Vaccines and Public Health in India

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Outline

- The impact of vaccines
- Challenges in India
- The future of vaccines
  - The valley of death
  - Outbreaks and global responses

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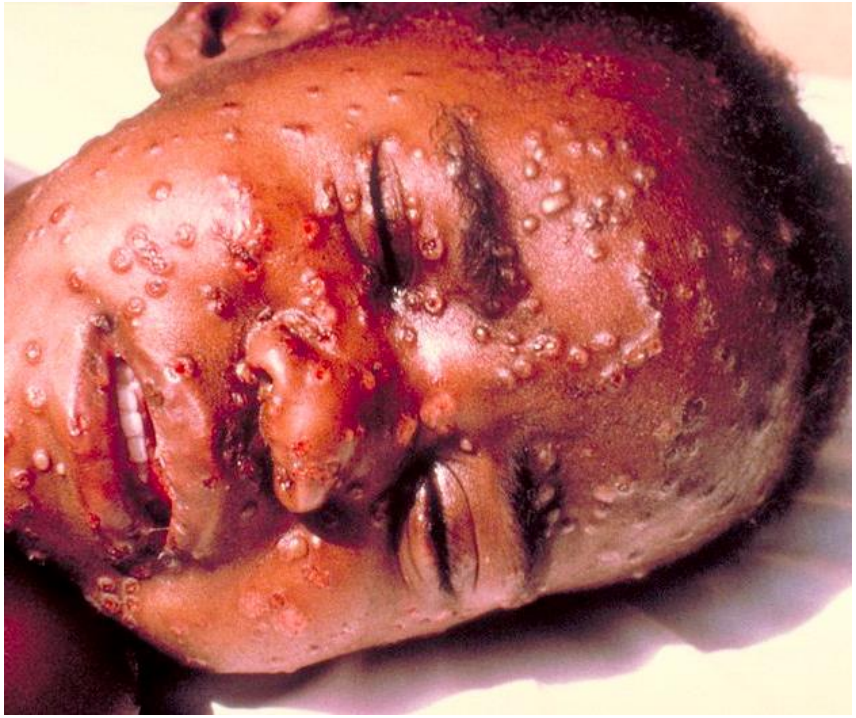
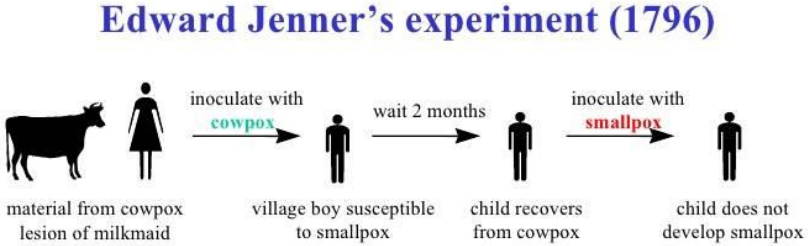
In a world without vaccines



- In the 1700s, in Europe alone 400,000 people died every year of small pox



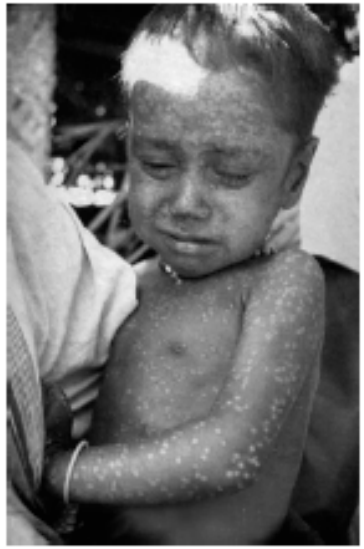
By 1800, vaccines administered across Europe and North America

By 1900: smallpox eliminated from much of industrialized world

1950: Pan Am Health Org - eradication program throughout Americas

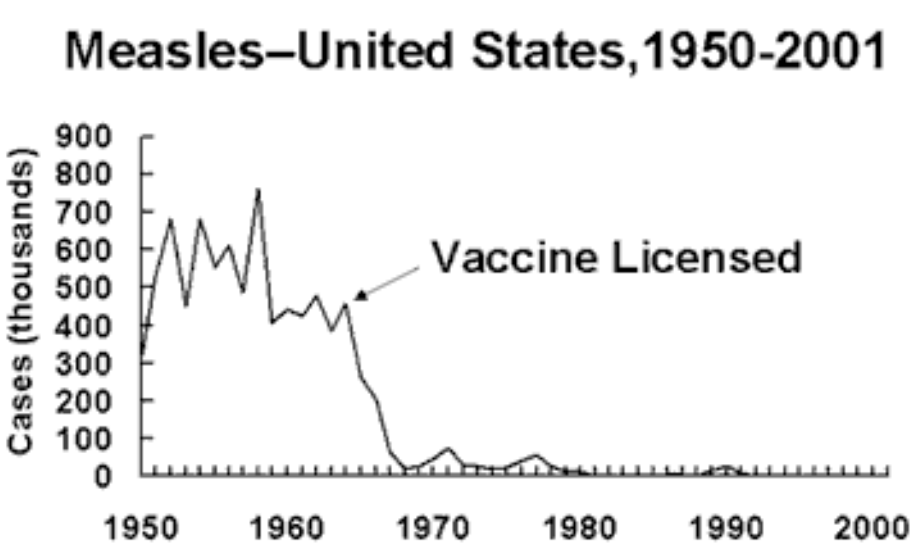
1959: Beginning of global smallpox eradication program

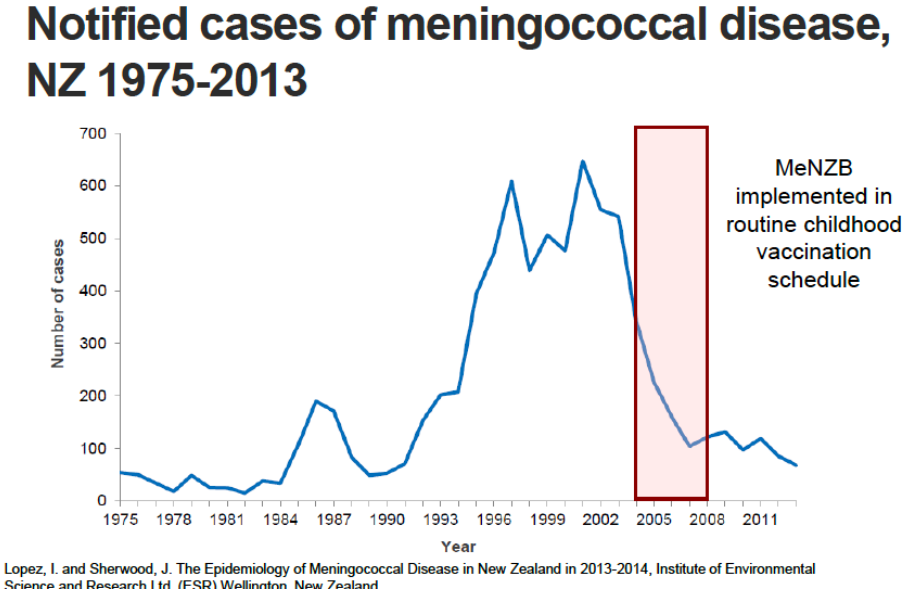
1975: Rahima Banu, one of the last people naturally infected by smallpox



12/9/1979: WHO declared smallpox eradicated

What can vaccines do to disease?





Lopez, I. and Sherwood, J. The Epidemiology of Meningococcal Disease in New Zealand in 2013-2014, Institute of Environmental Science and Research Ltd. (ESR) Wellington, New Zealand

Bacterial vaccine preventable diseases

- Tetanus
- Diphtheria
- Typhoid
- Cholera
- Botulism
- Anthrax
- Plague

- Pertussis
- Pneumococcus
- Meningococcus
- Haemophilus influenzae B
- Q fever
- Tuberculosis

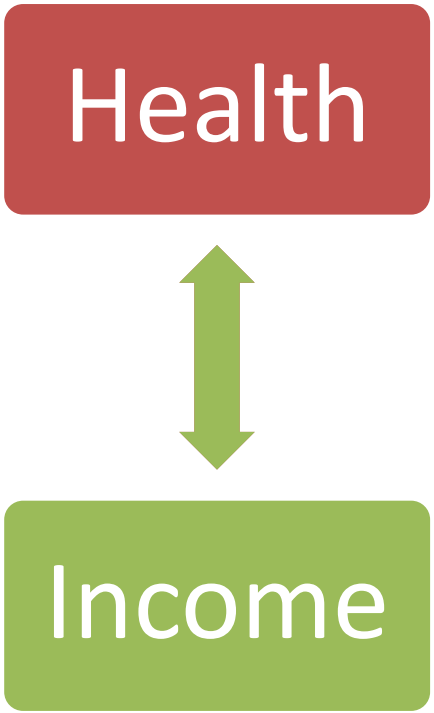
Viral vaccine preventable diseases

- Polio 1,2,3
- Hepatitis B virus
- Measles
- Mumps
- Rubella
- Varicella zoster virus
- Rotavirus
- Influenza A and B
- Hepatitis A
- Hepatitis E
- Rabies
- Japanese encephalitis
- Dengue
- Yellow fever
- Small pox
- Human papillomavirus

Vaccines are a best buy

- Vaccination currently saves between 2 and 3 million lives every year.
- The impact of vaccines goes far beyond saving lives and improving health. Vaccination is in every sense an investment, with wider benefits that accrue across a lifetime.

