

07 Oct 2019

# 2<sup>nd</sup> 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



## Historical context

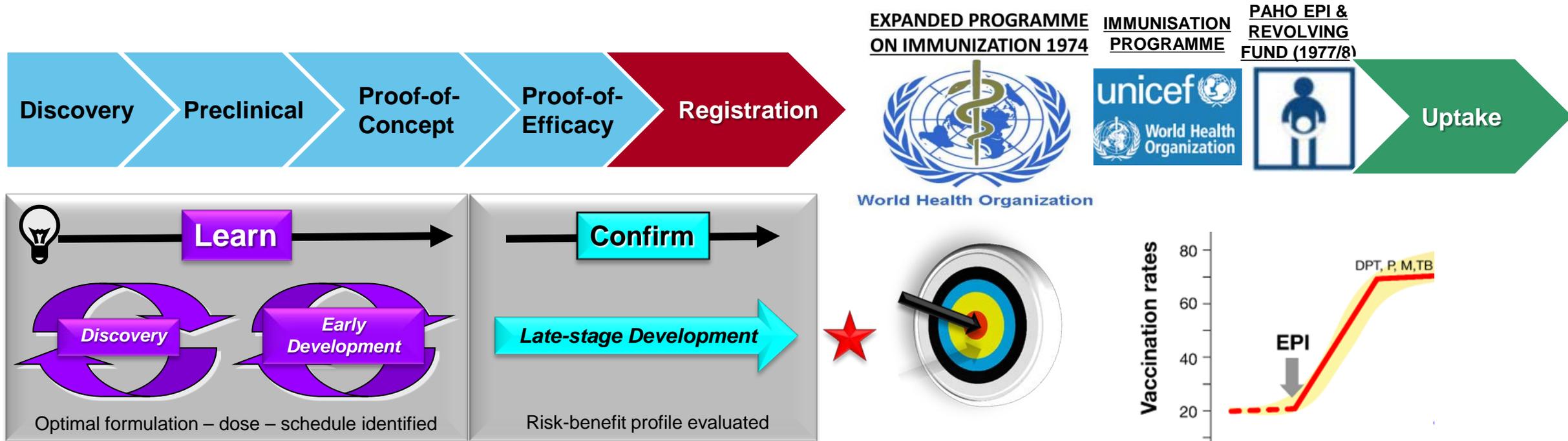
Barriers in Late Stage & Introduction Gap

An assumption-based framework?

Fit into IA2030?

# Progression of vaccine development and introduction for LMICs

## Conventional pathway to impact (circa 1997)

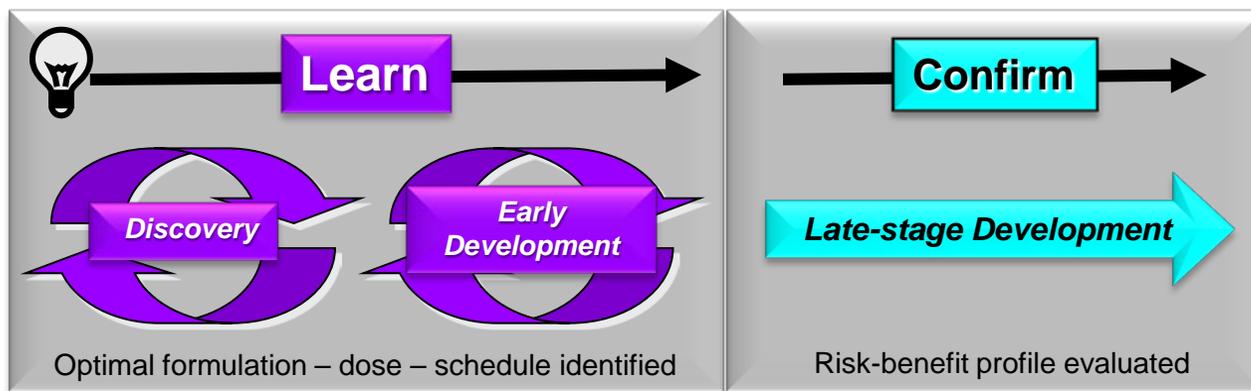


Sheiner, L. *Clin. Pharm. Therap.* **61**: 275–91, 1997  
doi:10.1016/S0009-9236(97)90160-0

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.**

# Progression of vaccine development and introduction for LMICs

## Conventional pathway to impact (circa 2000)



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

The Children's  
Vaccine Initiative

(1990)

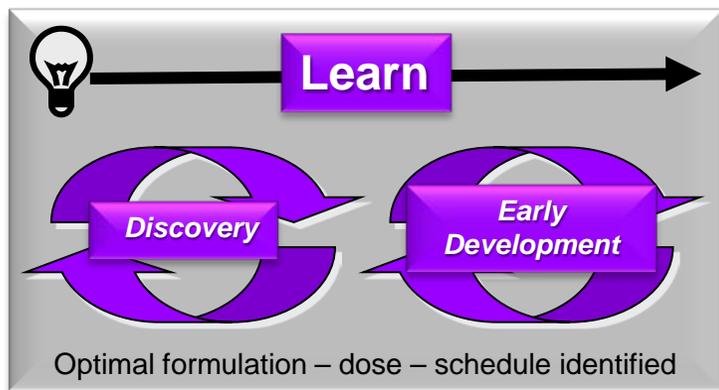


Global Alliance for Vaccines  
and Immunization (2000)

