# Typhoid CHIM

Andrew J Pollard FMedSci

# 2020

My mother can't forgive me for being alive.
The typhoid made me stooped, legs short,
never to be wed, but my hands are quick,
my voice strong, and I look up as I walk icy streets –

I may trip over frozen excrement
or sighing heaps of rags but I remember my brother's
hand in mine as he said, look at the planets,
that's Jupiter, and there's Mars, there.....

**Caroline Lucretia Herschel**
16 March 1750 – 9 January 1848
German astronomer
First woman to be awarded a Gold Medal of the Royal Astronomical Society

World Health Organization

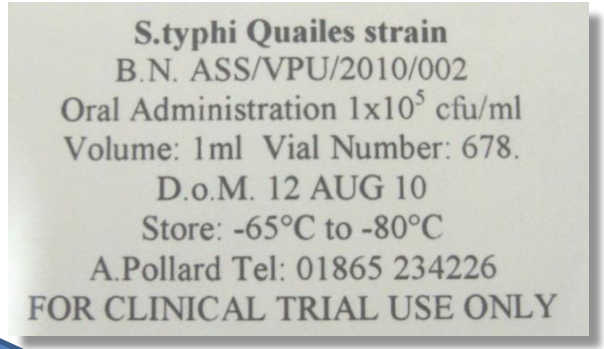
FINAL
ENGLISH ONLY

**Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines:**

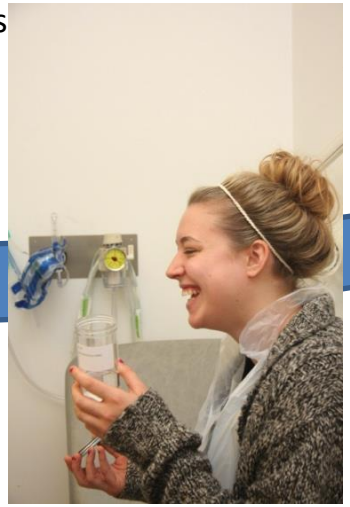
Nevertheless, successful typhoid challenge studies conducted in healthy adults using an appropriate and validated model (i.e. one in which some protective efficacy of unconjugated Vi vaccines is detectable) could provide considerable supporting evidence of the efficacy of a Vi conjugate vaccine. Human challenge studies may also provide at least limited information on the relationship between the immune response and various efficacy parameters. If, in consultation with

