February 2021

GVIRF Workshop 6:

Vaccine development to access: is there a role for early policy consideration?

Vaccine development to access: Opportunities, risks and potential valleys of death

Photo: PATH/Gabe Bienczycki

David C. Kaslow, MD
CSO
PATH Essential Medicines

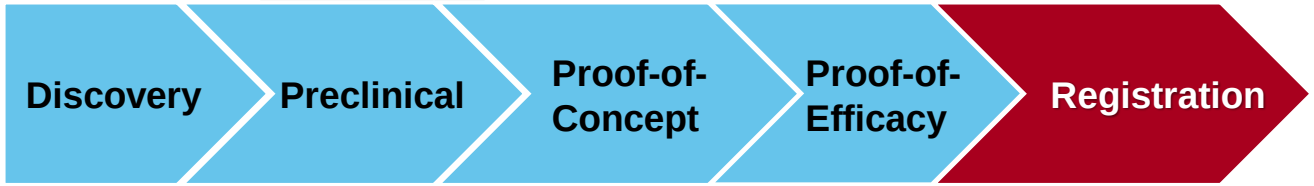
Historical context

Barriers in Late Stage & Introduction Gap

An assumption-based framework to bridge the gaps

Progression of vaccine development and introduction for LMICs

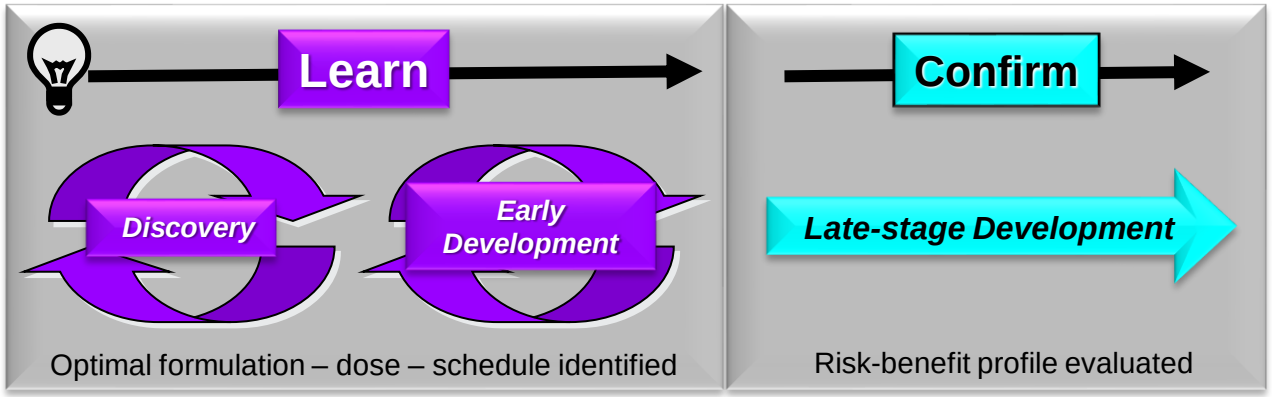
Conventional pathway to impact (circa 1997)

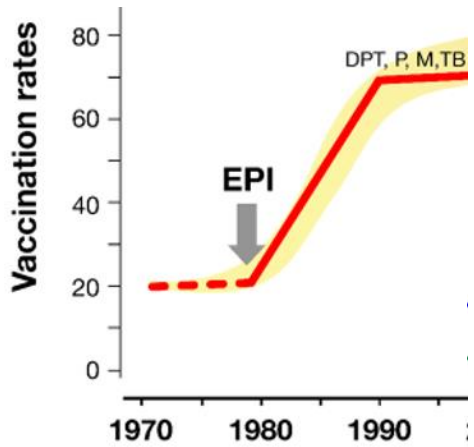


EXPANDED PROGRAMME ON IMMUNIZATION 1974

IMMUNISATION PROGRAMME

PAHO EPI & REVOLVING FUND (1977/8)





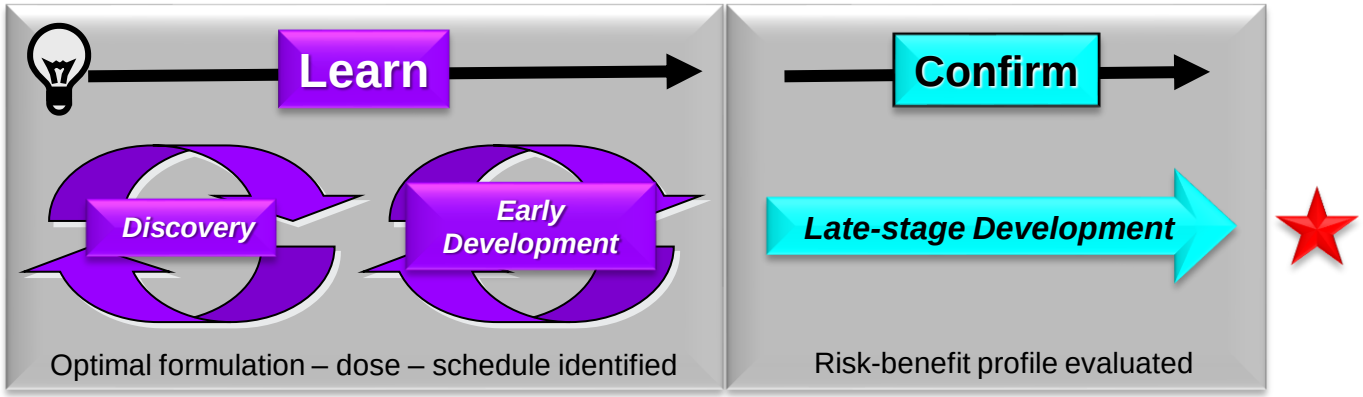
Sheiner, L. *Clin. Pharm.Therap.* **61**: 275–91,1997
doi:10.1016/S0009-9236(97)90160-0