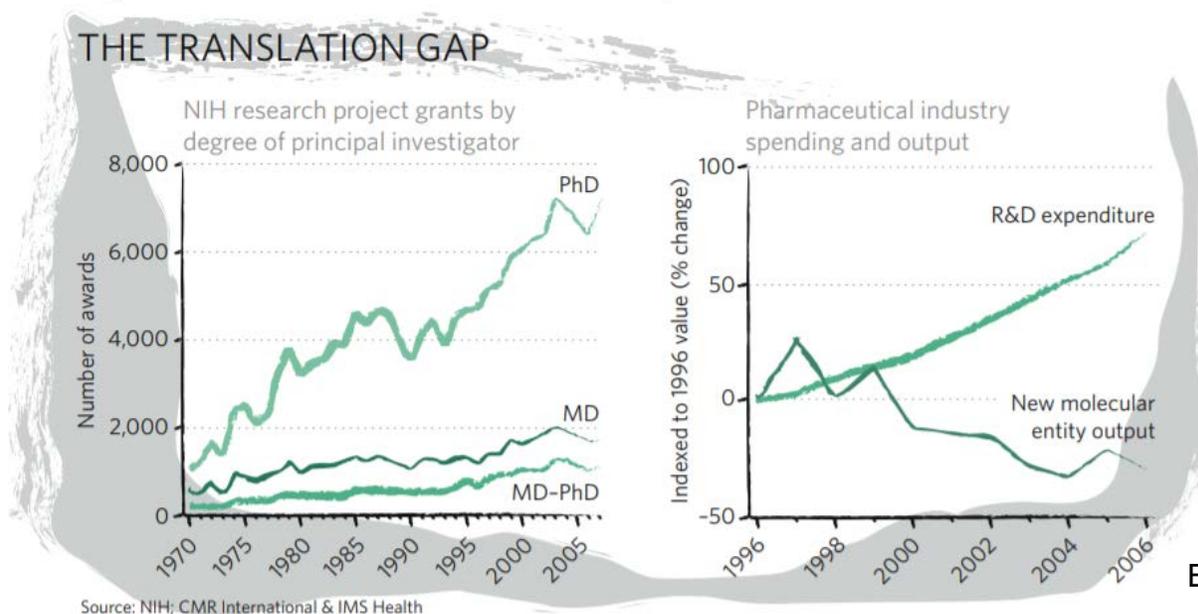


# Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2008)



