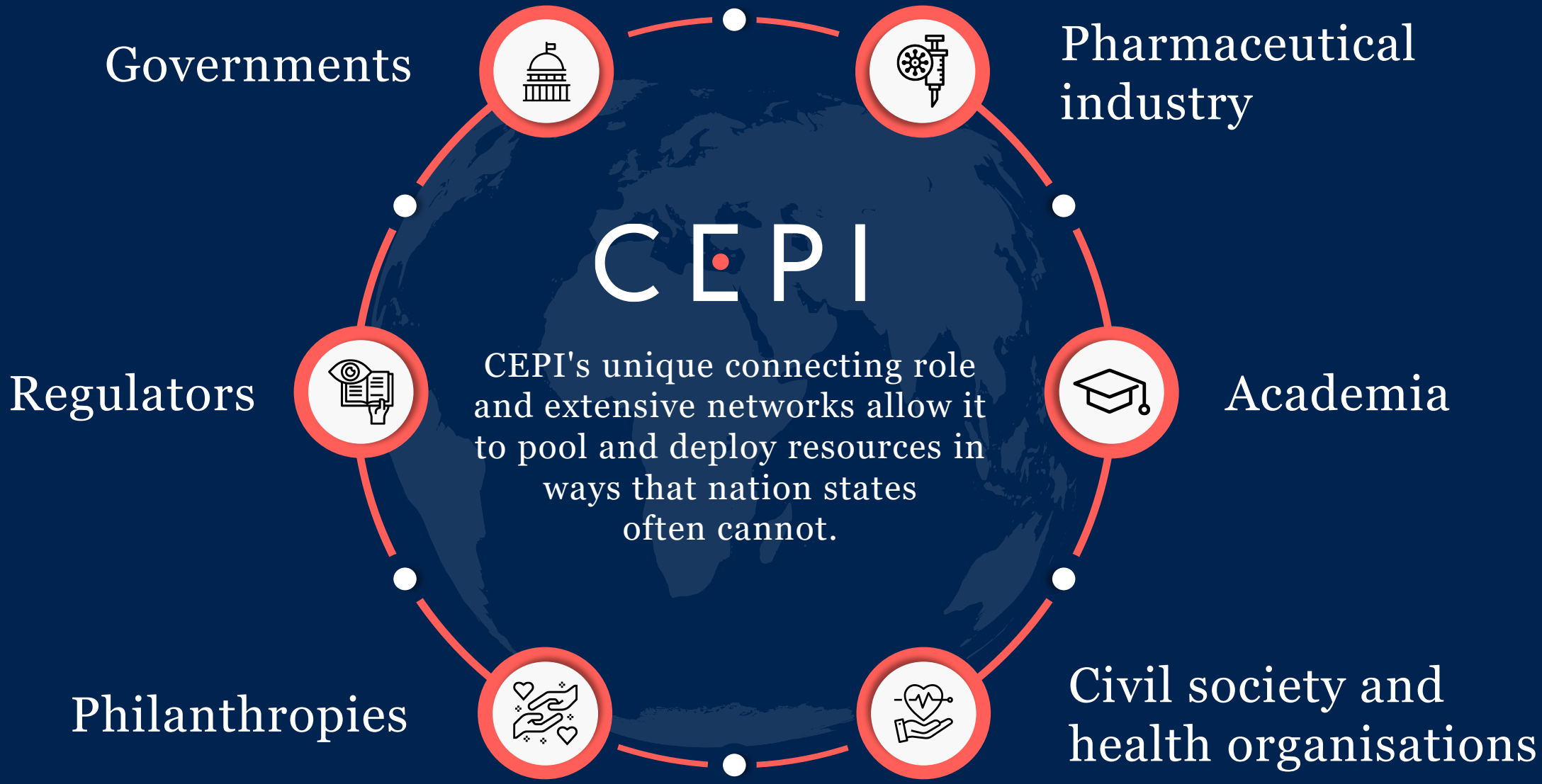
CEPI

Vaccines Licensed Without Phase 3 Efficacy Trials – A Historical Overview

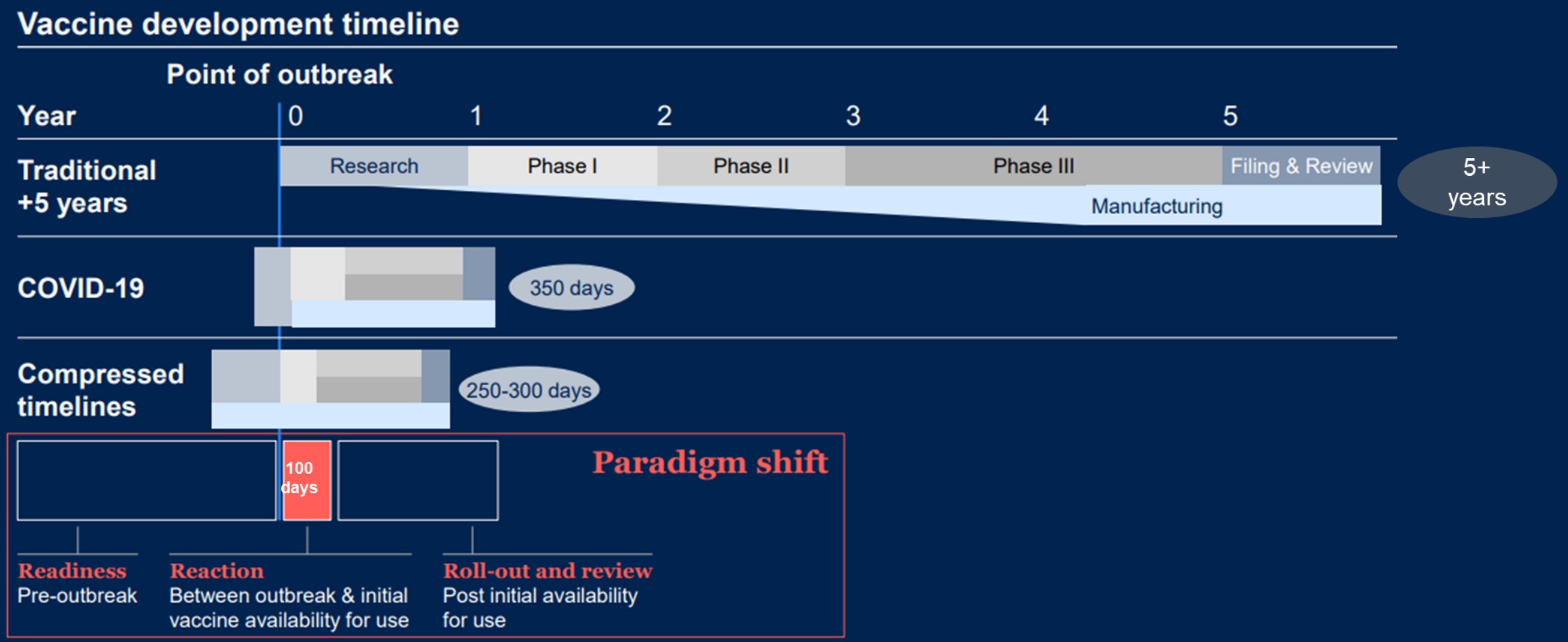
Danielle Craig, CEPI

2nd IABS REAL WORLD EVIDENCE WORKSHOP :
THE ROLE OF ALTERNATIVE APPROACHES TO PHASE 3 CLINICAL TRIALS FOR VACCINE EFFICACY AND LICENSURE

10-11 Dec 2025


Governments
Pharmaceutical industry
CEPI
CEPI's unique connecting role and extensive networks allow it to pool and deploy resources in ways that nation states often cannot.
Regulators
Academia
Philanthropies
Civil society and health organisations

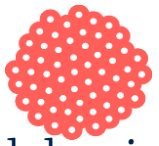
Paradigm shift towards preparedness



Is 100-days possible?