The value of health



Health contributes to income

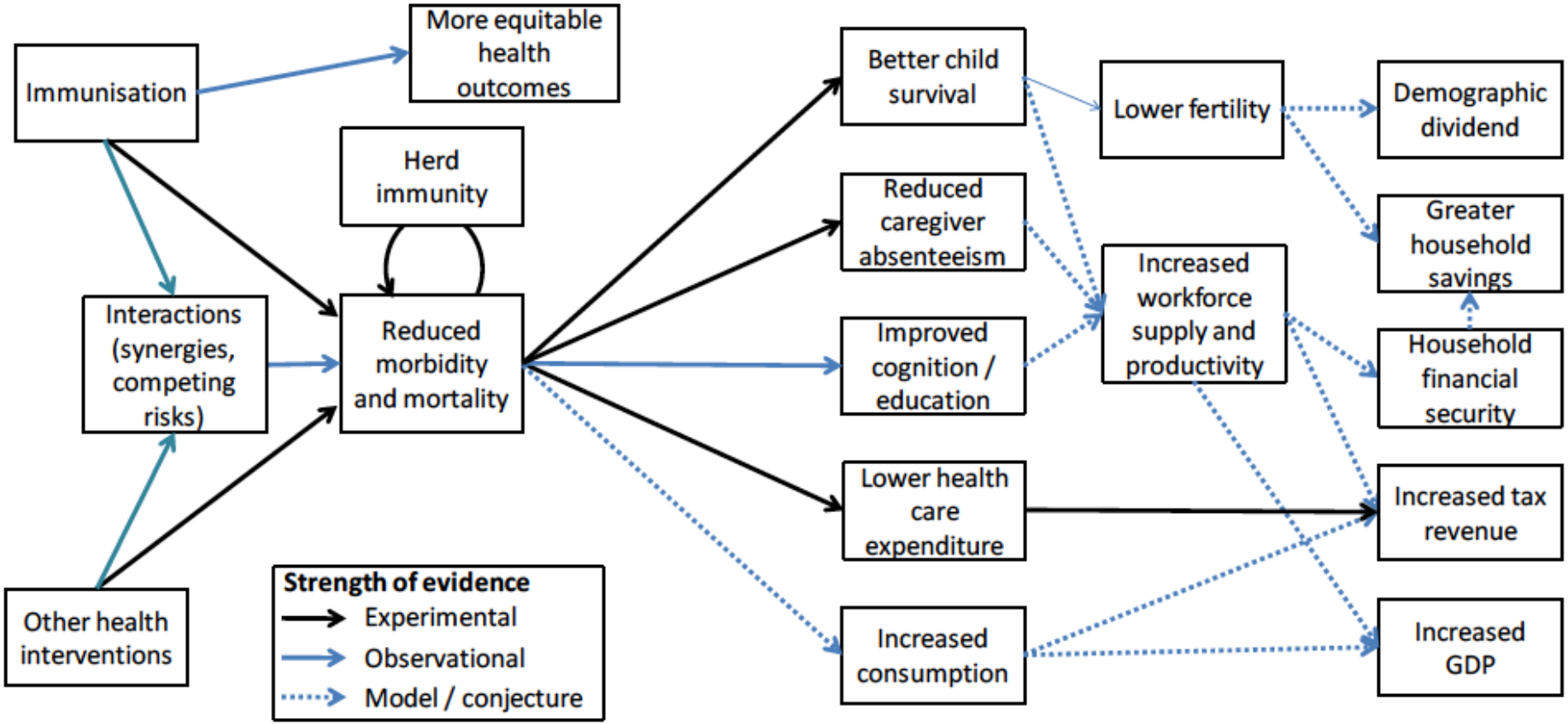
Productivity
Education
Investment
Demographic dividend

Income contributes to health

Nutrition
Safe water
Sanitation
Health care
Psycho-social resources

A 10 year gain in life expectancy translates into up to 1 additional percentage point of annual growth of income per capita

Capturing the value of vaccines



Outline

- The impact of vaccines
- Challenges in India
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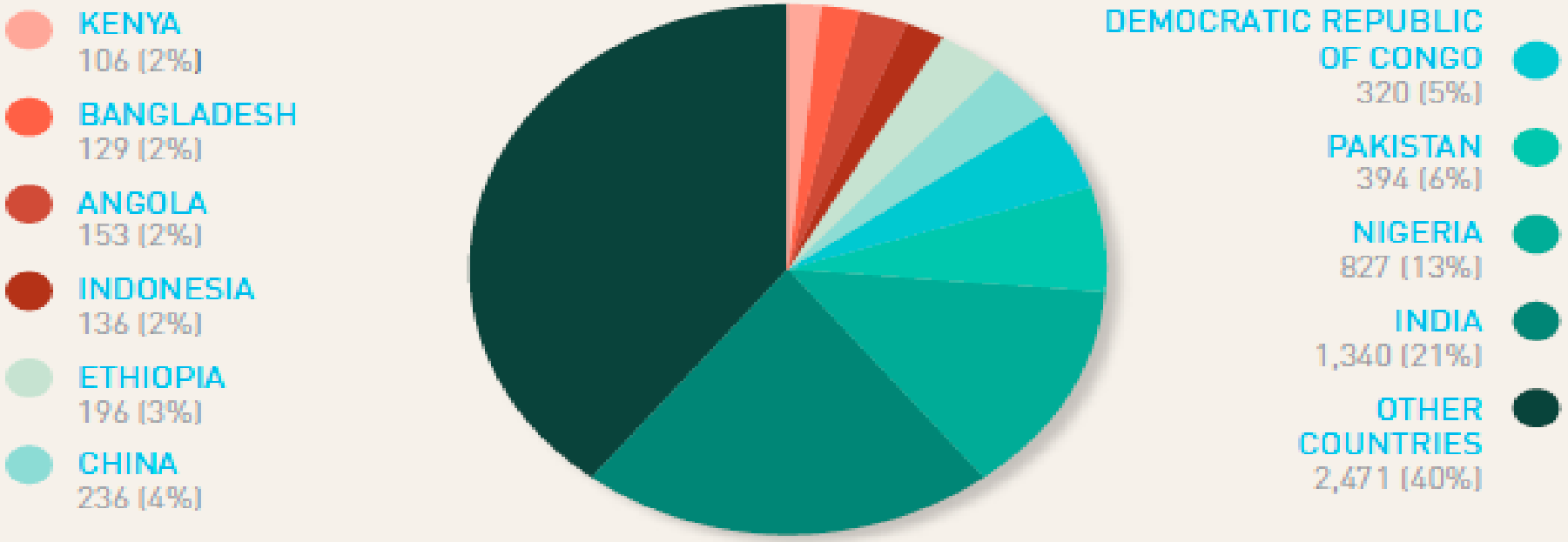
  - The valley of death
  - Outbreaks and global responses

WHO Key Facts About Immunization

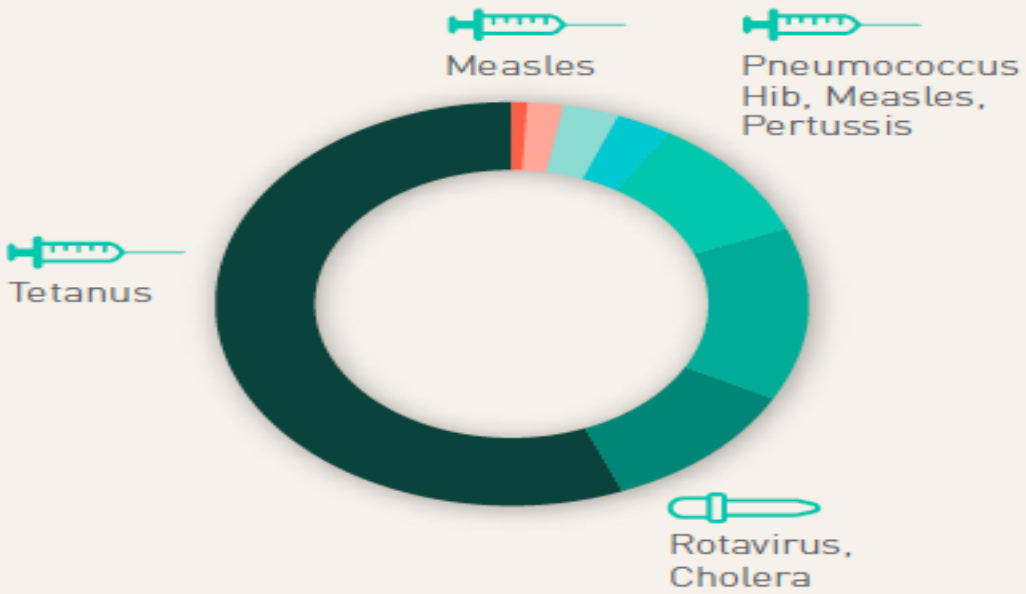
- Immunization currently averts an estimated 2 to 3 million deaths every year.
- An additional 1.5 million deaths could be avoided, however, if global vaccination coverage improves.
- An estimated 19.4 million infants worldwide are still missing out on basic vaccines.
- India has the most unimmunized and incompletely immunized children in the world.