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

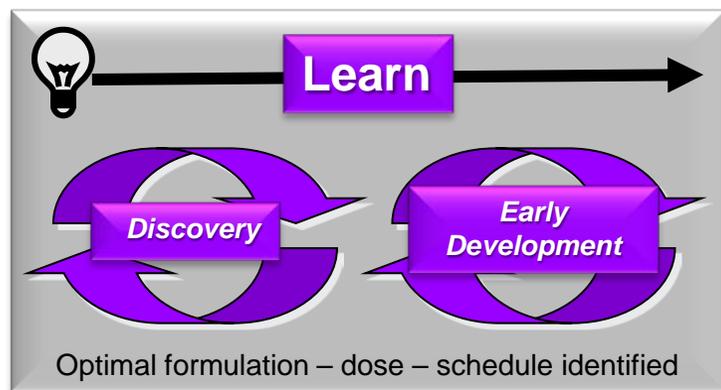


- Scarce expertise
- Increasing development costs



# Progression of vaccine development and introduction for LMICs

## Bridging the translational R&D gap



National Center for Advancing Translational Sciences

Biomedical Catalyst



Innovate UK



Strategic Health Innovation Partnerships



CEPI

GATES MRI

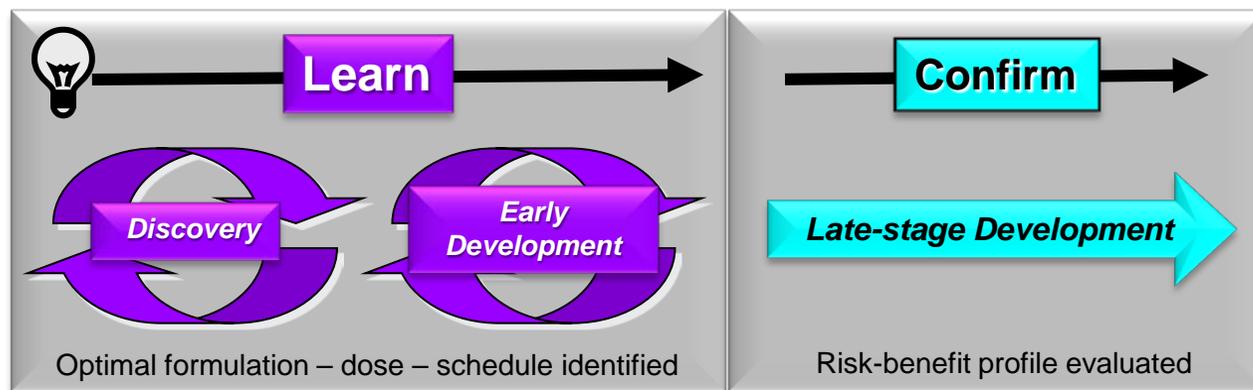
thsti

ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान

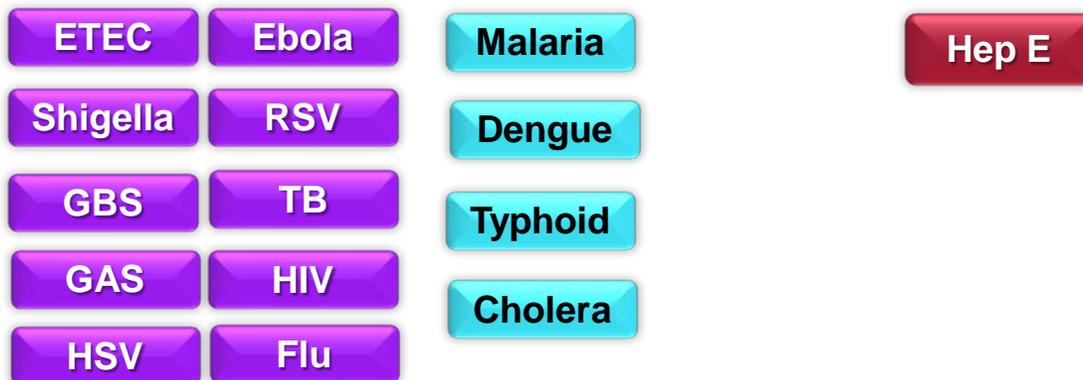


# Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2014-15)



## PDVAC/SAGE PIPELINE (Illustrative)



# Progression of vaccine development and introduction for LMICs

## Conventional pathway to impact (circa 2016)

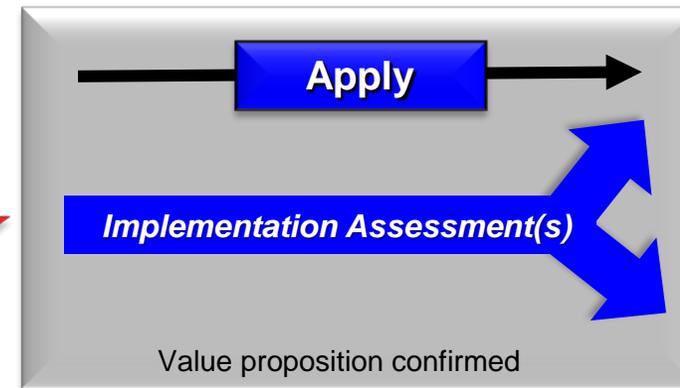


COMMENT | VOLUME 387, ISSUE 10031, P1887-1889, MAY 07, 2016

### 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](https://doi.org/10.1016/S0140-6736(16)30394-4)

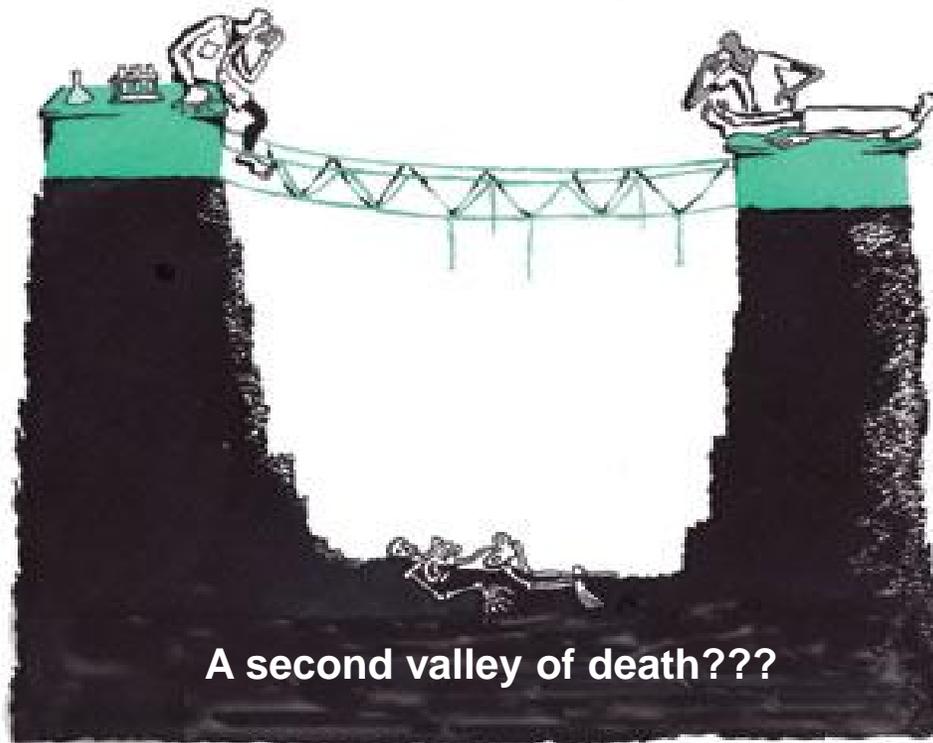
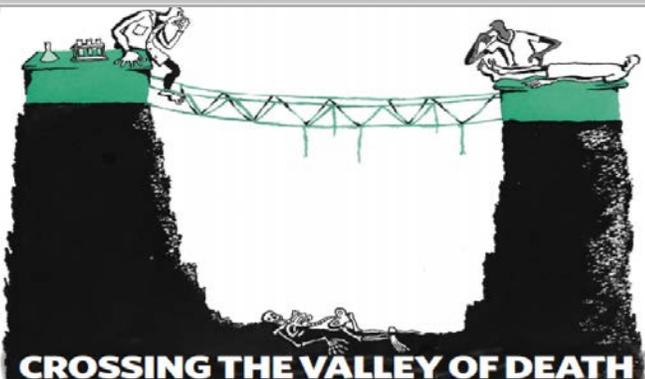
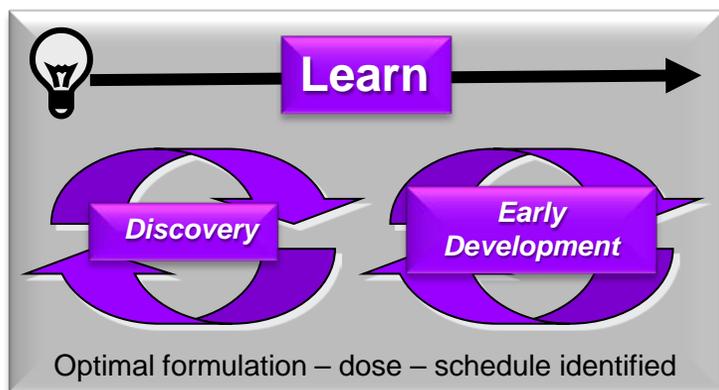