- Collaboration and preparedness is key!
- Only specific circumstances
- Requires:
  - Maximal use of prior knowledge and platform data
  - Risk-based framework for immune correlates of protection
  - Assessment of anticipated benefit-risk and high-risk populations
- Case studies support the "reason to believe"

Pandemic Flu



- pre-approved dossiers
- extensive prior knowledge

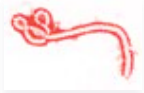
Covid

- immunobridging licensure
- utilising platform data and positive benefit risk for approval of strain adapted vaccines

Chikungunya

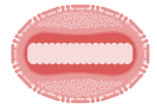
- use of correlates of protection in the absence of efficacy data

Filovirus



- use of platform data,
- bridging data across different diseases
- benefit-risk

Mpox



- use of platform safety data
- bridging data across different diseases
- licensure in paediatric population
- benefit-risk

Regulatory Requirements for Vaccine Licensure

Safety, Purity, Potency

Regulators mandate vaccines be safe, free from contaminants, and potent to ensure public health protection.

Efficacy Data Requirement

Phase 3 clinical trials provide robust efficacy data essential for demonstrating vaccine efficacy.

Biologics License Application / Marketing Application

The BLA/MAA compiles all clinical and manufacturing data required for vaccine licensure approval.

Considerations on Feasibility of Clinical Efficacy Trials

- Ethical feasibility of doing a trial
- Practical feasibility of conducting clinical trials will take into consideration these disease/condition factors:
  - Prevalence or incidence
  - Unpredictable incidence rate
  - Unpredictable outbreak locations
  - Occurrences limited to areas lacking critical infrastructure
  - Occurrences limited to areas with extraordinary threat to subject or investigator safety
- The above factors may change over time, impacting applicability of the primary use of preclinical efficacy data for a given disease/condition

Overview of regulation and guidelines enabling use of preclinical surrogate data

US FDA

- "Animal Rule"
  - Regulations became effective in July 2002 under 21 CFR 314.600-650 for drugs and 21 CFR 601.90-95 for biologics
  - Guidance document: Product Development Under the Animal Rule, October 2015 (final)
- Accelerated Approval
  - Section 506(c)(1)(B) of the FD&C Act, 21 CFR 314.500 – 314.560 for drugs and 21 CFR 601.40 – 601.46 for biologics

EMA

- Conditional or Exceptional Circumstance authorization
- Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1)

WHO

- Correlates of vaccine-induced protection: methods and implications, 2013

When is Immunogenicity used?

Clinical

- Provided a vaccine has demonstrated efficacy in clinical endpoint trial, vaccine effectiveness can be inferred through immunobridging to:
  - Extend the indication to a different age or other demographic group
  - Authorize a new a formulation or antigen composition of the same vaccine
  - Authorized an alternate dose or dose schedule
  - Evaluate immune interference with concomitant administration with other vaccines
  - Serve as an active comparator to authorize new vaccines within the same platform and, if justified, across platform

→ **Clinical**

Pre-clinical

- When efficacy cannot be shown through a Ph3 efficacy study, a surrogate may be used to show a **reasonable likelihood of clinical benefit**