The incidence of global under-5 deaths has reduced by half between 1990 (12.6 million) and 2013 (6.3 million).

India's share of global child mortality (figures in thousands)



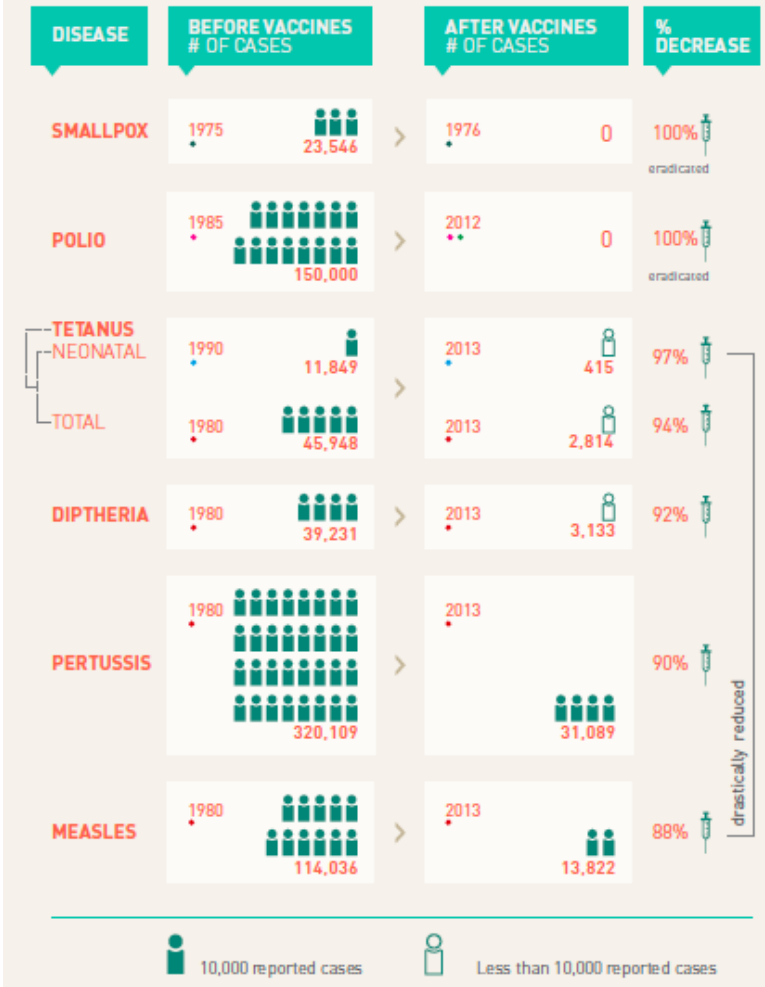
Causes of under-5 child mortality in India



Malaria	1%
Meningitis	2%
Measles	3%
Injury	3%
Diarrhoea	10%
Others	14%
Pneumonia	11%
Neonatal causes	56%

Vaccines available to help protect against forms of diseases are highlighted

Reference: Committing to Child survival – a Promise renewed. Progress report 2014. UNICEF, 2014.



Vaccines in India

- Small pox is gone (global eradication)
- Polio is gone (2011)
- Maternal and neonatal tetanus elimination (less than 1 case per 1000 live births)
- Measles decreased after 2nd dose introduction
- Diphtheria at less than 3000 cases (but outbreaks last year in Kerala and UP)
- Pertussis reduced by 86% in 20 years

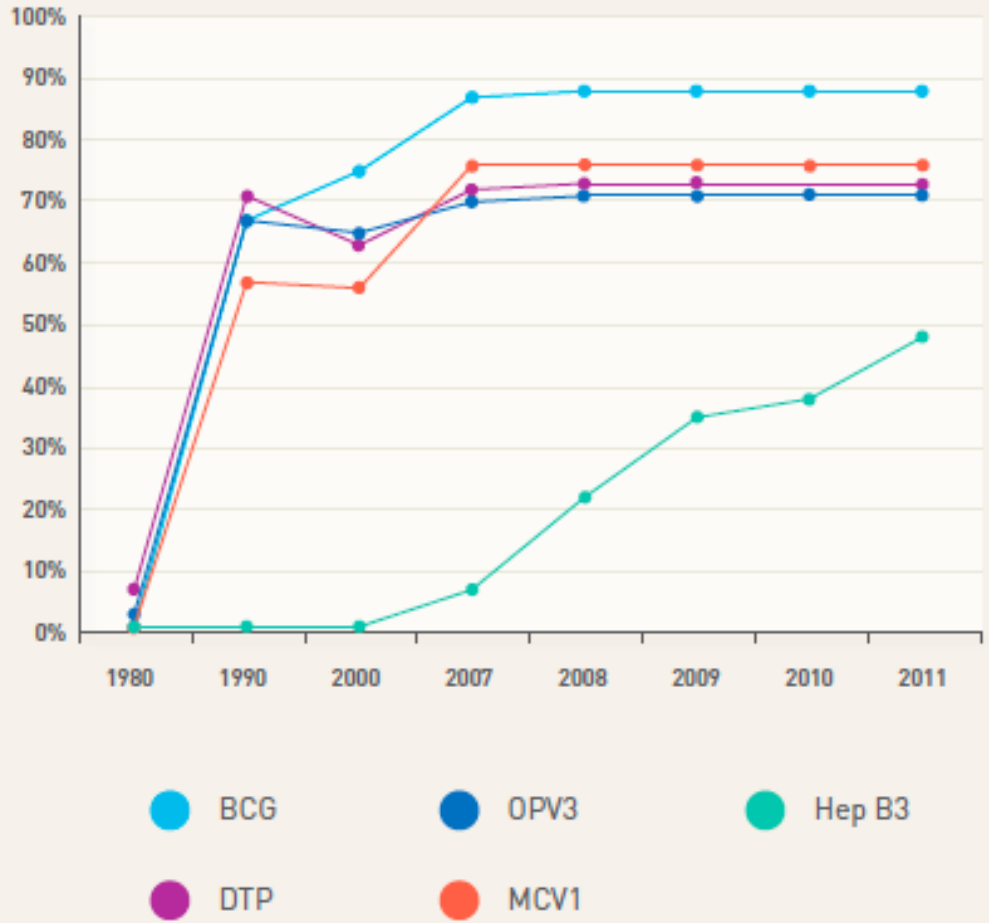
A sense of scale

- Routine immunization targets 26 million children and 30 million pregnant women.
- Nine million routine immunization (RI) sessions are organized in India each year
- The sessions are served through 27,000 cold chain stores.
- The national average for full immunization is 61 per cent, and for DPT-3 coverage, 72 per cent.
- Each National Immunization Day, 172 million children are immunized for polio.
- India's polio vaccination campaigns cover 800 million children a year.
- A three-year campaign to ensure children receive the second measles vaccination targeted almost 150 million children.

http://unicef.in/Whatwedo/3/Immunization#sthash.zGCHyxYd.dpuf

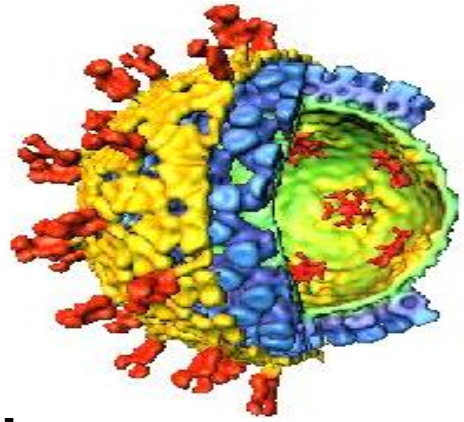
Challenges

- Scale
- Focus of childhood vaccination and maternal tetanus
  - No life course approach
- Heterogeneity in performance
- Approaches (routine vs. vertical and periodic intensification of routine immunization)

