Industry Perspective on Vaccine Innovation Environment

National Vaccine Advisory Committee meeting
September 12, 2018

Phyllis Arthur
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Infectious Diseases & Diagnostics Policy
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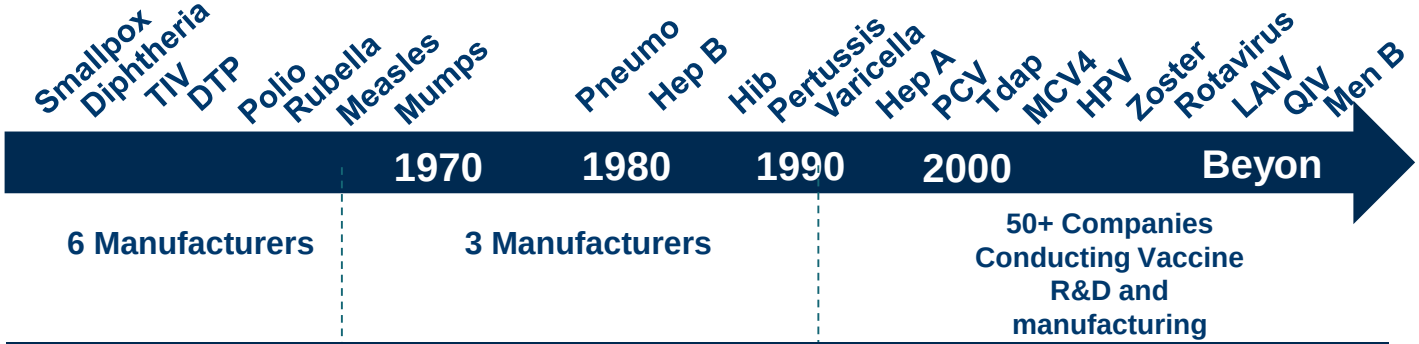
Biotechnology Innovation Organization



Over the next decade, we <u>may see</u>:

Innovative Technologies

- New cell lines
- Platform technologies
- Skin patches
- Heat-stability tech
- Reverse genetics
- More complex regimens for difficult targets

New Adult or Pediatric Vaccines

- Universal influenza
- Zoster
- Norovirus
- CMV
- RSV
- Streptococcus vaccines
- Norovirus
- HIV
- New combinations of existing pediatric vaccines

New Healthcare-acquired Infection Vaccines

- *Clostridium difficile*
- *Staphylococcus aureus*
- Tuberculosis
- *Pseudomonas aeruginosa*
- Candida
- *Escherichia coli*

Innovative Vaccine Technologies

Cell-based vaccine
Micro-dermal delivery system
Bacteria proteins combined with influenza virus for greater efficacy
Insect cells
Reverse genetics
Skin patch
Needle-less shot

The Environment For Vaccine Development Is Broader And More Complex And Thus The Vaccine Business Has Unique Risks

Development Risk

- No correlates of protection for new targets
- Complexity of immune system, especially in certain populations
- Lack of burden of disease data or uncertain epidemiology leads to complicated clinical trial designs

High Capital Needs

- High safety bar requires large, sometimes global, clinical studies
- Finalization of manufacturing processes is complex and lengthy

"Exit" Risk

- Limited number of potential acquirers
- Difficult to fund "go it alone" strategy if not acquired
- Investor returns on previous vaccine investments are not always stellar

Commercial Risk

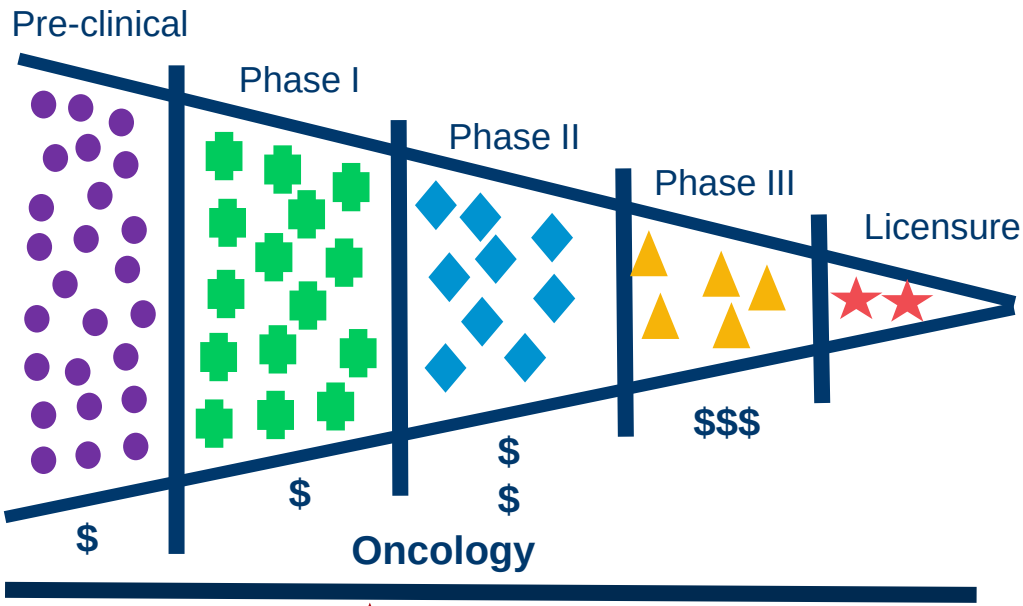
- Strong bargaining power of vaccine purchasers
- Uncertainty of ACIP recommendations
- Increasing vaccine hesitancy
- Key populations have insurance coverage or access issues (Medicare, Medicaid)

All of the above can make other investments more attractive

The Issue Of Opportunity Cost When Considering Preventive Vaccines Has Affected The Portfolio Decision-Making Process

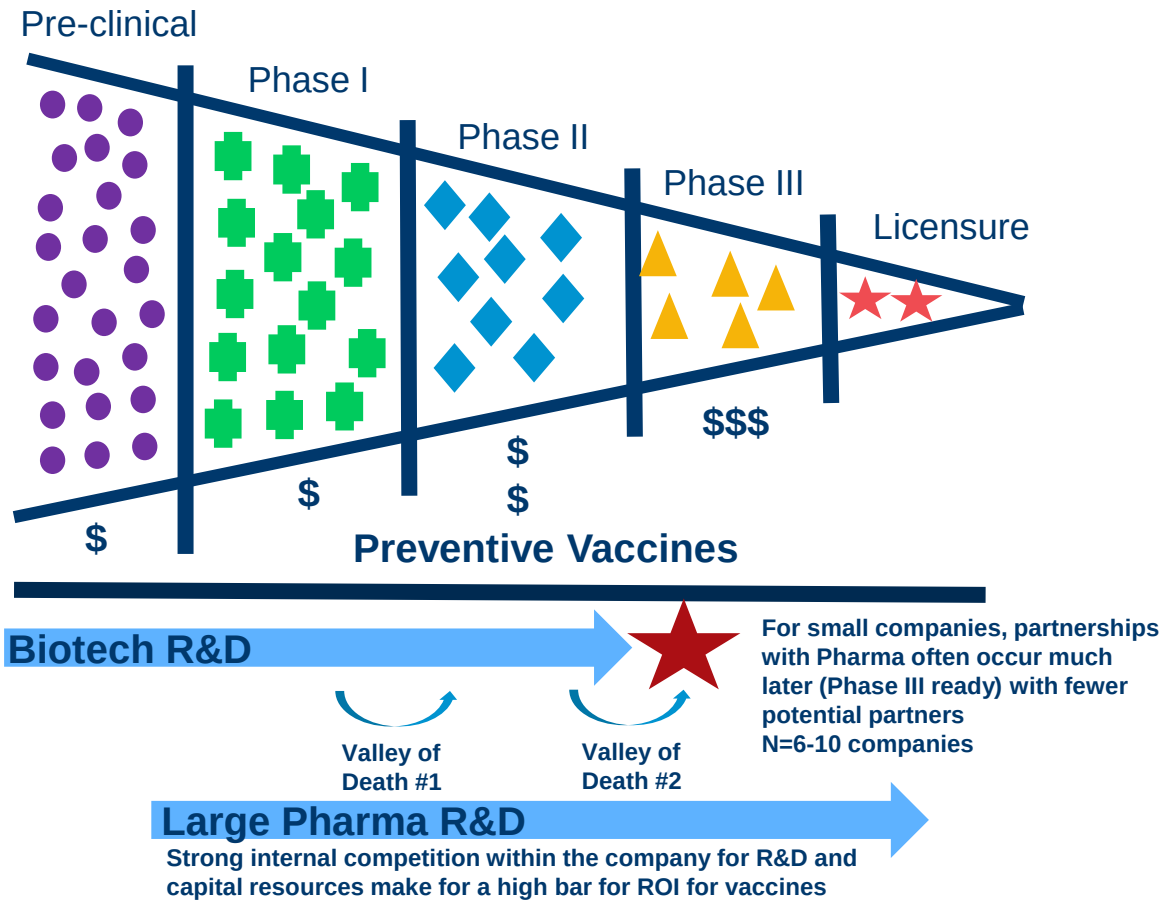
- Research in HIV revolutionized R&D related to immunology
- The role of the immune system in many non-infectious diseases increased research in immune therapies for:
  - Cancer
  - Auto-immune disorders
  - ID therapies
- The technologies that stemmed from immune therapy research could be applied to both infectious disease vaccines and therapeutics, changing the way companies assessed vaccine R&D
- Investors and shareholders weigh the potential return on investment (ROI) and compare projects for investment which disadvantages preventive vaccines, especially if the market has uncertainty.

The Ecosystem for Therapeutics



High level of partnerships with Pharma through deals and acquisitions with many potential partners N= many

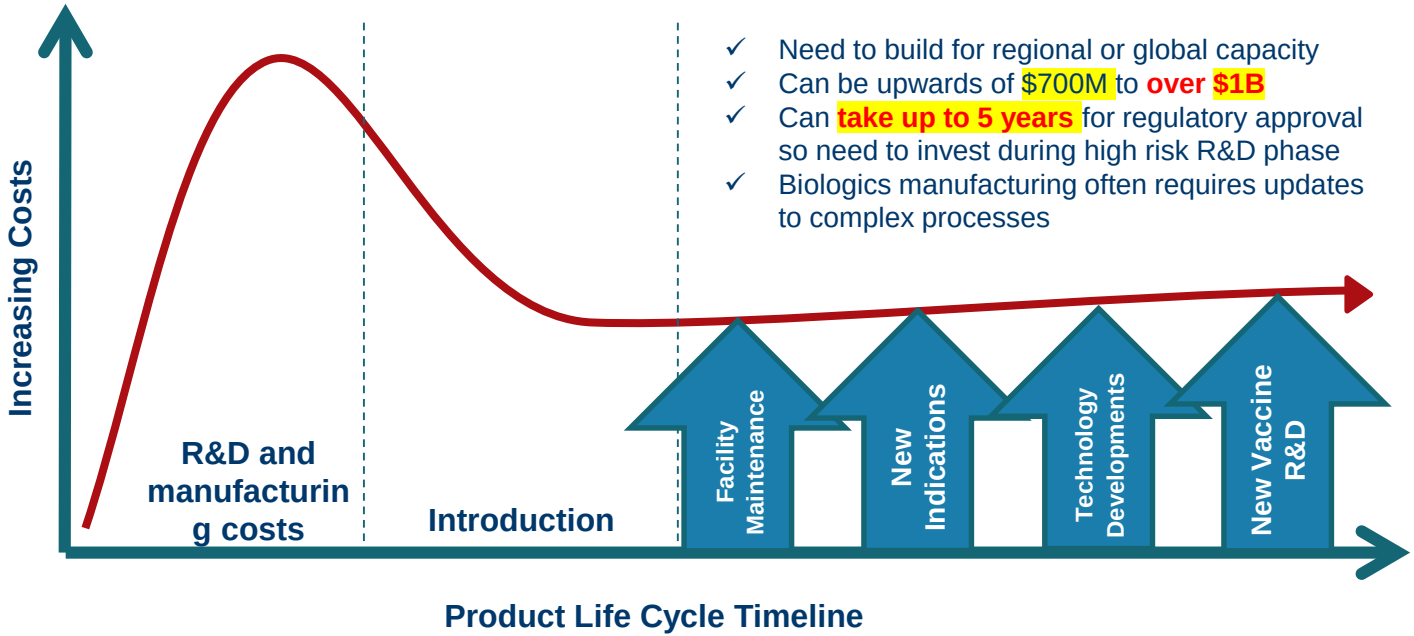
The Ecosystem for Infectious Disease Vaccines



High Number of Subjects Required in Pivotal Vaccine Efficacy Clinical Trials

Trial	Number subjects enrolled	Year trial completed
PCV7	~38,000	1998
HPV4	~18,000	2004
HPV4	~19,000	2005
Rotavirus (pentavalent)	~70,000	2006
Influenza high dose	~32,000	2013
PCV13 (CAPiTA) **	~85,000	2014
Dengue	~40,000	2014

Vaccines Present a Unique Need for High Initial Capital Plus Continuous Investment



- ✓ Need to build for regional or global capacity
- ✓ Can be upwards of $700M to **over $1B**
- ✓ Can **take up to 5 years** for regulatory approval so need to invest during high risk R&D phase
- ✓ Biologics manufacturing often requires updates to complex processes

For Vaccines, the U.S. Market Size is Defined by CDC Recommendations

- Uncertainty over a vaccine recommendation, combined with increasing resource intensity of development, has increased the risks associated with vaccine R&D
- ACIP deliberations take into account a host of factors:
  - What populations and indications will be recommended?
  - Is the epidemiology / burden well understood?
  - Will there be public funding for the vaccine?
  - Is the intervention cost-effective? Are there pricing pressures?
  - What else is already in the market? How important is competition?
- In recent years companies have had increasing concerns regarding the consistency and predictability of the ACIP process, which raises new questions:
  - Remaining pathogens likely to need new approaches – adjuvants, novel delivery vehicles. Is there a willingness to "pay" for translation and use of new technologies?
  - What will recommendations look like for niche vaccines or those with limited use?
  - How early can companies get an indication of the potential for positive (or less positive) recommendations as part of the development process?

