IMPERIAL

Controlled Human Infection Models to Accelerate Vaccine development

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Introduction

- What human infection challenge/controlled human infection studies are
- Why CHIMs are needed and their unique strengths
- Accelerating vaccine development using CHIM
- Limitations & bottlenecks
- Enteric CHIMs
  - Pathogenesis, immunity & transmission
  - Development of next-generation vaccines

Terminology

All are (mostly) synonymous

Human Challenge Study (**HCS**)

Controlled Human Infection Model (**CHIM**)

Controlled Human Malaria Infection (**CHMI**)

Experimental Human Infection Model (**EHIM**)

Controlled Clinical Infection Model (**CCIM**)

Human Infection Challenge (**HIC**)

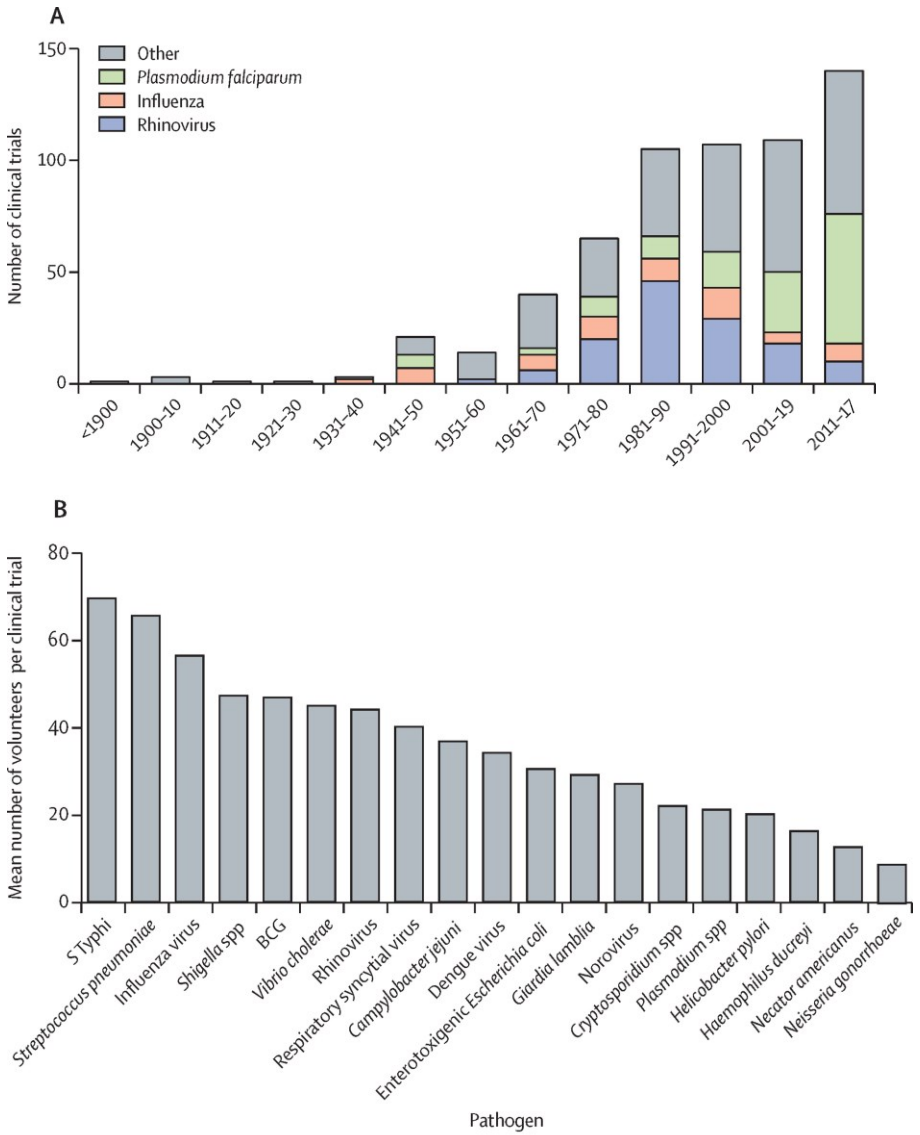
Controlled Human Infection Study (**CHIS**)

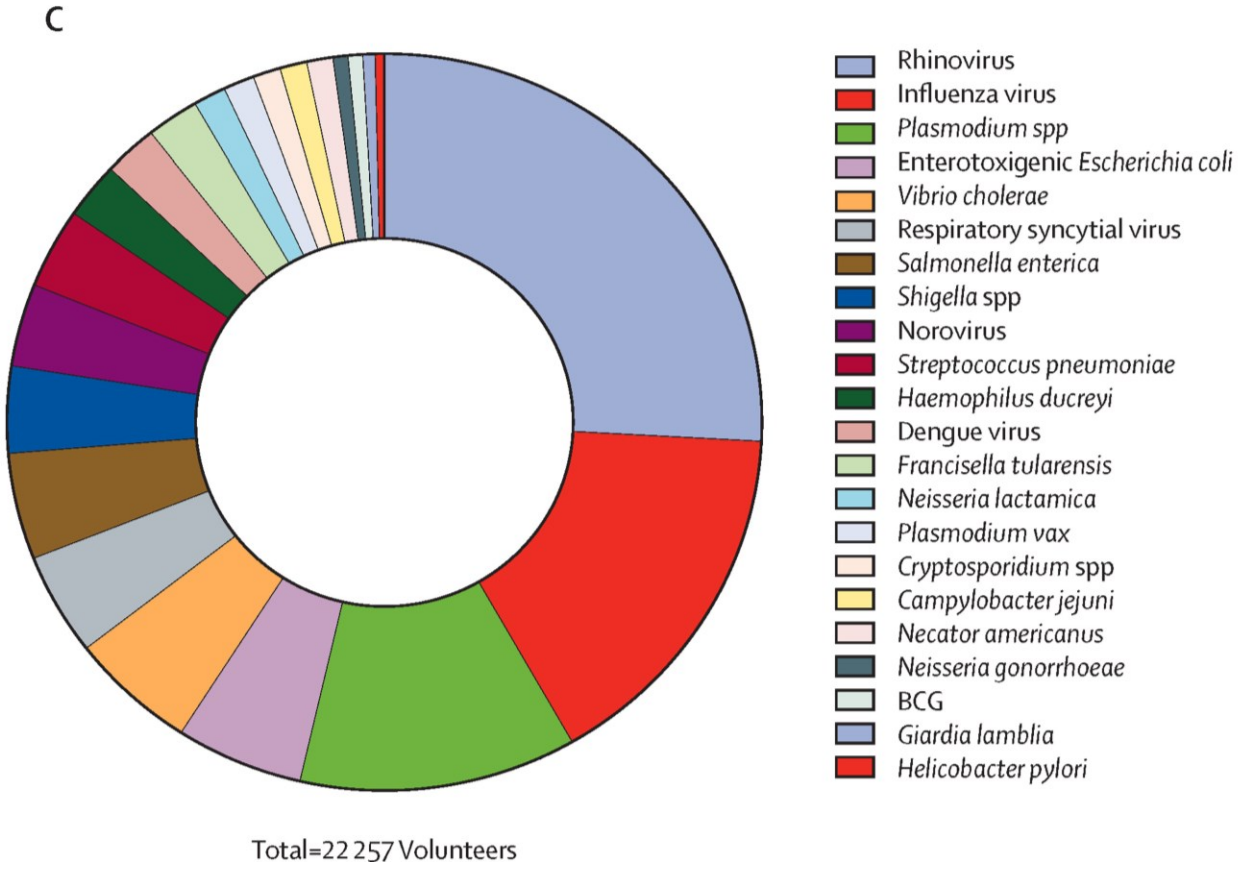
Experimental Human Infection Challenge (**EHIC**)

Etc.

A clinical model in which healthy, fully informed adult volunteers are deliberately exposed to a well-characterised infectious agent under strictly controlled conditions, within a robust ethical, regulatory and safety oversight framework.

Human challenge studies exist for a broad range of pathogens





The Lancet Infectious Diseases 2018 18e312-e322DOI: (10.1016/S1473-3099(18)30177-4)

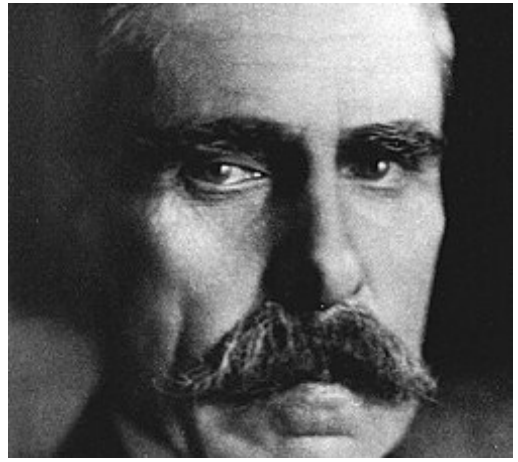
Historical Context

Edward Jenner’s Smallpox Vaccine Challenge (1796)

- Empirical proof of cross-protective immunity

Walter Reed’s Yellow Fever Commission (1900–1901)

- Mechanisms of Yellow Fever transmission.



Wagner-Jauregg Malariotherapy (1917)

- *P. vivax* in treatment of neurosyphillis.

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Historical context

Inform contemporary ethical, regulatory and safety norms

Nazi Concentration Camps

- Typhus, Typhoid

Unit 731

- Plague, cholera and anthrax. Survivors endured vivisection without anaesthesia.

Malariotherapy

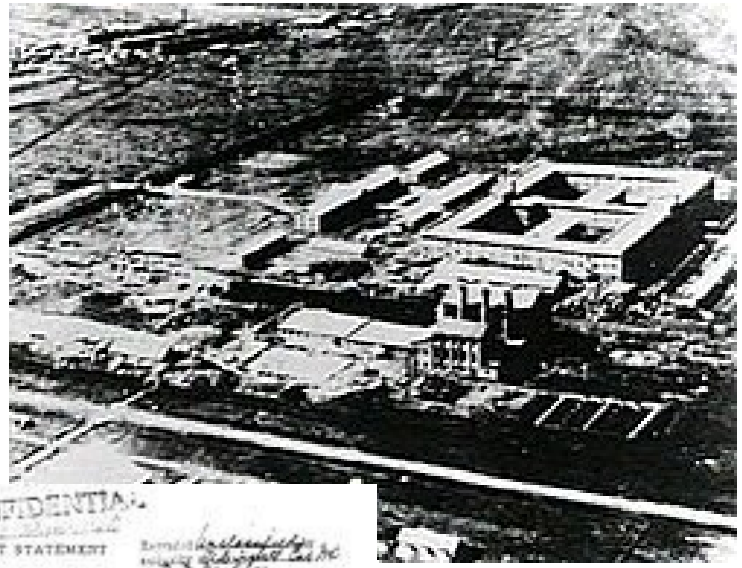
- Documented mortality

Stateville Study

- Prisoners promised reduced sentences.

Operation Whitecoat:

- Conscientious objectors as volunteers - military context inherent power imbalances.



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CONSENT STATEMENT

A program of investigation, sponsored by the United States Army, aimed toward determining the amount of a disease agent necessary to produce illness in man, has been explained to me. I understand that the only way in which this essential information can be obtained is by the exposure of volunteers to known amounts of the agent. I understand that such volunteers may become ill and that the program is not without hazard.

I further understand that the agent to be studied is Coxiella burnetii, which is the cause of Q fever. I understand that the organism(s) causing the disease will be suspended in air, and that by breathing this air I will expose myself to infection with this disease agent. I understand that within three (3) to twenty-one (21) days after the exposure I may become ill and that the expected symptoms are fever, headache, and generalized aching. I understand that the course of the disease may be from one (1) to three (3) weeks. I understand the decision as to appropriate treatment will be made by the attending physicians. I understand that such treatment, if employed, may have to be given in two (2) or more phases.

I further understand that I will be restricted to a single area for the period of this study, probably four (4) to six (6) weeks. I understand that various diagnostic procedures will be required.

There has been no exercise of force, fraud, deceit, duress, over-reaching, or other ulterior forms of constraint or coercion in order to obtain this consent from me.

Of my own free will, and after consideration for a period of more than four (4) weeks, I affix my signature hereto, indicating my willingness, as a soldier, to serve voluntarily as a subject for these studies, with the understanding that I will not be required to participate in studies which, in themselves, are contrary to my religious beliefs.

Signature

WITNESS:

ASN

Date JUN 29 1955

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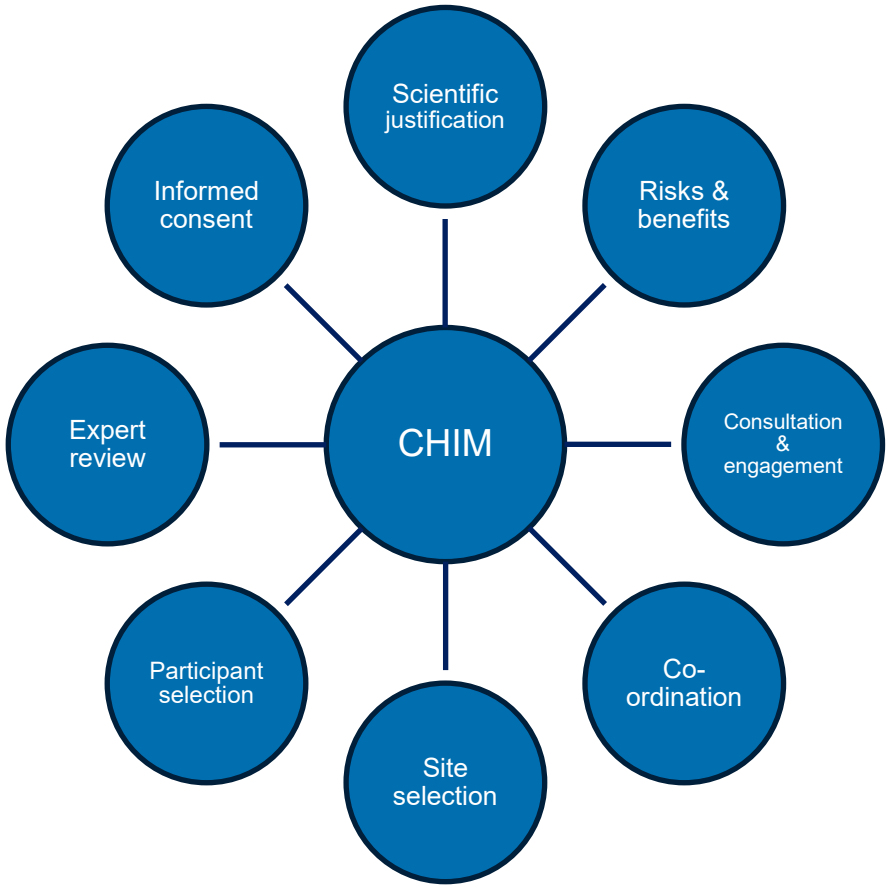
Ethical acceptability of CHIM



1. Clearly articulated need
   - What can be gained? Can results be achieved in other ways?
2. Consensus between public, government, academia, healthcare, industry
3. Careful participant selection
   - Lowest possible risk
   - Diversity & inclusion
4. Highest standards
   - High quality challenge agent
   - Quarantine capacity & strict discharge criteria
   - Close clinical monitoring & rescue treatment

WHO Working Group for Guidance on Human Challenge Studies in COVID19. Vaccine. 2021;39(4):633
Levine *et al.* Clin Infect Dis. 2021;72:2035
https://www.who.int/publications/i/item/9789240037816

Accelerating vaccine development using CHIM

Limitations of conventional vaccine development pathway

$31-68 million >15 years (no failure)

Basic research → Applied research → Preclinical development → Phase I development → Phase II development → Large scale efficacy trials

$2.8-3.7 billion (accounting for failed candidates)

Animal models
- Limited permissiveness
- Disease not recapitulated
- Variable predictive accuracy

