Strategies to accelerate vaccine approval and de-risk investments

Controlled human infection models & correlates of protection

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What is the problem?

The problem: Vaccine development can stall without feasible pathway for development.

- RCTs are not always feasible and alternative approaches to licensure need to be considered
- Limited funding available for phase 3 studies

Situations include where:

- **Disease incidence is low** e.g. Nipah – 516 years and over 163,000 vaccine doses under current epidemic conditions.
- **Large trials are required** e.g. maternal GBS vaccine to prevent neonatal diseases: 80K pregnant women
- **Outbreaks of EIDs are unpredictable in size and location** e.g. Lassa, Ebola Sudan
- **Unpredictable market demand and return on investment** fail to attract necessary investment e.g. TB / AMR high risk pathogens)

Supporting development of tools such as HIS and discovery and use of correlates of protection has the potential to provide a pathway to licensure and reduce time and cost of phase 3 testing.

Human Infection Studies

Human Infection Studies – Overview

Goals of Programme

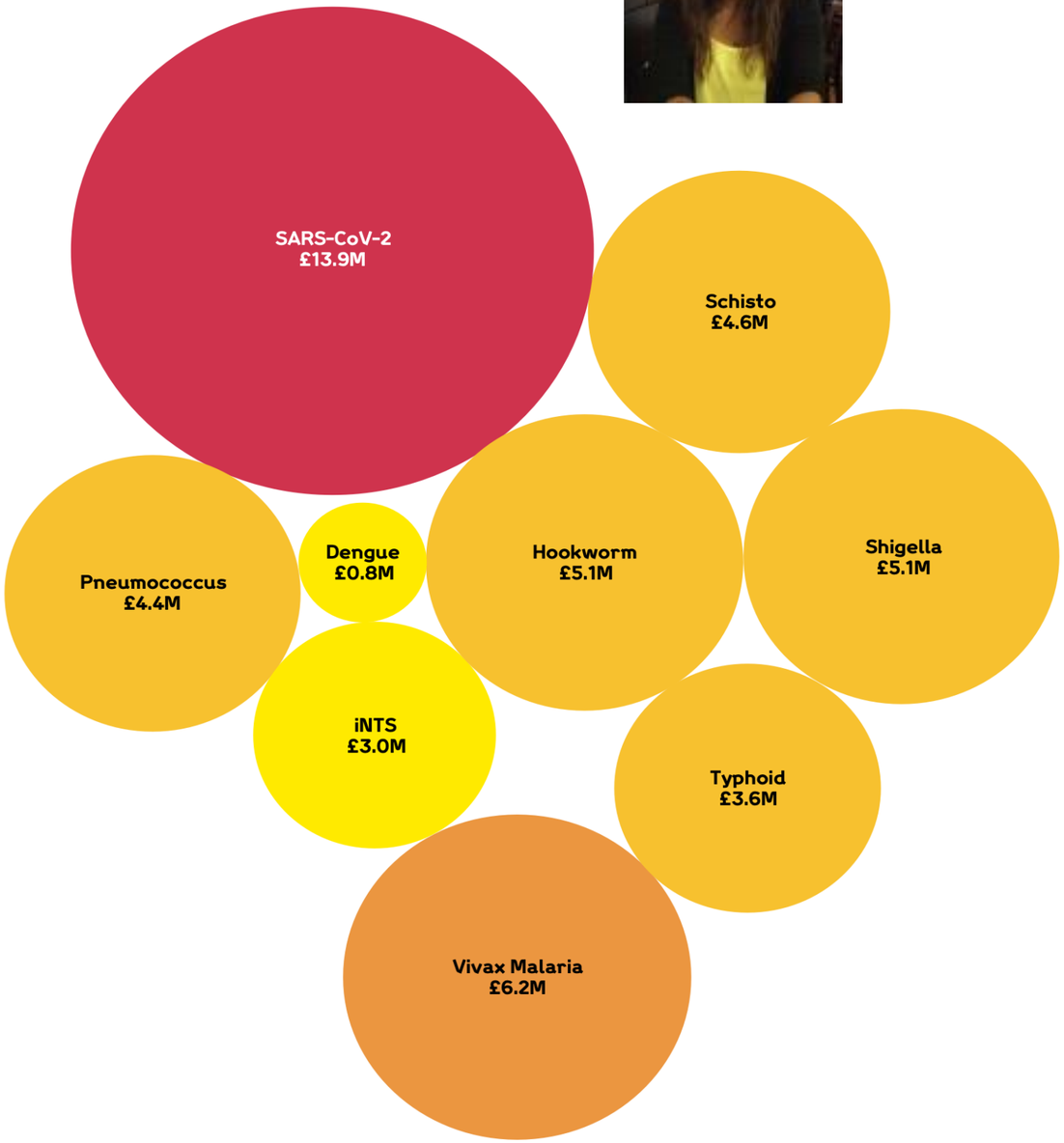
Challenge studies are effectively used to assess vaccine candidates in target populations in endemic areas

