activism

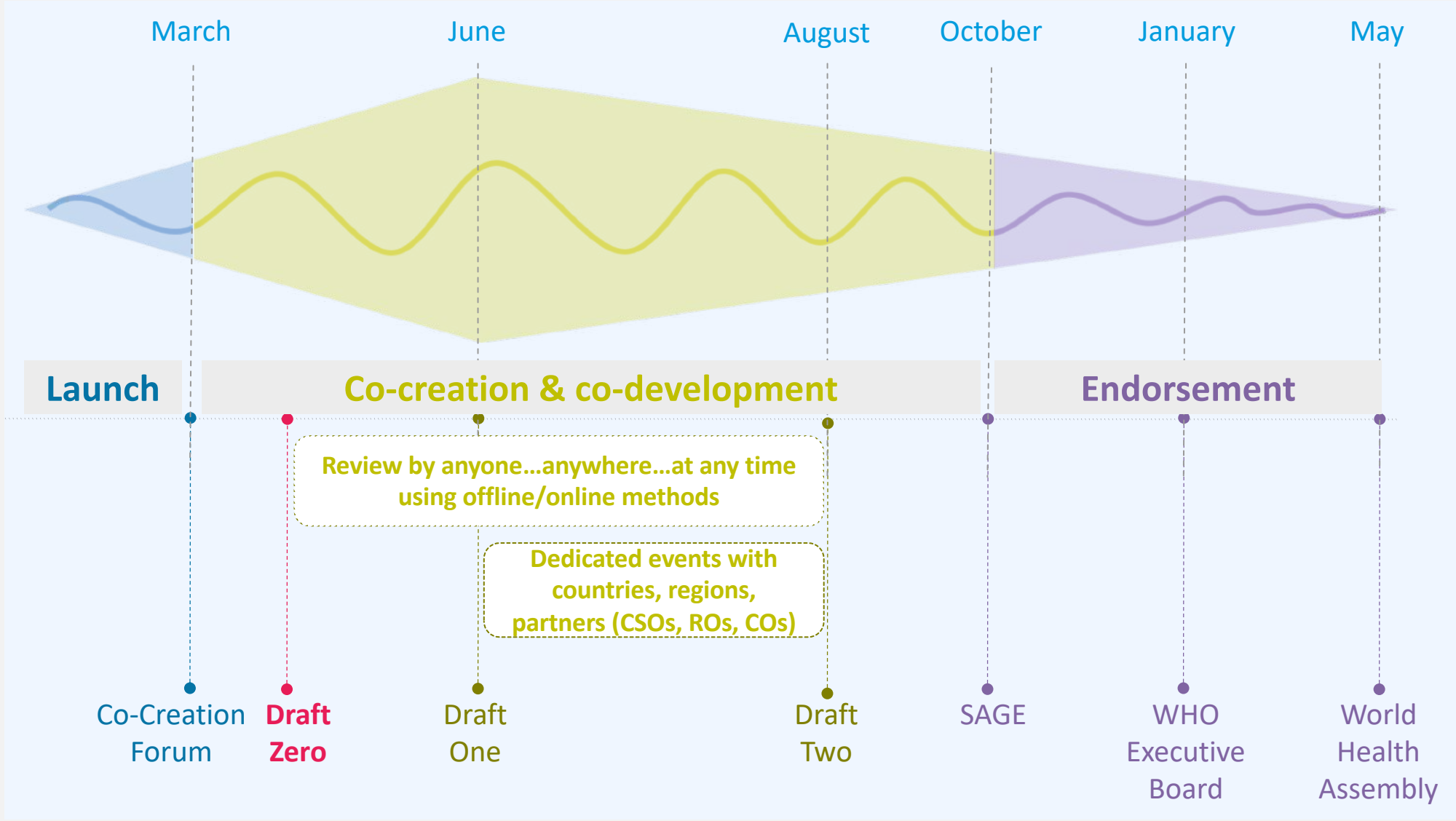


Ensuring global vaccine supplies meet national needs

Uncertain programmatic and financial self-sustainability

Source: Gavi (health systems photo)

The way towards WHA endorsement



"Immunization Agenda 2030" will include two components

Immunization Agenda 2030

IA2030 Online Resources

Living throughout 2021-2030

- Technical guidance
- Operational plans
- Disease specific documents

"Draft Zero"

Immunization Agenda 2030 Vision & Strategic framework

Vision (1-2 page document, for everybody)

- Vision 2030 and beyond – to inspire and rally
- Values & high-level strategic priorities

Strategic framework (15-20 page document, for immunization community & wider stakeholders)

- Strategic priorities, ways and means to guide development of global, regional, national strategies and plans

Documents to be endorsed at WHA 2020

IA2030 Online Resources

- Technical guidance documents "living" throughout 2021-30
- Existing or new global, regional, country plans & goals (e.g., regional strategies)
- Existing or new disease- and topic-specific technical guidance and best-practice documents (e.g., Measles strategy)

"Living" throughout the decade

Draft Title

"Immunization Agenda 2030"

Draft Vision statement

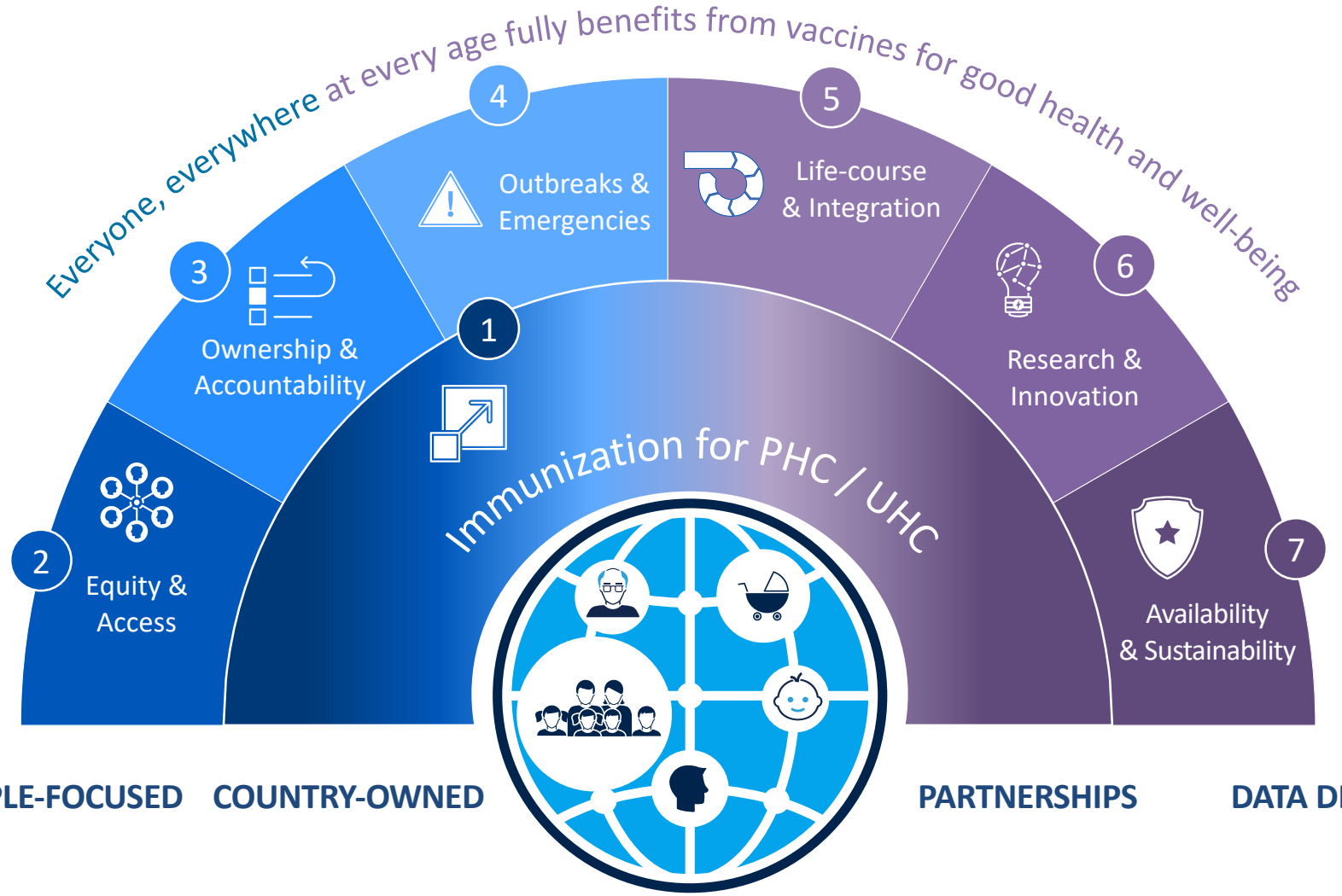
A world where everyone, everywhere, fully benefits from vaccines to improve health and wellbeing

What do you think about title and vision?
Any alternative suggestions?

UPDATED

For reference: Latest visual for strategic framework

Fig. 6 – The seven strategic priorities for 2021-2030.



Adaptive Ways & Means will guide implementation

Country-driven: Placing countries at the center

All efforts – at local, regional or international levels – adopt tailored approaches to strengthen country vaccination programmes that are shaped by local contexts and supported by communities.

Broad partnerships: Building on existing and new alliances

Maximizing coordination and collaboration for collective results, and expanding partnerships to include a wider range of CSOs, the private sector and other sectors beyond immunization.

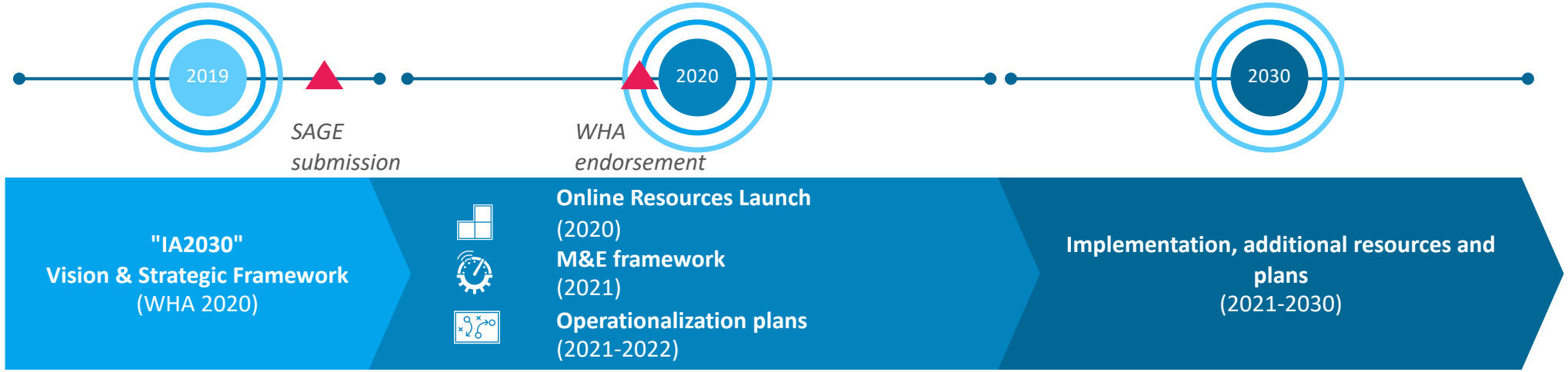
People-focused: Placing people at the heart of vaccination

The design, management, implementation and delivery of vaccination services are shaped by and responsive to the dynamic needs of people and families.

Data driven: Using data, evidence, and enhanced monitoring & evaluation

Emphasizing the use of subnational data to guide programme interventions; generating evidence from implementation research, delivery science, and social and behavioural research; and tracking progress with enhanced monitoring and evaluation.

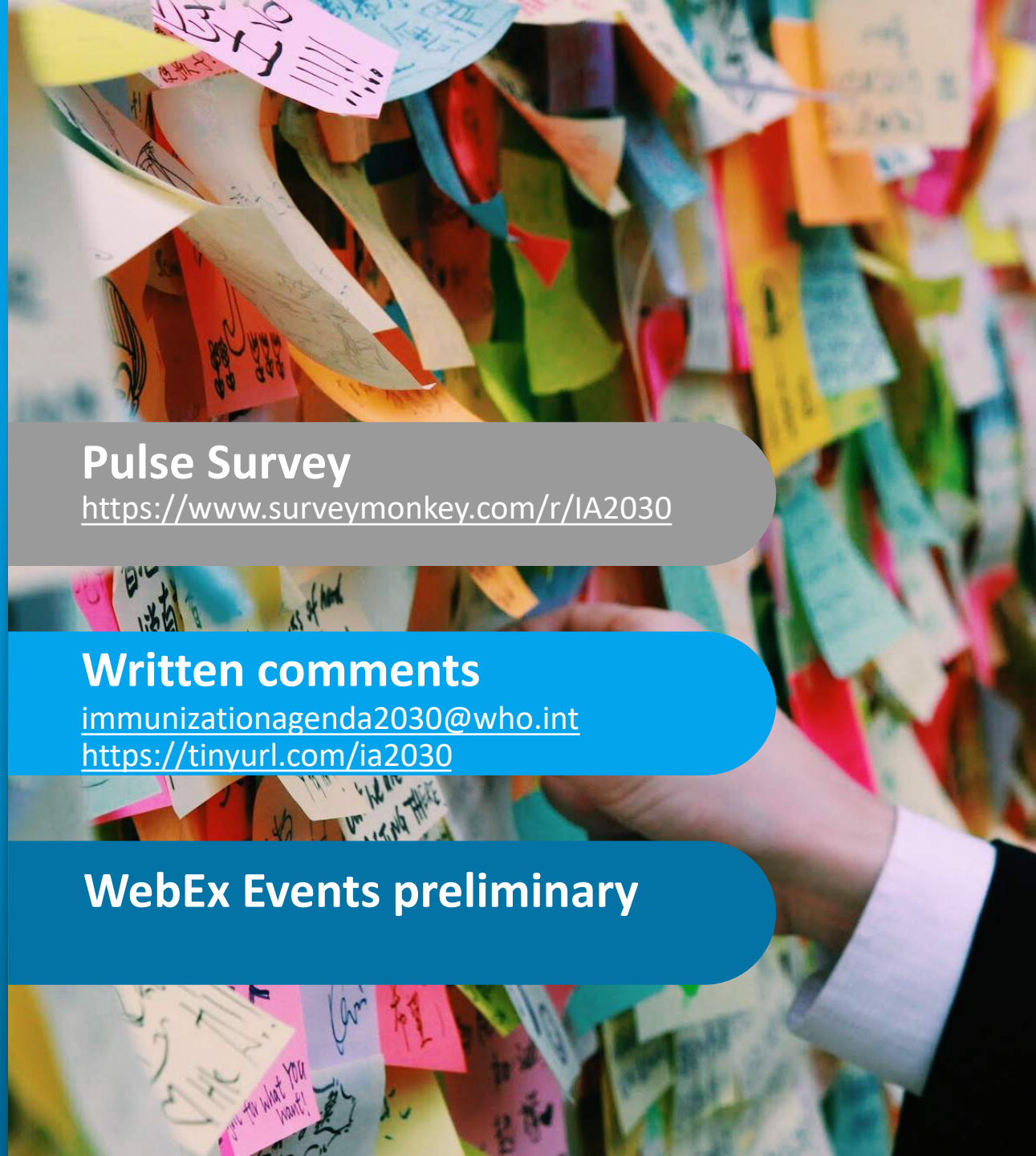
The strategic framework will be implemented through actions at global, regional and country levels



Level			
Global	• Develop global strategy, focusing on alignment among global development agencies, support for regional and country activities, and strategic priorities with a strong global element	• Develop monitoring and evaluation frameworks	
Regional		• Develop regional plans, to operationalize "IA2030" • Support the development of national vaccine action plans.	• Provide support according to the maturity status of national immunization programmes • Coordinate partner support at a national level • Develop regional resources and structures to advance the immunization agenda
Country			• Develop and implement integrated national vaccination action plans • Provide a roadmap with milestones towards achieving "IA2030" vision

Feedback on Draft One from 1 July

1. How well do you think this document succeeds in **providing a new vision and strategic framework** for maximizing the benefits of immunization for all?
2. Are the **6 strategic priorities** the right areas of focus?
3. Are any critical **barriers and obstacles** insufficiently addressed?
4. What are your main **recommendations** for improvement?
5. How could we make it optimally **relevant for countries and communities**?



Pulse Survey
https://www.surveymonkey.com/r/IA2030

Written comments
immunizationagenda2030@who.int
https://tinyurl.com/ia2030

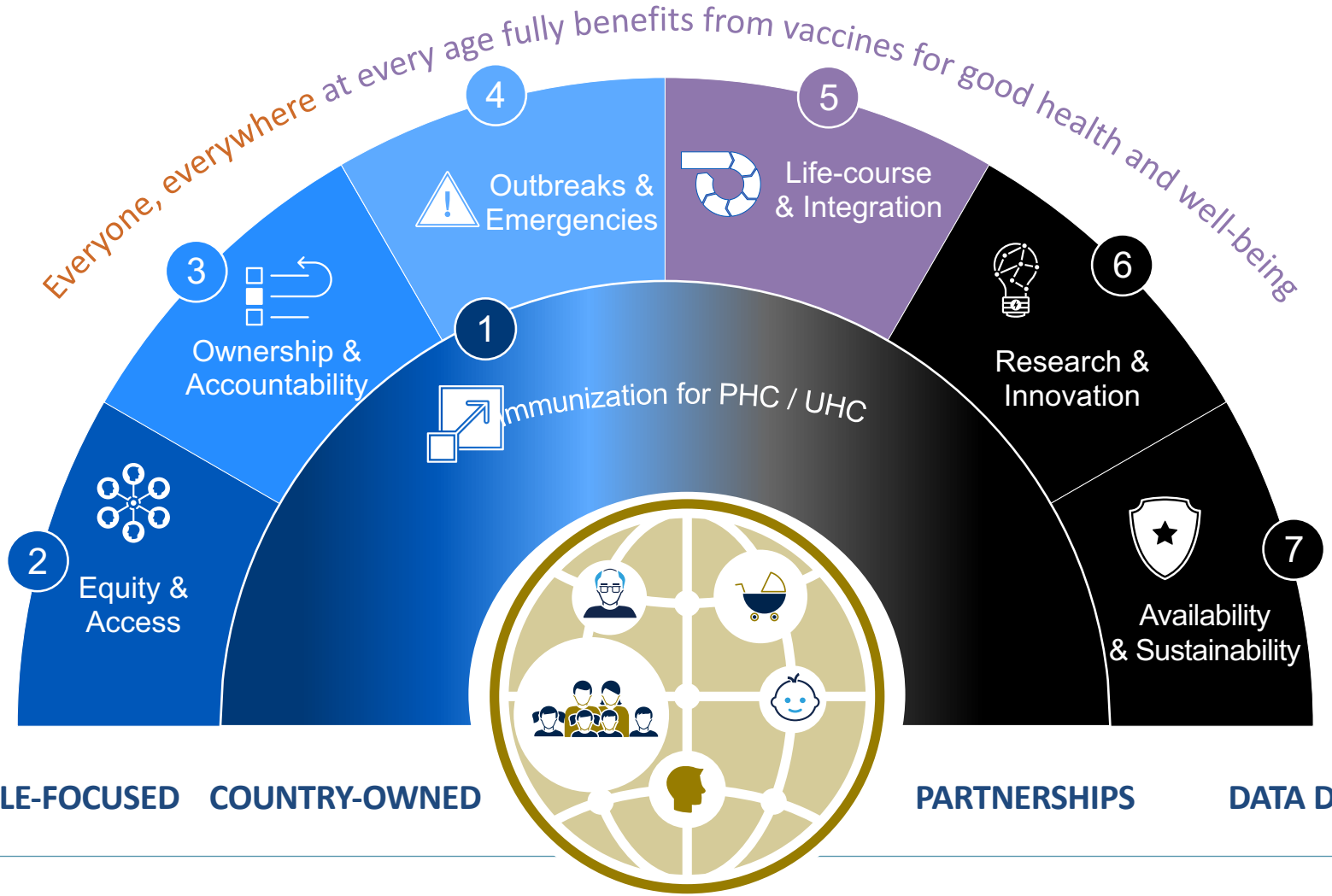
WebEx Events preliminary

Thank you

IMMUNIZATION AGENDA 2030 FRAMEWORK

FIG. 6 – THE SEVEN STRATEGIC PRIORITIES FOR 2021-2030.

Aligned with Draft One

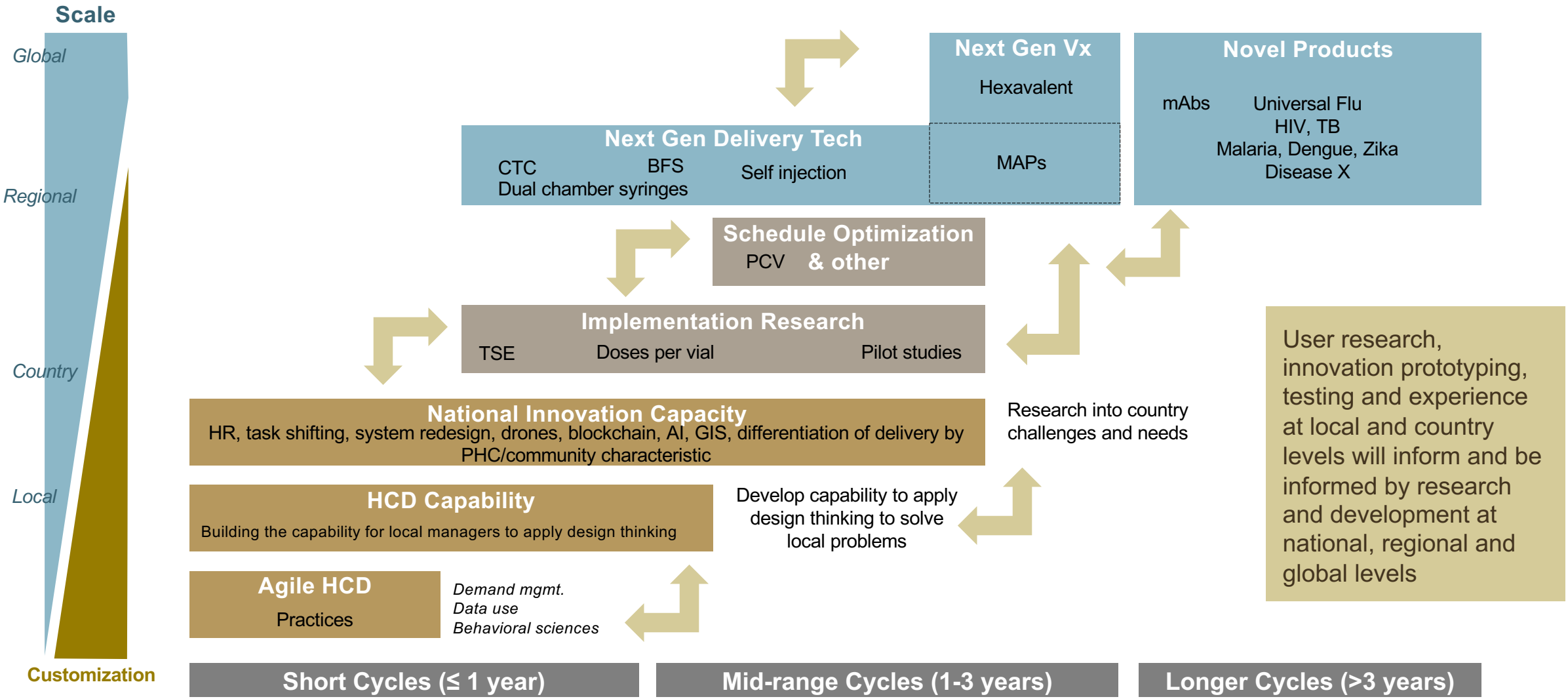


SP6 CHALLENGES

- Creating a collaborative work space
- Getting country engagement
- Differences in R&D and downstream innovation
- RCT versus rapid test fail, and learn cycles
- Top down versus bottom up innovation
- Cross SP consultation – innovation is a cross cutting issue

INNOVATION SPACE

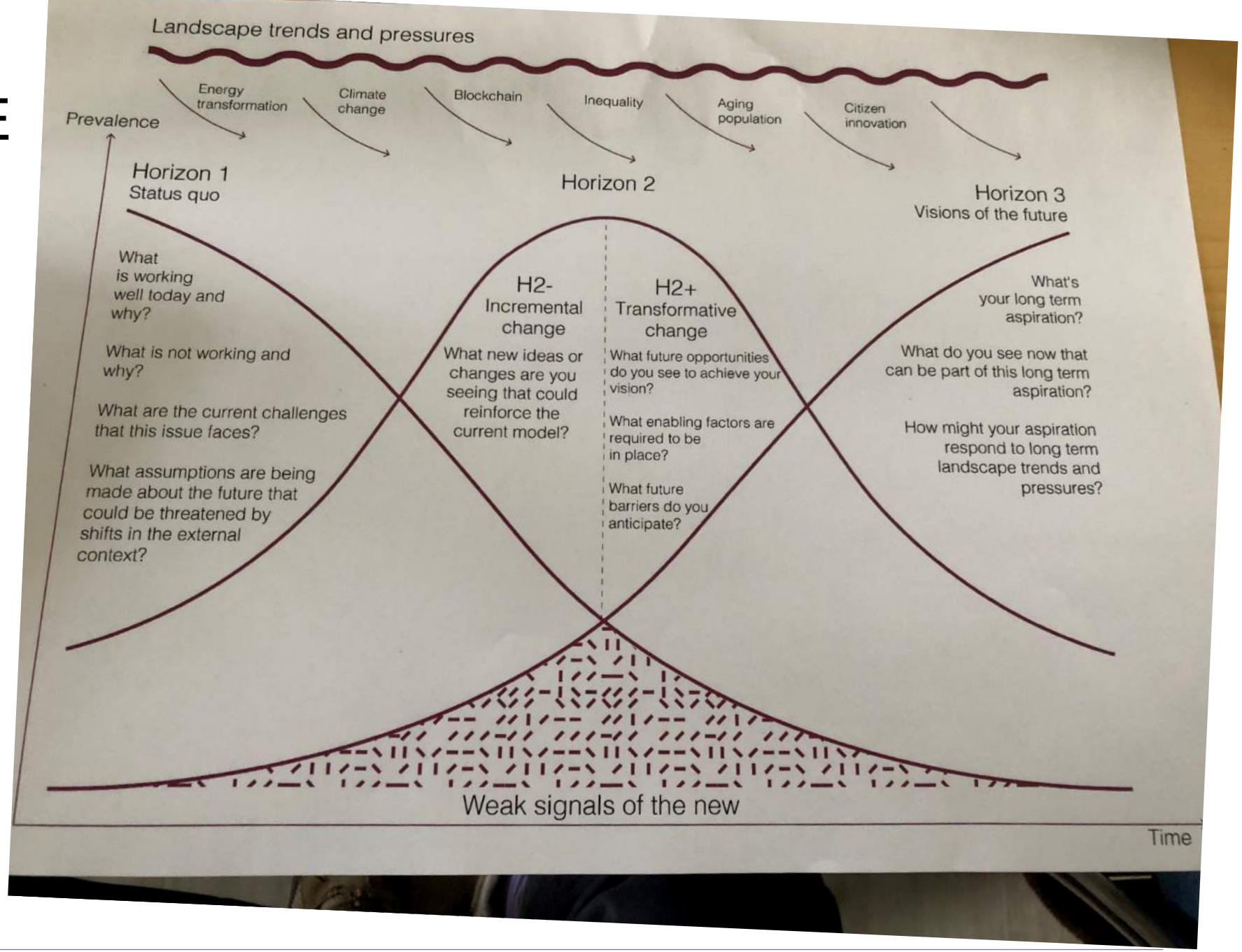
What is missing?
Do the 2 dimensions make sense? Are they clear?
How do we need to adjust the buckets?
Do the feedback loops make sense?



User research, innovation prototyping, testing and experience at local and country levels will inform and be informed by research and development at national, regional and global levels

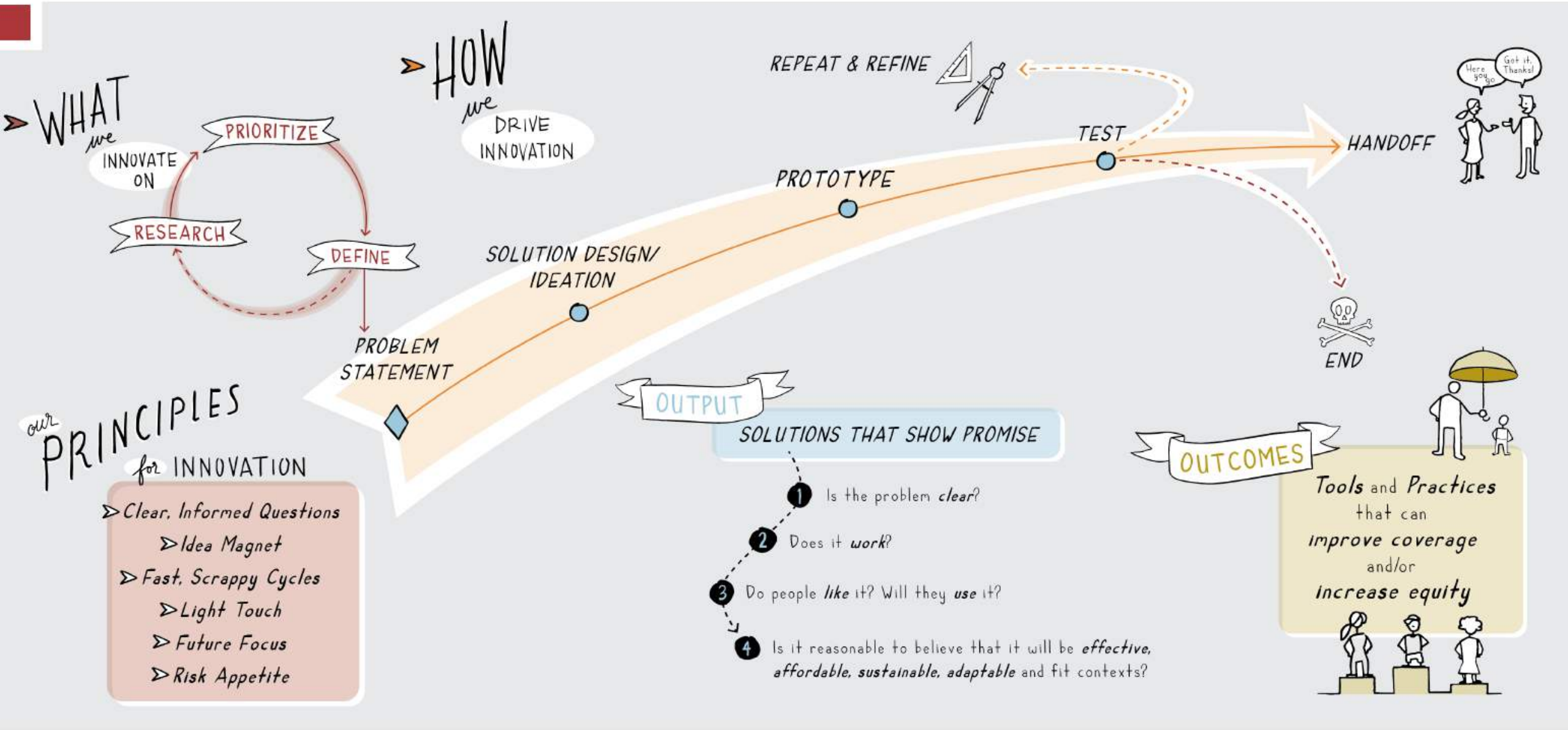
PREDICTING THE FUTURE IS IMPOSSIBLE

How do we identify test and scale transformative innovations rather than incremental innovations?

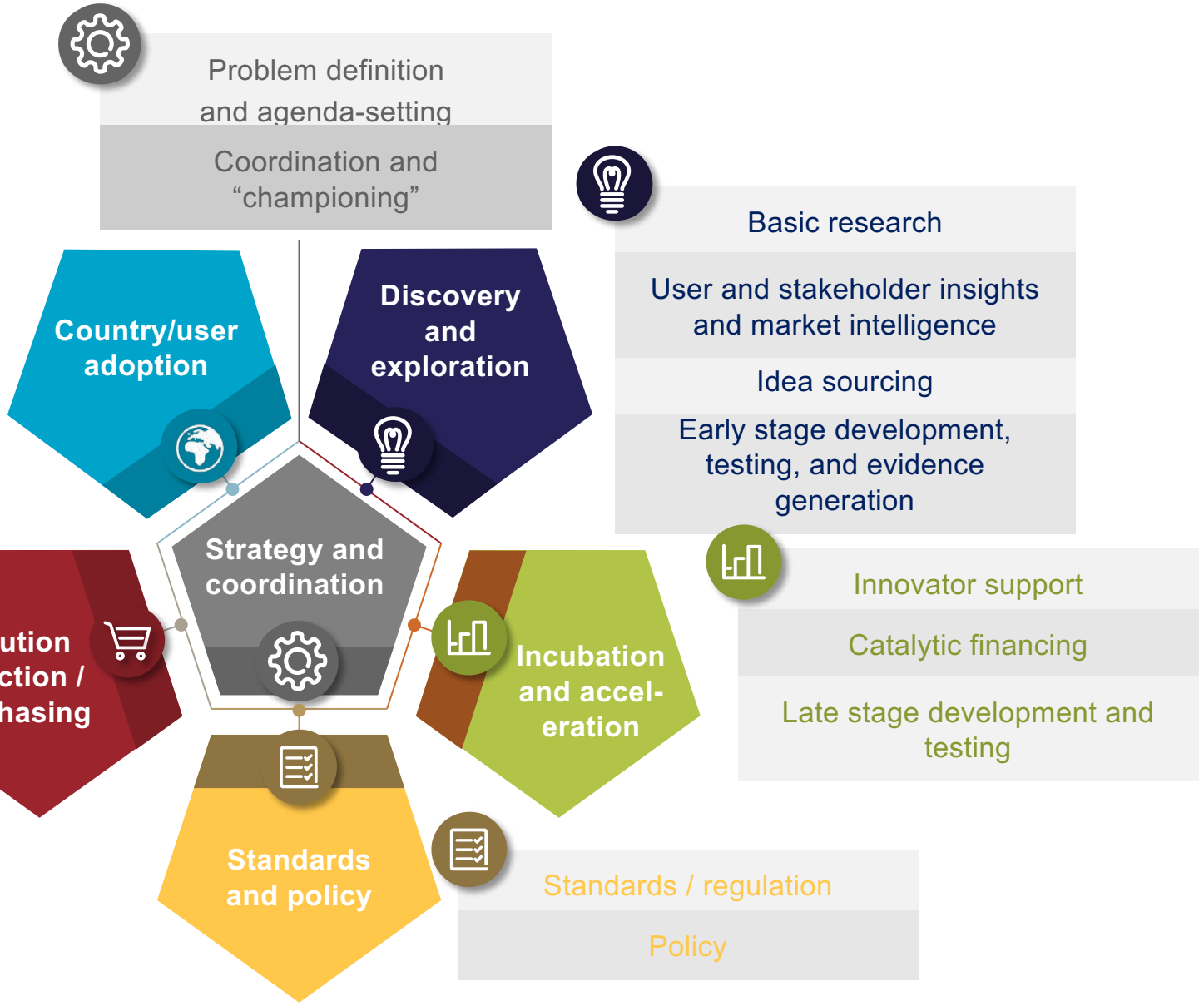


ANNEX – ADDITIONAL SLIDES

How we are thinking about innovation… (this is evolving)



I2S - KEY ENABLERS OF THE IDEAS2SCALE ECOSYSTEMS FRAMEWORK



What do we mean by the Full Public Value of Vaccines?

Alejandro Cravioto
WHO Product Development for Vaccines Advisory Committee

26-28 June 2019

What is the concept of the Full Public Value of Vaccines?

- The FPVV for vaccines is *a concept* that describes **the global value of a vaccine**, including from an LMIC perspective. It aims to articulate the **full direct** (individual) and **indirect** (population) **effects** of a vaccine.
- The intent of FPVV assessment is **to support decision-making** across the continuum of vaccine development and uptake, **with a line-of-sight to sustainable socio-economic *and* public health impact**
- They are particularly important for **vaccines targeted to LMICs** because:
  - Dual market vaccines often target HIC markets, initially;
  - These vaccines require additional resources to concomitantly develop and introduce vaccines suitable for LMIC uptake;
  - Several vaccines in development do not have a dual market… and require incentives

Pathway to vaccine uptake in LMICs

World Health Organization

WHO's Strategic Advisory Group of Experts (SAGE)

global policy recommendations and strategies

WHO Prequalification (PQ)
Programmatic suitability (PSPQ criteria)

Financing provides the mechanism for **procurement,**

GAVI, PAHO Revolving Fund or in ministries of finance

Product development investments to licensure

World Health Organization

- Small scale mfg
- Clinical assays
- Toxicology

Manufacturing consistency lots & capacity building

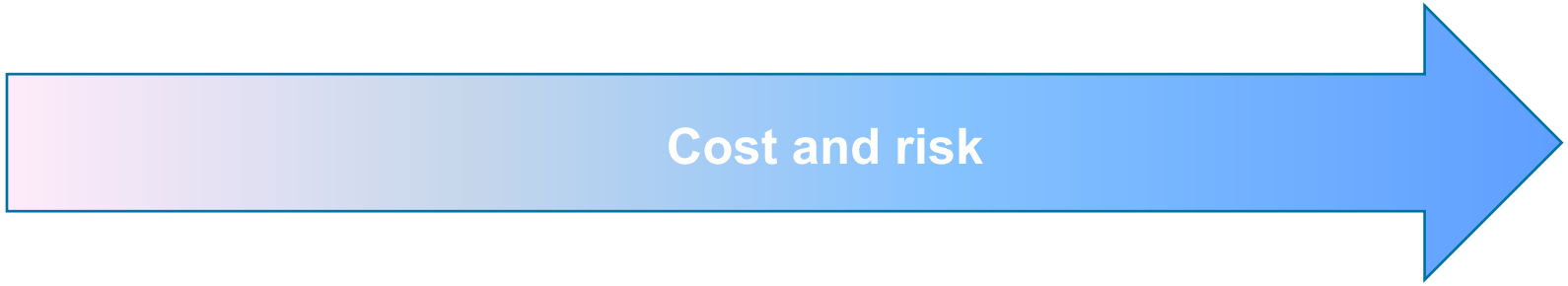
- Antigen targets
- Preclinical models
- Assays

Process development & scale up

Multi-centre trials

Launch! (often HIC)

World Health Organization



How do we incentivize product development to meet LMIC policy and PQ requirements?

What is conceptualized in the FPVV approach?