Global Health and Tropical Diseases Partners

World Health Organization

TARGETS

R&D FUNDING

ACCESS

INFRASTRUCTURE

PATH

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

unicef

Gavi

Pan American Health Organization
World Health Organization
Americas

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

- Vaccines targeted to global diseases affecting many countries, primarily developing ones, although many of these vaccines can serve as travel vaccines in developed countries
- R&D for these vaccines is generally funded through global public-private partnerships with the Bill & Melinda Gates Foundation, PATH, Wellcome Trust, the Global Fund and other global funding partners.
- These vaccines are vital for global public health and would normally be made available through programs like UNICEF, PAHO and Gavi or US government programs.
- Investment is required in large scale global clinical trials and manufacturing facilities in preparation for global demand.

Emerging Infectious Diseases (EID) Partners

TARGETS

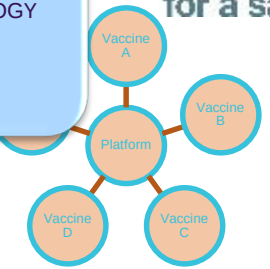
R&D FUNDING

MARKET

TECHNOLOGY

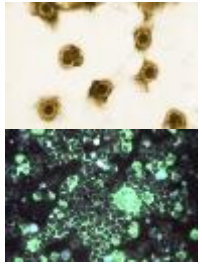
CEPI

New vaccines for a safer world



- Vaccines targeted to global diseases with pandemic or outbreak potential in multiple countries or globally.
- R&D for these vaccines is generally funded through public-private partnerships with government agencies such as the Department of Defense, NIH or BARDA or with international groups such as the Bill & Melinda Gates Foundation or Wellcome Trust.
- This is an area where new platform technologies are expected to play a key role. Platforms, such as unique cell lines, may help speed development and manufacturing; allow for fast transitions from one pathogen to another; build cross-pathogen safety profiles.
- These vaccines have a more uncertain market than other vaccines. They could be purchased by governments for stockpiles or held in late Phase 2 in the event of an outbreak.

Partnerships for New Vaccines with Commercial Markets



RSV

Norovirus

TARGETS

POPULATIONS

NEW TECHNOLOGY

Academia to Industry
Biotech to Large Pharma

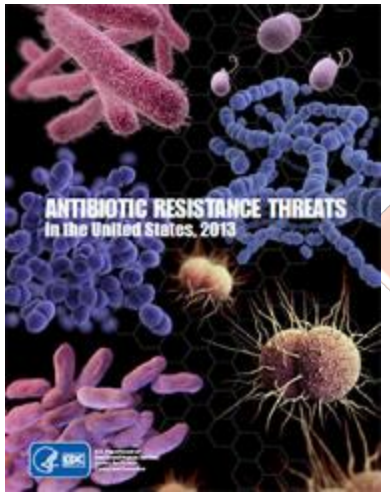
NIAID

BARDA

CDC

- Some of these vaccines will be targeted to specific populations or sub-sets of existing recommended populations or cover additional strains.
- Many vaccines in this category use novel technologies, such as novel adjuvants, in their development or production.
- Novel adjuvants will be used to help boost immune responses in special populations (elderly), extend the duration of immunity or reduce the number of doses needed.
- This category could include clinical activities undertaken by vaccine companies in support of maternal immunization recommendations.
- In addition, this could include new ways to improve the way vaccines are stored or delivered, for example, improved heat stability, patches, use in multiple injection technologies, nasal spray delivery, etc.

Vaccines For Combating Antimicrobial Resistance (AMR)



- PREVENTION
- RESISTANCE RISK
- DURATION OF PROTECTION
- EFFECTIVENESS

CARB-X
Combating Antibiotic Resistant Bacteria

BARDA

W

CDC

NIAID

DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA

79% of deaths reported in 2013 CDC AMR Report are due to HAIs

These vaccines may help with prevention of infections in humans and animals

- Reduce downstream antibiotic use and further resistance
- Includes viral vaccines that could prevent antibiotic use (flu, RSV)

There is a low risk of resistance to AMR vaccines

- Prophylaxis can be widely used without generating resistance

These vaccines may demonstrate a longer duration of protection when compared to antibiotics

- Reduce recurrent infections and hospital readmissions

Vaccines are effective against susceptible & AMR strains

- Demonstrated with Hib and pneumococcal vaccines

Potential Ways to Reduce Barriers

- Continue to strengthen the consistency and clarity of the ACIP process
- Share epidemiology and burden of disease data more readily with industry to encourage prioritization and development
- Increase vaccine confidence in the U.S. and globally
- Continue to build the adolescent, maternal, adult and elderly immunization platforms, especially with regard to accessing vaccines
- Encourage the use of push and pull incentives for emerging infectious disease vaccines and vaccines targeted to antimicrobial resistant pathogens
- Continue to work with providers to encourage strong recommendations and also to alleviate business pressures
- ***In the end, the value of working on the development of preventive vaccines needs to be somewhat comparable to other therapeutic areas to encourage continued and increased participation by industry***


Bio
Biotechnology
Innovation
Organization

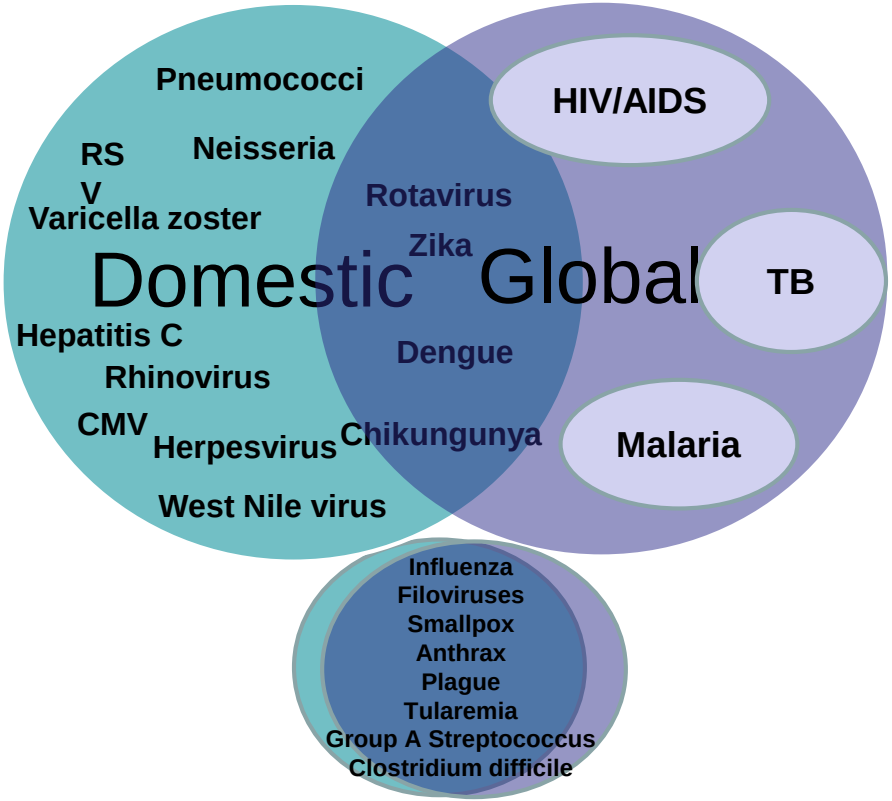
Vaccine Research & Development: The Role of Public Private Partnerships in Enabling Innovation

Annie Mo, Ph.D.
Program Officer
Parasitology & International Programs Branch
Division of Microbiology & Infectious Diseases
NIAID, NIH, DHHS

Sept. 12, 2018
NVAC Presentation

National Institute of Allergy and Infectious Diseases

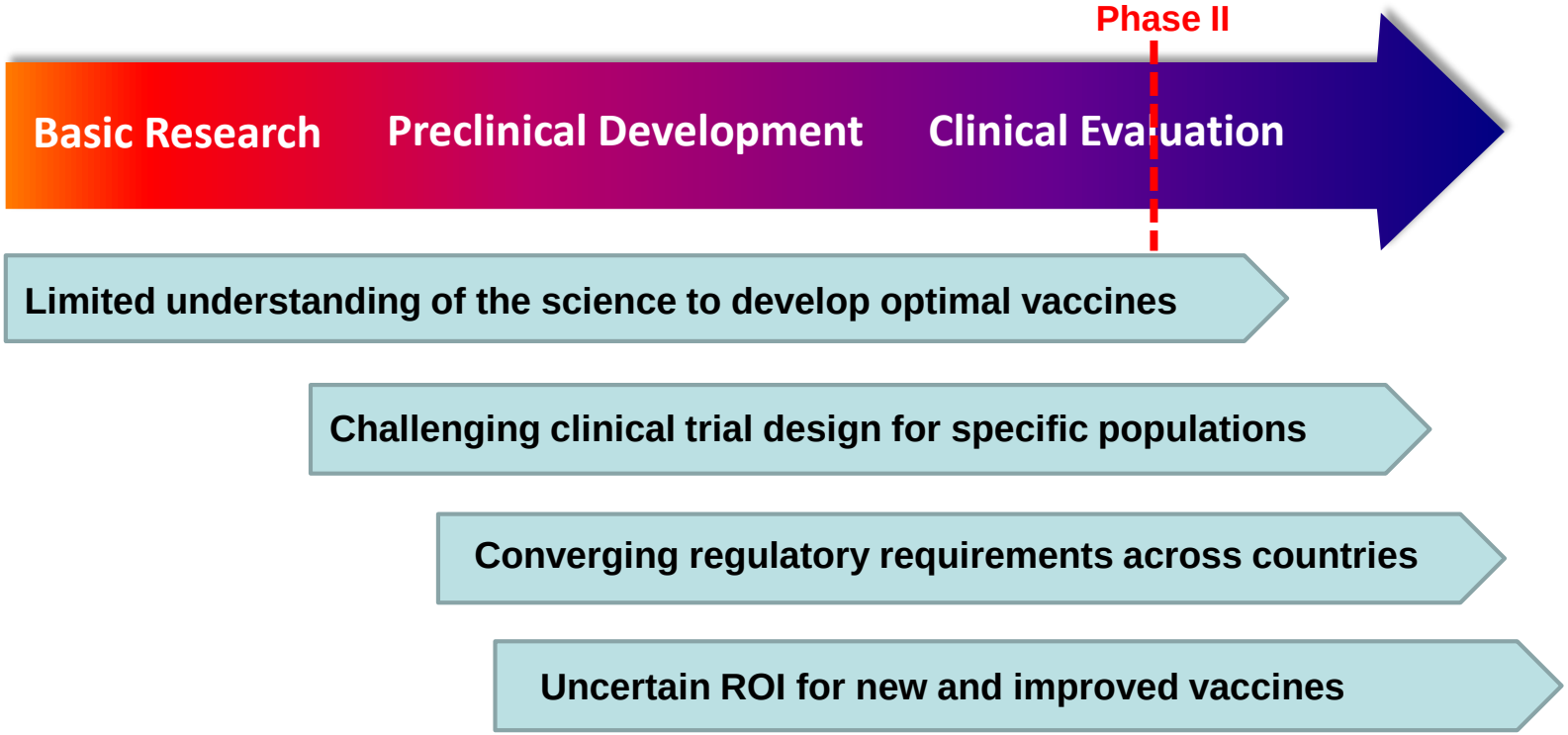
Vaccine R&D at NIH



Biodefense
Pandemic Response
Antimicrobial Resistance

Note: These are select examples. The list of pathogens is not comprehensive.