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)



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)

Gavi The Vaccine Alliance

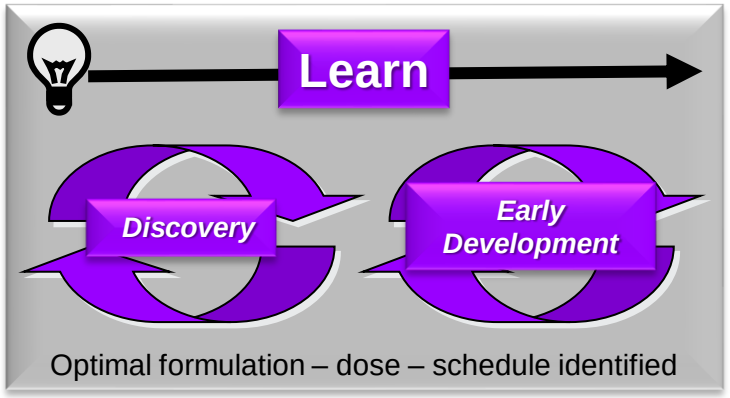
Progression of vaccine development and introduction for LMICs

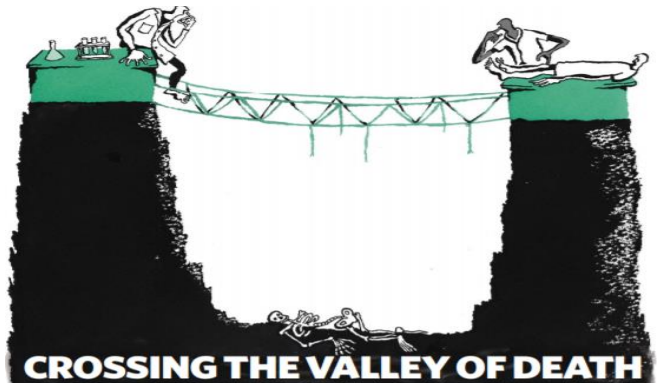
Conventional pathway to impact (circa 2008)

Translation R&D gap

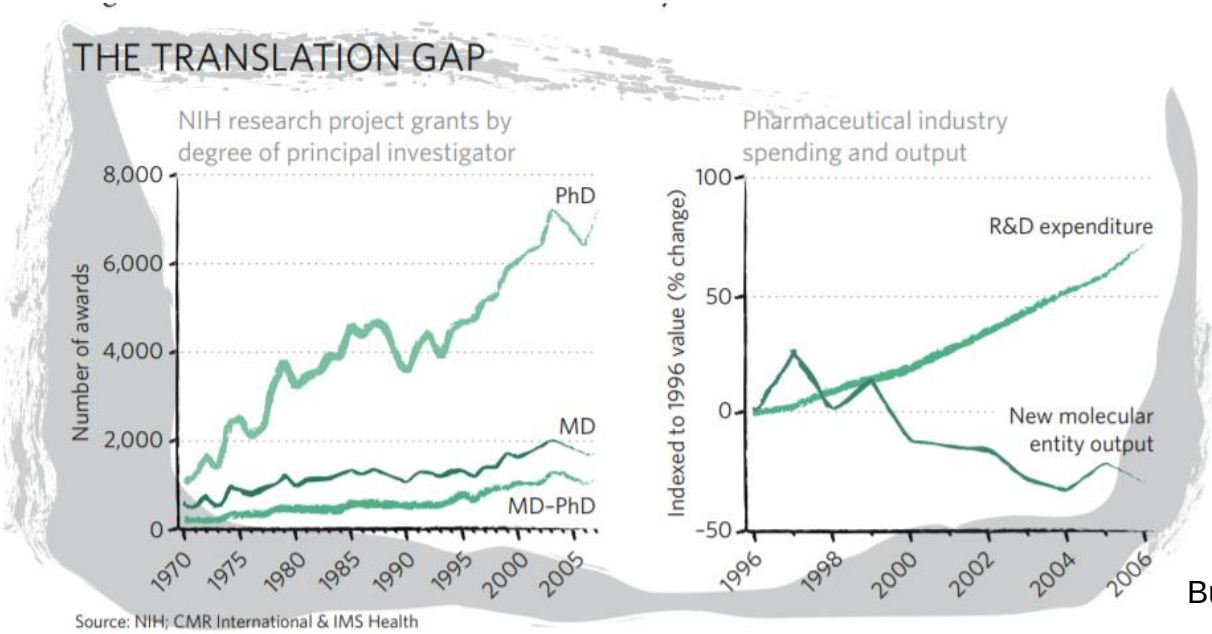
Coverage & Equity gap

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

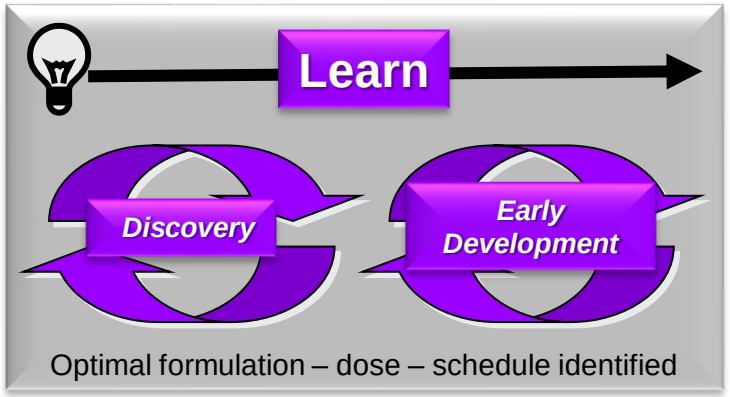
Progression of vaccine development and introduction for LMICs