Rational harmonisation of challenge protocols and comparability of datasets is achieved

Functional challenge study sites are established in endemic areas

Portfolio of funded sites:

SARS-CoV-2- United Kingdom
***Plasmodium vivax* – Thailand**
***Pneumoccocus* – Malawi**
Typhoid – India (supportive only)
Dengue – Vietnam (supportive)
Hookworm – Brazil (stopped)
***Shigella* – Kenya**
Schistosomiasis – Uganda
Cholera – India (redacted)
NTS - United Kingdom



HIS in de-risking clinical development of an RSV vaccine

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Vaccine Efficacy in Adults in a Respiratory Syncytial Virus Challenge Study

Schmoele-Thoma B et al. DOI: 10.1056/NEJMoa2116154

CLINICAL PROBLEM

Respiratory syncytial virus (RSV) can cause severe disease in older adults, especially those who are frail or have coexisting conditions. However, no RSV vaccine has been licensed.

STUDY

Design: A phase 2a, single-center, randomized, double-blind, exploratory study tested a bivalent RSV prefusion F (RSVpreF) candidate vaccine in healthy adults 18 to 50 years of age.

Intervention: 70 adults were randomly assigned to receive 120 μg of nonadjuvanted RSVpreF vaccine or placebo intramuscularly; 62 of the participants were challenged 28 days later with intranasal RSV A Memphis 37b (4.5 $\log_{10}$ plaque-forming units), and 60 were observed for 12 days, with follow-up visits at 28 days and 155 days. The per-protocol primary end points were reverse-transcriptase–quantitative polymerase-chain-reaction (RT-qPCR)–confirmed detectable RSV infection on 2 or more consecutive days with at least one clinical symptom, the total symptom score from day 1 to discharge, and the area under the curve (AUC) for the RSV viral load in nasal-wash samples, measured by RT-qPCR, from day 2 after challenge to discharge.

RESULTS

Efficacy: Vaccine efficacy according to RT-qPCR–confirmed detectable RSV infection was 86.7%. The geometric mean sum of the total symptom scores and the median AUC for the RSV viral load were lower in the vaccine group than in the placebo group.

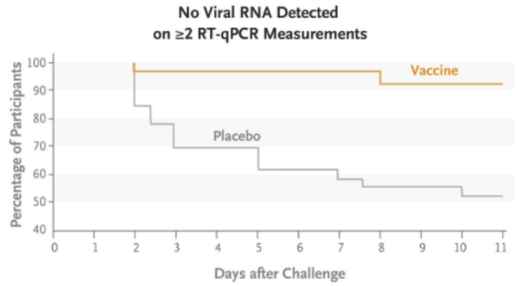
Safety: Local reactions and systemic events (most often fatigue or tiredness) within 7 days after injection were more common in the vaccine group and were mild. One vaccine recipient had temporarily enlarged submandibular lymph nodes, starting on day 26 after vaccination, that were considered to be related to the vaccine.