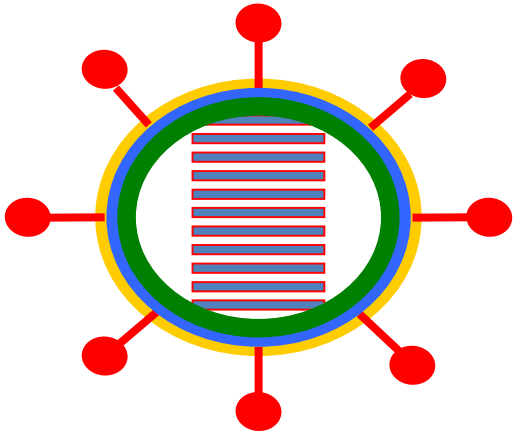


Nonetheless, we have finally begun to introduce new vaccines

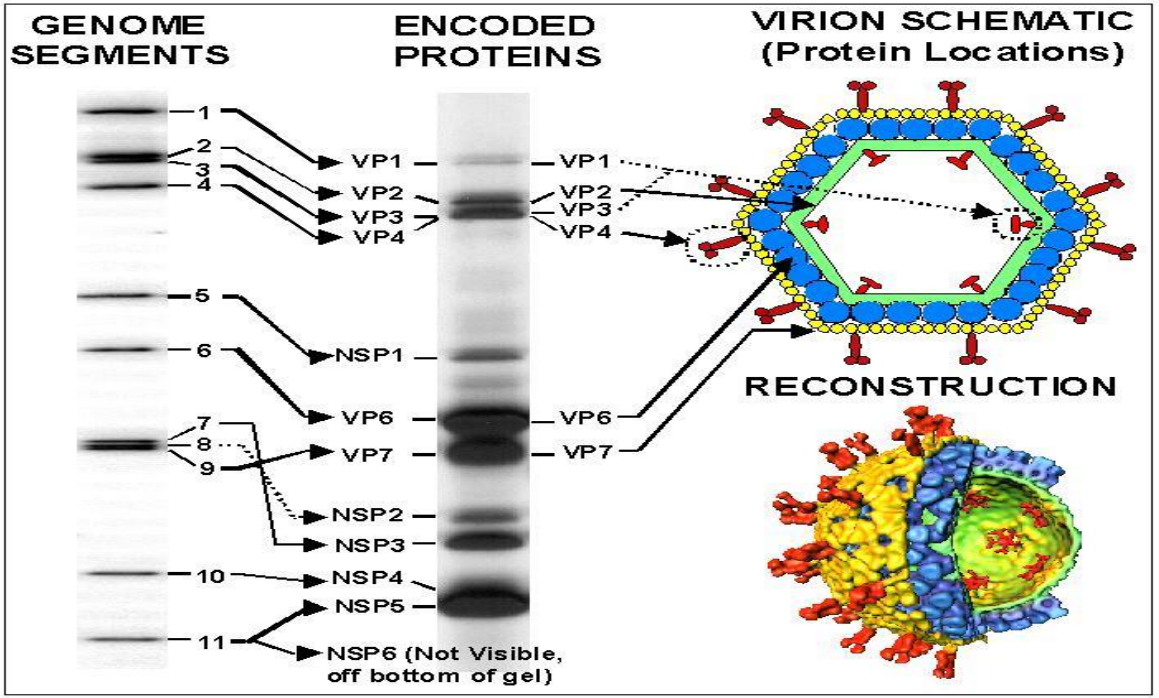
- Pentavalent (now country wide)
- Japanese encephalitis (partial expansion and adult immunization
- Rotavirus (8 states and planned expansion)
- Pneumococcal (introduced for 2017)
- Human papillomavirus (Punjab 2017, other states planning introduction)



The Story of an Indian Rotavirus Vaccine

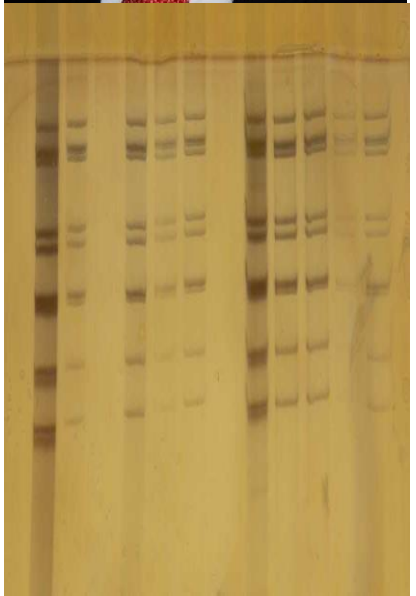


Group A rotaviruses are the most common cause of dehydrating gastroenteritis in children



Indian neonatal strain

- In 1985, an “outbreak” of asymptomatic rotavirus infections was observed in the newborn unit of the All India Institute of Medical Sciences (AIIMS) I
- 50% for newborns hospitalized for 3 days and 75% for newborns hospitalized for a full week
- All asymptomatic
- All 11 gene segments of the neonatal strains appeared to be identical on the basis of the results of electrophoresis
- Persisted for several years in the newborn unit



The Indo-US Vaccine Action Program

- Supported strain characterization in the US and India
- Based on the clinical studies, both strains taken forward as vaccine candidates
- Hypothesized that both strains would replicate well because mothers would not have antibodies against P[11]
- Pilot lots prepared in the US by serial passage in cell culture
- Licensed to Bharat Biotech Intl Ltd

Phase 3 Study Sites

Study sites: In three states

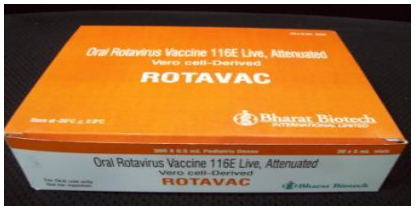
Sample size: 6800

Recruitment Target

- 3800 (Site 1, Society for Applied Studies, Delhi)
- 1500 (Site 2, King Edward Memorial Hospital and Research Centre, Pune, Maharashtra)
- 1500 (Site 3, Christian Medical College, Vellore, Tamil Nadu)

Efficacy of Rotavac

	Number of Cases			
Disease Severity	RVV (N=4354)	Placebo (N=2187)	% Efficacy	95% CI
Severe	93	102	**55.1**	39.9, 66.4
Hospitalized	92	102	**55.6**	40.5, 66.8



Bhandari et al. Lancet 2014

Rotavirus Disease Burden Estimates for India

78,583
(76,019 – 81,206) deaths

1 in every 345 (334 – 356) children*

872,315
(596,662 – 1,231,452) hospitalizations

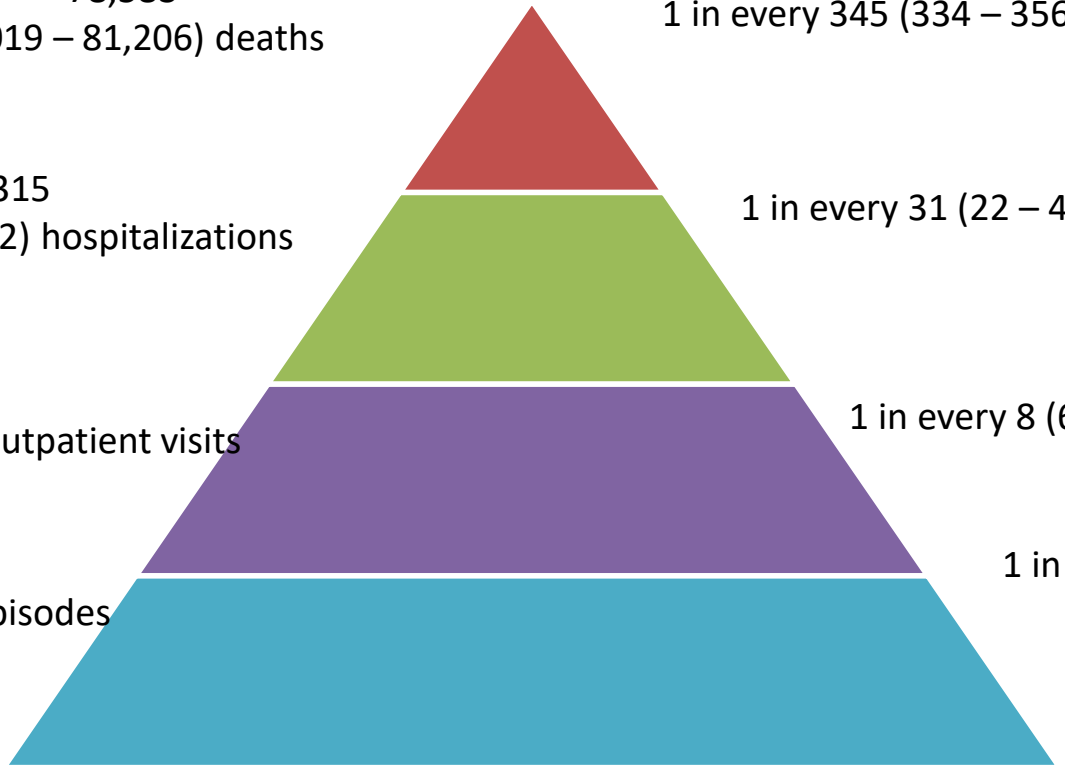
1 in every 31 (22 – 45) children*

3,271,187
(2,237,486 – 4,617,948) outpatient visits

1 in every 8 (6 – 12) children*

11,373,098
(9,745,967 – 13,194,028) episodes

1 in every 2 (2 – 3) children*



* Estimates based on 2011 birth cohort of 27,098,000 children (UNICEF India Statistics)