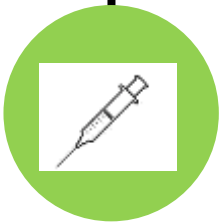
Overcoming Vaccine R&D Huddles



Information from: Encouraging vaccine innovation: promoting the development of vaccines that minimize the burden of infectious diseases in the 21st century. Report to Congress, 2017

Innovations for Vaccine R&D

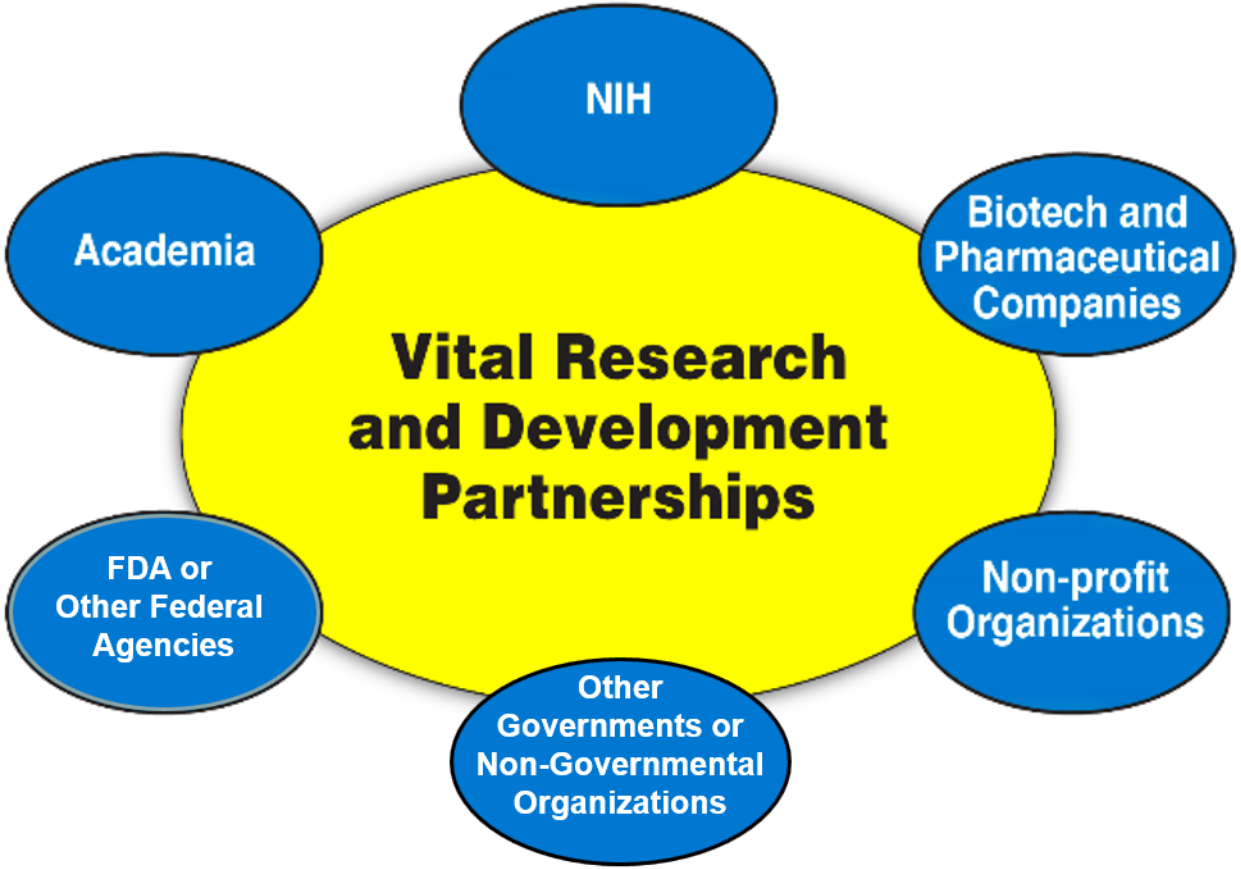
Vaccine R&D



Improving Existing Vaccines
(storage, coverage, effectiveness, etc.)

Developing New Vaccines
(against difficult pathogens/diseases)

Advancing Vaccine Development



Modified from A. S. Fauci's slide

Supporting Vaccine R&D: Enabling Public Private Partnerships

Grants
(Solicited & Unsolicited)

Cooperative Agreements
(Solicited & Unsolicited)

Contracts
(Solicited)

Other Mechanisms for Engaging in Public Private Partnership

- Material Transfer Agreement (MTA)
- Licensing Agreement
  - Collaboration Agreement
  - Cooperative Research and Development Agreement (CRADA)
    - Non-clinical Evaluation Agreement
    - Clinical Trial Agreement

Partnerships with Private Sector to Develop Universal Influenza Vaccines

Icahn School of Medicine at Mount Sinai

GSK

MSSM/GSK/NIAID VRC Chimeric HA

- Phase I DNA prime (chimeric H8/1, N1 NA) & IIV boost (chimeric H5/1, N1 NA) in healthy adults
- Analysis of humoral NA and HA stalk-specific responses

FluGen

RedeeFlu (M2SR LAIV)

- Phase I H3N2 M2SR prime & IIV4 boost in pediatric subjects
- Analysis of humoral & CMI responses including NA immune responses & HA stalk-specific responses

BiondVax

M-001 Peptide Vaccine

- Phase II M-001 prime & seasonal IIV3/IIV4 boost in healthy adults
- Analysis of CMI responses

SANOFI

Imiquimod (Aldara) Topical Adjuvant

- Phase II: Imiquimod with H5N1 vaccine in healthy adults
- Analysis of humoral & CMI responses

MS/GSK/NIAID - vaccine strategy that stimulates an immune response to conserved regions of the HA stalk region using chimeric HAs in prime-boost approach.

Flugen – designed to test whether H3N2 M2-deleted SR LAIV priming elicits stem, NA, CMI, sIGA boosted by QIV

Biondvax - repetitions of 9 conserved linear epitopes HA, NP, M1 protein that are prepared as a single recombinant protein.

Imiquimod – f/u to 2 clinical trials in Hong Kong –very high seroconversion rates and more robust responses to drifted variants of H1, H3 and B

A Prime/Boost Vaccine (Ad26.ZeBov/MVA-BN-FILO) for Preventing Ebola

(AdVac®)
Jassen/Crucell

Oxford Vaccine Group

NIH National Institute of Allergy and Infectious Diseases

Bavarian Nordic
(MVA-BN® Filo)

PREVAC Consortium

Inserm

NIH National Institute of Allergy and Infectious Diseases

LSHTM

ALIMA

MINISTRY OF HEALTH

MINISTRY OF HEALTH AND SANITATION

Jassen → World Health Organization

EUAL Submission

BARDA

Project BioShield
Late Stage Development & Procurement

MVA-BN: multivalent, glycoprotein from Zaire, Sudan, and Marburg

Insert: French National Institute of Health and Medical Research

Other Health Authorities

Guinea, Liberia, Sierra Leone

A Successful Public Private Partnership

-Innovation through Patenting and Licensing

1980's

Wyeth Lederle

CRADA

NIH National Institute of Allergy and Infectious Diseases

Reassortant Rotavirus

1990's

Wyeth

RotaShield On/Off Market

Wyeth

NIH National Institute of Allergy and Infectious Diseases

All Materials & Docs Transferred

2000's

P1

P2

SERUM INSTITUTE OF INDIA PVT. LTD.

NIH National Institute of Allergy and Infectious Diseases

Px

P11

Non-exclusive License Agreements to 11 Industrial Partners in Developing Countries & US

2010's

SERUM INSTITUTE OF INDIA PVT. LTD.

Thermostable ROTASIIL®

Universal Immunization Programme (India)

WHO Pre-qualification expected

2018

The U.S. Patent and Trademark Office

Patents for Humanity

IT'S NOT JUST AN INVENTION.

Human & Bovine

Reassortant Rotavirus

Summary

- Partnerships have the potential to accelerate the translation of promising concepts into effective public health interventions.
- PPP have enabled innovations at diverse stages of the vaccine R&D process.
- Successful PPP require
  - Aligned goals
  - Leveraging comparative advantages of partners
  - Shared risk, responsibility, and accountability
  - Careful strategic planning
  - Flexible mechanisms

Acknowledgement

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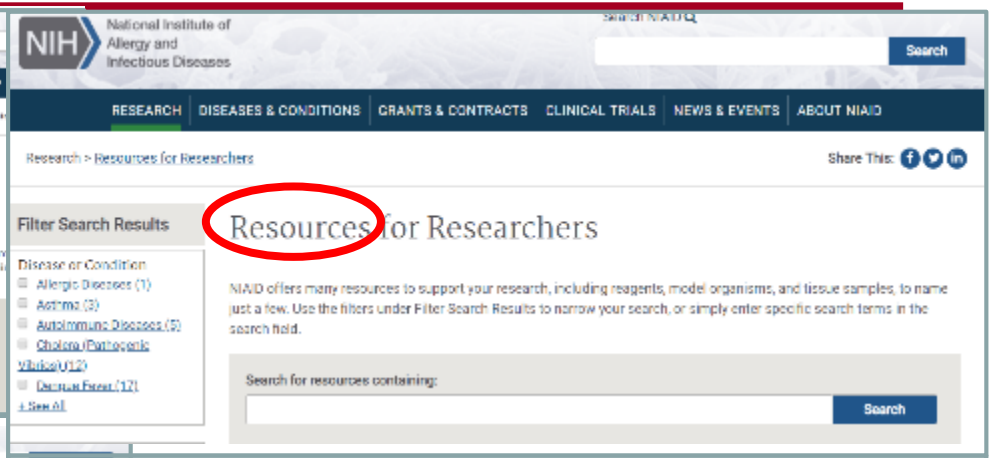
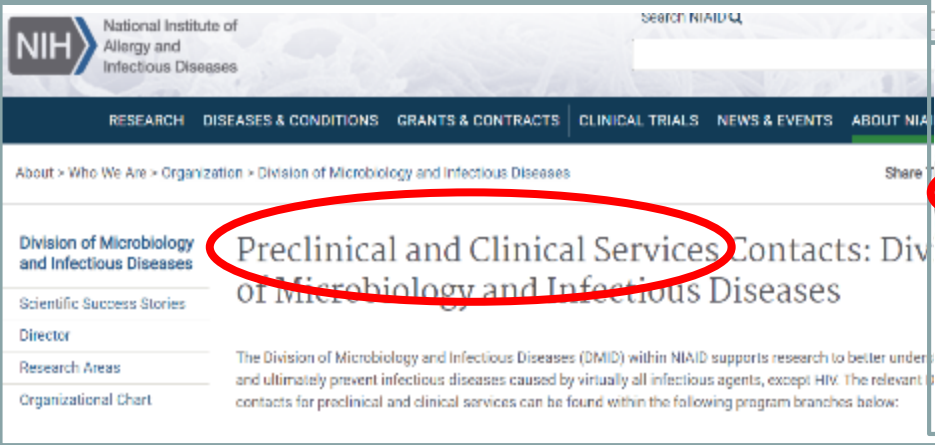
Colleen Sico
Kimberly Taylor
Christopher Roberts

Opportunities and Resources





Public-Private Partnerships

Dr. Linda C. Lambert
Deputy Assistant Secretary
Director, Medical Countermeasures Research Support Services
BARDA/ASPR

ASPR's Mission

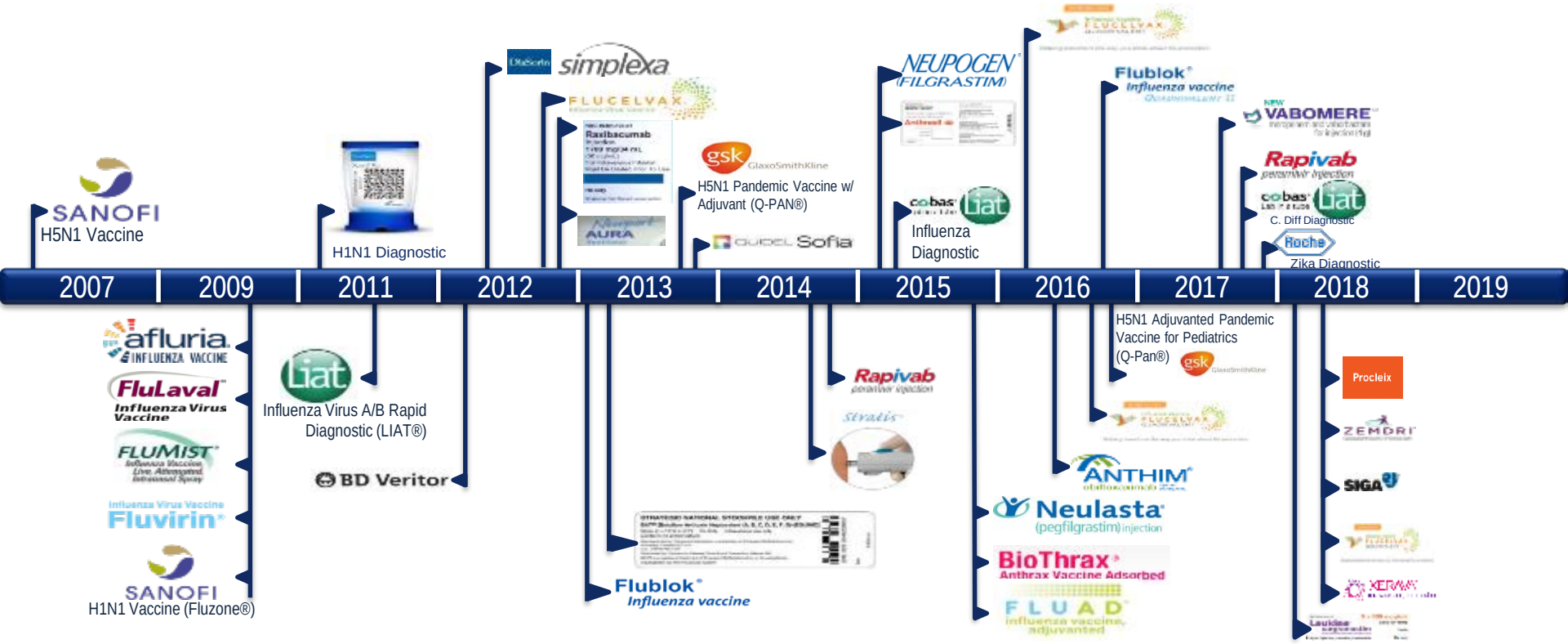
•Our mission is to save lives and protect Americans from 21st century health security threats.

