New clinical / regulatory framework: Acceleration of vaccine licensure

ARVAC, 5th and 12th June 2024

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The 100-day Mission Requires A Paradigm Shift

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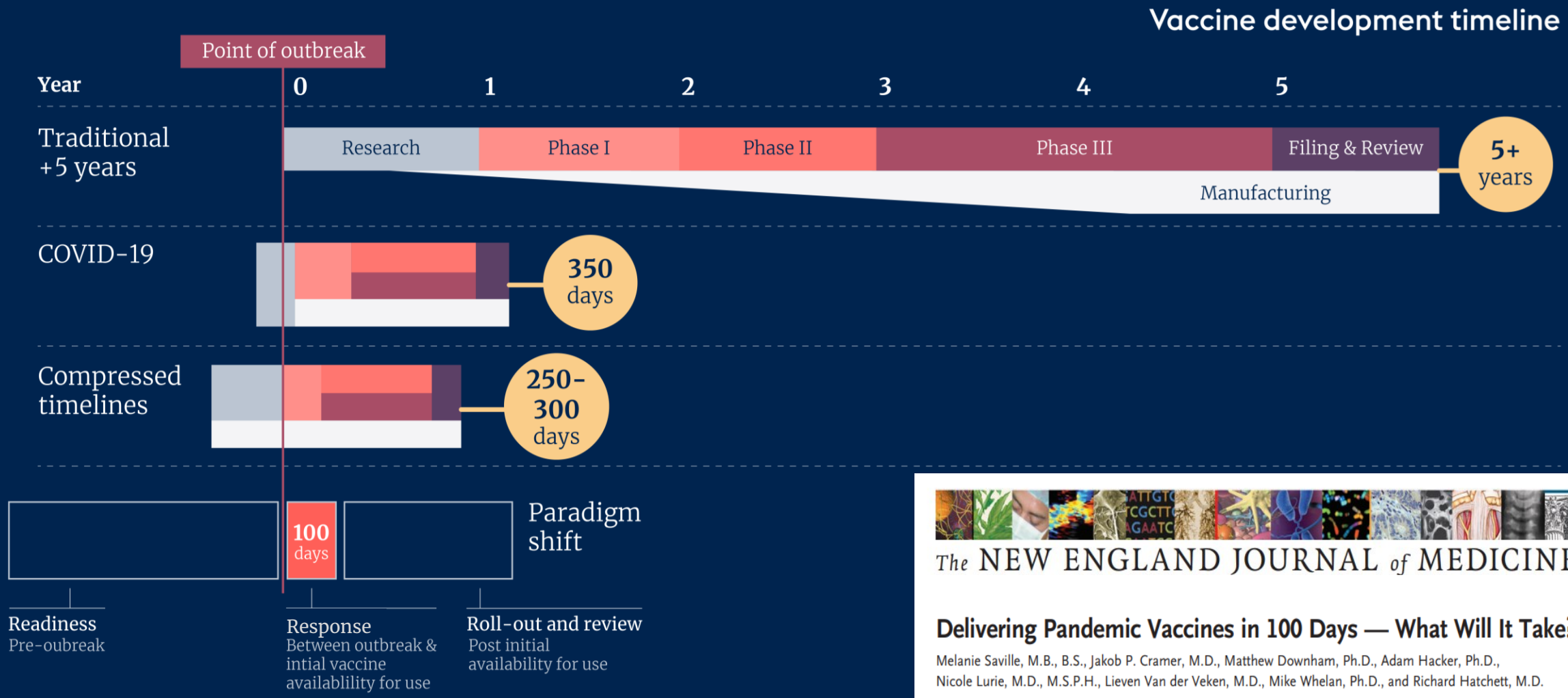

The NEW ENGLAND JOURNAL of MEDICINE

Delivering Pandemic Vaccines in 100 Days — What Will It Take?

Melanie Saville, M.B., B.S., Jakob P. Cramer, M.D., Matthew Downham, Ph.D., Adam Hacker, Ph.D., Nicole Lurie, M.D., M.S.P.H., Lieven Van der Veken, M.D., Mike Whelan, Ph.D., and Richard Hatchett, M.D.