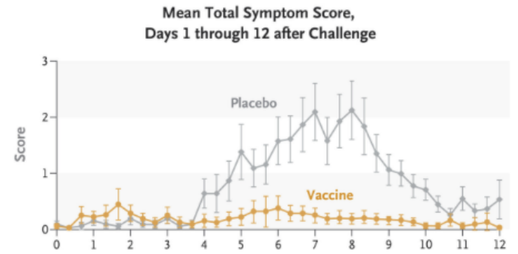
LIMITATIONS AND REMAINING QUESTIONS

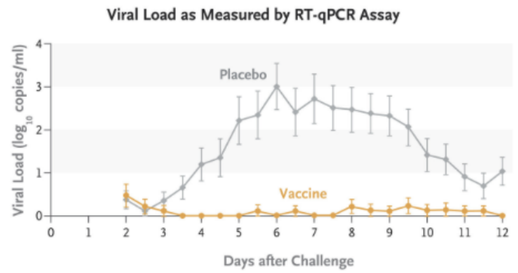
Study limitations include the following:

- Vaccine efficacy was tested with a challenge rather than with real-world virus exposure.
- The number of participants was small.
- Trial participants were prescreened for low RSV-neutralizing titers and were younger than the population at risk for severe RSV infection.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In this challenge study, the candidate RSV vaccine RSVpreF was effective against symptomatic RSV infection and viral shedding, with no evident safety concerns, in young and middle-aged adults.

WHO PDVAC recommendations

For bivalent typhoid-paratyphoid vaccine:

Typhoid: non-inferior immunogenicity to licensed vaccine

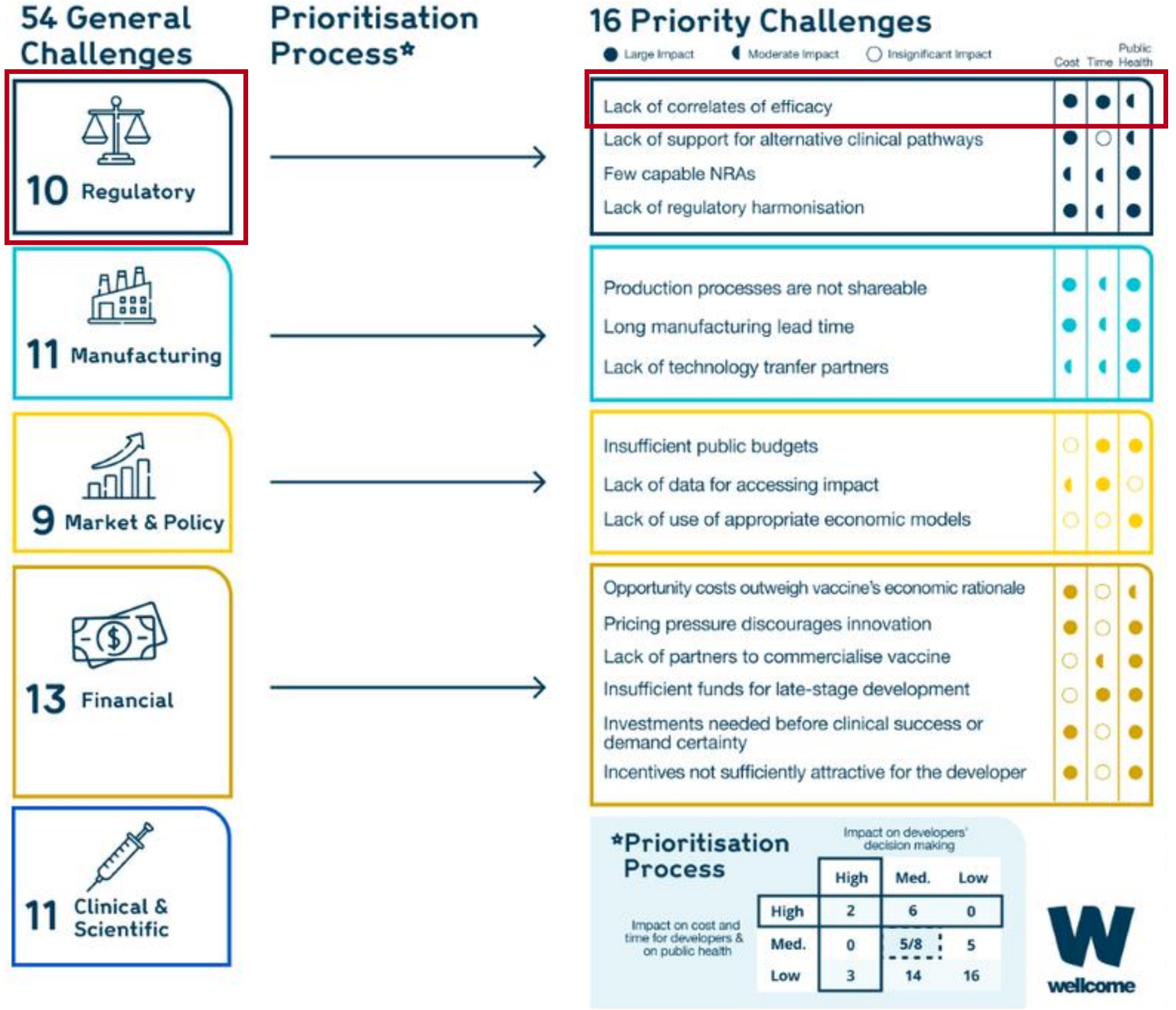
Paratyphoid:

- Protective efficacy in CHIM (adults)
- Immunogenicity in endemic settings (children)
- Vaccine effectiveness in post-approval study

Correlates of Protection

Prioritisation of identified challenges

Challenges identified by vaccine developers were prioritised according to impact on cost, time and public health impact.



Wellcome CoP workshop, Sept 2022

1. Our working definition was that **CoP are immune responses associated with protection (predictors of efficacy)**.

2. CoPs have multiple roles to play at various stages in vaccine development.

3. **Standardisation** of assays, protocols and sampling is critical to facilitate correlates discovery and their use of CoPs in licensure decision-making.

4. CoPs studies often focus on serum biomarkers: **gaps in understanding** (e.g. T cells and mucosal immunity).

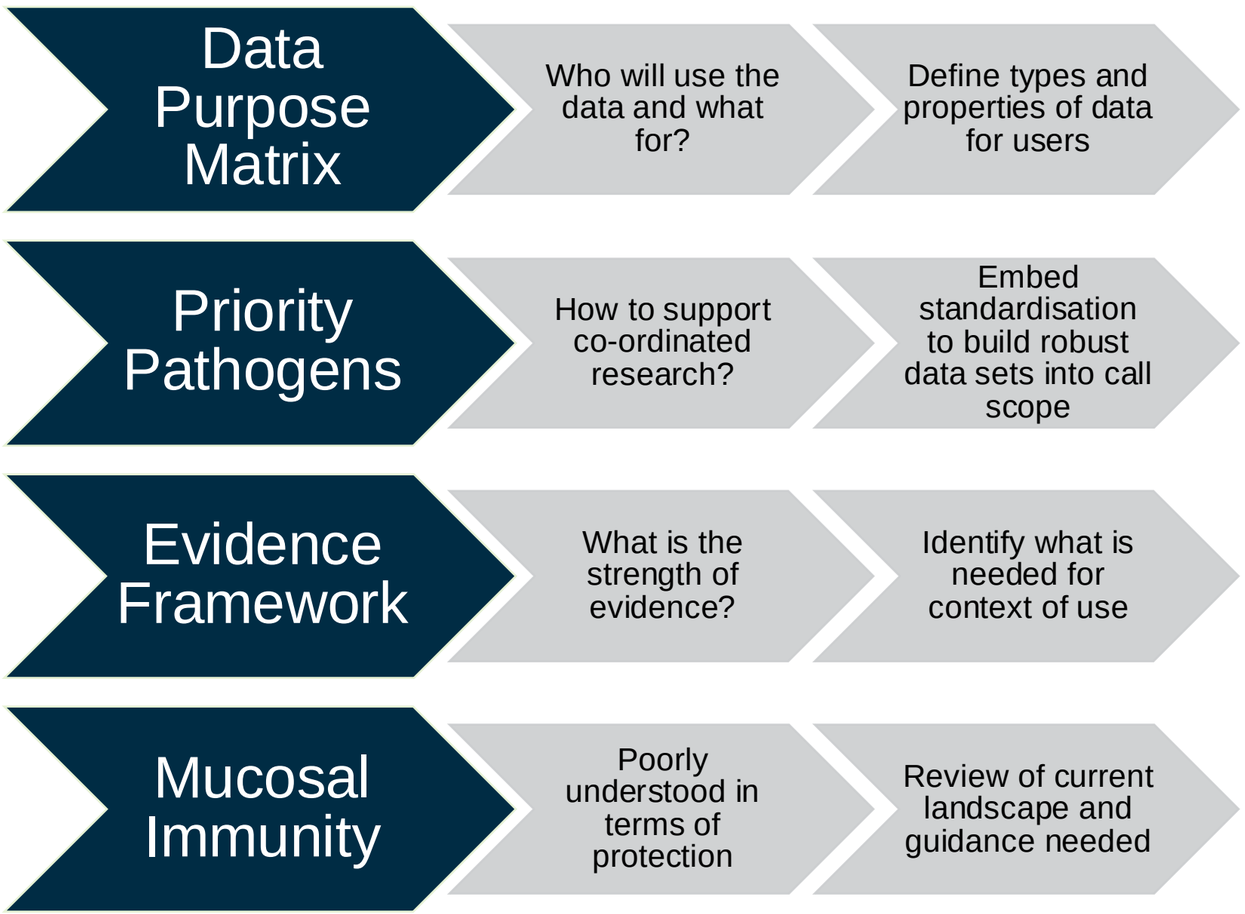
5. **Collaborations** are required to advance CoPs for specific pathogens/indications.