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



Vaccine Research Center

Strategic Health Innovation Partnerships

BARDA

NIH
National Center for Advancing Translational Sciences

Biomedical Catalyst

MRC Medical Research Council

Innovate UK

Gavi The Vaccine Alliance

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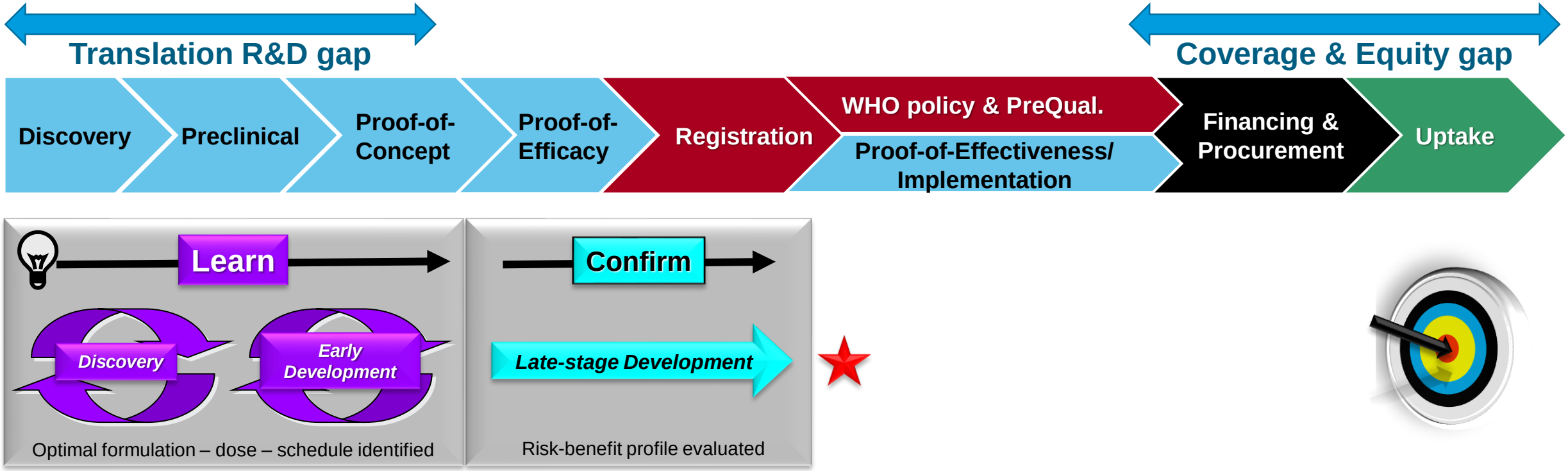
Progression of vaccine development and introduction for LMICs

Conventional pathway to impact (circa 2014-15)

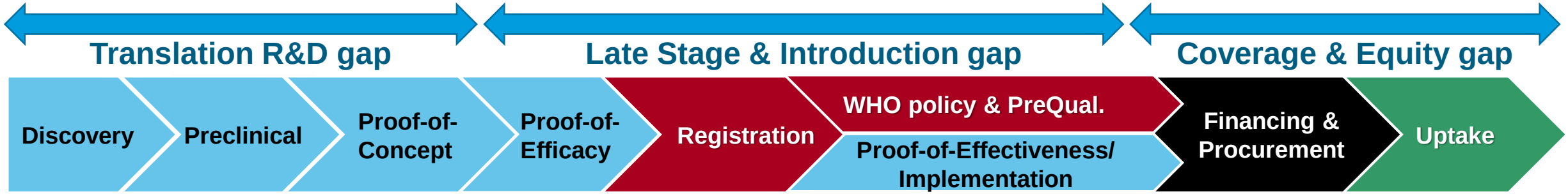


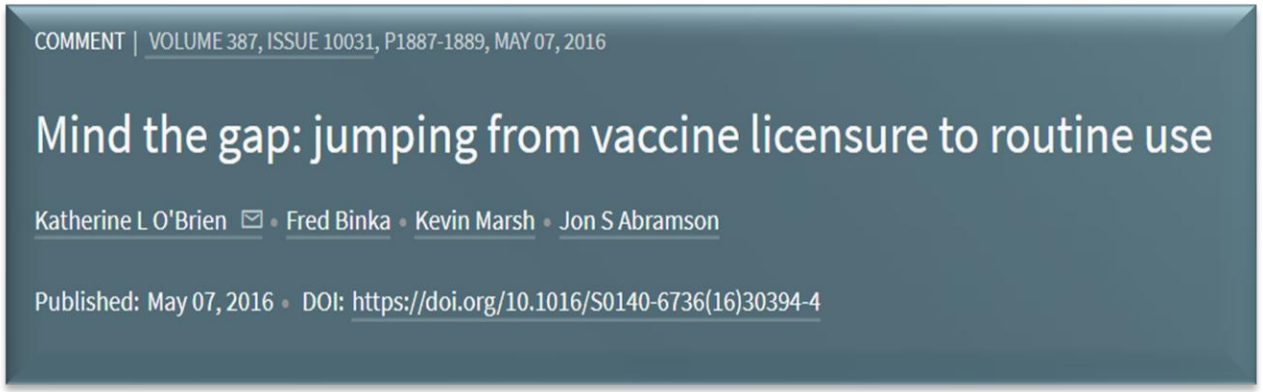
PDVAC/SAGE PIPELINE (Illustrative)

- 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)