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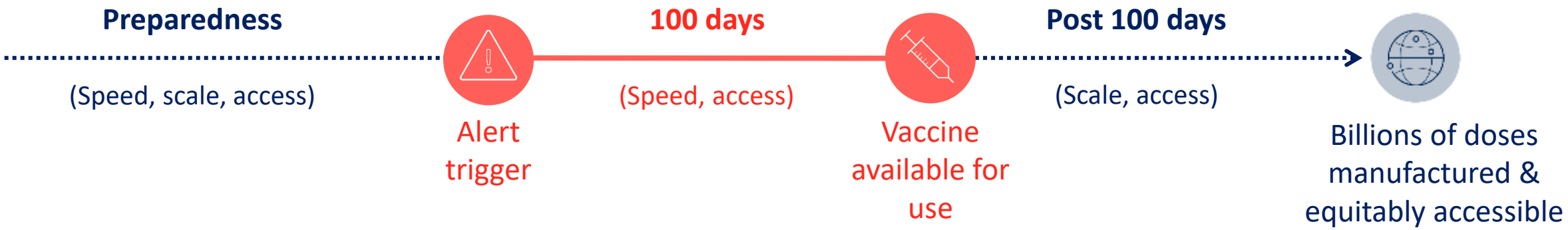
Pathway towards 100 Days Mission

→ Paradigm shift: significant front-loading in preparedness, and breaking the firewall between development and intervention



- Prototype vaccine & platform development
- Manufacturing readiness
- Enabling tools & networks

- Outbreak characterisation
- Accelerated development, manufacturing, & authorization

- Expansion of clinical evidence (clinical trials, Real World Evidence (RWE)
- Scale-out and large-scale manufacturing

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100 Days Mission: What will it take?

Creating **a library of prototype vaccines** & establishing **vaccine platforms**

Establishing **global manufacturing capacity** to make top-quality, safe, and effective new vaccines quickly

➡ **PRODUCT (vaccine)**

Getting **clinical trials and laboratory networks** ready for rapid evidence generation (incl. RWE)

Identification and implementation of **appropriate reliable tools & technology** functioning in resource-poor settings

Developing **evidence generation strategies** incl. (pre-approved mock-up) protocols

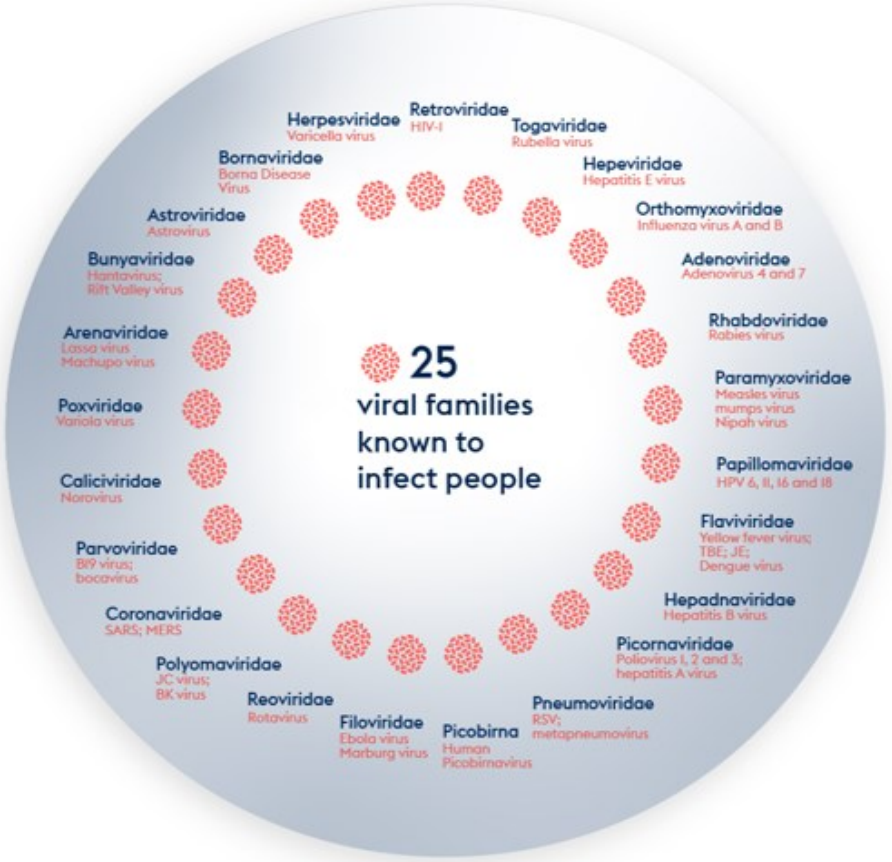
➡ **EVIDENCE (approval & use)**

Thinking out of the box**:** **Open up for flexibility re clinical-regulatory strategies**

