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
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)

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)

Discovery → Preclinical → Proof-of-Concept → Proof-of-Efficacy → Registration

WHO policy & PreQual. → Proof-of-Effectiveness/Implementation → Financing & Procurement → Uptake

Coverage & Equity gap

Learn

Optimal formulation – dose – schedule identified

Confirm

Risk-benefit profile evaluated

doi:10.1016/S0009-9236(97)90160-0

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

doi:10.1038/453840a
Progression of vaccine development and introduction for LMICs

Bridging the translational R&D gap

Translation R&D gap

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

Coverage & Equity gap

Learn

Optimal formulation – dose – schedule identified

Strategic Health Innovation Partnerships

Vaccine Research Center
BRIDGING THE GAP
DARPA
Vaccine Alliance
CEPI
GATES
MRI
Biomedical Catalyst
Innovate UK

National Center for Advancing Translational Sciences
Biomedical Catalyst
Medical Research Council
Innovate UK

Gavi
The Vaccine Alliance
Progression of vaccine development and introduction for LMICs
Conventional pathway to impact (circa 2014-15)

PDVAC/SAGE PIPELINE (Illustrative)
“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)???
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

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

Translation R&D gap

Discovery → Preclinical → Proof-of-Concept

Late Stage & Introduction gap

Proof-of-Efficacy → Registration → WHO policy & PreQual. → Proof-of-Effectiveness/Implementation

Coverage & Equity gap

Financing & Procurement → Uptake

Coverage & Equity gap

Late Stage & Introduction gap

What’s else?
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

Vaccine manufacturing is complex and capital-intensive

Translation R&D gap

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical</th>
<th>Proof-of-Concept</th>
<th>Proof-of-Efficacy</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO policy &amp; PreQual.</td>
<td>Proof-of-Effectiveness/Implementation</td>
<td>Financing &amp; Procurement</td>
<td>Uptake</td>
<td></td>
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</tbody>
</table>

Late Stage & Introduction gap

Coverage & Equity gap

### Review

The complexity and cost of vaccine manufacturing – An overview

Stanley Plotkin, James M. Robinson, Gerard Cunningham, Robyn Iqbal, Shannon Larsen

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

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**

Additional resources:

- [WHO policy & PreQual.](https://www.nature.com/articles/d41586-018-07758-3)
- [Uptake](https://stm.sciencemag.org/content/11/497/eaaw2888.full)
An assumption-based framework?
Fit into IA2030?

Historical context

Barriers in Late Stage & Introduction Gap
An assumption-based framework?
Fit into IA2030?
Barriers in the Late Stage & Introduction Gap

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

- Technical
  - 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:

It's 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

**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

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The Theory Of Moral Sentiments
(Part IV, Chapter I)
Progression of vaccine development and introduction for LMICs

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

Translation R&D gap
- Discovery
- Preclinical

Late Stage & Introduction gap
- Proof-of-Concept
- Proof-of-Efficacy
- Registration
- WHO policy & PreQual.
- Proof-of-Effectiveness/Implementation

Coverage & Equity gap
- Financing & Procurement
- Uptake

Strategic Health Innovation Partnerships

Biomedical Catalyst
NIH
BARDA
MRC
Innovate UK
CEPI
Gavi
Vaccine Research Center
Darpa
Gates Mri

???
Progression of vaccine development and introduction for LMICs

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

- Translation R&D gap
- Late Stage & Introduction gap
- Coverage & Equity gap


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

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

<table>
<thead>
<tr>
<th>Critical Attributes</th>
<th>Quality</th>
<th>Safety (Risk)</th>
<th>Effectiveness (Benefit)</th>
<th>Supply</th>
<th>Demand</th>
<th>Value</th>
</tr>
</thead>
</table>

**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

Accessibility
Availability
Affordability
Acceptability

Sustainability

Favorable and sustainable value proposition
Traditional Direct Risk/Benefit v Full Public Value

- **Health**
  - Direct
  - Indirect
- **Non-health (Societal/Economic)**
  - Direct
  - Indirect

- **Individual**
  - Traditional Direct Risk/Benefit

- **Population**
  - Full Public Value
Key assumption:

*Public sector championship required (political will)*
Full Public Value of Vaccines as driver of sustainable vaccine development and access

- 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
Potential “needle-movers”

Challenge strongly held vaccine development dogmas

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

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)
    - Target Policy Profiles (?)
    - Target Financing Profiles (?)

**THE PULL**: Full public value of vaccines
- Country perspectives of value (TSE)