O'Brien, KL. et al., *Lancet*. **387**::1887-9.  
doi: 10.1016/S0140-6736(16)30394-4

“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

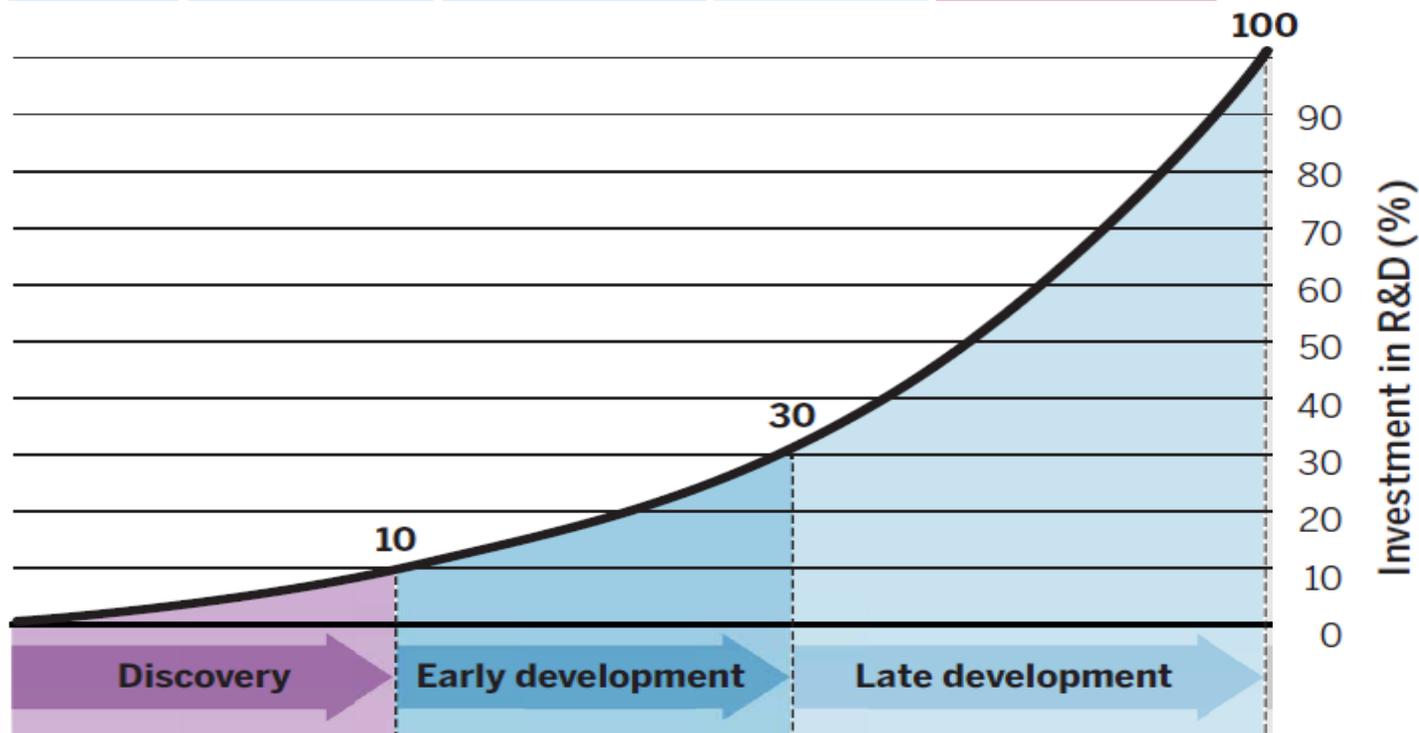
Conventional pathway to impact (circa 2019)???