➡ **APPROVAL (licensure / authorisation)**

Platform Technology & Manufacturing
Disease X: Vaccine Library concept

Virus Families



Disease X vaccine library for each virus family needs:

✓ **Knowledge base and Materials**

- "Tested and proven" **rapid response platforms** (e.g., mRNA, Adenoviral vector)
- State of the art **immunogen design**
- Preclinical/clinical testing for safety, immunogenicity and efficacy for a subset of viruses/designs ➔ **preclinical and clinical exemplar vaccines**
- **...**

Multiple virus families will be targeted in CEPI 2.0:

- 2 pilots already selected (**paramyxoviridae**, **arenaviridae**)
- More to be selected

Evidence Generation: Vaccine Efficacy in the Context of Epidemic Preparedness

Objective	Endpoint
Shape the epidemic curve (end, shorten, …) or the outbreak itself	→ Transmission → [Infection (= sterile immunity …)]
Impact on public health (prevent mortality, morbidity, medical care system from decompensation, …)	→ Disease

[note: theoretically, a vaccine effective against 'disease' can increase transmission (because people can be infectious but not sick)]!

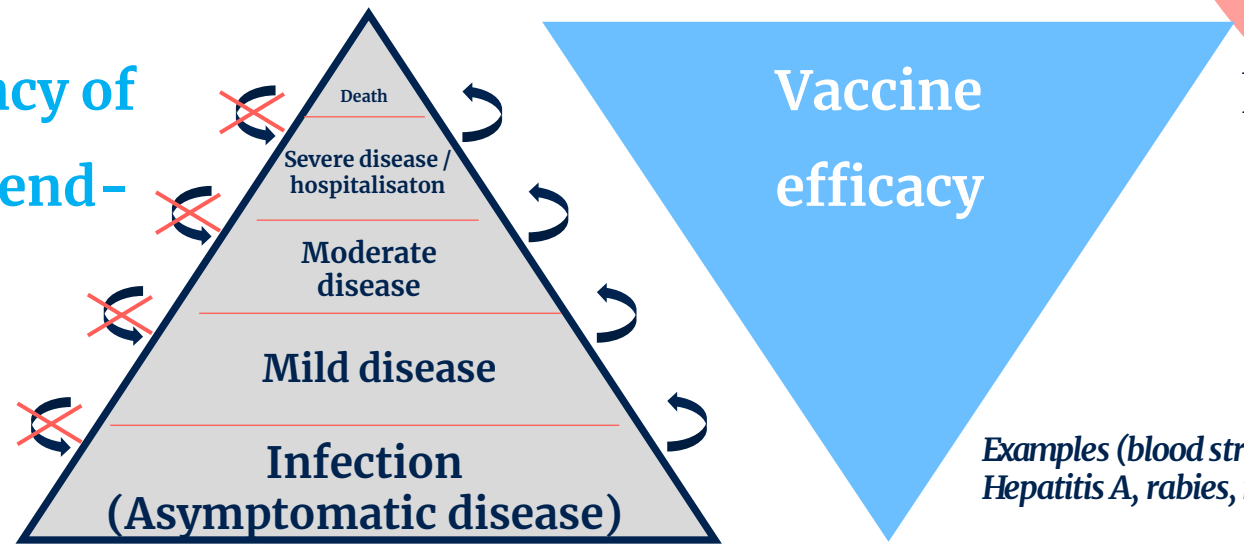
Misleading terms in this context:

- ~~'Asymptomatic disease'~~ → infection! (endpoint: infection+ / symptom-)
- ['Symptomatic infection'] → disease! (endpoint: infection+ / symptom(s)+)

What is Meant by ‘Vaccine Efficacy’ ?

A) … **DISEASE** → to reduce BoD
(Tool: classical controlled vaccine efficacy trials)

B) … **TRANSMISSION** (≠ infection!) → required to stop further spreading / end an outbreak
(Tool: household transmission trials, studies to address indirect parameters (viral load / shedding etc.), CHIM)



