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)


Coverage & Equity gap

The Children's Vaccine Initiative (1990)

Global Alliance for Vaccines and Immunization (2000)

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

Coverage & Equity gap

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

Optimal formulation – dose – schedule identified

Strategic Health Innovation Partnerships

Biomedical Catalyst
CEPI
GATES
MRC
NIH
Vaccine Research Center
BARDAR
BARDA
BRIDGING THE GAP
INNOVATE UK
Medical Research Council
National Center for Advancing Translational Sciences

Proof-of-Concept
Proof-of-Efficacy
Registration
WHO policy & PreQual.
Financing & Procurement
Uptake
Progression of vaccine development and introduction for LMICs
Conventional pathway to impact (circa 2014-15)


Translation R&D gap

Covered & Equity gap

- **Learn**: Optimal formulation – dose – schedule identified
- **Confirm**: Risk-benefit profile evaluated

**PDVAC/SAGE PIPELINE (Illustrative)**

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


- Optimal formulation – dose – schedule identified
- A second valley of death???

https://www.nature.com/articles/d41586-018-07758-3
https://stm.sciencemag.org/content/11/497/eaaw2888.full

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.

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

|-----------|-------------|-------------------|-------------------|--------------|-----------------------|---------------------------------------|------------------------|--------|

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

What’s else?
Progression of vaccine development and introduction for LMICs

Vaccine manufacturing is complex and capital-intensive

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

The complexity and cost of vaccine manufacturing – An overview

Stanley Plotkin¹, James M. Robinson¹,², Gerard Cunningham³, Robyn Iqbal⁴, Shannon Larsen⁴

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

Translation R&D gap
Discovery
Preclinical
Proof-of-Concept

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

Financing & Procurement

Coverage & Equity gap

Uptake

The complexity and cost of vaccine manufacturing – An overview

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

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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


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

• Human-controlled

  • Funding
  • Political Will
  • Stakeholder Alignment
  • Regulatory-Policy-Financing Pathway

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.
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

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
- Proof-of-Concept
- Proof-of-Efficacy
- Registration
- WHO policy & PreQual.

Late Stage & Introduction gap

- Proof-of-Effectiveness/Implementation
- Financing & Procurement
- Uptake

Coverage & Equity gap

Strategic Health Innovation Partnerships

- NIH
- BARDA
- MRC
- Innovate UK
- CEPI
- Gavi

???
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

**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>
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**Regulatory**

**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

<table>
<thead>
<tr>
<th>Health</th>
<th>Non-health</th>
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<tr>
<td>Direct</td>
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<td>Indirect</td>
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<tr>
<th>Individual</th>
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<td>Traditional Direct Risk/Benefit</td>
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<tr>
<th>Population</th>
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<tr>
<td>Full Public Value</td>
</tr>
</tbody>
</table>
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
An assumption-based framework?

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)