*Drawn to scale*

# 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

# 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<sup>a</sup>, James M. Robinson<sup>b,\*</sup>, Gerard Cunningham<sup>c</sup>, Robyn Iqbal<sup>d</sup>, 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](https://docs.gatesfoundation.org/Documents/Production_Economics_Vaccines_2016.pdf)

\*Cost of Goods Sold



# Progression of vaccine development and introduction for LMICs

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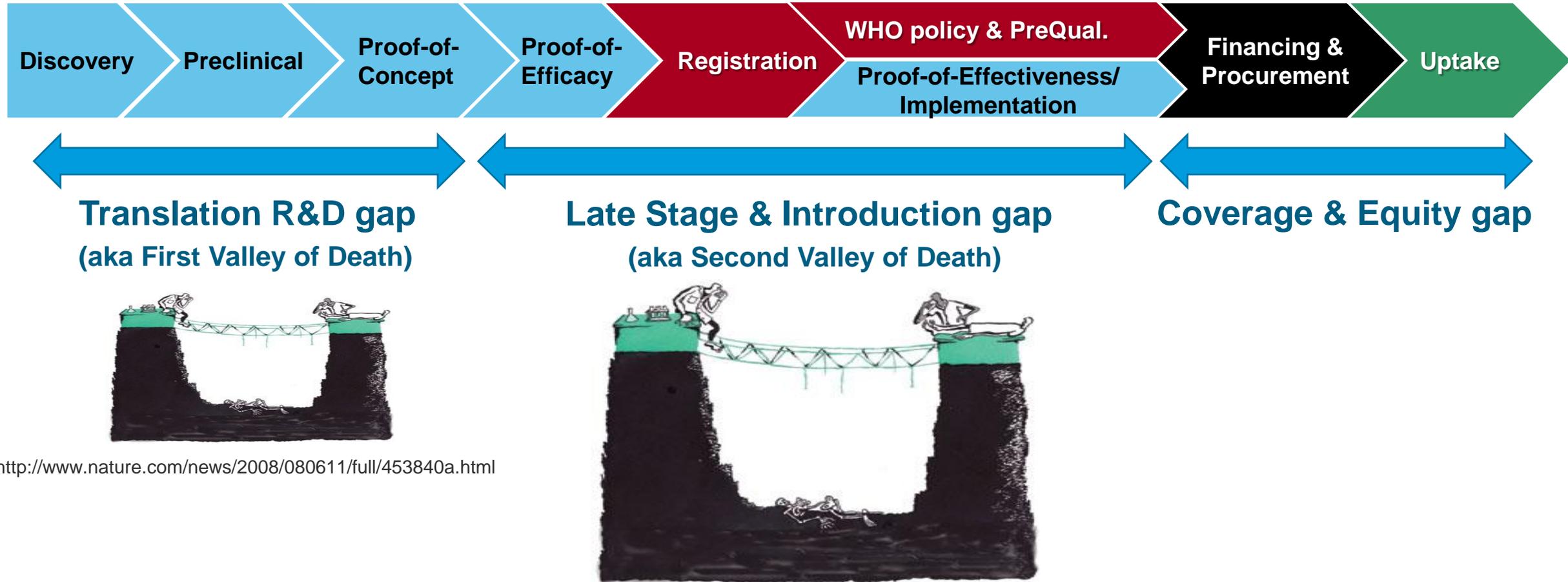
Ave. cost of Phase 1 for CMC elements **12 M USD**