Human observational studies & field efficacy trials
- Uncontrolled (often unmeasurable) confounders
- Heterogeneity of patients
- Subject to low or erratic transmission
- Inaccurate clinical readouts

High risk of late-stage failure

Very large studies required to power

Poor ability to resolve Correlates of Protection

Company News | March 1, 2019

Novavax RSV vaccine ResVax fails in Phase III trial

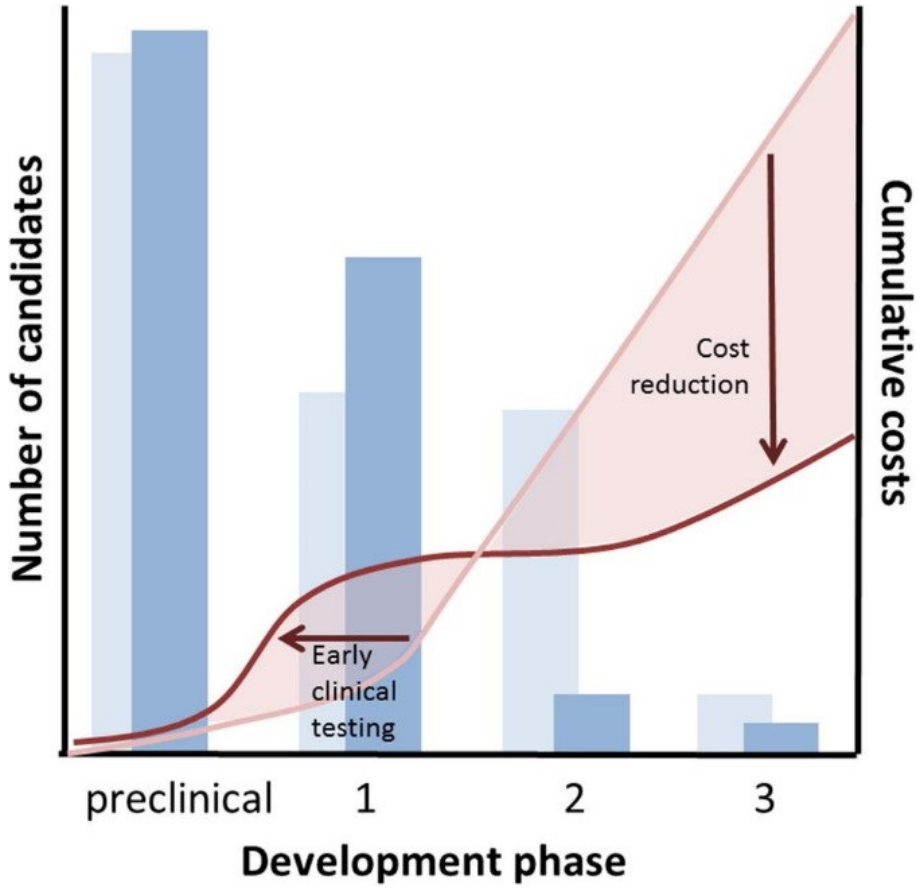
Novavax has reported negative top-line results from the Phase III Prepare clinical trial of its ResVax vaccine being developed to prevent respiratory syncytial virus (RSV) disease in infants through maternal immunisation.

admin

This scanning electron micrograph image depicts RSV particles, coloured blue. Credit: NIAID.

Failing Faster (?)

Screening Candidate Vaccines & Prioritizing Promising Candidates



Roestenberg M, Mo A, Kremsner PG, Yazdanbakhsh M. *Vaccine* 2017; **35**: 7070–6.

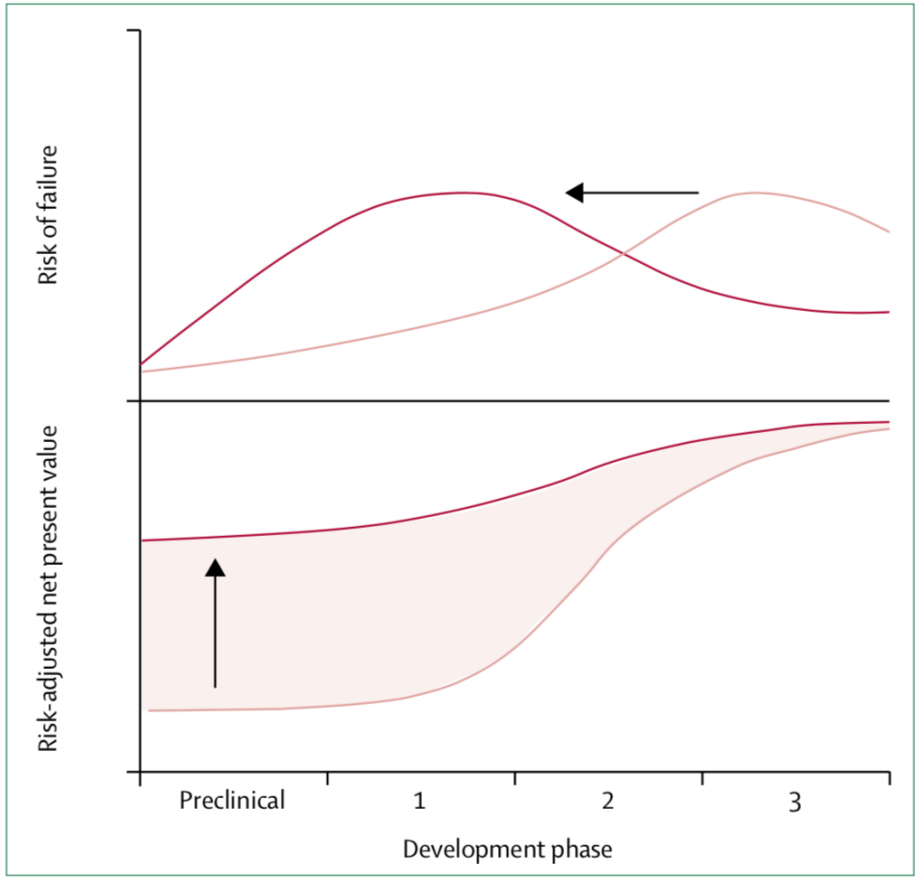
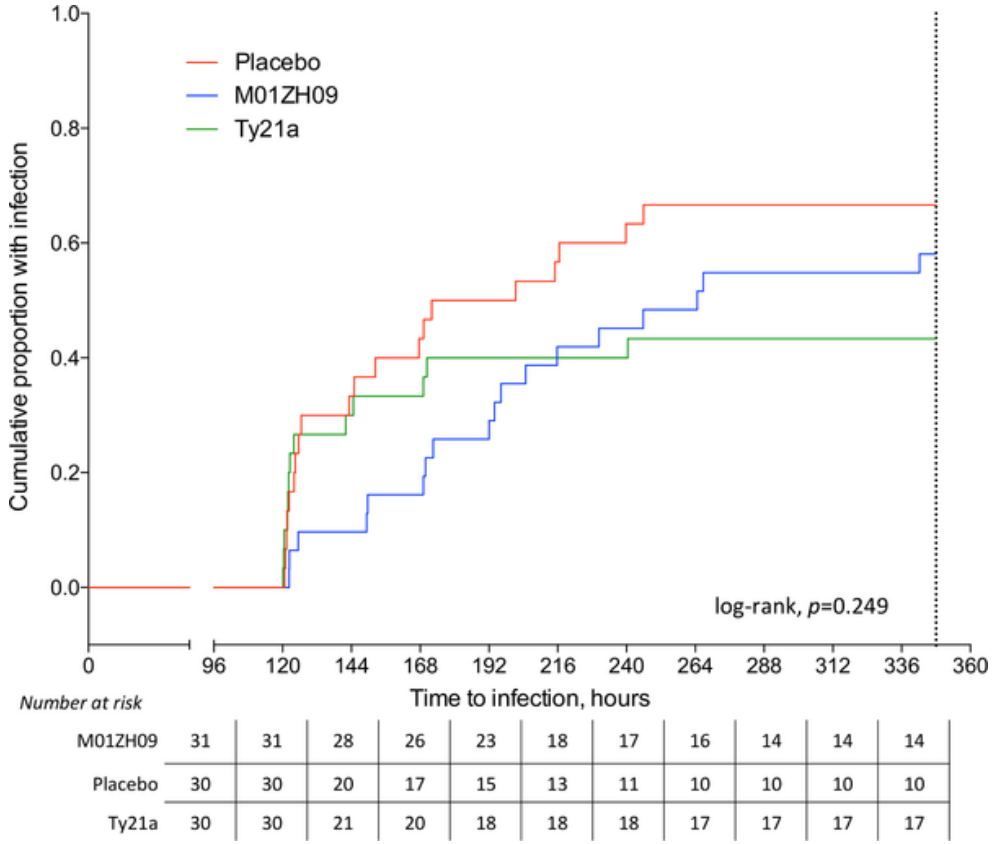


Figure 1: **Graphic representation of the risk of failure and the risk-adjusted net present value of a product before (light red) and after (dark red) introduction of a controlled human infection (CHI) model**

Roestenberg M et at, Lancet ID, http://dx.doi.org/10.1016/ S1473-3099(18)30177-4

Failing faster

Is there a risk of prematurely halting product development?



Attack Rate		Vaccine Efficacy
Placebo	67%	
M01ZH09	58%	19% (-7 to 43%)
Ty21a	43%	31% (-8 to 55%)

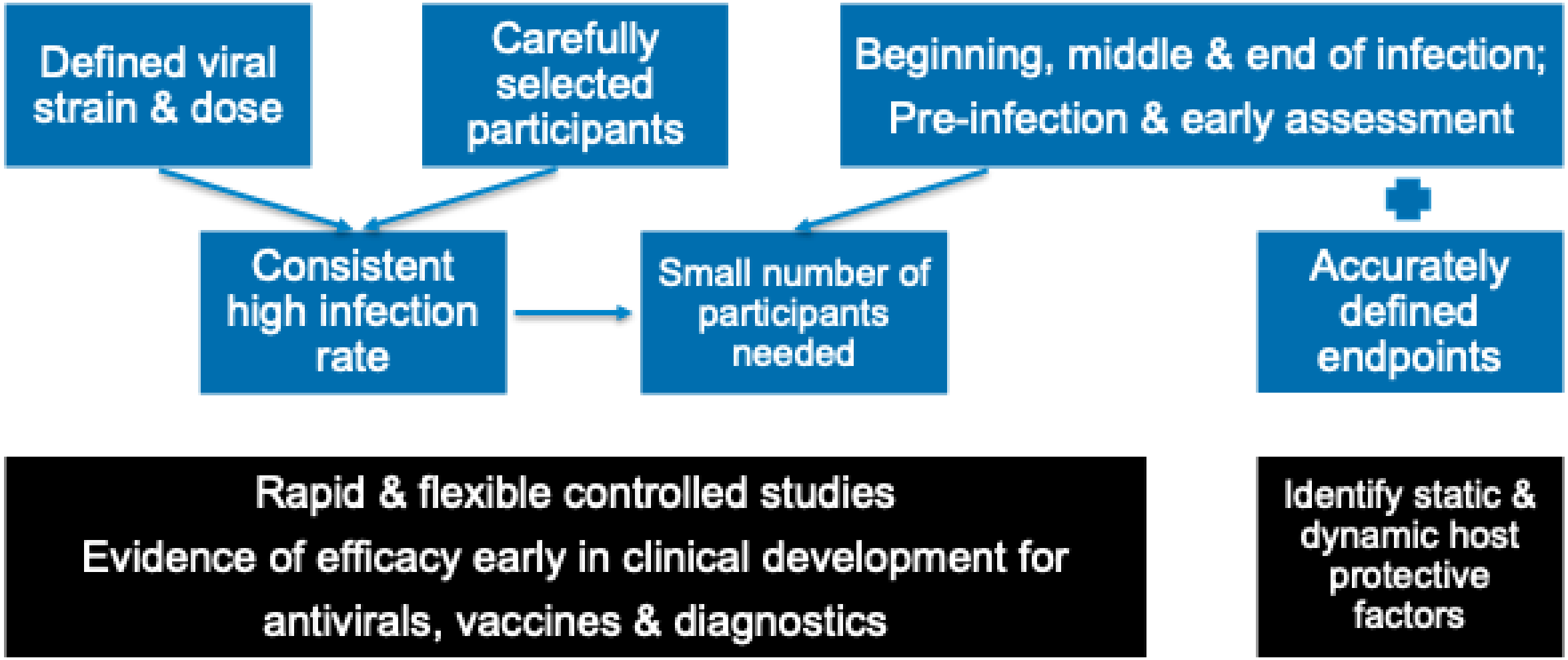
Live attenuated oral typhoid vaccine M01ZH09 product development stalled by lack of efficacy in a typhoid CHIM.

Could vaccine developers may be wary of testing candidate vaccine in a CHIM?

Primary Endpoint -*Typhoid Diagnosis* defined as fever ≥38ºC for >12 hours or positive blood culture

Darton TC, Jones C, Blohmke CJ, et al, PLoS Negl. Trop. Dis. 2016

Key & unique features of controlled human infection models



The role of CHIM in pandemic response & preparedness

Development of the SARS-CoV-2 CHIM

Short-term

Pathogenesis & kinetics
Assessment of diagnostics

Medium-term

Triaging vaccine candidates
If first-gen vaccines suboptimal, rapid efficacy testing of products inc. new formulations/regimes/adjuvants; H2H comparison

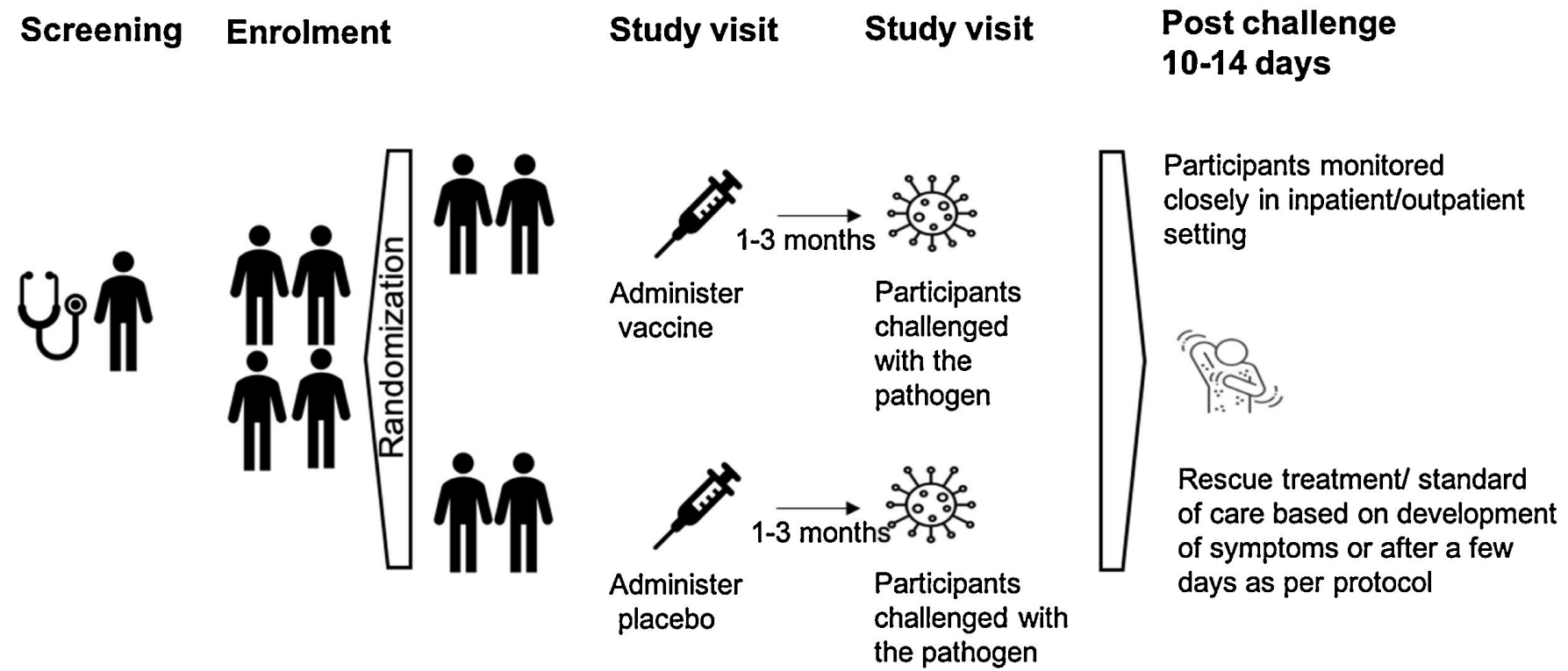
Long-term

Advanced vaccine development: transmission, durability, breadth
Provide efficacy data as phase III studies become unfeasible