Traditional approach based on:

- Efficacy & effectiveness
- Risk/safety (individual)
- Morbidity and mortality at individual level
- Cost-benefit analysis

FPHVV approach based on:

- Disease reduction directly and indirectly by reducing pathogen transmission
  - Vaccine preventable disease incidence
  - All cause mortality
  - Under 5 mortality
  - Long term sequellae
  - Anti-microbial resistance
- Reduce frequency and size of outbreaks
- Social and economic benefits
- Equity, access, affordability and acceptance, sustainability
- Protection against financial risk

Adapted from: Wilder-Smith et al. BMC Medicine (2017) 15:138, DOI 10.1186/s12916-017-0911-8

GLOBAL HEALTH POLICY

By Angela Y. Chang, Carlos Riumallo-Herl, Nicole A. Perales, Samantha Clark, Andrew Clark, Dagna Constenla, Tini Garske, Michael L. Jackson, Kévin Jean, Mark Jit, Edward O. Jones, Xi Li, Chutima Suraratdecha, Olivia Bullock, Hope Johnson, Logan Brenzel, and Stéphane Verguet

DOI: 10.1377/hlthaff.2017.0861
HEALTH AFFAIRS 37,
NO. 2 (2018): 316–324

The Equity Impact Vaccines May Have On Averting Deaths And Medical Impoverishment In Developing Countries

EXHIBIT 1

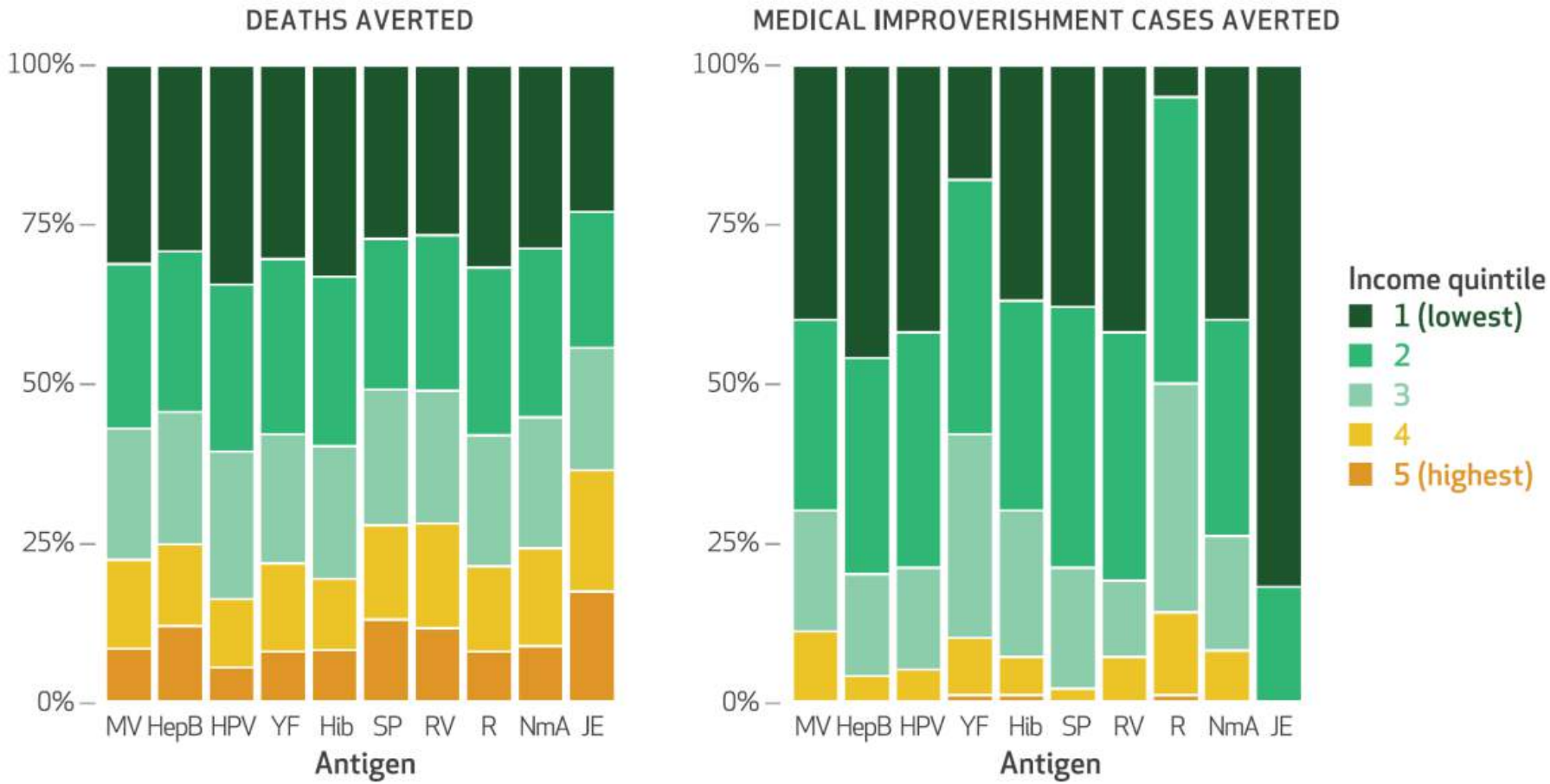
Numbers of deaths and cases of medical impoverishment averted by vaccines to be administered in 41 low- and middle-income countries, 2016–30

Antigen	Deaths averted (thousands)	Number of deaths averted (per million people vaccinated)	Medical impoverishment cases averted (thousands)
Measles	22,204	11,339	4,787
Hepatitis B	6,639	10,751	14,034
Human papillomavirus	2,522	11,990	112
Yellow fever	1,804	4,551	835
Hemophilus influenzae type b	1,242	1,998	1,054
Streptococcus pneumoniae	782	1,337	248
Rotavirus	454	819	242
Rubella	355	897	141
Neisseria meningitidis serogroup A	137	81	2,684
Japanese encephalitis	13	35	8

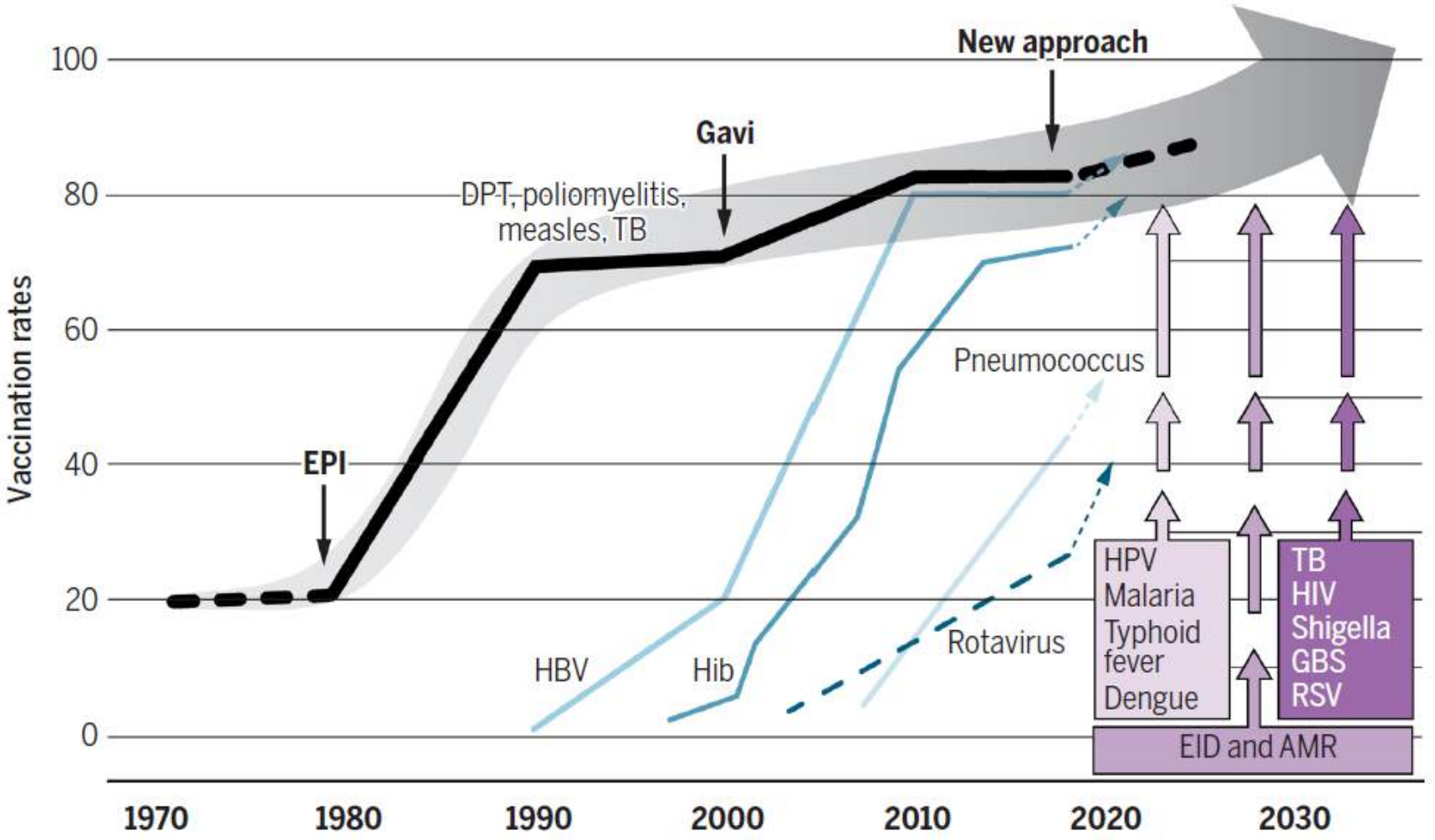
SOURCE Authors' analysis.

EXHIBIT 2

Distribution, by income quintile, of deaths averted and cases of medical impoverishment averted by vaccines to be administered in 41 low- and middle-income countries, 2016–30

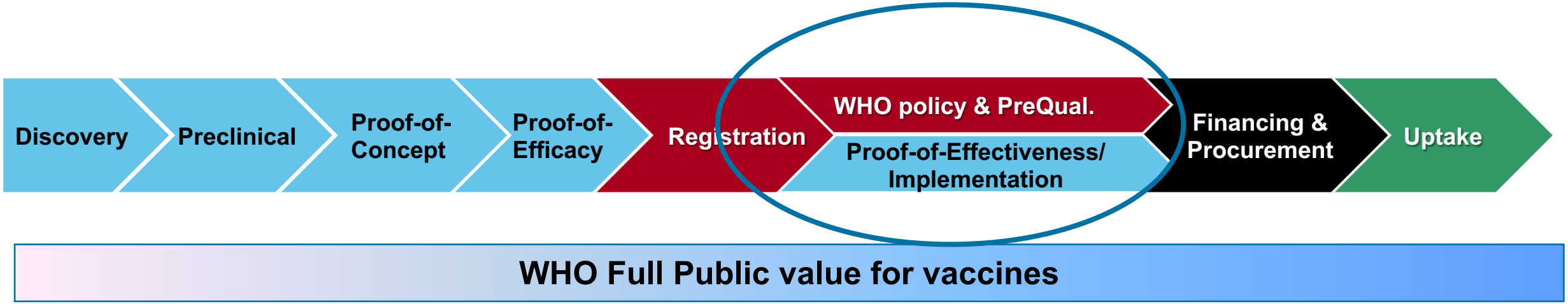


Why do we need to define the FPVV?



Source: Rappuoli et al, Vaccines and global health: In search of a sustainable model for vaccine development and delivery, STM, 2019

What is the rationale for FPVV for vaccines?

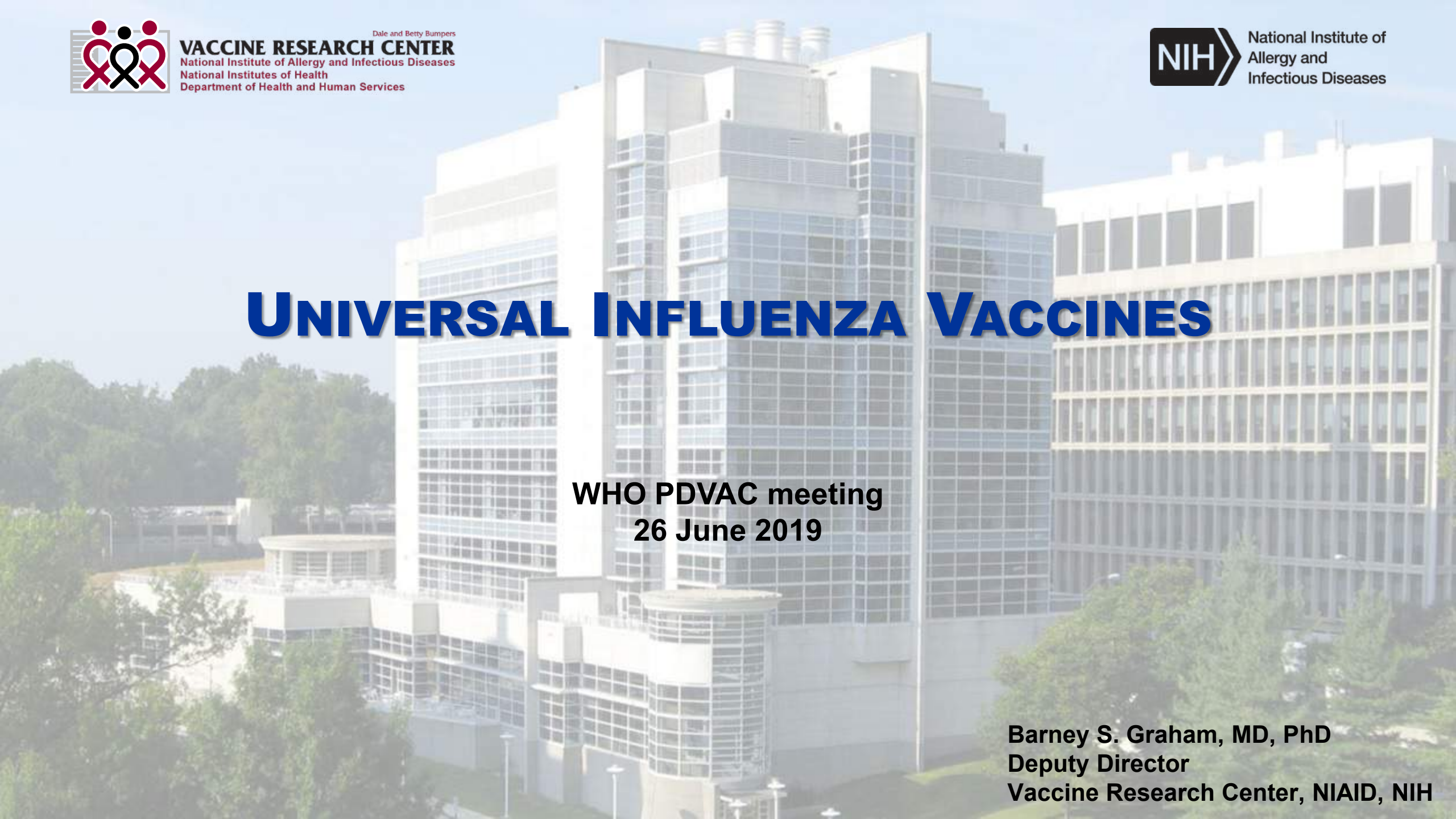


- Considers evidence of vaccine impact from a **population/societal** perspective
- Describes data that support SAGE and in-country policy decision making
- Broadens the potential market for vaccines in development

Overview of this session

- Consider the value of vaccines in reducing the need for antibiotic use – Value attribution framework for antimicrobial resistance
- Value of vaccines for diseases that have low mortality but high morbidity
- What is the need and rationale for vaccine product innovation
- What is the manufacturers' perspective of vaccine value
- What is the perspective of vaccine value for global financing agencies

➢ Discussion



Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

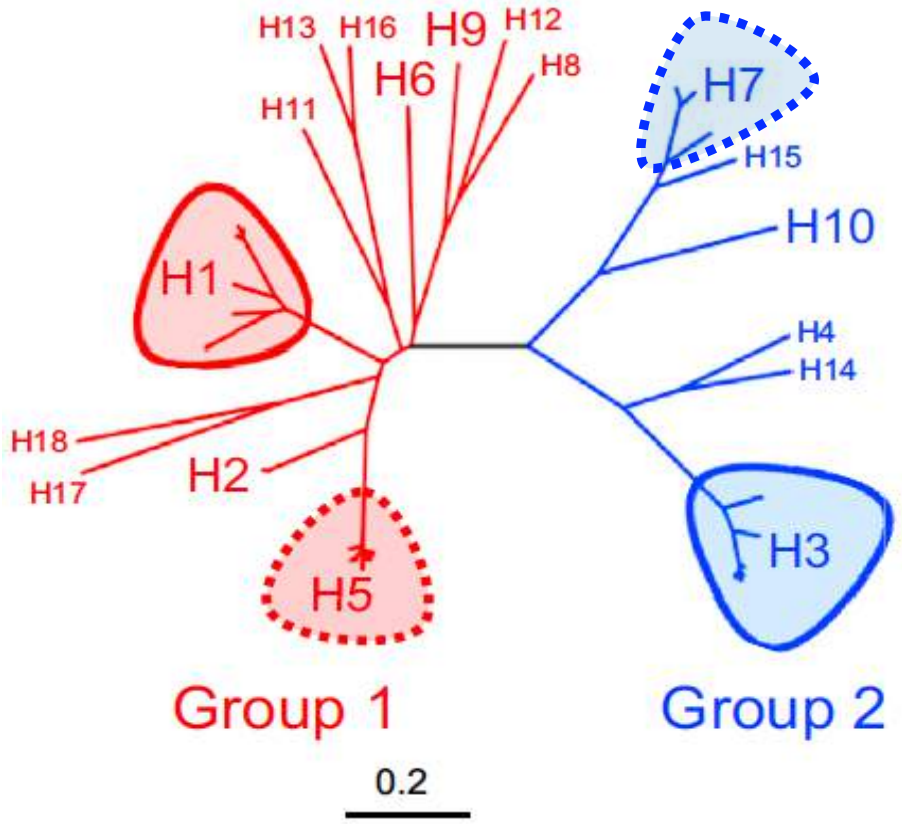
NIH National Institute of Allergy and Infectious Diseases

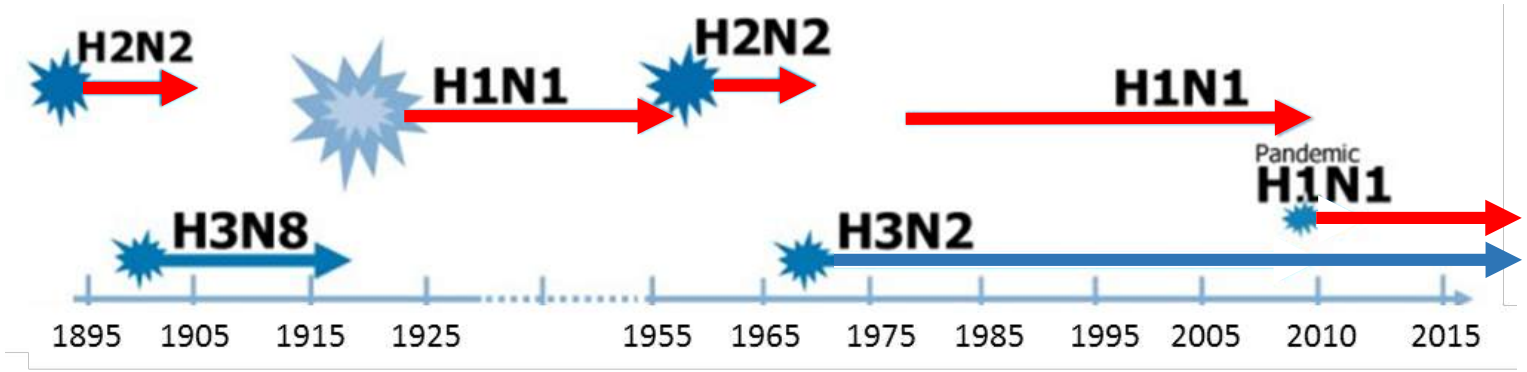
UNIVERSAL INFLUENZA VACCINES

WHO PDVAC meeting
26 June 2019

Barney S. Graham, MD, PhD
Deputy Director
Vaccine Research Center, NIAID, NIH

Influenza A has been the cause of prior pandemics





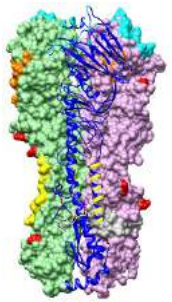
Need For a Universal Influenza Vaccine

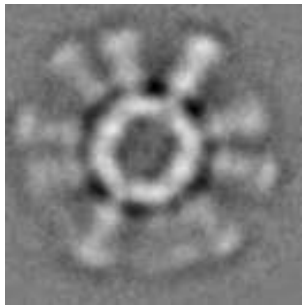
Current Influenza Vaccines:

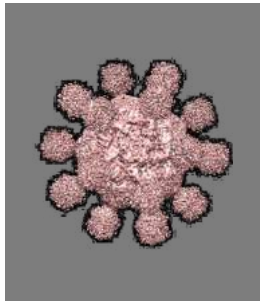
- Use 1940's technology - inactivated virus grown in chicken eggs
- Only 50-60% effective in good years
- Need to be reformulated every year to match circulating influenza strains
- Not effective against new pandemic strains and response is too late

Future Influenza Vaccines:

- Will use mammalian and insect cell manufacturing of recombinant proteins
- Apply new technologies and endpoints







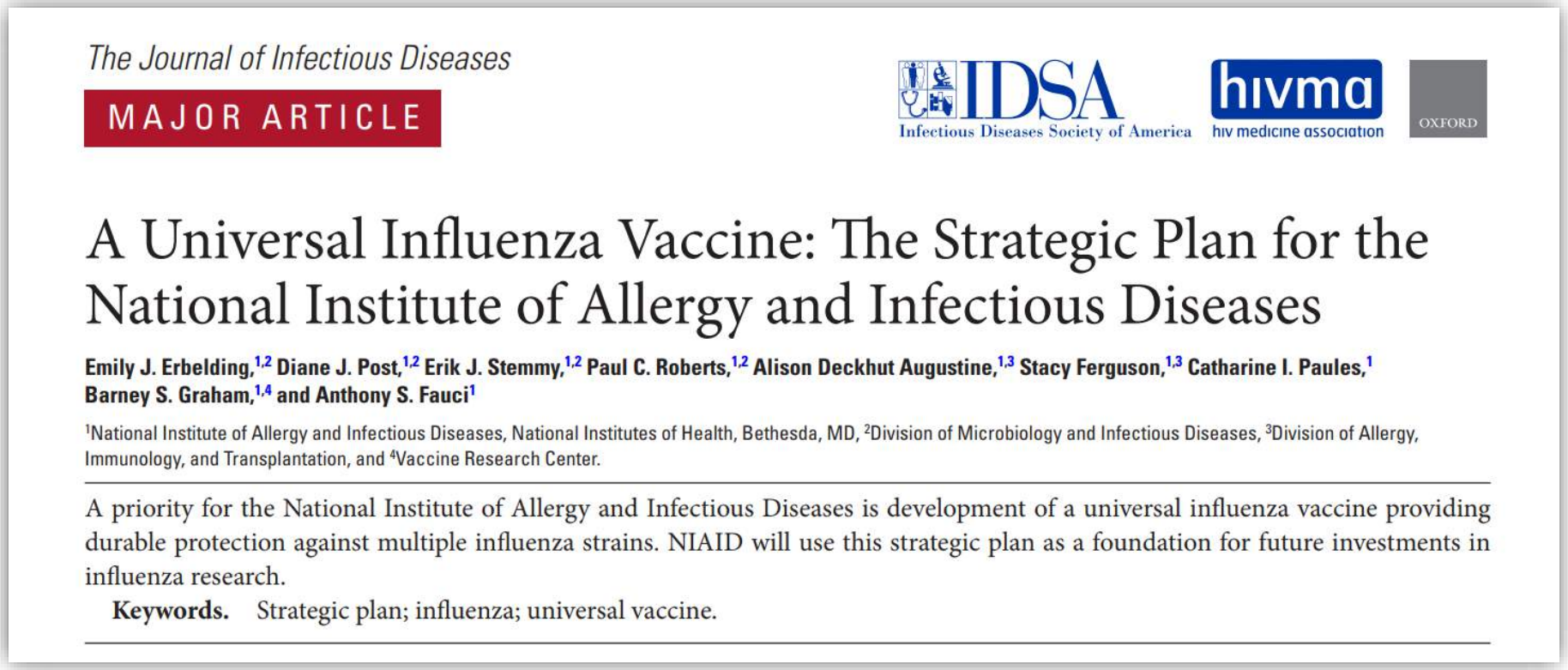
Major Biological Challenges for Universal Influenza Vaccine

- **Antigenic variation and genetic plasticity**
  - Extensive zoonotic reservoir, reassortment, adaptive mutations
- **Pre-existing immunity**
  - Immunodominance of serotype-specific epitopes
  - Immunodominance of antibody lineages with limited breadth
  - Influence on B cell phenotypes

Influenza Vaccine Strategies

	Strategy	Phase	Theoretical Mechanism
Leading universal vaccine concepts	HA stem or head-stem chimera	Phase I	Broad NAb (no HAI) and ADCC
	HA head chimera (COBRA)	Pre-clinical	Broad NAb (with HAI)
Additional concepts	M2 ectodomain	I/II	Broad cross-reactive Ab; ADCC (no NT)
	Co-assembled HA on NP	Pre-clinical	Favors cross-reactive B cells
Improved seasonal vaccines	HA rosettes, individual full-length HA nanoparticles, VLP	I/II	Potency from particle display, breadth from multiple strains mixed or sequential delivery
	Add neuraminidase antigen	Pre-clinical	Additional antigen for NT breadth/potency
	Live-attenuated or single-round virus or gene-based delivery	Phase I	Additional antigens, T cell responses, and mucosal immunity
	Mammalian cells, high-dose, adjuvants, LAIV or DNA prime	Post-marketing	Improved manufacturing or immunogenicity of conventional vaccine

NIAID Universal Influenza Vaccine Strategic Plan



The Journal of Infectious Diseases

MAJOR ARTICLE

A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases

Emily J. Erbelding,[1,2] Diane J. Post,[1,2] Erik J. Stemmy,[1,2] Paul C. Roberts,[1,2] Alison Deckhut Augustine,[1,3] Stacy Ferguson,[1,3] Catharine I. Paules,[1] Barney S. Graham,[1,4] and Anthony S. Fauci[1]

[1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]Division of Microbiology and Infectious Diseases, [3]Division of Allergy, Immunology, and Transplantation, and [4]Vaccine Research Center.

A priority for the National Institute of Allergy and Infectious Diseases is development of a universal influenza vaccine providing durable protection against multiple influenza strains. NIAID will use this strategic plan as a foundation for future investments in influenza research.

Keywords. Strategic plan; influenza; universal vaccine.

- NIAID priority to develop a universal influenza vaccine that provides durable protection against multiple influenza strains
- Foundation for future investments in influenza research (CIVIC grants)

National Institute of Allergy and Infectious Diseases

Goals for a Universal Influenza Vaccine

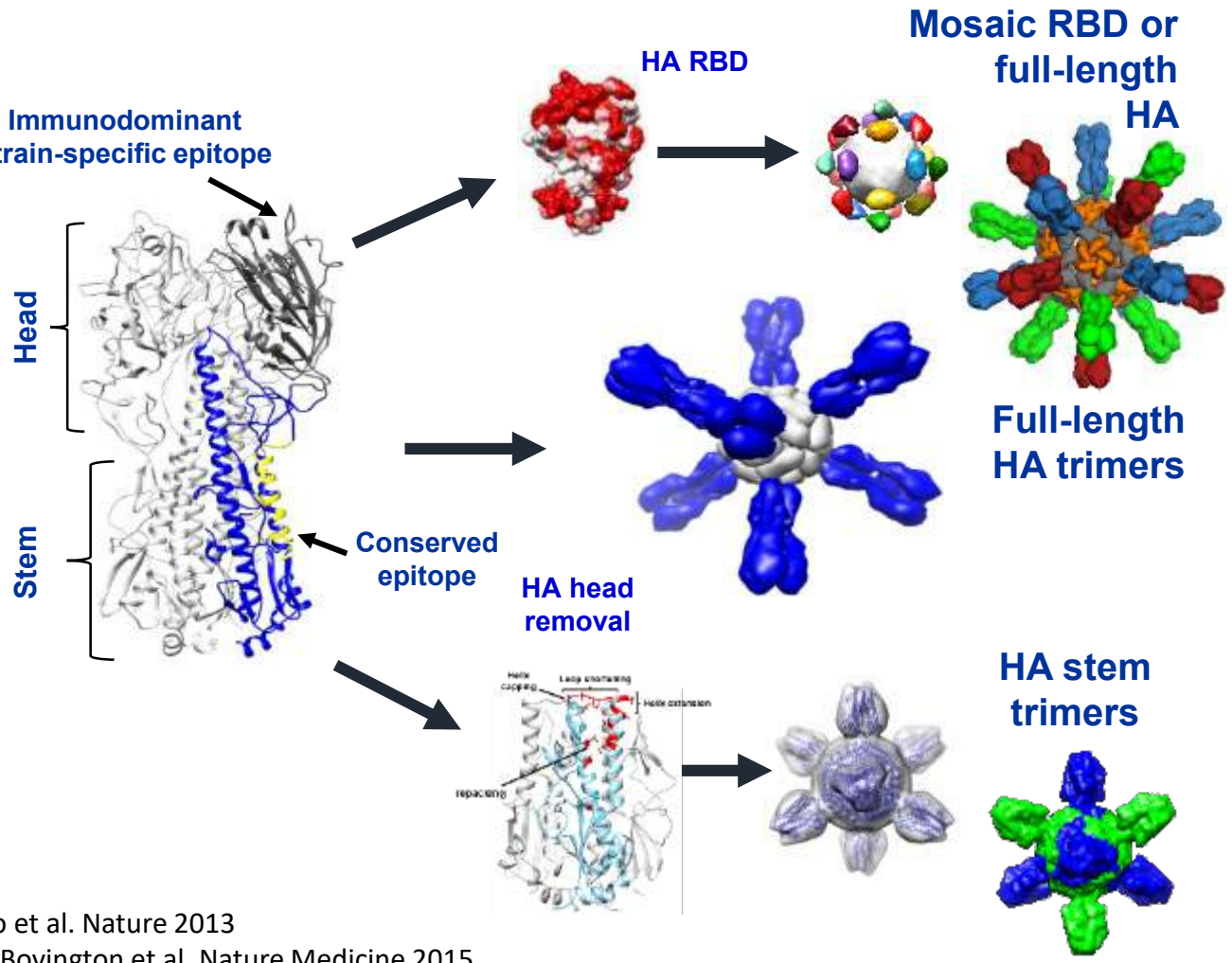
- Consistent efficacy >75% against medically-attended illness caused by seasonal and pandemic strains of influenza
- Single product that does not require annual revision
- Durable immunity for greater than 1 year

New Technologies Have Changed the Options for Universal Influenza Vaccine Development

- **Design** - Structure-guided approach for antigens and probes
- **Display** – Natural and designer nanoparticles
- **Delivery** – Proteins, nucleic acid, vectors
- **Detection** of specific immunological endpoints
  - Define and target specific antibody lineages with cross-neutralizing activity
  - Analysis of B cell phenotype and repertoire at single-cell level
  - Development of high-throughput functional serological assays

VRC Universal Influenza Vaccine Development

HA is primary antigenic target | **Structure-guided antigen design** | **Nanoparticle display** | **Strategy for achieving protective antibodies against future drifted and pandemic strains**



Avoiding immunodominance

Mosaic full-length HA on custom nanoparticles

Accumulation of breadth

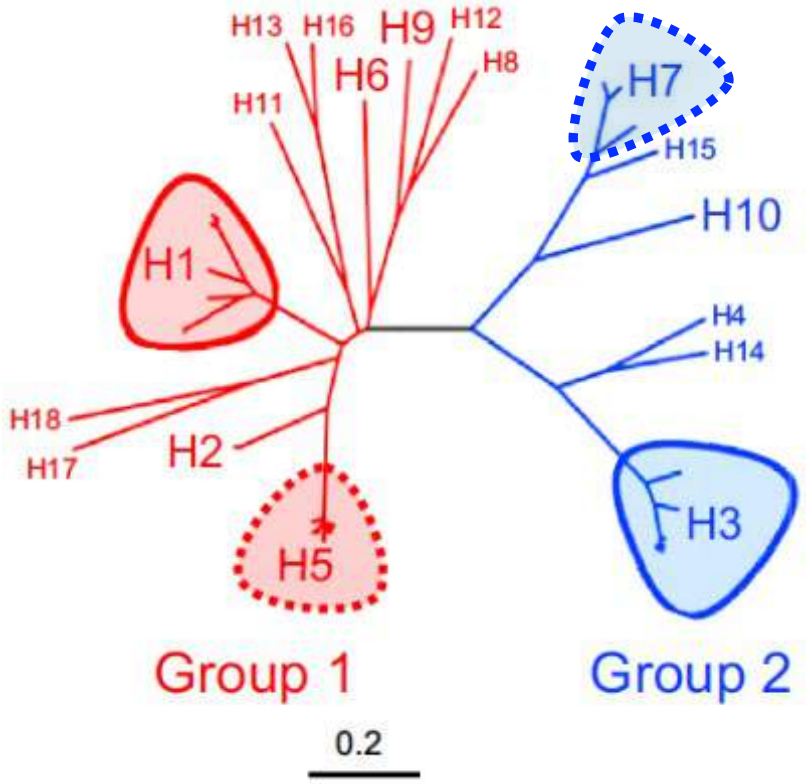
Targeting conserved sites

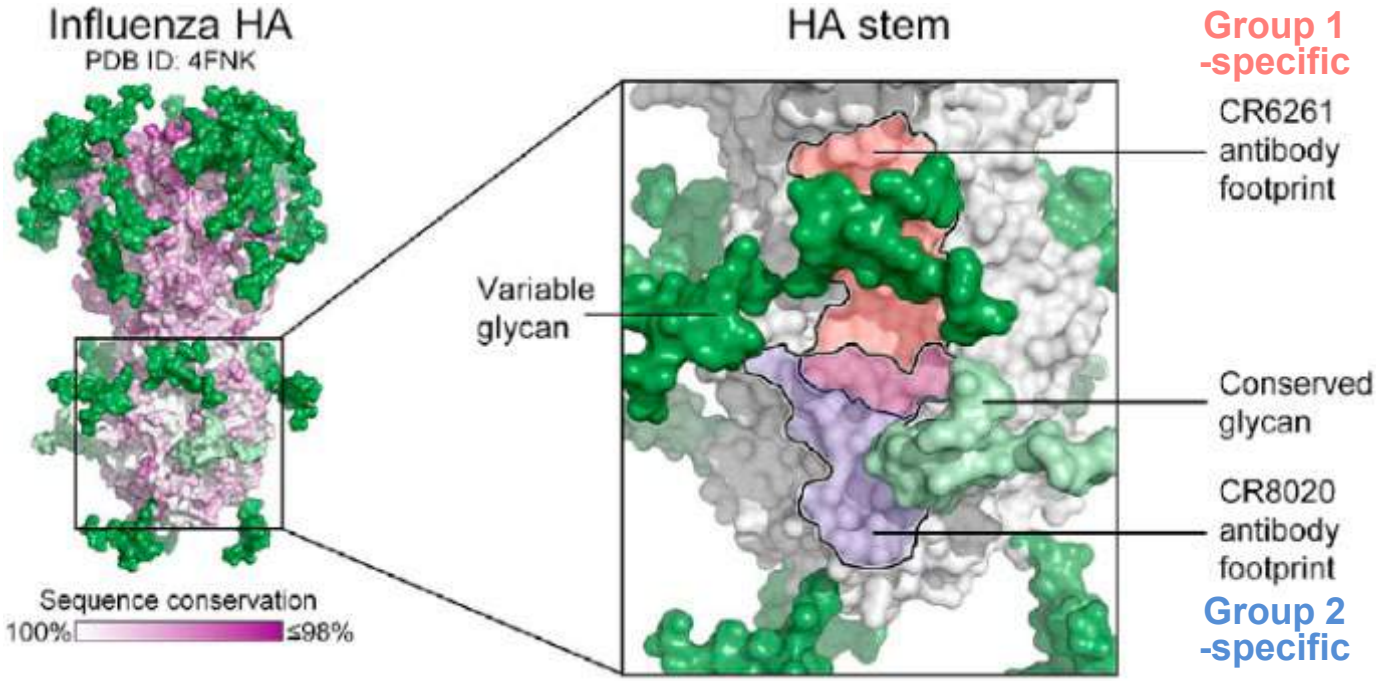
Group 1 & 2 on insect ferritin

Kanekiyo et al. Nature 2013
Yassine, Boyington et al. Nature Medicine 2015
Kanekiyo et al. Nature Immunology 2019

Influenza virus HA – sites of vulnerability

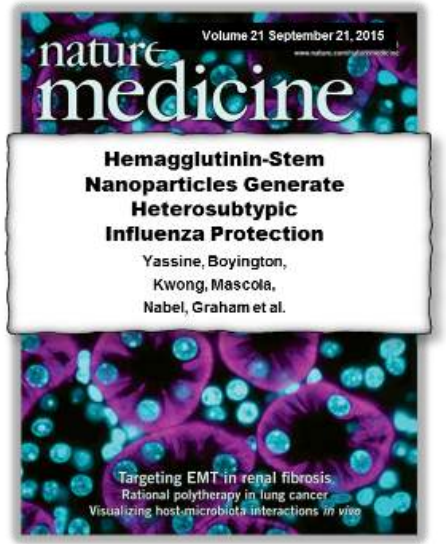
Diversity of influenza A hemagglutinins

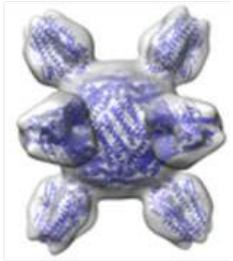


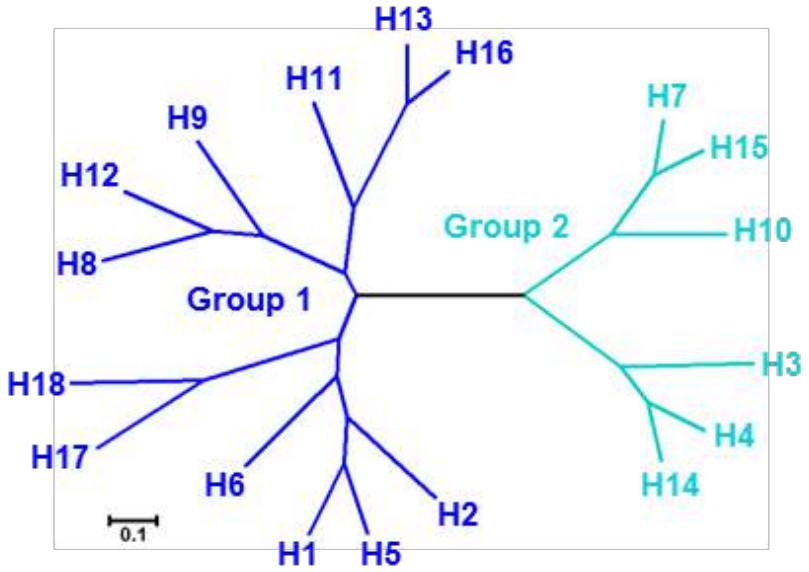


Joyce et al. *Cell* (2016)

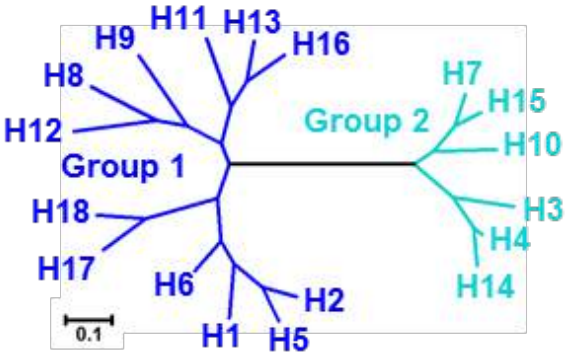
Headless HA-stem antigens achieve heterosubtypic protection and induce multi-donor cross-neutralizing antibody lineages



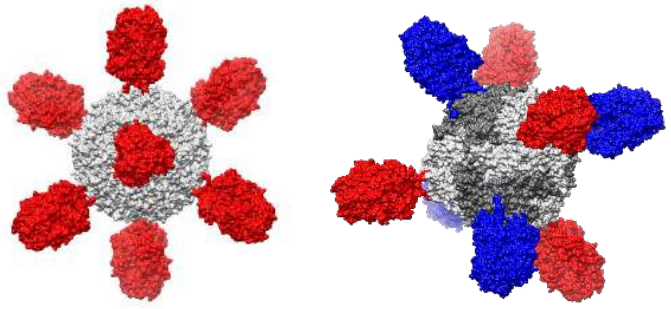




Full length HA

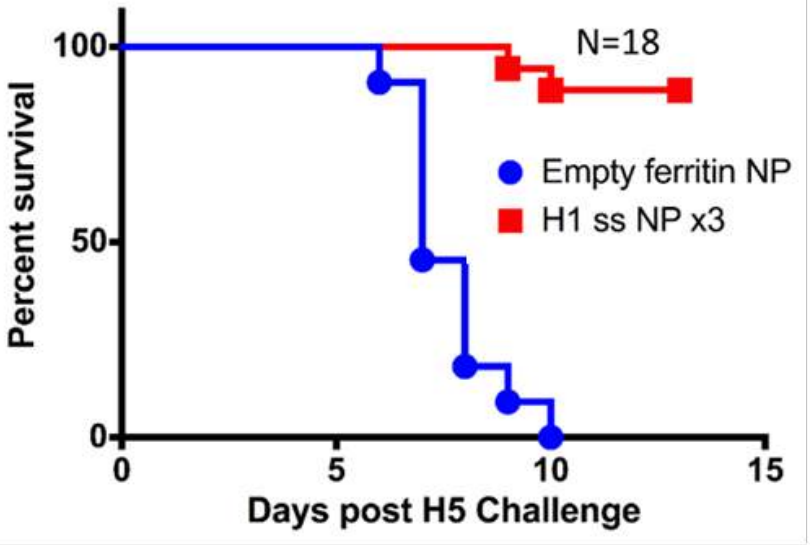


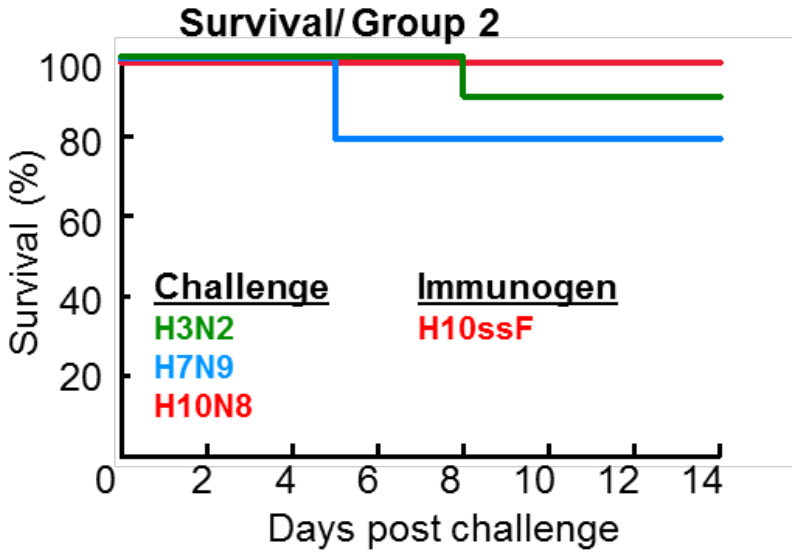
HA stem



H. pylori ferritin

Insect ferritin

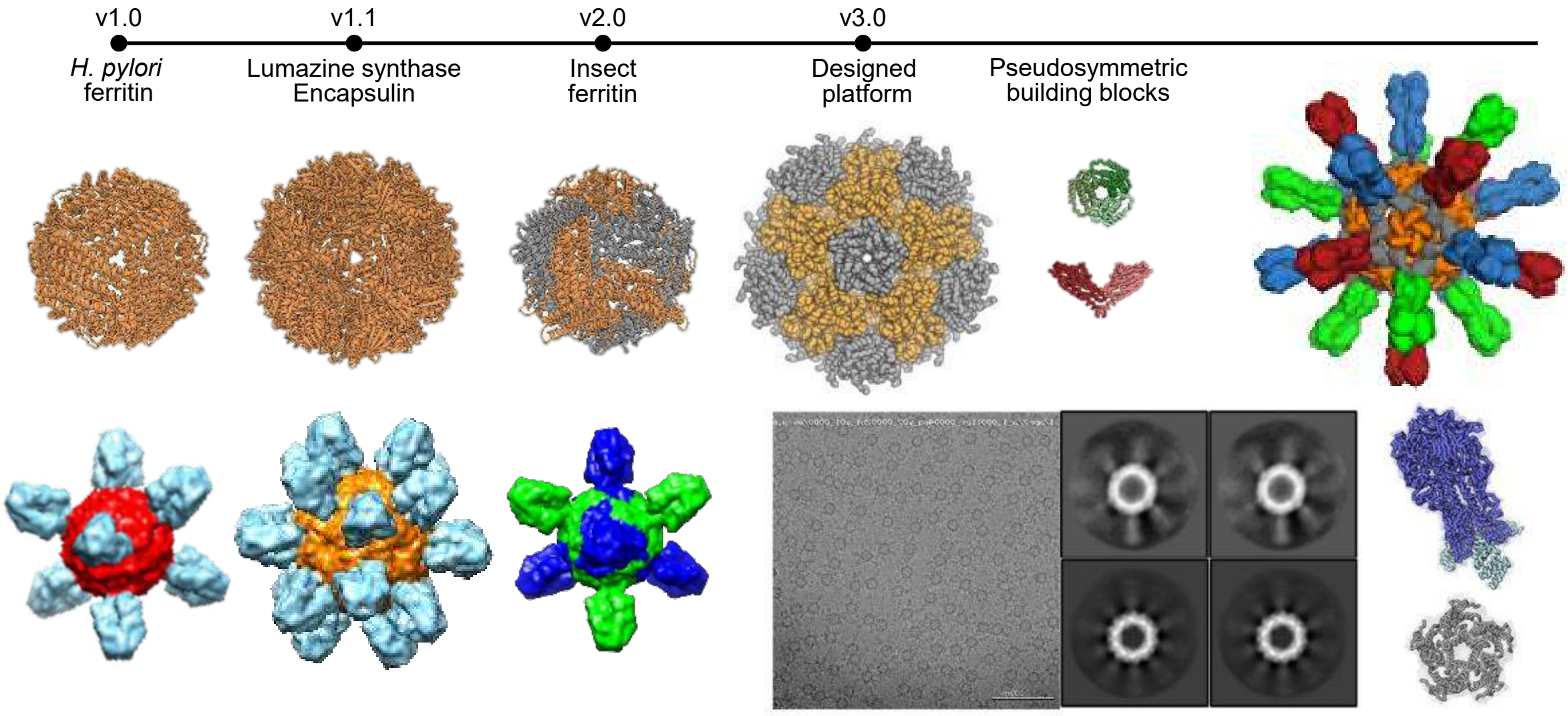




Yassine, Boyington, et al. Nature Medicine 2015

Corbett, Moin et al. mBio 2019

Evolution and Development of Self-Assembling Proteinaceous Nanoparticle-based Vaccines



Neil King, Daniel Ellis – UWash Institute for Protein Design

Co-display of heterotypic antigens in mosaic arrays

Mosaic antigen concept

Homogeneous antigens
(viruses, vaccines, etc.)