Examples (mucosal infections):
Influenza, COVID-19, RSV, noro, …

Examples (blood stream infections):
Hepatitis A, rabies, measles, …

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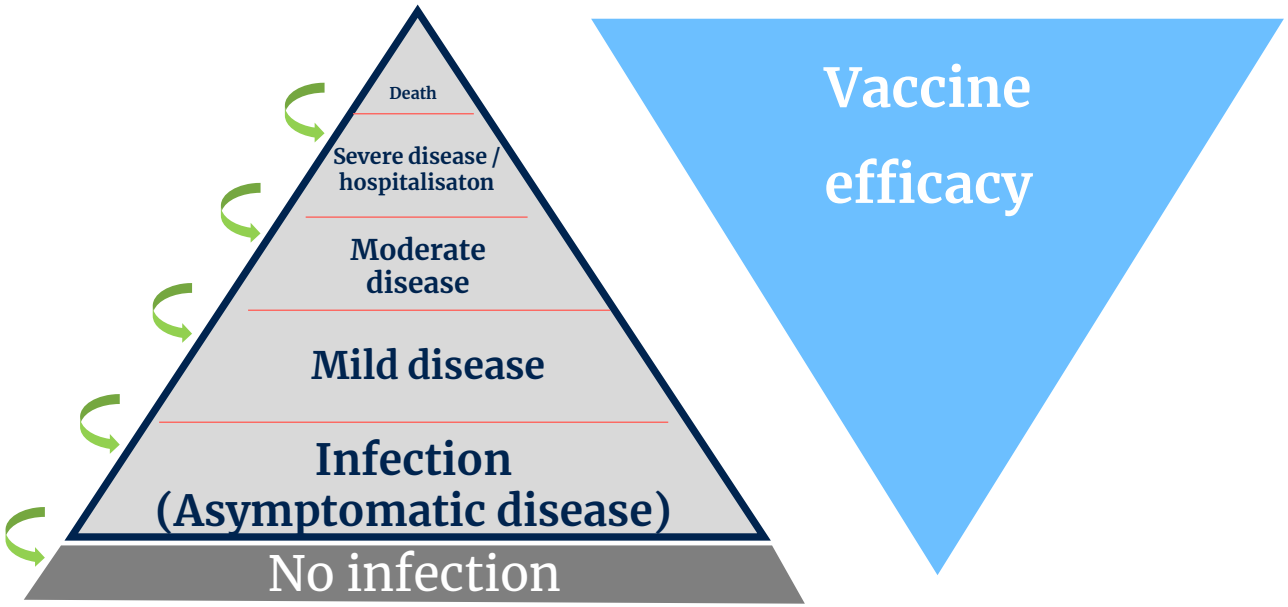
↻ = progression as well as protection (example: if you do not get infected you cannot develop symptoms etc. but a vaccine that protects against (severe) disease does not necessarily prevent against infection)

Testing Vaccines against Disease …

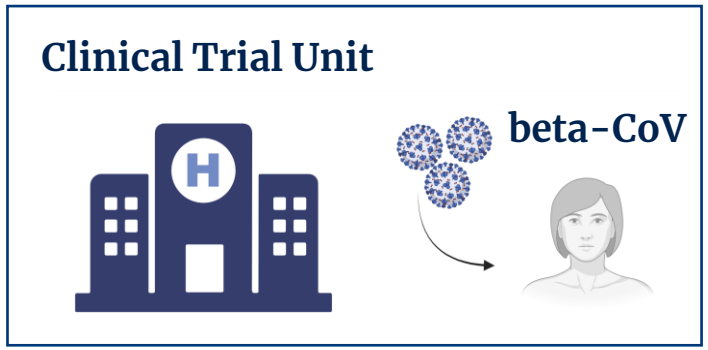
- … Combining conventional & innovative clinical trial designs tailored for specific pathogens / outbreaks
  - ✓ Conventional randomised controlled trials with adaptive case-driven trial
  - ✓ Early versus delayed ring vaccination trials
  - ✓ Etc.
- … using innovative clinical research concepts
  - ✓ For example, Burden of Disease (BoD) endpoints



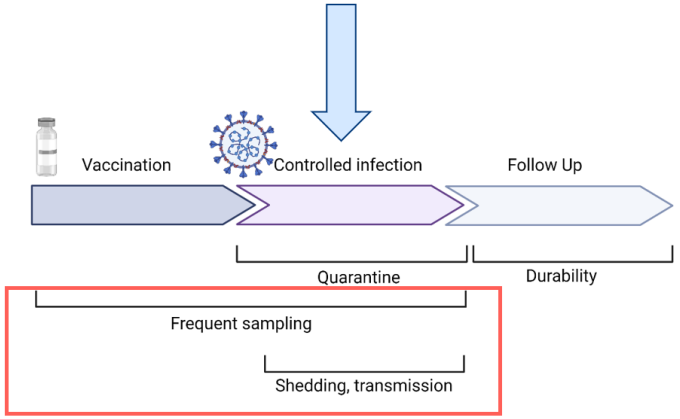
Scoring reduction in **Burden of Disease** rather than **disease y/n** counting