Slides Courtesy of Professor Chris Chiu

Study Design & Strain selection

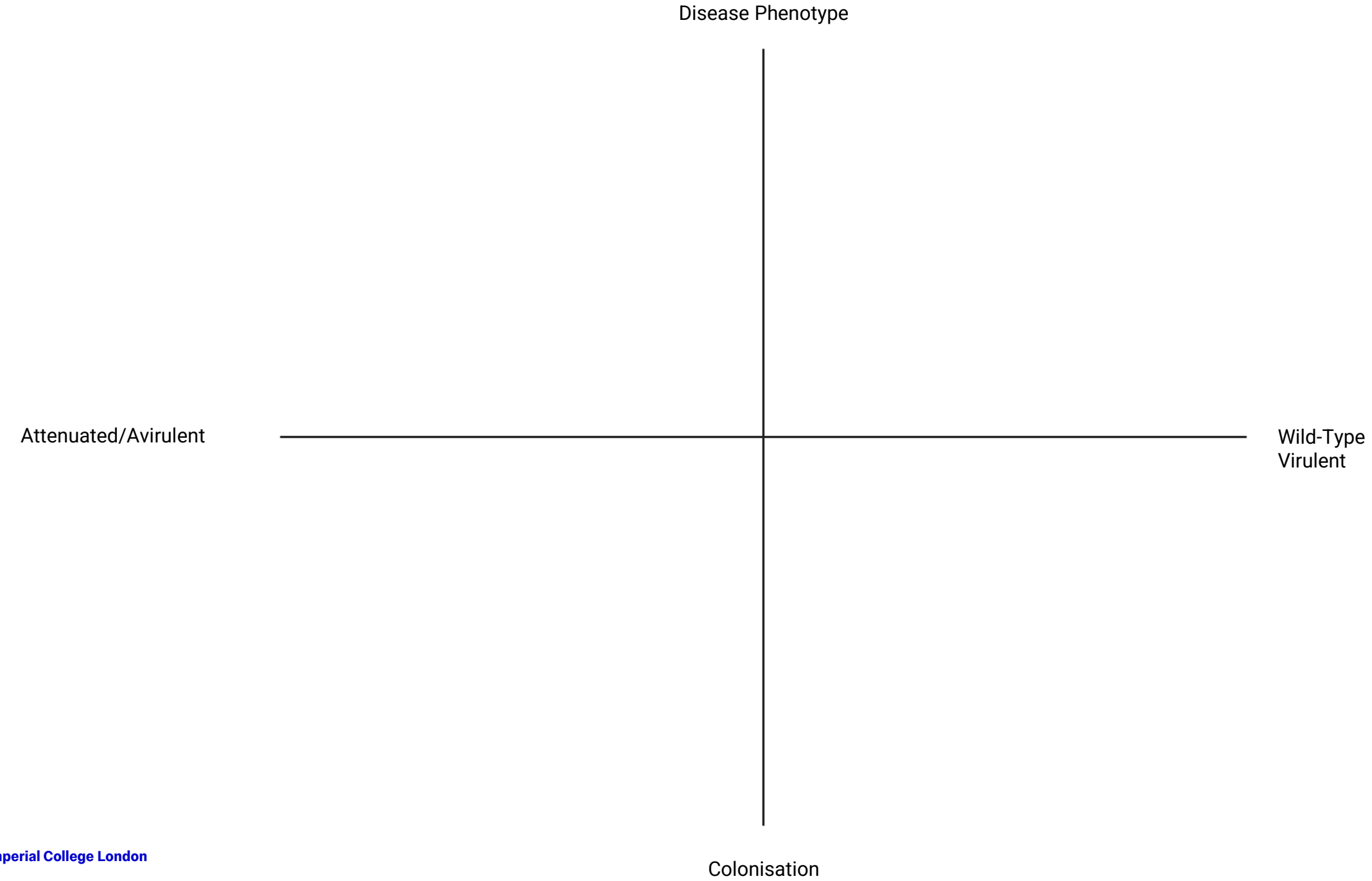
General Schematic

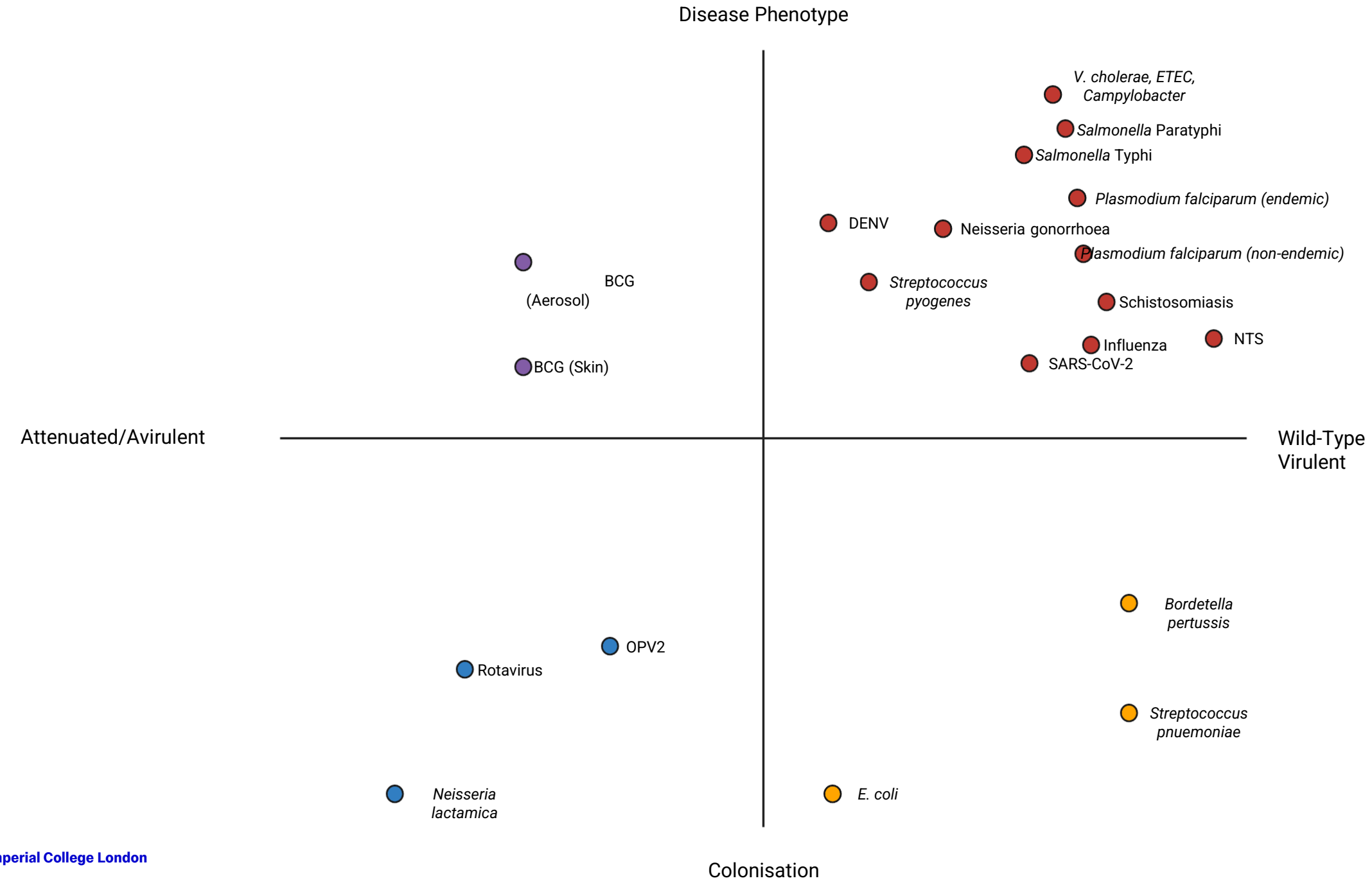


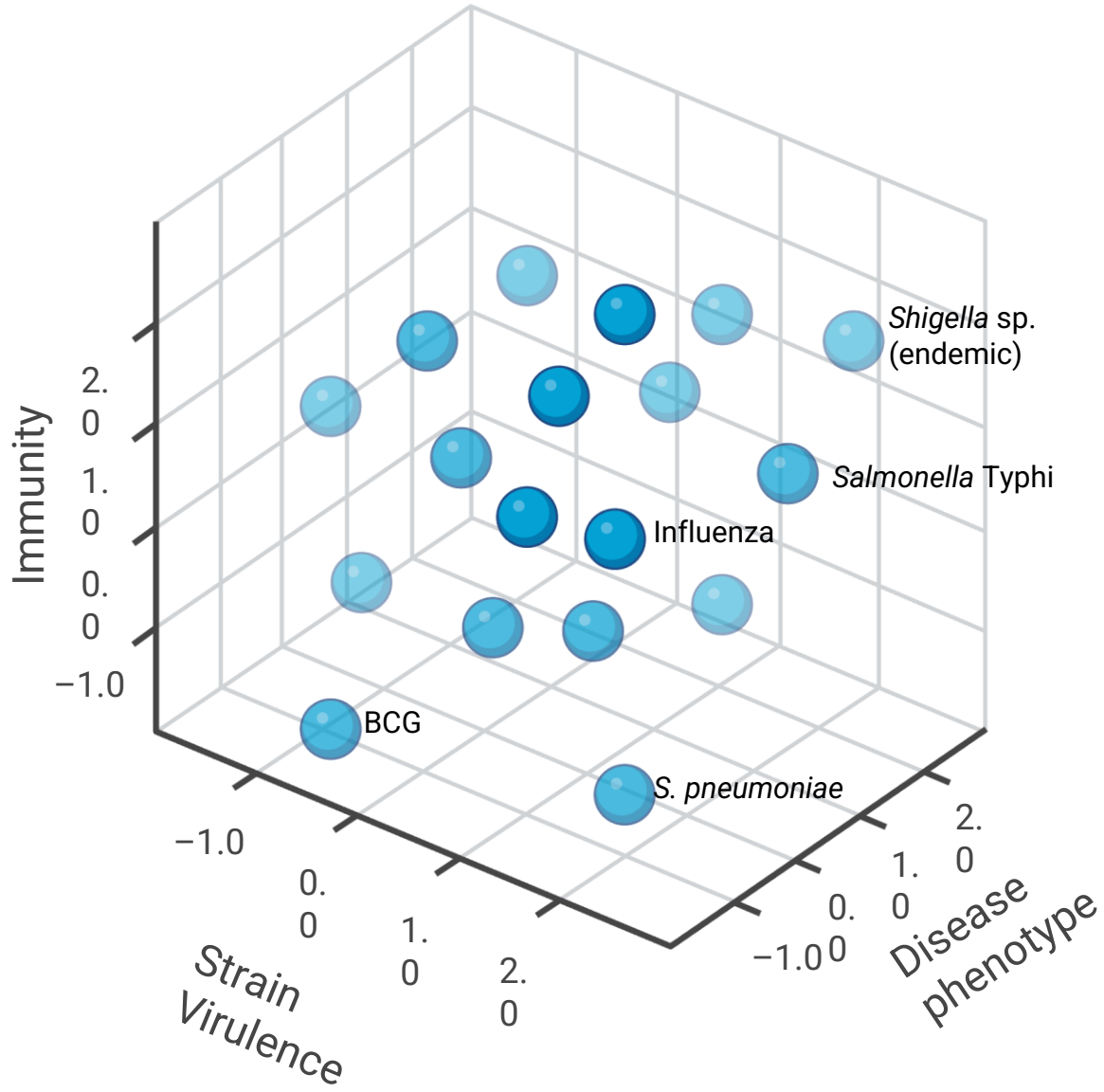
Samples (blood, stool, urine, saliva etc.) collected for laboratory testing and analysis during screening, post vaccination, post challenge on daily follow up and for long-term follow up.

- Proof-of-concept early in clinical development
  - Difficult pathogens and/or uncertain correlates of protection
- Head-to-head or quasi-H2H trials
- Up- & down-selection of vaccine candidates
- Vaccine licensure

Sekhar *et al.* Sem Immunol 2020


Disease Phenotype
Attenuated/Avirulent
Wild-Type
Virulent
Colonisation


Disease Phenotype
V. cholerae, ETEC, Campylobacter
Salmonella Paratyphi
Salmonella Typhi
Plasmodium falciparum (endemic)
DENV
Neisseria gonorrhoea
Plasmodium falciparum (non-endemic)
Streptococcus pyogenes
Schistosomiasis
NTS
Influenza
SARS-CoV-2
BCG (Aerosol)
BCG (Skin)
Attenuated/Avirulent
Wild-Type Virulent
Bordetella pertussis
OPV2
Rotavirus
Streptococcus pnuemoniae
Neisseria lactamica
E. coli
Colonisation

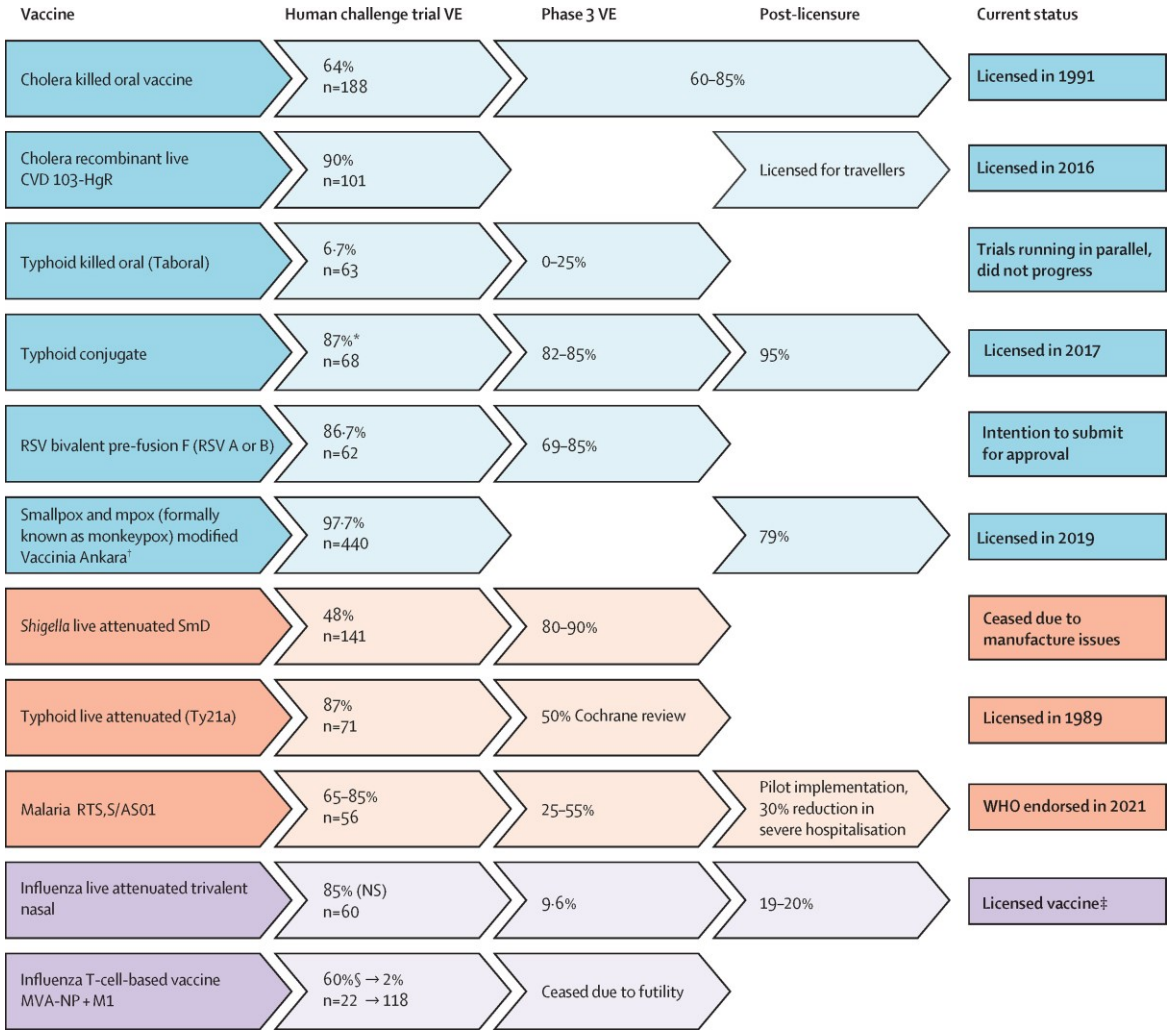

Immunity
2.0
1.0
0.0
−1.0
Strain Virulence
−1.0
0.0
1.0
2.0
Disease phenotype
−1.0
0.0
1.0
2.0
Shigella sp. (endemic)
Salmonella Typhi
Influenza
BCG
S. pneumoniae

Safety & regulation

- Balancing of key ethical principles
  - Scientific/public health need vs participant safety
- Risk considerations overlap with early phase clinical trials
  - Potential for adverse events (expected & unexpected)
  - Risk mitigation
- Third party risks
  - Infection control/containment
  - Genetically modification
- Regulation varies globally
  - FDA requires IND (same as any investigational medicinal product)
  - EMA treats as Auxiliary Medicinal Product
  - MHRA does not regulate unless part of CT-IMP

CHIM for Vaccine Licensure

Prediction of Vaccine Efficacy?