The BARDA Model

BARDA develops and makes available medical countermeasures **(MCMs)** by forming unique public-private partnerships with industry partners

Our Industry Partners

FDA Approvals, Licensures, and Clearances



Public-Private Partnerships

- BARDA considers every contract, other transactional authority, or cooperative agreement as a partnership with the company
- BARDA brings our subject matter experts and funding to work with our partners to develop and make available medical countermeasures
- Specific examples of PPP:
  - Centers for Innovation and Advanced Development and Manufacturing
  - Other Transactional Authority
  - CARB-X
  - DRIVe

Centers for Innovation and Advanced Development and Manufacturing (CIADMs)

- Establishment of the CIADMs was a result of the 2010 PHEMCE review – highlighting the need to expand domestic manufacturing for pre-pandemic vaccines

HHS: Seqirus
Holly Springs, NC

HHS: Emergent BioSolutions
Baltimore, MD

HHS: Texas A&M
College Station, TX

Other Transactional Authority

2014

2015

2016

2016

2017

2017

Antibiotics and Diagnostics

Influenza
Antivirals
and Emerging
Infectious Diseases

Influenza
Vaccines
and Antivirals

- All Other Transactional Agreements have cost-share efforts. Meaning the company and BARDA share in the costs for development of the candidates under the portfolios

CARB-X

Xccelerating global antibacterial innovation

FUNDERS

ASPR ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA

wellcome

NIH National Institute of Allergy and Infectious Diseases

Department of Health

ALLIANCE PARTNERS

BILL & MELINDA GATES foundation

ACCELERATORS

BOSTON UNIVERSITY

RTI INTERNATIONAL

MassBio

CLSI California Life Sciences Institute

BROAD INSTITUTE

- *A private sector approach to funding and portfolio management*
- *Portfolio currently contains **35** candidates*
- *For every $1 provided by funders and alliance partners – $7-8 in private equity follow on investments*

BARDA Division of Research, Innovation, and Ventures (DRIVe)

DRIVe Mission: Driving Life-Saving Innovation

Accelerate the research, development, and availability of transformative countermeasures to protect Americans from natural and intentional health security threats.

DRIVe Transforming Health Security

DRIVe-Ready

CAPTURE

Set targets & research agenda Coordinate with "deep thinkers" across USG, academia, industry, and other stakeholders.

SOLUTION MAPPING

Establish Integrated Solutions for Intelligent Acceleration

DRIVe-X

ACCELERATE

Investors: BARDA, DoD

DRIVe-Launch

INITIAL SUSTAINMENT

(1-18 Months)

Investors: BARDA, MCIP

DRIVe VENTURES

STRATEGIC SUSTAINMENT

Corporate Venture Capital Model Investment in Products

PHEMCE 2.0 Industry DoD

DRIVe-X

Initial Emphasis:

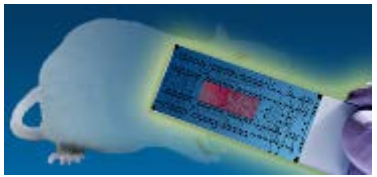
- Prevent illness from infectious exposures through early identification and action
- Save lives by solving sepsis

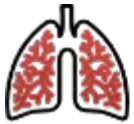
SOLVING SePSIS

ENACT
Early Notification to Act, Control, and Treat

Future Areas:

- *Create universal treatment options for broad classes of pathogens*
- *Ensure access to life-saving medical countermeasures for all Americans*
- *Transform the process by which medical countermeasures are developed (non-animal testing)*
- *Opioid Defense*





- Viral
- Bacterial
- Fungal

Response Framework

Situational Awareness/Recognize
How do we know something is happening, an agent has entered the community?

Design
How do we stop the spread of the disease? Drugs, vaccines, PPE, social distancing?

Produce
On demand manufacturing of X?

Administration
Everyone who needs X is provided X

Identification/Characterize
What is it, is it drug resistant, are certain subpopulations more susceptible, will it become an epidemic?

Validate
Methods under design are evaluated, clinical trials, non-clinical trials, epidemiology, surveillance

Distribute
Novel ways to get product/information to those who need it.

BARDA has had a Successful Decade Based on our Successful Partnerships

How to Contact BARDA

https://www.medicalcountermeasures.gov/home.aspx

- Portal to BARDA: **Register to request a TechWatch meeting!**
- **Learn about and register for BARDA Industry Day (October 29-30, 2018)**

https://www.fbo.gov/ ("FedBizOpps")

- Official announcements and info for all government contract solicitations

https://www.usajobs.gov/

- Join the team!

https://www.phe.gov/about/BARDA/Pages/default.aspx

- Program description, information, news, announcements

www.drive.hhs.gov

- DRIVe questions


SCIENCE
MEDICAL
HEALTH CARE
BARDA INDUSTRY DAY
October 29-30, 2018
Grand Hyatt • Washington, D.C.
ONLINE REGISTRATION OPENED
ASPR

12 September 2018

National Vaccine Advisory Committee

PUBLIC-PRIVATE PARTNERSHIPS: SUCCESSES AND FAILURES IN FINANCING VACCINE INNOVATION

PATH

David C. Kaslow, M.D.
PATH Essential Medicines

CENTER FOR VACCINE INNOVATION & ACCESS

PATH

Photo: PATH/Gabe Bienczycki

1 About PATH & CVIA (Center for Vaccine Innovation & Access)

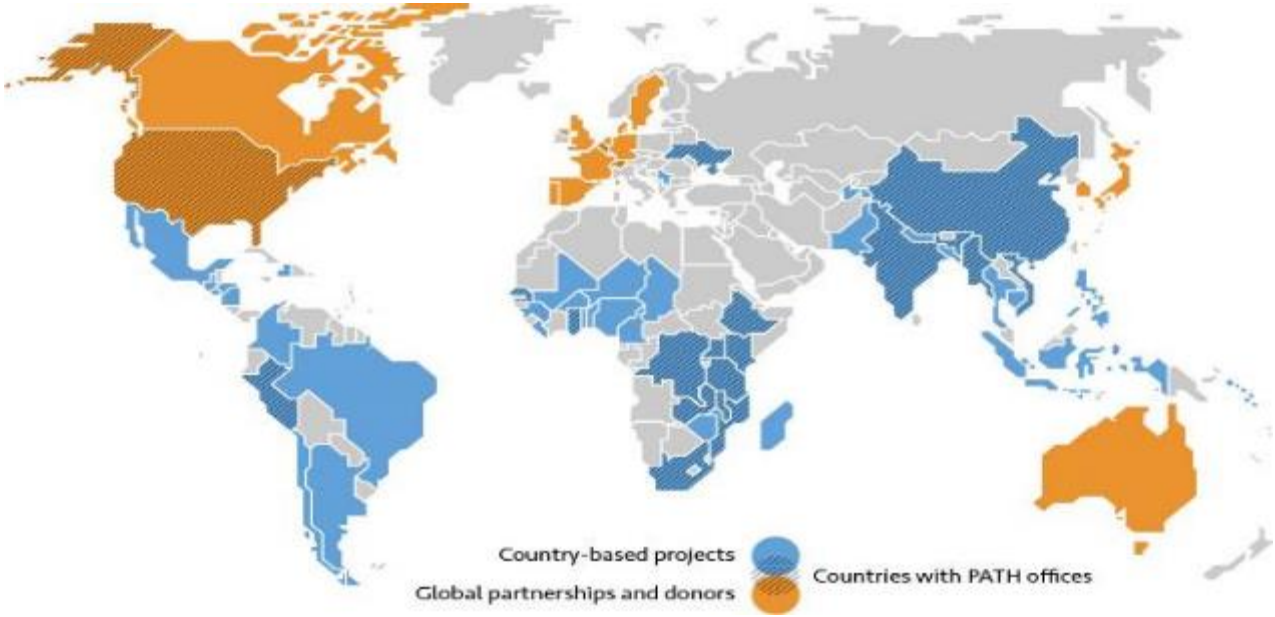
2 PDP models

3 Another valley of death

4 Full Public Value of Vaccines (for panel discussion)

PATH—a global organization

Work in more than 70 countries. 150 million people reached each year on average.



7+ billion vaccine vials
with **Vaccine Vial Monitors** (VVMs) to ensuring vaccines potency when given

6+ billion autodisable syringes
used to deliver single use (**Soloshot**) vaccines potency when given

300+ million people
immunized with **MenAfriVac®** in the African meningitis belt

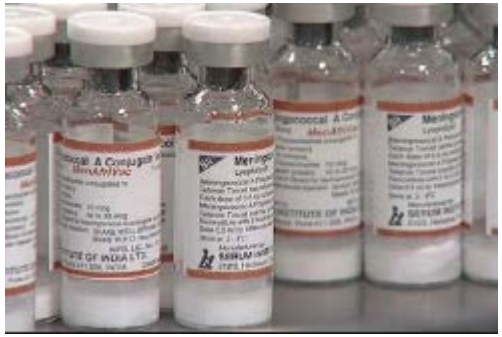
310+ million children
vaccinated in 6 countries with **Japanese Encephalitis Virus Vaccine**

PATH

With expertise in science, health, economics, technology, advocacy, and dozens of other specialties, PATH develops and scales solutions—including vaccines, drugs, diagnostics, devices, and innovative approaches to strengthening health systems worldwide.

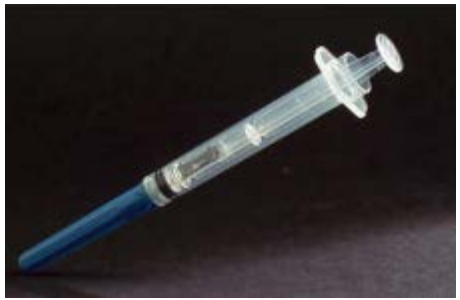
PATH

Vial Vaccine Monitor



Meningitis A conjugate vaccine

RTS,S malaria vaccine



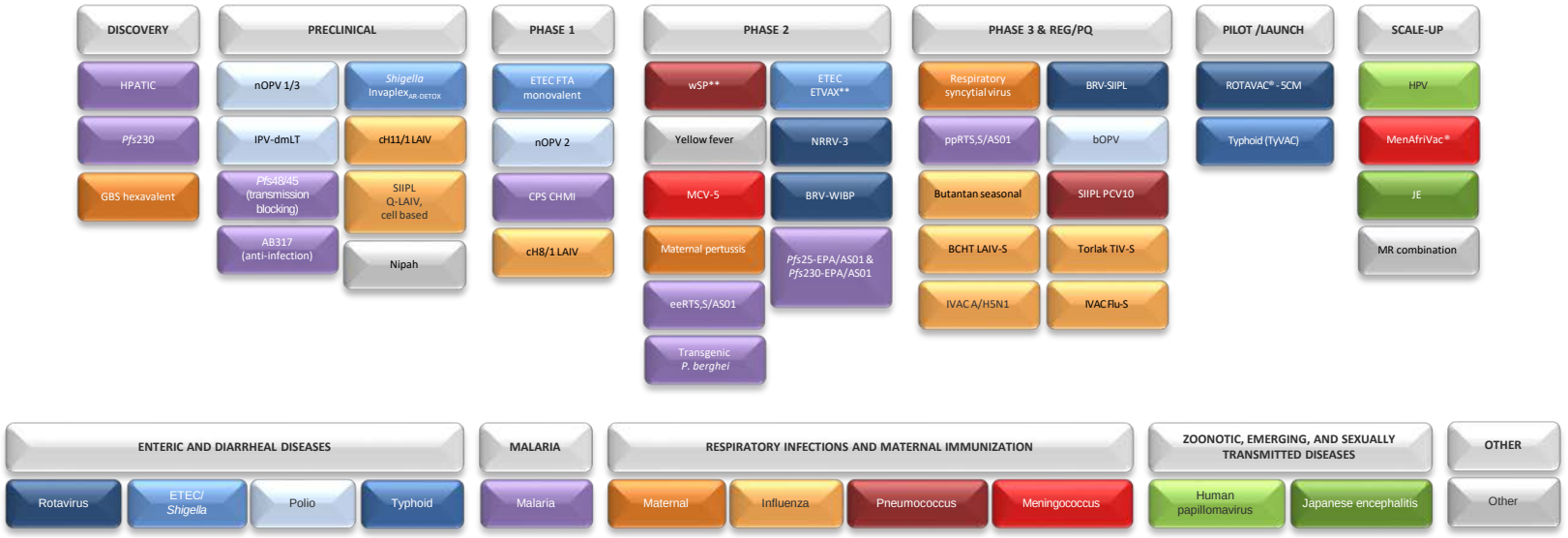
Autodisable syringe

Japanese encephalitis vaccine

Rotavirus vaccine

PATH

CVIA portfolio includes over two dozen vaccines in development and use across 17 disease targets

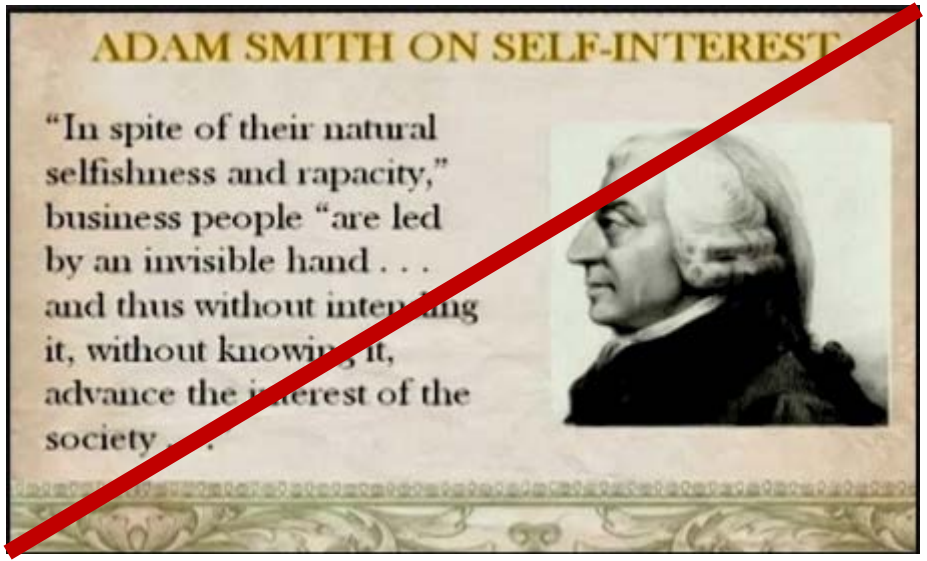


Portfolio snapshot current as of August 2018; does not include new/ongoing proposal development work, nor ongoing support to the Expanded Programme on Immunization in multiple countries.
**Reflects wind-down activities.