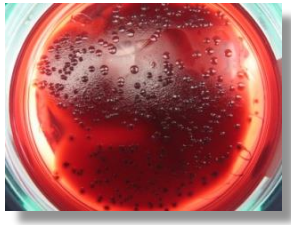
# Oxford Challenge Model

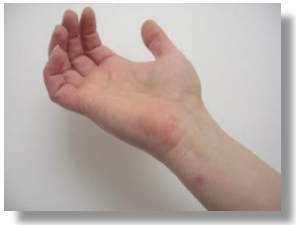
Mrs Quailes





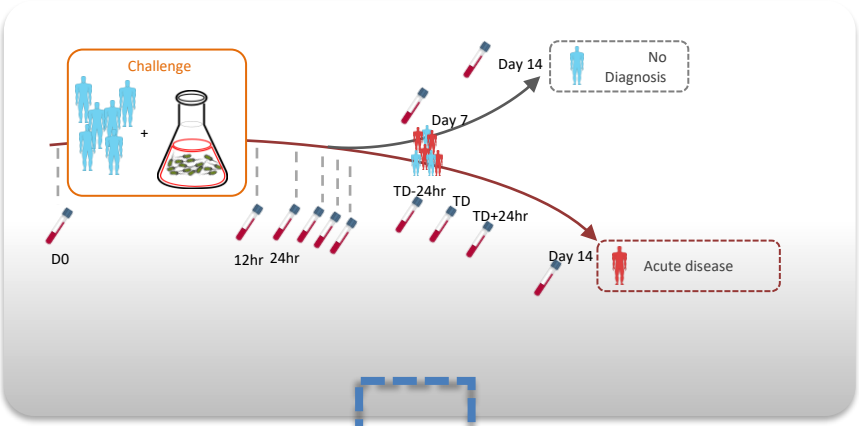






wellcome trust

# Using CHIM to Accelerate Discovery

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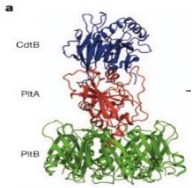
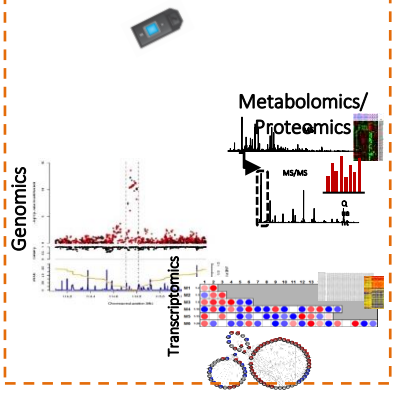
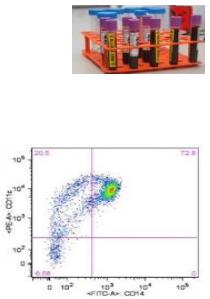