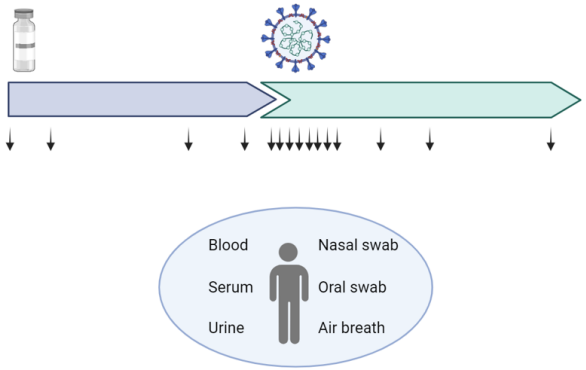
Testing Vaccines against Infection / Transmission …

- … using Controlled Human Infection Models (CHIM):



- CHIM offer possibility to analyse vaccine-induced mucosal immune responses (incl. potential CoP)
- CHIM offer possibility to analyse vaccine efficacy against infection / transmission
- CHIM may open new options for the regulatory approval of novel vaccines (e.g. intranasal)
- CHIM can be used to compare efficacy of multiple vaccine candidates and select the most promising one





- … via innovative field vaccine efficacy trial concepts (incl. household transmission trials etc.)

Testing Vaccines against Disease, Infection and Transmission

FDA Definition [US FDA; August 2023]

- **Real World Data:** data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- **Real World Evidence:** clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD

- **Phase 4**: "*These trials are done after a drug has been shown to work and has been licenced.*" [https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/]

  Phase 4 trials aim to find out:

  - ✓ more about the side effects including the rarer side effects and safety of the drug
  - ✓ what the long-term risks and benefits are
  - ✓ how well the drug works when it's used more widely for people not included in the phase 3 trial

New vaccine / CEPI's 100 DM: Phase 2 → Phase 4 (RWE) ?? … will not work in every outbreak scenario!

We cannot use conventional terms and approaches to do something (completely) new

Evidence Generation: Before / After Licensure …

RCTs versus RWE

Evidence generation on:

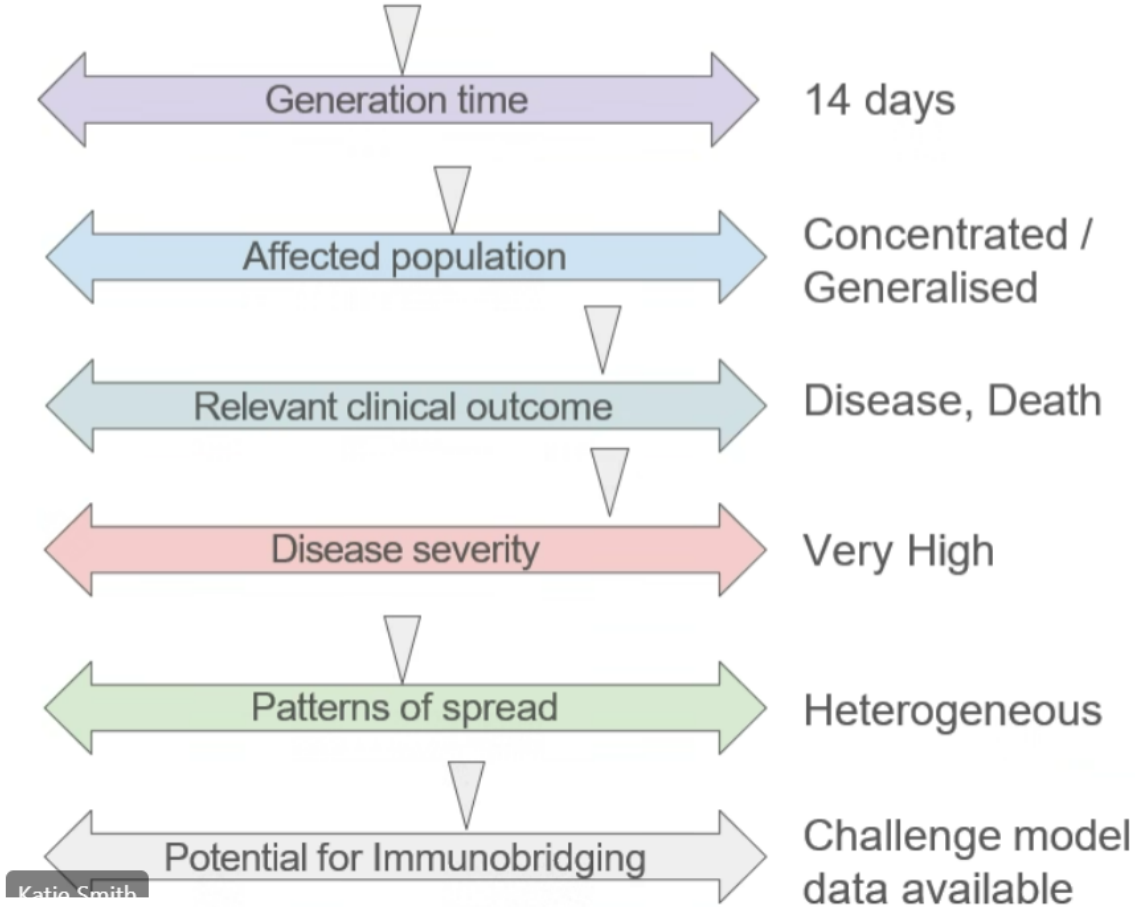
1. Vaccine Efficacy (= stat. significant evidence on **PRESENCE** of vaccine efficacy):
   - … via RCTs = conventional controlled vaccine efficacy trials
   - … via protective immune response: CoP
   - … via RWE (='Real World *Effectiveness*')