CVIA's goal

To fix John Snow's pump without the "invisible hand" of Adam Smith

Cholera outbreak
Soho, London (1854)



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

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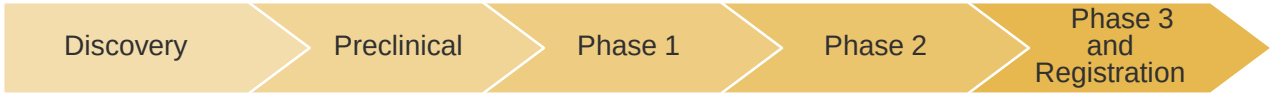
“Development” valley of death



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

1 About PATH & CVIA

2 PDP models

3 Chapter Title

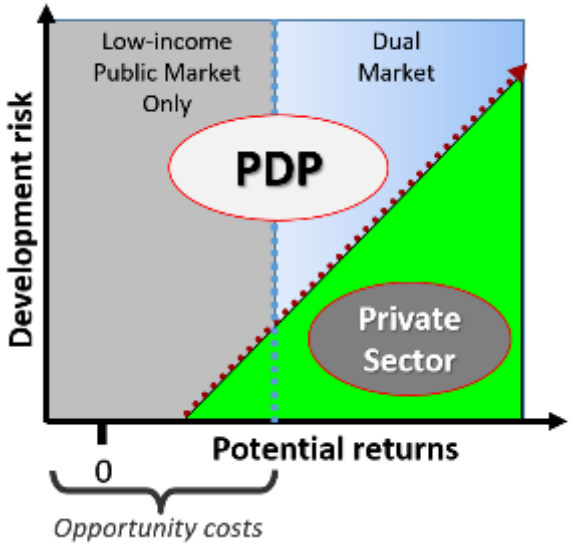
4 Full Public Value of Vaccines

PDP

Product Development Partnership:

A unique, **non-profit business model bringing together public, private, academic and philanthropic sectors to develop technologies for global health**. PDPs pave the way for new research on infectious diseases and accelerate the development of safe and effective vaccines, drugs and diagnostics for the most vulnerable populations as quickly and cheaply as possible.

- Sharing the risk
- Sharing the cost



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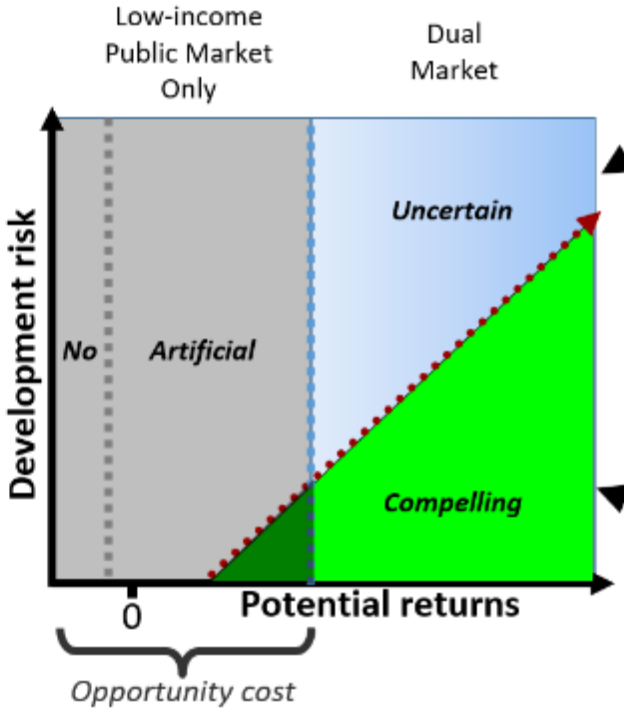
Product Development Partnerships (PDPs): *Four models (at least)*

***Assisted* business case (Outbreak)**
Examples: Ebola, MERS, Nipah, Lassa Fever
Solutions:
- **Coalition for Epidemic Preparedness Innovations (CEPI)**
- BARDA
- DARPA

***Assisted* business case (LMIC only)**
Examples: Cholera, Malaria, Men A, Non-typhoidal salmonella, Shigella
Solutions:
- **Public funding**
- Priority Review Vouchers
- LMIC Manufacturers
- Push & Pull mechanisms
  - GAVI financing



***Uncertain* business case (LMIC ↔ HIC)**
Examples: Grp A Strep, Grp B Strep, TB
Solutions:
- **Reverse tiered pricing**
- Push & Pull mechanisms
  - Advanced Market Commitments
  - GAVI financing

***Compelling* business case (HIC → LMIC)**
Examples: CMV, HiB, HPV, PCV, RSV, Rota
Solutions:
- **Tiered pricing**
- Push & Pull mechanisms
  - Advanced Market Commitments
  - GAVI financing

Developing products for low resource settings: *Principles of global access*

PATH's Guiding Principles for Private-Sector Collaboration

Purpose and Scope

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A clear link to mission

Collaborations with private sector must lead to positive impact in low resource settings on:

- **Availability**
- **Accessibility**
- **Affordability**
- **Acceptability**

With recognition of private sector needs

To apply their development, manufacturing, and distribution strengths toward innovative technologies that, in the absence of PATH involvement, would not be a private-sector priority

- **Sustainability**

http://www.path.org/publications/files/ER_gp_collab.pdf

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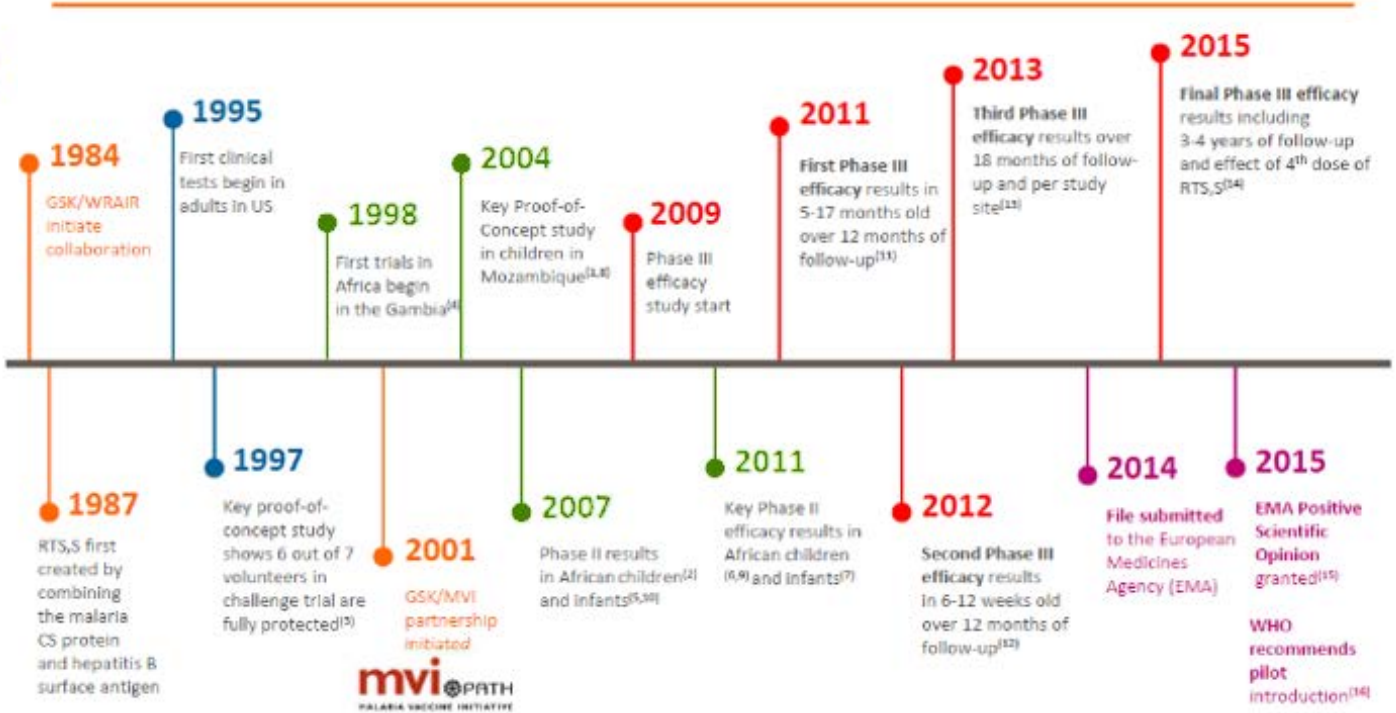
1 About PATH & CVIA

2 PDP models

3 Another valley of death

4 Full Public Value of Vaccines

Case Study: RTS,S/AS01$_E$ (Mosquirix®): *30+ years in development*



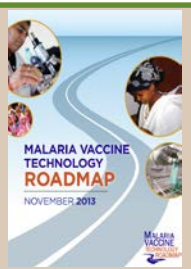
(1) Alonso P et al. Lancet 2004; (2) Aponte J et al. Lancet 2007; (3) Stoute J et al. NEJM 1997; (4) Doherty J et al. AJTMH 1999; (5) Bejon P et al. NEJM 2008; (6) Olotu A et al. Lancet ID 2011; (7) Asante KP et al. Lancet ID 2011; (8) Sacarlal J et al. JID 2009; (9) Agnandji ST et al. JID 2010; (10) Abdulla S et al. NEJM 2008; (11) RTS,S Clinical Trials Partnership. NEJM 2011; (12) RTS,S Clinical Trials Partnership. NEJM 2012; (13) RTS,S Clinical Trials Partnership, PLoS Med 2014; (14) RTS,S Clinical Trials Partnership, Lancet 2015; (15) www.ema.europa.eu; (16) www.who.int/immunization/research/development/malaria_vaccine_qa/en/

- **What:** Product Development Partnership established in 2001 by GlaxoSmithKline (GSK) and PATH.
- **Why:** To develop a vaccine that will protect infants and children residing in malaria endemic regions of sub-Saharan Africa from clinical disease and severe malaria resulting from *Plasmodium falciparum* infection.

Consistent with the

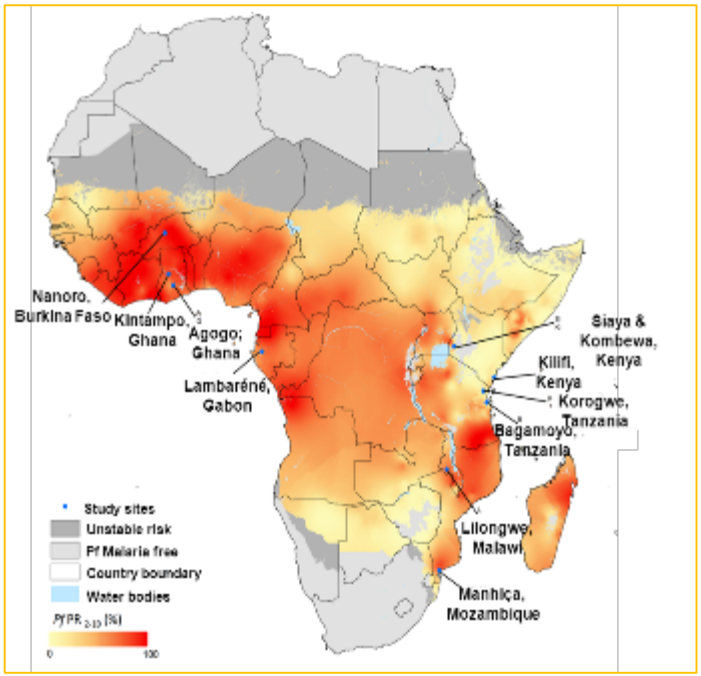
2015 Landmark goal from the Malaria Vaccine Technology Roadmap (circa 2006 and 2013)

and



"By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year."