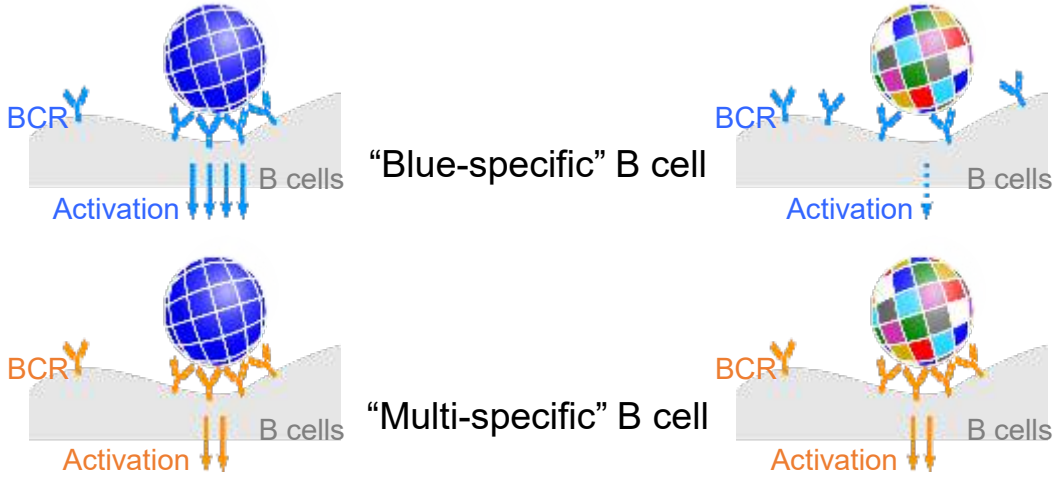
Building blocks

Particulate Ag

Heterogeneous antigens
(non-natural array)

Building blocks

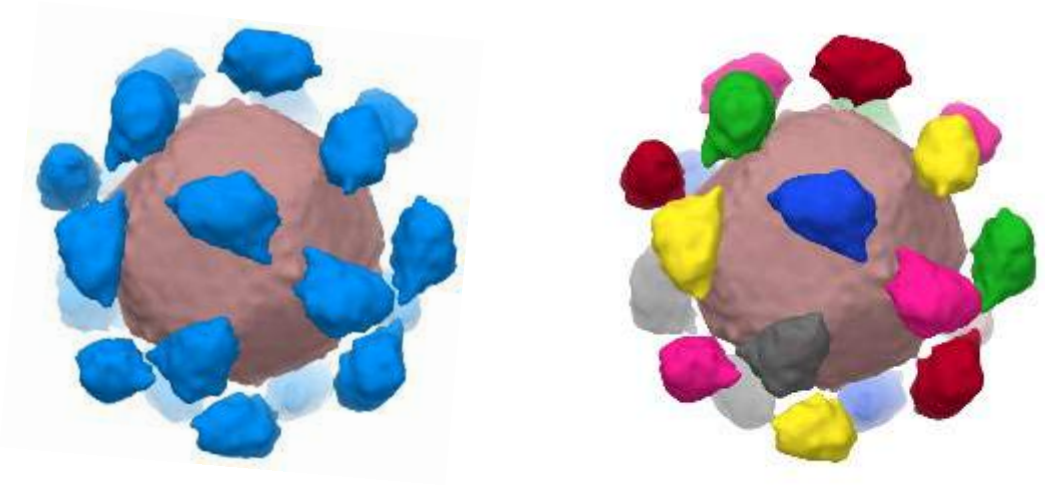
Particulate Ag



Experimental approach

Monotypic display

Mosaic display



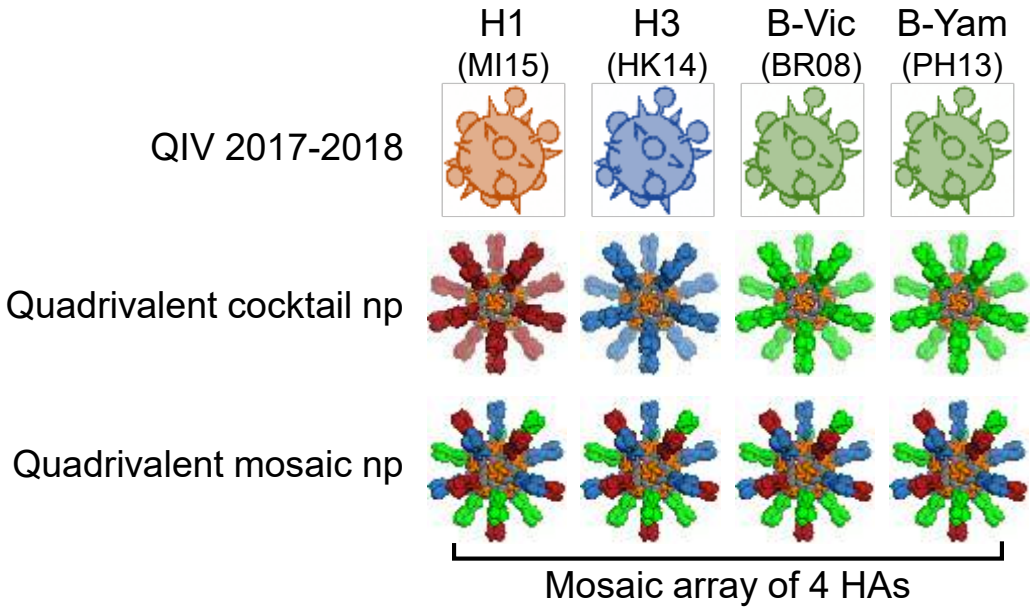
Per-particle antigen density of blue

Antigen heterogeneity

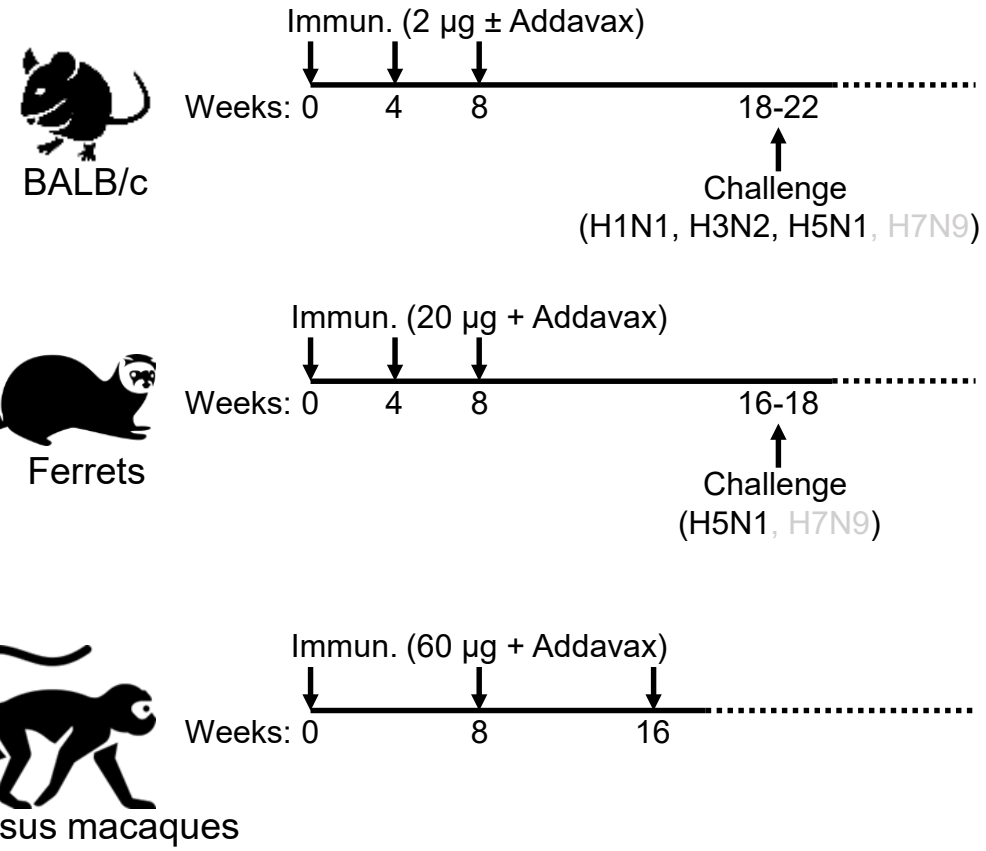
Kanekiyo et al., Nat Immunol (2019)

Full-length HA mosaic nanoparticle vaccine

Immunization groups

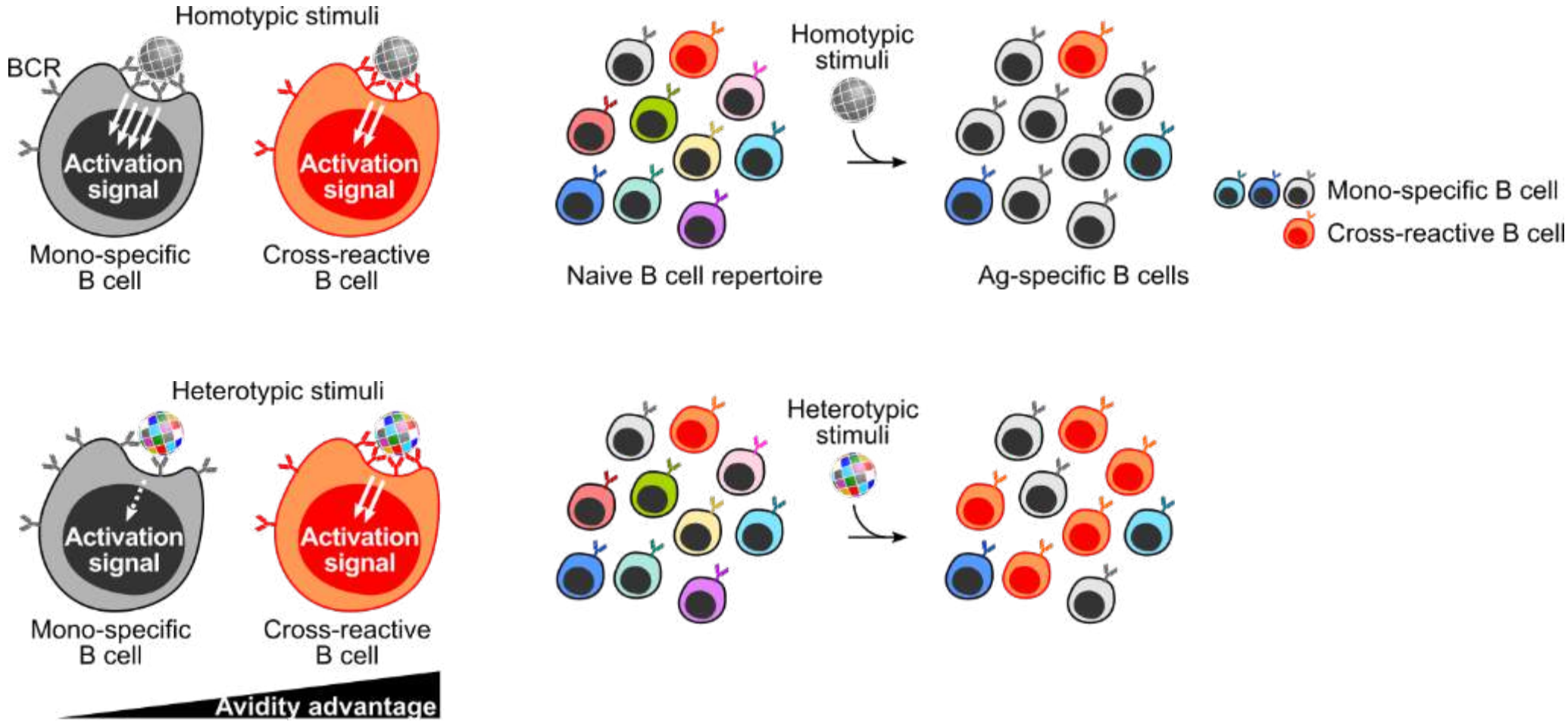


Animal models



Boyoglu-Barnum, Ellis et al., in preparation

Mosaic nanoparticle vaccine principle



Kanekiyo et al., Nat Immunol (2019)

Summary

- New technologies are transforming vaccinology providing solutions for long-standing problems and emerging viral diseases
- Targeting structurally-defined sites of vulnerability, defining specific antibody lineages, and advances in protein engineering have provided new options for influenza vaccines
- Mosaic antigen display may provide a way to overcome antigenic diversity and immunodominance
- In the short-term improved seasonal vaccines using cell-based manufacturing, dose-adjustments, adjuvants, and added neuraminidase, synthetic vaccinology for rapid manufacturing
- WHO PDVAC could help:
  - define and facilitate acceptable regulatory and logistical pathways to compare with conventional vaccines, e.g. new biomarkers and surrogate endpoints
  - Clarify pathway to replace current manufacturing technology
  - Define key target populations and priorities

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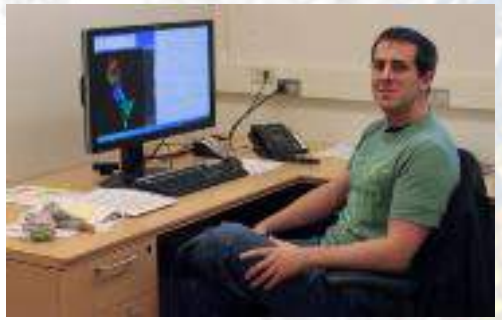

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NIDVD

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Natalie Jones

Value Attribution Framework For Vaccines Against Antimicrobial Resistance

Mateusz Hasso-Agopsowicz (WHO, Geneva, Switzerland)

Holly Prudden (WHO)
Johan Vekemans (WHO)

The Problem of AMR and the role of vaccines

- Global estimates suggest that drug-resistant infections result in **700,000 deaths per year**
- Could rise to **10 million annual deaths** by 2050
- Economical expenditure of **US$10 trillion** by 2050
- Mobilisation of efforts by WHO, UN, international organizations, member states, public health stakeholders to produce **a list of recommendations to combat AMR**
- **Vaccines** highlighted as having an **important** role in the process:
  - Vaccines prevent the infection and reduce carriage and transmission of AMR pathogen
  - Vaccines reduce the presence of clinical symptoms, reducing the pathogen associated antibiotic use

The role of WHO in vaccines and AMR

- Call from the AMR community to work on vaccines and AMR
- The aim of WHO is to highlight the role of vaccines and their impact against AMR
- To highlight priority activities around vaccines and AMR

Through:

- Creation of a roadmap that summarises priority actions around vaccines and AMR
- Developing a value attribution framework to articulate the value of vaccine against AMR
- Creation of a Working Group to oversee both processes, provide technical expertise and endorsement.

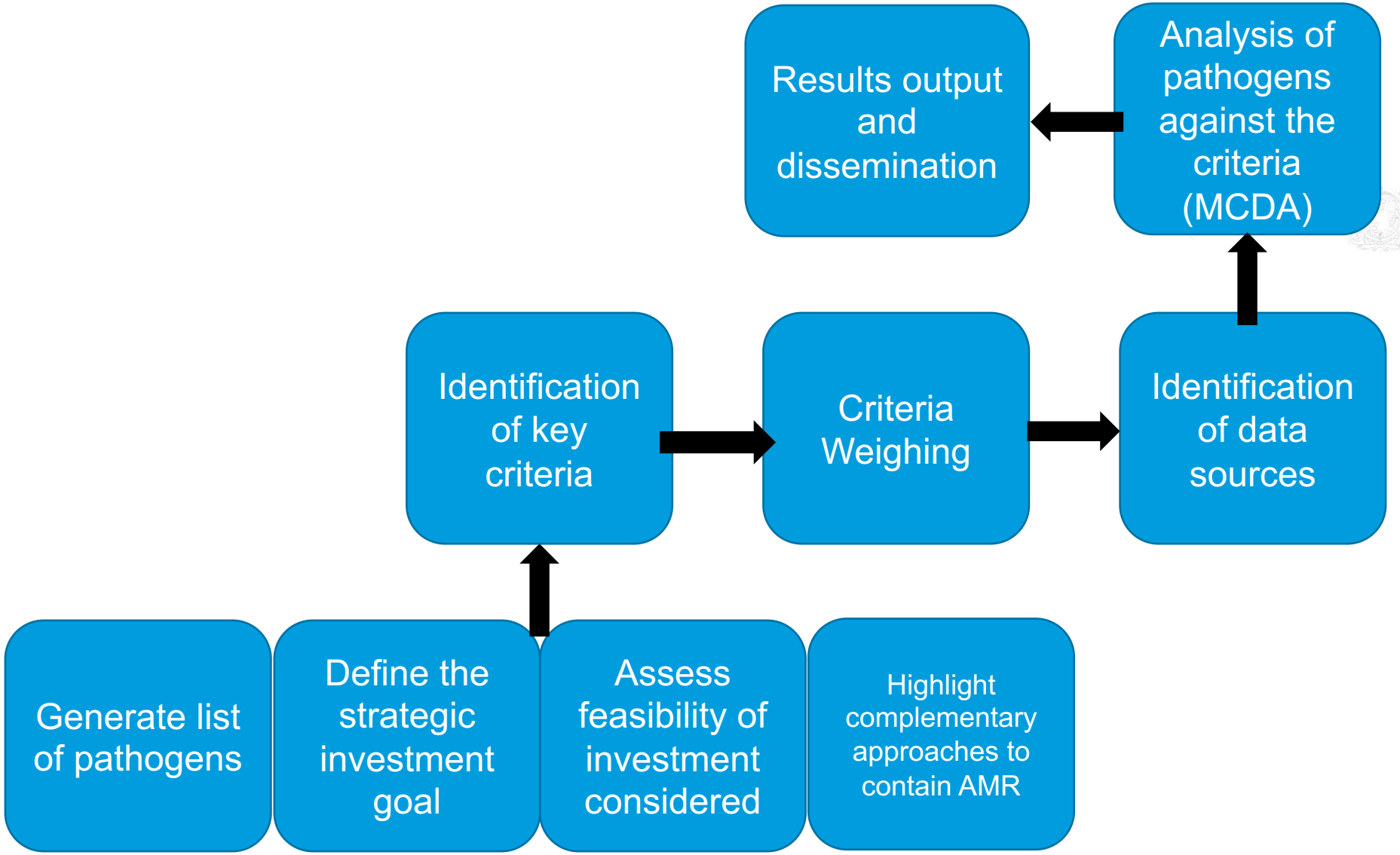
Aim

To create a semi-quantitative framework to assess the value of vaccine investments for their impact on AMR.

This framework will:

- Support the prioritisation of decisions and investments about vaccine development and use.
- Complement and inform the generation of a WHO technical roadmap expressing priority actions aimed to strengthen the role of vaccines against AMR.
- Support the narrative of pathogen specific priority activities

Methodology Outline



Generate list of pathogens

Bacteria:

Acinetobacter baumannii
Campylobacter
Chlamydia
Cholera
Clostridium difficile
Enterococcus faecium
E. coli
GAS
GBS
Haemophilus influenzae nt, b
Helicobacter pylori
Klebsiella pneumoniae
Meningococcus
Mycobacterium tuberculosis
Neisseria gonorrhoeae
Pseudomonas aeruginosa
Salmonella typhi
Salmonella paratyphi
Salmonella, non-typhoid
Shigella spp
Staphylococcus aureus
Streptococcus pneumoniae

Viruses:

HIV
Influenza virus
Measles virus
Norovirus
Rotavirus
RSV

Fungi/Parasites:

Malaria

Define the strategic investment goal

For each pathogen area, we will specify the strategic investment goal

- **Existing vaccines:** known effectiveness profile, use case being considered
  - Reaching expressed public health goals in terms of coverage rates
  - Consider a new target population (expanded use case)
  - Consult WHO IVB, GAVI, UNICEF, vaccine implémentation experts
- **Future vaccines, or pathogens with no vaccines in development:**
  - Putative target population, effectiveness profile
  - WHO product characteristic preferences (tuberculosis, GBS, RSV, GAS, others) or other publicly available target product profile documents
  - Consult WHO IVR, PDVAC, vaccine R&D experts
- **Example, Mycobacterium tuberculosis:**

TB vaccine with 50% vaccine efficacy for prevention of adult pulmonary TB, implemented through routine adolescent immunization and adult vaccination campaigns.

Feasibility of reaching strategic goal

- **Working with PDVAC/PATH, considering:**
  - Biological Feasibility
  - Product Development Feasibility
  - Access and Implementation Feasibility

Themes Considered	Indicators
Biological Feasibility	Existence of immunity from natural exposure The most advanced vaccine candidate Understanding mechanisms of immunity Multiplicity of pathogenic strains
Product Development Feasibility	Existence of animal models to facilitate vaccine development Existence of in vitro assays to facilitate vaccine development Ease of clinical development Availability of clinical tools to facilitate vaccine development
Access and Implementation Feasibility	Possibility of implementation within existing delivery systems Commercial attractiveness Barriers to uptake Clarity of licensure and policy decision pathway

Identification of Key Criteria

- A set of defined criteria will be used to assign overall value on investment goals being considered.
- Both qualitative and quantitative metrics will be used.
- The evidence will be graded.
- Ideally, the criteria should be complete, non-redundant, non-overlapping and independent, as is the case in multi-criteria decision analysis (MCDA) methodologies.

Identification of Key Criteria

Criteria	Definition	Data sources
Vaccine-averted AMR fraction of the disease	The ability of a vaccine to reduce AMR caused mortality and morbidity	CDDEP IHME Cassini et al. Experts opinions
Reduction of antibiotic use	The ability of a vaccine to reduce antimicrobial consumption	SPA PPS
Economic and Societal Burden	Cost of illness due to an AMR pathogen (direct, indirect, societal costs)	Systematic review
Sense of Urgency	The urgency of a pathogen to cause a threat due to AMR	Resistance Map
Ethical and Equity considerations	Vector of stigma, exclusion, poverty, inequity and discrimination	Systematic Review

Data collection, analysis and standardisation

- Weights will be assigned for each of the criteria depending on importance
- For each pathogen or vaccine, the data needs to be identified and extracted to support the criteria
- Evidence-based with a focus on high-quality studies, supported by experts opinion
- Strength of evidence documented throughout
- Collection of qualitative and quantitative data, translation of qualitative evidence to quantitative

Results Dissemination

Online tool that allows for adjustable, modular, flexible, user-centred view

Similar to IHME visualisations

Supported by narrative sections and case studies

Publication

Excel spreadsheet

Thank You

World Health Organization

Mateusz Hasso-Agopsowicz, WHO

20, Avenue Appia
1211 Geneva

Switzerland

WHO Roadmap for Strengthening the Role of Vaccines Against AMR

World Health Organization

Holly Prudden, Johan Vekemans, Robert Taylor, Mateusz Hasso-Agopsowicz

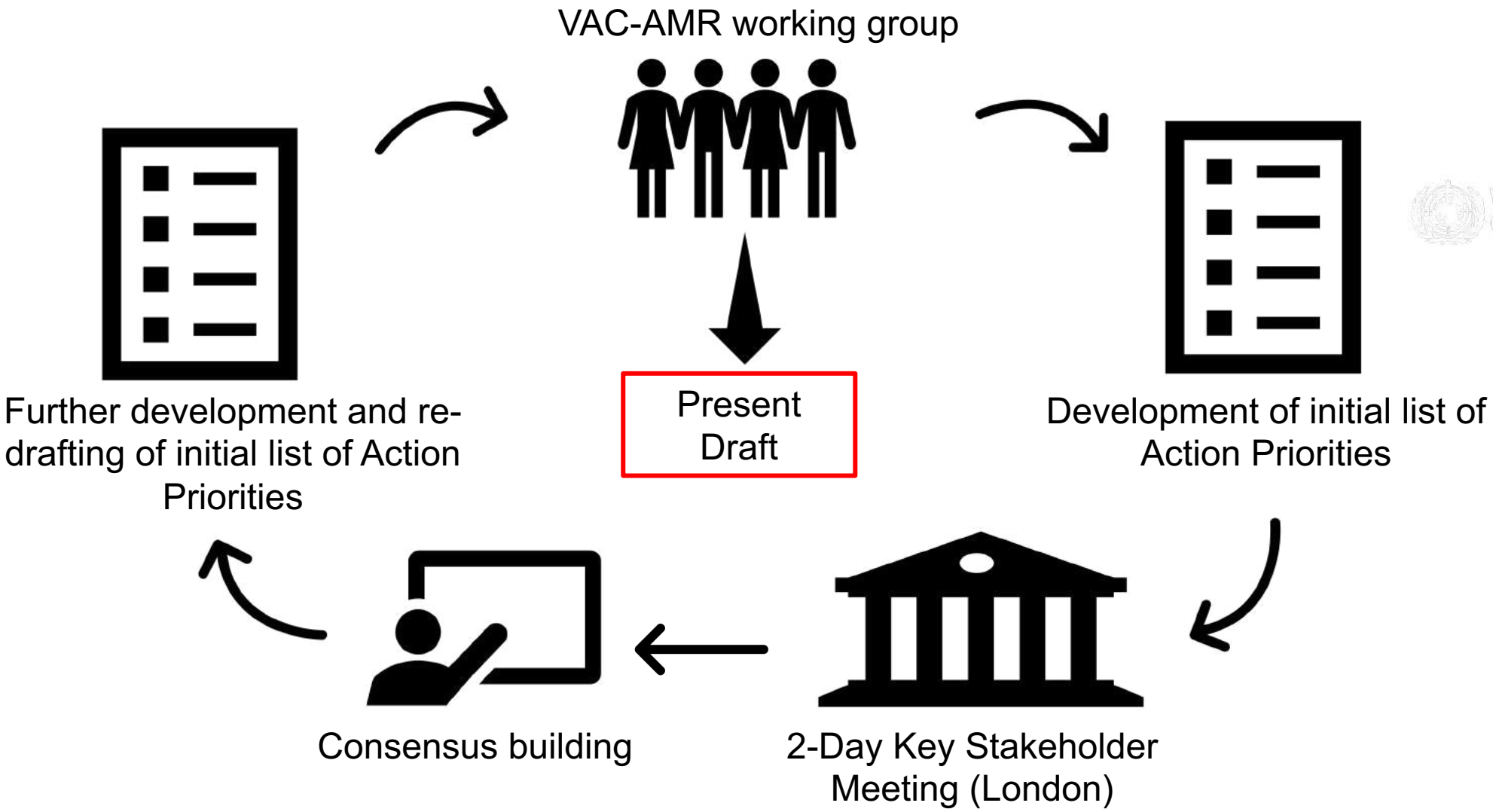
Development of a Roadmap Highlighting Priority Actions for the use of Vaccines against AMR

World Health Organization

Purpose of project:

To produce an overarching guidance document (‘Roadmap’) highlighting priority actions that will aim to highlight gaps and opportunities in a diverse set of topics.

Consultation Process



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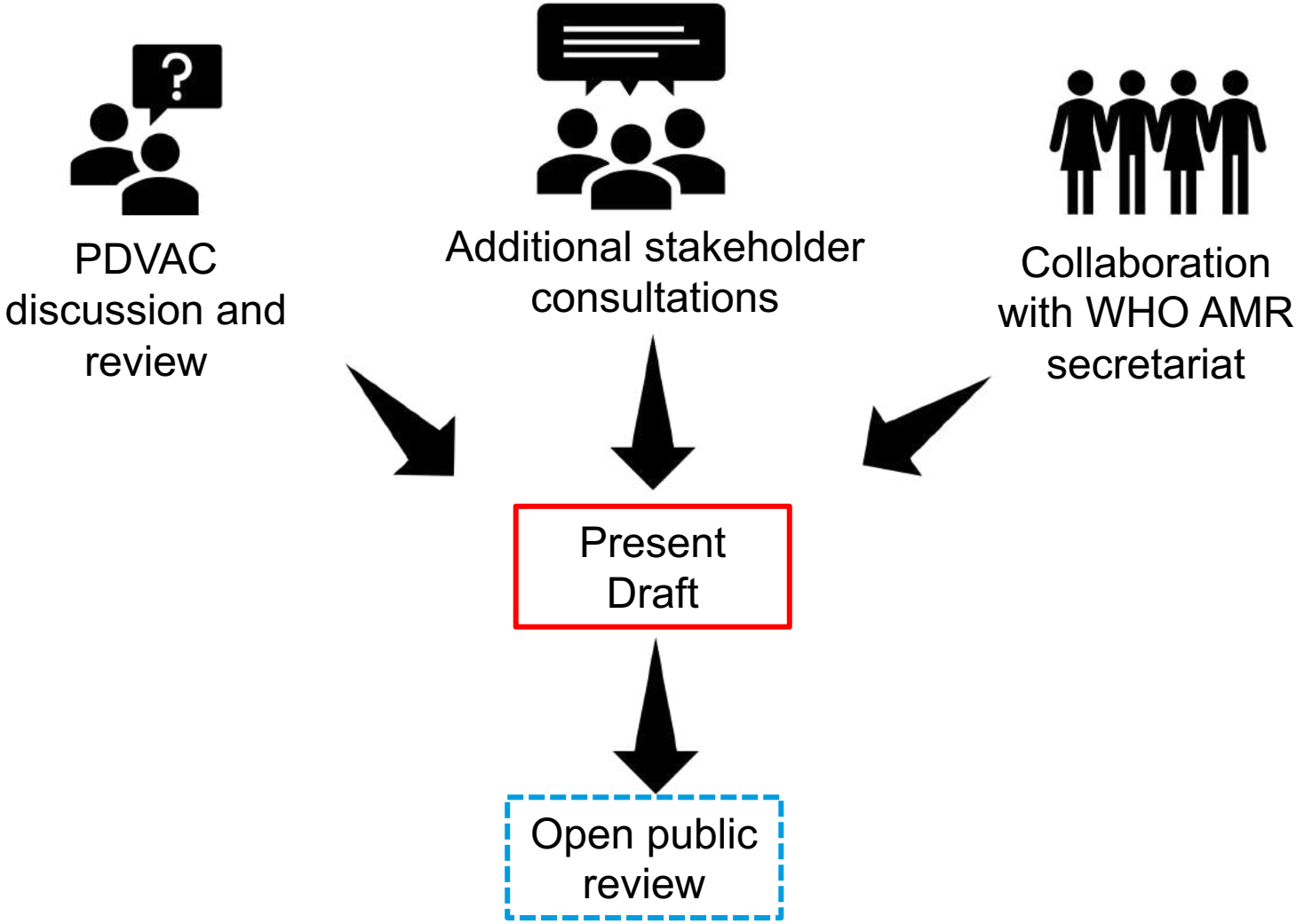
Consultation Process: Next Steps



Four Over-Arching Categories Identified

1. Policy and Communication
2. Research and Development
3. Evidence Generation
4. Animal Vaccines

10 Priority Actions were constructed from these.

1. Policy and Communication

1. Include vaccine recommendations when formulating global AMR strategy and prioritizing interventions.

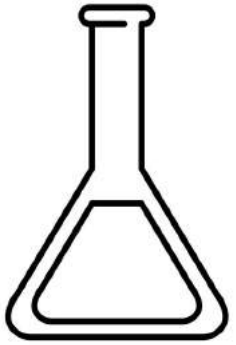
- **Within the context of other interventions e.g. wastewater infrastructure and hygiene.**

2. Make policy and financing decisions to ensure equitable and affordable access to vaccines that reduce AMR.

- **An example of this is the recent inclusion of AMR threat in Gavi's Vaccine Investment Strategy.**

3. Raise public awareness about the role of vaccines against AMR.

Research and Development



4. Increase direct support for research and development of vaccines against priority AMR pathogens.

5. Develop regulatory and policy mechanisms that hasten approval of vaccines that will impact AMR.

- **Consider options in regulatory and policy space to ease the path to licensure for vaccines with high AMR potential without undermining safety.**

6. Strengthen incentives and risk-sharing strategies to encourage the large investments needed to license and affordably deploy vaccines that will impact AMR.

- **Long delays between initial licensure and wide-scale introduction are often observed in low- and middle-income countries.**

3. Evidence Generation

7. Use available datasets and expand pathogen surveillance programs, epidemiological studies and randomized clinical trials to assess vaccine impact on AMR

8. Develop a model-based framework to assess the full public health, societal and economic value of vaccines in the prevention and control of AMR

- **Herd immunity, transmission patterns, pathogen carriage rates, bacterial population dynamics, vaccine-driven reductions in antibiotic use and various molecular drivers of resistance must be evaluated.**

4. Animal Vaccines

9. Expand use of existing animal vaccines to reduce antibiotic use in farming.

10. Increase research and development support for animal vaccines that would reduce antibiotic use in food production.

Supporting Evidence: Case Studies

Case study examples are included in support of the Action Priorities:

Gavi Adds AMR Impact to its Vaccine Investment Strategy

Gavi formally redevelops its guiding Vaccine Investment Strategy (VIS) document every five years……. In 2018, Gavi decided to include impact of vaccination on AMR as a main indicator of a vaccine's value…..

CARB-X funds innovation in antimicrobial development

CARB-X is a non-profit organisation expressly founded to support R&D to tackle AMR……. its mission is to support "early development of antibiotics, diagnostics, vaccines and other products to combat the most serious drug-resistant bacteria."

Setting Priorities Among Vaccines to Tackle AMR

A recent report from the Wellcome Trust and The Boston Consulting Group investigated which vaccines, among those for pathogens on the WHO AMR-priority pathogen list, would be both useful in the fight against AMR and be likely to be successfully brought to market.

Supporting Evidence: Current Vaccines and AMR-Related Vaccine R&D

Two additional tables outlining the role of Current Vaccines and Current AMR-related Vaccine R&D are included in the introduction. These highlight considerations about the role of current key vaccines and potential impact on AMR, and about priority vaccine candidates with the potential to have a high impact on AMR, that are in development.

Current Vaccines

Target Pathogen	WHO Recommended Use	Global Coverage	Coverage target	Vaccine impact on AMR	Source
S. Pneumoniae (Pneumoccus)	All children under 5 years of age	44%	90% nationally, 80% at district level	Proportionally reduces resistant and nonresistant pneumococcal disease; pooled estimates from >50 publications indicate PCV use reduces antibiotic use in children.	(1)(2)(3)

AMR-Related Vaccine Research and Development

Some Priority Candidates in AMR-Related Vaccine R&D

Many vaccines now in development have the potential to substantially impact AMR; efforts to prioritize these candidates for further funding are ongoing. We describe here the status of some of these candidates.

Tuberculosis. Tuberculosis (TB) causes more deaths annually than any other single infectious agent. A third of the world's population is latently infected with *Mycobacterium tuberculosis.* In 2017, 10 million people developed active TB, and 1.6 million died of the disease……


World Health
Organization






2019 WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Session: How is the perceived value of vaccines and associated technologies evolving?