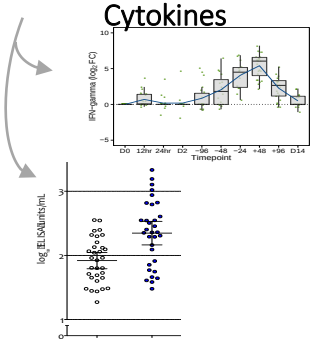

**Omics**




**CMI**



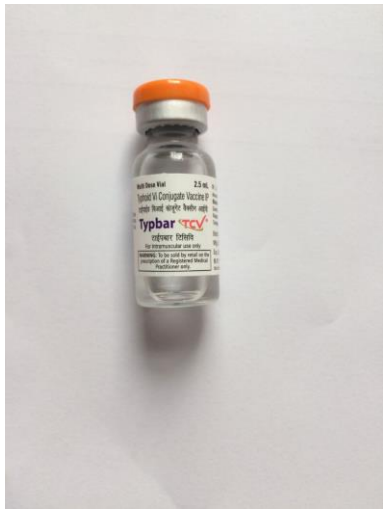
**Serology & Cytokines**

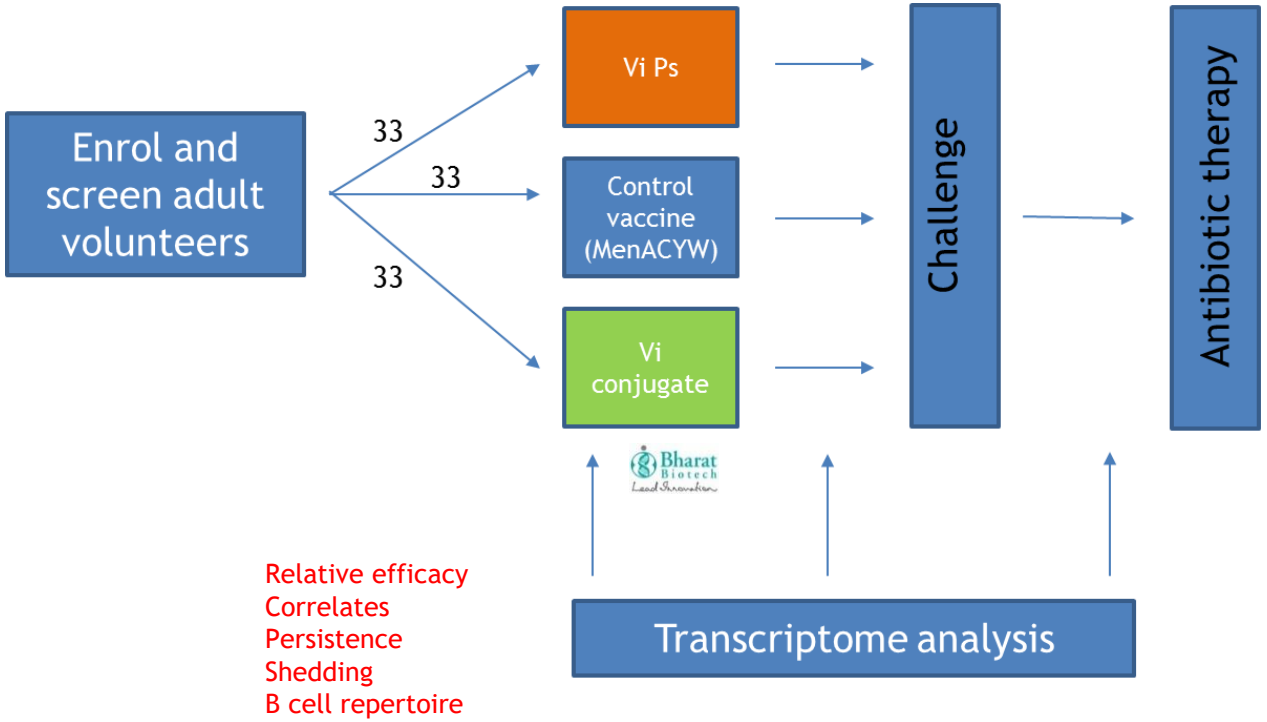


**Vaccines**

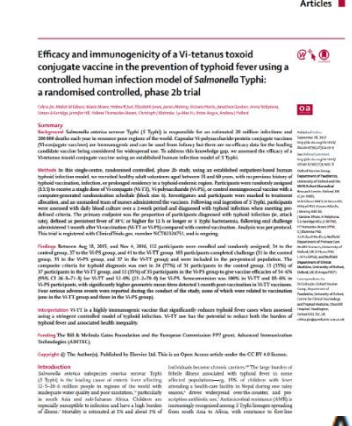
Slide courtesy of C. Blohmke

# New Vi conjugate vaccine




Celina Jin


Articles

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

# VE in CHIM

UNIVERSITY OF OXFORD

A

Cumulative proportion of participants with S Typhi infection (%)

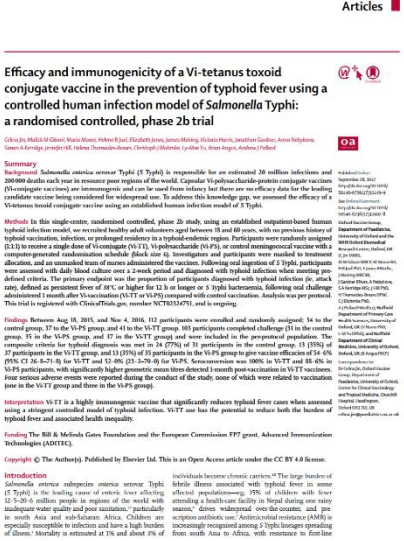
Control group
Vi-TT group
Vi-PS group

Log-rank
Vi-TT p=0·0001
Vi-PS p=0·0002

77%

52-54%

| Number at risk | | | | |
|---|---|---|---|---|
| Control group | 31 | 16 | 7 |
| Vi-TT group | 37 | 30 | 24 |
| Vi-PS group | 35 | 29 | 23 |



Articles

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

Summary

Background *Salmonella enterica* serovar Typhi (*S* Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a Vi-tetanus toxoid conjugate vaccine using an established human infection model of *S* Typhi.

Methods In this single-centre, randomised controlled, phase 2b study, using an established outpatient-based human typhoid infection model, we recruited healthy adult volunteers aged between 18 and 60 years, with no previous history of typhoid vaccination, infection, or prolonged residency in a typhoid-endemic region. Participants were randomly assigned (1:1:1) to receive a single dose of Vi-conjugate (Vi-TT), Vi-polysaccharide (Vi-PS), or control meningococcal vaccine with a computer-generated randomisation schedule (block size 6). Investigators and participants were masked to treatment allocation, and an unmasked team of nurses administered the vaccines. Following oral ingestion of 5 TyphI, participants were assessed with daily blood culture over a 2-week period and diagnosed with typhoid infection when meeting pre-defined criteria. The primary endpoint was the proportion of participants diagnosed with typhoid infection (ie, attack rate), defined as persistent fever of 38°C or higher for 12 h or longer or 5 TyphI bacteraemia, following oral challenge administered 1 month after Vi-vaccination (Vi-TT or Vi-PS) compared with control vaccination. Analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT02324751, and is ongoing.