Efficacy of the RTS,S/AS01$_E$ in a Phase 3 multicenter safety, efficacy and immunogenicity trial in two age categories



Vaccine efficacy over 12 months following the first 3 doses in 5–17 months and 6–12 weeks of age at first vaccination

Endpoint	5-17 months	6-12 weeks
% VE against all clinical malaria episodes (with 95% CI)	**51.3%** (47.5–54.9)	**32.9%** (26.3–38.9)
% VE against severe malaria (with 95% CI)	**44.5%** (23.8–59.6)	**38.5%** (7.8–59.0)

As published in Malaria vaccine: WHO position paper
WHO WEEKLY EPIDEMIOLOGICAL RECORD, NO 4, 29 JANUARY 2016

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in accordance with Article 58 (23 July 2015)

RTS,S is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B.

- The use of RTS,S should be based on official recommendations considering *Plasmodium falciparum* malaria epidemiology in different geographical areas.
- Vaccination in children from 6 weeks up to 17 months of age (at first dose):
  Three doses, each of 0.5 ml, should be given at monthly intervals.
  A fourth dose is recommended 18 months after the third dose.

"…it is important that established protective measures, for example insecticide-treated bed nets, continue to be used in addition to the vaccine."

RTS,S "should not be used for the prevention of hepatitis B in settings where prevention against malaria caused by *P. falciparum* is not sought."

*Summary of Opinion, 23 July 2015 (*EMA/CHMP/464758/2015); *press release, 24 July 2015; http://www.ema.europa.eu.*

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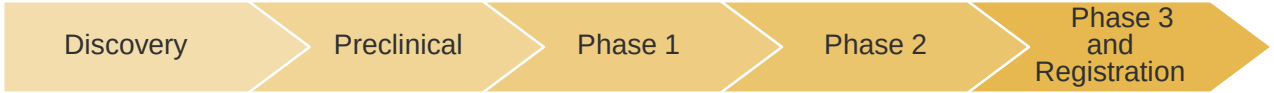
RTS,S crossed the valley of death



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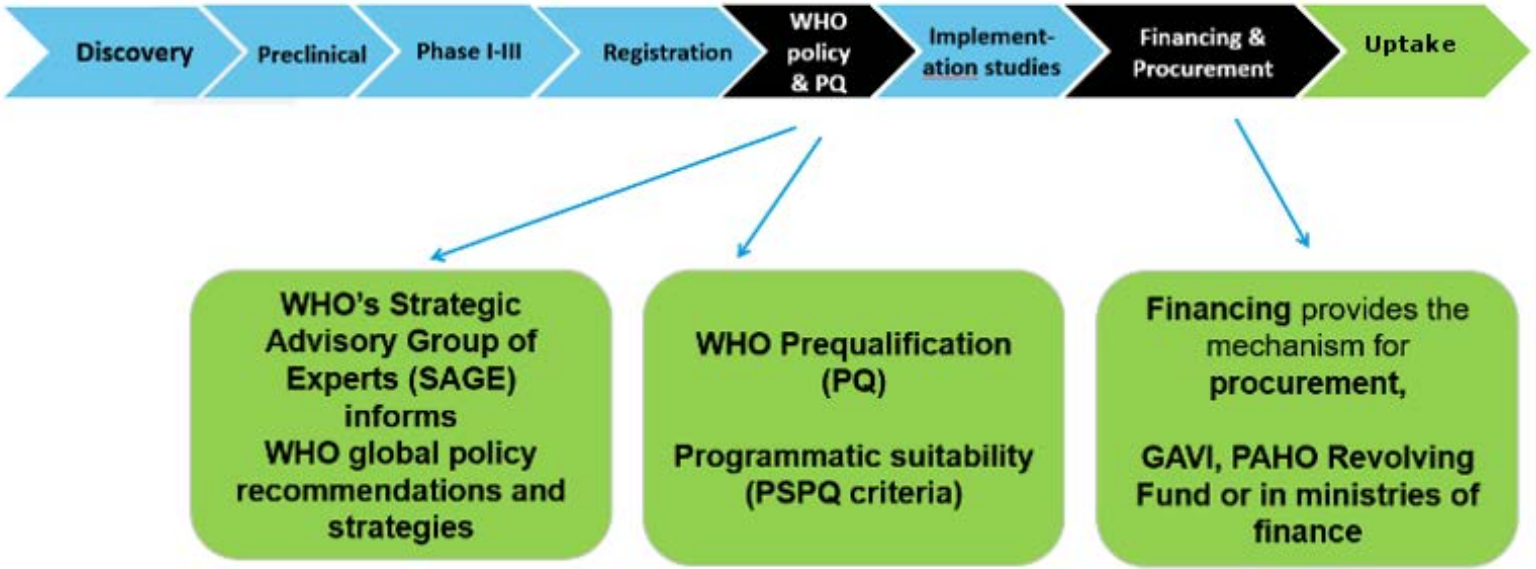
Additional steps for vaccine uptake in LMICs

World Health Organization



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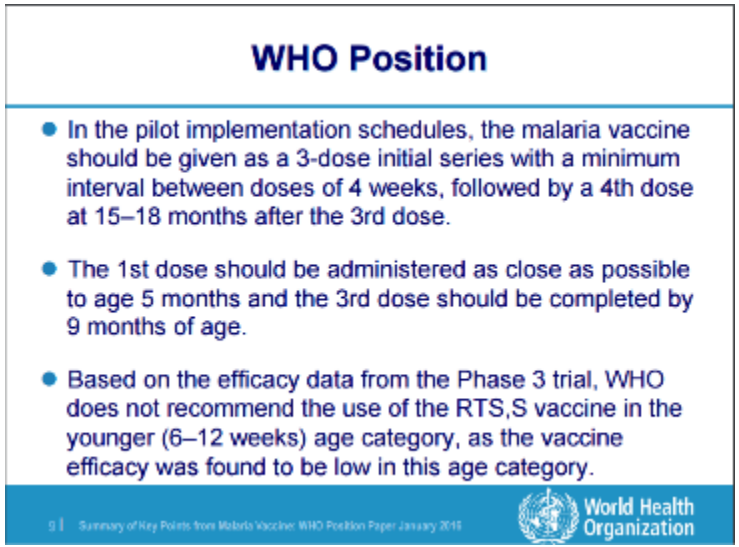
World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

29 JANUARY 2016, 91th YEAR / 29 JANVIER 2016, 91e ANNÉE
No 4, 2016, 91, 33–52
http://www.who.int/wer



WHO *"recommends further evaluation of RTS,S/AS01 in a series of pilot implementations, addressing several gaps in knowledge, before considering wider country level introduction."*

- Feasibility of administering 4-dose schedule
- Impact on all-cause mortality (including gender-specific mortality)
- Further assess causal relationship to excess cases of meningitis and cerebral malaria
- Evidence of any adverse effects of vaccine implementation on other malaria control measures

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Mind the gap: jumping from vaccine licensure to routine use

Failure to tackle this implementation phase with the same commitment shown to the licensure phase will pose greatest risk for vaccines developed mainly for the world's poorest people (eg, malaria, typhoid, haemorrhagic fevers). Thus, implementation assessments must become the third component of the core vaccine evaluation tripod, joining safety and efficacy. The essential value of this third phase has not been fully appreciated…

www.thelancet.com Vol 387 May 7, 2016

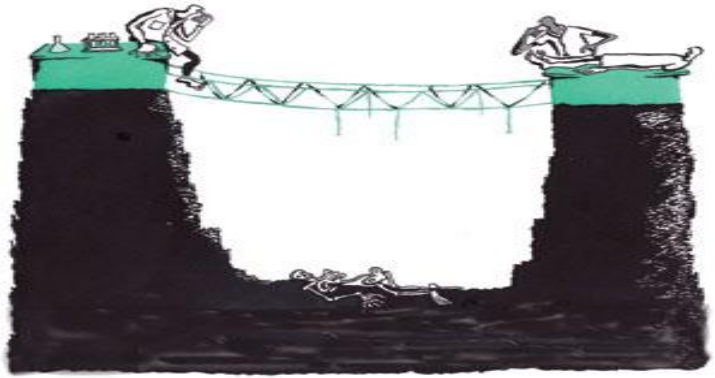
*Katherine L O'Brien, Fred Binka, Kevin Marsh, Jon S Abramson

1887

“Mind the gap”: A second “valley of death”?

Mind the gap: jumping from vaccine licensure to routine use

The first valley of death



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

A second valley of death?

www.lancet.com Vol 387 May 7, 2016

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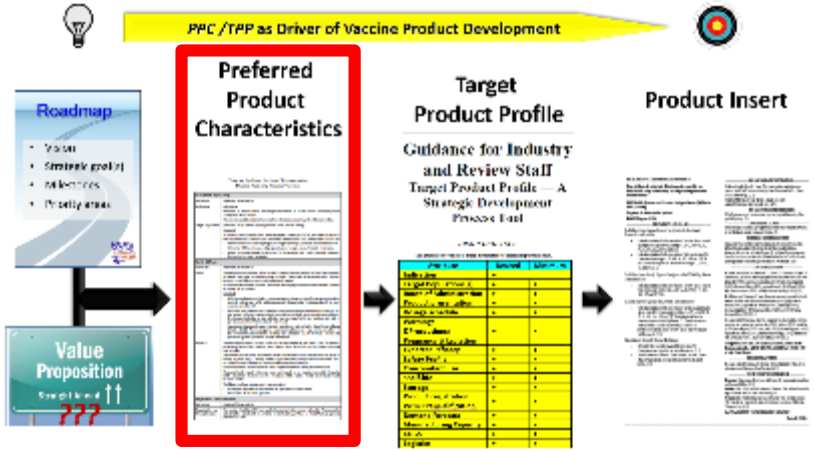
1 About PATH & CVIA

2 PDP models

3 Another valley of death

4 Full Public Value of Vaccines (for panel discussion)



If we build it, will anyone want to use it???

Favorable
value proposition
as driver of
vaccine development
and
access

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Traditional v Full Public Value of Vaccines

Traditional approach based on:

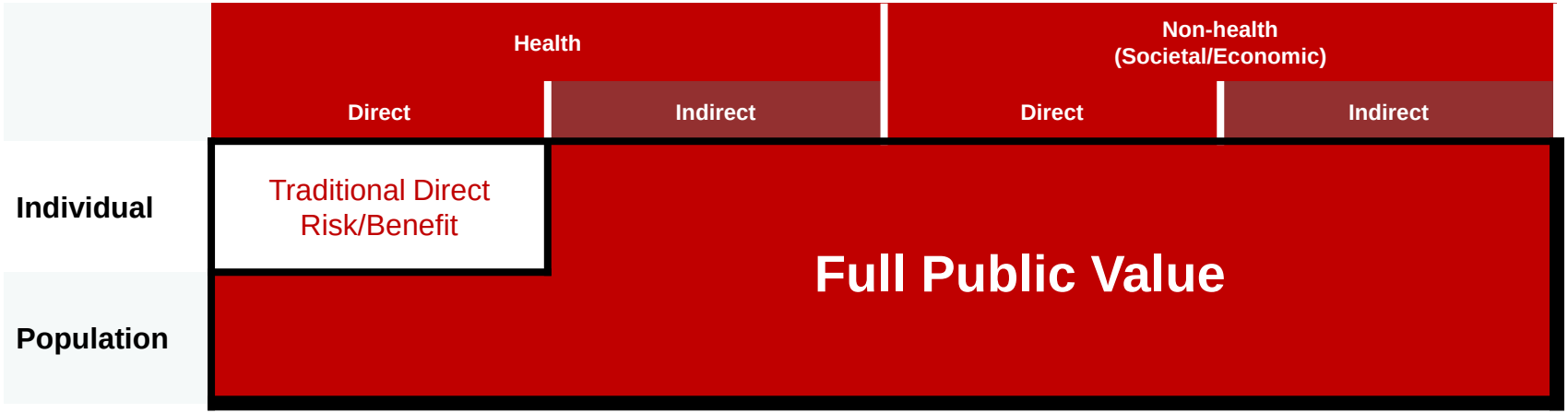
- Efficacy (individual direct benefit) & effectiveness (direct and indirect health benefits)
- Risk/safety profile (individual)
- Cost-benefit analysis

FPVV approach also based on:

- Disease reduction directly and indirectly by reducing:
  - Vaccine preventable disease incidence
  - All cause mortality
  - Under 5 mortality
  - Long-term sequelae
  - Pathogen transmission
  - Anti-microbial resistance
- Reducing frequency and size of outbreaks
- Stabilizing health systems
- Social and economic benefits
- Equity, access, affordability, acceptance and sustainability
- Protecting against financial risk

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

Traditional Direct Risk/Benefit v Full Public Value



- Create alignment across a range of stakeholders, with respect to global health priorities
- Provide a resource to effectively advocate for development and introduction of vaccines
- Inform investment decisions at all stages of development and implementation
- Accelerate suitability for and accessibility of vaccines to LMICs

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

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Leveraging Public-Private Partnerships to Move the Needle in Product Development

Biotechnology Company Perspective

National Vaccine Advisory Committee
September 12, 2018

Timothy Cooke, Ph.D.
Chief Executive Officer, NovaDigm Therapeutics

Biotechnology Industry Representative, National Vaccine Advisory Committee, 2015-2019
Member, Incentives for Vaccines Working Group, PACCARB 2017
Member, Biotechnology Innovation Organization (BIO)
- Antimicrobial Resistance Working Group
- Vaccines Policy Advisory Committee

Advisory Board, CARB-X

Disclosure Statement

Timothy Cooke has the following affiliations:

Chief Executive Officer, Board Director and shareholder in NovaDigm Therapeutics, a company developing vaccines against *Candida* and *Staphylococcus aureus*.