6. **Regulators** are willing to consider CoP data in licensing applications, as part of a wider data package, case-by-case.

7. A rigorous **framework** is needed to evaluate the strength of evidence supporting use of a biomarker as a CoP.

8. The evidence needs of policymakers extend beyond those of regulators.

Correlates of Protection Workshop Outputs



Workshop report
https://doi.org/10.1038/s41541-024-00872-6

Funding call to generate biomarker data from multiple sources

Evidence Framework to evaluate biomarker data packages

Mucosal landscape to improve understanding of mucosal responses

Data Purpose Matrix for CoP Data

	Vaccine objective		
	Clinical development	Regulatory and licensure	Vaccine policy and introduction
Key stakeholder / audience **User of the CoP data**	Clinicians Epidemiologists, microbiologists, immunologists Statisticians Manufacturers / Developers (pharma and biotech, PPPs) Funders and donors Consortium members	NRAs WHO Vaccines Pre-Q Manufactures / Developers (pharma and biotech, PPPs) Funders and donors	WHO, SAGE, GNN RITAGs NITAGs Ministries of Health / Finance Industry / manufacturers
Data purpose: **What do the stakeholders use the CoP data for?** **What decisions are made using the CoP data?**	Identify correct/best choice of vaccine antigen based on pathogen biology Confirm lot-to-lot consistency Confirm lack of interference in concomitant use Provide early insight into efficacy Enable design of go/no-go criteria for Ph1 to determine progress to Ph2 De-risk or down-size phase 3, Extend indication Validate success of tech transfer Inform formulation, schedule and dose.	To establish biomarkers for Immunobridging, and infer effectiveness in: - Different age groups or demographic groups, - Change of dose, regimen or need for boosters - Change in formulation - Bridge manufacturing changes - Establish lack of interference in concomitant vaccine use Immunobridging of a new product by comparing immune responses to a licenced comparator Inclusion of additional strains to a licenced product without efficacy data Essential part of data package where efficacy studies are not ethical or feasible Definition of endpoints for phase IV evaluation if required.	To reduce delays in vaccine introduction by establishing immunogeneicity in local populations where direct efficacy data is not available. Inform design of phase 4 studies to gather safety and effectiveness data in local populations and link to immunogenicity (and validate correlate). Prioritising limited vaccine stocks to key target groups Refining dosing or boosting regime Determine susceptibility of population to disease where a threshold is established. duction

https://doi.org/10.1038/s41541-024-00872-6

Funding call to accelerate vaccine development through identification of correlates of protection

Correlates of Protection Funding Call

High-level goals:

1. **To accelerate development of vaccine candidates in early phase by generating evidence to support decision-making for diseases where new vaccines are needed in LMIC's**
2. **To establish co-ordination between stakeholders to develop standardised approaches to data collection and analysis**