Findings Between Aug 18, 2015, and Nov 4, 2016, 112 participants were enrolled and randomly assigned; 34 to the control group, 37 to the Vi-PS group, and 41 to the Vi-TT group. 103 participants completed challenge (31 in the control group, 35 in the Vi-PS group, and 37 in the Vi-TT group) and were included in the per-protocol population. The composite criteria for typhoid diagnosis was met in 24 (77%) of 31 participants in the control group, 13 (35%) of 37 participants in the Vi-TT group, and 13 (35%) of 35 participants in the Vi-PS group to give vaccine efficacies of 54·6% (95% CI 26·6–71·8) for Vi-TT and 52·4% (23·2–70·8) for Vi-PS. Seroconversion was 100% in Vi-TT and 88·6% in Vi-PS participants, with significantly higher geometric mean titres detected 1-month post-vaccination in Vi-TT vaccinees. Four serious adverse events were reported during the conduct of the study, none of which were related to vaccination (one in the Vi-TT group and three in the Vi-PS group).

Interpretation Vi-TT is a highly immunogenic vaccine that significantly reduces typhoid fever cases when assessed using a stringent controlled model of typhoid infection. Vi-TT use has the potential to reduce both the burden of typhoid fever and associated health inequality.

Funding The Bill & Melinda Gates Foundation and the European Commission FP7 grant, Advanced Immunization Technologies (ADITEC).

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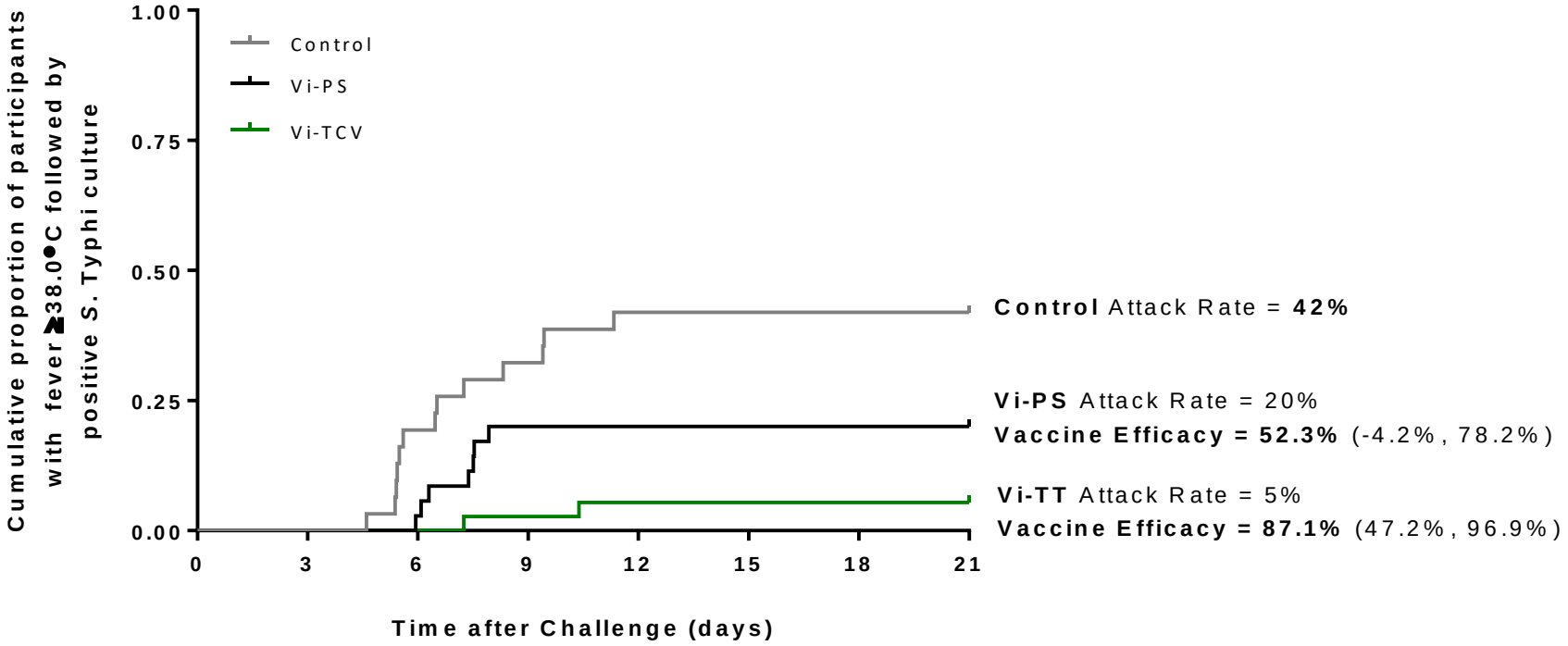
Introduction