Value of Vaccines with High Morbidity and Low Mortality

Maria Elena Bottazzi PhD
Associate Dean and Professor
Co-Director, TCH CVD

Texas Children's Hospital Center for Vaccine Development (TCH CVD)

Leading the development and testing of low-cost and effective vaccines against emerging, neglected tropical diseases and other diseases of unmet need

Features and Impact of Global Morbidity Diseases

Neglected Tropical Diseases with vaccines under development

Most common diseases globally with ~400 M people affected (1.5B + other STHs)

Major increases due to conflict and political instability

Leading cause of morbidity > 30 M DALYs

Beyond DALYs – promote and cause the "spiral" of Poverty

Leading productivity losses > $ 8 B

Major co-factors for other diseases i.e. malaria, HIV/AIDS

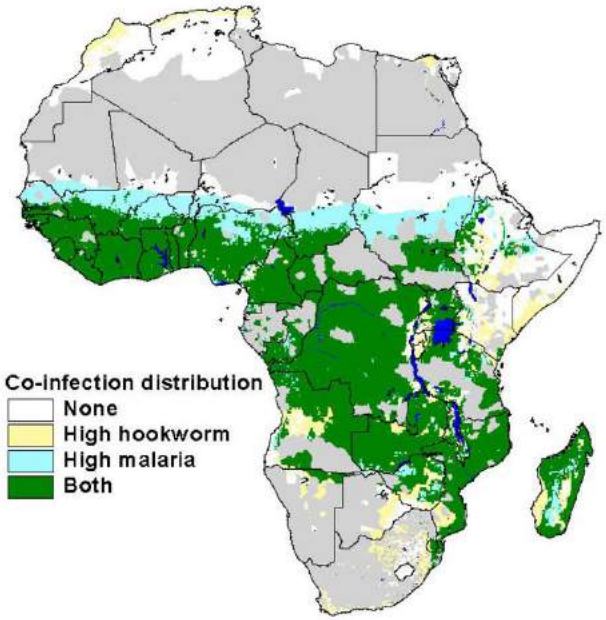
Baylor College of Medicine

Texas Children's Hospital

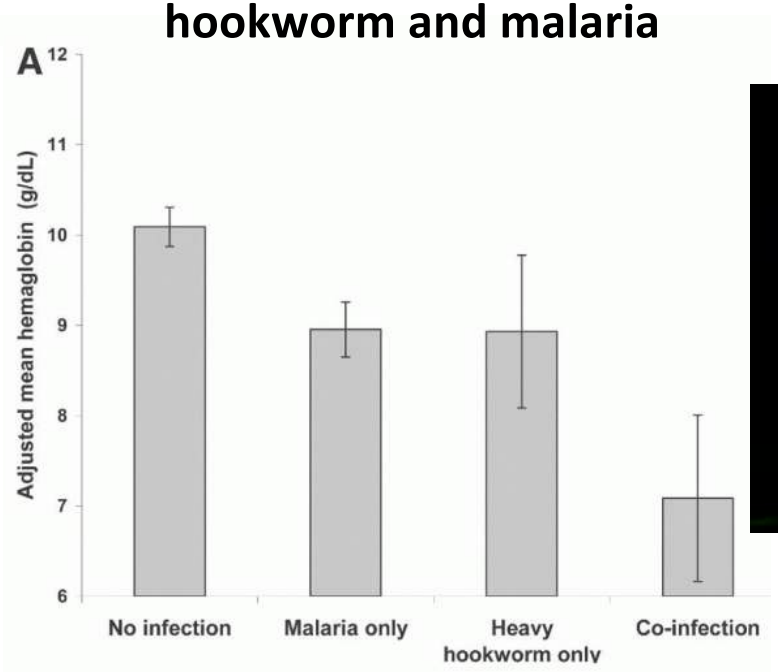
Disease	Stage of Vaccine Development	Prevalence in 2017[7]	Incidence in 2017[7]	Estimated DALYs in 2017[8]	Alternative disease burden estimates in DALYs
Hookworm Infection	**Phase 1-2**	**229 million**	**Not Determined**	**845,000**	**4.1 million[9]**
Schistosomiasis	**Phase 1-2**	**143 million**	**Not Determined**	**1.4 million**	**13-15 million[10]**
Dengue	Licensed (Dengvaxia)	6.3 million	105 million	2.9 million	0.3-5 million (+ arboviral diseases)[11]
Onchocerciasis	Preclinical	21 million	Not determined	1.3 million	128,000 additional[12]
Chagas disease	**Preclinical**	**6.2 million**	**162,500**	**232,000**	**806,170[13]**
Leishmaniasis	**Phase 1-2**	**4.1 million**	**669,100**	**774,000**	**>2 million just for cutaneous leishmaniasis[14]**
Leprosy	Phase 1	518,500	48,500	31,500	Local or regional estimates only
Yellow Fever	Licensed	2,600	97,400	314,000	0.3-5 million (+ arboviral diseases)[11]
Rabies	Licensed	500	13,400	634,000	3.7 million canine rabies[15]
Total NTDs	**-**	**~400 million**	**Not determined**	**8.5 million**	**> 30 million**

A Perfect Storm: Hookworm + Malaria = Severe Anemia

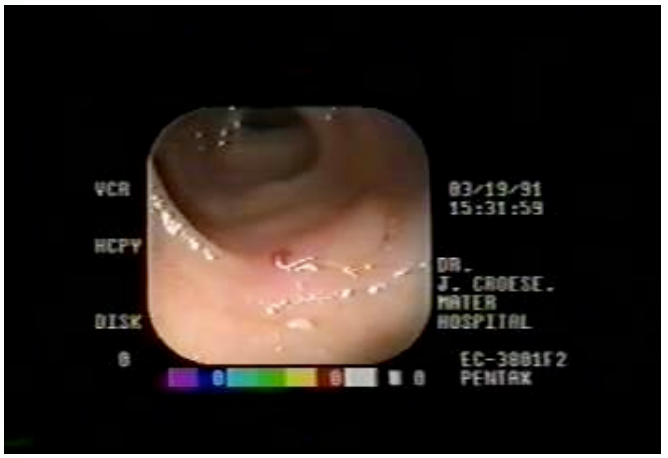
Co-endemicity of hookworm and malaria



Additive anemia of hookworm and malaria



Hookworm blood feeding



"Courtesy of John Wiley and Sons"

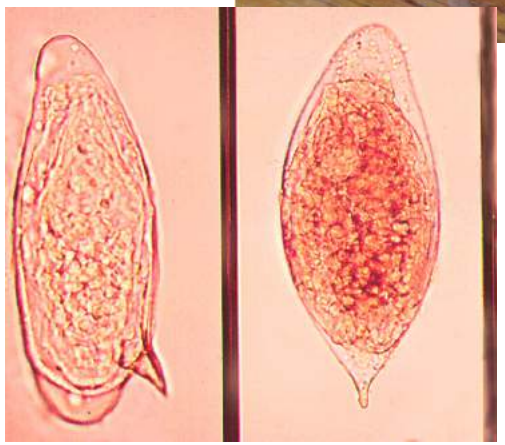
25 *Necator* worms = 1 ml blood loss = 0.55 mg Fe = Child's daily iron intake

Baylor College of Medicine

Texas Children's Hospital

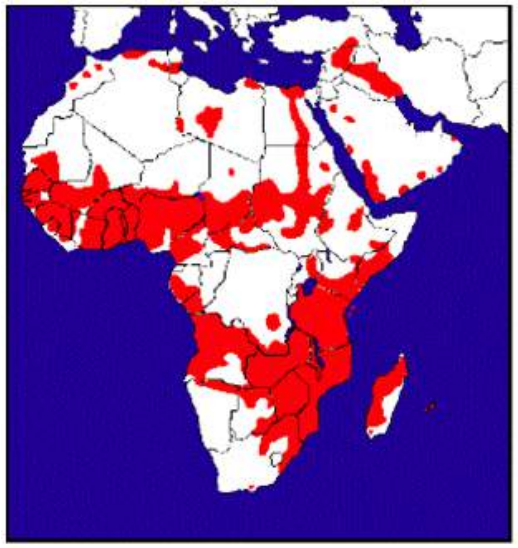
Bartsch et al (2016), Hotez PJ et al. (2010) ; Murray et al, (2012); Smith and Brooker, (2010); Keenan JD et al., (2013) Brooker et al., (2007), Brooker et al., (2006); Smith et al., (2010)

Another Perfect Storm: Schistosomiasis & HIV

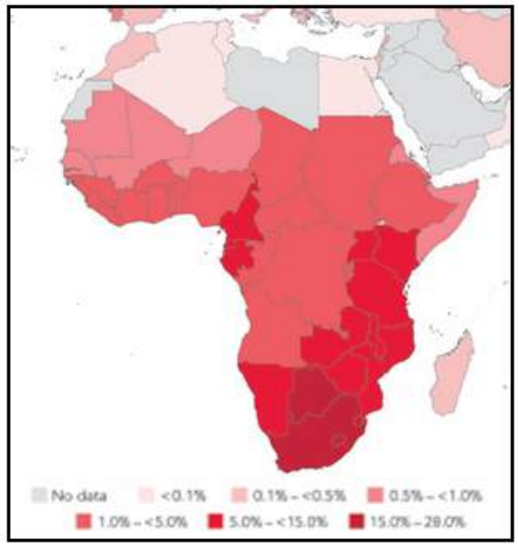


Intestinal schistosomiasis & anemia

Co-endemicity of urogenital schistosomiasis and HIV



Urogenital Schistosomiasis
King C, 2001



HIV Prevalence in Adults Aged 15-49
UNAIDS, 2010

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Current Control Strategies Alone are Not Sufficient

Vaccines are a strategic necessity and can complement conventional MDA

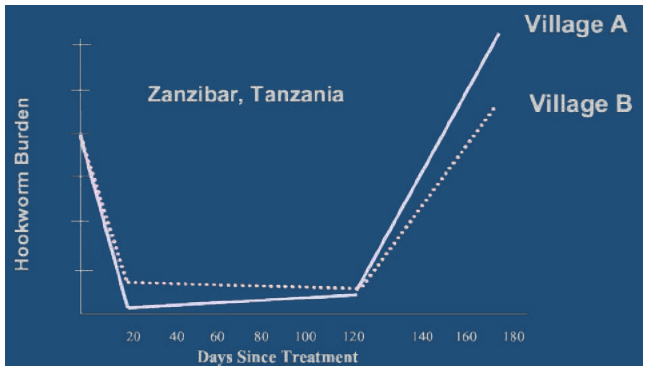
Current treatment: Small molecule drugs

- MDA impact shown only in areas of <20% prevalence; LT impact in >40-50% prevalence unknown
- % Target coverage is below threshold
- Do not prevent re-infection
- Lack of improvement in anemia
- Low cure rates, variable efficacy, and increasing drug failure

DISEASE	% Change of YLDs since 2006
LF	-44%
Ascariasis	-37%
Onchocerciasis	-33%
Schistosomiasis	-33%
Trichuriasis	-28%
Hookworm	-13%

Post-treatment Re-infection

Albonico et al



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The Golden Age for NTD and Anti-poverty Vaccine Development

Product Development Partnerships (PDPs) launched with robust funding support

Period 2000-2015 generated a modest but promising pipeline of NTD candidates that entered the vaccine development critical path

- Three hookworm vaccines entered clinical development (*Na*-GST-1, *Na*-APR-1 and Co-admin *Na*-GST-1/*Na*-APR-1)
- Three schistosomiasis vaccine candidates (Bilhvax, *Sm*-TSP-2 and *Sm*-14) plus 6 in preclinical stage
- Two leishmania vaccine candidates (LeishF2 and LeishF3) plus several 2nd or 3rd generation and several sand-fly-derived candidates in preclinical stage

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Post-2015 the priorities have shifted to:

Vaccines for pandemic threats and future epidemics (CEPI)

Vaccines for high mortality in children < 5 yo (Gates)

Develop/fund products with lower risk and greater effects on profitability and financial realization (GHIT & RIGHT)

An Accelerated Strategy for Rapid Entry into Phase 1

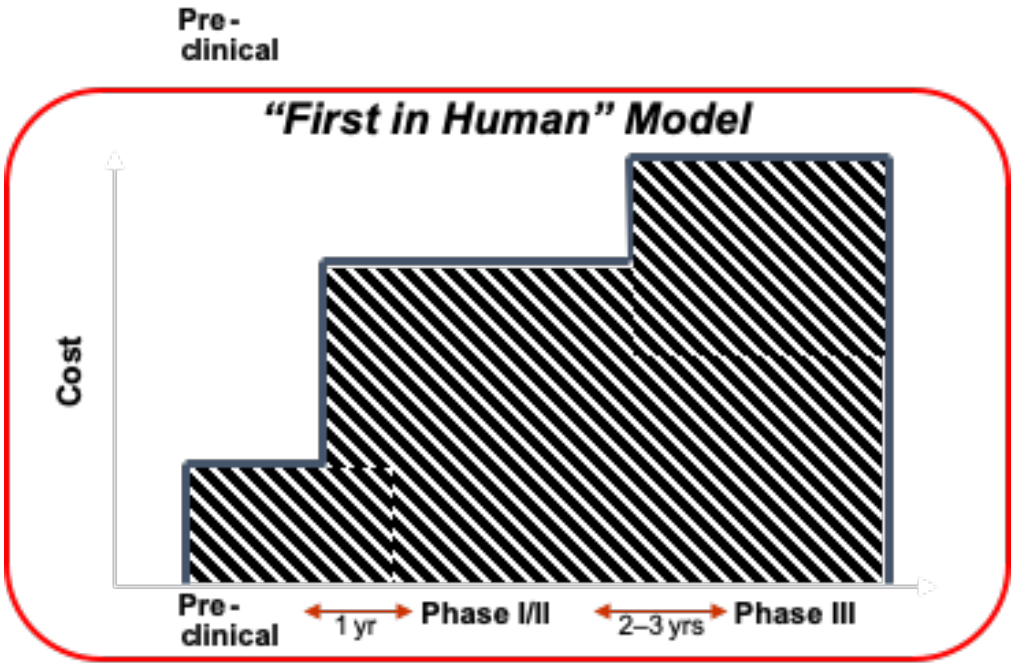
Running through the first set of gauntlets

PDP infrastructure established: virtual, in-house or hybrid models

Candidates were selected and prioritized from proof-of-principle preclinical models

Focused on rapid entry into FIH studies

- Smaller up-front investment in regulatory-enabling CMC (process development, characterization, tech transfer and GMP)
- Funds limited to 1-2 vaccine candidates with 1-2 types of formulations/adjuvants
- One shot on goal for GLP-Tox and FIH study
- Committed for the long-run: QA/RA, stability



* Source: Figure obtained from PRTM/PWC Consultants

Hookworm and Schistosomiasis Vaccines

Safe, well-tolerated and immunogenic

Evaluated in a series of Phase I clinical trials

- Adult volunteers from non-endemic (USA) and endemic areas [Brazil, Gabon (HW) and Uganda (Schisto)] and children from endemic area (Gabon for HW)
- Formulation - Recombinant protein adsorbed to Alhydrogel® +/- immuno-stimulants (TLR Agonists: GLA-AF or CpG10104)
  - *Na*-GST-1 vaccine tested in 160 volunteers
  - *Na*-APR-1 vaccine in 70 volunteers
  - Co-administration in 110 adult volunteers
  - Co-administration in 48 children volunteers
  - *Sm*-TSP-2 vaccine tested in 132 volunteers

Developed a Controlled Human Hookworm Infection (CHHI) model (in USA under US FDA IND)

Currently in proof-of-concept Phase 2 trials

- Hookworm *Na*-GST-1 vaccination + CHHI in 48 healthy, hookworm-naïve adults in US
- Schistosomiasis *Sm*-TSP-2 randomized, double-blind Phase IIb trial in 200 Ugandan adults

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Technical Gaps and Current Challenges

Running the next set of gauntlets

- **Gaps to scale and improve manufacturing processes**
- **Replenish aged vaccine lots**
- **Limited adjuvant access and novel formulation & delivery platforms**
- **Difficult pivotal Phase 2/3 clinical trials**
- **No support for QA/RA & PM**
- **No alignment & fragmented vaccine portfolios**
- **Short and inadequate funding schemes**
- **Transparent and trustworthy partnerships**
- **Lack of key stakeholder engagement**

Traversing the Second "Valle of Death": Towards Licensure

The **funding need accumulates to > $151 million** for each vaccine

Initial estimates predict an **internal rate of return of 11.7%** probability adjusted

With a discount rate of 15%, the probability unadjusted **net present value is $11.6 million**

Vaccination could result in **>$77 million in healthcare savings** and avert **>500,000 total DALYs** per target countries

Vaccination linked to annual MDA **highly cost-effective** (ICERs ≤ $790/DALYs averted)

An Urgent Call to Action

New and sustainable vaccine development roadmap for NTD vaccines

- Urgent need of partnership(s) with **vaccine manufacturers** (DCVMN, Pharma)
- Convene key technical and operational **stakeholder engagements**: partnerships, alignment & risk management strategies
- Access to **tools and models** to **predict** economic and public health **returns on investments - FPHV**
- **Innovative funding** for late-stage development and delivery beyond gov. subsidies (GAVI) or philanthropy (Gates)
- More **R&D funding** to fill the knowledge gaps: mechanisms of action, correlates and end-points, pathogenesis, etc.

COMMENT

EXPLORATION Seafarers' journals are a rich record of discoveries p.340 | CRISPR Time to redefine misleading meanings in genome editing p.345 | OUTBREAKS WHO drafts code on pathogen sequence sharing p.345 | OBITUARY Aaron Klug, electron-tomography Nobel laureate, remembered p.346

REPORTERS/JEVONNE

Women in a hospital ward with malaria bed nets in Bunia, the Democratic Republic of the Congo.

Vaccine candidates for poor nations are going to waste

Promising immunizations for diseases that affect mostly people in low- and middle-income countries need help getting to market, urge **David C. Kaslow** and colleagues.

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An eco-system to align portfolios, identify opportunity costs and reduce development risks

Thank You

Partners

Funders

The value of vaccine delivery innovations

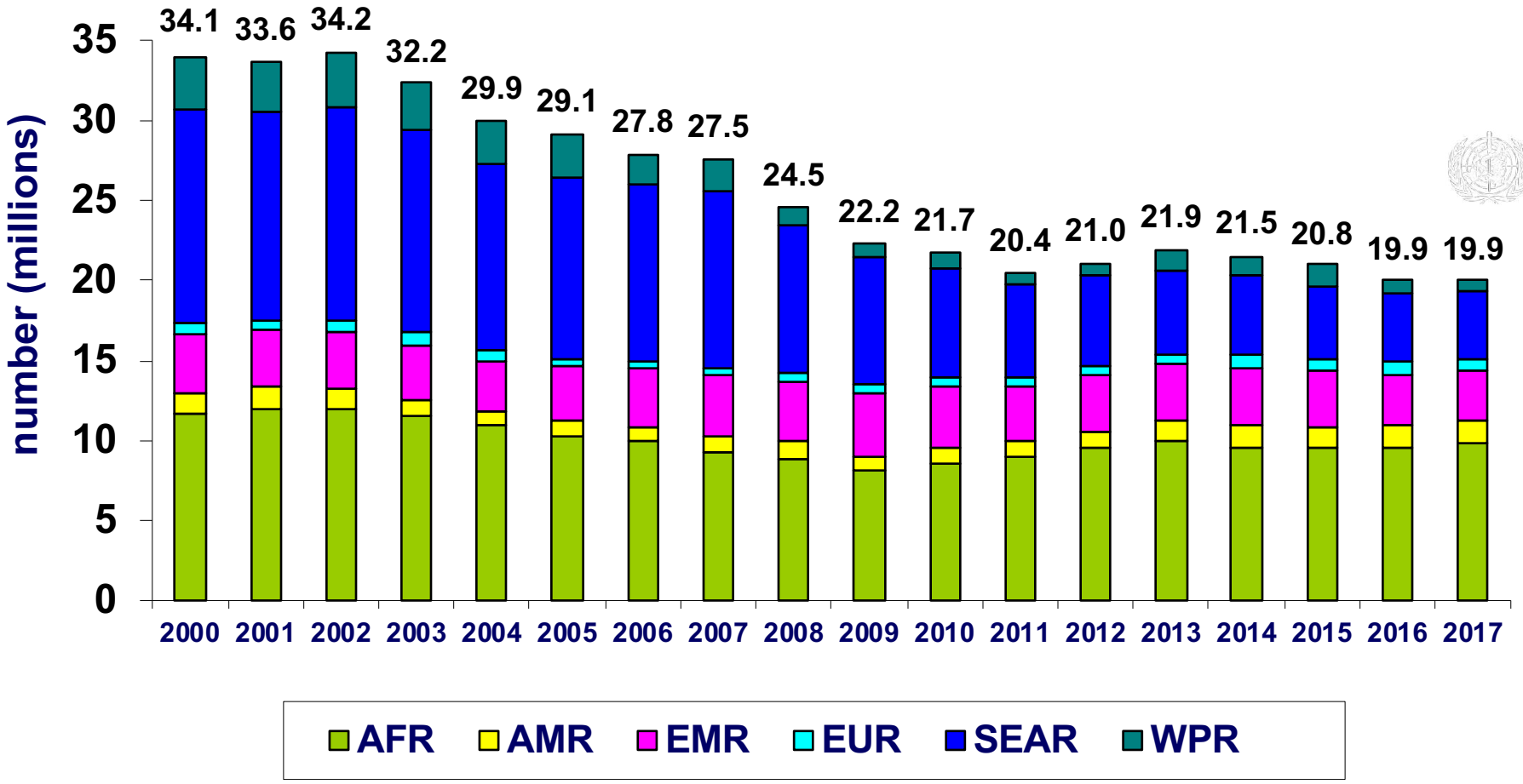
World Health Organization

Birgitte Giersing, PhD

Product Development for Vaccine Advisory Committee meeting

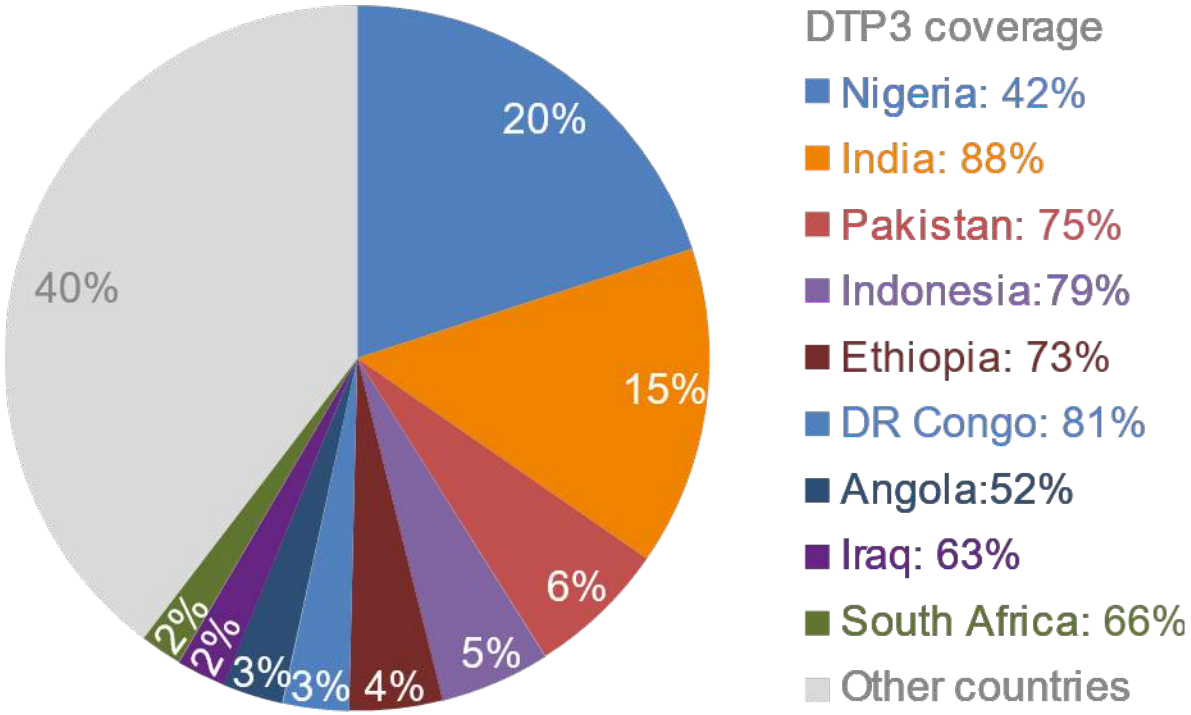
26-28 June 2019

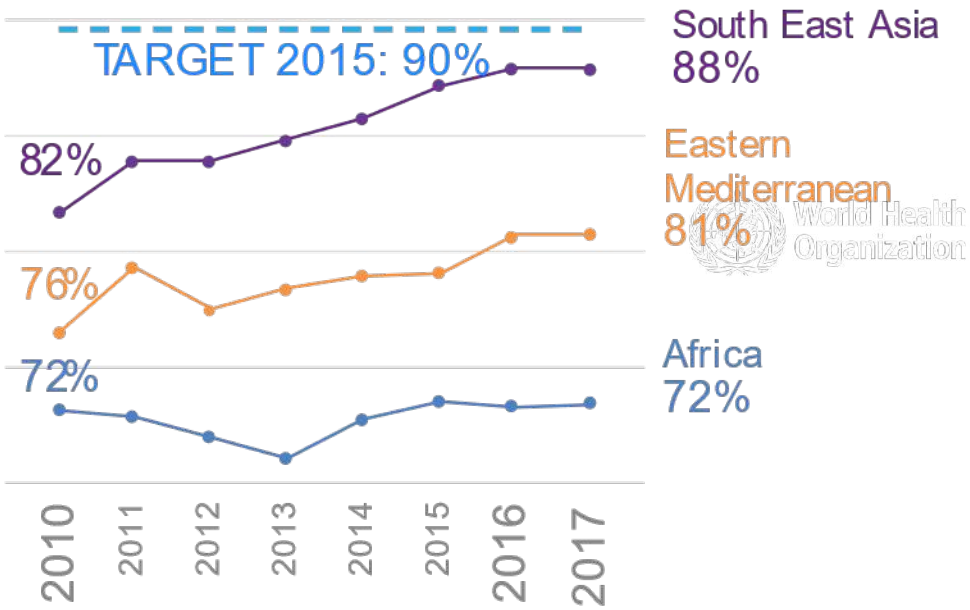
While more children are being reached, there are 20 Million under vaccinated children



Source: WHO/UNICEF coverage estimates 2017 revision, July 2018. United Nations, Population Division. The World Population Prospects - 2017 revision. New York, 2017.
Immunization Vaccines and Biologicals (IVB), World Health Organization.
194 WHO Member States. Date of slide: 12 December 2018.

While more children are being reached, there are 20 Million under vaccinated children

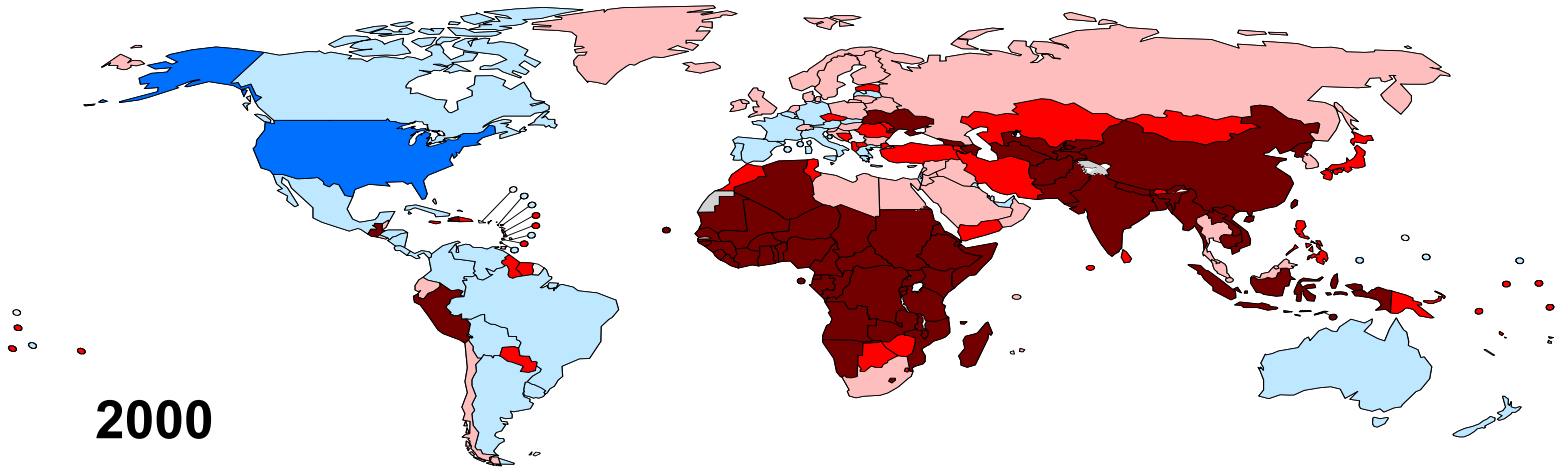




Source: WHO/UNICEF coverage estimates 2017 revision, July 2018. United Nations, Population Division. The World Population Prospects - 2017 revision. New York, 2017.
Immunization Vaccines and Biologicals (IVB), World Health Organization.
194 WHO Member States. Date of slide: 12 December 2018.

Number of vaccines/antigens introduced 2000 vs July 2017

World Health Organization

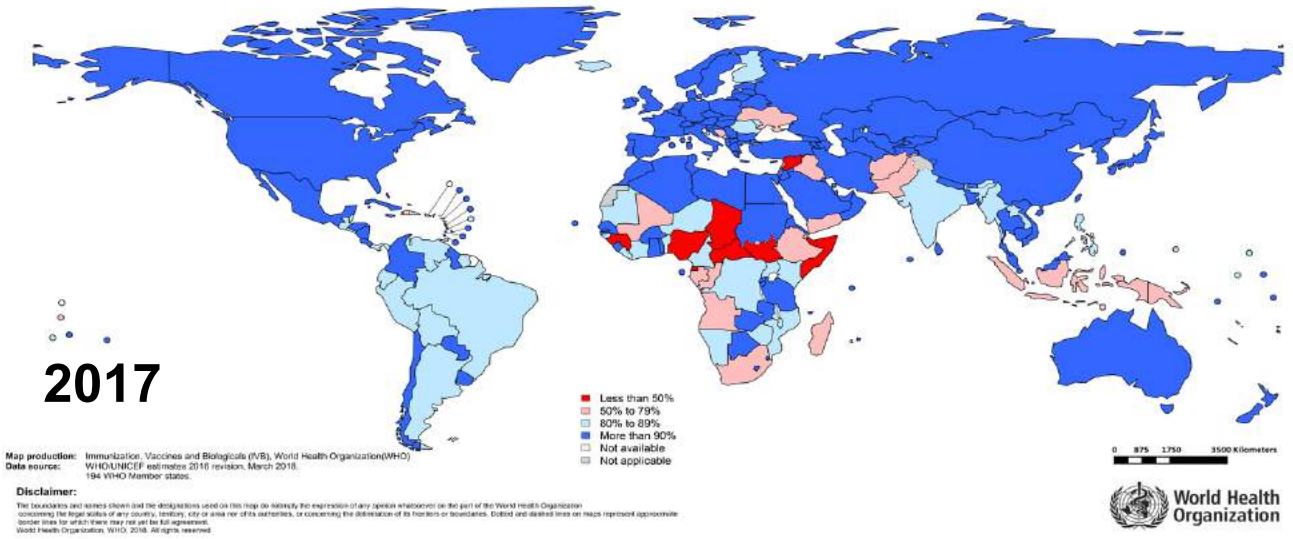


2000

Selected antigens are :
Diphtheria, Tetanus, Pertussis, Measles, Polio - universal use
Hepatitis B,
Heamophilius Influenza type B,
Pneumococcal conjugate
Rotavirus
Rubella

World Health Organization

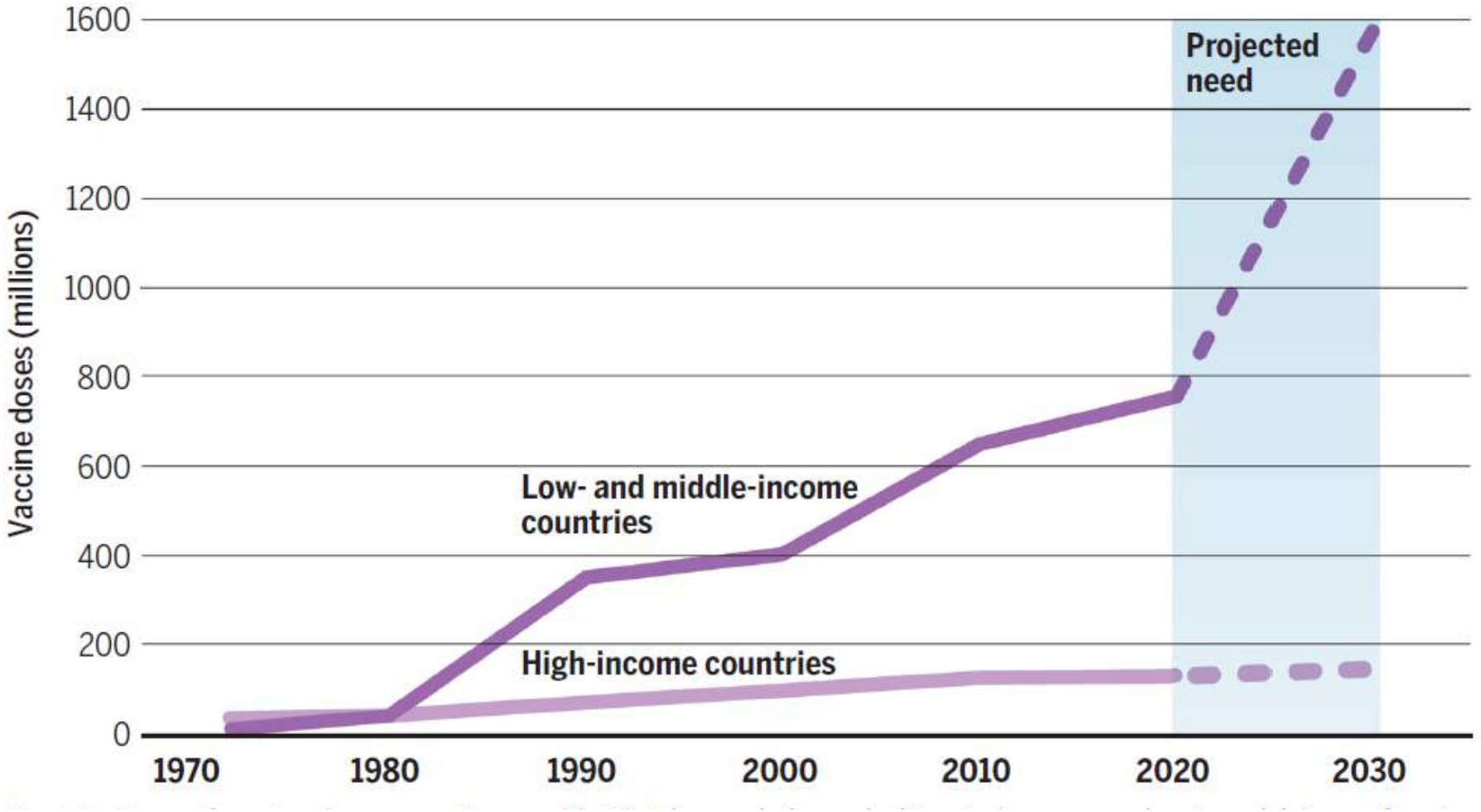
- 5 antigens (DTP, Measles and Polio)
- 6 antigens
- 7 antigens
- 8 antigens
- 9 antigens
- ≥10 antigens
- Not applicable
- Not available



2017

World Health Organization

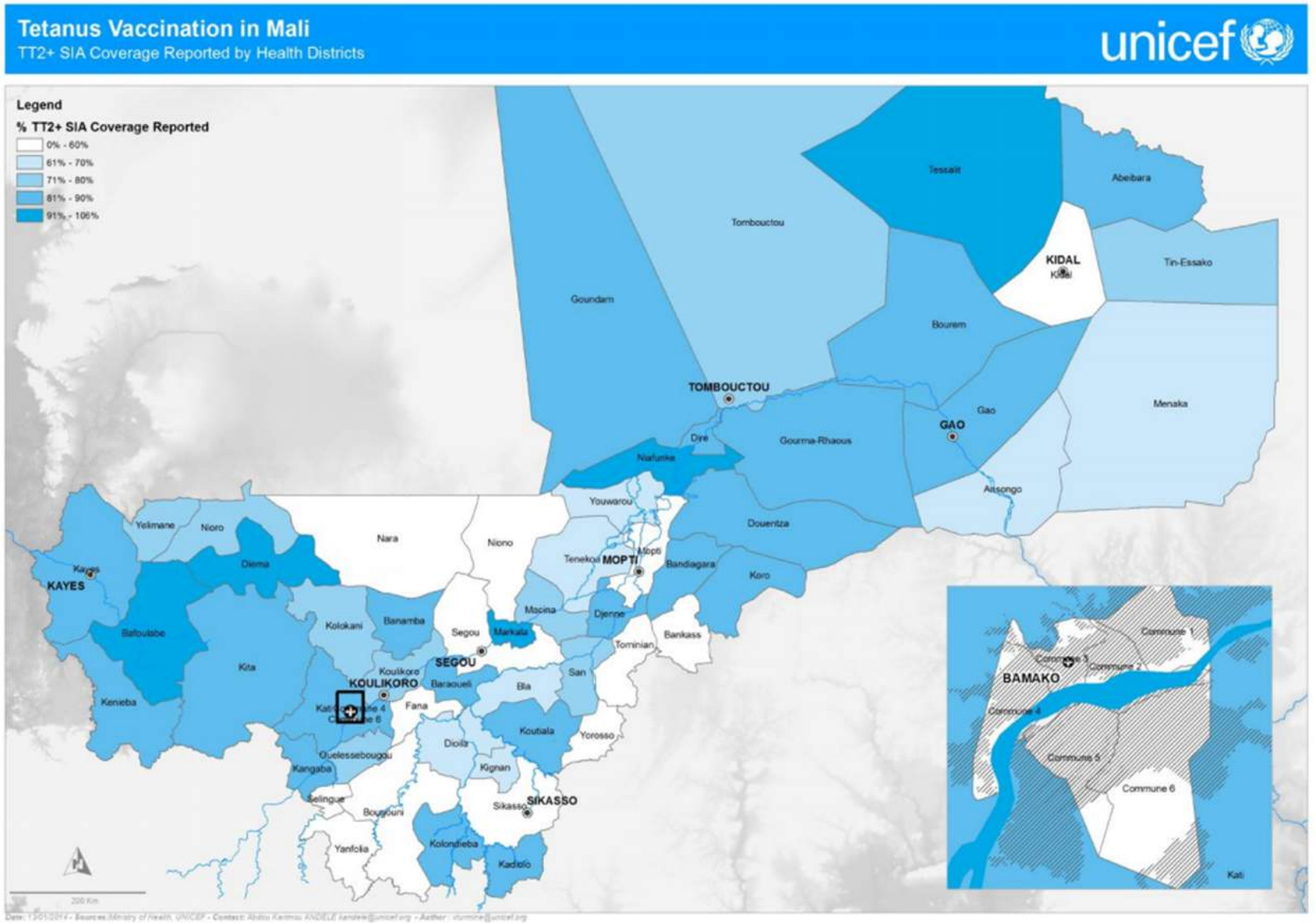
Projected delivery of vaccine doses over time worldwide



Source: Rappuoli et al, Vaccines and global health: In search of a sustainable model for vaccine development and delivery, STM, 2019

It's not only about increasing coverage.
We need improvements in *equitable* coverage