→ **Clinical**

CEPI

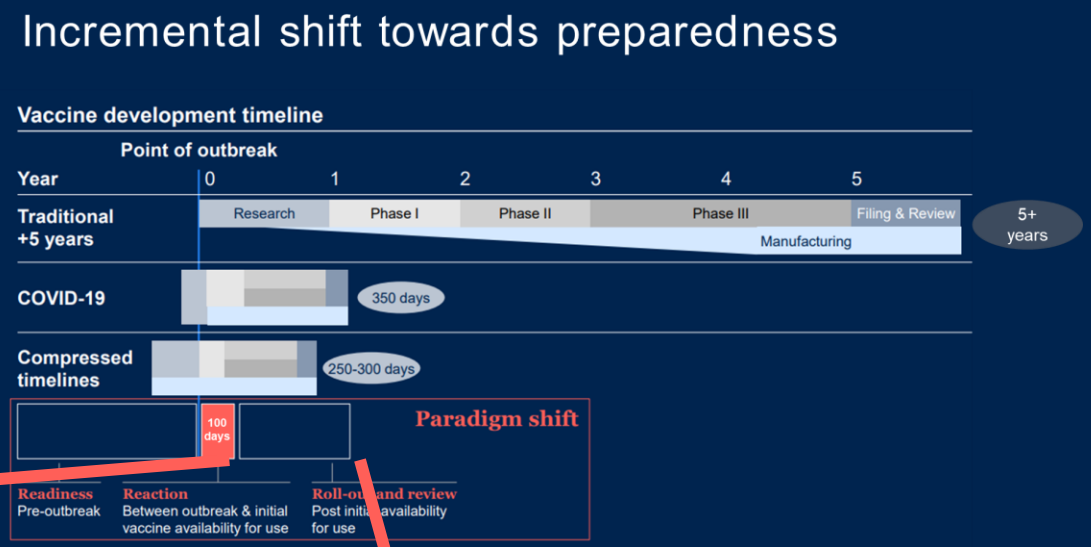
Slides courtesy of Jenny Hendriks

Alternative Pathways to Estimate Vaccine Efficacy

Method	1) Correlate of Protection (CoP)	2) Clinical Immuno-bridging	3) *Passive transfer* followed by animal challenge	4) Animal challenge post *active immunisation*	5) CHIM and other supportive data
	CoP established	***No immune CoP established (yet)***			
Approach	• Immune biomarker **predictive of** clinical protection established allowing the assessment of sero-protection rates • No comparator vaccine necessary	• Comparing immunogenicity (non-inferiority) of candidate vaccine with established vaccine for which clinical efficacy has been established – using one (or more) biomarkers reasonably likely to predict benefit without protective threshold (same antigen / similar platform technology*)	• Animal challenge post passive transfer of different concentrations of antibodies isolated from immunised humans to establish a biomarker level that is reasonably likely to predict protection. • Proportions of subjects achieving this antibody level in clinical trials then used to estimate protective efficacy. • Animal disease model resembles human disease.	• Animal challenge post vaccination → immunological biomarker demonstrating clinical protection derived from correlation of immune response levels with protective effect in animals. • Vaccine-induced immune responses in clinical trials bridged to animal responses using that biomarker. • Animal immune response and disease model resembles human immune response and disease.	Regulators will consider the totality of data; hence other supportive data can be important… • Controlled human infection models (CHIM) → endpoint mostly *infection*, rarely *disease* but can sometimes be used for licensure e.g. cholera • Sero-epidemiological studies • Disease natural history studies
Examples where primary data source used for licensure	Polio, rabies, HBV, Influenza (based on HA antigen)	COVID-19 2nd wave vaccines & variant updates, pneumococcal conjugate (multivalency); Vaccine updates for population, schedule and #doses	Chikungunya, Japanese encephalitis	Ebola-Zaire (Janssen), Anthrax	Vaxchora cholera, CHIM Malaria, CHIM Influenza, CHIM Chikungunya, sero-epidemiological study
Comments	• Very hard to establish • Usually requires a Ph3 study and/or a comprehensive sero-epidemiological study • Vaccine-independent	• Needs to be in comparison to same vaccine (in case of valency updates) • For COVID, cross platform bridging was allowed (BIMERVAX protein vs mRNA)	Preferred approach by regulators: as it estimates the protective potential of human antibodies		• CHIM – important to use wild-type virus for challenge to increase regulatory acceptability

*) acceptability by regulatory authorities to be explored on a case-by-case basis (e.g. same antigen, different platform technology)

Connecting to the 100 Days Mission



"Next 100 days"

continues clinical development for additional populations

Additional population authorizations

real-world data generation and real-world evidence studies

Full approval