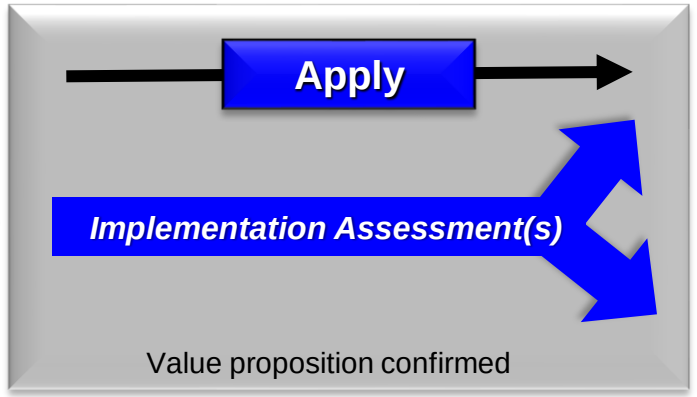


COMMENT | VOLUME 387, ISSUE 10031, P1887-1889, MAY 07, 2016

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**

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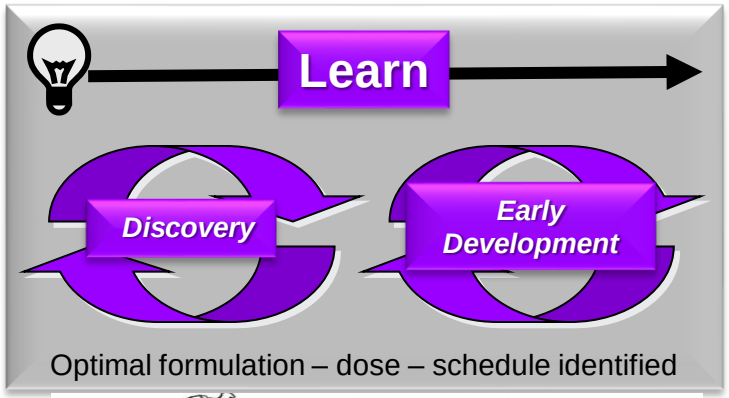
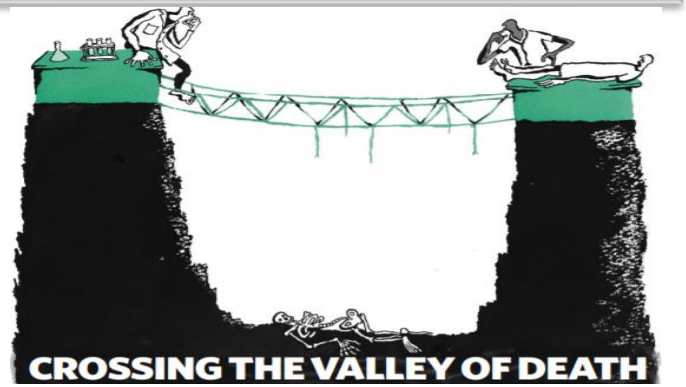
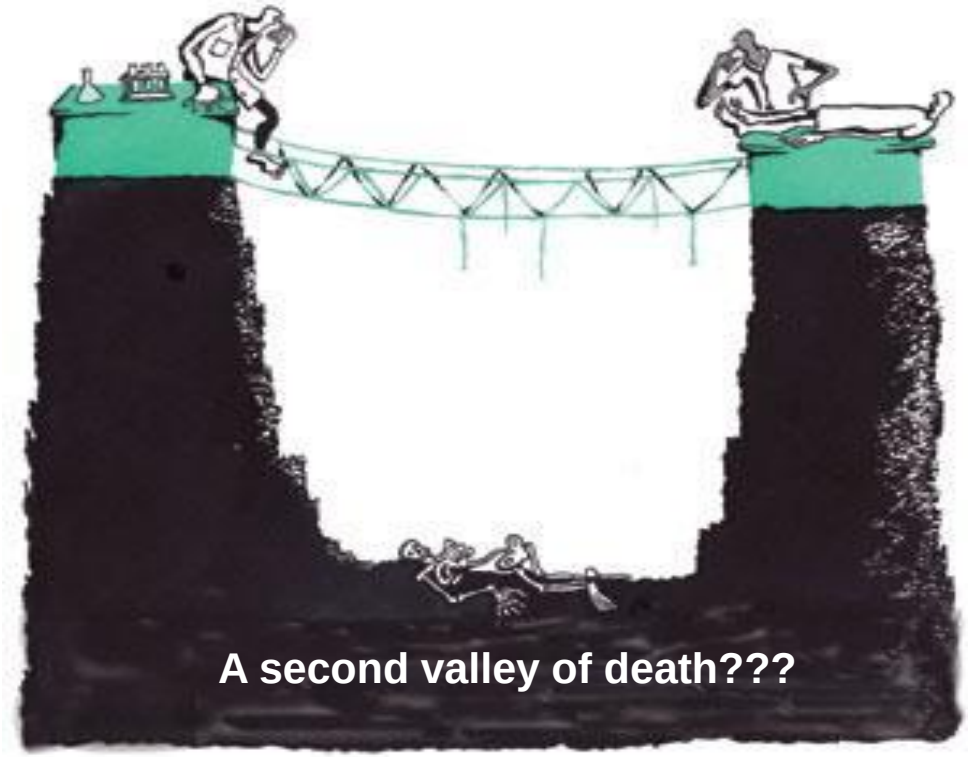