"The contribution of human challenge trials to vaccine development depends on pathogen-specific and product-specific factors that should be explicitly considered when designing models and trials"

The Lancet Infectious Diseases 2023 23e533-e546DOI: (10.1016/S1473-3099(23)00294-3)

Use of CHIM data for licensure

Vaxchora

- Vaxchora's FDA approval
  - largely based on data from CHIM
  - regulatory first for a U.S. vaccine.
- Pivotal trial:
  - single vaccine dose,
    - 90.3% and 79.5% efficacy against moderate/severe cholera at 10 days and 3 months, respectively.
- Direct measurement of vaccine protection when traditional field studies were impractical.
- Immunobridging with vibriocidal antibody seroconversion enabled extension of efficacy data to children and older adults.
- Vaxchora is now indicated for travelers aged 2-64 years to cholera-affected regions

Clinical or Bacteriological Endpoint	All Vaccinees	Vaccine Day 10	Vaccine 3 mo	All Placebos	Day 10	3 mo
Total challenged	68	35	33	66		
No. with severe cholera (%)	3 (4.4)	1 (2.9)	2 (6.1)	28 (42.4)	93.3% (56.2%–100%)	85.7% (46.2%–100%)
No. with moderate or severe cholera (%)[a]	6 (8.8)	2 (5.7)	4 (12.1)	39 (59.1)	90.3% (61.7%–100%)	79.5% (49.1%–100%)

Clinical Infectious Diseases, Volume 62, Issue 11, 1 June 2016, Pages 1329–1335, https://doi.org/10.1093/cid/ciw145

Use of CHIM data for licensure

Vaxchora

- Phase IIa CHI data often included as supportive data
- Field efficacy data required by regulators wherever possible
- Vaxchora (live attenuated cholera vaccine) for travellers
  - Long Hx of clinical development
    - Earlier formulation approved outside US but FDA licensure not completed
    - Re-developed 2009 using new Master Cell Bank
  - Pivotal challenge study in naïve subjects to confirm efficacy
    - n=197 (1:1 vaccine:placebo)
    - 68 challenged at 10d; 66 at 3 months post-vaccination
    - VE 84.8% at 10d & 78.4% at 3 months
  - FDA approved 2016

Limitations and bottlenecks

- Prioritisation of safety so no severe disease or significant risk factors
  - Some models cause no disease (e.g. pneumococcus) or treated before symptom onset (e.g. malaria)
- Relatively healthy adult participants may not reflect high-risk target populations
- Slow & costly challenge agent manufacture
  - Requirement for GMP production
  - Issues with access
- Limited global capacity & expertise
  - Clinical infrastructure limits use in LMIC settings
  - Still relatively few sites
- Public & ethical acceptability & regulatory uncertainty globally

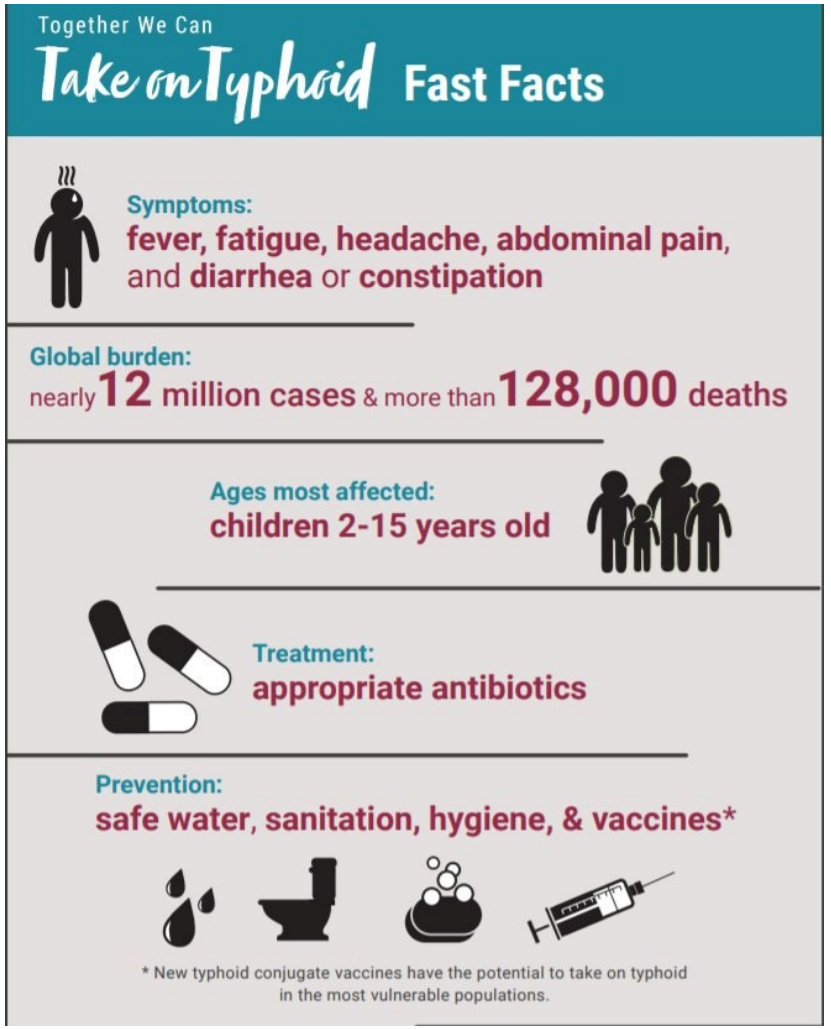
Accelerating vaccine development using CHIM

Case Study: Vaccines for *Salmonella* Typhi

Vaccines for *Salmonella* Typhi

Past Decade

- ~10-12 million cases annually
- Associated with poor sanitation and hygiene
- High burden in South Asia and SSA
- Amenable to vaccination
  - Travel vaccines have moderate efficacy and are not suitable for programmatic use

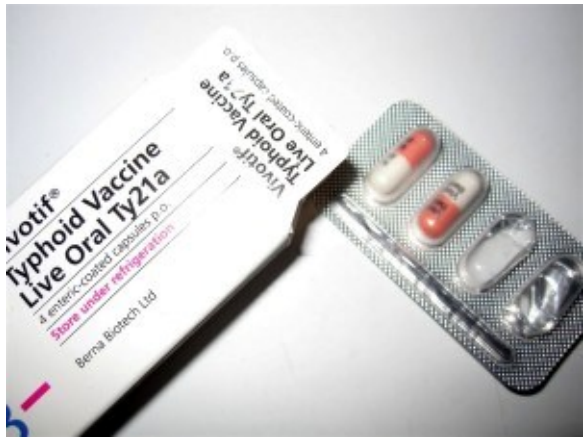


Typhoid Vaccines – the past decade

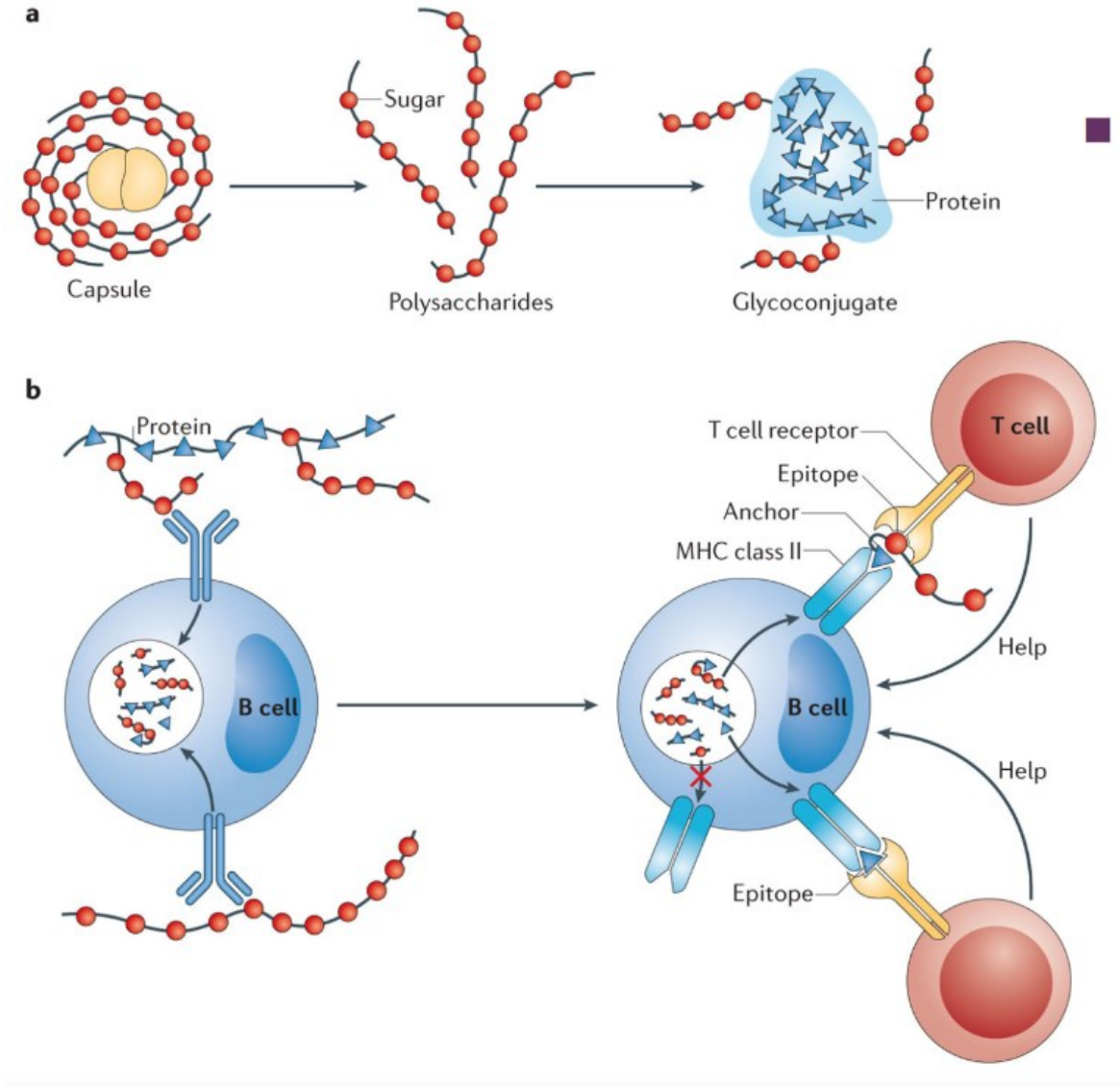
Live attenuated oral Ty21
Parenteral plain Vi-capsular polysaccharide

Limitation of earlier generation typhoid vaccines include:

- Modest efficacy;
- Failure to induce durable immunity (and memory);
- Are non-immunogenic and/or unsuitable for use in the population with the highest burden of disease (i.e. children <5 years);
- Uncertain effect on herd immunity.
- No protection against S. Paratyphi A



Typhoid Conjugate Vaccines



Lin, F. Y., Ho, V. A., Khiem, H. B., Trach, D. D., Bay, P. V, Thanh, T. C., … Szu, S. C. (2001). The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. *The New England Journal of Medicine*, *344*(17)

Typhoid Conjugate Vaccines

The New England Journal of Medicine

VOLUME 344 APRIL 26, 2001 NUMBER 17

THE EFFICACY OF A *SALMONELLA TYPHI* Vi CONJUGATE VACCINE IN TWO-TO-FIVE-YEAR-OLD CHILDREN

FENG YING C. LIN, M.D., M.P.H., VO ANH HO, M.D., HA BA KHIEM, M.D., DANG DUC TRACH, M.D., PH.D., PHAN VAN BAY, M.D., TRAN CONG THANH, M.D., ZUZANA KOSSACZKA, PH.D., DOLORES A. BRYLA, M.P.H., JOSEPH SHILOACH, PH.D., JOHN B. ROBBINS, M.D., RACHEL SCHNEERSON, M.D., AND SHOUSUN C. SZU, PH.D.

TABLE 3. EFFICACY OF Vi-rEPA CONJUGATE VACCINE.

VARIABLE	VACCINE GROUP	PLACEBO GROUP	VACCINE EFFICACY (95% CI)*	P VALUE†
			%	
Children who received two correctly labeled injections — no.	5525	5566		—
Children with typhoid fever — no.	4	47	91.5 (77.1–96.6)	
Attack rate (cases/1000 children)	0.72	8.44		
All children — no.‡	5991	6017		—
Children with typhoid fever — no.	5	56§	91.1 (78.6–96.5)	
Attack rate (cases/1000 children)	0.83	9.31		
Children with typhoid fever				
Sex — no. (%)			—	0.05
Male	5 (100)	29 (52)		
Female	0	27 (48)		
Age at vaccination — no. (%)			—	0.58
2 Yr	2 (40)	16 (29)		
3 Yr	1 (20)	7 (12)		
4 Yr	0	16 (29)		
5 Yr	2 (40)	17 (30)		
Date of isolation of *S. typhi* — no. (%)			—	0.36
3/98–2/99 (12 mo)	2 (40)	33 (59)		
3/99–5/00 (15 mo)	3 (60)	23 (41)		

*CI denotes confidence interval.

†P values were calculated by Fisher's exact test.

‡The numbers of children include those who received two injections from vials with correct codes and those who received one or two injections from vials with incorrect codes.

§One child with typhoid fever who received two injections of placebo from a vial with an incorrect code is included.

Lin, F. Y., Ho, V. A., Khiem, H. B., Trach, D. D., Bay, P. V, Thanh, T. C., … Szu, S. C. (2001). The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. *The New England Journal of Medicine*, *344*(17)

Typhoid Conjugate Vaccines

Why aren't Vi-rEPA vaccines part of routine infant vaccination schedules in endemic countries?