2. Vaccine Safety (= stat. significant evidence on **ABSENCE** of safety-related risks):
   - … via RWE only

   (RCTs can only clarify if a vaccine is unsafe → exclude a relatively high frequency of safety-relevant events)

Multiple Factors Determine Clinical Trial Design

Example: Nipah transmission / disease



	iRCT	cRCT	2-stage	Ring
Sample size				
Duration				
In-trial deaths				
Endpoint 1				
Endpoint 2				
Score	15	17	18	70
Ranking	4	3	2	1

low medium high

AI ...

PREpare using Simulated Trial Optimisation (PRESTO): CEPI-funded programme at the Pandemic Science Institute, University of Oxford

Immunobridging: How can we identify a Correlate of Protection (CoP)?

FAQ.
Examples

Do we have validated and robust assays?

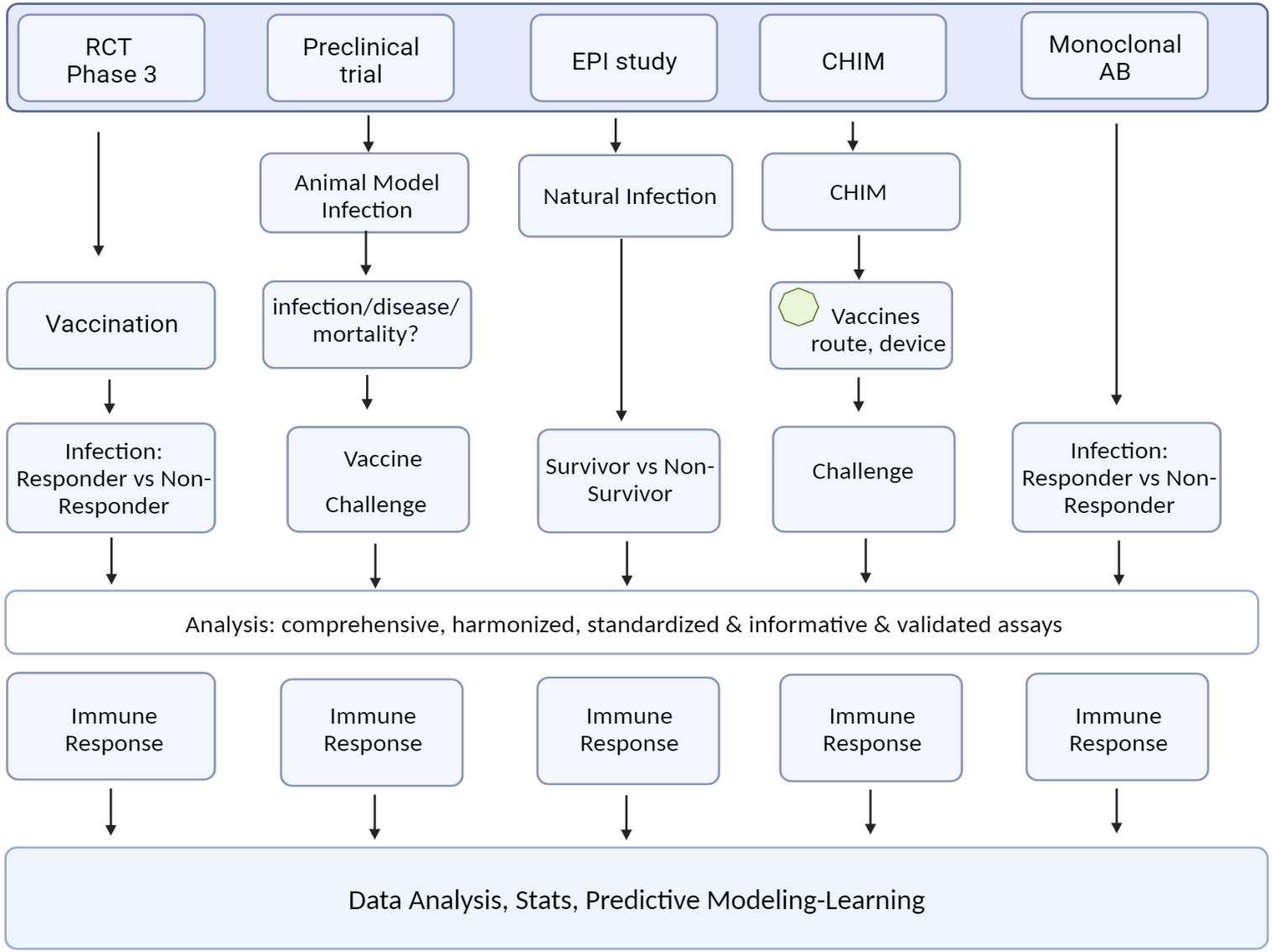
What do we know about protective immunity