India first country to state in guidance that upper age limit is 12 months for first dose

In March and April 2016, India introduced the indigenous rotavirus vaccine for 9% of the birth cohort—Odisha, Andhra, Haryana and Himachal Pradesh
Now expanded to another 20%

Summary of rotavirus vaccine development

- India developed a rotavirus vaccine made by India for India
- Now being used in the national programme in 4 states
- Potential to save 30,000 children's lives every year
- Much work still to be done
  - Special populations
  - Improving performance in developing countries
  - Monitoring impact and safety

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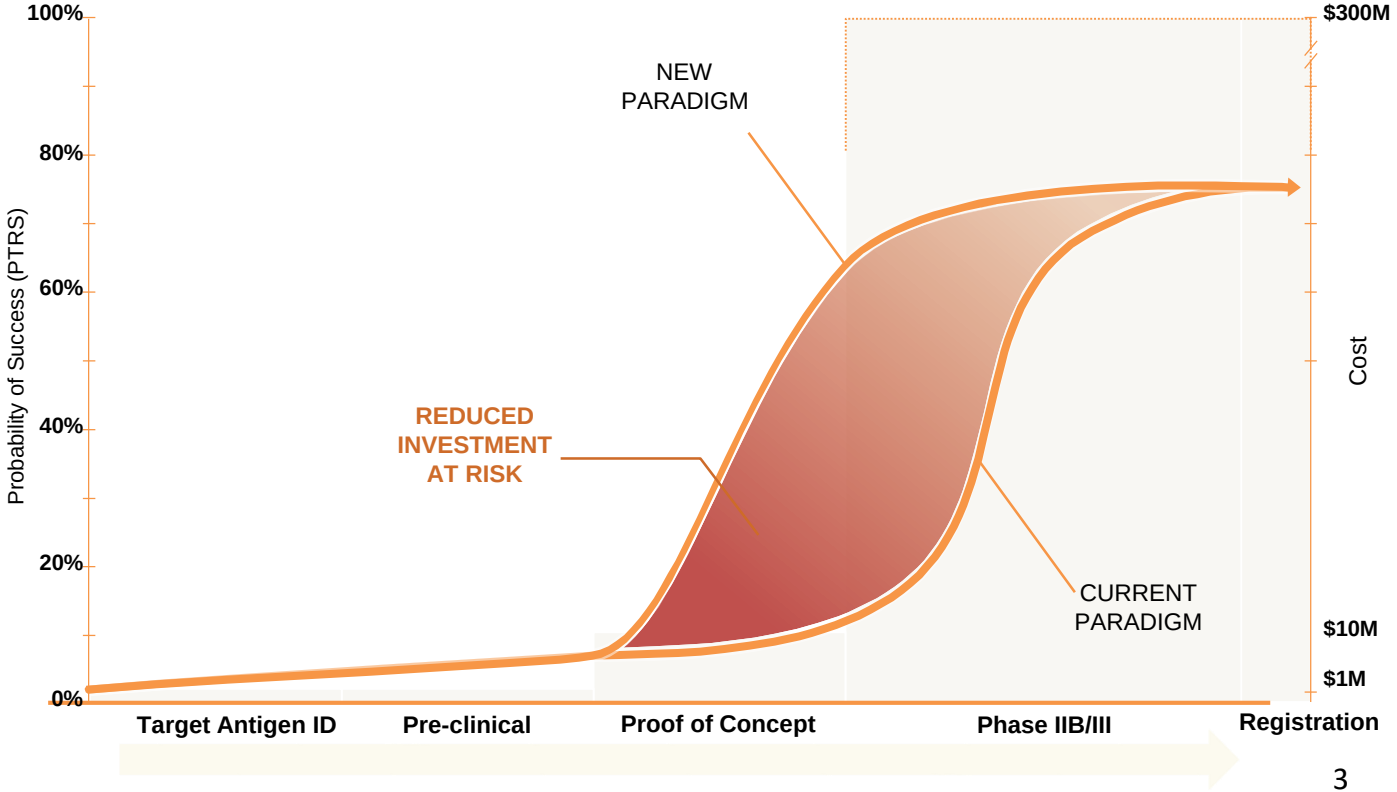
Newer strategies for vaccine development

- Strategy
  - Live recombinant
  - Recombinant proteins
  - Replicative defect/virus like particles
  - Alpha virus replicons
  - Naked DNA plasmid
  - Recombinant vectors
  - Prime boost using DNA
  - Reverse genetics
  - Peptides
  - T cell receptor
- Examples
  - Dengue, parainfluenza
  - Hep B, Pertussis toxin
  - HPV, HSV
  - HIV, haemorrhagic fevers
  - Hepatitis B
  - CMV, HIV
  - HIV, malaria
  - Influenza, RSV
  - Cancer
  - Multiple sclerosis

The valley of death results from costs

Shift decision making to the left



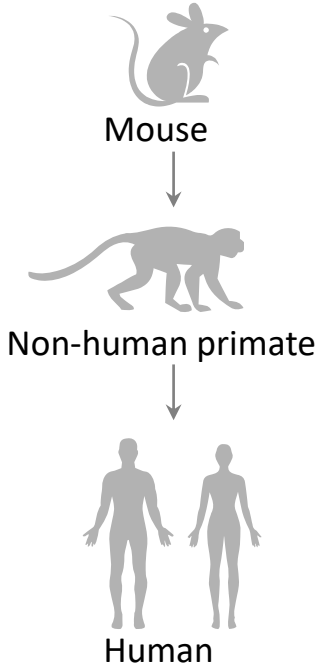
Slide from Lynda Stuart

How do we left-shift vaccine R&D?

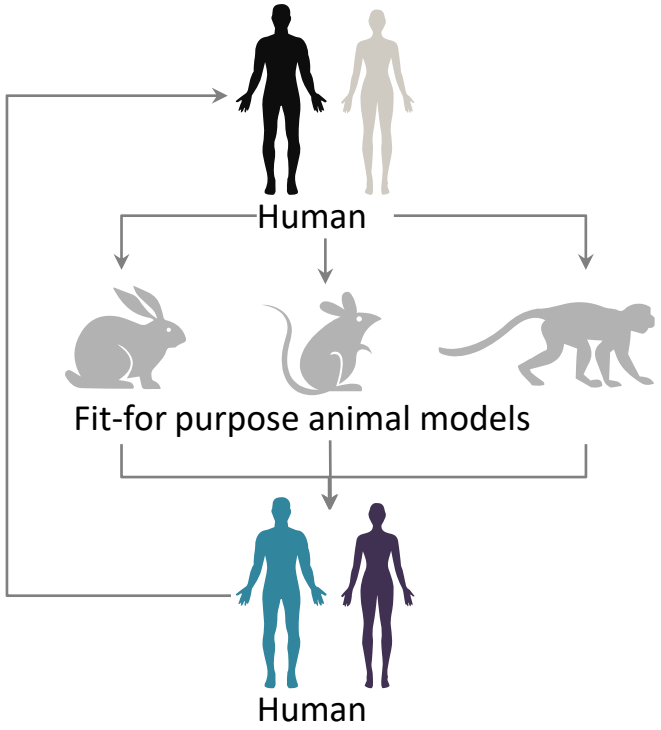
- Time it takes to develop and deliver a new vaccine to market remains too slow.
- A number of issues contribute to the delay:
  - Limitation of animal models to predict and mimic vaccine-induced immunity
  - Limited ability to generate novel, but physiologically relevant and testable hypotheses about the mechanisms of vaccine-induced immunity
  - Difficulties in defining correlates of protection
  - Poor strategies to rationally up and down select different vaccine candidates in an affordable and timely manner
- **Exploratory clinical studies could circumvent many of these problems BUT major logistical barriers to this approach**

Inverting the experimental paradigm

Current paradigm



New paradigm



What are exploratory clinical studies?