Scope

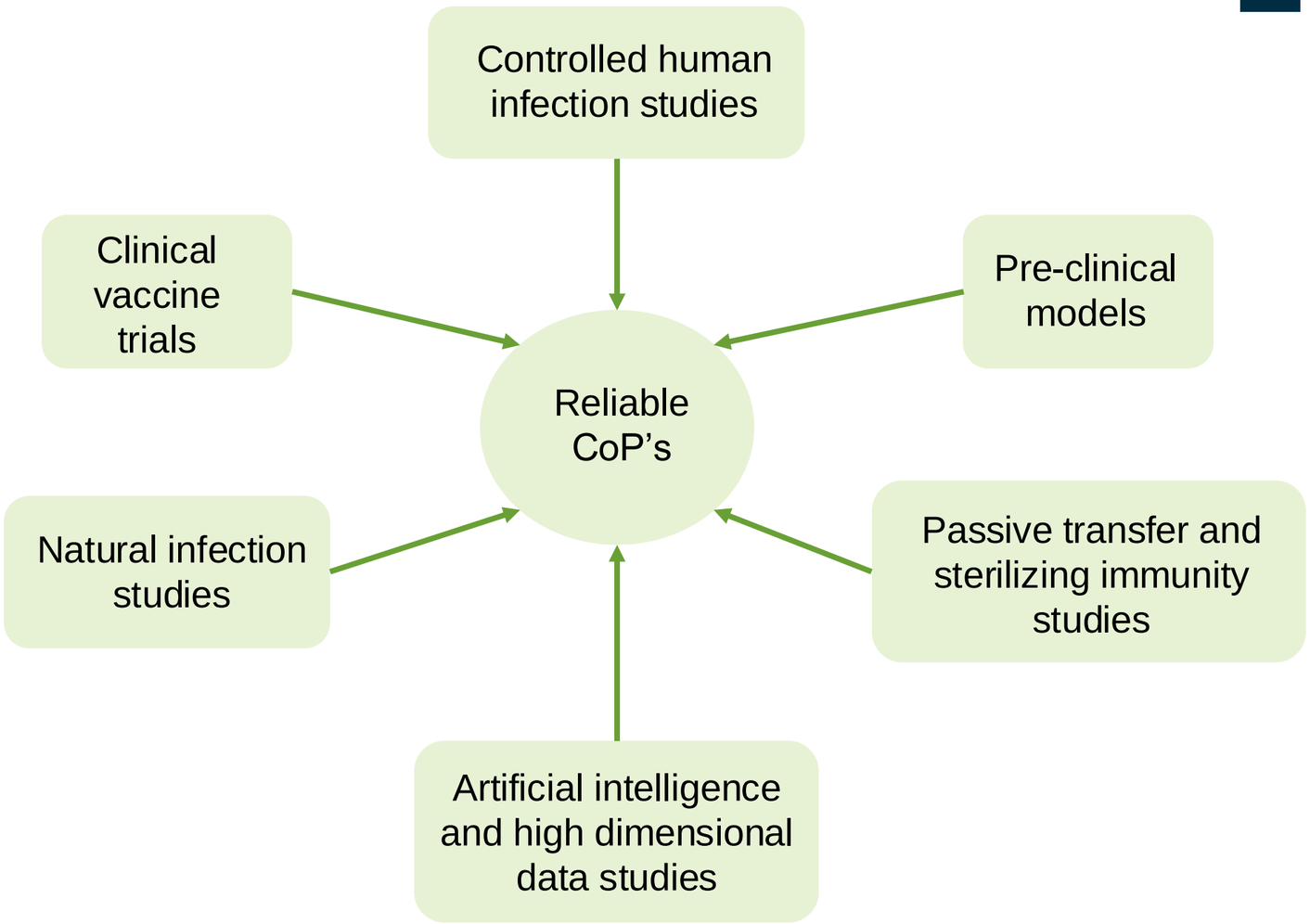
- Generate data to discover, establish or validate correlates of protection for defined diseases that will support clinical development decision-making of new vaccines suitable for target populations.
- To harmonise approaches to data analysis to enable comparison of data from different sources through the use of standardized reagents, assays protocols and analysis technologies