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*



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

[www.lancet.com](http://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

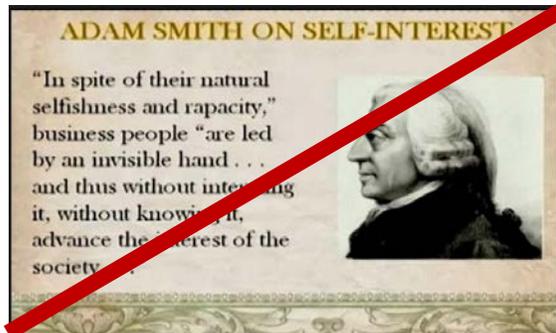
*Compelling—Uncertain—Assistance—No*

## Assistance-dependent business case (LMIC only; Outbreak)

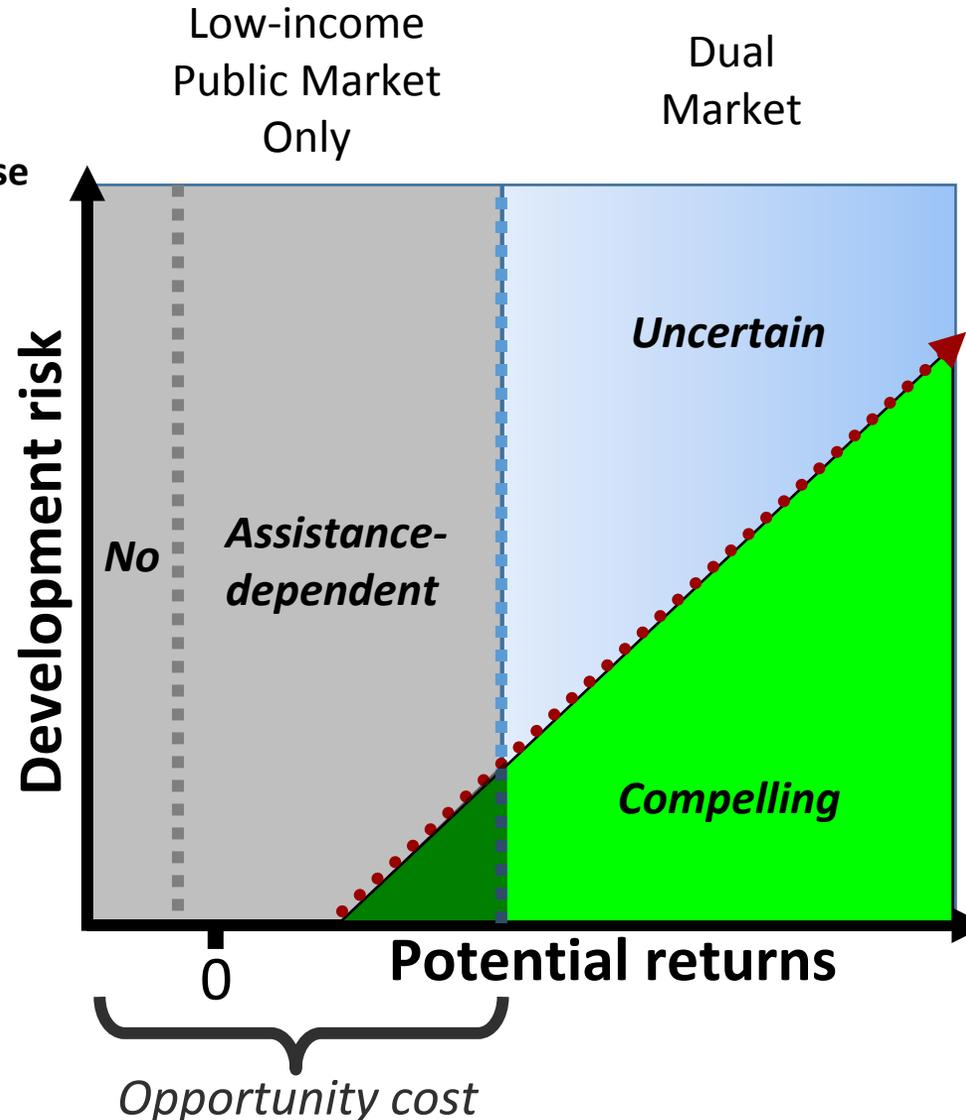
(e.g., LMIC: Cholera, Malaria, Men A, Shigella; Outbreak: Ebola, MERS, Nipah, Lassa Fever)

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



# 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 Initiative)

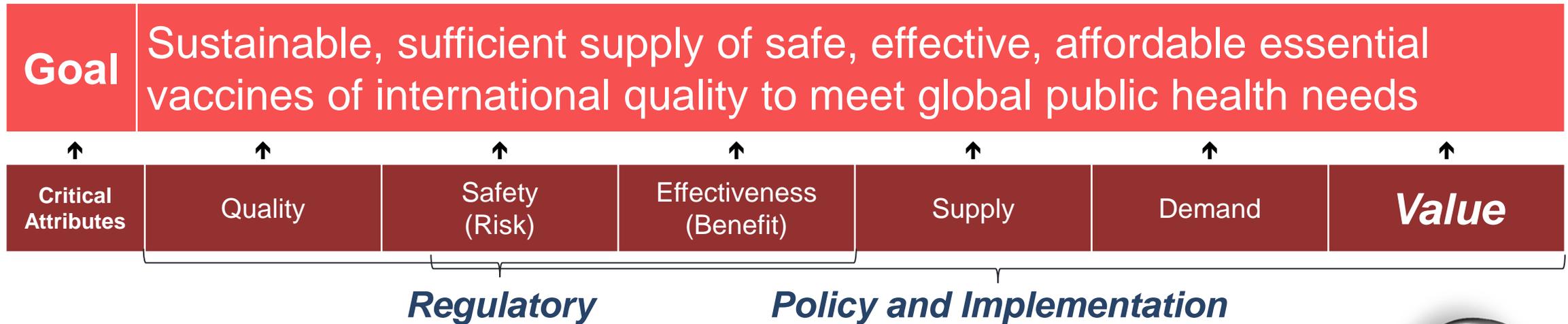


A single entity?

Key assumption:

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

# Critical vaccine attributes to optimally achieve strategic goal



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



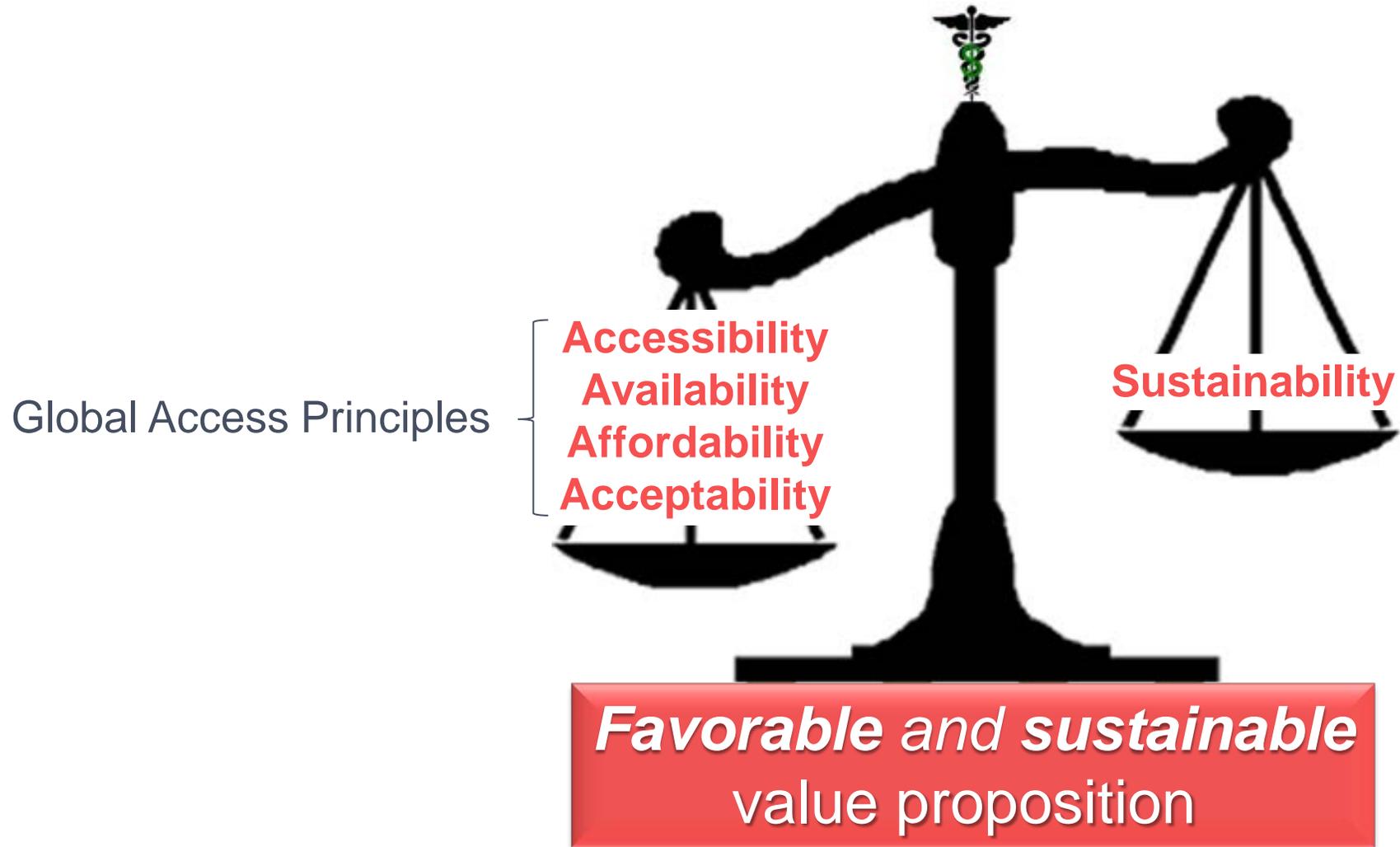
*Typical stakeholders include:*

- 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.