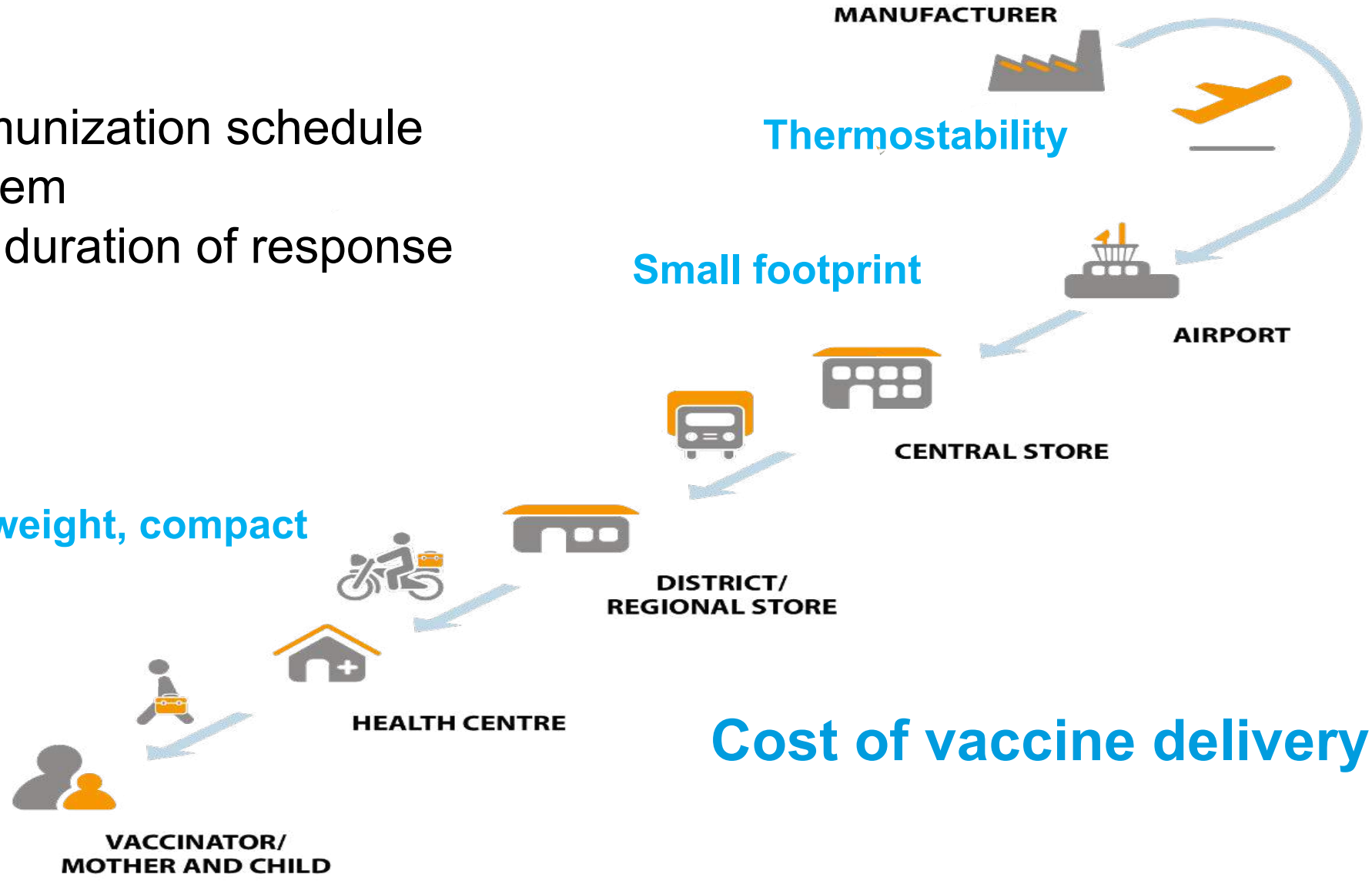
World Health Organization



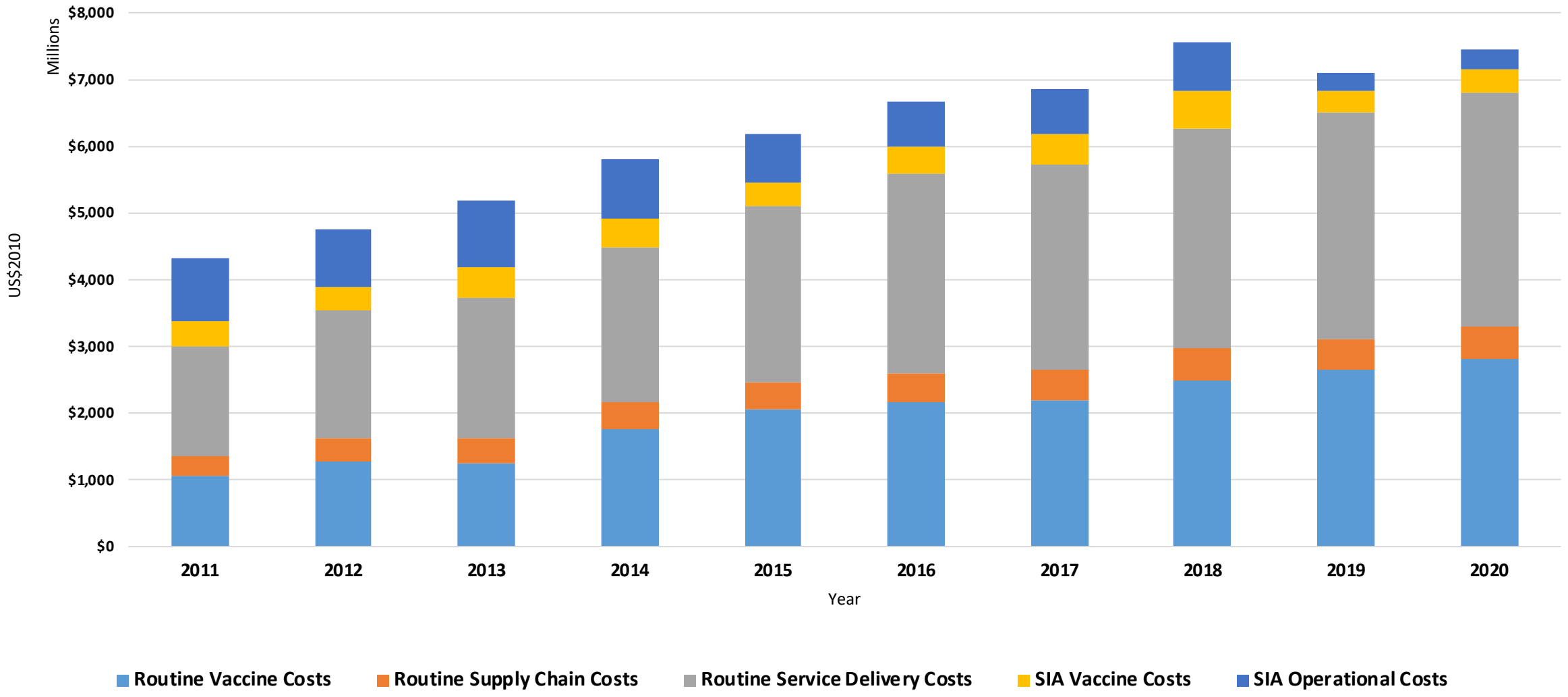
World Health Organization

What are the challenges when developing vaccines for LMIC contexts?

- Fit within the immunization schedule and delivery system
- No of doses and duration of response
- Acceptability
- Cost of goods



The total cost to immunize a child = cost to procure the vaccine + the cost to deliver it



Source: Portney A et al, 2015.

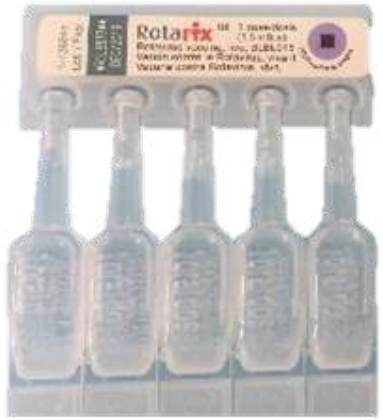
Several delivery technologies already exist; many in development

Disposable-syringe jet injector

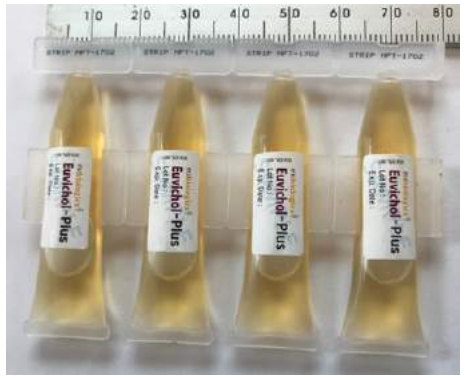
Controlled temperature chain

Integrated reconstitution technology

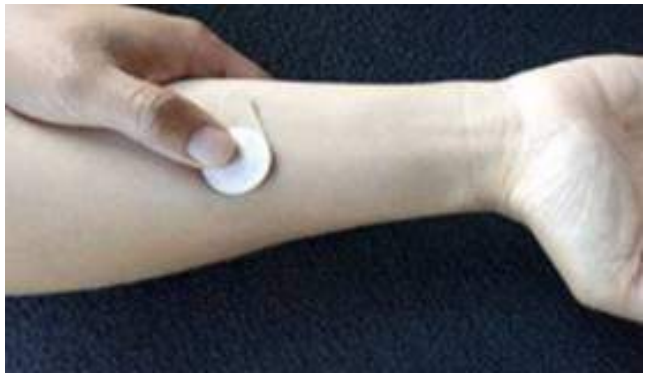
Compact Prefilled Autodisable Device



Rotarix™ rotavirus vaccine

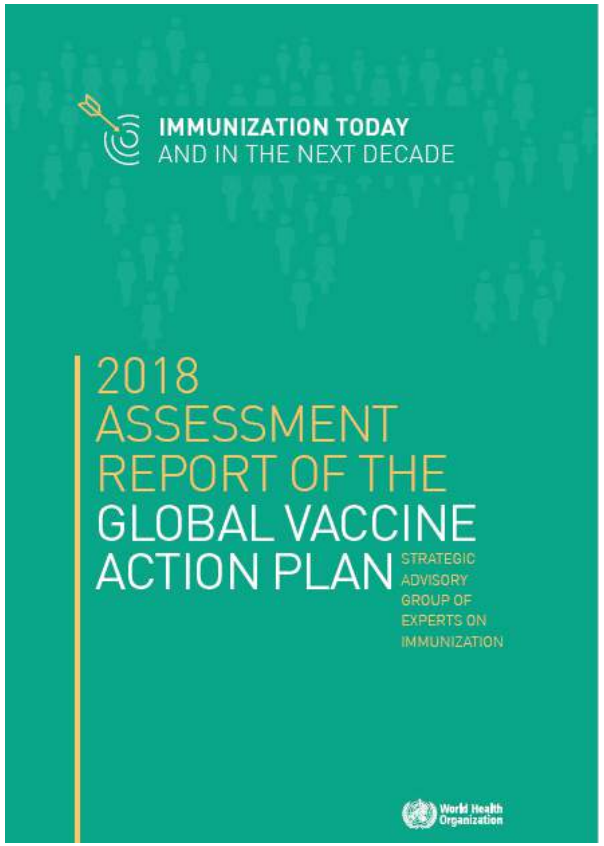


Euvichol® oral cholera vaccine

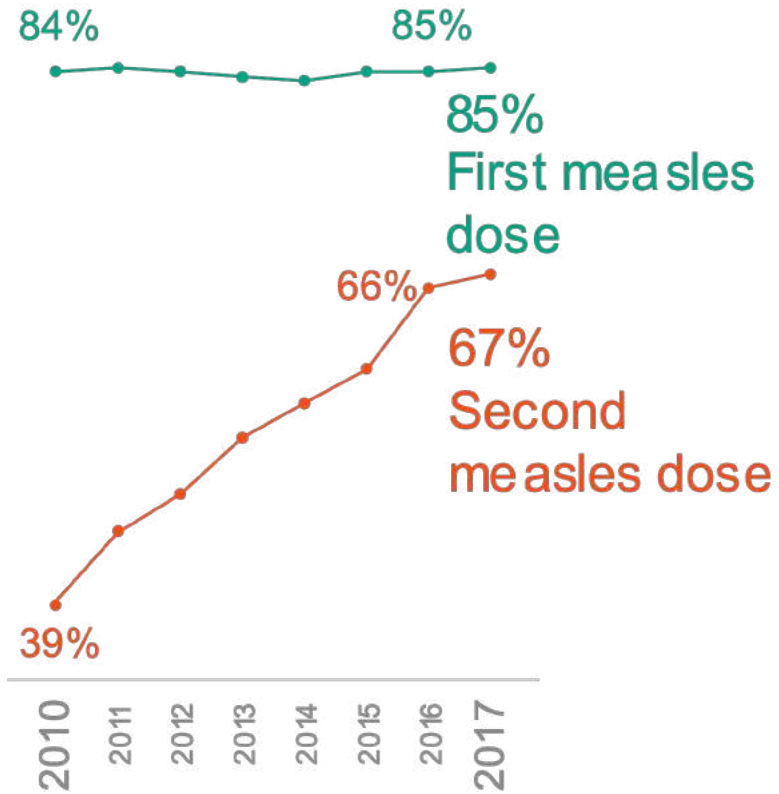


Dissolving microarray patch

Market opportunities for traditional vaccines

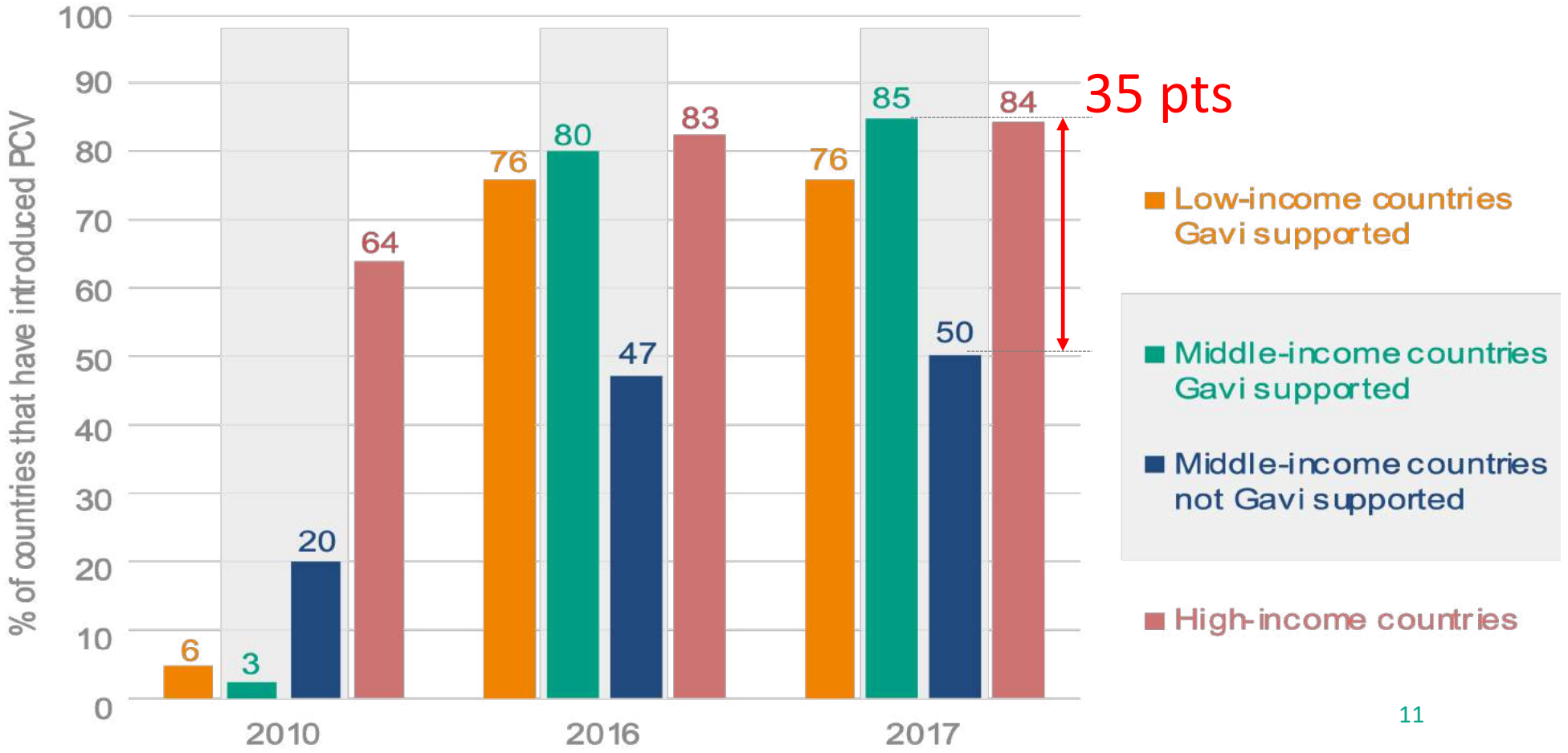


GLOBAL COVERAGE OF FIRST-DOSE MEASLES VACCINE HAS PLATEAUED BUT SECOND-DOSE COVERAGE HAS INCREASED SIGNIFICANTLY



Slide courtesy of Tania Cernuschi, WHO

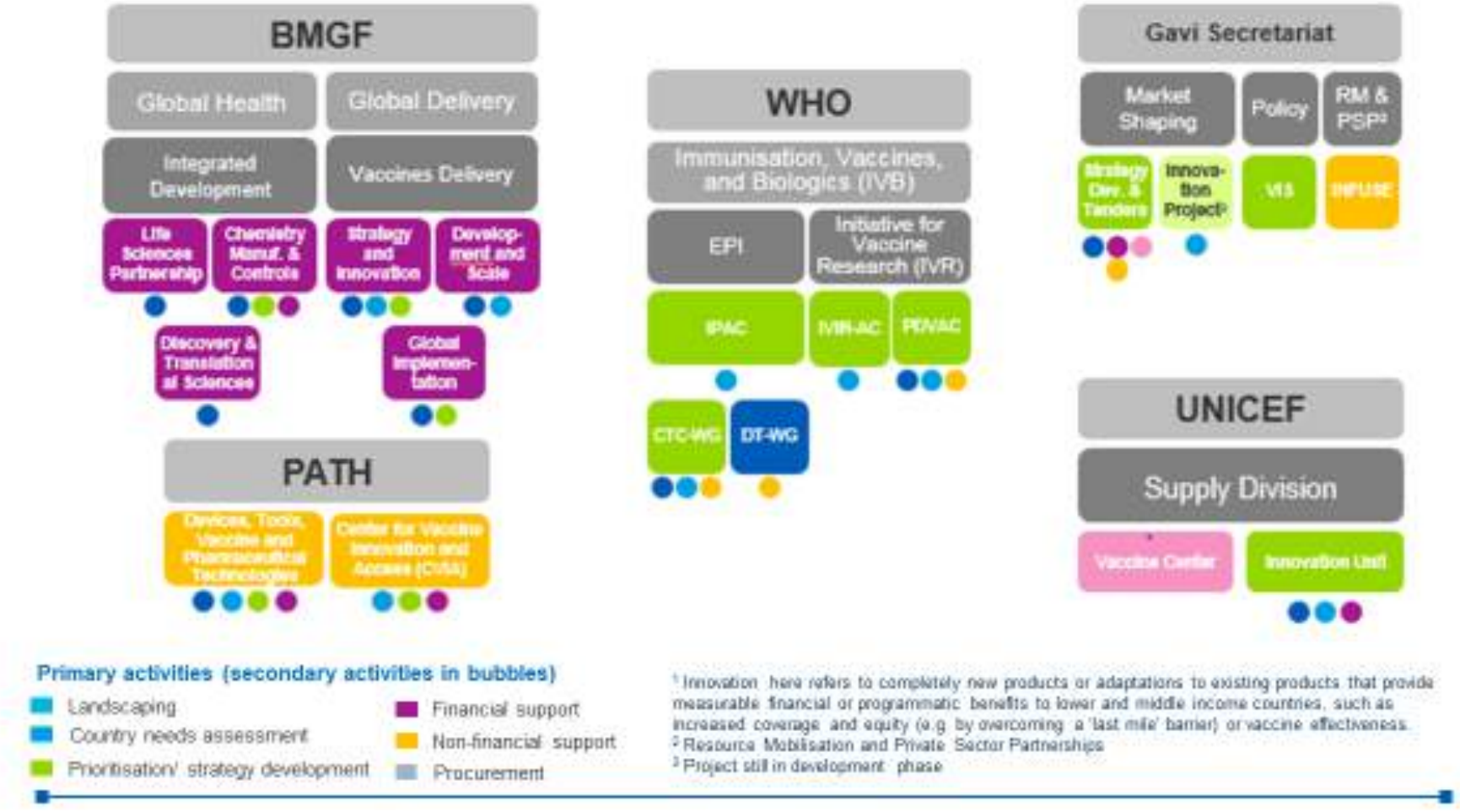
The unfinished business with newly introduced vaccines



Source: GVAP 2018

Slide courtesy of Tania Cernuschi, WHO

A mapping of innovation-related activities across the various partners was conducted to understand existing capabilities and gaps



Slide courtesy of the VIPS Alliance

Across the Alliance, a number of initiatives have tackled vaccine product innovation, but key gaps remain…

Vaccine product innovation

Vaccine product development and introduction continuum

Vaccine product development → **Procurement**

Innovation conundrum

Lack of understanding which product innovations countries need

Uptake conundrum

Lack of decision making and procurement mechanisms for innovations:

- No Alliance aligned perspective on the benefits of innovations
- No space for innovations coming with a cost premium

Slide courtesy of the VIPS Alliance

....creating key risks

Although vaccine product innovations have been identified as a key lever to achieve the Alliance coverage and equity goals and despite several initiatives, key gaps may result in **market inefficiencies for countries and manufacturers**:

Innovative products may not be developed due to lack of clear communication of desired attributes

Innovative products may be developed, however with undesirable profiles due to lack of guidance, thus may not be procured/used

Suitable innovations may be developed and brought to market, but not met by demand because of other market dynamics' attributes (e.g., programmatic trade-offs, pricing, supply security, etc.).

Slide courtesy of the VIPS Alliance

VIPS is a close Alliance-wide collaboration effort

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

World Health Organization

Gavi The Vaccine Alliance

unicef

BILL & MELINDA GATES foundation

PATH

CLINTON HEALTH ACCESS INITIATIVE

Gavi The Vaccine Alliance
World Health Organization
BILL & MELINDA GATES foundation
PATH
unicef

VIPS: Vision and goal

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

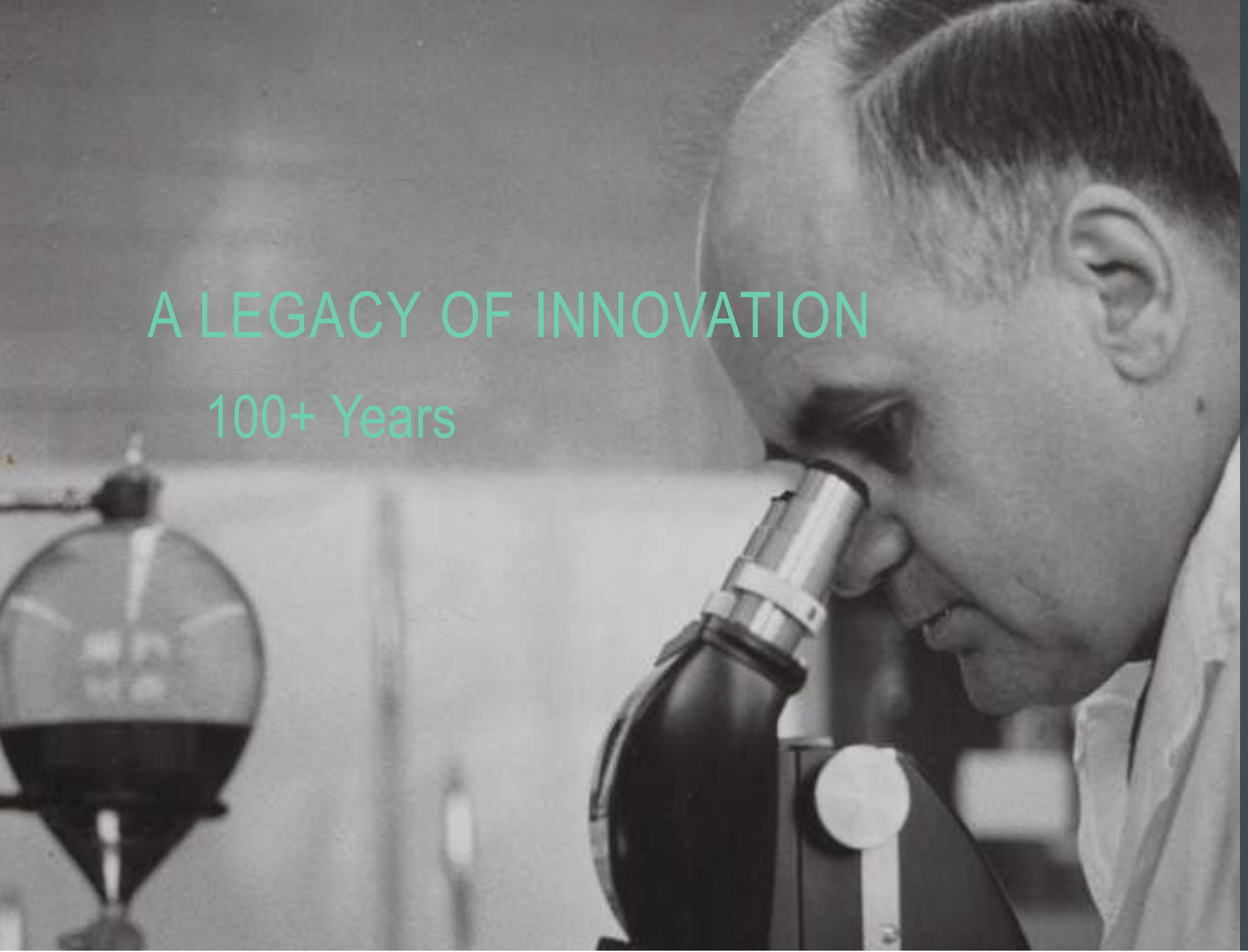
VISION

- **Innovation** is one of the **Alliance priorities** for shaping markets to the benefit of Gavi-supported countries.
- The Alliance aims to pursue a common agenda of:
  - **Driving vaccine product innovation to better meet country needs**
  - **Support Alliance goals on immunisation coverage and equity.**

GOAL

- **Prioritise innovations in vaccine product attributes to provide greater clarity to manufacturers and partners to make investment decisions.**

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef



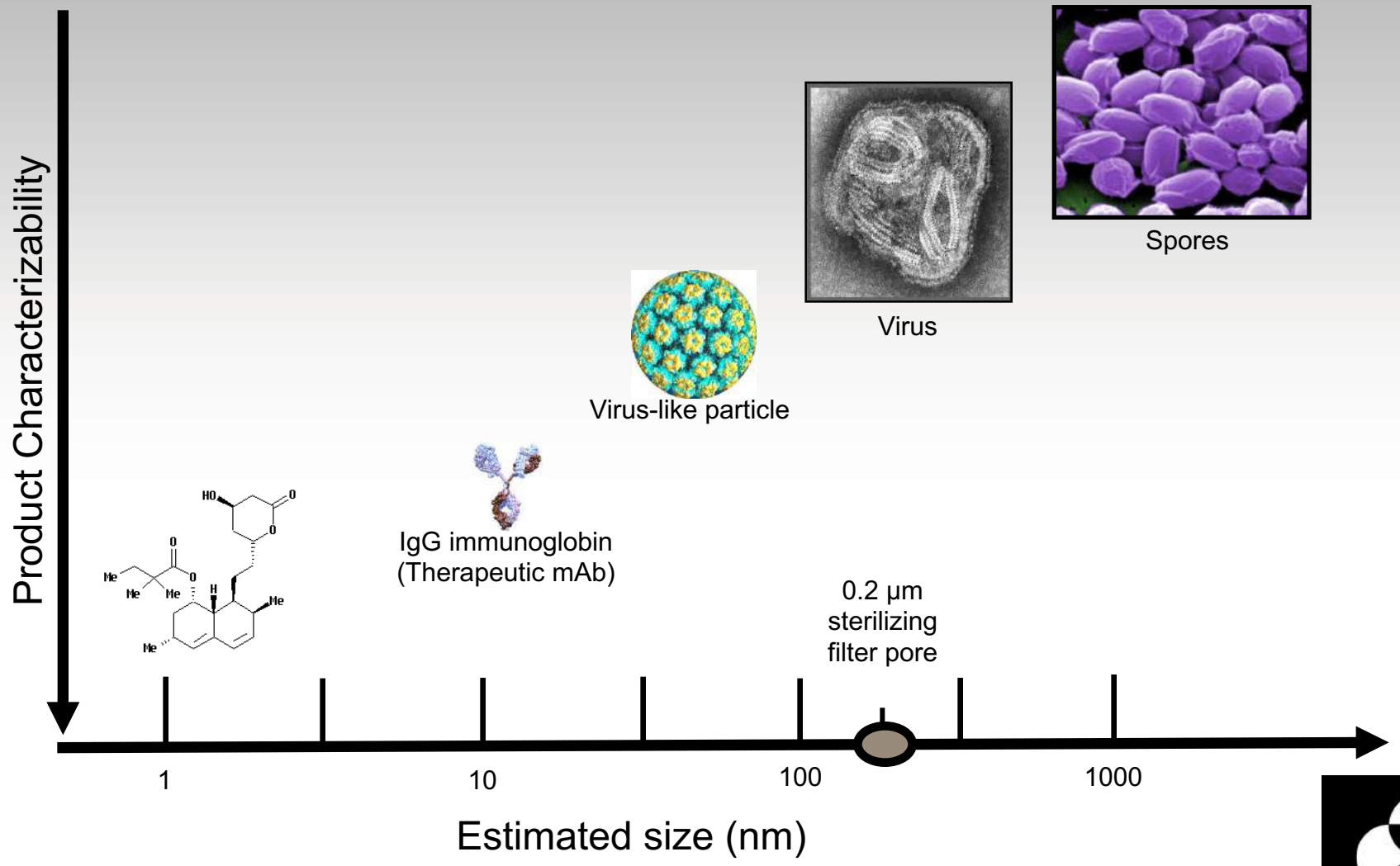
A LEGACY OF INNOVATION

100+ Years

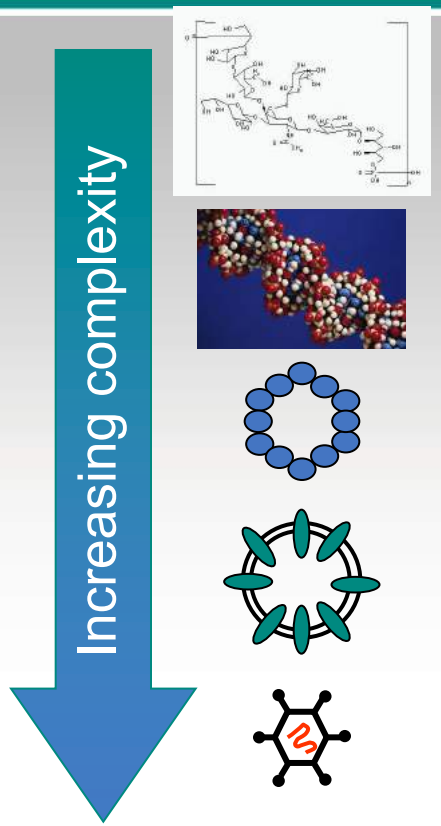
MSD

VACC-1251970-0000 04/18

Complexity of Vaccine Product Development



Vaccines Are Diverse



Polysaccharide:

mRNA vaccines:

Virus Like Particles:

Viruses:

Combinations:

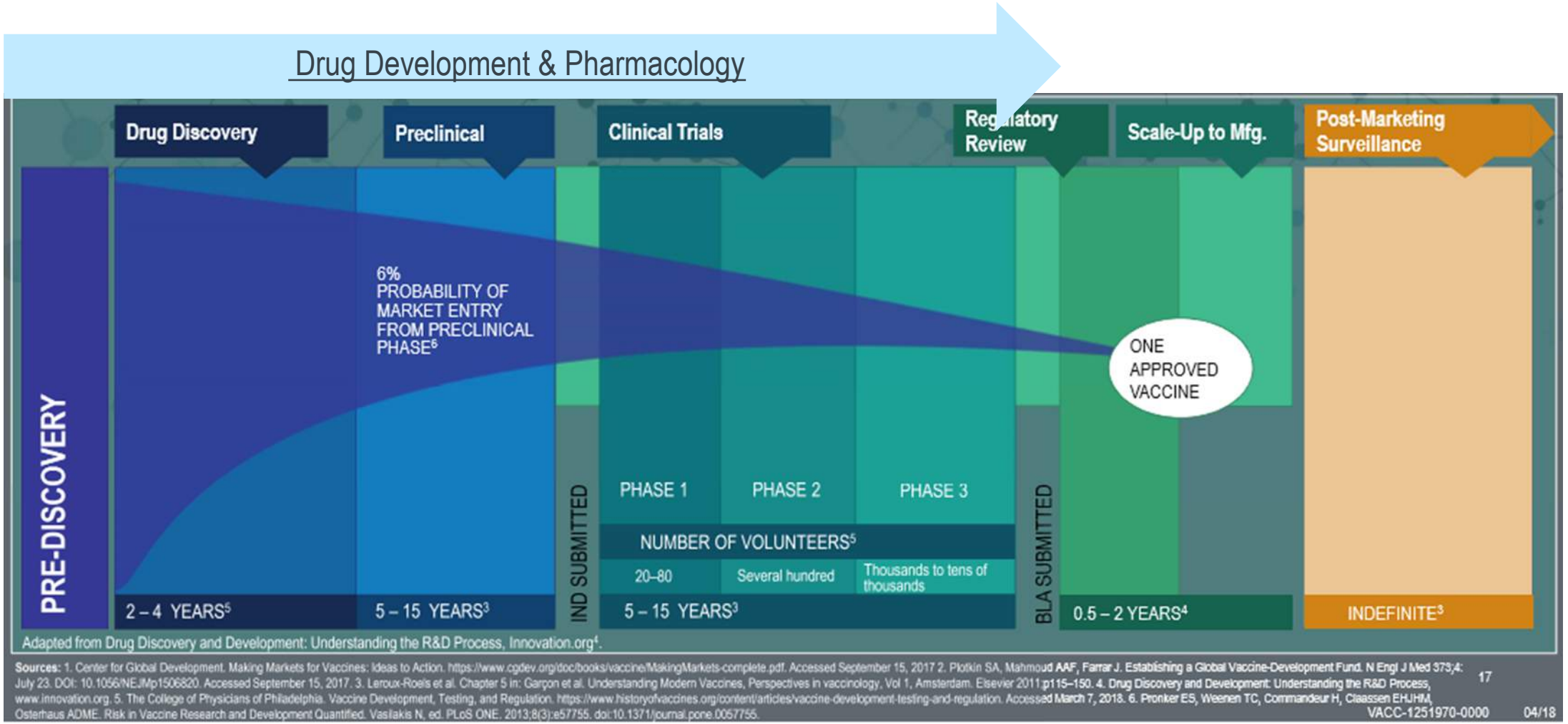
Adjuvants:

Wide variations in properties, product “characterize-ability”
There are few platform processes

MSD

Vaccine Development is Lengthy and Costly with No Guarantee of Success

Live the Legacy.
Protect the Future.



Sources: 1. Center for Global Development. Making Markets for Vaccines: Ideas to Action. https://www.cgdev.org/doc/books/vaccine/MakingMarkets-complete.pdf. Accessed September 15, 2017 2. Plotkin SA, Mahmoud AAF, Farrar J. Establishing a Global Vaccine-Development Fund. N Engl J Med 373;4: July 23. DOI: 10.1056/NEJMp1506820. Accessed September 15, 2017. 3. Leroux-Roels et al. Chapter 5 in: Garçon et al. Understanding Modern Vaccines, Perspectives in vaccinology, Vol 1, Amsterdam. Elsevier 2011;p115–150. 4. Drug Discovery and Development: Understanding the R&D Process, www.innovation.org. 5. The College of Physicians of Philadelphia. Vaccine Development, Testing, and Regulation. https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation. Accessed March 7, 2018. 6. Pronker ES, Weenen TC, Commandeur H, Claassen EHJHM, Osterhaus ADME. Risk in Vaccine Research and Development Quantified. Vasilakis N, ed. PLoS ONE. 2013;8(3):e57755. doi:10.1371/journal.pone.0057755.

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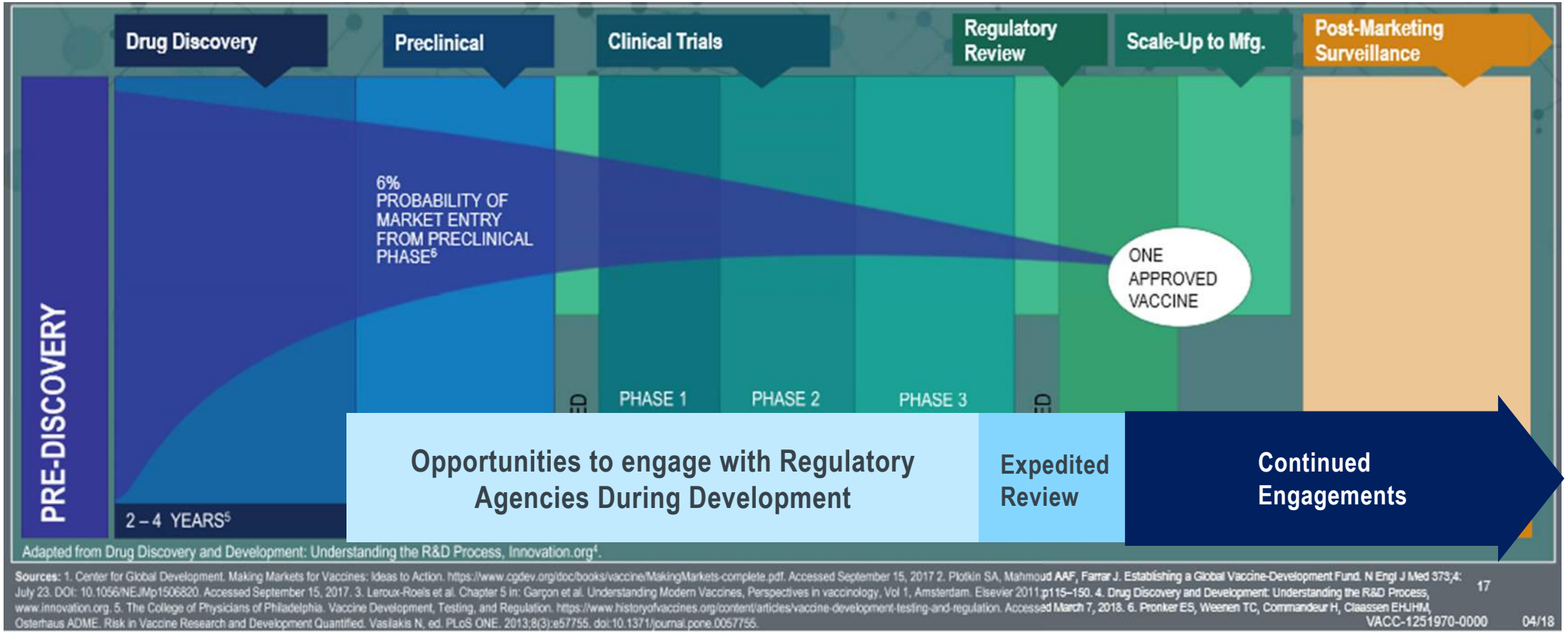
VACC-1251970-0000 04/18

INVENTING FOR LIFE

Public

Interactions with regulatory agencies are needed throughout vaccine development and continue throughout the lifecycle of the vaccine…

Live the Legacy.
Protect the Future.