Do we have samples with an adequate quality?

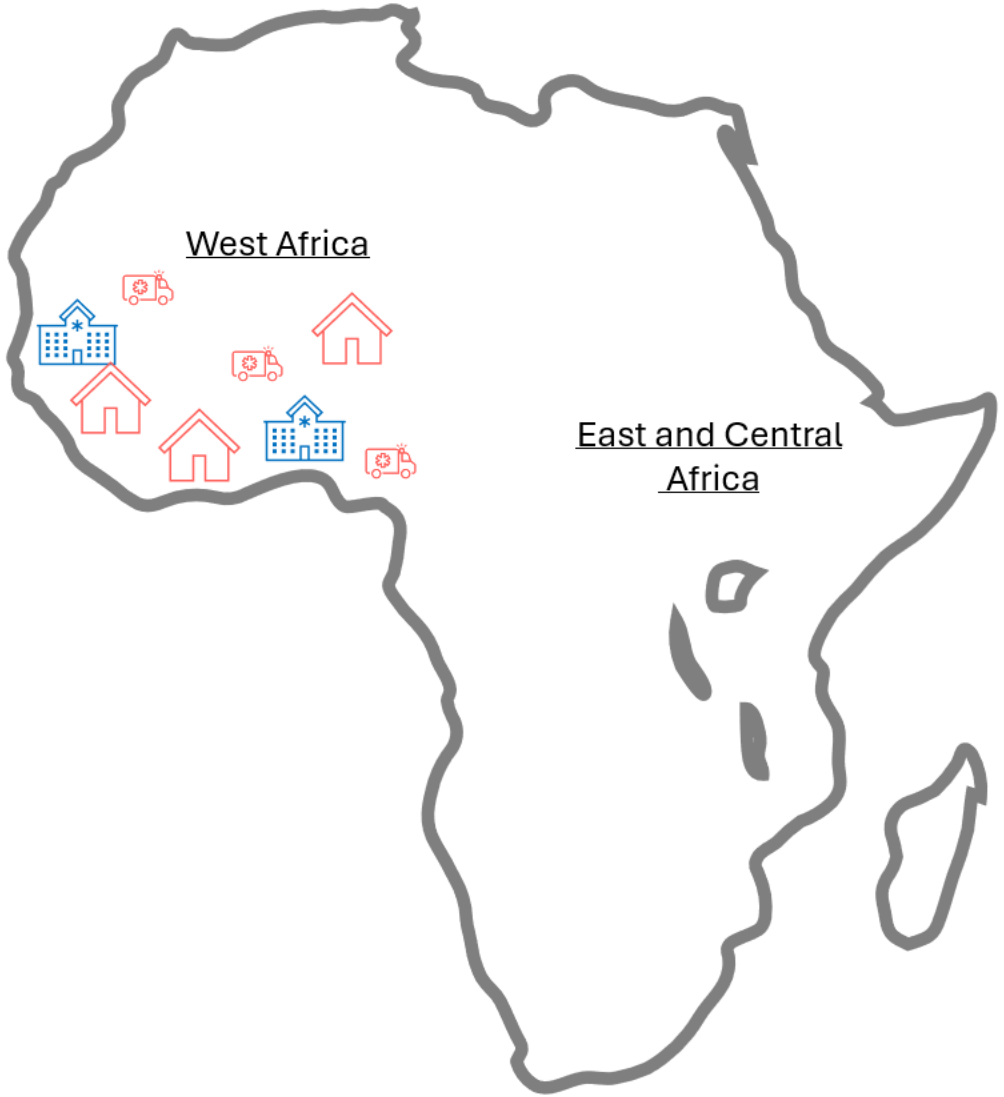
Do we have adequate animal models?