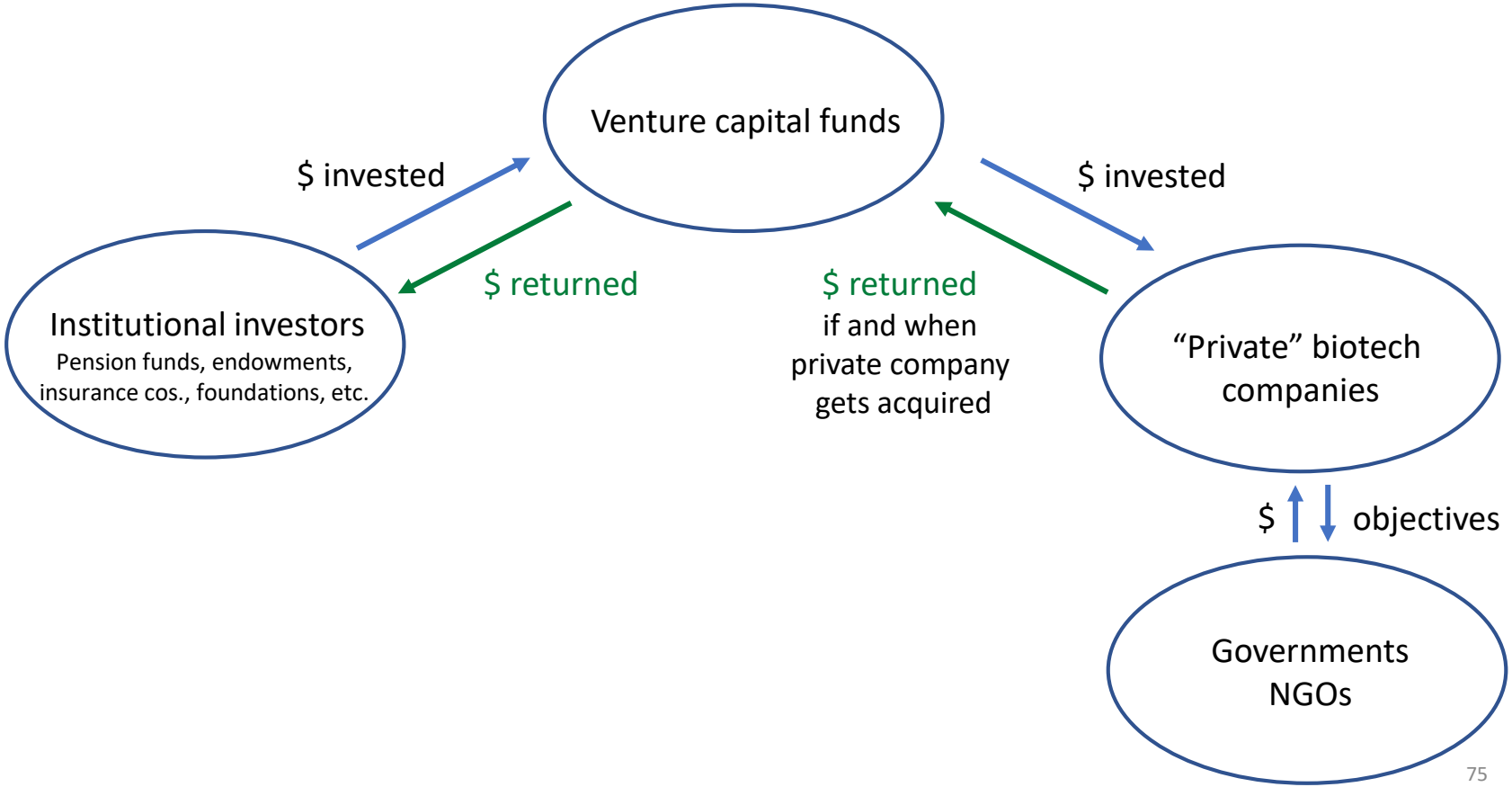
Consultant to Ology Bioservices, a contract development and manufacturing organization.

Consultant to Fina Biosolutions, an R&D service organization focused on polysaccharide conjugate vaccines.

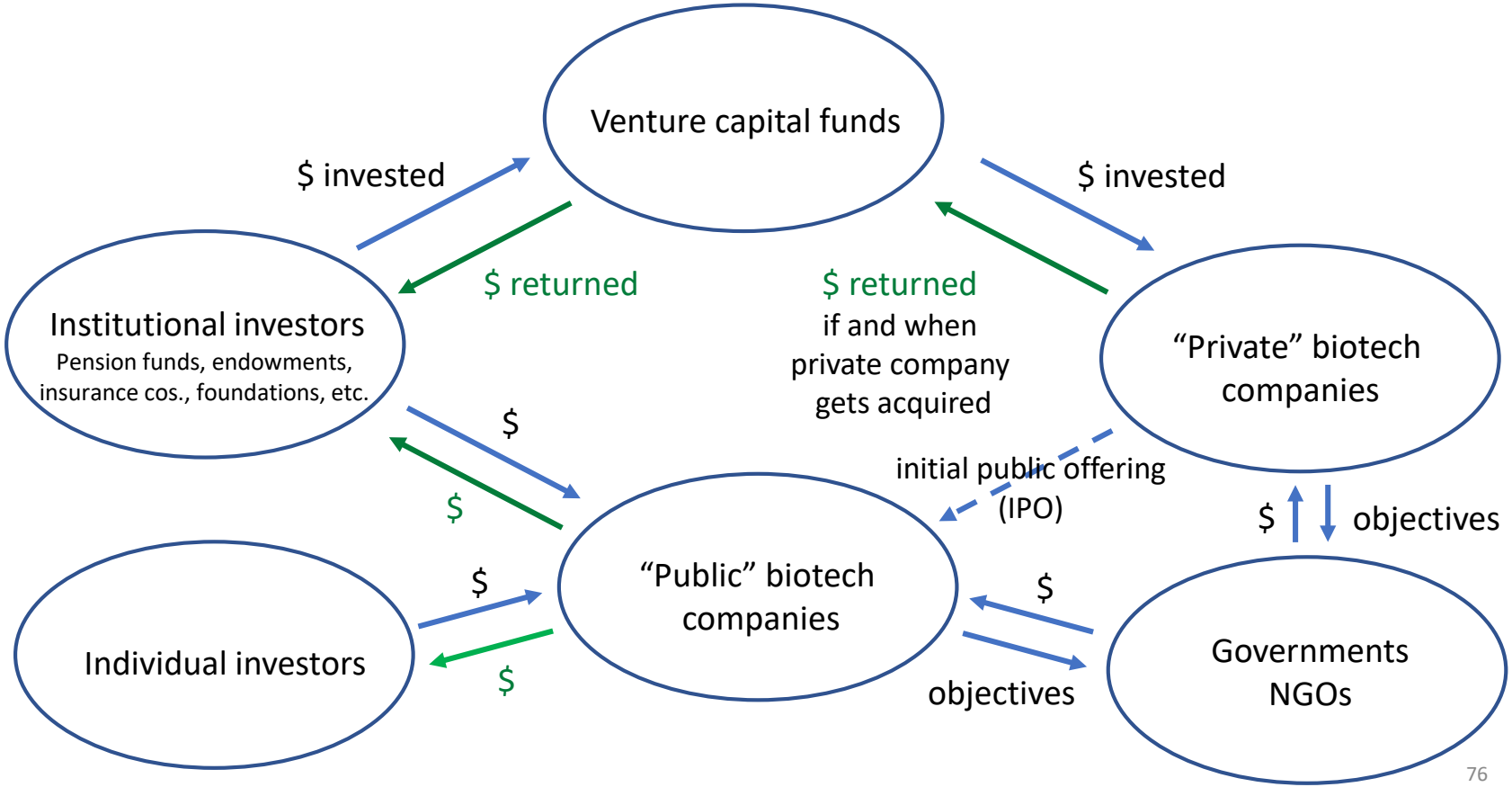
Biotechs developing infectious disease vaccines

- These biotechs would not exist without public-private partnerships
  - Especially uncertain/unattractive markets (biodefense, pandemic, global health)
- New biotechs cannot attract investors without robust commercial markets
  - Need to maintain/expand Big Pharma interest in infectious disease vaccines
- Historical venture-capital model for creating biotechs under severe stress
  - High costs of vaccine development (especially Phase 2 to 3 transitions)
  - Consolidated industry reduces acquisition opportunities (4 dominant pharmas)
  - ID vaccines (and antibiotics) have relatively low pricing expectations
  - Investments are relative and are going elsewhere (e.g., immuno-oncology, orphan)

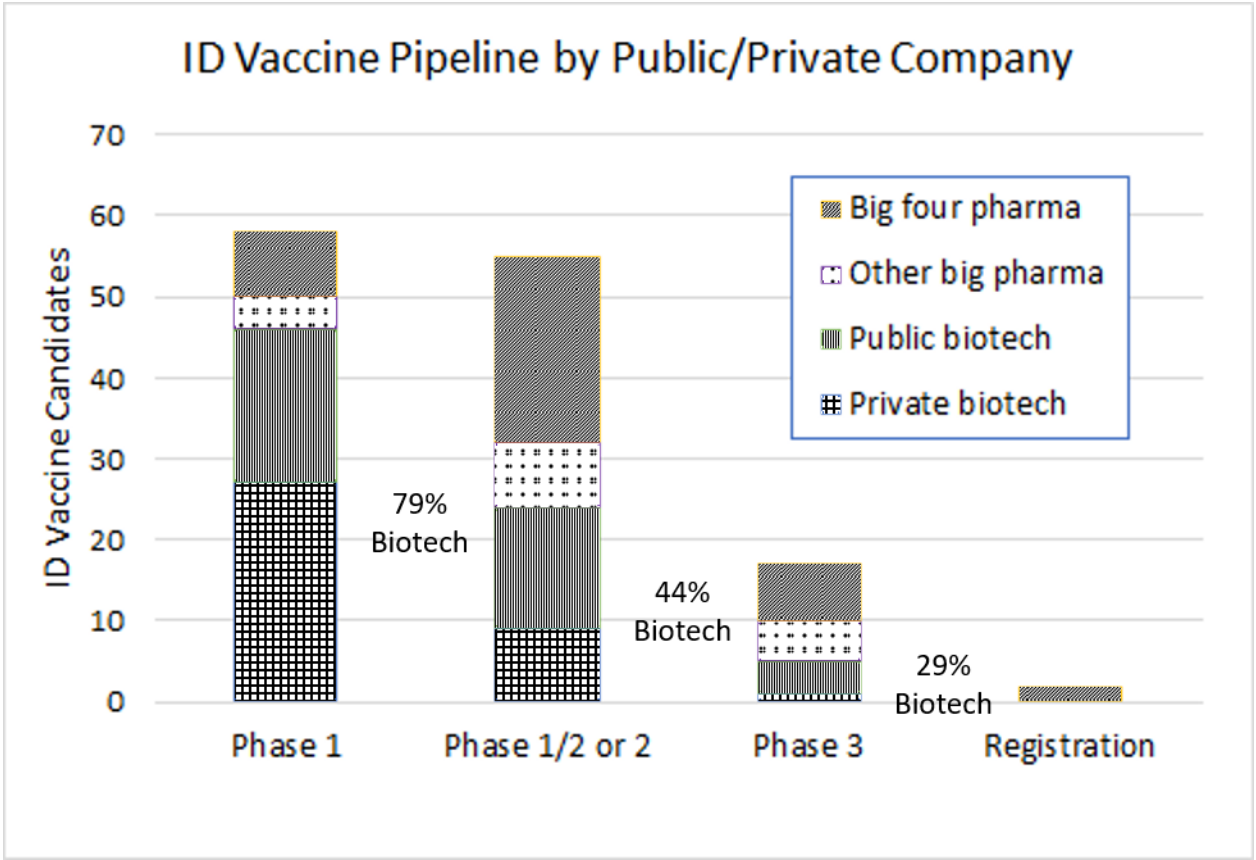
Venture Capital Funding



Venture Capital Funding



“Big Pharma” and biotech infectious disease vaccine pipeline



Big four pharma:
- GSK
- Merck
- Pfizer
- Sanofi Pasteur

Other big pharma:
- CSL/Seqirus
- J&J/Janssen
- Mitsubishi Tanabe/Medicago
- Takeda

Public biotech:
17 companies

Private biotech:
22 companies

Pipeline adapted from PhRMA Pipeline Oct 2017 and updated Feb 2018
(n = 132 candidates from US, EU, Japan, Korea, Canada, Australia)

Startup biotech to marketed vaccines
Only 7 companies over 20 years

- Emergent – acquired BioThrax®/anthrax from BioPort (1998)
- Crucell – acquired marketed products from Berna (2005)
- Valneva – Ixiario®/Japanese encephalitis (2009)
- Bavarian Nordic – Imvamune®/small pox (2010 US sales)
- Protein Sciences* – Flublok®/seasonal influenza (2016)
- PaxVax* – VaxChora®/cholera (2016)
- Dynavax – Heplisav®/hepatitis B (2017)