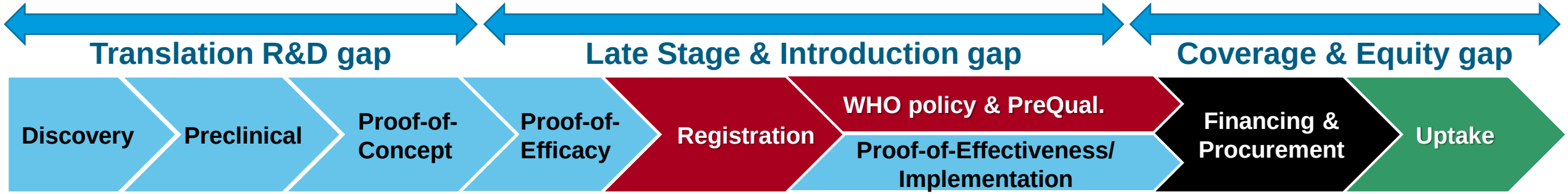


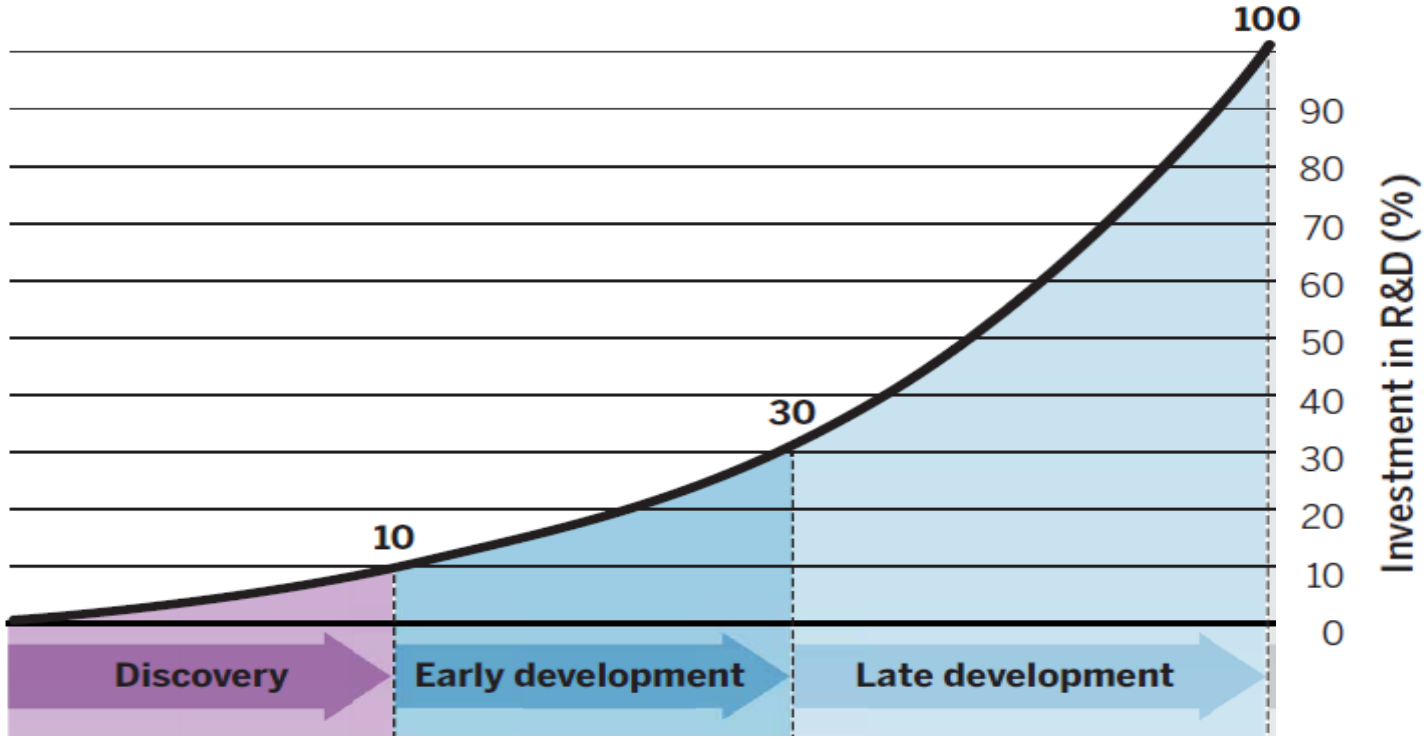
Drawn to scale

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



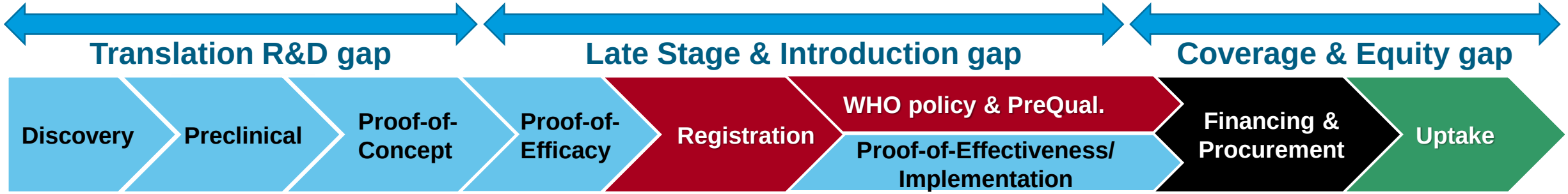


70% of the total R&D budget

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

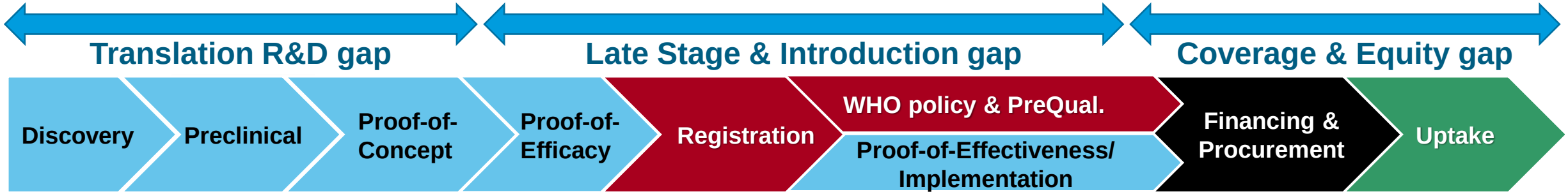
Late development is the most labor- and budget-intensive phase of vaccine development