Eligibility
- Must include co-applicants from a disease-affected country
- Any study design including both prospective and retrospective data collection

Disease scope
- High priority in AFRO and SEARO regions
- Viral: Lassa, Marburg, Sudan Ebola, Nipah, RVF
- Non-Viral: Paratyphi A, iNTS, GAS, Schistosomiasis, ExPEC, Shigella

Standardisation support:
- Budget for development and testing of standards, assays and analysis plans
- Convening of stakeholders to align an analysis

Research to identify correlates of protection



Co-ordination, Collaboration, Consistency, Communication

Based on Wang et al, 2024.
https://doi.org/10.1038/s41541-024-01004-w

Impact

Range of pathogens for which vaccines are in development but not licenced :

- 4 non-viral – Paratyphi A, Group A Strep, Shigella, invasive Non-Typhoidal Salmonella
- 4 viral – Marburg, Lassa, Nipah, Rift Valley Fever

Diversity of approaches: HIS, sero-epidemiology and incidence data, survivor cohorts, passive transfer of humoural immunity, vaccine studies and animal models.

Assays: Cellular and humoural immune responses including functional responses, assay transfer and validation, systems serology.

Diversity of leadership: 6 female PI's and 2 male PI's, 2 female PI's based in Africa.

Relevance to vaccine development: Proposals include samples from 9 candidate vaccines.

Filling evidence gaps: samples sourced and research conducted in 18 countries, including 12 disease affected LMIC's and 6 HIC's.

Evaluating biomarker data packages

Strategies for licensure including biomarkers

Gold standard	Well-established biomarker (with threshold)	Biomarker reasonably likely to predict clinical benefit (with previously licensed vaccine)	Biomarker to compare immune responses (with previously licensed vaccine)	Biomarker reasonably likely to predict clinical benefit (no previously licensed vaccine)
Randomised, double blind, placebo-controlled efficacy trial is possible and feasible; CoP not needed for licensure but should be identified in phase 3 clinical and phase 4 effectiveness studies.	**Clinical efficacy trial is not possible or feasible & scientifically well-established biomarker (with threshold) to predict protection that can be reliably measured in a validated assay is available**	**Controlled clinical trial comparing immune response of candidate vaccine compared to immune response of licensed vaccine using a biomarker thought reasonably likely to predict clinical benefit but not robustly established**	**Absent an agreed upon serological cut-off or threshold value, an immune response associated with protection and proportional to other protective components of the immune response, compared between candidate and licensed vaccines**	**Controlled clinical trial using a biomarker thought reasonably likely to predict clinical benefit but not robustly established, *in the absence of a previously licensed vaccine with demonstrated effectiveness***
Examples: RSV, TB, Dengue Malaria, Shingles	**Examples: Hep B**	**Examples: Influenza**	**Example: Next Gen COVID-19**	**Examples: Group B streptococcus Group A Streptococcus (ARF/RHD) Nipah**