*Salmonella enterica* subspecies *enterica* serovar Typhi (*S* Typhi) is the leading cause of enteric fever affecting 12·5–20·6 million people in regions of the world with inadequate water quality and poor sanitation,[1] particularly in south Asia and sub-Saharan Africa. Children are especially susceptible to infection and have a high burden of illness.[2] Mortality is estimated at 1% and about 3% of individuals become chronic carriers.[3,4] The large burden of febrile illness associated with typhoid fever in some affected populations[5–7] means, 15% of children with fever attending a health-care facility in Nepal during one rainy season,[7] drives widespread over-the-counter, and pre-scription antibiotic use.[7] Antimicrobial resistance (AMR) is increasingly recognised among *S* Typhi lineages spreading from south Asia to Africa, with resistance to first-line

# VE in CHIM

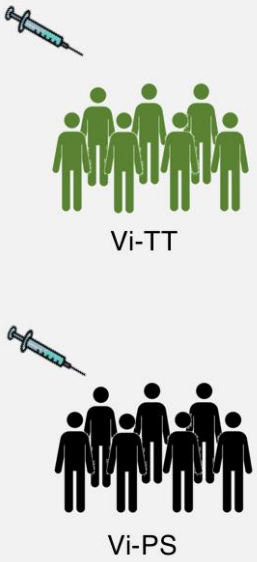
VE 54-87%

**Fever ≥38.0°C followed by positive *S.* Typhi blood culture**

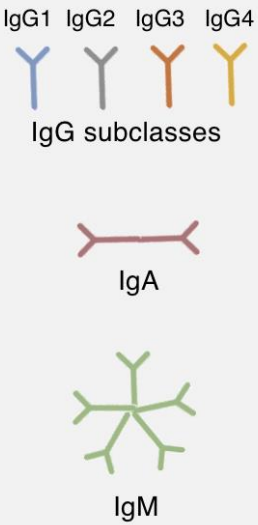


# correlates of protection

## Vaccination

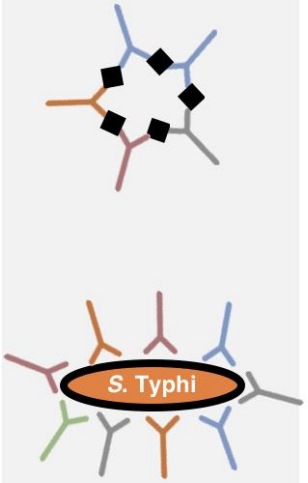



## Polyclonal Antibody Production



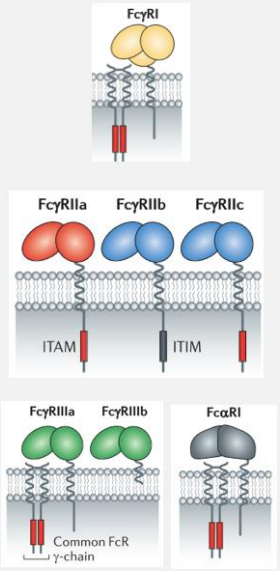

**Dependent on Antigen Type**
(T-dependent versus T-independent)

## Immune Complex Formation/ Opsonisation



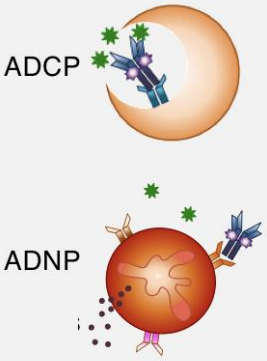

**Dependent on Avidity**

## Fc Receptor Binding




**Dependent on Binding Affinity**
(Antibody quantity
IgG subclasses
Genetic polymorphism of FcR)

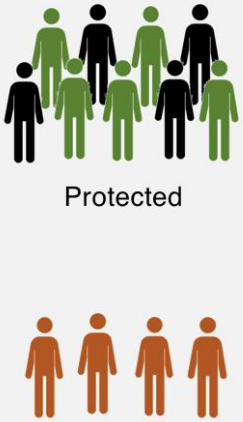
## Fc Triggering of Effector Innate Functions