- Costs
- Scalability
- Lack of advocacy
- Competing priorities
- Uncertain epidemiology – who to vaccinate, when and how frequently.

WHO - ***"...Successful typhoid challenge studies conducted in healthy adults using an appropriate and validated model (that is, one in which some protective efficacy of unconjugated Vi vaccines is detectable) could provide considerable supporting evidence of the efficacy of a Vi conjugate vaccine."***

Typhoid Challenge

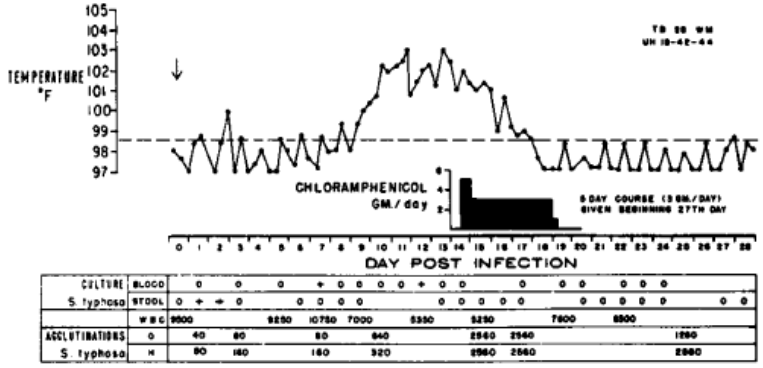
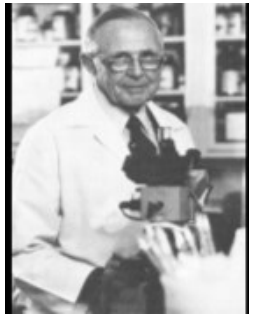


Table 4. Development of clinical disease and fecal excretion of virulent *Salmonella typhi* in controls and in recipients of *S. typhi* Ty21a vaccine.

Vaccine trial, group*	No. of men	Percentage with typhoid fever	Percentage excreting *S. typhi*	
			0–3 days	4–30 days
Trials 1 and 3				
Vaccinees	28	7 ($P = 0.0002$)	36 (NS)†	11 ($P = 0.00009$)
Controls	43	53	49	60
Trial 2				
Vaccinees	27	19 (NS)	19 (NS)	19 (NS)
Controls	21	38	24	38

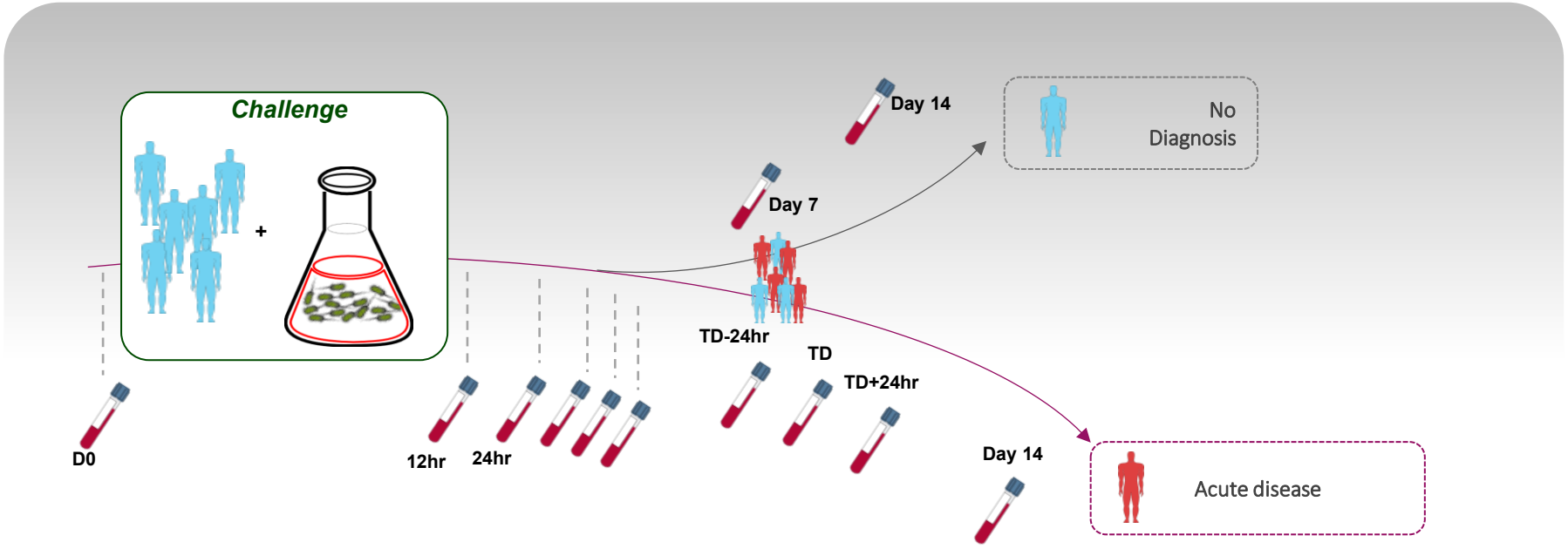
*Volunteers in trials 1 and 3 were given vaccine strain grown with galactose, and those in trial 2 were given vaccine strain grown without galactose.
†NS = not significant.



Photos courtesy of M. Levine

Hornick RB, Greisman SE, Woodward TE, DuPont HL, Dawkins AT, Snyder MJ. Typhoid fever: pathogenesis and immunologic control. *N Engl J Med* 1970; **283**: 686–9

OVG Human Challenge Studies



Typhoid Diagnosis **defined as fever ≥38ºC for >12 hours or positive blood culture collected ≥72 hours from challenge**

Salmonella Typhi vaccines: A decade of progress

Significant reduction in the rate of typhoid fever following controlled challenge

Vaccination with Vi-TT results in a significant reduction in the rate of typhoid fever following controlled challenge

Vaccine efficacy

- Composite diagnostic endpoint) **55%** (26.8 – 71.8%) p=0.0005
- Secondary endpoint **89%**

- Provided key supporting data to progress to Phase 3 efficacy/effectiveness studies

	Control group (n=34)	Vi-TT group (n=41)	Vi-PS group (n=37)
Primary outcome			
Completed challenged	31	37	35
Total diagnosed (composite definition, clinical or microbiological typhoid diagnosis)	24/31 (77%)	13/37 (35%)	13/35 (37%)
Relative risk (95% CI)	..	0·45 (0·28–0·73)	0·48 (0·30–0·77)
Vaccine efficacy (%, 95% CI)	..	54·6% (26·8–71·8)	52·0% (23·2–70·0)
p value	..	0·0005	0·0010
Secondary outcomes			
Time to diagnosis (days)	6·0 (5·1–7·8)	6·5 (6·1–8·6)	7·2 (5·9–10·2)
Microbiological diagnosis	16/31 (52%)	12/37 (32%)	9/35 (26%)
Time to microbiological diagnosis (days)	6·0 (4·6–8·0)	6·3 (6·0–8·3)	6·1 (5·1–10·2)
Clinical diagnosis	8/31 (26%)	1/37 (3%)	4/35 (11%)
Time to clinical diagnosis (days)	6·8 (5·4–7·8)	10·4	8·5 (6·5–10·0)
Clinical outcomes			
Fever ≥37·5°C (any duration)	20/31 (65%)	13/37 (35%)	18/35 (51%)
Fever ≥38·0°C (any duration)	17/31 (55%)	6/37 (16%)	11/35 (31%)
Fever ≥38·5°C (any duration)	14/31 (45%)	4/37 (11%)	9/35 (25%)
Time to first fever ≥38·0°C (any duration; days)	7·2 (5·4–8·5)	10·4 (10·2–15·5)	7·5 (6·2–8·7)
Microbiological outcomes			
S Typhi bacteraemia	24/24 (100%)	13/13 (100%)	11/13 (85%)
Time to first positive blood culture (days)	6·1 (5·0–7·6)	6·5 (6·1–8·6)	6·1 (5·0–10·2)
Participants with positive S Typhi stool culture	22/31 (71%)	22/37 (59%)	21/35 (60%)
Diagnosed participants with positive S Typhi stool culture	19/24 (79%)	12/13 (92%)	10/13 (77%)
Median quantitative blood culture (CFU/mL; range)	0·4 (0·05–22·7)	0·075 (0·05–1·2)	0·1 (0·05–5·6)

Data are n, n/N (%), or median (IQR) unless otherwise stated. Vi-TT=Vi-tetanus toxoid conjugate vaccine. Vi-PS=Vi-polysaccharide vaccine. S Typhi=*Salmonella* Typhi. CFU=colony forming units.

***Table 2*: Primary and secondary outcomes**

Jin C, Gibani MM, Moore M, *et al.* Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* 2017. D (17)32149-9

Supporting data for typhoid vaccine deployment

World Health Organization

Typhoid vaccines

SAGE noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (*S.* Typhi) in low- and middle-income countries. SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of typhoid conjugate vaccine(TCV) for infants and children over 6 months of age as a single dose in typhoid endemic countries. Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant *S.* Typhi. SAGE also recommended catch-up vaccination wherever feasible, with priority for catch-up in the youngest age groups (up to 15 years of age), depending on local epidemiology.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

Decisions on the preferred immunization strategy should be based on an analysis of disease burden, availability and quality of surveillance data, affordability, and operational feasibility. The experiences and impact of different vaccination strategies, as well as integration with water, sanitation and hygiene (WASH) or other interventions, should be monitored and documented in order to support a learning agenda for typhoid control.

WHO SAGE October 2017 -
Recommendation for programmatic use of Vi-TCV in high-burden countries from 6 months of age

Gavi
The Vaccine Alliance

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Millions of children set to be protected against typhoid fever

Gavi Board approves US$ 85 million funding window for 2019-2020 to support the introduction of typhoid conjugate vaccine in developing countries

Vientiane, 30 November 2017 – Millions of children in the poorest countries could soon be protected against typhoid fever following the Gavi Board's approval today of a support window for typhoid conjugate vaccines (TCVs).

"Typhoid fever imposes a dramatic burden on children in the poorest nations affecting countries, communities and families," said Dr Ngozi Okonjo-Iweala, Gavi Board Chair. "This disease has long been eliminated from most industrialised nations, but it is still a serious threat in developing countries where the vast majority of deaths occur," she said. "I lost my cousin and nearly lost my son because of typhoid. This vaccine will be a lifesaver for millions of children, especially those living without access to clean water or sanitation."

An immunisation session for the Hmong community at Nasala Village during a visit by the Gavi Board. Credit: Gavi/2017/Amanda Mustard.

Commitment for **Gavi** support November 2017

Embargoed for release up to

3rd January, 2018, 8:00 AM hrs CET
3rd January, 2018, 12:30 PM hrs IST
2nd January, 2018, 11:00 PM hrs PST
3rd January, 2018, 2:00 AM hrs ES

World Health Organization

Typbar TCV® from Bharat Biotech, World's First Typhoid Conjugate Vaccine Prequalified by WHO

Hyderabad, Genome Valley, January 3, 2018: Bharat Biotech's Typbar TCV®, the world's first clinically proven Typhoid Conjugate Vaccine against typhoid fever has received prequalification from World Health Organisation (WHO). This enables the procurement and supplies of this life saving vaccine to UNICEF, Pan-American Health Organization (PAHO) and GAVI supported countries. Typbar TCV® has been evaluated in Human Challenge Studies at Oxford University and typhoid conjugate vaccines have been recommended by WHO's Strategic Advisory Group of Experts on Immunization (WHO-SAGE).

Typbar TCV® is the first typhoid vaccine, clinically proven to be administered to children from 6 months of age to adults and confers long term protection against typhoid fever.

International Health Metrics and Evaluation (IHME) estimates that in 2016, there were approximately 12 million cases of typhoid fever resulting in around 130,000 deaths. Typhoid fever is caused by the bacterium *Salmonella* Typhi (*S.* Typhi), which infects humans due to contaminated food and beverages from sewage and other infected humans. Currently a third of the global population is at risk of typhoid fever, which results in reduced school attendance, loss of work and wages, lowered pregnancy outcomes and impaired physical and cognitive development of children. In most developing countries the cost of a course of treatment for typhoid fever ranges from $50 to $5000 for outpatient and inpatient treatments.

WHO Pre-qualification January 2018

$ViCRM_{197}$ prequalified 2020

TyVAC Consortium

Accelerating Typhoid Conjugate Vaccine Introduction

- TyVAC Study
- Assessing the effectiveness of Vi-TT in typhoid endemic countries
- Three sites
  - Blantyre, Malawi – Individual RCT. 22,000 Children 9 months – 12 years.
  - Kathmandu, Nepal – Individual RCT. 20,000 Children 9 months – 15 years
  - Dhaka Bangladesh – Cluster RCT. Population 180,000 (43,000 eligible for vaccination)

TyVAC Typhoid Vaccine Acceleration Consortium

University of Maryland School of Medicine Center for Vaccine Development

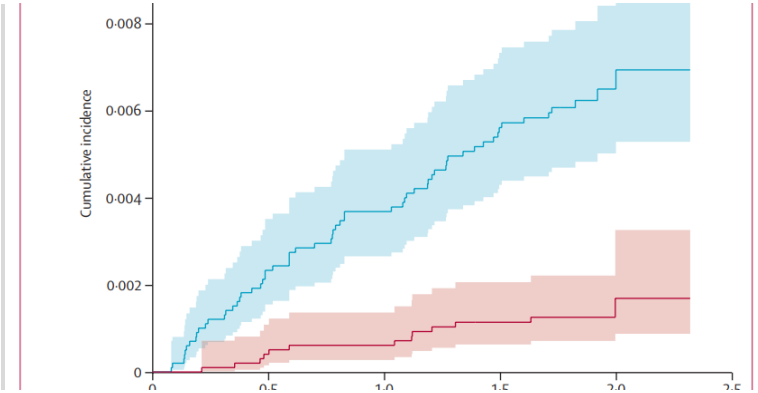
University of Oxford

PATH

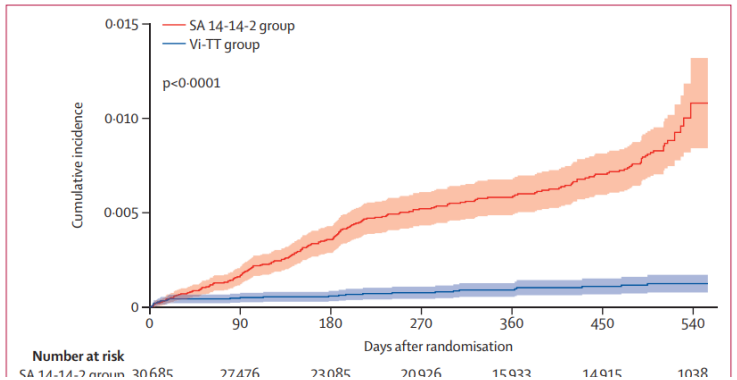
Bill & Melinda Gates foundation

TyVAC team meeting: Kampala, Uganda.