Based on Gruber et al., 2023

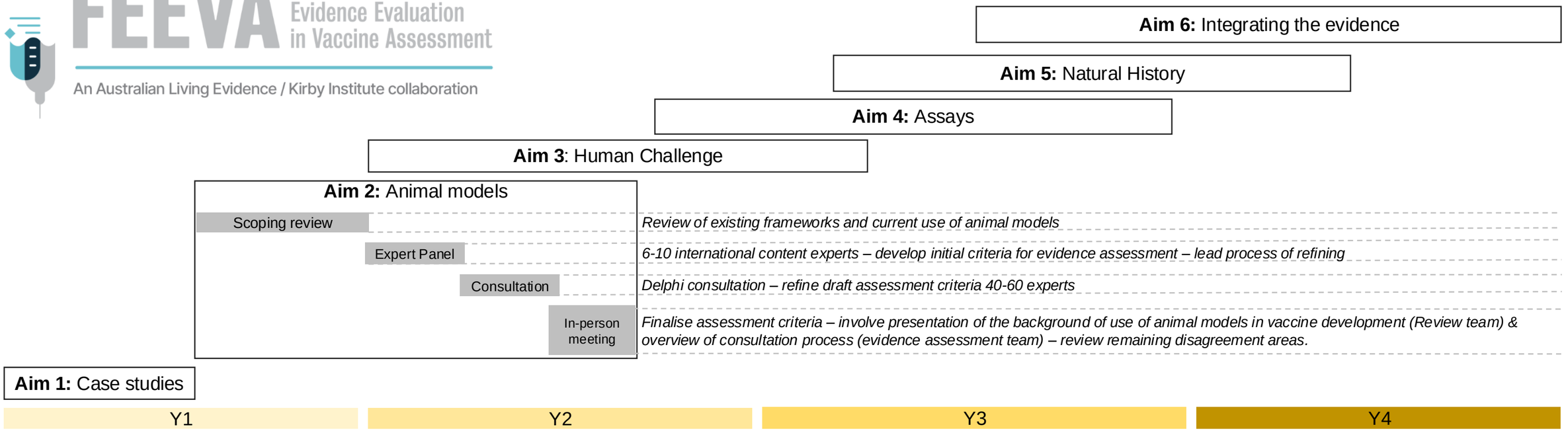
The problem statement

What constitutes sufficient evidence to arrive at a biomarker that can be used to infer vaccine effectiveness where efficacy trials are not feasible and a comparator vaccine is not available

Whereas globally accepted standards exist for assessment of candidate vaccines by clinical efficacy (e.g. RCTs), no globally accepted standards exist for assessment of predictive biomarker data packages (e.g., immune responses) for situations where efficacy trials are not feasible and a licensed comparator vaccine with demonstrated clinical efficacy and/or effectiveness is not available

FEEVA A Framework for Evidence Evaluation in Vaccine Assessment

An Australian Living Evidence / Kirby Institute collaboration



Goal: Develop and disseminate a consensus framework for grading the reliability and certainty of indirect evidence arising from pre-clinical or early clinical studies (e.g. animal studies, human challenge studies, natural history studies, and in vitro studies of immune responses to vaccination and infection) to inform decision making on vaccine approval and use recommendations.

Deliverables:

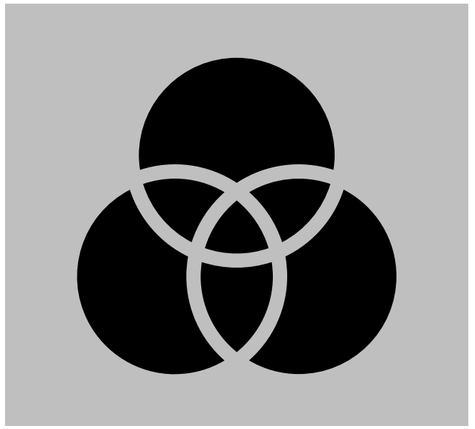
1. Review of the historical use of indirect data to support vaccine effectiveness. *Aim 1*
2. A review of the current use of indirect studies to support vaccine development and approval across four domains. *Aim 2-5.*
3. Consensus frameworks for evidence assessment (x 4). *Aim 2-5.*
4. Framework for assessment of integrated portfolios of evidence: A transparent, systematic framework for assembling portfolios of pre-clinical or indirect clinical evidence of vaccine effectiveness to underpin decisions on vaccine approval. *Aim 6.*

Summary

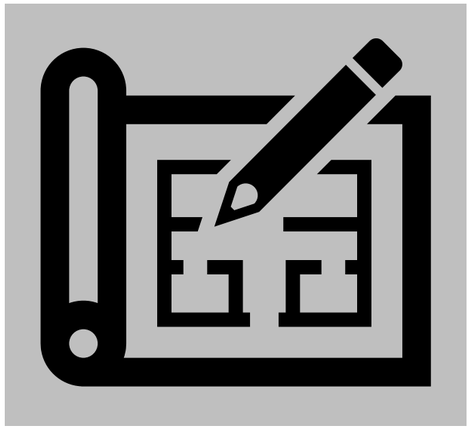
Summary

Standards and co-ordination can improve consistency in data at early stages

HIS are a valuable tool and can provide data to support licensure and de-risk investments



Multiple data sources can be integrated to ensure robustness and relevance of biomarkers



Tools that allow objective evaluation of biomarker data packages can improve confidence in biomarker data packages

Thank you

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