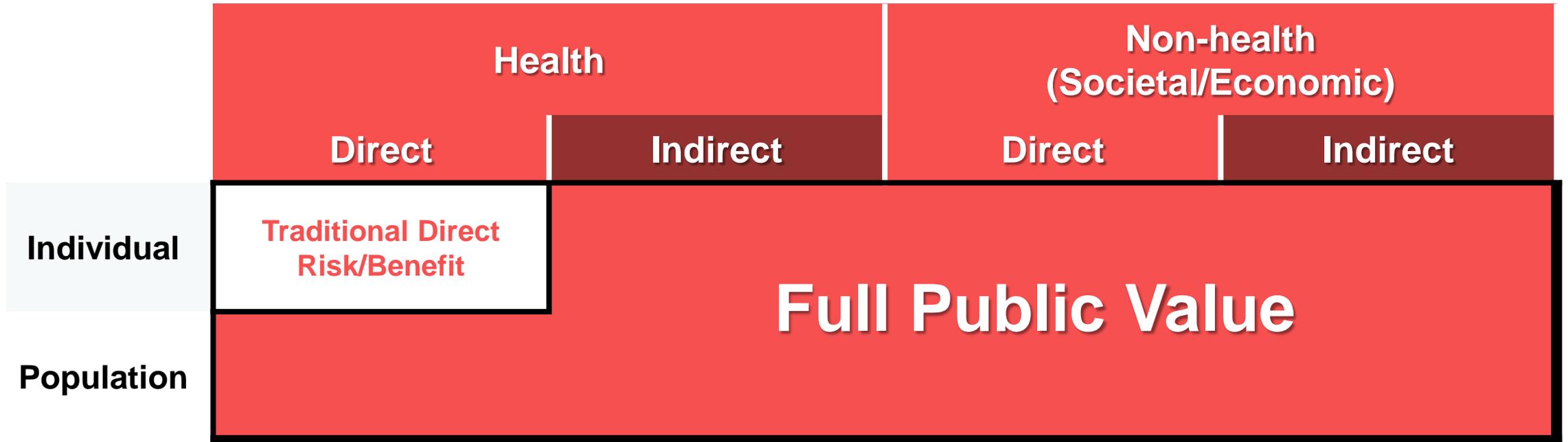
*Other stakeholders:*

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

# Finding the optimal balance of value for all key stakeholders



# 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

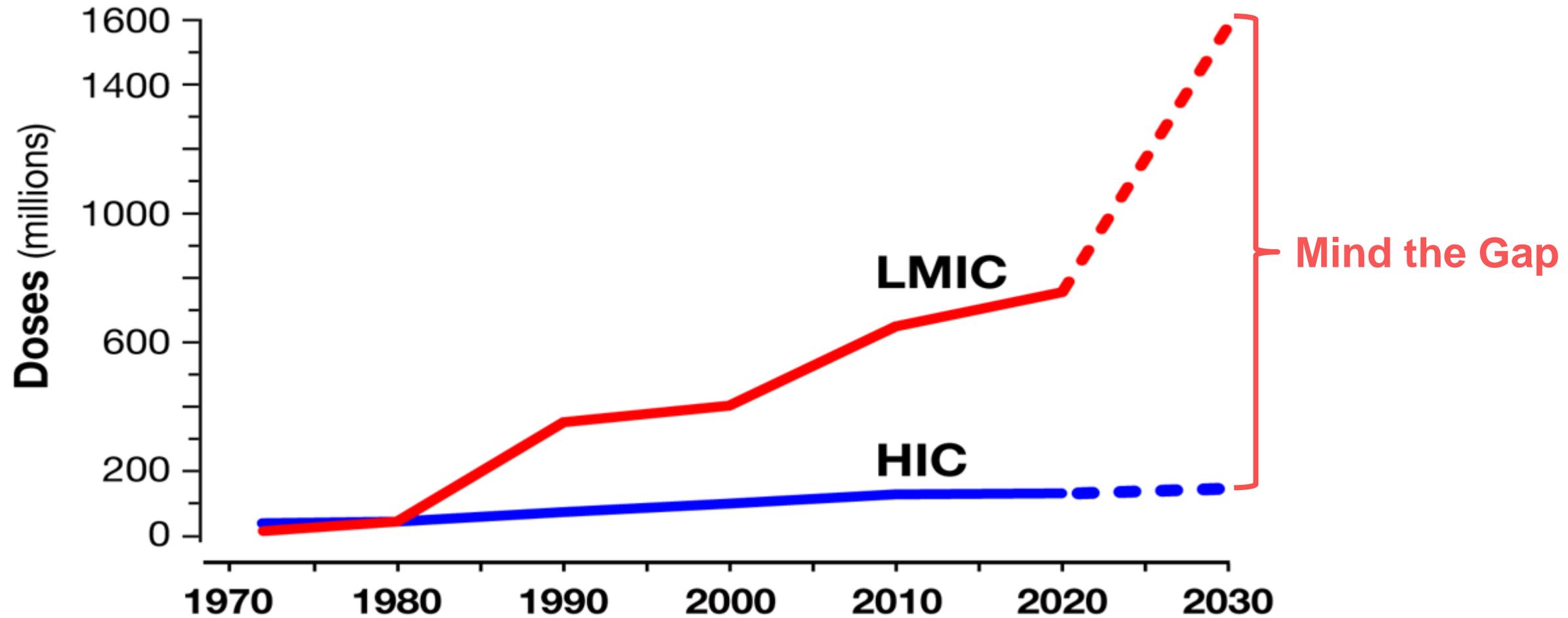
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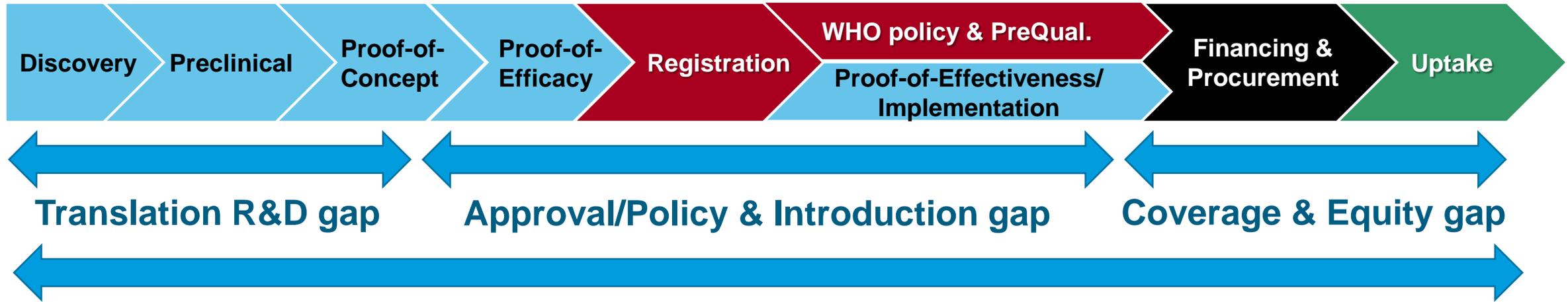
**Fit into IA2030?**

# Next decade of vaccine



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



## Delivery and vaccine-associated technology gaps

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)
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    - Target Financing Profiles (?)

**THE PULL:** Full public value of vaccines

- Country perspectives of value (TSE)