TyVAC - Nepal

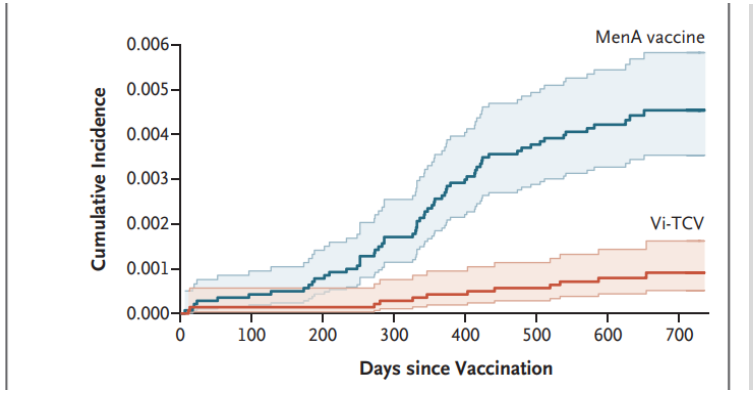


TyVAC Nepal
VE against culture confirmed typhoid fever 2 years – **79%** (95%CI 62-89%)



TyVAC Bangladesh
Overall against culture confirmed typhoid fever 2 years – **85%** (95%CI 76-91%)

Lancet 2021; 398: 675–84



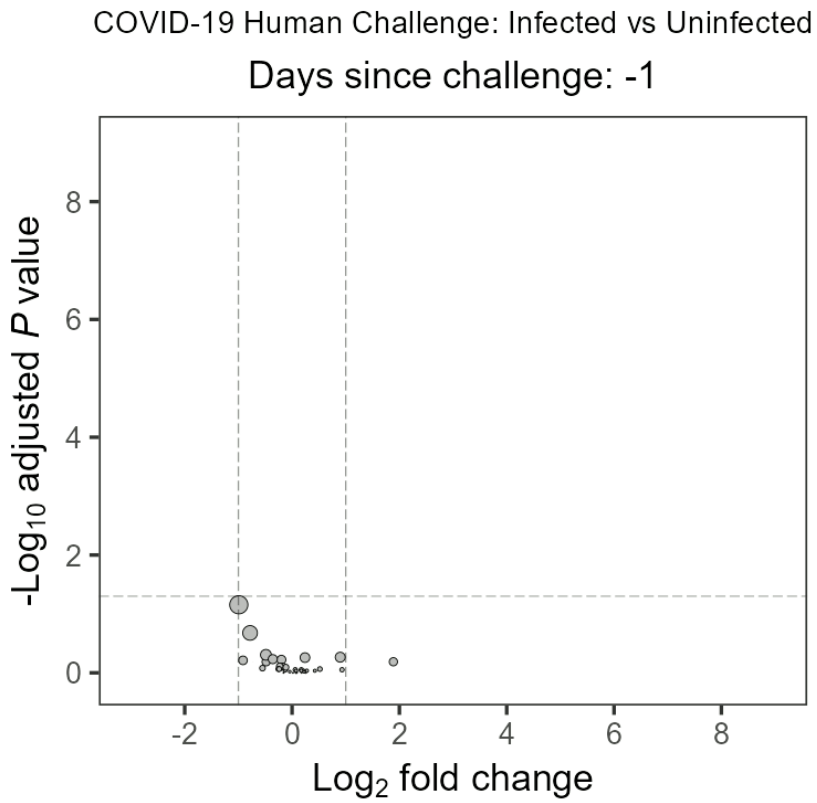
TyVAC Malawi
Overall efficacy against culture confirmed typhoid fever 2 years – **81%** (95%CI 64-90%)

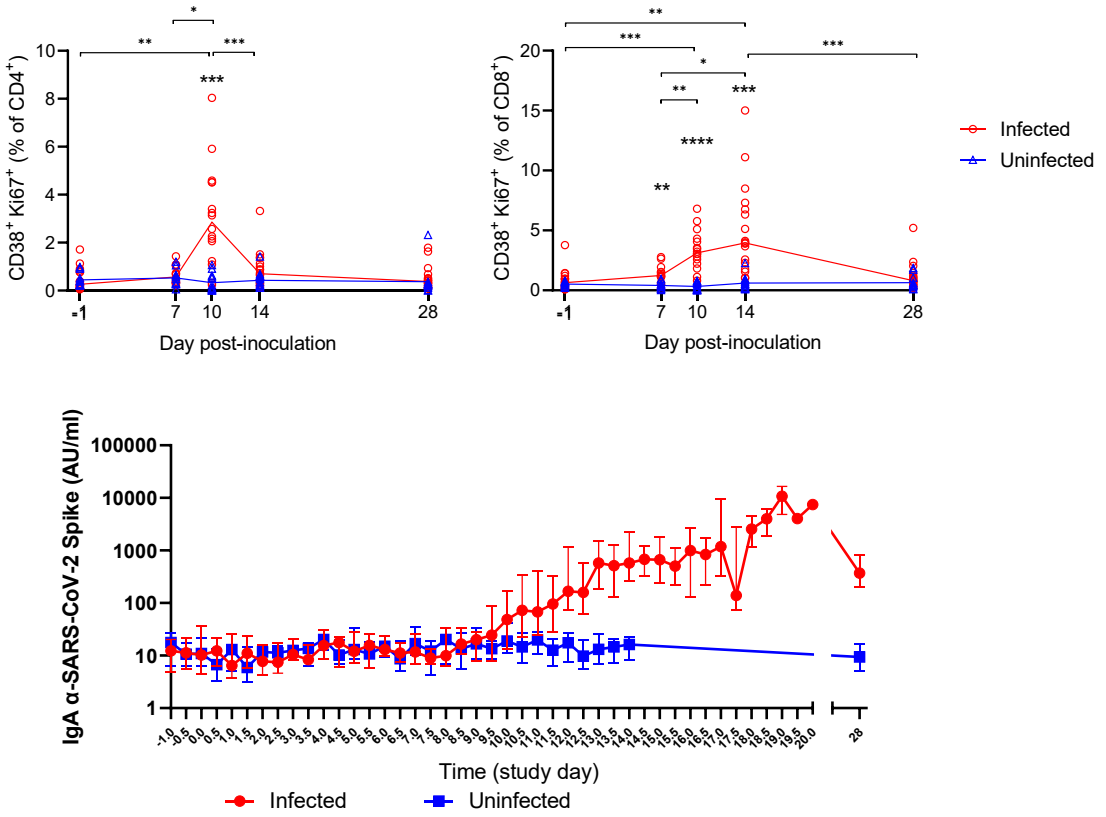
N Engl J Med 2021; 385:1104-1115

Lancet Glob Health 2021; 9: e1561–68

Opportunities for Mechanistic Insights

Immune response to primary SARS-CoV-2 infection



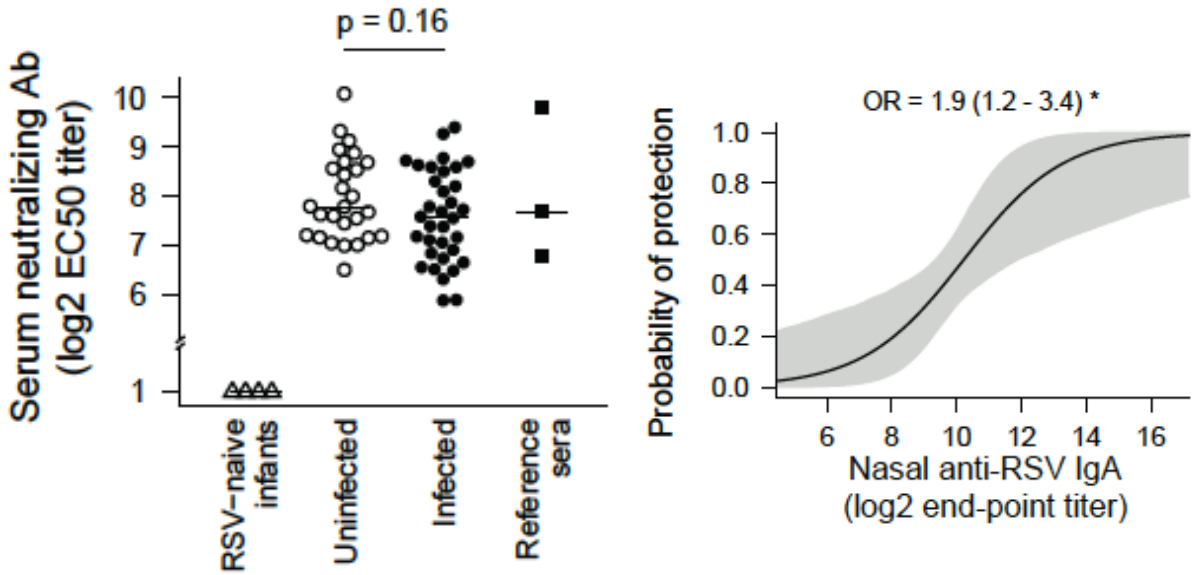


Slides Courtesy of Professor Chris Chiu

Wagstaffe *et al.* Science Immunol 2024

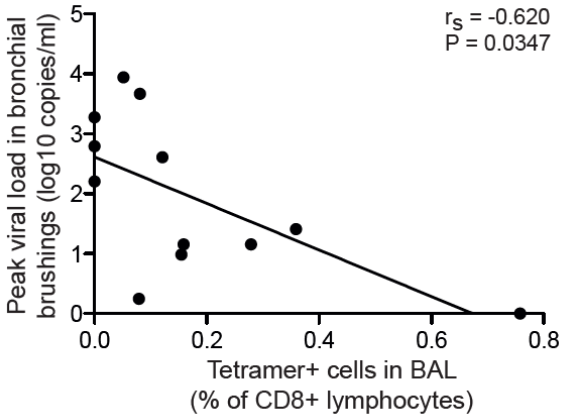
Identifying correlates of protection

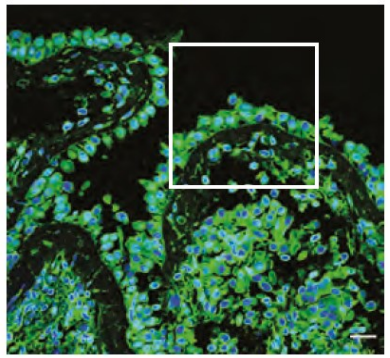
Mucosal vs systemic antibody



Habibi *et al.* AJRCCM 2015

Pulmonary Trm cells



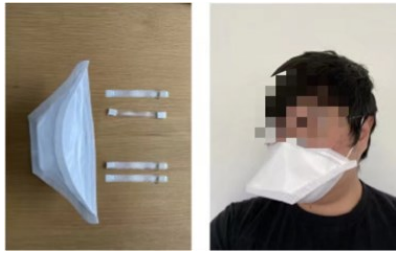


Paterson *et al.* AJRCCM 2021
Jozwik *et al.* Nat Commun 2015

Slides Courtesy of Professor Chris Chiu

Identifying improved readouts of transmission

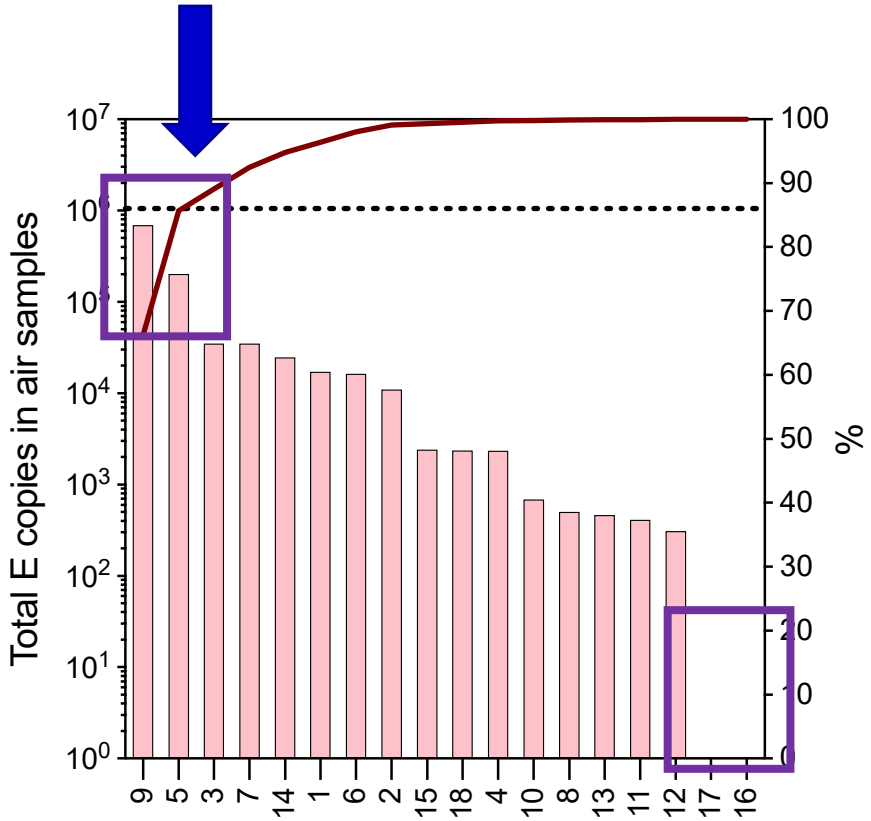
Facemask sampling
60 mins

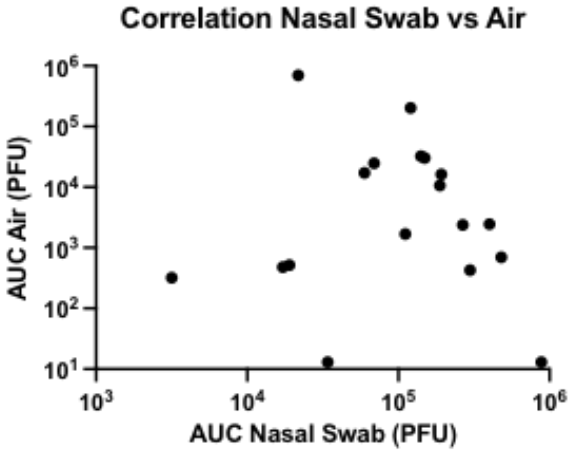


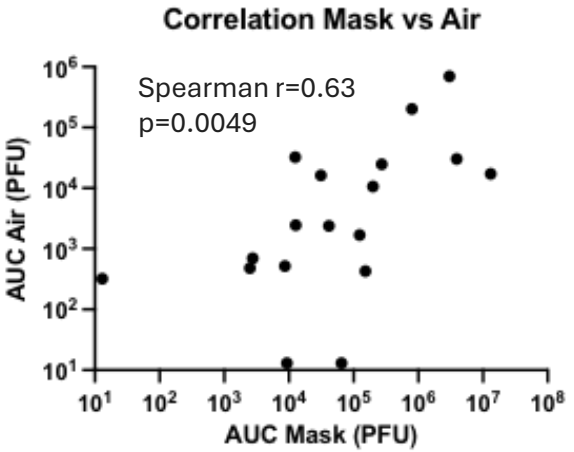
(Mike Barer)