* Private biotech companies

Venture capital funded to acquisition

Pace of acquisitions has slowed over last 5 years

Date	Company	Acquirer	Amount
May 2008	Iomai	Intercell	$190M
July 2008	Acambis	Sanofi Pasteur	$546M
Mar 2011	Crucell	J&J Janssen	$2,400M
Oct 2012	LigoCyte	Takeda	$60M upfront + milestones
May 2013	Inviragen	Takeda	$35M upfront + $215M milestones
May 2013	Okairos	GSK	$325M
June 2013	Isconova	Novavax	$30M
Sept 2013	Medicago	Mitsubishi Tanabe	$357M
Feb 2015	GlycoVaxyn	GSK	$212M
Aug 2017	Protein Sciences	Sanofi Pasteur	$650M upfront + $100M milestones
Aug 2018	PaxVax	Emergent	$270M

6 acquisitions/3 years

3 acquisitions/5 years

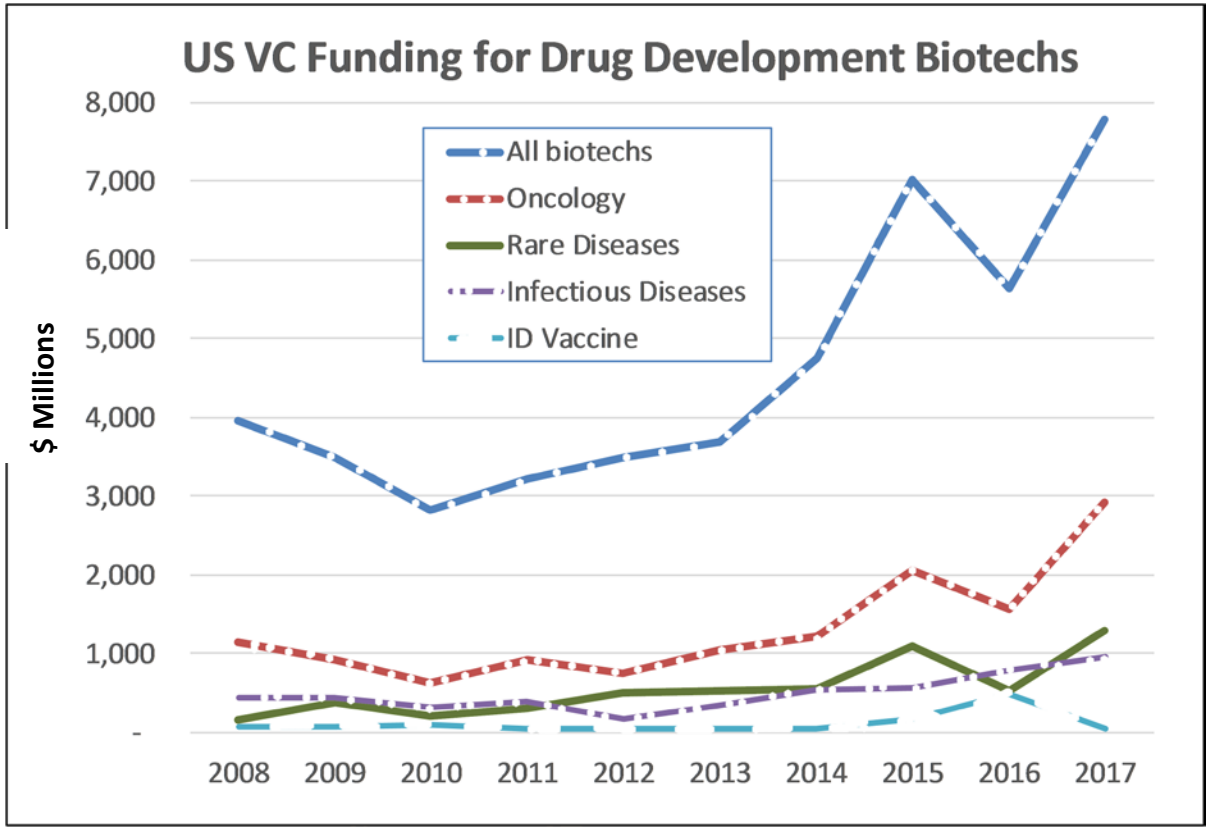
Venture capital funded to initial public offering

ID vaccine-focused biotechs had difficulty becoming public companies

- Strong opportunity for biotech initial public offerings 2013-2017
- 179 IPOs for drug development biotechs in US
- 19 IPOs infectious disease companies (11%)
- 2 IPOs ID vaccine companies (1%)
  - Argos Therapeutics & Genocea Biosciences in 2014
- 3 biotechs acquired public companies to become publicly traded
  - VBI Vaccines in 2014, Altimmune & Vaxart in 2017

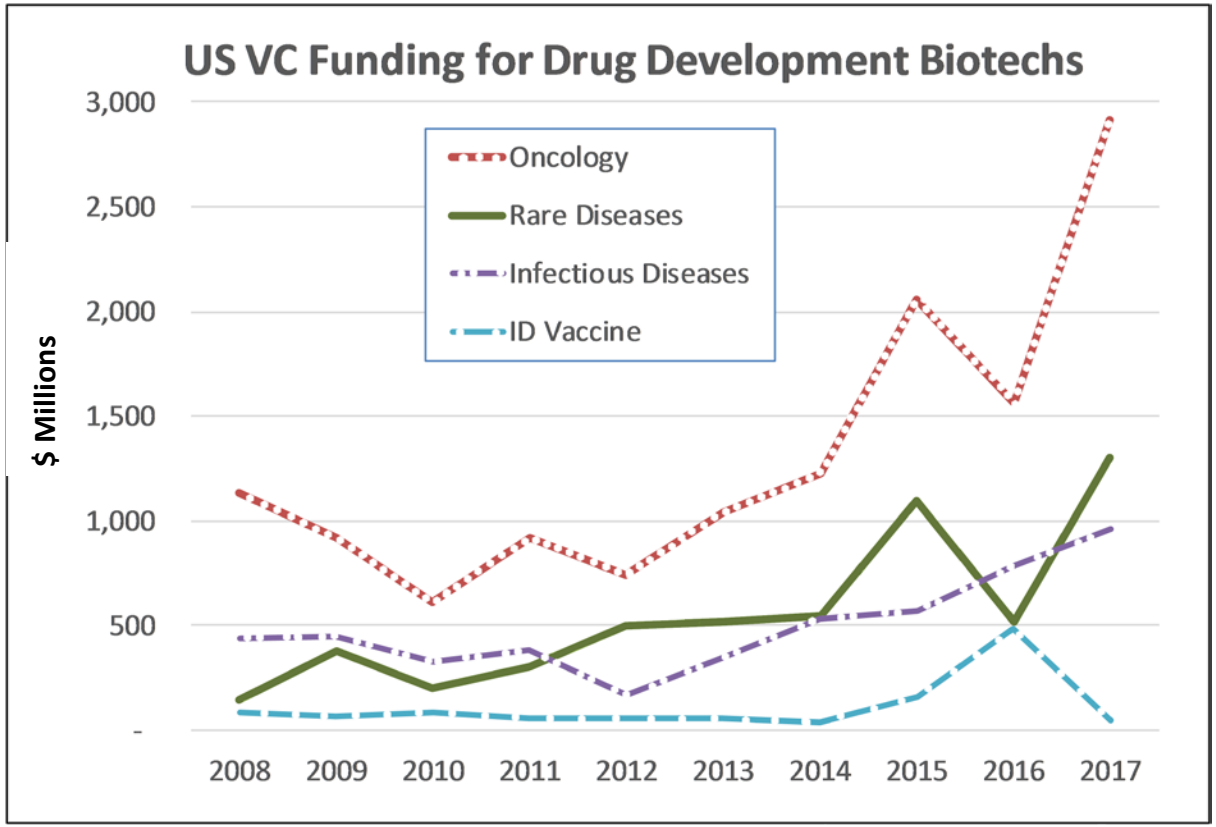
Dave Thomas & Chad Wessel, BIO Emerging Therapeutic Company Investment and Deal Trends, 2008-2017

Venture capital funding for US drug development biotechs



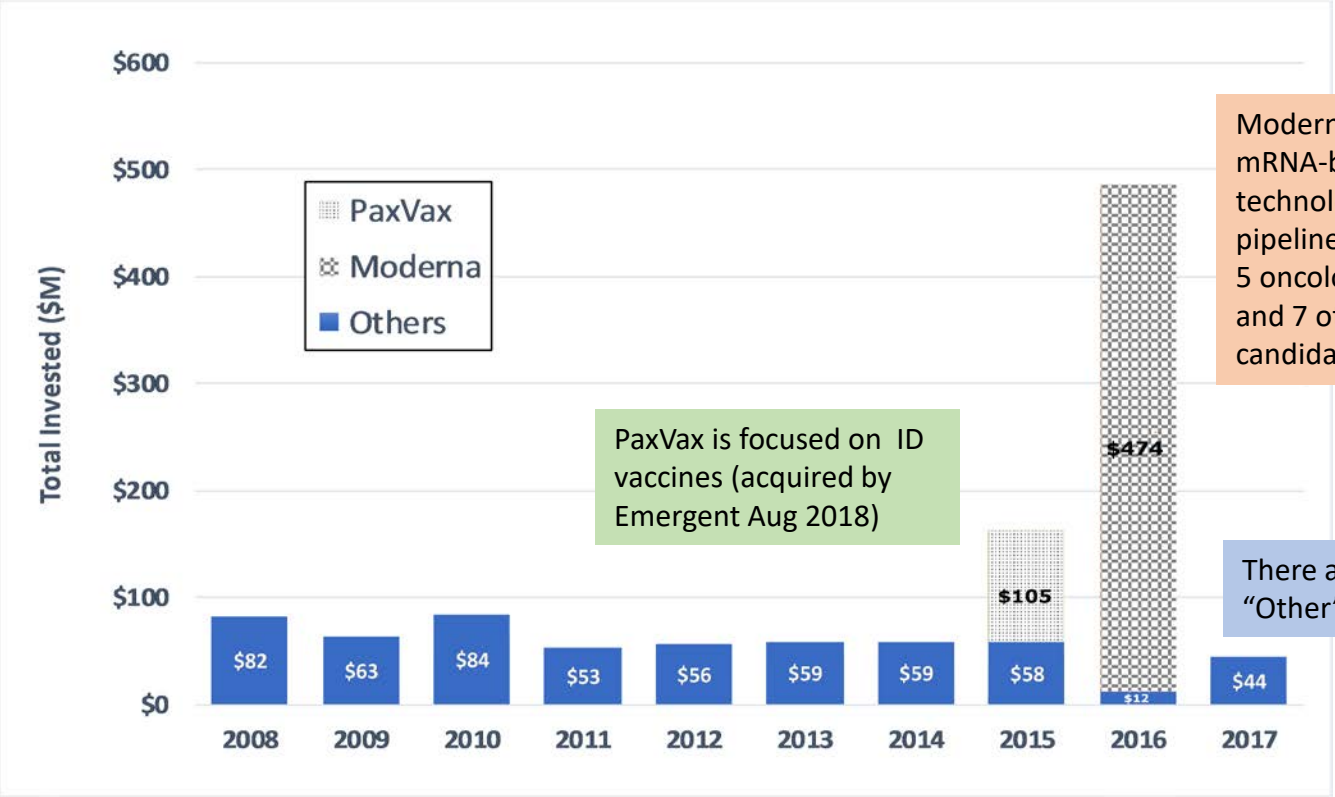
Dave Thomas & Chad Wessel, BIO Emerging Therapeutic Company Investment and Deal Trends, 2008-2017

Venture capital funding for US drug development biotechs



Dave Thomas & Chad Wessel, BIO Emerging Therapeutic Company Investment and Deal Trends, 2008-2017

Venture capital funding for US ID vaccine biotechs



Moderna has a broad mRNA-based platform technology with a pipeline of 9 ID vaccines, 5 oncology candidates and 7 other therapeutic candidates (July 2018).

PaxVax is focused on ID vaccines (acquired by Emergent Aug 2018)

There are about 20 "Other" private biotechs

Dave Thomas & Chad Wessel, BIO Emerging Therapeutic Company Investment and Deal Trends, 2008-2017 & unpublished data

Biotechs developing infectious disease vaccines

- Public-private partnerships are more important than ever to mitigate VC and public investor funding gaps for biotechs
  - NIH, DoD, Gates, PATH, CEPI and CARB-X play important roles usually up to Ph2
  - Transitioning from Phase 2 to 3 requires “BARDA-scale” funding (≥$100M)
- Need commercially successful infectious disease vaccines
  - Maintain/expand Big Pharma interest in funding internally and acquiring biotechs
  - Success stories for investors in ID vaccines (venture capital, institutional, individual)
- Need government policies that can support vaccine use & development
  - Expand coverage and reimbursement for existing vaccines (esp. adult, adolescent)
  - Lower development cost/risk (regulatory innovation, ACIP predictability)

Public biotechs with clinical-stage/marketed ID vaccines
Government intervention has been successful in sustaining biotechs