Which clinical trial design is adequate?

What data package would regulator accept?



Research Preparedness: Re-thinking Clinical Trial Networks



Africa CDC

Tier 1

Africa CDC - HUB

- as part of Africa CDC's Execution Roadmap
- according to ACDC selection criteria

Tier 2

Clinical Trial Site

- supported by CEPI's Research Preparedness Program
- based on ACDC selection criteria
- ensure presence of CEPI's priority pathogens in the region

Tier 3

Mobile Elements / Clinical Trial Units

- supported by CEPI's Research Preparedness Program

Innovative Tech & Tools in Clinical Trials

Site Access/Data Collection	Subject recruitment and retention	Local general logistics
How much direct access to sites and data will we have; in person or remote? Internet connectivity impact?	**How to identify the applicable patients and to mitigate retention problems?**	**How to solution for the logistical needs in case of closed borders? Remote areas, how do we reach them?**
• Direct Data Capture, eDC • Direct EMR access • Secure document sharing • IRT and Mobile IP review • eCOA, ePRO • CTMS • eISF • eTMF	• eConsent with or without video • Connected devices • Decentralized Trial solutions/remote patient visits • Patient facing communication platforms • Iris scanners	• Internet capabilities/Satellite uplink • In country storage of clinical supplies and IP vs import • Lab strategy central/local • Tablet based data collection vs cloud based • In time delivery to epidemic/pandemic hotspots • Mobilization strategy

EMR = electronic med. Record; IRT = interactive response technology; IP = Internet Protocol; CTMS = clin. trial management system; ISF = investigator site file

Innovative Tech & Tools in Clinical Trials

Site Access/Data Collection	Subject recruitment and retention	Local general logistics
How much direct access to sites and data will we have; in person or remote? Internet connectivity impact?	**How to identify the applicable**	**How to solution for the logistical needs in case of closed borders? Remote areas, how do we reach them?**

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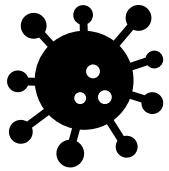
EMR =
system; ISF

Artificial Intelligence will catalyse this evolution

- Transforming start-up timelines
- Fostering diverse and patient-centric recruitment,
- Facilitating faster and meaningful data analysis (inc. safety signal detection
- Enabling more streamlined trial processes and faster decision-making

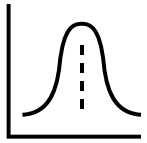
Different outbreak scenarios may have different response timelines



Pathogen

(known vs unknown)

✘



Scale

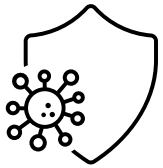
(small outbreak to pandemic)

✘

Severity

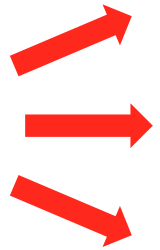
(mild to severe)

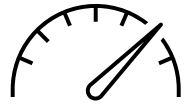
✘



Transmissibility

(low to high)





Wide range of response scenarios

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Regulatory Pathways

Vaccine licensure / authorisation

A) Phase 1 → Phase 2 → Phase 3 → Phase 4 / RWE

Conventional field vaccine efficacy trial

B) Phase 1 → Phase 2 → Phase 3 → Phase 4 / RWE (!)

… to immunobridge
… to supplement the safety database

CoP

… e.g via passive transfer animal studies

C) Phase 1 → Phase 2 → Phase 3 → Phase 4 / RWE (!)

CoP

CEPI's 100 DM: pre-licensure evidence generation based on **prototype vaccines**

Similar to influenza: Product-specific evidence generated only **after starting to use it**

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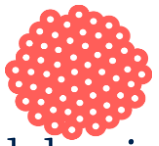
CEPI 2.0: Is 100-days possible?

- 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

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