Air sampling
Coriolis 300L/min
10 mins

>80% of airborne virus emitted by 2 participants



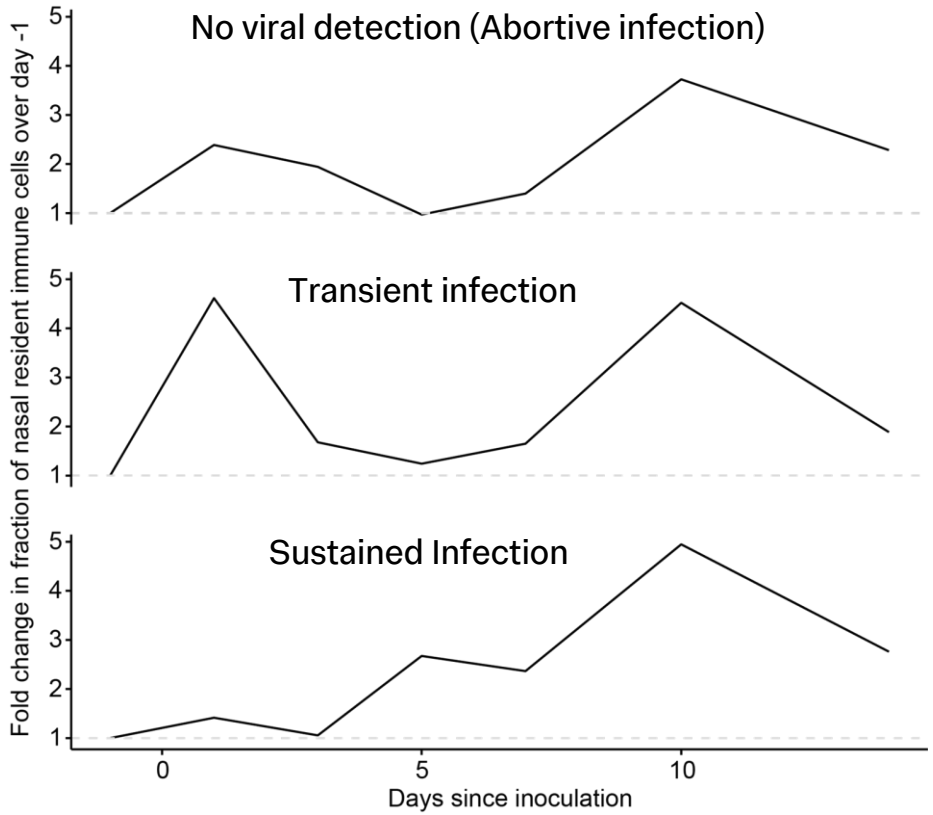


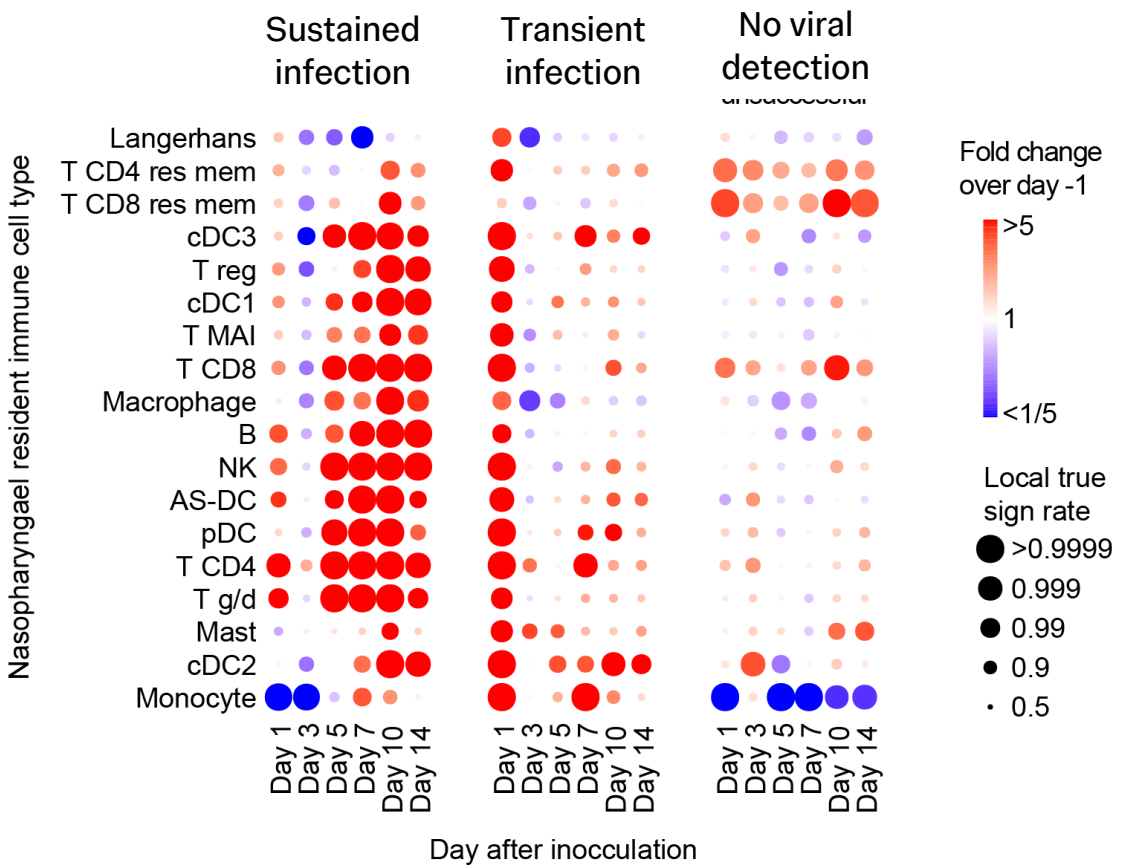


Slides Courtesy of Professor Chris Chiu

Jie Zhou, Anika Singanayagam & Wendy Barclay *et al.* Lancet Microbe 2023

Early cellular recruitment associated with “protection”





Lindeboom, Nikolic, Teichmann *et al.* Nature 2024

Slides Courtesy of Professor Chris Chiu

Conclusions

- Increasingly used to address difficult-to-solve vaccine gaps
- Unique investigation of correlates of protection pre- and early post-exposure
- Ethics of CHIM have been considered very comprehensively
- Can de-risk clinical development if appropriately used
- Additional use cases
  - Infections with low or erratic incidence
  - Transmission-reduction
    - Pandemic preparedness
  - Cross-strain protection

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Thank You

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Peter Hill
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Gauri Godbole
Jacob Lee
Dominic Smith
Stephanie D'Arc
DSMC
- Tom Darton
- Daniella Ferreira
- Melissa Kapulu
- Moreno Ursino
- Adam Dale

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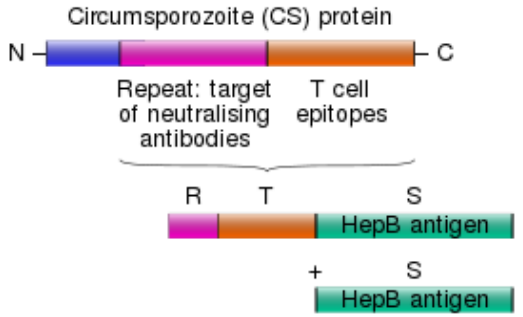
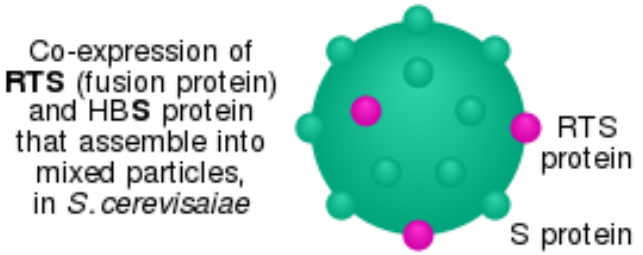
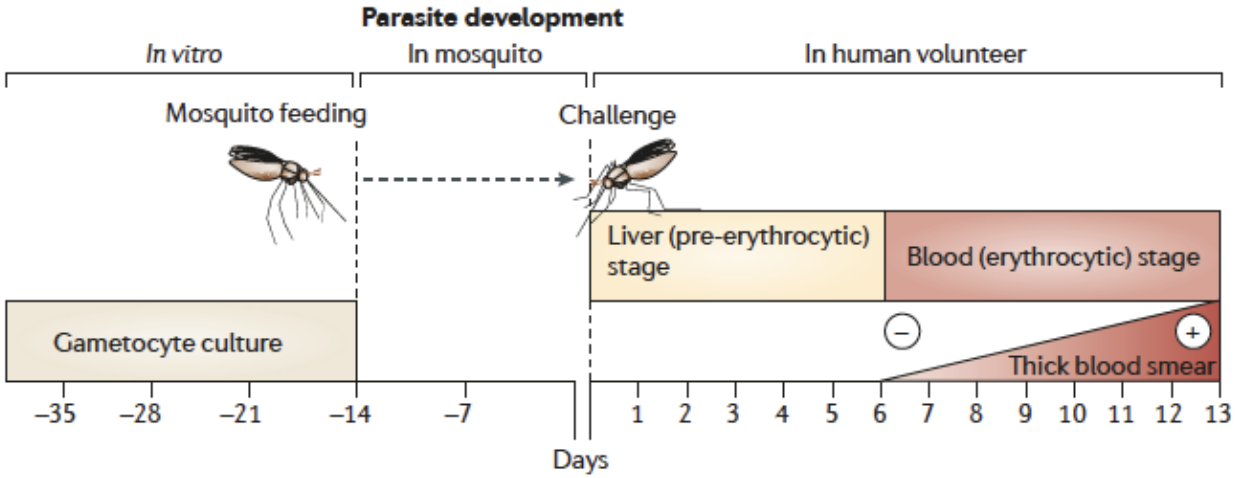
Supplementary Slides

Malaria challenge for vaccine development

- *P. falciparum*: 229 million cases, 409,000 deaths (2/3 in children <5y)
- Difficult immune target
  - Complex organism
  - Multi-stage lifecycle
- Correlates of protection unclear
- Animal models limited
- First attempts in 1980s with protein subunit (circumsporozoite protein)

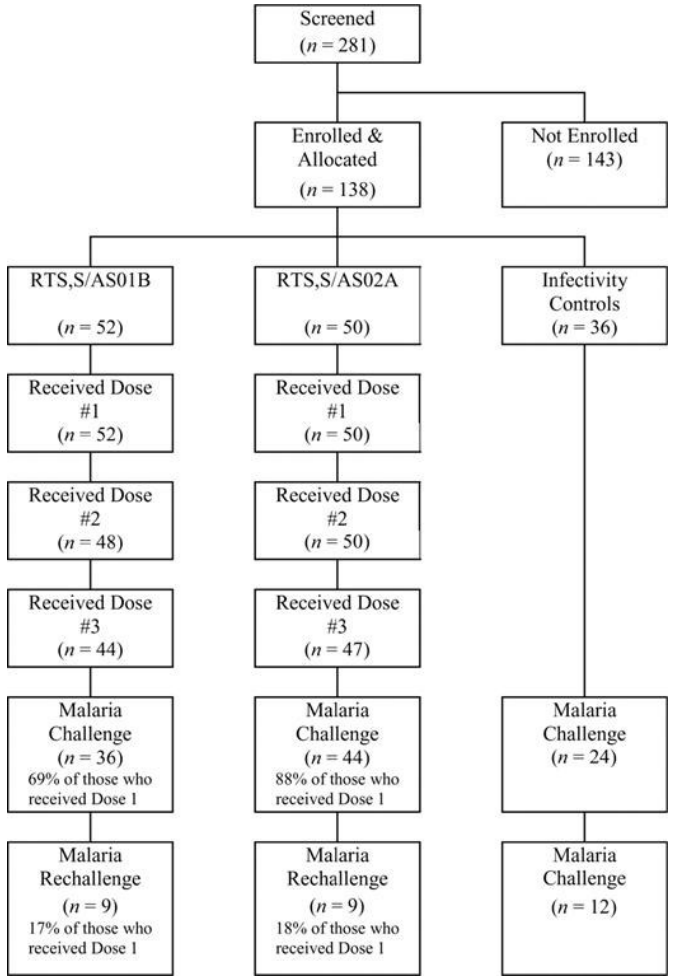


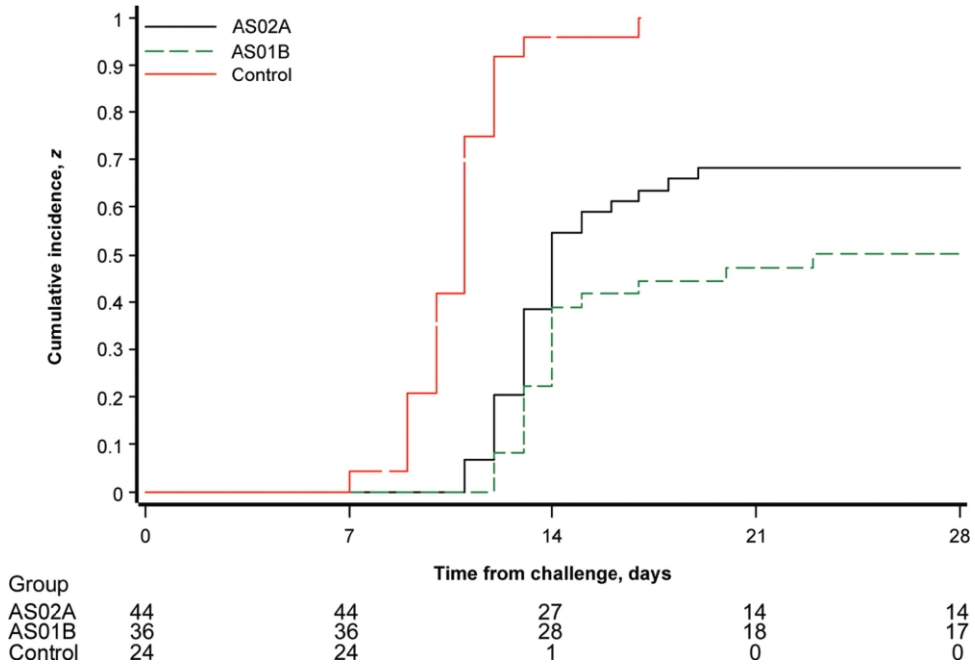




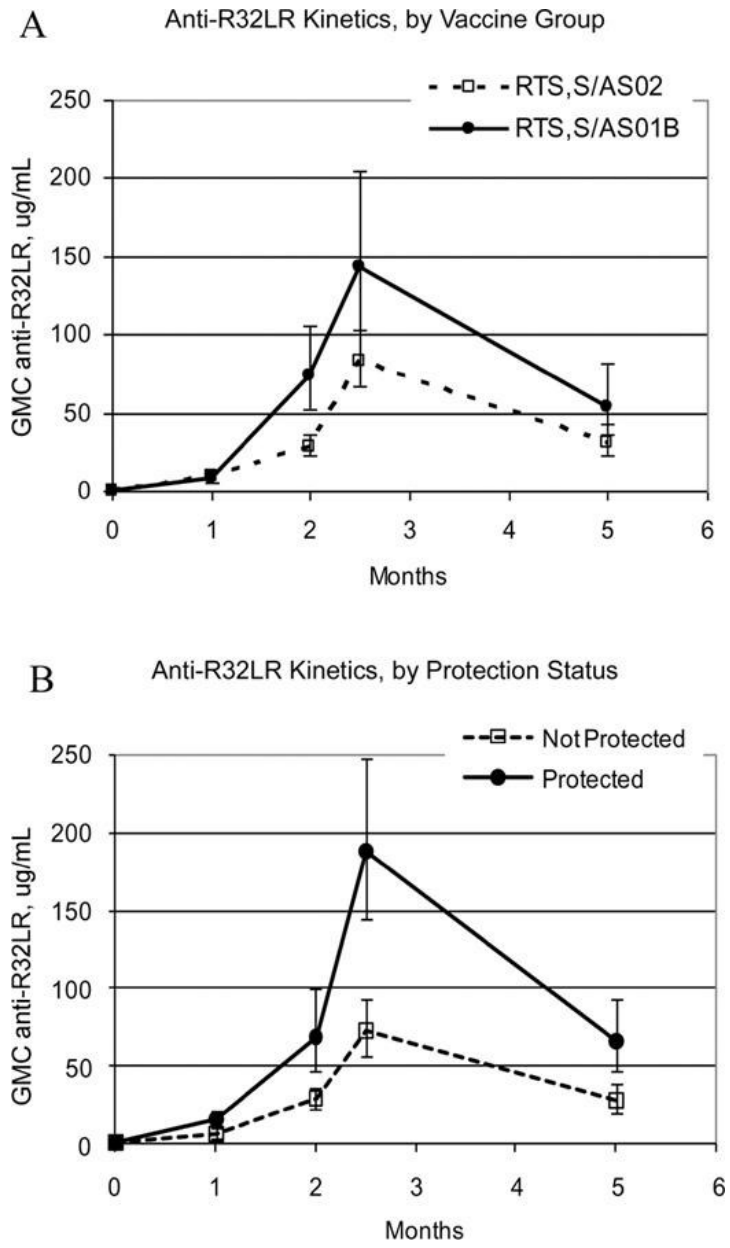
Sauerwein *et al.* Nat Rev Immunol 2011

Efficacy of RTS,S by malaria challenge





- Small sample size
- Direct comparison of formulations
- Vaccine Efficacy AS01B ~50%
- Provided important immunology data



Kester *et al.* J Infect Dis 2009

Malaria challenge predicts field efficacy

Table 1 | **Summary of published Phase IIa sporozoite challenge trials with *Plasmodium falciparum* candidate vaccines**