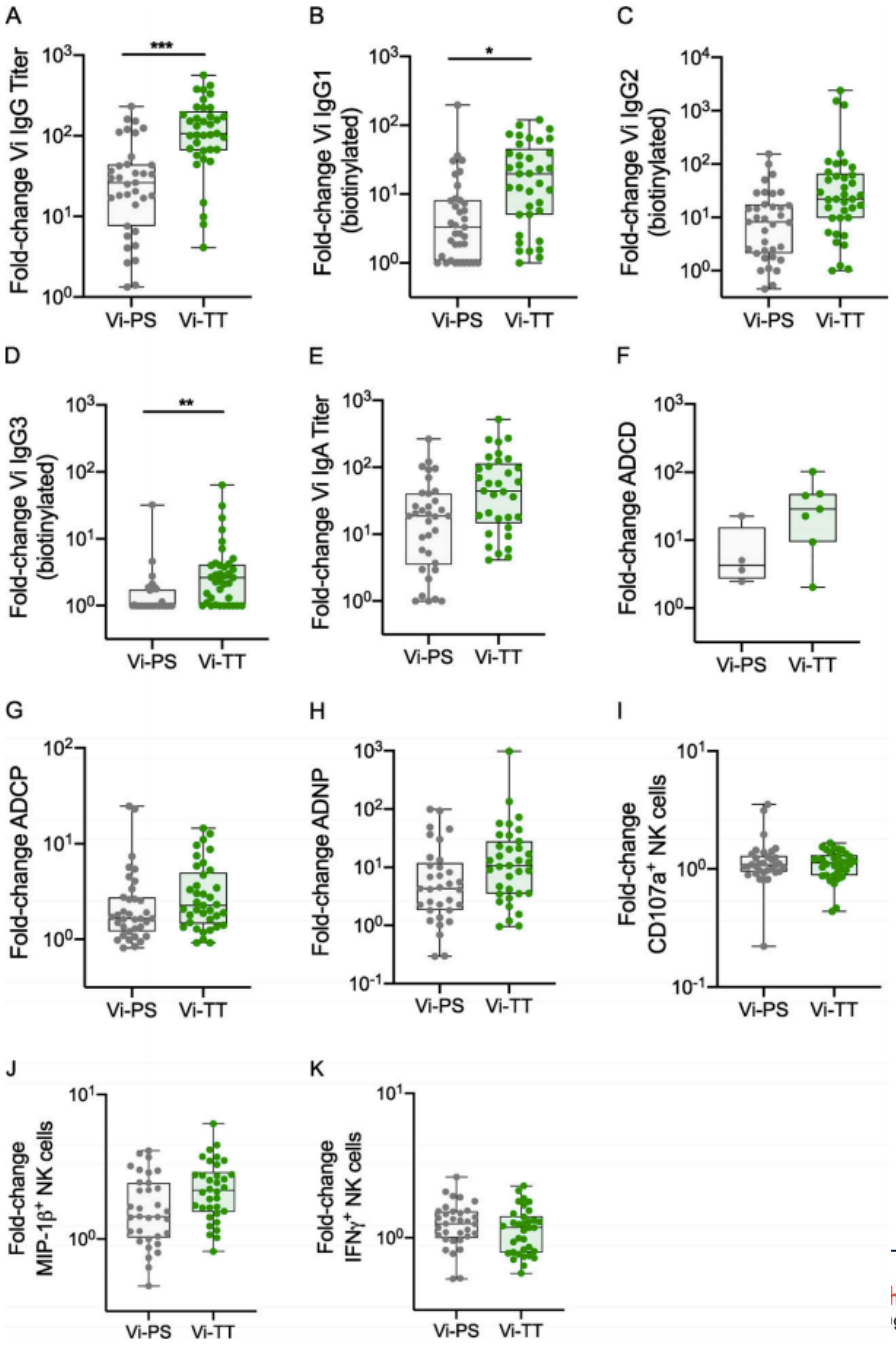



ADCC
ADNKA
ADDCP

**Dependent on Binding of FcRs on innate cells**
(activation vs inhibition)