Small, flexible studies that can be used either to ***generate or test a hypothesis*** early in humans in order to provide critical information that contributes to accelerating discovery and/or vaccine product development

Key characteristics

Scope

- Up to a phase 1 study
- Smaller number of subjects than a typical phase 1 (~10-15 subjects)
- Includes **Controlled Human Infection Models**

Types

- Hypothesis generation and testing
- Not necessarily on a product development path
- **Exploratory studies e**.g.:
  - Identification of correlates of protection,
  - Antigen discovery
  - Validation of effectors

Potential Differentiation from Phase I Studies

- Iterative nature of EM projects between early clinical and preclinical research
- Not necessarily intended to progress beyond early human studies
- Used in both the a preclinical and **precompetitive space**

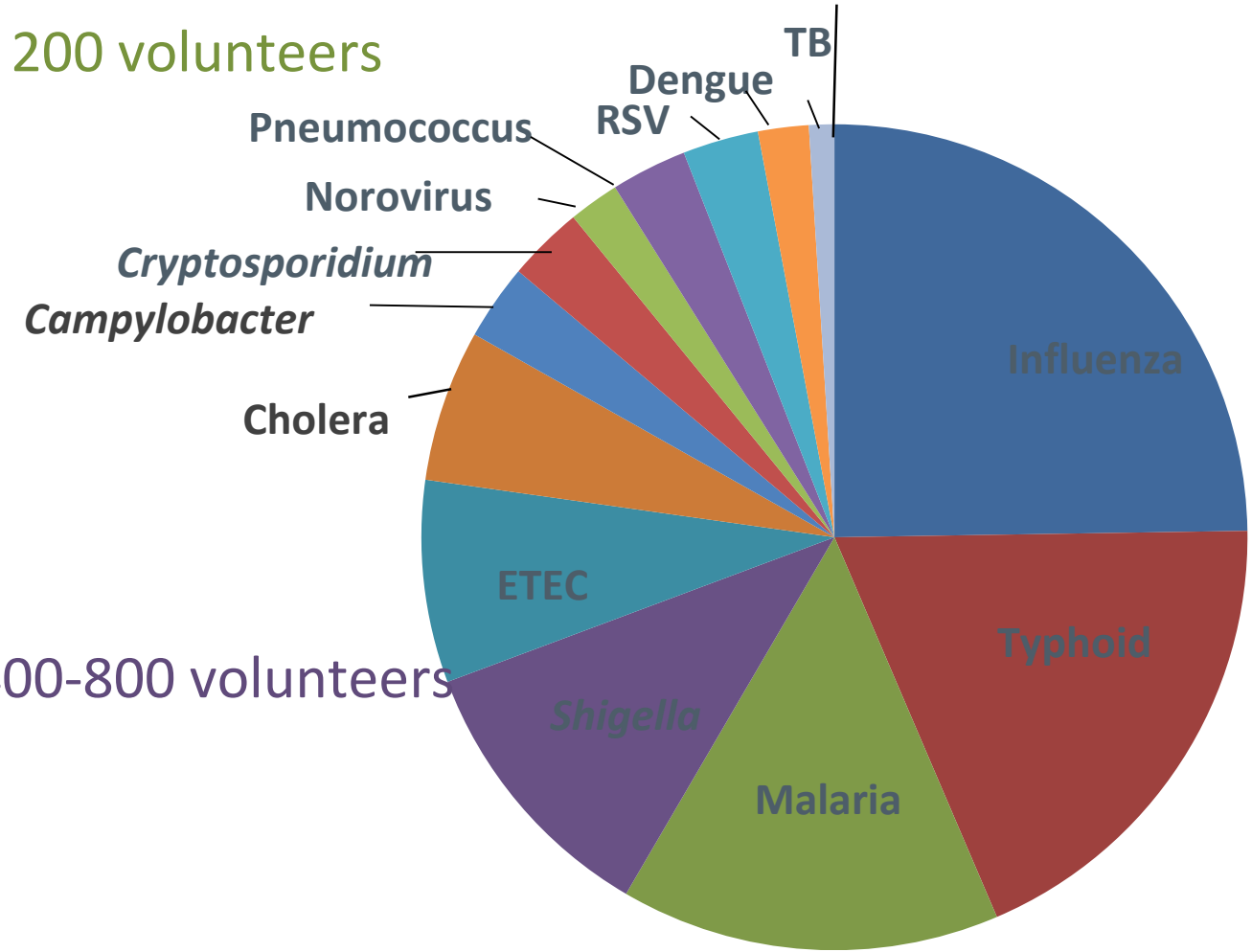
Controlled Human Infection Models

Slides from Lynda Stuart and Francine McCutchan

CHIM and their utilization

- In use for more than 70 years.
- More than 6,500 volunteers have participated.
- Nearly 60 different challenge strains used.
- Some models are more widely used than others.
- Limited spectrum of disease and lack of protective immunity are drawbacks for some models.
- Application to vaccine development has been variable.
- Utilization often increases when models meet current guidelines, standardize procedures, and support a robust pipeline of candidate vaccines.

> 200 volunteers



1,000-2,000 volunteers

400-800 volunteers

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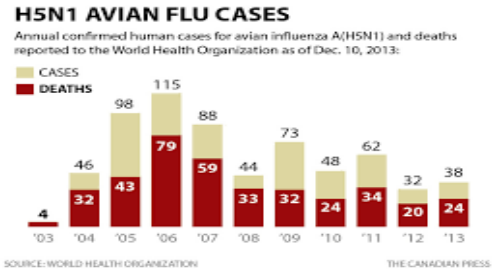
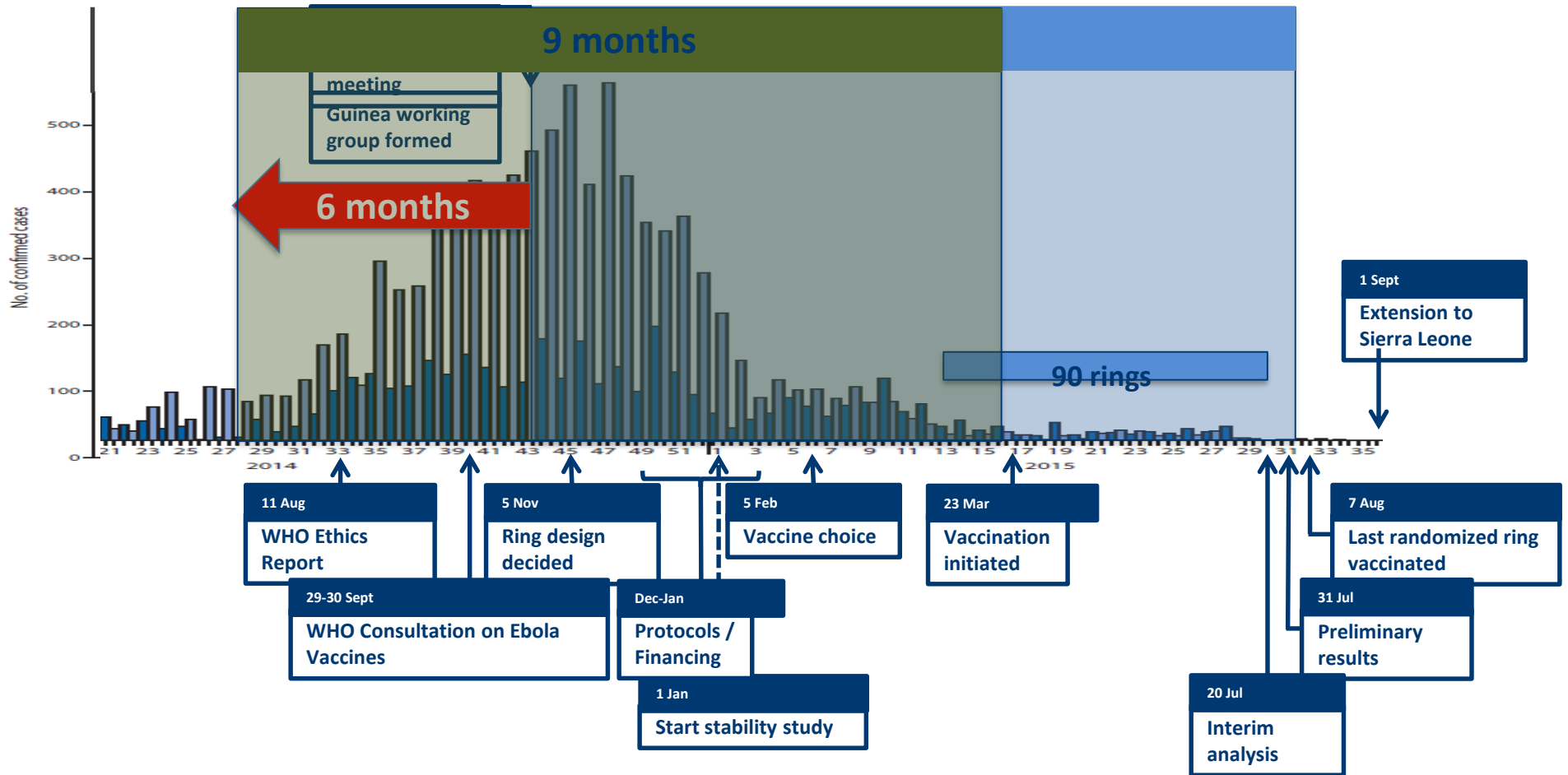
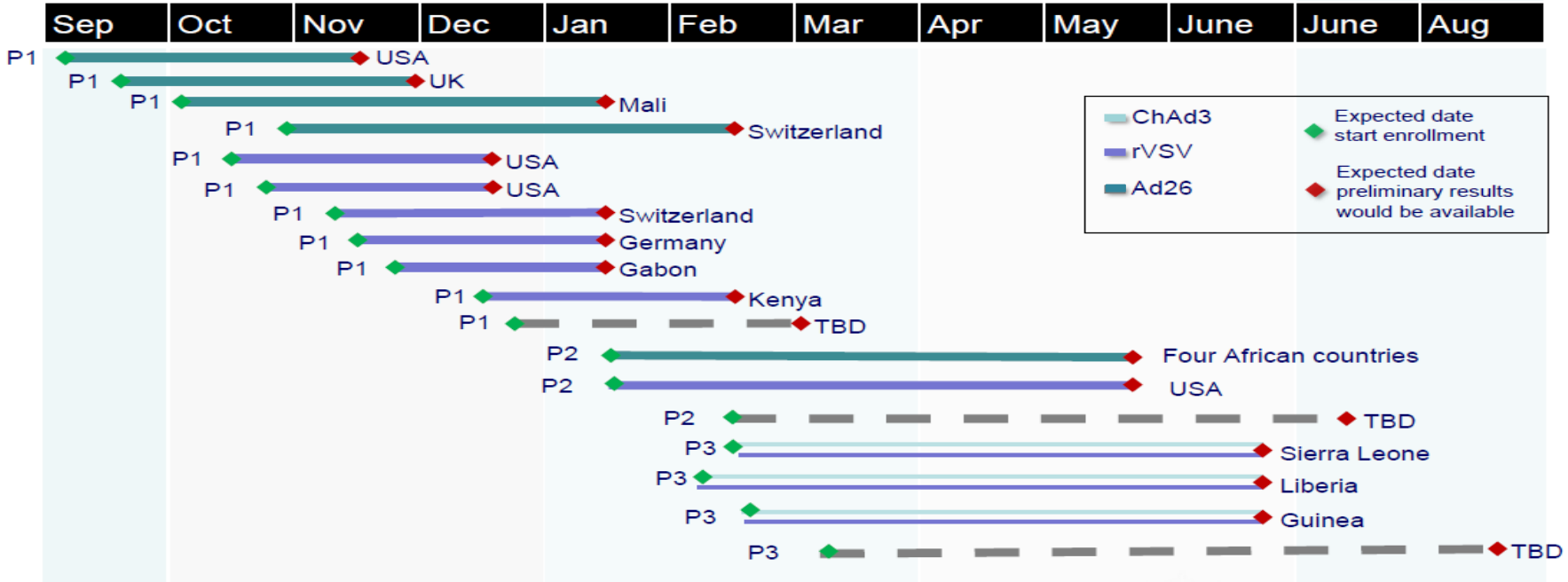
The challenge of epidemics