Vaccine	*Plasmodium* protein	Category	Number of volunteers challenged	Number of volunteers protected	Year of publication	Institution or company	Refs
Irradiated sporozoites	Whole parasite	Pre-erythrocytic	37	20 (54.05%)	1970s–1993	NMRI* and WRAIR*; University of Maryland, USA; University of Sydney, Australia	60–65
Several products	CSP	Pre-erythrocytic	317	94 (29.65%)	1987–2009	University of Maryland; WRAIR*; University of Oxford, UK; Johns Hopkins University School of Hygiene and Public Health, Maryland, USA; NMRI*; University of Lausanne, Switzerland	12,13,16, 18,20,22, 40,45,62, 66–73
Several products	TRAP	Pre-erythrocytic	74	3 (4.05%)	2003–2006	University of Oxford	22,74,75
AMA1 with AS02A or AS01B	AMA1	Asexual erythrocytic	16	0 (0%)	2009	US Military Malaria Vaccine Program	35
LSA1-NRC with AS01 or AS02	LSA1	Pre-erythrocytic	22	0 (0%)	2010	WRAIR*	76
NYVAC-Pf7	CSP, SSP2, LSA1, MSP1, SERA, AMA1, Pfs25	All stages	35	1 (2.86%)	1998	WRAIR*	77
FFM ME-TRAP plus PEV3A	CSP, TRAP and AMA1	Pre-erythrocytic and asexual erythrocytic	24	0 (0%)	2008	University of Oxford	78
SPf(66)30 or SPf(105)20 with Alum	MSP	Asexual erythrocytic	9	0 (0%)‡	1988	Universidad Nacional de Colombia	79
MuStDO 5	CSP, EXP1, SSP2, LSA1, LSA3	Pre-erythrocytic	31	0 (0%)	2005	Naval Medical Research Center*	80
FMP1 with AS02A	MSP1	Asexual erythrocytic	Unknown	0 (0%)	2005	WRAIR*	81

Alum, aluminium hydroxide adjuvant (Alhydrogel; Brenntag biosector); AMA1, apical membrane antigen 1; AS01, GlaxoSmithKline adjuvant system 01; CSP, circumsporozoite protein; EXP1, exported protein 1; FFM ME-TRAP, multi-epitope string fused to TRAP that is delivered in fowlpox virus strain FP9 and modified vaccinia virus Ankara vectors in prime–boost combinations; FMP1, carboxy-terminal region of MSP1; LSA, liver-stage antigen; LSA1-NRC, full-length carboxy- and amino-terminal flanking domains and two of the 17 amino acid repeats from the central repeat region of LSA1; MSP, merozoite surface protein; MuStDO 5, multi-stage DNA vaccine operation 5 antigens; NMRI, Naval Medical Research Institute, USA; NYVAC-Pf7, a highly attenuated vaccinia virus with seven *P. falciparum* genes inserted into its genome; PEV3A, virosomal formulation of CSP and AMA1; Pfs25, 25kDa ookinete surface antigen; SERA, serine-repeat antigen protein; SSP2, sporozoite surface protein 2; SPf, synthetic *P. falciparum* peptides of MSP; TRAP, thrombospondin-related adhesion protein; WRAIR, Walter Reed Army Institute of Research, USA. *Currently the US Military Malaria Vaccine Program. ‡Three of five volunteers immunized with SPf(66)30 eventually cleared parasitaemia after they experienced asexual parasitaemia that was detectable by microscopy.

RTS,S

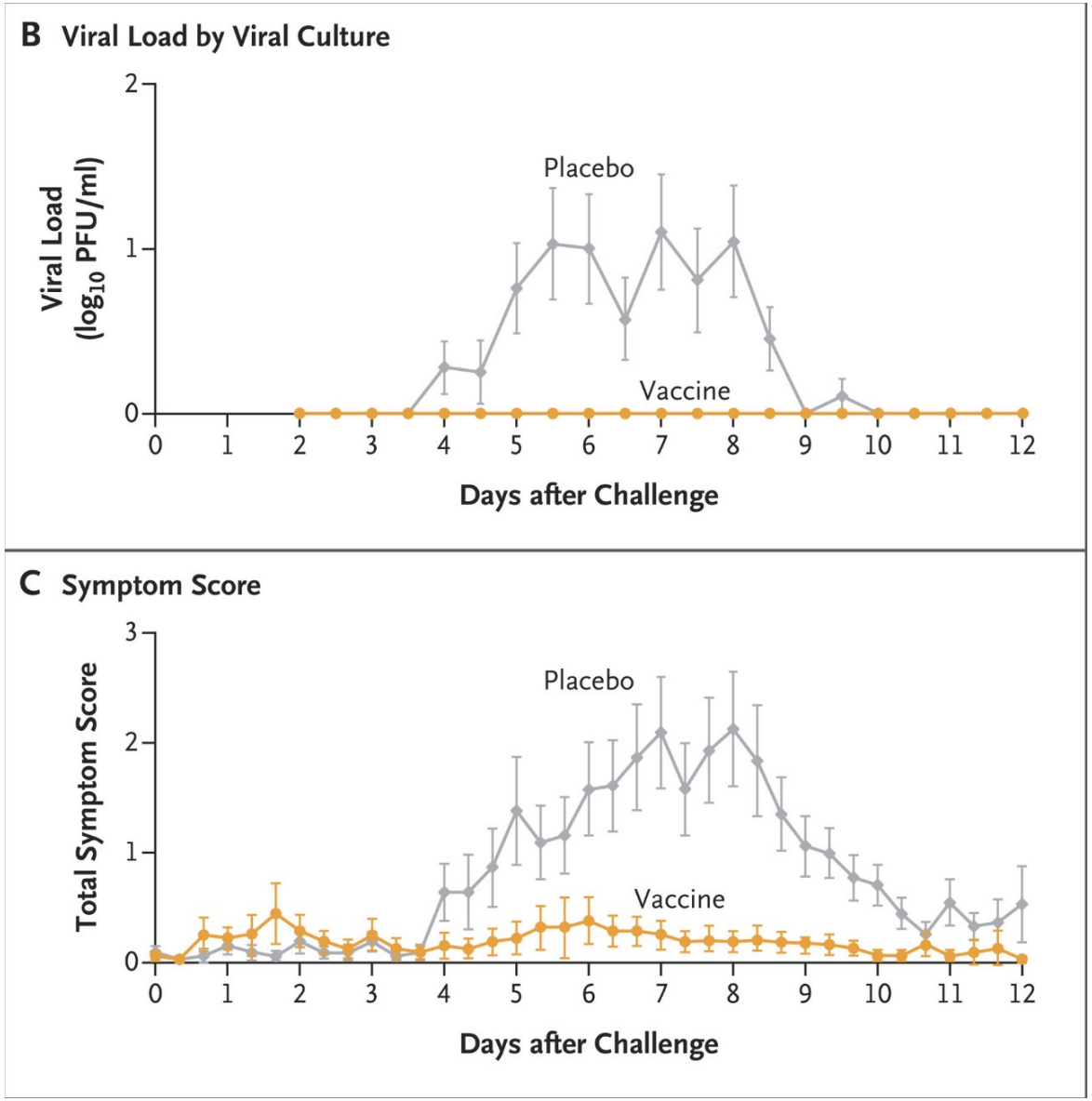
- Alonso *et al.* Lancet 2005
  - Phase IIb RCT Mozambican children 1-4yo
  - VE 35.3% for infection; 48.6% for severe malaria
- RTS,S Clinical Trials Partnership. Lancet 2015
  - VE 36.3%; 32.2% for severe malaria

R21 (Matrix-M, higher CSP:HbS ratio)

- ~82% VE in CHIM
- Datoo *et al.* Lancet 2024
  - Phase III in 5-36mo (Burkina Faso, Mali, Kenya, Tanzania)
  - VE 75% at seasonal sites; 67% at perennial transmission sites
  - Antibodies correlated with protection

Sauerwein *et al.* Nat Rev Immunol 2011
Am J Trop Med Hyg Conference 2017; Nov 5–9, 2017 (abstr 5 supp 1)

RSV young adult challenge predicted field efficacy in elderly



Pfizer

Pfizer Press release | Vaccines | Vaccines

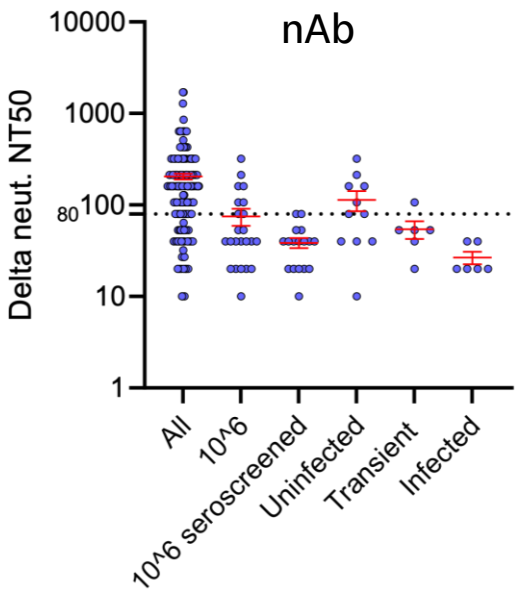
Pfizer Announces Positive Top-Line Data from Phase 3 Trial of Older Adults for its Bivalent Respiratory Syncytial Virus (RSV) Vaccine Candidate

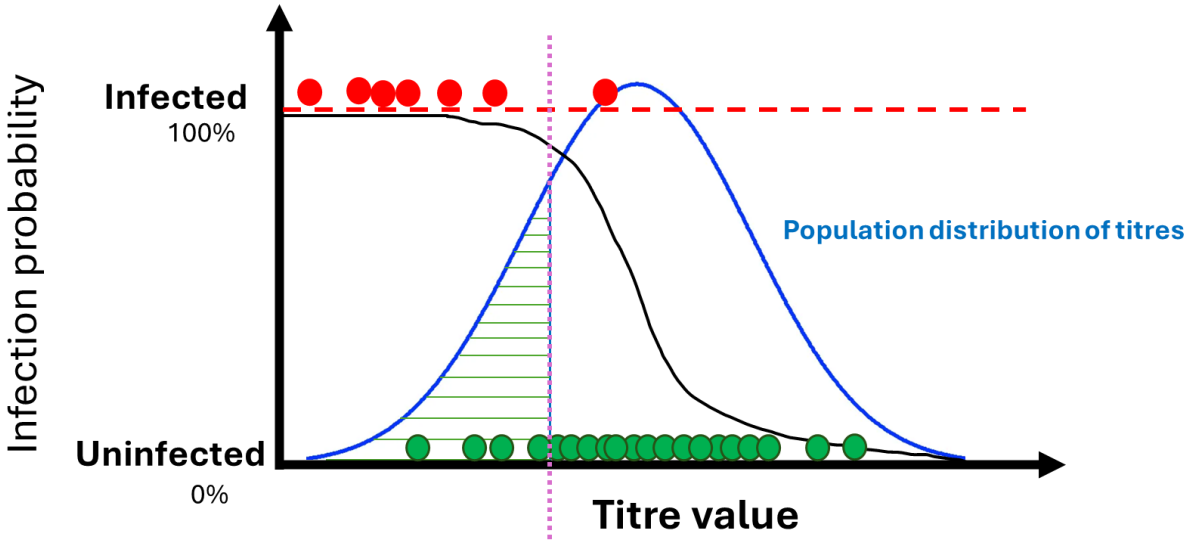
Thursday, August 25, 2022 - 06:45am

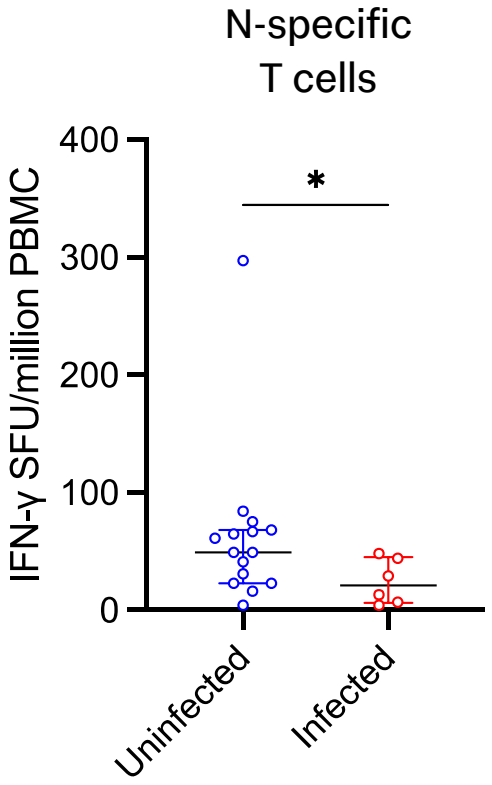
- *Vaccine efficacy of 85.7% was observed in participants with more severe disease primary endpoint of lower respiratory tract illness (LRTI-RSV) defined by analysis of three or more RSV-associated symptoms*

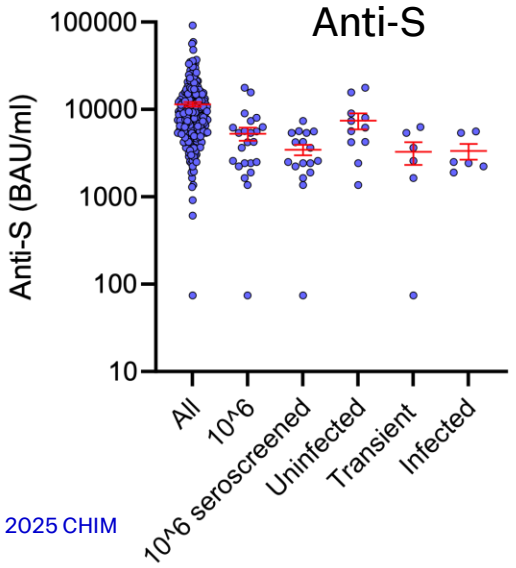
Schmoele-Thoma *et al.* NEJM 2022

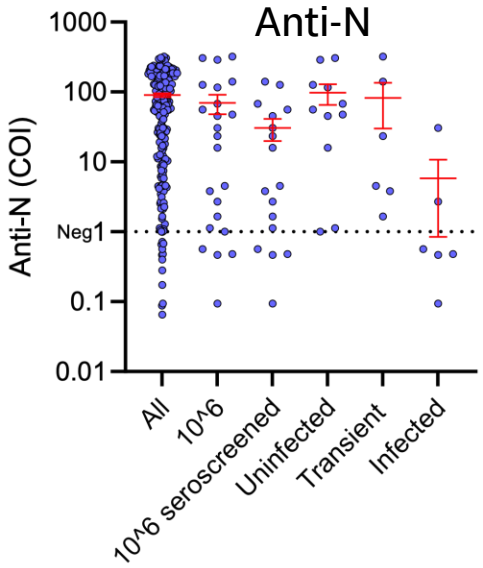
Protection from breakthrough infection associated with N-specific immunity











CEPI/EU Mucosal Immunity in Coronavirus Challenge (MUSICC) consortium

CEPI

News

Global consortium plans coordinated human challenge studies in hunt for transmission-blocking coronavirus vaccines

CEPI • 11th March 2024

- 21 institutional partners, 40 PIs
- Further call to build capacity in LMICs upcoming

Optimising betaCoV CHIM & assays for measuring mucosal immunity

- Accelerated challenge agent manufacturing
- New CHIM models
  - Omicron BA.5
  - Omicron EG.5.1
  - Seasonal CoV OC43
- Optimised sampling & assays for nasal IgA & T cells

Testing next-gen mucosal vaccines

- Non-conventional approaches
  - Mucosal
  - T cell inducing?
- Identify optimal vaccine platform for pandemic preparedness
  - Transmission reduction/ blockade

Establishing correlates of transmission

- Mathematical modeling
- Translating high-dimensional data into usable CoPs