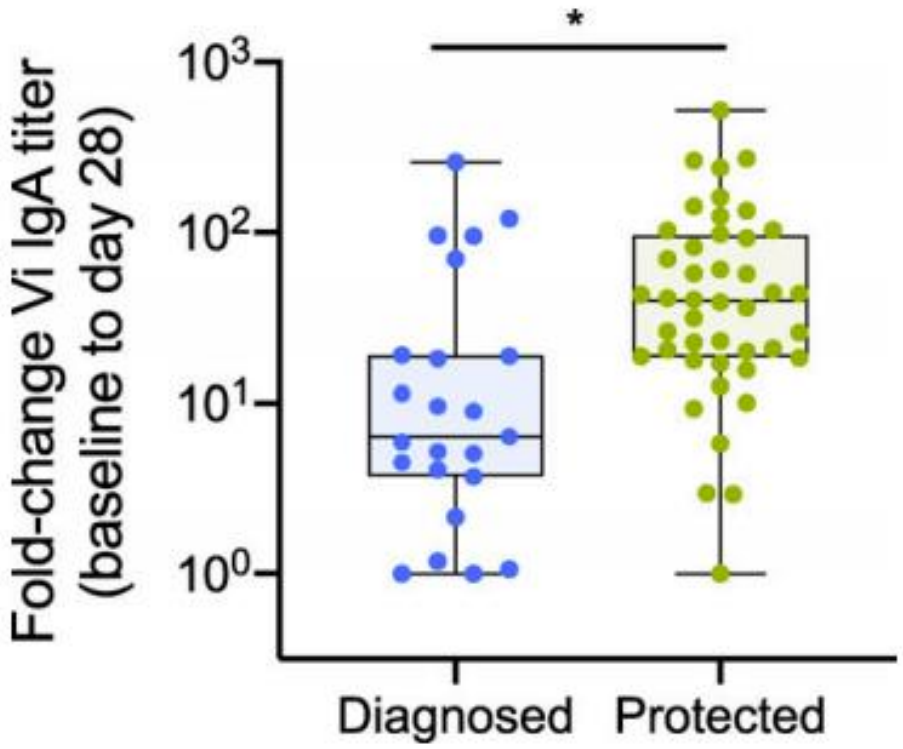
## Clinical Protection





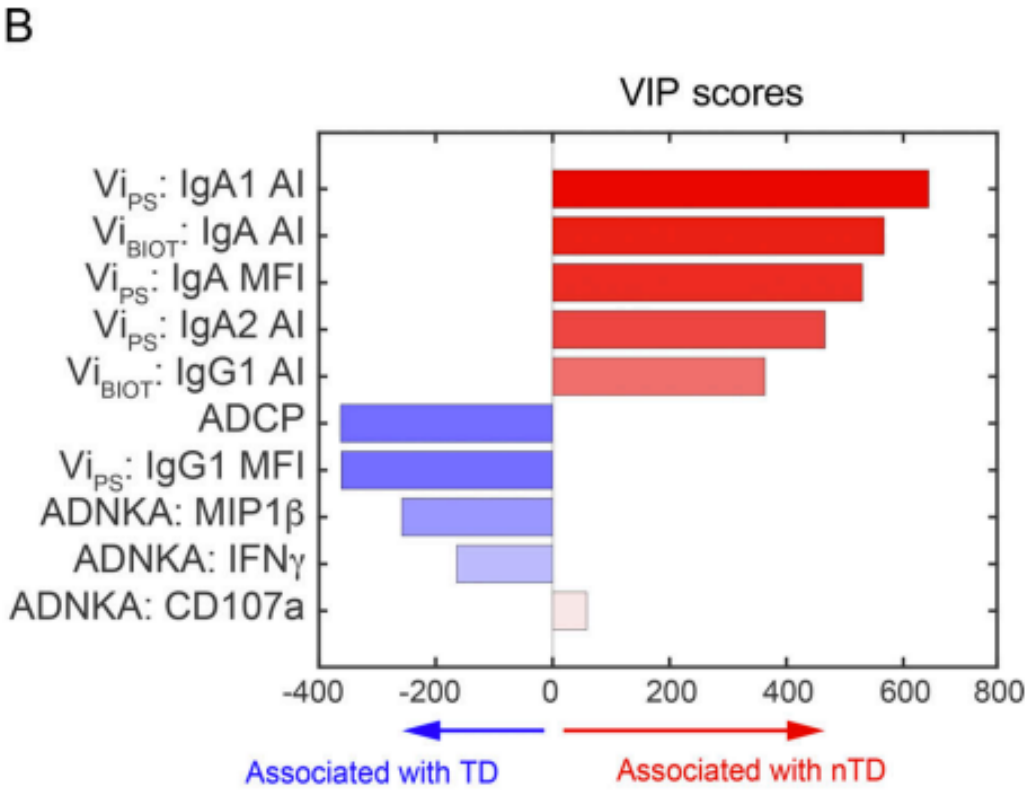

Vi-TT induces higher levels functional antibody than Vi-PS