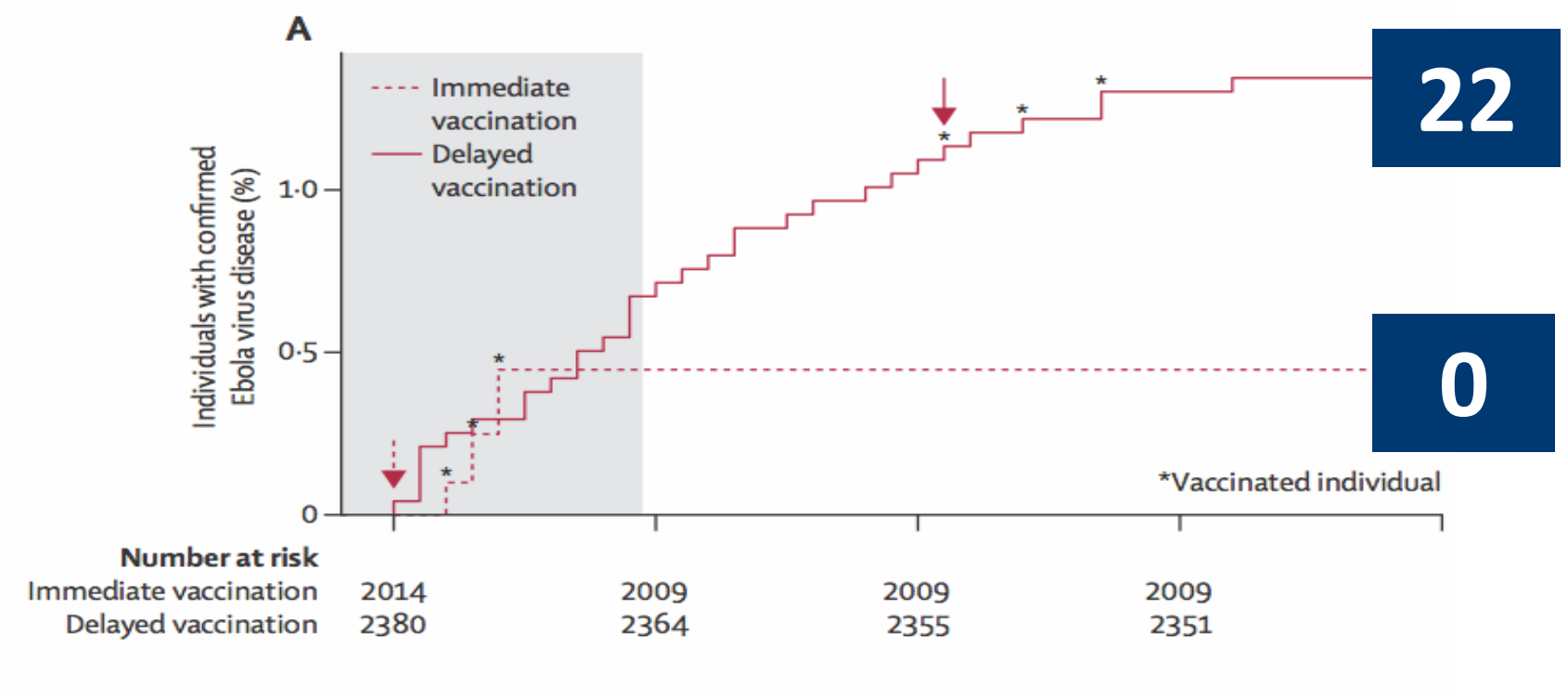
Timing of phase III trials



More than 15 clinical trials



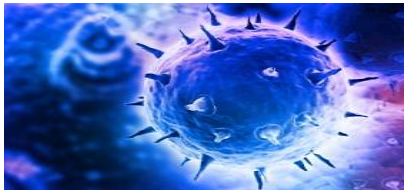
Efficacy data, Guinea trial



Timely vaccine development – objectives for efficient global R&D preparedness

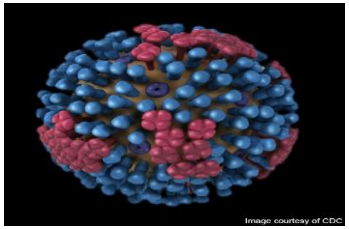
1. "Just in Case" – Preparedness	Advance **vaccine candidates** through late preclinical studies to proof of concept and safety in humans during non-epidemic periods
2. "Just in Time" – Response speed	Validate and sustain **technology platforms** to support the rapid development of vaccines in known and unknown pathogen emergencies

Live attenuated virus vaccines

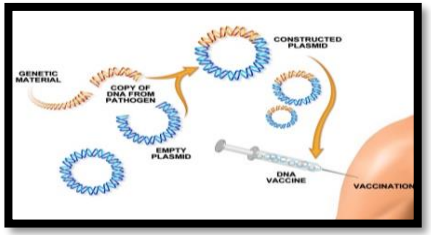


Whole killed virus vaccines (other forms of protein-particulate vaccines)