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*

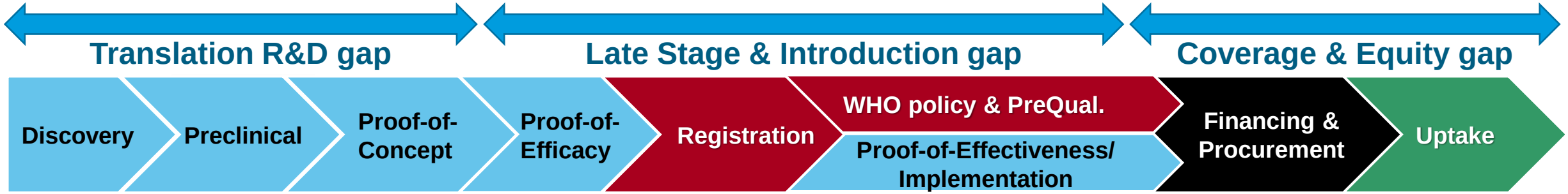
- Development
- **Facilities & Equipment CAPEX**
- Consumables/raw materials
  Direct Labor
- Overhead
- Licensing/Regulatory and commercialization

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



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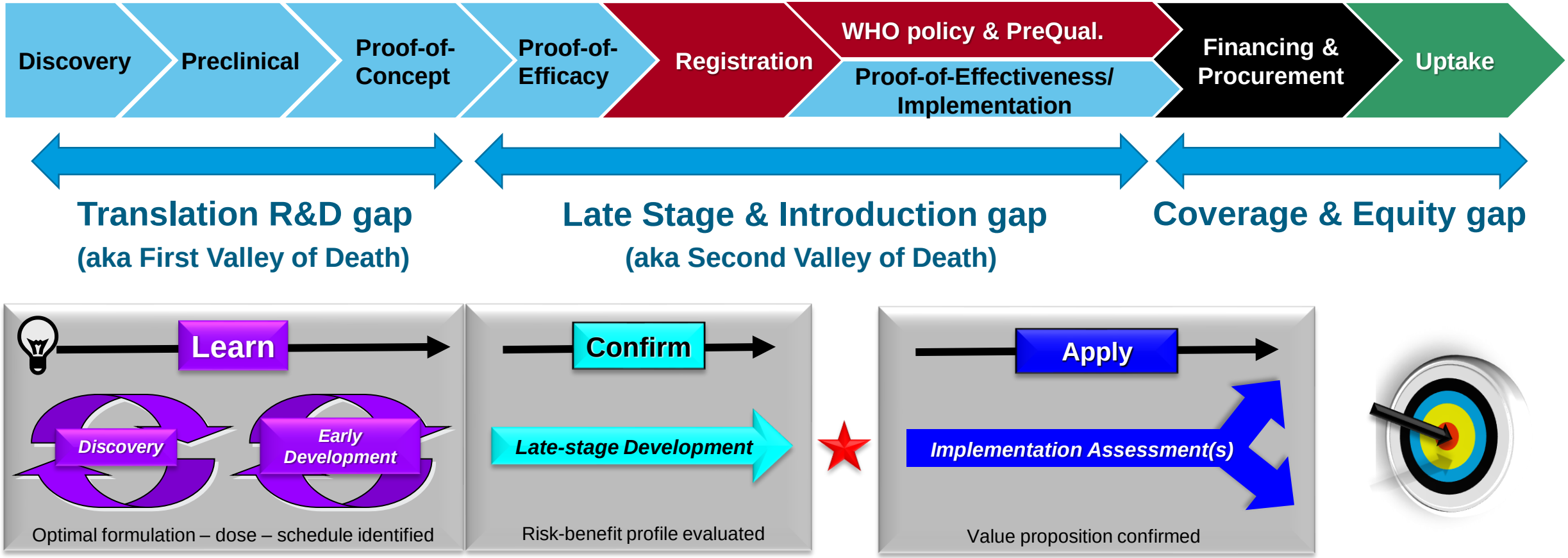
Ave. cost of Phase 1 for CMC elements **12 M USD**

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



Historical context

Barriers in Late Stage & Introduction Gap

An assumption-based framework to bridge the gaps

Three 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 and certainly by the time of exiting 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 to bridge the gaps

Key assumption:

Its not just about the money

Human-controlled bridges across the second valley of death: *ABCs beyond just funding*

- **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:

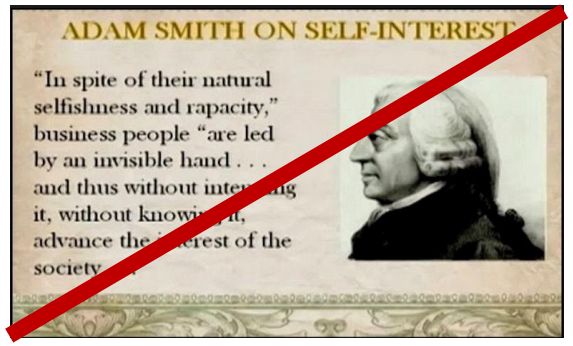
“One size” won’t fix all cases

Four Vaccine Business Cases

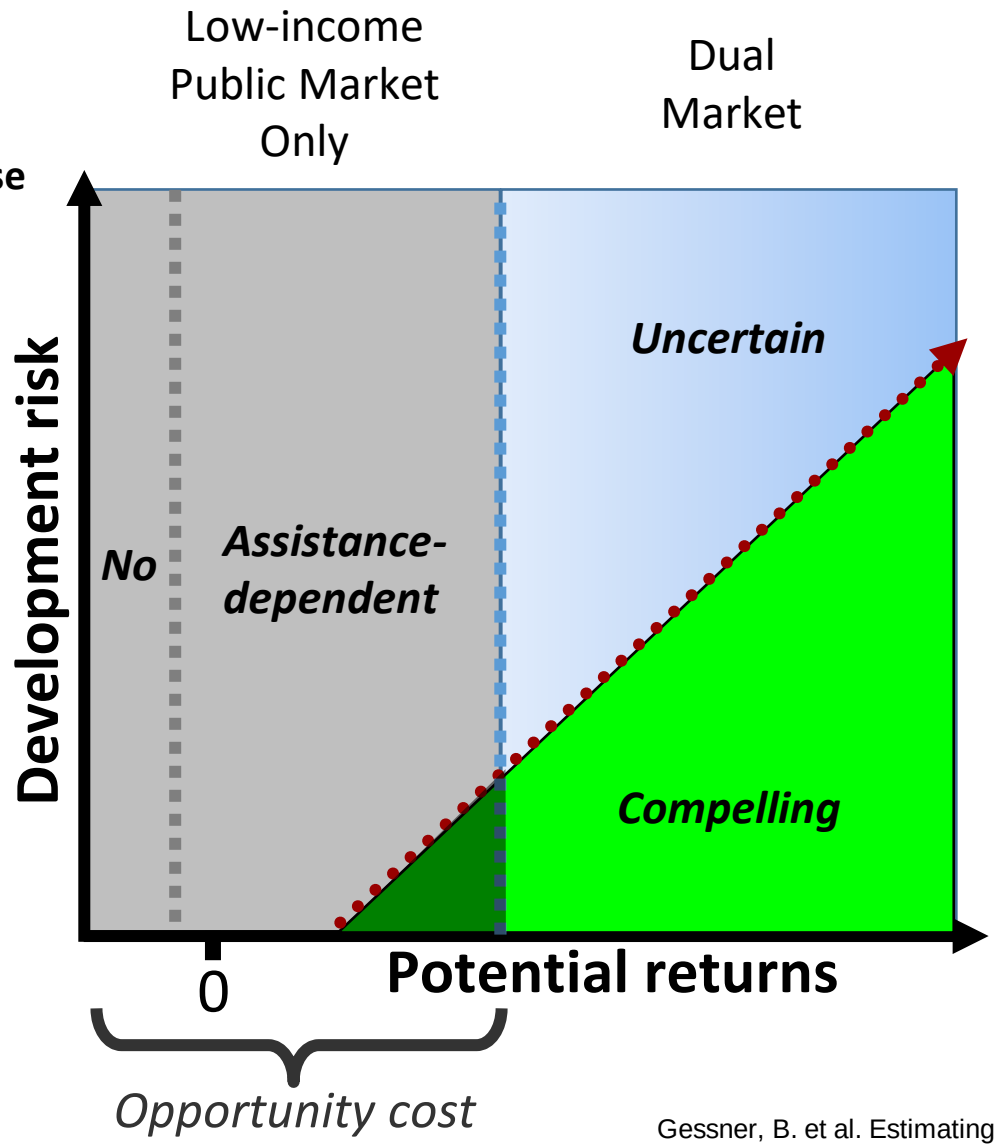
Compelling—Uncertain—Assistance—No

***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

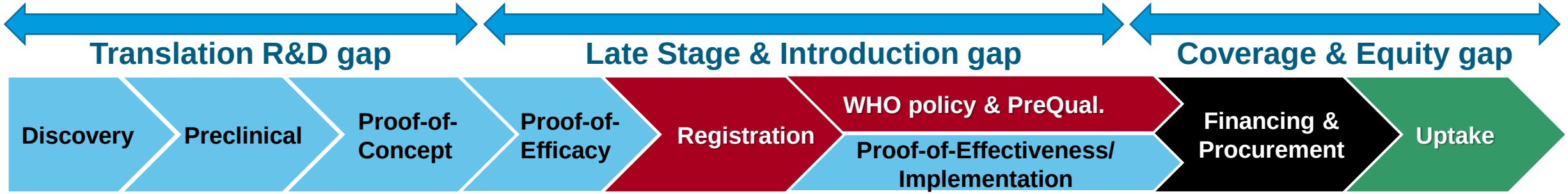
***Compelling* business case (HIC → LMIC)**
(e.g., HBV, HiB, HPV, PCV, RSV, Rota)
Solutions:

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

Gessner, B. et al. Estimating the full public health value of vaccination *Vaccine* 35:6255-6263, 2017
Kaslow, et al. Vaccine candidates for poor nations are going to waste *Nature* **564**: 337-339, 2018

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

BARDA Biomedical Advanced Research and Development Authority

CEPI

???

Gavi The Vaccine Alliance

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thsti ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान

DARPA Bridging The Gap Powered By Ideas

GATES MRI

Progression of vaccine development and introduction for LMICs

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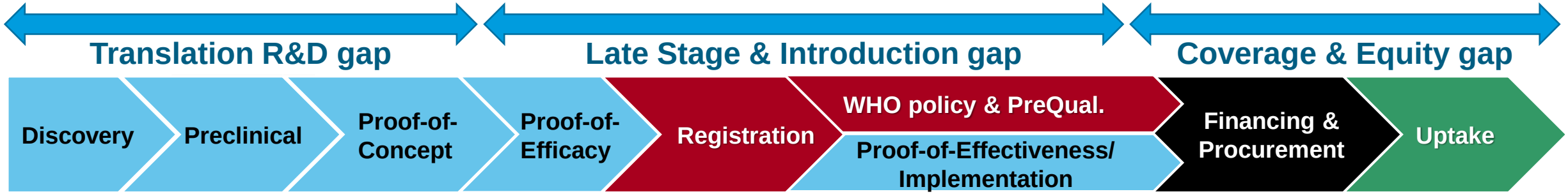


Pathogen-specific?
(Pneumo and Rota ADIPs, Hib Initiative)

A single entity?