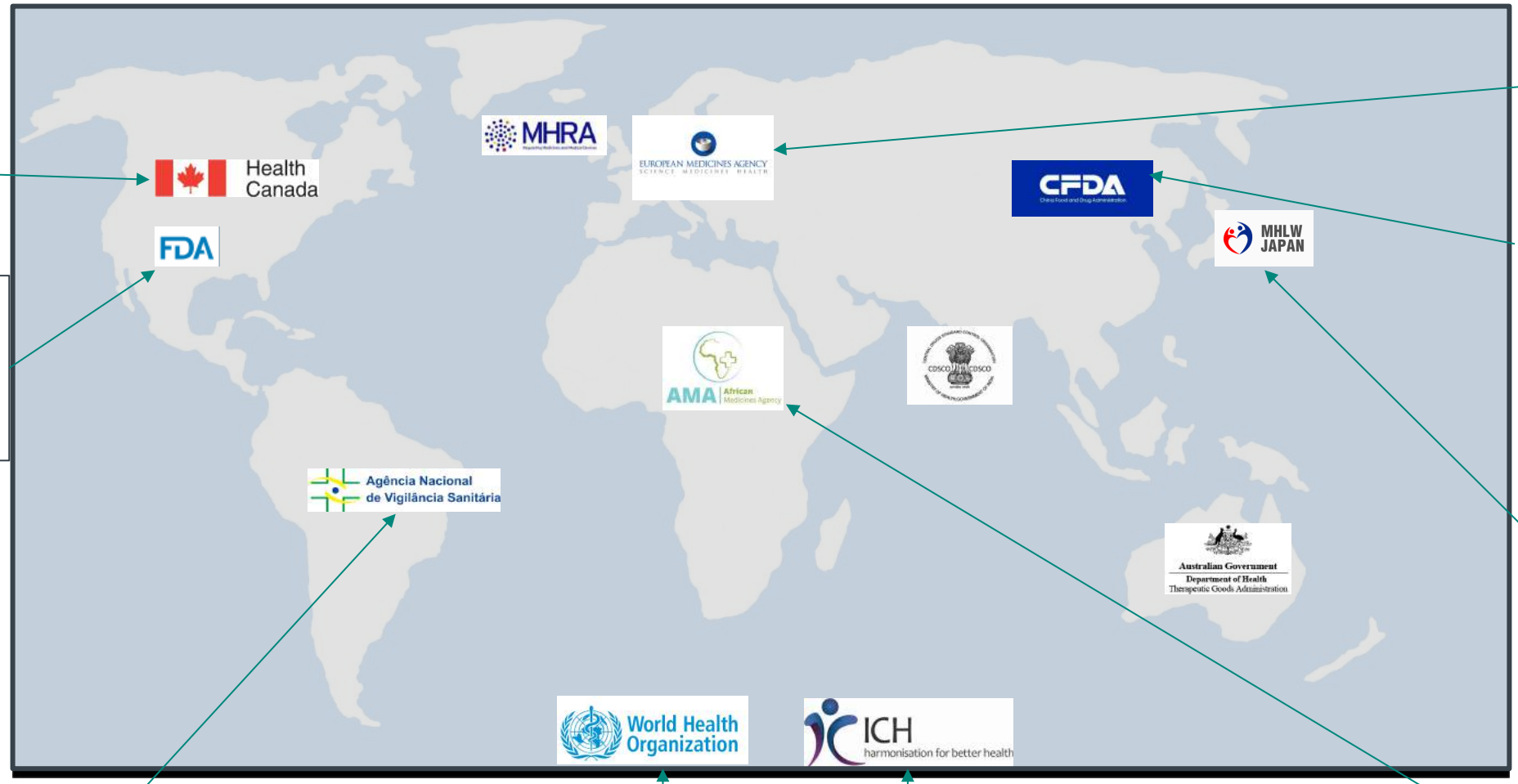


Sources: 1. Center for Global Development. Making Markets for Vaccines: Ideas to Action. https://www.cgdev.org/doc/books/vaccine/MakingMarkets-complete.pdf. Accessed September 15, 2017 2. Plotkin SA, Mahmoud AAF, Farrar J. Establishing a Global Vaccine-Development Fund. N Engl J Med 373;4: July 23. DOI: 10.1056/NEJMp1506820. Accessed September 15, 2017. 3. Leroux-Roels et al. Chapter 5 in: Garçon et al. Understanding Modern Vaccines, Perspectives in vaccinology, Vol 1, Amsterdam. Elsevier 2011:p115–150. 4. Drug Discovery and Development: Understanding the R&D Process, www.innovation.org. 5. The College of Physicians of Philadelphia. Vaccine Development, Testing, and Regulation. https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation. Accessed March 7, 2018. 6. Pronker ES, Weenen TC, Commandeur H, Claassen EHJHM, Osterhaus ADME. Risk in Vaccine Research and Development Quantified. Vasilakis N, ed. PLoS ONE. 2013;8(3):e57755. doi:10.1371/journal.pone.0057755.

Global regulations and requirements need to be considered when developing vaccines

Live the Legacy.
Protect the Future.

Note: This figure only shows a small subset of the agencies that MSD needs to work with for global vaccine clinical trials and registrations



Biologics and Genetic Therapies Directorate (BGTD), within the Health Products and Food Branch (HPFB) of Health Canada, is responsible for Canada's vaccines regulatory program.

Vaccines are regulated by the Center for Biologics Evaluation and Research within the US Food and Drug Administration. Accelerated pathways are possible including fast-track and breakthrough therapy designation, and priority review.

Brexit is having a major impact on our industry with the future separation in regulatory reviews between the UK's Medicines and Healthcare Regulatory Agency (MHRA) and the European Medicines Agency.

China is undergoing major reform in the regulatory space including new laws for vaccine administration after a vaccine safety scandal involving local manufacturers in 2018.

Japan's Ministry of Health, Labor and Welfare (MHLW) is the regulatory body that oversees food and drugs in Japan, which includes creating and implementing safety standards for medical devices and drugs. In conjunction with the MHLW, the Pharmaceutical and Medical Device Agency (PMDA) is the agency that is responsible for reviewing drug. vaccine and medical device applications.

ANVISA - the Brazilian Health Surveillance Agency, linked to the Ministry of Health of Brazil, is the regulatory agency in charge of health products, such as drugs and vaccines

Prequalification of vaccines by the World Health Organization (WHO) is needed prior to procurement by United Nations agencies. The WHO also publishes guidelines and standards for vaccines.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) publishes guidelines that are followed in many regions of the world.

Regional harmonization is starting in Africa with a commitment to form an African Medicines Agency. Currently there is an African Vaccines Regulatory Forum (AVAREF) performing coordinated product reviews in collaboration with the World Health Organization.

Trends in global regulations

Live the Legacy.
Protect the Future.

- **Importance of value evidence:**
  - Parallel advice procedures (e.g. European Medicines Agency, Health Technology Assessment programs and National Immunisation Technical Advisory Groups) could enable vaccine development plans to better address the needs of all the stakeholders involved in vaccine authorization, reimbursement and deployment.
- **Importance of real world data (RWD) and real world evidence (RWE):**
  - Playing an increasing role to support coverage decisions and to support clinical trial designs and observational studies.
- **Regulatory harmonization and divergence:**
  - Although some regions are trying to harmonize regulations (e.g. in Africa) there is also a trend towards implementation of new vaccine-specific regulations (e.g. in Asia).

It is an Internal Race to Bring Products to the Market
Meet the Drivers:

Clinical Product Development constitutes the progressive clinical research studies to demonstrate the product is safe and efficacious.

Chemistry, **Manufacturing**, and **Controls** (**CMC**) constitutes that part of pharmaceutical development that deals with the nature of the **drug substance and drug product**, the manner in which both are made, and the manner by which the **manufacturing** process is shown to be in **control.**

What's the course of CMC during this race?

Process Definition & Analytical Development

- Define **raw materials, process operations, and parameter set-points**.
- Complete Analytical method development

Commercial Site Selection, Facility Readiness, Process Characterization, Analytical Validation

Process Characterization - Additional process experience to understand impact of raw material, components, and process parameters on critical quality attributes and process variability.

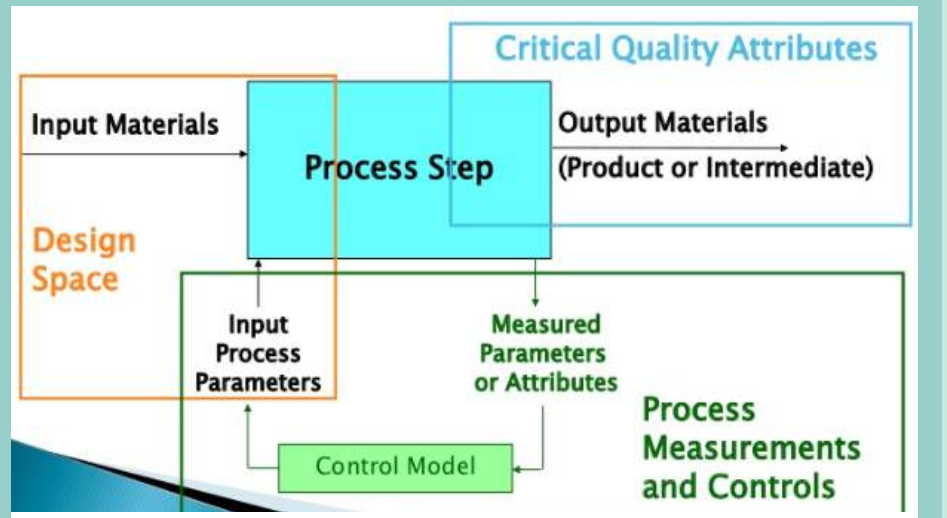
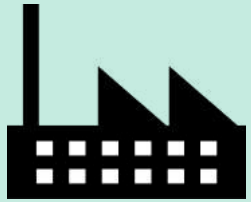


*Figure from Design Space Presentation prepared by Drug Regulations – a not for profit organization. www.drugragulations.org

Process Qualification

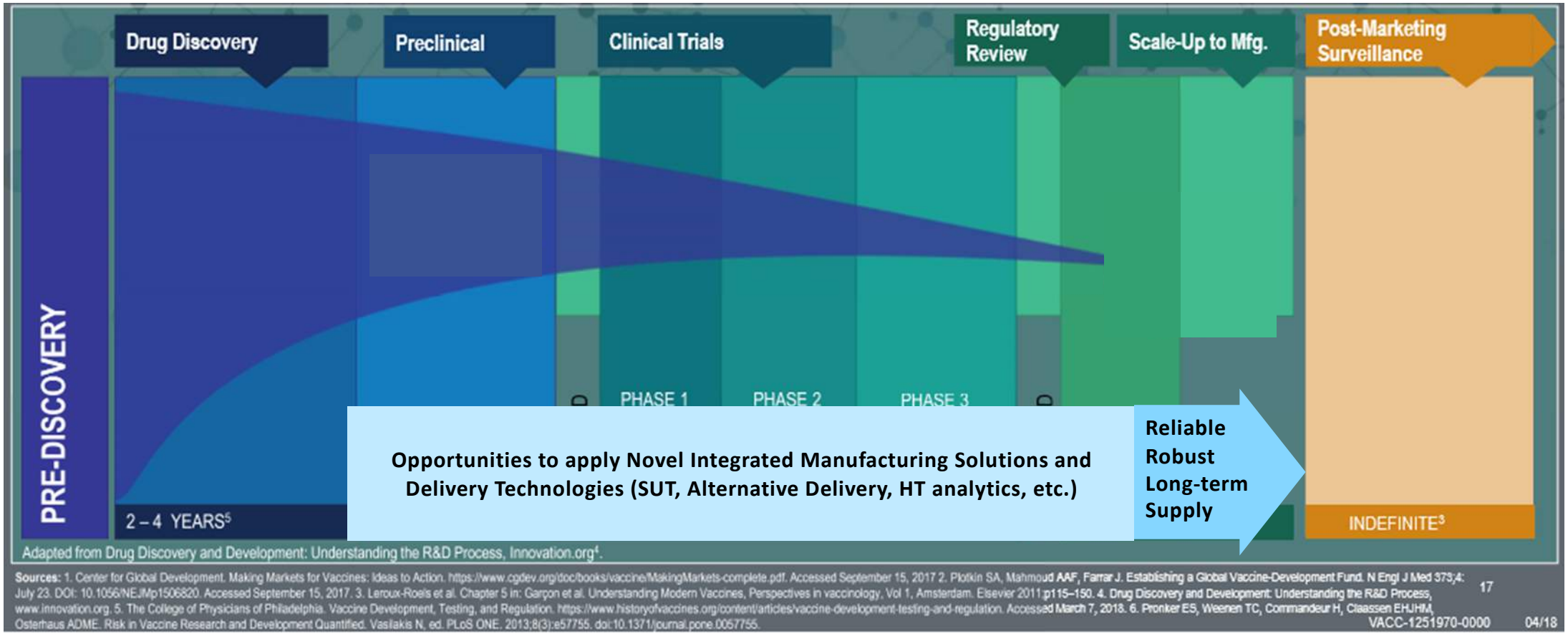


DS and DP process qualification lots are manufactured in **commercial facility** to demonstrate the process is capable of reproducibly meeting critical quality attributes.

Stability Data Prepare to File

Accumulate **minimum** of 6M of drug product accelerated and real-time stability data and prepare file for submission.

Vaccine CMC Development from Discovery to Post-Launch; Opportunities to Employ Novel Delivery Technologies



…to ensure reliable and robust supply through process, analytical and formulation

Biological E. Limited
Celebrating Life Every Day

PDVAC Meeting : Manufacturer's Perspective

26 June 2019
Geneva

Ramesh Matur, PhD
Biological E Ltd,
Hyderabad, India

Manufacturer's view: developing new vaccines

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- BE has been supplying vaccines to UNICEF and Govt agencies and is a DCVMN member
- Over the years we have seen price erosion and increased competition for some approved vaccines – not a surprise but expected : Limits the ability to continue to invest in R&D
- BE is committed to develop new vaccines using new / novel technologies
- Requires R&D commitment for full development and need Commercial Manufacture Capex investment while the product is in Phase 3 clinical trials

Manufacturer's view:
developing new vaccines

Biological E. Limited
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- Some challenges for developing new vaccines – there are uncertainties and hence risk the time and money invested
- Access to Available Technologies / Licensures / Agreements
- Opportunities for receiving funding
- Reasonable confidence in pricing on the approved new product

Manufacturer's view:
developing new vaccines

Biological E. Limited
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- Developing the vaccines for unmet need in preventing infectious diseases could lead to creating new intellectual property with rights on the invention
- IP Creates value – Innovation needs to be recognised and rewarded

Manufacturer's view
developing new vaccines

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New Leap for vaccines and understanding infectious diseases

- AMR is a big concern –
  - No new classes of antibiotics being approved
  - Regulatory approvals need demonstration of superiority over the existing antibiotics
  - New antibiotics will not be first line of therapy – hence smaller market
  - Safety study and clinical trials – expensive
  - Hospital-acquired MDR bacterial infection cases are on the rise
- It makes a strong case in developing vaccines for MDR bacterial infections : Pseudomonas; *S. aureus*; *Burkholderia cepacia*; *K. pneumoniae* ….

Manufacturer's view
developing new vaccines

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- Exciting Scientific Advancements, Second Phase of DoV will provide unforeseen opportunities
  - Using latest scientific tools
  - Speed in data analysis, genomics and proteomics information
  - Increased understanding of the interlinks in immunology, host-pathogen interactions, disease mechanisms, and
  - New abilities to manipulate the pathogen's genome to develop vaccine strains

All these help develop new vaccines

Manufacturer's view
developing new vaccines

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- Local development of new vaccines – preferred
- Encourage development of reagents suppliers and service providers locally; equipment; enabling materials; need to import
- Animal models for studying the disease and or animal challenge studies
- Access to global experts / expertise for the developing country manufacturers

All are key factors in development of new vaccines beyond the traditional vaccines

Manufacturer's view
developing new vaccines

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- BMGF, WHO, GAVI, GHIT, PATH, EVI, IVI, and Many academic institutes, NGOs
  - Provide support in various forms help addressing the issues and create a path for vaccines development
- Fast Emerging Challenge: Interchangeability of vaccines
  - Multiple versions of a vaccine for the same infectious agent
  - Subunit(s)
  - VLPs and or antigen display on VLP
  - Chimeric antigen
  - Live attenuated strains versus subunit antigens
  - Polysaccharide –Protein Conjugate vaccines (different carrier proteins)

Manufacturer's view

developing new vaccines

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Interchangeability of vaccines

- Establishing equivalency
- Conducting a clinical trial for equivalency –
  - who would do it
  - funding such clinical studies
  - Where efficacy trials are needed when no established correlates of protection available

While there are plenty of opportunities exist for new vaccines development against infectious diseases, manufacturers understand that they face high development costs, high capex needed and potential unknown on the product price

Biological E. Limited
Celebrating Life Every Day

Appreciate the opportunity to present ..

Thank You

How is the perceived value of vaccines and associated technologies evolving?

PDVAC

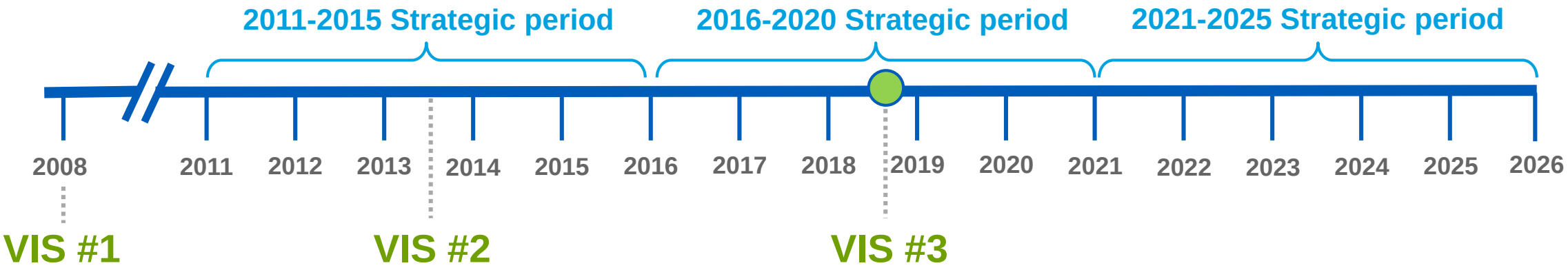
Sophie Mathewson
26 June 2019, Geneva

Gavi
The Vaccine Alliance

Overview

- **Gavi Vaccine Investment Strategy**
- **Key findings on value of vaccines from Gavi VIS consultations**
- **Evaluation of vaccines for epidemic preparedness and response**
- **Forward view**

What is the Vaccine Investment Strategy (VIS)? What are its objectives?



- The VIS takes place **every 5 years** to identify and evaluate **new opportunities for investment** in vaccines and other immunisation products
- Gavi identifies and **reviews the latest evidence** for each candidate investment along a number of criteria including: health & economic impact, value for money and equity amongst others
- The process is **highly consultative**, with partners and external stakeholders essential in helping to develop the recommendations

VIS assesses strength of investment case relative to other potential vaccine investments

21 investment candidates identified with WHO

Step 1: Evaluation

Evaluation Framework, e.g.:

- Health impact
- Value for money
- Equity
- Economic impact
- Global Health Security
- *secondary criteria

Candidates	Ranking Criteria		
	1	2	3
Vaccine A	🟢	🟢	🟡
Vaccine B	🔴	🔴	🔴
Vaccine C	🟡	🔴	🔴
Vaccine D	🟡	🟡	🟢
Vaccine E	🟢	🟡	🟡
Vaccine F	🔴	🟢	🟢

- Vaccination strategy
- Disease burden
- Target population
- Vaccine efficacy
- Price

Step 2: short list

Further analysis, e.g.:

- Financial implications
- Programmatic feasibility / design

Investment case(s)

* See next slide

Gavi The Vaccine Alliance

VIS 2018 evaluation criteria and indicators for vaccines for endemic disease prevention

	Criteria	Proposed indicators
Ranking criteria:	Health impact	Total future deaths averted 2020-2035, and per 100,000 vaccinated Total future cases averted 2020-2035, and per 100,000 vaccinated
	Value for money	Vaccine procurement cost per death averted Vaccine procurement cost per case averted
	Equity and social protection impact	Disproportionate impact of disease on vulnerable groups Special benefits of vaccination for women and girls
	Economic impact	Financial risk protection
	Global health security impact	Epidemic potential of disease Impact of vaccination on antimicrobial resistance (AMR)

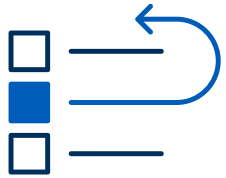
	Criteria	Proposed indicators
Secondary criteria:	Other impact	Total U5 deaths averted 2020-2035, and per 100,000 vaccinated Total DALYs averted 2020-2035, and per 100,000 vaccinated Vaccine procurement cost per DALY averted
	Gavi comparative advantage	Degree of vaccine market challenges Potential for Gavi support to catalyse additional investment
	Broader health systems benefits	*Only assessed contextually*
	Implementation feasibility	Ease of supply chain integration Need for health care worker behaviour change Feasibility of vaccination time point Need for demand promotion Long-term fiscal space implications
	Alternate interventions	Optimal use of current and future alternative interventions (prevention and treatment)
Financial implications:	Vaccine cost	Total procurement cost to Gavi and countries, 2020-2035
	Operational cost	Incremental in-country operational costs per vaccinated person
	Additional implementation costs	Additional costs for introduction

Green = Same as VIS 2013
Orange = Similar to VIS 2013
Black = New for VIS 2018

For VIS 2018, three themes relevant to value of vaccines surfaced from Board consultations

Ranking criteria

Health impact (deaths averted) mostly weighted highest (avg. 40%); similar weighting for value for money (20%), equity (15%) and economic impact (10%); wide range of answers on global health security (15%)



Secondary criteria

Consensus to use secondary criteria to adjust ranking (emphasis on Gavi comparative advantage/ market shaping and implementation feasibility)

Total vs. relative

Preference for total impact vs. per 100k vaccinated

Source: Consultations with Gavi Board members representing 17 constituencies/seats in February 2018

Additional considerations around value of vaccines from Board consultations

Context

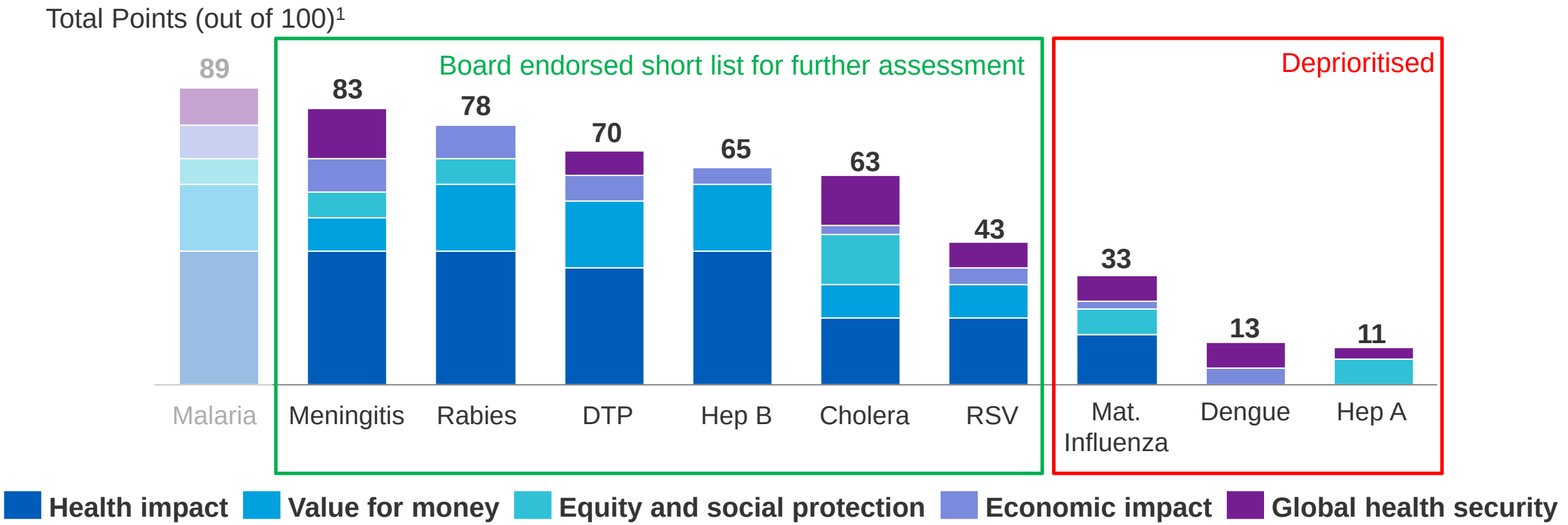
- Changing **global health landscape**
- Greater diversity of candidates in the **vaccine pipeline**
- Forward look towards contribution to **integration and SDGs/ UHC**

Measuring impact of investments

- **Health impact and deaths prevented** prioritised over cases averted
- **Value for money** over cost effectiveness
- **Consolidation** (improving coverage of current Gavi-supported vaccines) vs **new vaccine investments**
- **Equity impact** important but recognised that programme implementation could also deliver similar impact
- **Economic impact** would be rated higher if it more fully reflected the value of vaccines
- Divergent views on importance of **global health security**
- **Lack of feasibility** would be a strong reason to deprioritise a vaccine
- Board guidance to **be pragmatic where data quality is weak**

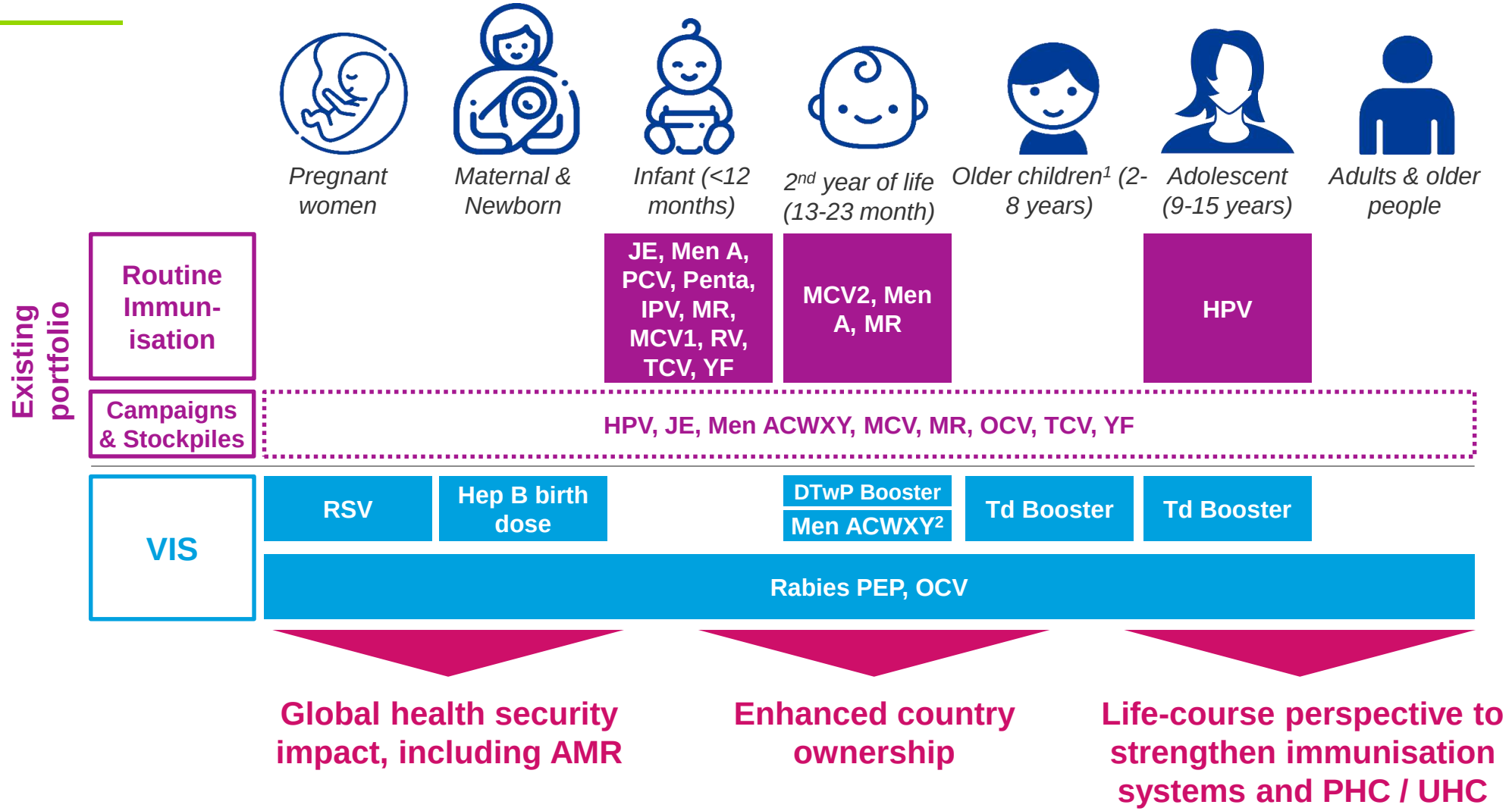
Gavi The Vaccine Alliance

Board shortlisted six 2018 VIS candidates for investment case development



1. Maximum 40pts for health impact (30pts for total deaths averted, 10pts for deaths averted per 100k), 20pts for value for money (cost per death averted), 15pts for equity and social protection impact, 10pts for economic impact and 15pts for global health security
Note: Malaria not up for investment decision. Used as comparator with Health impact and economic impact based on high-level estimates

2018 VIS candidates add value to countries' current portfolio



1. Mostly corresponds to school entry; In theory, Gavi is supporting MCV2 at school entry, but Gavi countries have so far chosen to introduce MCV2 in the second year of life
2. Assumed 1 dose (15-18 months)

Epidemics framework tailored for evaluation of stockpile/similar investments

	Situation 1: traditional Gavi investments	Situation 2: stockpile/ similar investments
Disease epidemiology	Endemic with outbreak/ epidemic potential	Sporadic outbreaks only, not endemic
Vaccination strategy	Routine / preventive campaigns in high risk/endemic areas, with stockpile for outbreak response	Outbreak response and preparedness (e.g., stockpile)
Examples	Measles, yellow fever, typhoid conjugate vaccine	e.g. licensed vaccines for R&D Blueprint priority pathogens
Approach to evaluate potential Gavi investment	"Classic VIS criteria" including: • Projected deaths averted • Cost per deaths averted • Other impact, cost and feasibility considerations	Not suited for "classic VIS criteria" given uncertainty of disease burden, and thus impact and value for money projections Alternative approach to gauge magnitude of risk, relevance to Gavi; also assess cost and feasibility

Strategy / investment may evolve over time (e.g., changing disease epidemiology or understanding of epidemiology; new vaccines that are more suitable for prophylactic use)

‘Living assessments’ & full investment cases to consider four questions

Disease Burden & Risk	1. Is the epidemic potential sufficient to prioritise a stockpile or similar investment?	**Questions to be answered by the ‘Living Assessment’**
Vaccine Impact & Feasibility	2. Would the vaccine be feasible to use and impactful as part of epidemic preparedness and response?	
Fit for Gavi & Partners	3. What is Gavi’s comparative advantage and how can Gavi’s expertise contribute to the funding and delivery of this vaccine?	
Financial Implications	4. What is the appropriate scale of the stockpile (or related intervention) and what would be the financial implications of an investment?	**Determined as part of subsequent full investment case**

Gavi
The Vaccine Alliance

Forward view – value of vaccine technology?

VIPS work, ongoing

- (to be presented at PDVAC on Friday)

Innovation in Gavi 5.0 (2021-2025 strategy)

- Discussions are ongoing but emphasis on importance of innovation across next strategic period
- Interest in using market shaping capabilities to drive innovation in vaccine-related products

Summary

Evolving value of vaccines but…

- Importance of prevention of morbidity and mortality
- Incremental changes in how certain characteristics are valued and measured (e.g. contribution to global health security/ AMR, gender, broader measures of economic impact)
- Update indicators and analysis to reflect advances in methodology, modelling, data availability and priorities

Whose investment?

- Decision making needs to be highly consultative
- Countries' preferences, priorities and view to transition
- Importance of a robust and compelling case to funders

Gavi The Vaccine Alliance

THANK YOU

Total Systems Effectiveness

Evaluating all trade-offs to inform choice

WHO Product Development for Vaccines Advisory Committee

Birgitte Giersing

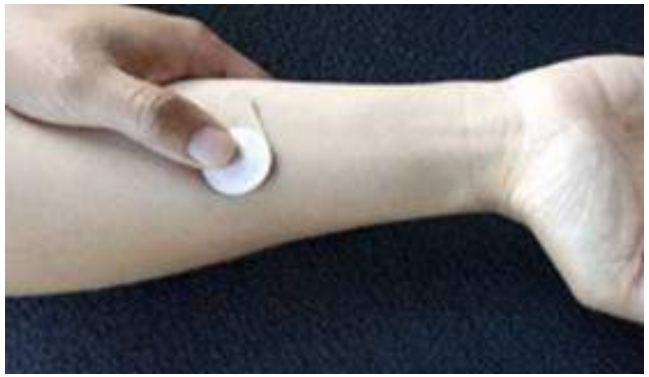
26-28 June 2019



What has been the impact – to coverage and equity *in countries* – of recent vaccine product innovations?

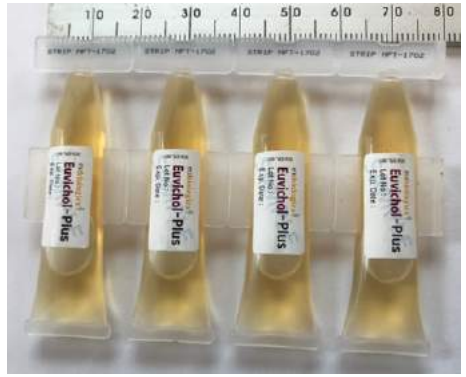
PQ'd – little uptake

Slow uptake



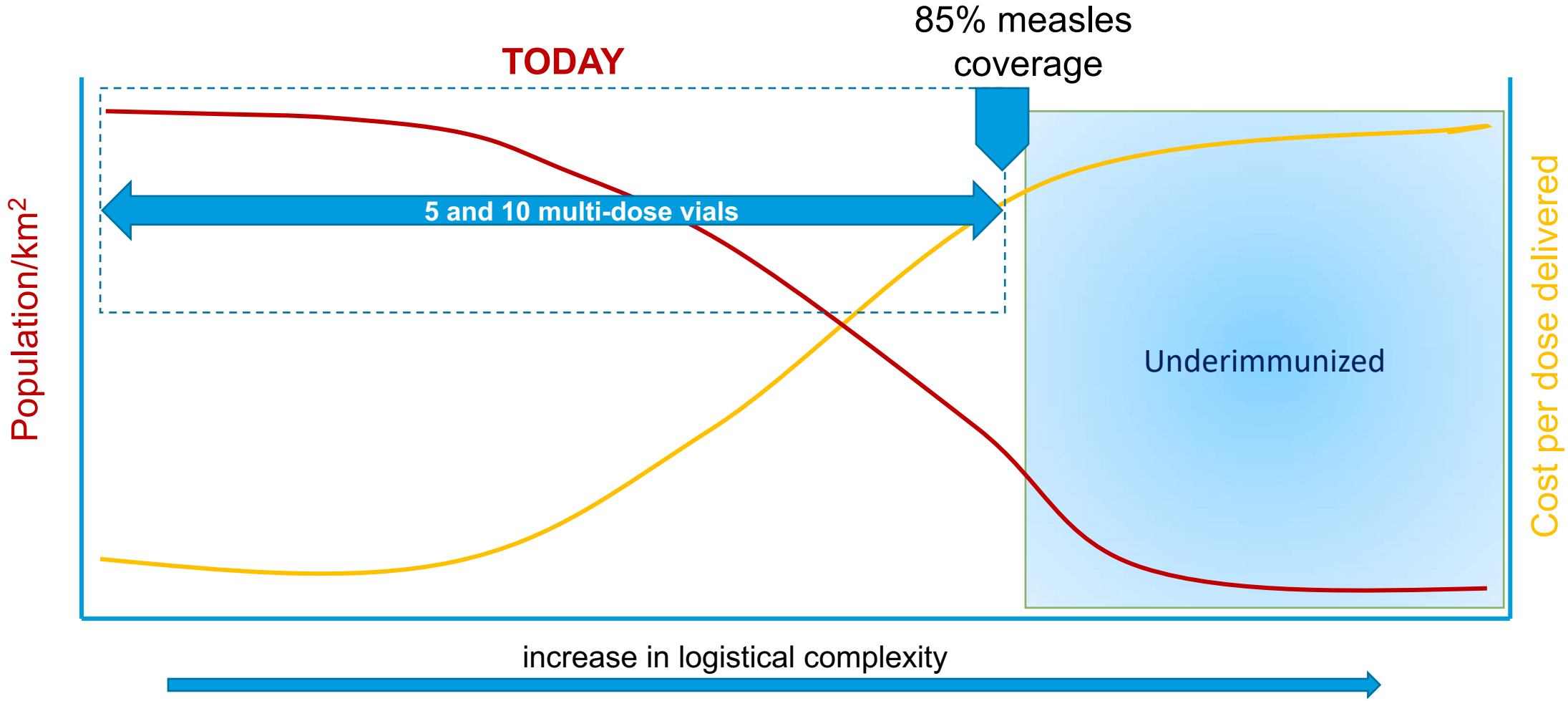
VERY slow development of a potentially game-changing innovation

PQ'd – little uptake

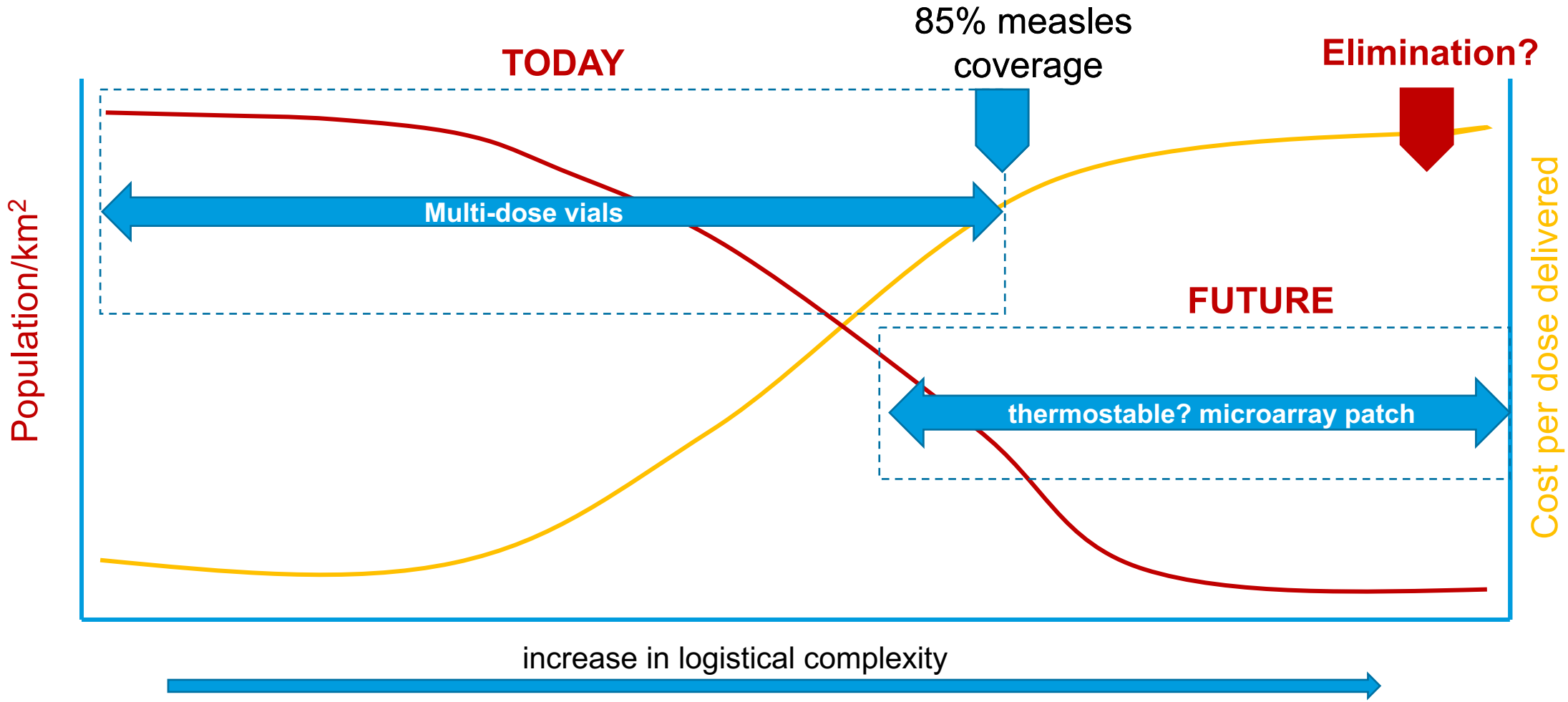


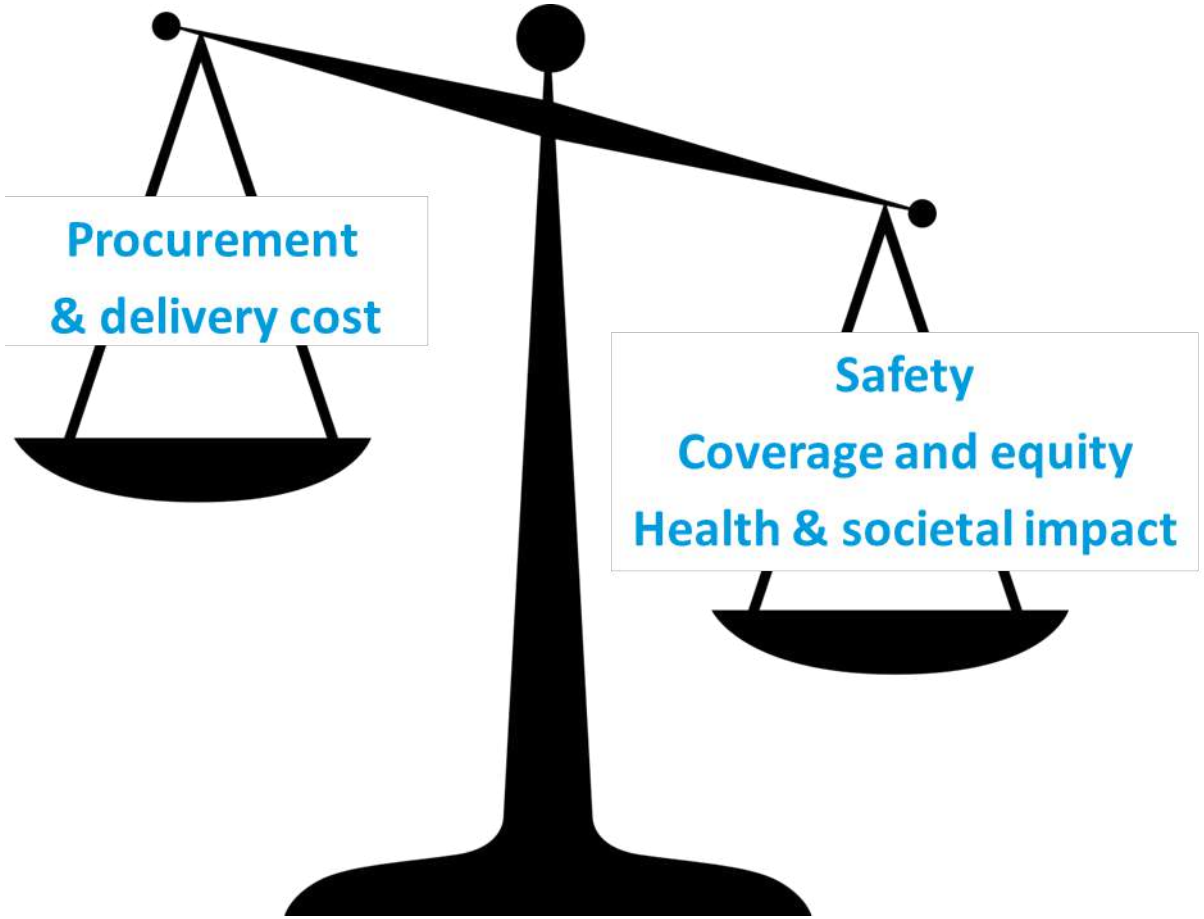
Product optimization needed for uptake

Conceptual utilization of multiple delivery strategies



Conceptual utilization of multiple delivery strategies





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What is the willingness to pay for a vaccine delivery innovation that may improve coverage and equity?