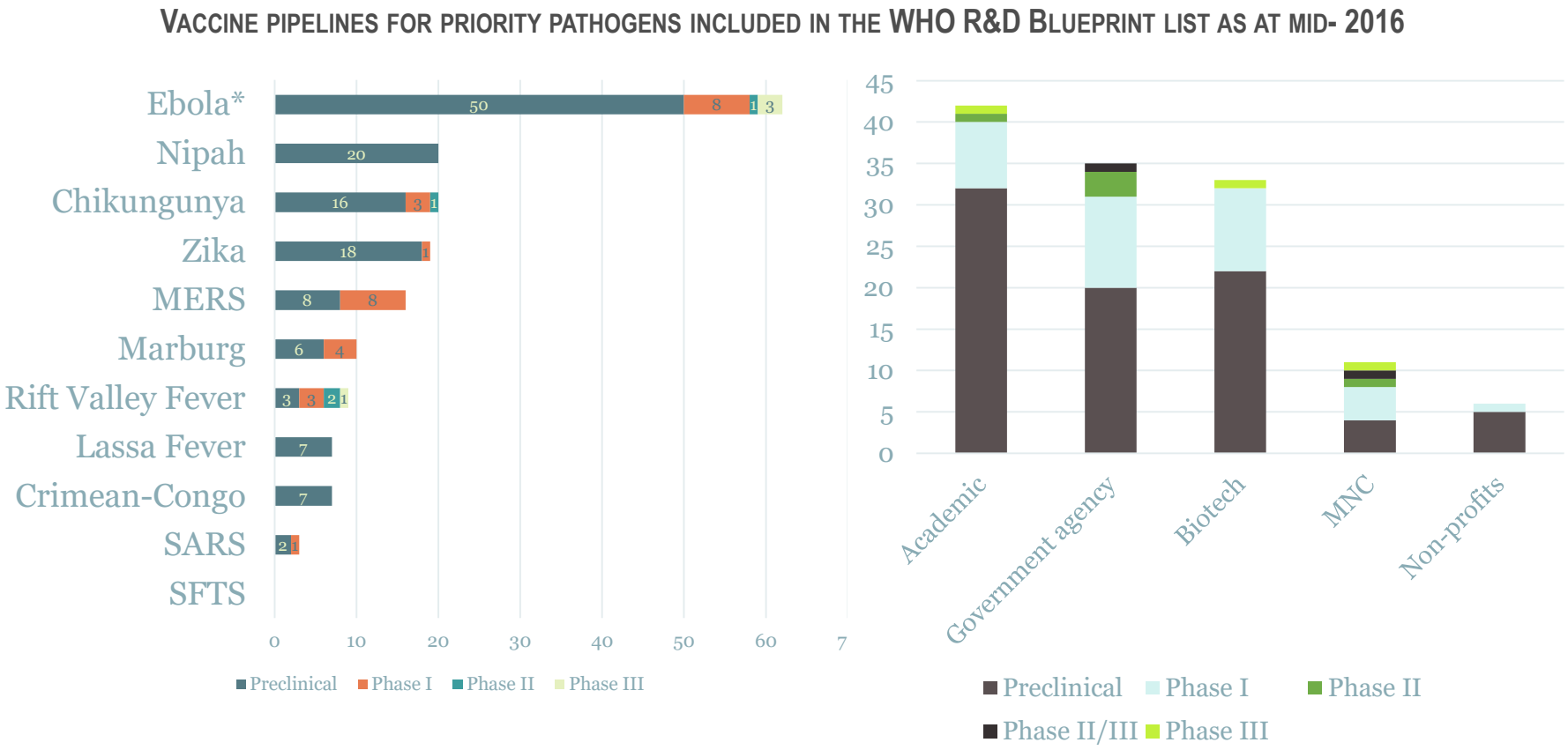
VLP (Virus-Like-Particle) vaccines, other non-living technologies (e.g.liposomes)



DNA/RNA vaccines Self-Amplifying-Material (SAM®)



Epidemic infectious diseases - weak clinical pipelines and multiple vaccine R&D actors



CEPI

Coalition for Epidemic Preparedness Innovations

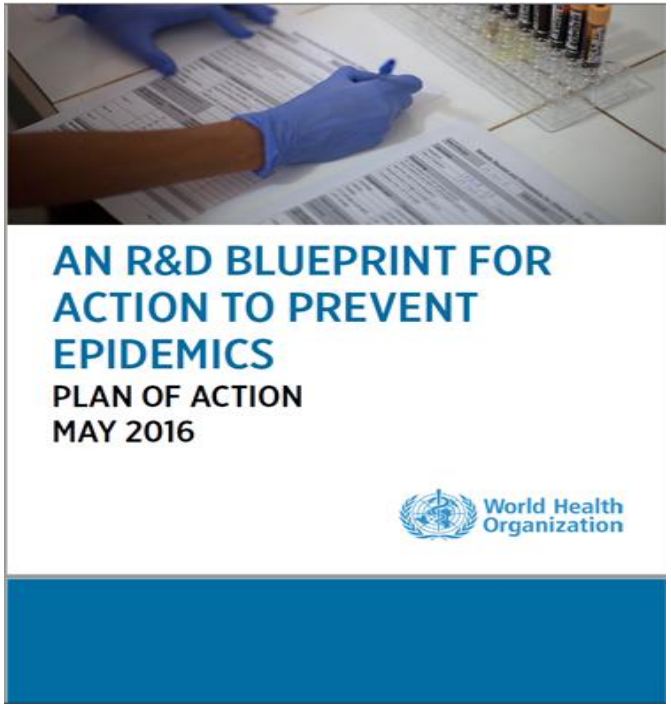
New vaccines for a safer world

- Based on broad consultations in the global health community there is recognition of the unmet gaps in the current architecture that requires a new dedicated global initiative, which has been named the Coalition for Epidemic Preparedness Innovation (CEPI).

- Coalition for Epidemic Preparedness Innovations (CEPI) is a partnership of public, private, philanthropic and civil society organisations

- CEPI will *stimulate, finance and coordinate* vaccine development
  - against priority threats,
  - particularly when development is unlikely to occur through market incentives alone

WHO – CEPI partnership



What is CEPI's model for response?

- CEPI will move vaccine candidates through late preclinical studies to proof of concept and safety in humans before epidemics begin
  - larger effectiveness trials can begin swiftly in an outbreak
  - small stockpiles are ready for potential emergency use

- CEPI will build technical platforms and institutional capacities that can be rapidly deployed against new and unknown pathogens

CEPI's Gap-Filling Role

Phase	1 Discovery	2 Development/Licensure	3 Manufacturing	4 Delivery/Stockpiling
Current Stakeholders	• Academia • Governments • WT/NIH • GLOPID-R • Industry • Regulators • Biotech	• Industry • National Governments • Regulators • Bill and Melinda Gates Foundation • BARDA/DTRA etc. • WHO • Biotech • PDPs	• Industry • BARDA • CMOs • Regulators • National • Governments • WHO • GHIF	• GAVI • UNICEF • PAHO • National Governments • WHO • Industry • Pandemic Emergency Facility (World Bank) • WHO Contingency Fund

CEPI will complement existing efforts by focusing on advanced **vaccine development for priority EIDs, bridging the gap** between discovery research and vaccine delivery as part of an **end-to-end approach** that will address global calls for:

1) **a global mechanism to align EID R&D** funders, developers, and regulators;
2) **coordinated and proactive R&D for and access to EID vaccines**;
3) clear, predictable, and coordinated **regulatory processes**; and
4) stronger **advanced development and manufacturing capabilities**.

India’s engagement

- Leadership in founding CEPI
  - Government of Norway, DBT, Wellcome Trust, World Economic Forum, Bill and Melinda Gates Foundation
  - Proposal to host one node of CEPI Secretariat
- Consultation with stakeholder ministries
  - Health and Family Welfare (including ICMR and DCGI), External Affairs, Defence
- Consultation of industry stakeholders
  - Through CII and ABLE
- Preparation for participation
  - DBT, working with NCR-Biotech Cluster institutions and stakeholder ministries

Scope of Indian engagement

- Strategic plan for long-term, flexible global engagement with CEPI and with stakeholders in LMICs and the vaccine industry
- An end to end approach from vaccine development to application, to move new vaccines from preclinical to proof of principle in humans, and the development of new technology platforms for vaccines
- Development of ethical and regulatory frameworks and plans for rapid response and testing of potential interventions

Why is this essential?

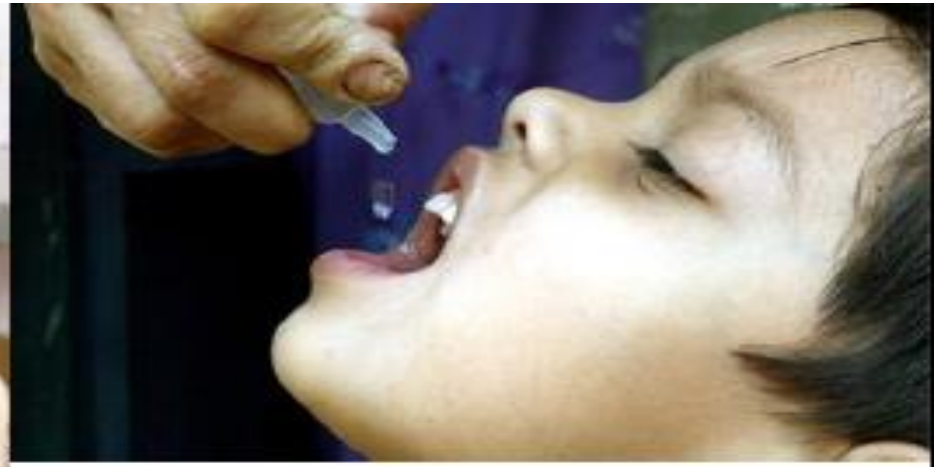
- **Vision**
- By 2025, India will have a rapid, scalable response to infectious threats through a well-coordinated, prepared public health system and a globally competitive vaccine industry which addresses existing and emergent public health problems in India and worldwide

An opportunity to lead globally in an area that is, and will continue to be, important for health security

Summary

- Vaccines are a clear best buy for public health
- India has implementation challenges and development challenges
- Taking on new vaccine development offers opportunities for the advancement of science, the Indian vaccine industry and public health
- Experimental medicine and platform technologies are possible
- There will be hurdles, but we must get to work

Thank you



Two-thirds of the world's children receive at least one vaccine made in India