Key assumption:

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

Critical vaccine attributes to optimally achieve strategic goal

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.

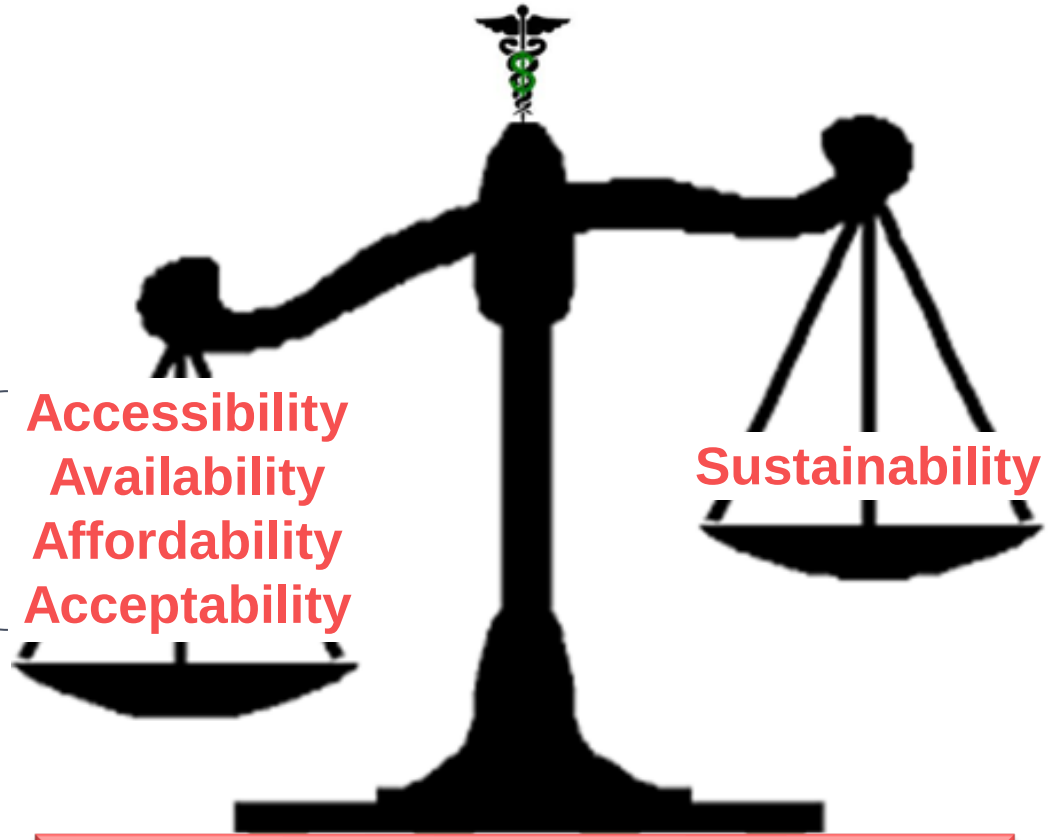
Other stakeholders:

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

From: WHO Public Health Value Proposition: DRAFT Template

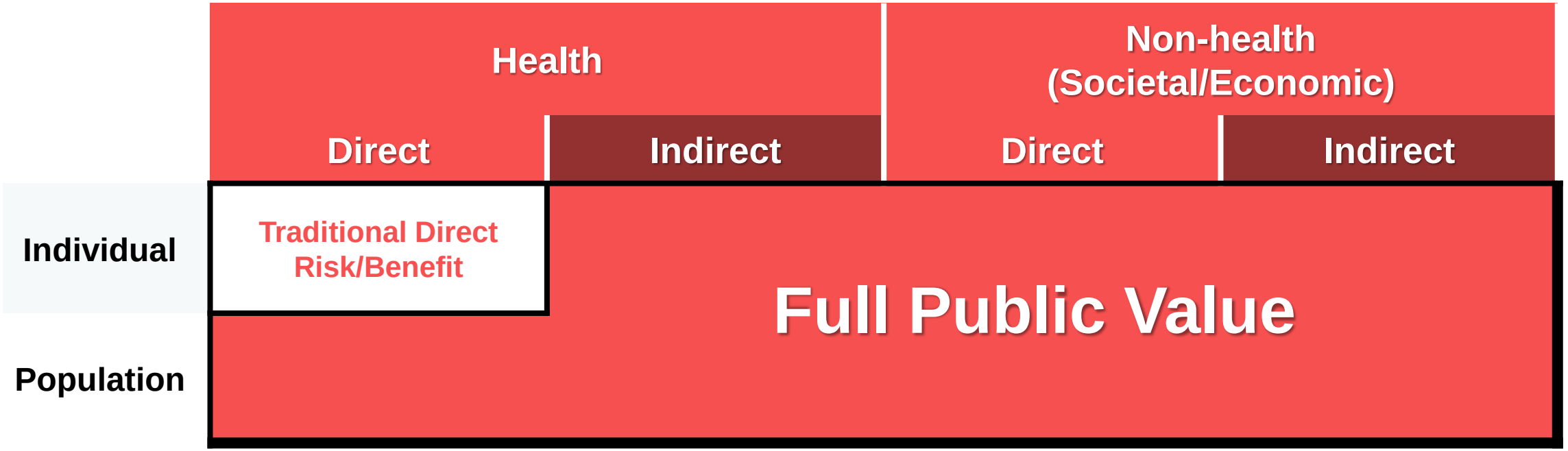
Finding the optimal balance of value for all key stakeholders

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