Why have delivery innovations not had impact?

At the country level:

Vx products do not reflect country preferences so there is poor uptake

Programme context/challenges are not always factored into country product selection

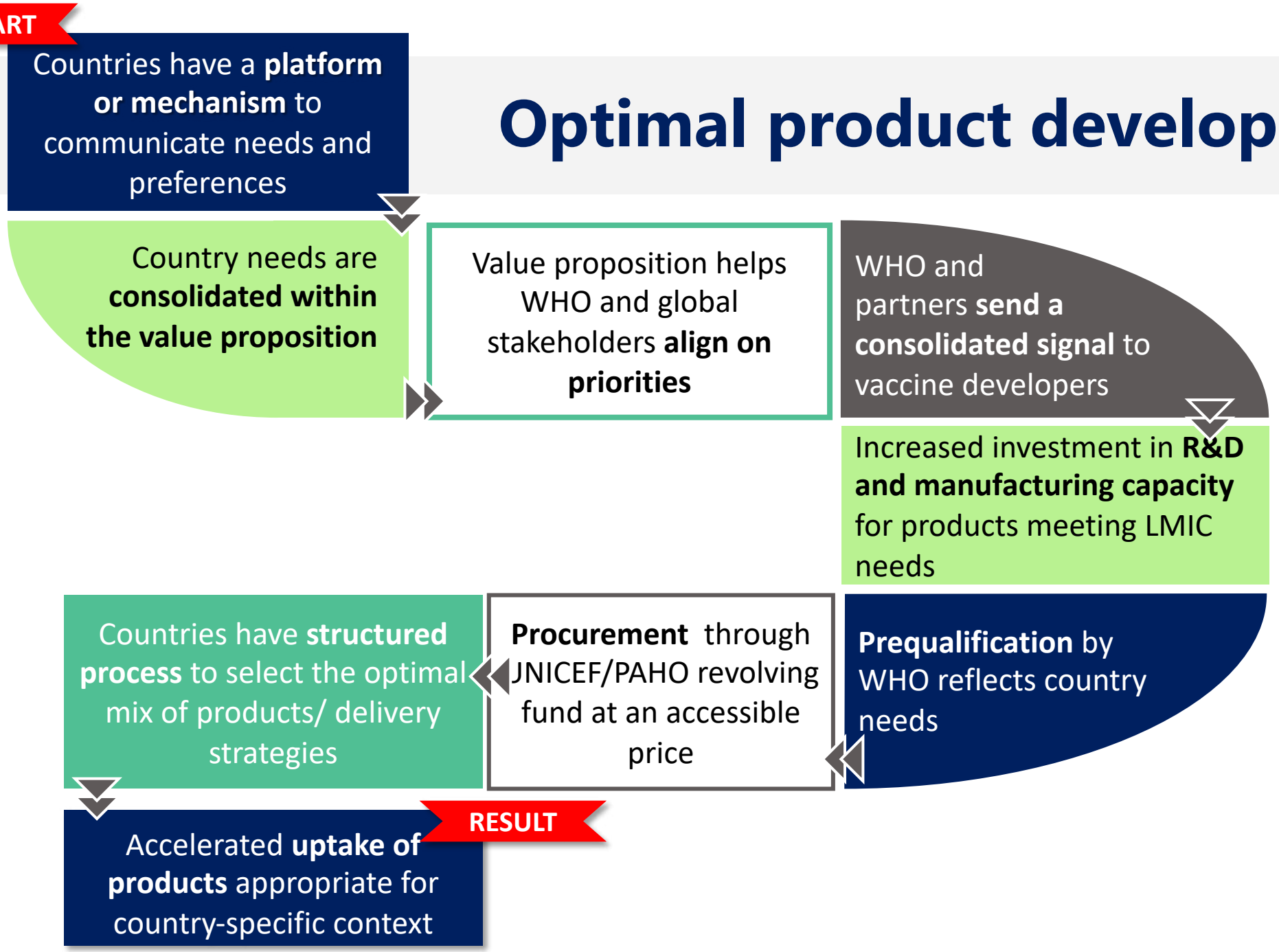
For vaccine supply and R&D:

Lack of investment in products that meet LMIC needs as the value proposition for developers, and countries, is unclear

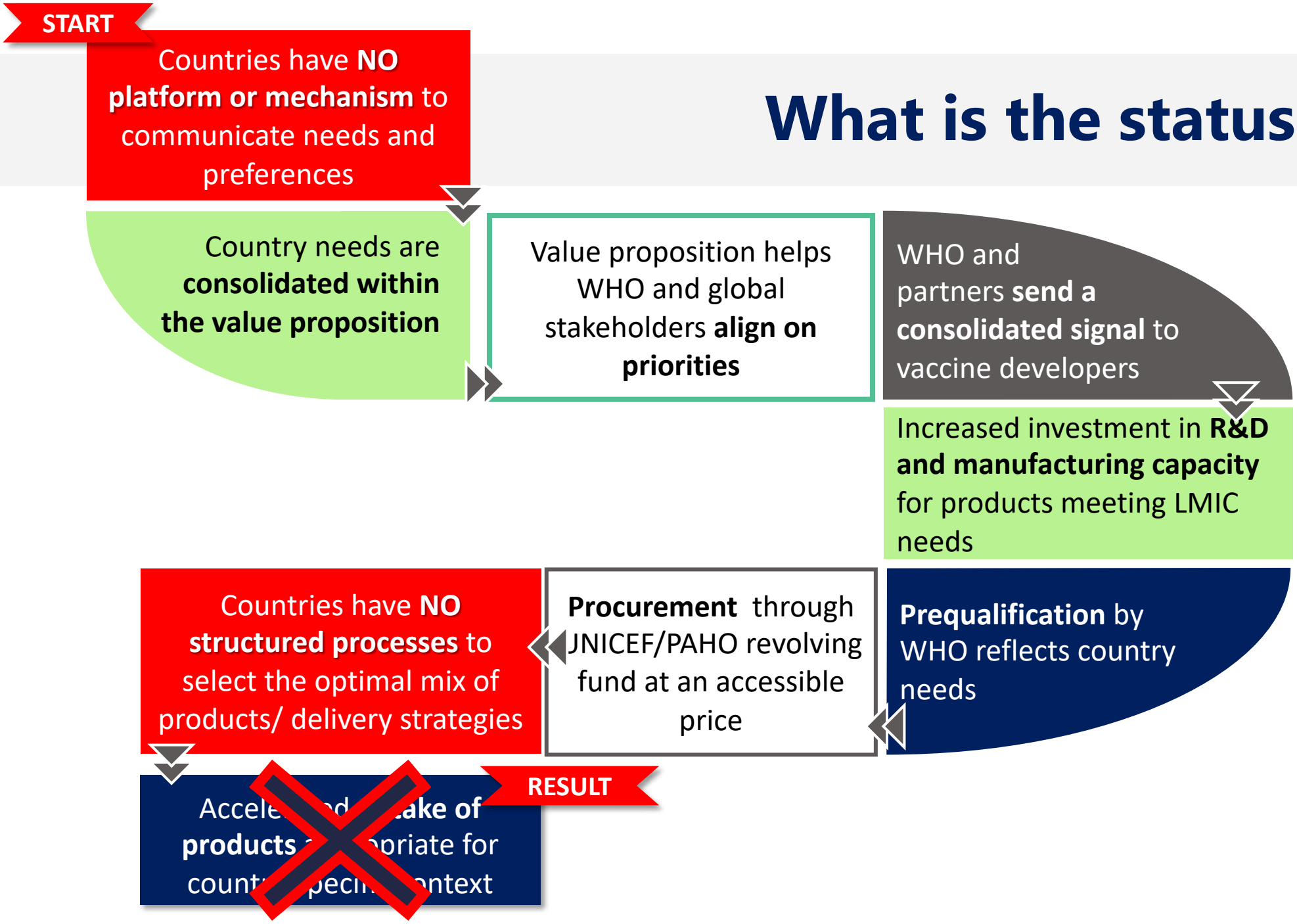
Due to:

- Limited, ad-hoc country engagement in R&D/supply priority setting
- Assumptions around country preferences are not always evidence based
- Lack of continuous monitoring of changes in programme needs or country preferences over time

Optimal product development



What is the status quo?



Where does TSE fit?

START

Countries have **NO platform or mechanism** to communicate needs and preferences

Country needs are **consolidated within the value proposition**

Value proposition helps WHO and global stakeholders **align on priorities**

WHO and partners **send a consolidated signal** to vaccine developers

Increased investment in **R&D and manufacturing capacity** for products meeting LMIC needs

Prequalification by WHO reflects country needs

Procurement through UNICEF/PAHO revolving fund at an accessible price

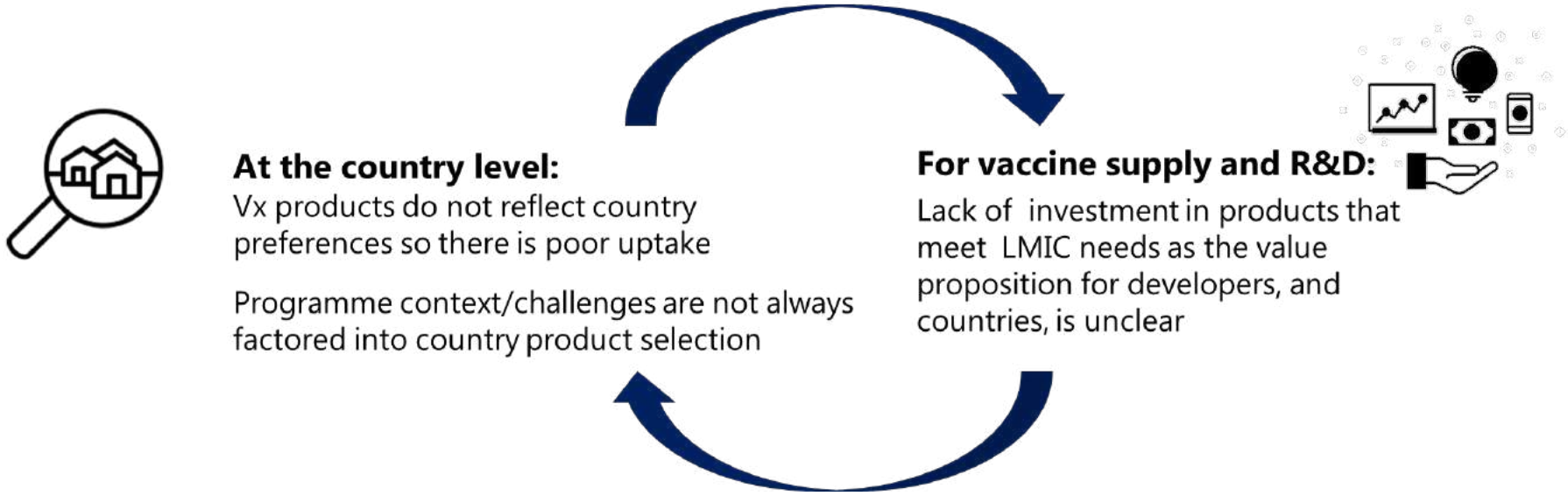
Countries have **NO structured processes** to select the optimal mix of products/ delivery strategies

RESULT

Accelerated **uptake of products** appropriate for country-specific context

We need a framework for countries to **systematically evaluate products** for selection, and use this as a platform to engage countries on product needs.

Aim is to ensure vaccine products are designed, and developed, according to country needs



An approach enabling countries to identify the value of products and product attributes for their own respective immunization programmes and communicate it to product development stakeholders for improved prioritization and better tailored product design.

TSE overview

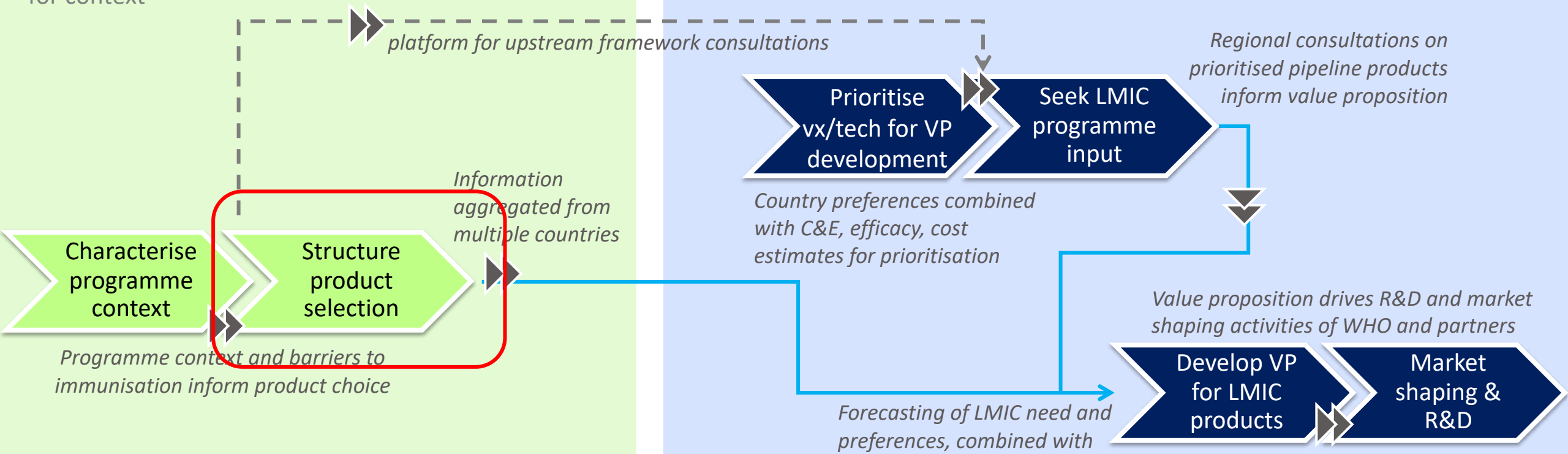
VP value proposition
C&E coverage and equity
Vx vaccines
Tech delivery technologies

Country programme framework

For **country** use; to select the optimal mix of products for context

Supply/R&D framework

Consolidate LMIC perspective within the value proposition



Purpose of the pilot (Jan 2018 – Mar 2019)

Is the concept of TSE **useful for immunisation programmes** to assess trade-offs between vaccine products?

The tool was developed iteratively with country consultations and experts

STARTING POINT: Quantitative MCDA tool

REVISION 1 based on PHE framework*

REVISION 2 w/ AFRO IST West & CDC

IVIRAC review
March 2018

Indonesia
Thailand
May 2018

IPAC
July 2018

Mali
August 2018

IVIR-AC
September 2018

Indonesia
December 2018

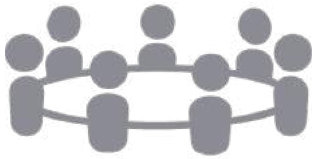
IST West & IST Central orientation
March 2019

Mali
HPV pilot
Q2 2019

"Exemplary in the way [TSE] has taken on board pilot country feedback"
- IVIRAC member, September 2018

https://www.gov.uk/government/publications/the-prioritisation-framework-making-the-most-of-your-budget

What does the TSE decision-support tool do?



Structures group discussions…

… to come to an **evidence-based**, **context-specific** recommendation…

…documenting the rationale at each step of the process

1. **Based on multi-criteria decision analysis (MCDA):**
   - makes explicit the values underlying decisions
   - brings together different types of evidence
2. Focus on the social aspects of the recommendation process

Other TSE Activities and timelines (2019)

11 MARCH 2019
TSE orientation for DRC and CAR during IST Central JRF

25 MARCH 2019
TSE orientation for 6 countries* during IST West JRF

MARCH - APRIL 2019
Pilot in Mali: HPV product selection by GTCV-Mali (for 2020 Gavi application)

* Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Nigeria

TSE overview – what next?

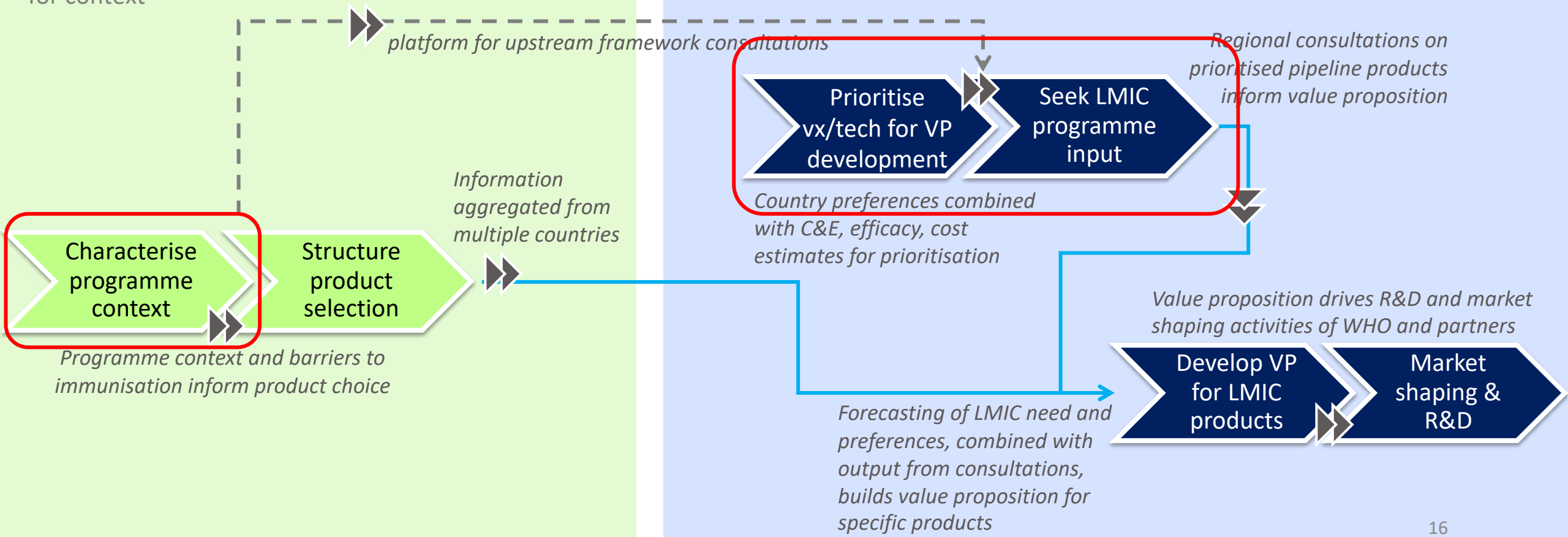
VP value proposition
C&E coverage and equity
Vx vaccines
Tech delivery technologies

Country programme framework

For **country** use; to select the optimal mix of products for context

Supply/R&D framework

Consolidate LMIC perspective within the value proposition



What next? In-country R&D workshops

- Can we build on product evaluation work, and leverage the TSE framework, to engage with country level stakeholders on hypothetical products?
- What barriers could these products address? What is the level of interest and acceptability? What product attributes are key?

➢ How do we create a PULL, from the countries where we need to improve C&E, for new products

Test case 1:
Novel delivery tech: microarray patch

- **Evaluate barriers** to MR delivery in country X
- **Socialise the MAP technology** and its benefits
- Use TSE to identify criteria for **preferential characteristics of MR-MAP vaccine**
- Measure preferences against MR-MAP TPP
- Identify **use case scenarios** for MR-MAP in the context of existing interventions
- Assess scenarios/strategies for use using MR-MAP to **inform demand (scale)**
- Identify which characteristics for MR-MAP are CRITICAL as opposed to nice to have

With THANKS!

TSE 1.0 Steering committee:
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Heather Deehan
Richard Duncan
Deborah Kristensen
Pascale Leroueil
Marion Menozzi-Arnaud
Mercy Mvundura
Anna Osbourne
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Jos Luttjeboer
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26 June 2019

2nd Valley of Death?

Is there a “second valley of death” for vaccines?
If so, how to approach bridging it?

David C. Kaslow, MD
VP PATH Essential Medicines

Photo: PATH/Gabe Bienczycki

Historical context

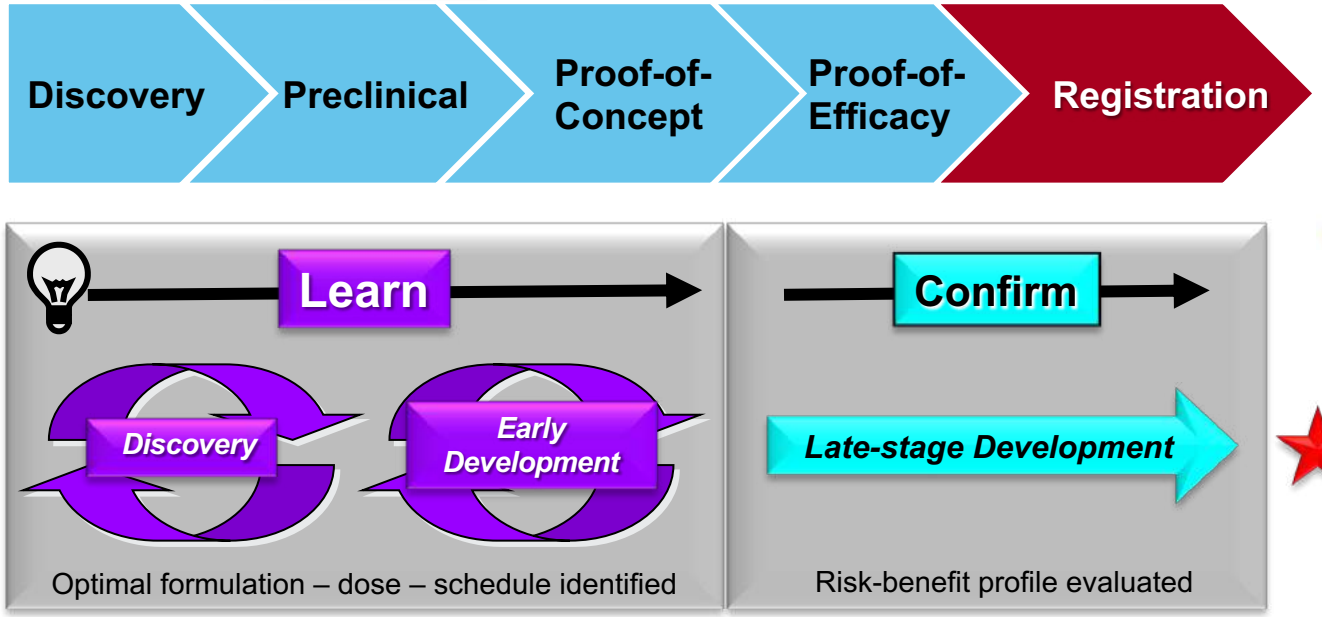
Barriers in Late Stage & Introduction Gap

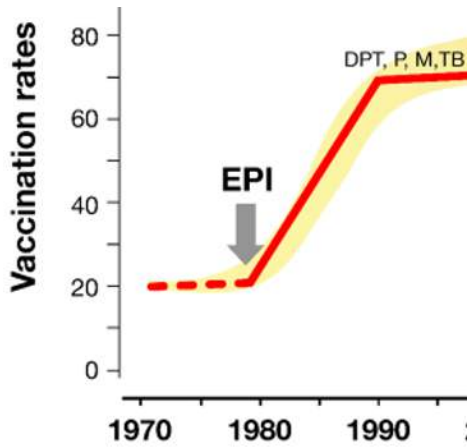
An assumption-based framework?

Fit into IA2030?

Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 1997)





Sheiner, L. *Clin. Pharm.Therap.* **61**: 275–91,1997
doi:10.1016/S0009-9236(97)90160-0

Less than 10 years after global vaccine coverage had soared to **80% coverage** in 1990, immunization rates in low resource settings stagnated -- nearly **30MM children were not fully immunized.**

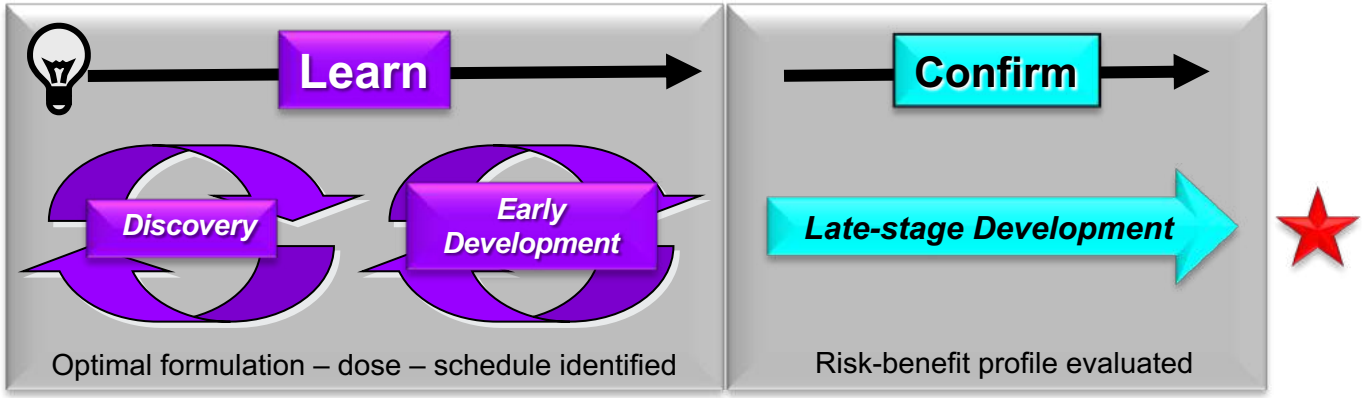
https://www.gavi.org/about/mission/history/

Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2000)

Coverage & Equity gap

Discovery → Preclinical → Proof-of-Concept → Proof-of-Efficacy → Registration → WHO policy & PreQual. / Proof-of-Effectiveness/ Implementation → Financing & Procurement → Uptake



The Children's Vaccine Initiative (1990)

Global Alliance for Vaccines and Immunization (2000)

Gavi The Vaccine Alliance

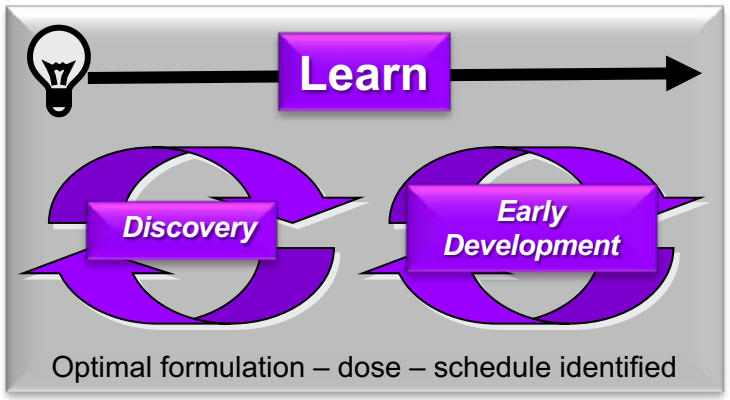
Sheiner, L. *Clin. Pharm.Therap.* **61**: 275–91,1997
doi:10.1016/S0009-9236(97)90160-0

Progression of vaccine development and introduction for LMICs

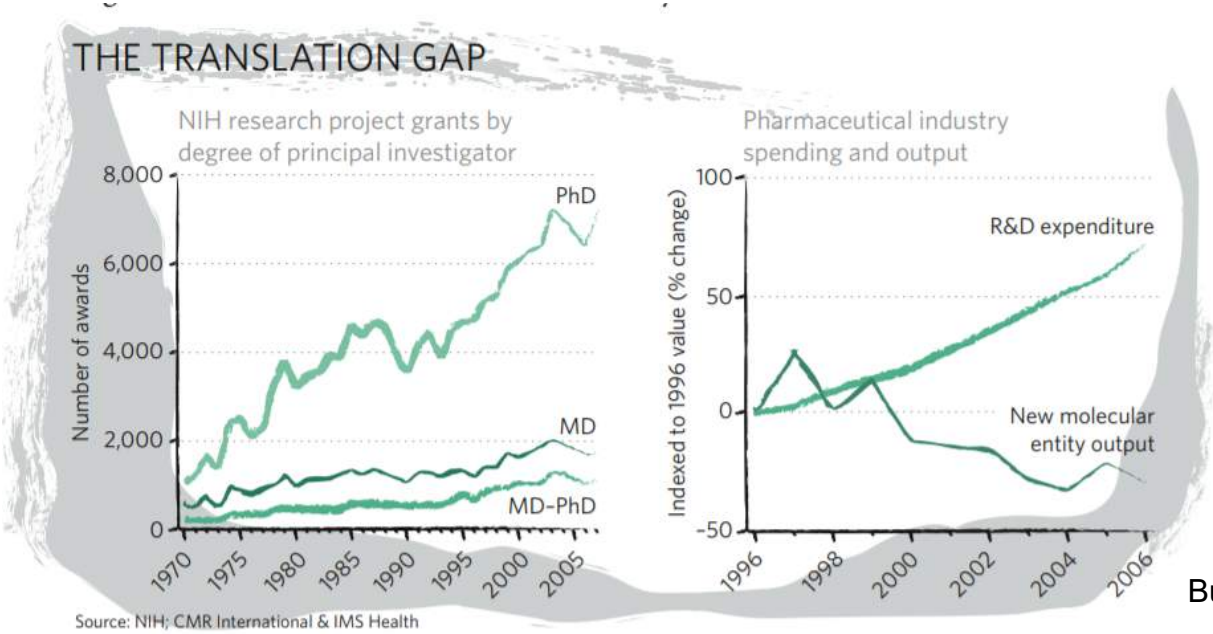
Conventional pathway to impact (circa 2008)

Translation R&D gap — **Coverage & Equity gap**

Discovery → Preclinical → Proof-of-Concept → Proof-of-Efficacy → Registration → WHO policy & PreQual. / Proof-of-Effectiveness/ Implementation → Financing & Procurement → Uptake



A widening chasm between biomedical researchers and the patients who need their discoveries.



- Scarce expertise
- Increasing development costs

Bulter, D. *Nature* **61**: 840-2, 2008
doi:10.1038/453840a

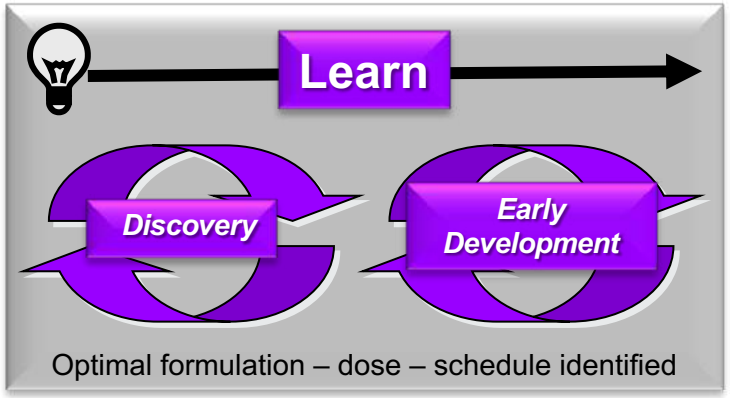
Progression of vaccine development and introduction for LMICs

Bridging the translational R&D gap

Translation R&D gap

Coverage & Equity gap

Discovery → Preclinical → Proof-of-Concept → Proof-of-Efficacy → Registration → WHO policy & PreQual. / Proof-of-Effectiveness/ Implementation → Financing & Procurement → Uptake



Strategic Health Innovation Partnerships

thsti
ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान

Biomedical Catalyst

MRC Medical Research Council

Innovate UK

CEPI

Vaccine Research Center

DARPA — Bridging the Gap — Powered by Ideas

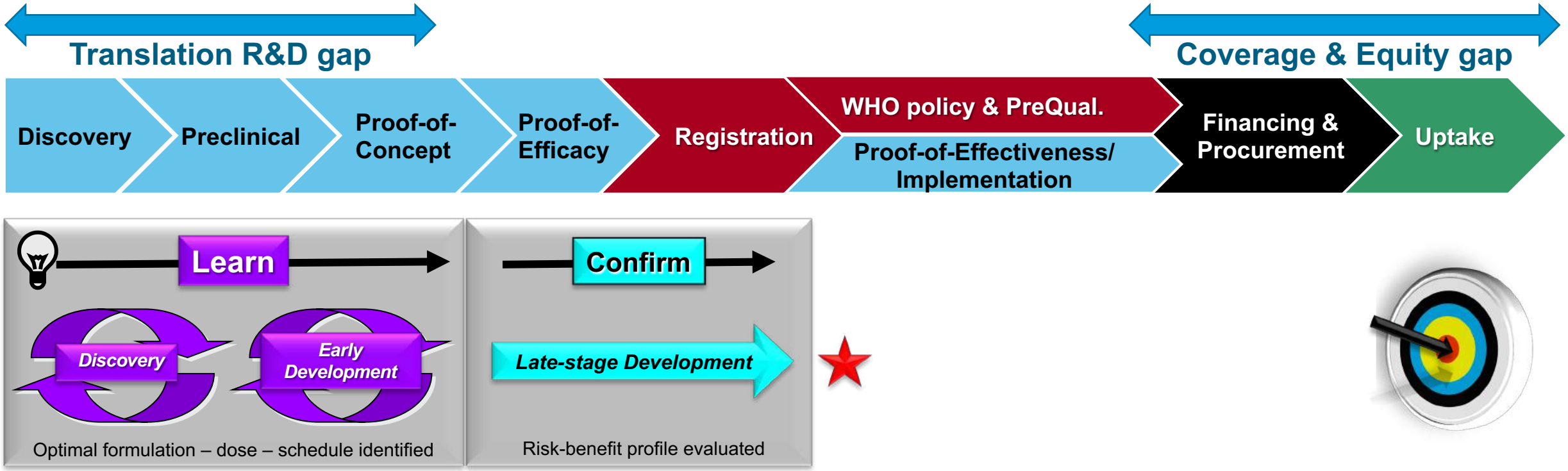
GATES MRI

BARDA — Biomedical Advanced Research and Development Authority

NIH
National Center for Advancing Translational Sciences

Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2014-15)

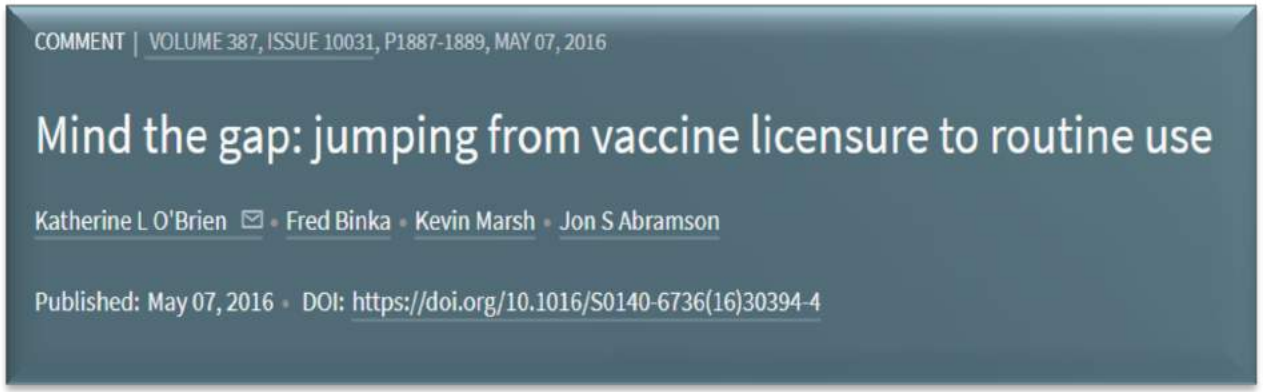


PDVAC/SAGE PIPELINE (Illustrative)

- ETEC
- Ebola
- Shigella
- RSV
- GBS
- TB
- GAS
- HIV
- HSV
- Flu
- Malaria
- Dengue
- Typhoid
- Cholera
- Hep E

Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2016)

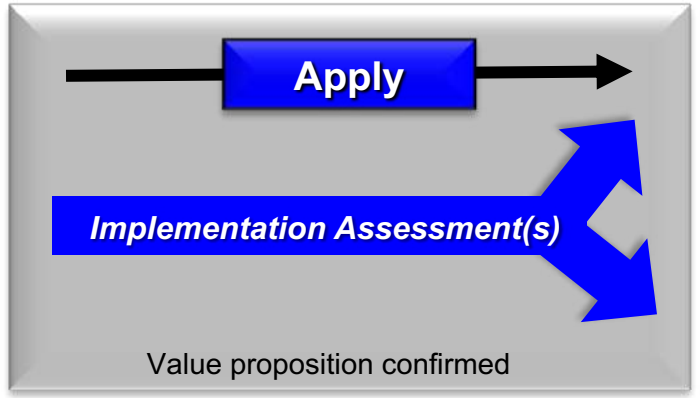


COMMENT | VOLUME 387, ISSUE 10031, P1887-1889, MAY 07, 2016

Mind the gap: jumping from vaccine licensure to routine use

Katherine L O'Brien • Fred Binka • Kevin Marsh • Jon S Abramson

Published: May 07, 2016 • DOI: https://doi.org/10.1016/S0140-6736(16)30394-4



O"Brien, KL. et al., *Lancet*. **387**::1887-9.
doi: 10.1016/S0140-6736(16)30394-4

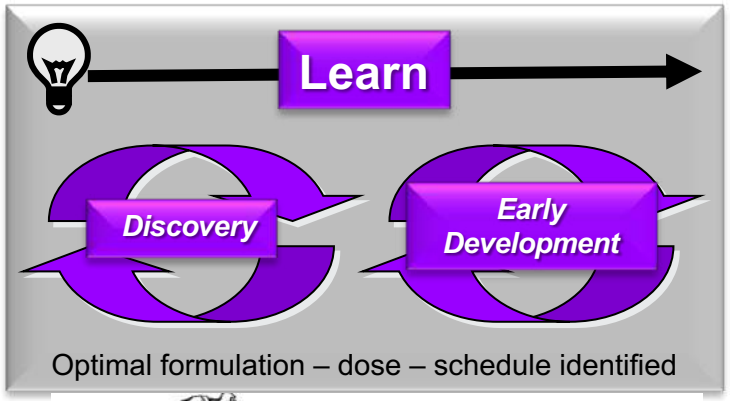
Vaccines against dengue, typhoid, respiratory syncytial virus, Ebola virus, and other infectious diseases will face a similar, ever widening gap between the evidence required for licensure and that needed to actually use them to their greatest effect (impact).

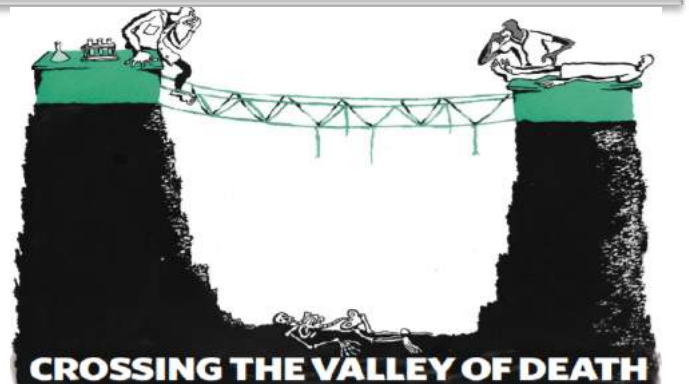
Progression of vaccine development and introduction for LMICs

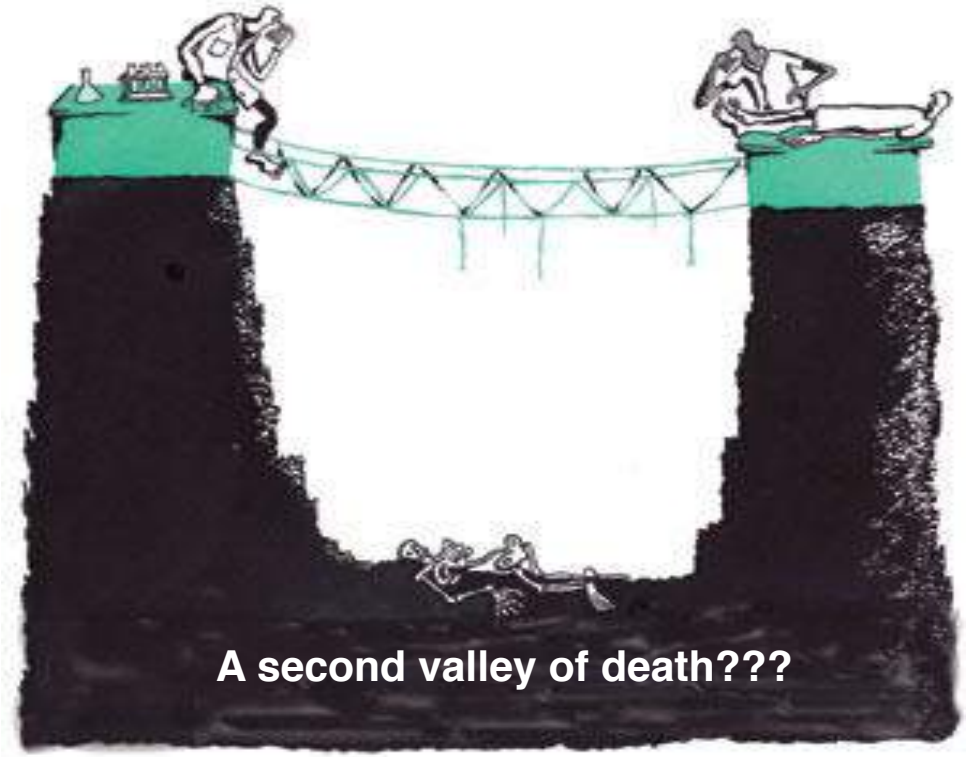
Conventional pathway to impact (circa 2019)???

Translation R&D gap | **Late Stage & Introduction gap** | **Coverage & Equity gap**

Discovery → Preclinical → Proof-of-Concept → Proof-of-Efficacy → Registration → WHO policy & PreQual. / Proof-of-Effectiveness/ Implementation → Financing & Procurement → Uptake





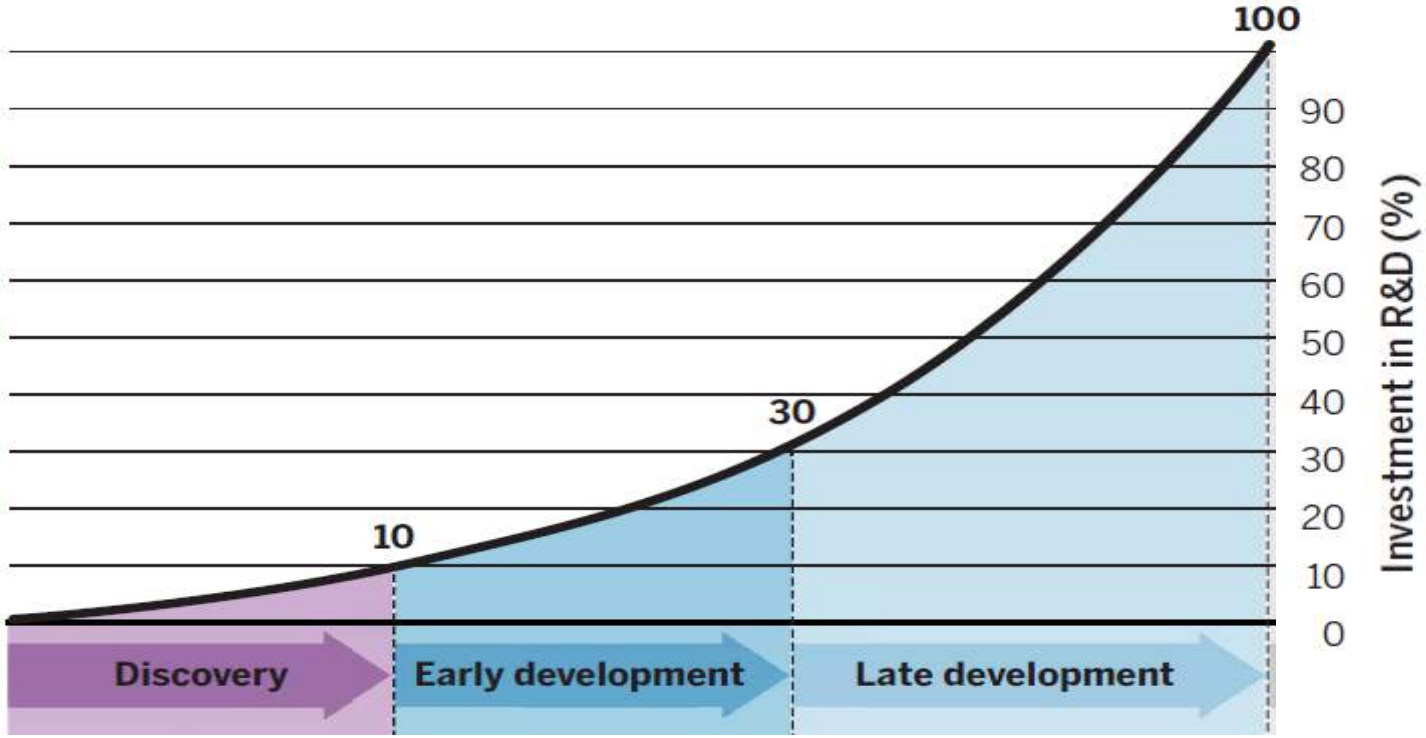


Drawn to scale

www.lancet.com Vol 387 May 7, 2016
https://www.nature.com/articles/d41586-018-07758-3
https://stm.sciencemag.org/content/11/497/eaaw2888.full

Progression of vaccine development and introduction for LMICs

Late stage development is the most labor- and budget-intensive phase of vaccine development



70% of the total R&D budget

Adapted from: Rappuoli et al., *Sci. Transl. Med.* 11, eaaw2888 (2019)
https://stm.sciencemag.org/content/11/497/eaaw2888.full

Progression of vaccine development and introduction for LMICs

Late development is the most labor- and budget-intensive phase of vaccine development

What's else?

Progression of vaccine development and introduction for LMICs

Vaccine manufacturing is complex and capital-intensive

Review

The complexity and cost of vaccine manufacturing – An overview

Stanley Plotkin [a], James M. Robinson [b,*], Gerard Cunningham [c], Robyn Iqbal [d], Shannon Larsen

Plotkin, S. *Vaccine* **35**:4064–71, 2017
doi:10.1016/j.vaccine.2017.06.003

Major cost drivers that impact on COGS*

- Development
- **Facilities & Equipment CAPEX**
- Consumables/raw materials
  Direct Labor
- Overhead
- Licensing/Regulatory and commercialization

See also:
https://docs.gatesfoundation.org/Documents/Production_Economics_Vaccines_2016.pdf

*Cost of Goods Sold

Progression of vaccine development and introduction for LMICs

Vaccine manufacturing is complex and capital-intensive

Review

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Ave. cost of Phase 1 for CMC elements **12 M USD**

Total costs can range from **200 - 500 M USD**

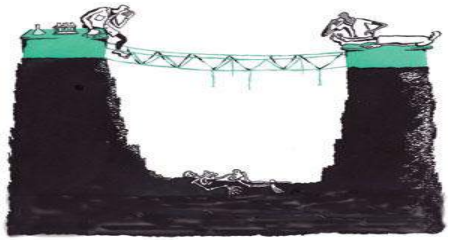
Progression of vaccine development and introduction for LMICs

Three apparent gaps across the product cycle for vaccines

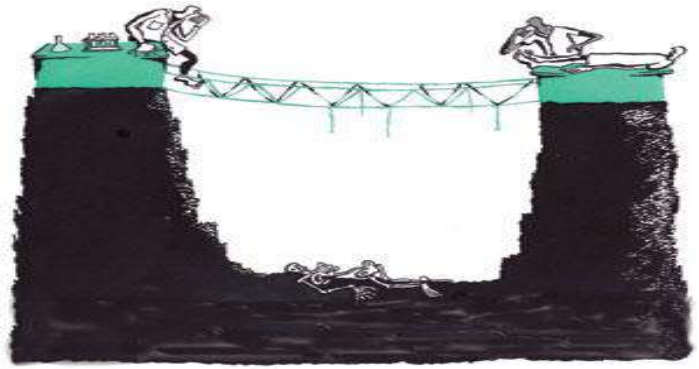
Translation R&D gap
(aka First Valley of Death)

Late Stage & Introduction gap
(aka Second Valley of Death)

Coverage & Equity gap



http://www.nature.com/news/2008/080611/full/453840a.html



www.lancet.com Vol 387 May 7, 2016
https://www.nature.com/articles/d41586-018-07758-3
https://stm.sciencemag.org/content/11/497/eaaw2888.full

Historical context

Barriers in Late Stage & Introduction Gap

An assumption-based framework?

Fit into IA2030?

Barriers in the Late Stage & Introduction Gap

- Biological
- Technical

Many ***but certainly not all*** of the biological and technical gaps and uncertainties should have been addressed before entering into late stage development

Current exception are **implementation evidence** gaps

- **Human-controlled**
  - Funding
  - Political Will
  - Stakeholder Alignment
  - Regulatory-Policy-Financing Pathway

Historical context

Barriers in Late Stage & Introduction Gap

An assumption-based framework?

Fit into IA2030?

Key assumption:

Its not just about the money

Human-controlled beyond just funding: ABCs

- **Acceptable** innovative approaches and tools to accelerate the pathway to licensure, (i.e. CHIMS, adaptive trial designs, bridging first and next generation candidates)
- **Binding alignment** of the regulatory-policy-financing pathway continuum—what evidence is needed when to accelerate the transitions?
  - Aligning profiles:
    - Target Product (licensure) Profiles (PDVAC)
    - Target Policy Profiles (?)
    - Target Financing Profiles (?)
- **Country-based** activities including understanding demand, and creating the required infrastructure and workforce capacity

Key assumption:

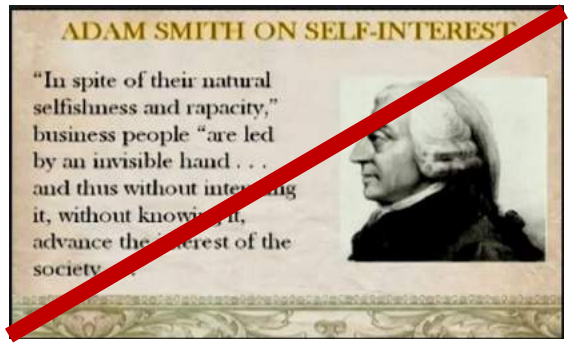
“One size” won’t fix all cases

Four Vaccine Business Cases

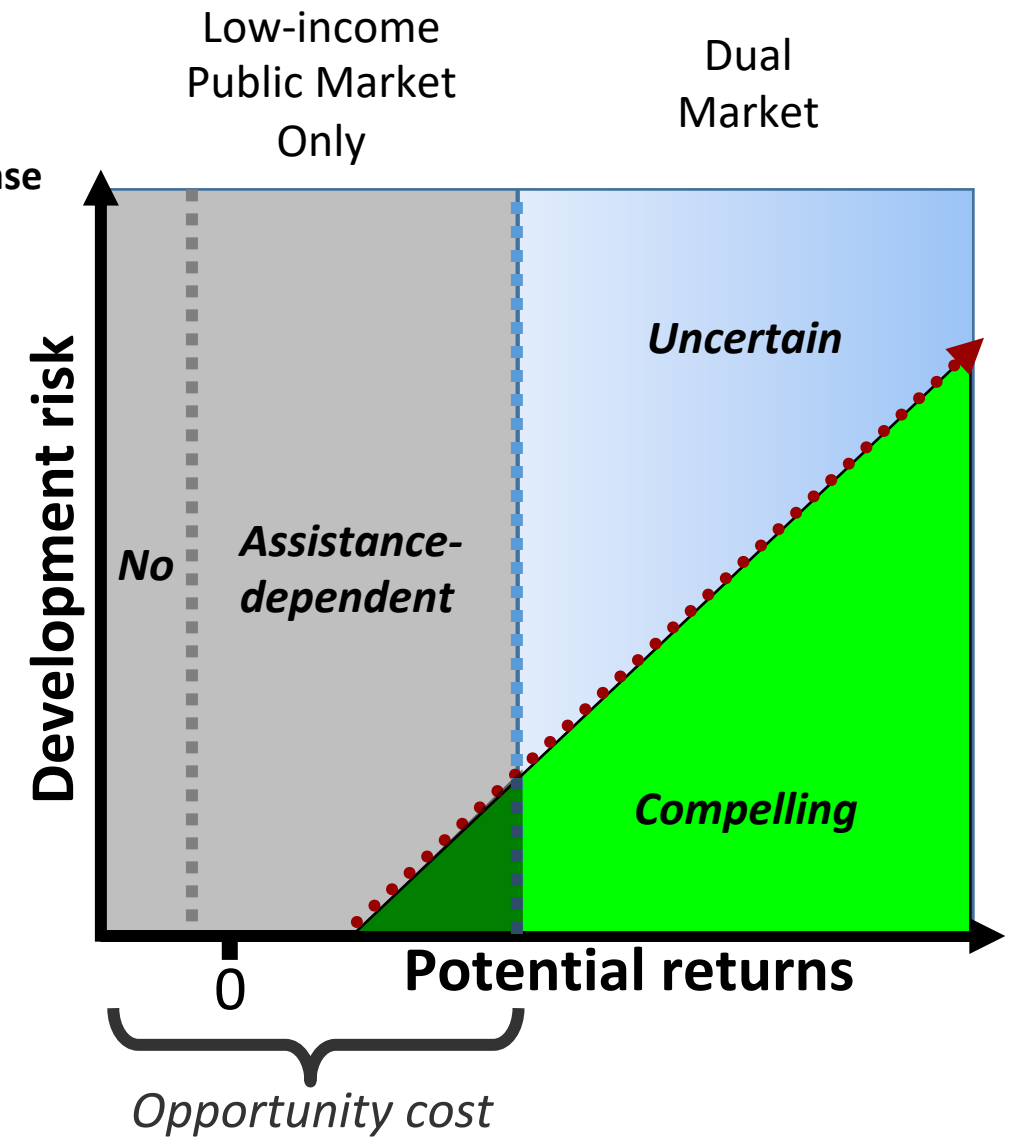
Compelling—Uncertain—Assistance—No

***Assistance-dependent* business case (LMIC only; Outbreak)**
(e.g., LMIC: Cholera, Malaria, Men A, Shigella; Outbreak: Ebola, MERS, Nipah, Lassa Fever)
Solutions:

- **Public funding**
- Priority Review Vouchers
- LMIC Manufacturers
- Push & Pull mechanisms



The Theory Of Moral Sentiments
(Part IV, Chapter I)



***Uncertain* business case (LMIC ↔ HIC)**
(e.g., Grp A Strep, Grp B Strep, TB)
Solutions:

- **Reverse tiered pricing**
- Push & Pull mechanisms

***Compelling* business case (HIC → LMIC)**
(e.g., HBV, HiB, HPV, PCV, RSV, Rota)
Solutions:

- **Tiered pricing**
- Push & Pull mechanisms

Progression of vaccine development and introduction for LMICs

Late development is the most labor- and budget-intensive phase of vaccine development

Strategic Health Innovation Partnerships

Biomedical Catalyst

MRC Medical Research Council

Innovate UK

NIH National Center for Advancing Translational Sciences

CEPI

???

Gavi The Vaccine Alliance

GATES MRI

Progression of vaccine development and introduction for LMICs

Late development is the most labor- and budget-intensive phase of vaccine development

Pathogen-specific
(Pneumo ADIP
Rota ADIP
Hib Initaitive)

A single entity?

Key assumption:

*A **favorable** and **sustainable** value proposition for all key stakeholders*

Critical vaccine attributes to optimally achieve strategic goal

Goal	Sustainable, sufficient supply of safe, effective, affordable essential vaccines of international quality to meet global public health needs

Critical Attributes	Quality	Safety (Risk)	Effectiveness (Benefit)	Supply	Demand	***Value***

Regulatory ***Policy and Implementation***

***Value* as Driver of Vaccine Product Development**

Typical stakeholders include:

- Public and private funders and donors;
- Developers (large pharma, biotech and academic) and manufacturers;
- Global and national policymakers including WHO;
- National/global advocacy groups including in countries with high disease burden.

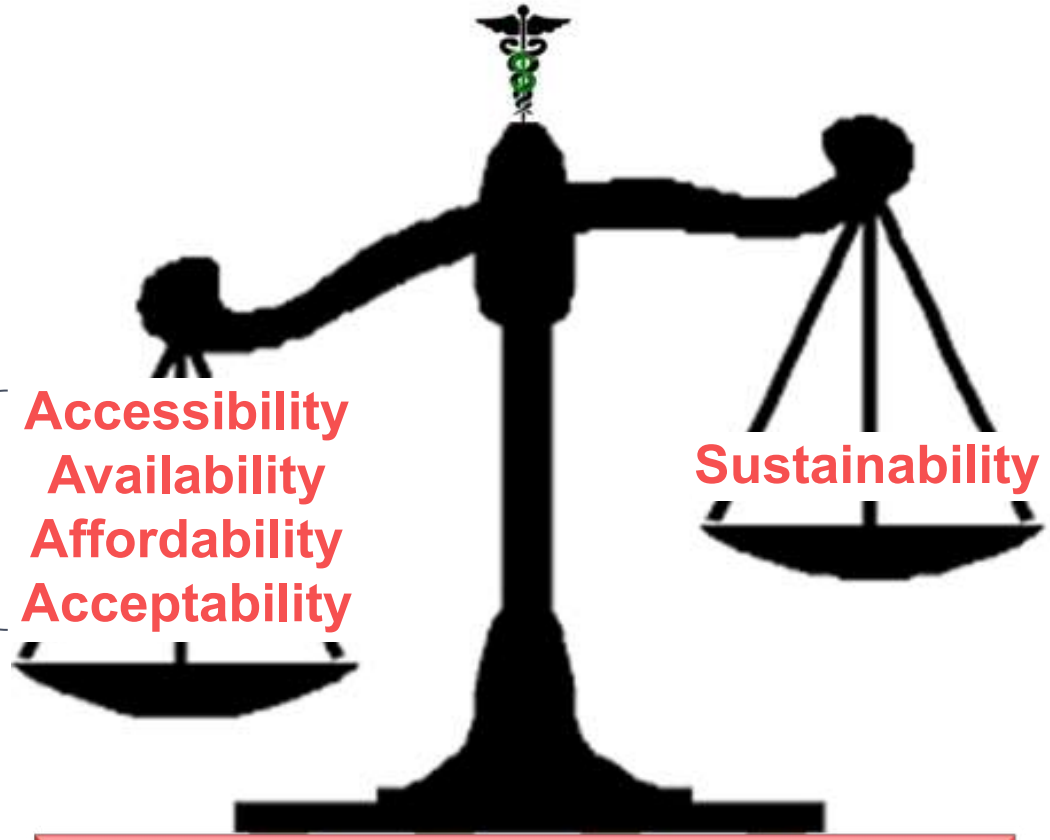
Other stakeholders:

- Households;
- Third-party payers;
- Government (e.g. MoH, MoF, MoD);
- Donors;
- Innovators;
- Society as a whole.

From: WHO Public Health Value Proposition: DRAFT Template

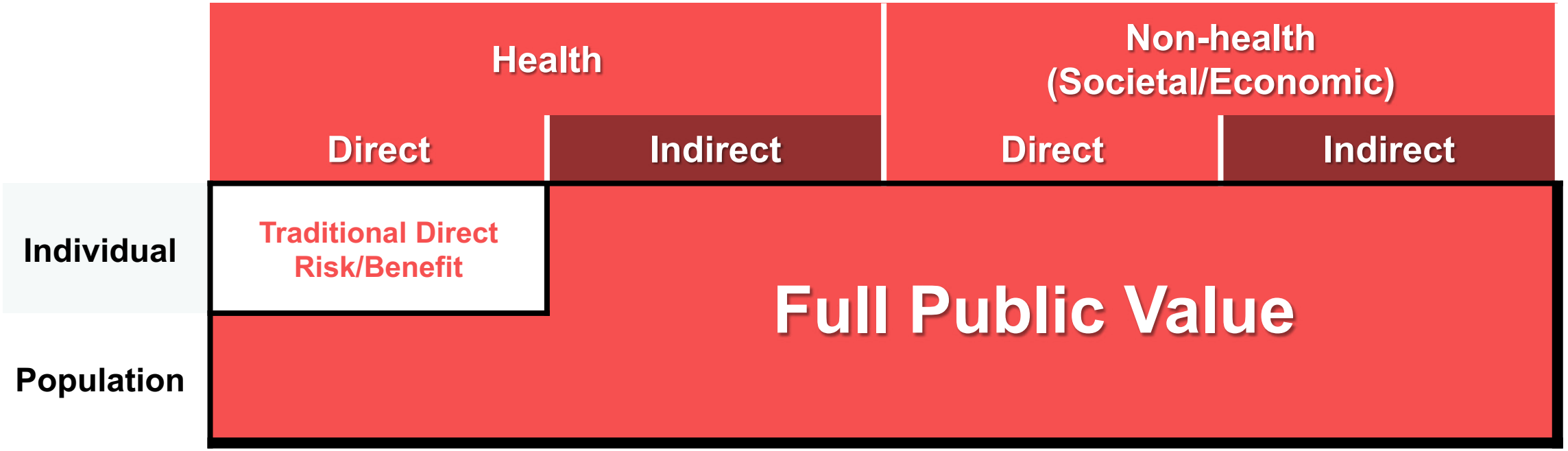
Finding the optimal balance of value for all key stakeholders

Global Access Principles



***Favorable** and **sustainable** value proposition*

Traditional Direct Risk/Benefit v Full Public Value



Key assumption:

Public sector championship required (political will)

- Creates alignment across a range of stakeholders, with respect to global health priorities
- Provides a resource to effectively advocate for development and introduction of vaccines
- Informs rapid, disciplined investment decisions at all stages of development and implementation
- Increases the likelihood of suitability for and access and sustainability of vaccines to LMICs

Full Public Value of Vaccines as driver of ***sustainable*** vaccine development and access

Potential “needle-movers”

Challenge strongly held vaccine development dogmas

Reject business as usual

Potential “needle-movers”

Resource line-of-sight through **binding long-term** multilateral partnerships between funders and developers

Potential “needle-movers”

Balance the current asymmetries in risk and uncertainties

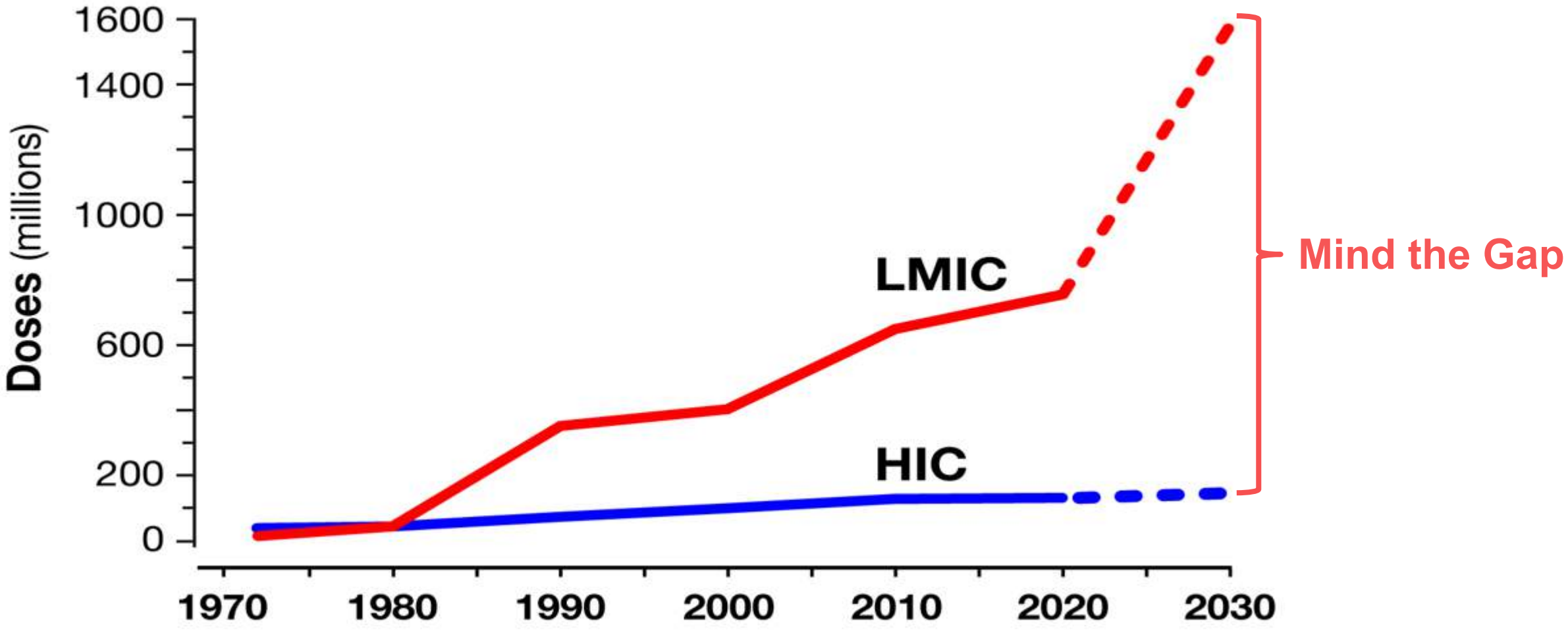
Historical context

Barriers in Late Stage & Introduction Gap

An assumption-based framework?

Fit into IA2030?

Next decade of vaccine



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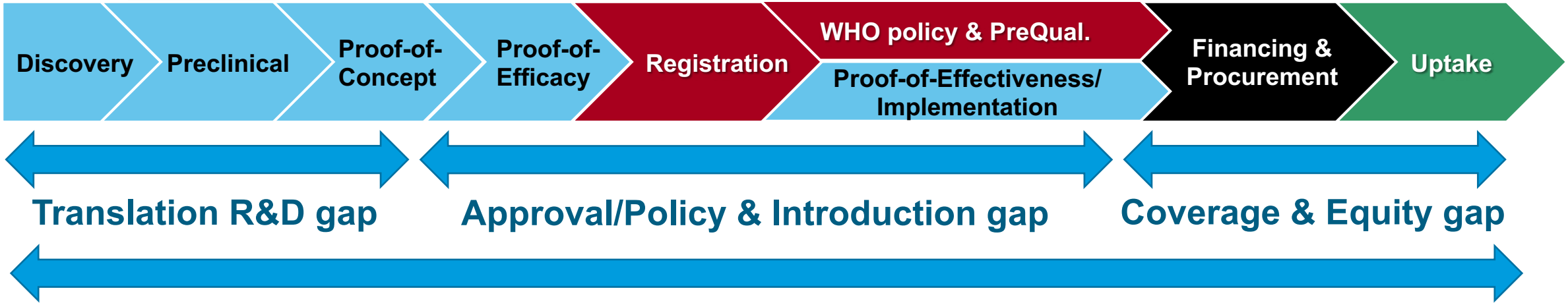
Progression of vaccine development and introduction for LMICs



Creating sustainable R&D models to ensure a healthy vaccine and tech pipeline

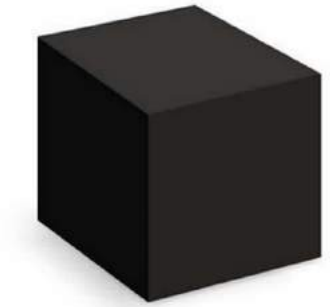
- Identifying and prioritizing early vaccine development pipeline gaps
- Mechanisms to incentivize investment in novel manufacturing and delivery platforms, including VIPS technology
- Valuing/incentivizing innovations?

Managing the risk in the 'second valley of death' for vaccines

- Innovative approaches and tools to accelerate the pathway to licensure, (i.e. CHIMS, adaptive trial designs, bridging first and next generation candidates)
- Alignment of the regulatory-policy-financing continuum—what evidence is needed when to accelerate the transitions?
  - Aligning profiles:
    - Target Product (licensure) Profiles (PDVAC)
    - Target Policy Profiles (?)
    - Target Financing Profiles (?)

THE PULL: Full public value of vaccines

- Country perspectives of value (TSE)



Regulatory support of vaccine development

Ralf Wagner,
Eberhard Hildt, Klaus Cichutek

www.pei.de

The views expressed in this presentation are not only personal views of the author. They may be understood or quoted as considerations of the Paul-Ehrlich-Institut.

The authors did not receive any funding or financial supplementation, neither by companies nor by Federations representing companies.

Clinical phases of vaccine development

goals

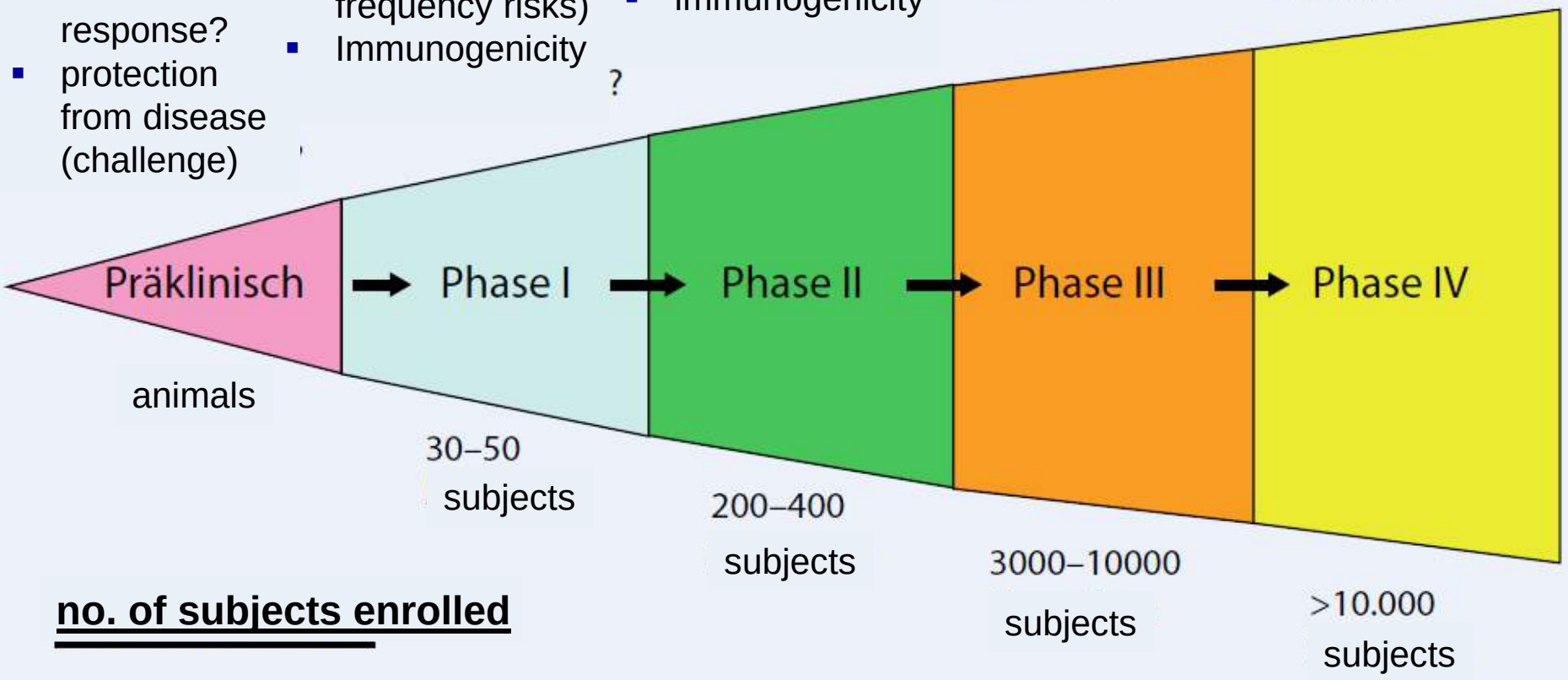
pre-clinical
- immune response?
- protection from disease (challenge)

proof of principle
- safety (1:10 frequency risks)
- Immunogenicity

dose finding
- optimal dose
- safety
- immunogenicity

pivotal clin. trial
- efficacy
- safety (1:1000 frequency risks)
- Immunogenicity (broader immune responses)

post-marketing
- effectiveness (field efficacy)
- safety (1:100.000 frequency risks)



no. of subjects enrolled

mod. from Pfleiderer und Wichmann, Bundesgesundheitsbl 2014

Basic regulatory approach for the evaluation of novel vaccines

Potential scenarios with increasing "regulatory challenging potential":

- LOW:
  Pertinent regulatory guidance available / licensed vaccines ☺
- INTERMEDIATE:
  Insufficient specific guidance / similar vaccines evaluated or licensed 😐
- HIGH:
  No or insufficient specific guidance / product represents an absolute novelty ☹

➢ The underlying regulatory rationale for the evaluation of novel vaccines and/or innovative technologies:

- "Transfer - as much as/whenever possible – existing knowledge, considerations
- and decisions made before for similar products or technologies"

- **Aim:**
  - consistent, reliable and transparent regulatory requirements for all products
  - scientifically sound decisions to assure safety and efficacy

Accelerated assessment

- **Shortened timelines for dossier review** and benefit-risk assessment suitable for medicinal product with
  - **major public health interest** and/or therapeutic innovations
  - **150 days assessment time instead of 210 days until CHMP opinion** (followed by decision on marketing authorisation by the European Commission)
  - may include rolling submission of dossier parts/modules

- In order to apply for accelerated assessment the applicant needs to submit a 5 to 10 page rationale explaining e.g.
  - unmet medical need
  - reasons underlying major public health interest

- During the review the CHMP may decide to switch back to the normal assessment procedure

- VSV-ZEBOV (currently PRIME and accelerated assessment)

“PRIME”(Priority Medicines) procedure

- To support development of medicines which
  - target an **unmet medical need**
  - offer a major **therapeutic advantage** over existing treatments

- Hallmarks of PRIME
  - **early designation of the rapporteur** (NCA leading the dossier review) responsible for continuous support and procedural help delivering
    - early dialogue
    - **more frequent scientific advice** and interactions with regulators,
    - support regarding clinical trial design
  - **aim is accelerated assessment procedure**

- Example: VSV-ZEBOV

Conditional marketing authorization

- **Benefits of immediate availability outweighs risks of less comprehensive data (mostly clinical data)**

- **Valid for 1 year** with possible annual re-assessment, can develop into normal MA when data are complete

- Suitable for medicines which are used
  - for **protection from**, treatment or diagnosis of **life-threatening diseases**
  - for **emergency use**
  - and for orphan medicines

- Conditional marketing authorisation may be provided, if
  - favourable benefit-risk balance and
  - **high probability of additional data to be provided** by the applicant and
  - **unmet medical need** is served and
  - the **benefit to public health of the medicinal product's immediate availability** on the market outweighs the risks due to need for further data.

- example: pandemic H5N1 influenza vaccine

Marketing authorization under exceptional circumstances

- **Unlikely that missing data can be provided after provision of the marketing authorisation**
  - In contrast to „conditional marketing authorization“ the possibility of providing a standard marketing authorisation is not expected in the future
- **Annual re-assessment** of the benefit-risk balance
- For medicines fulfilling the following criteria:
  - selected „orphan medicines“ for **extremely rare orphan disease** so that conclusive evidence for safety and effectiveness will not be obtained in the future.
  - **state of science does not allow to gather conclusive data**.
  - It would be against ethical standards to gather the necessary data.

- Marketing authorisation is provided in conjunction with certain **obligations**
  - clear definition of the proceedings in case of safety signal detection
  - information to the competent authority and
  - risk management plans

- Example: „Imvanex“ (pox, MVA) – epidemic control

Article 58 procedure

- **Art. 58 in Regulation (EG) No. 726/2004**
- Procedure in collaboration with **WHO** – for support of LMIC
- **Regulatory/scientific evaluation and opinion by EMA/CHMP** for medicines intended to be used in the non-EU market
- **Regulatory evaluation like in centralised EU-procedure by national regulatory authorities at EMA – but no official licensure through EC**
- Countries in which the medicine is intended to be licensed shall be involved in the procedure and have access to the assessment reports

  Licensure has to be granted by the respective country.

Regulatory flexibility regarding clinical efficacy data for licensure

- Efficacy to be shown as
  - protection from infection
  - protection from reactivation (e.g. VZV)
  - accepted correlate of protection
  - animal models in exceptional cases

- Efficacy needs
  - to be proven with statistical significance
  - to be of clinical relevance
  - no minimum level expected:
    benefit-risk balance needs to be favourable

- Safety
  - usually large studies of sufficient sample size (>>3000 subjects)

Additional regulatory support for vaccine development

- Regulators support the complete life-cycle management
  - from drug discovery
  - to post-licensure variations and surveillance
- One application/one authorisation principle in Europe for licensure and clinical trials established (ethics/reg. approval and mutli-national trials)
- PEI collaborates with a pan-German Health Research Centre on Infectiology (DZIF) to support translation to first clinical trials
  - Part of a Product Development Unit
    - Office for Scientific Regulatory Advice OSRA
    - Translational Product Management Organisation TPMO
- PEI offers a variety of interactions
  - kick-off meetings
  - national scientific advice
  - help to apply for an EMA scientific advice
  - Joint advice PEI/HTA in Germany
  - multi-national scientific advice with applicant-selected NCAs (HMA pilot)
- IMI funding for basic research questions in vaccine development
- PEI contributes to EMA Vaccine Working Party of the CHMP (GLs etc.)
- PEI´s Vacctrain mission in the Global Health Protection Program of Germany
  - Support and regulatory training to establish systems for the regulation and control of clinical trials for vaccines and biomedicines

Summary and discussion

- Regulatory systems offer a variety of supportive actions
  - to enable vaccine developments
  - while protecting individual and public health.

- Regulatory flexibility in concluding on a favourable benetif-risk balance of a product as the basis for licensure /marketing authorisation
  - depends on the experience of the regulatory agency/assessor and
  - is given by a variety of regulatory procedures and measures.

- Questions
  - Which parts of the current regulatory path to licensure can be simplified?
  - What kind of additional help and support from regulators would have an impact regarding
    - the speed of vaccine development and
    - the rate of failures?