# IgA and protection




Jin et al, JEM 2020

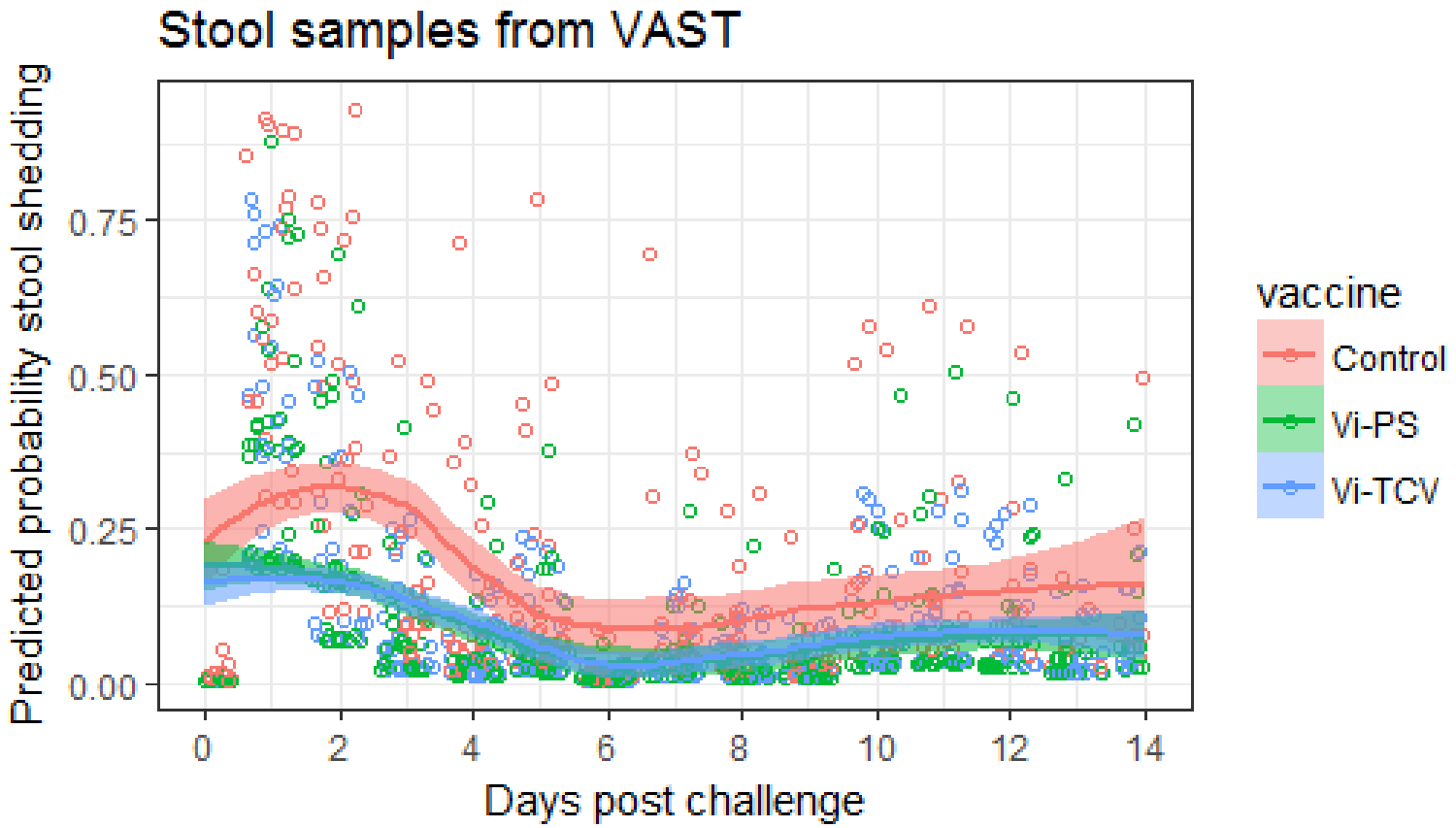
# ADNP and IgA predict protection within Vi-TT




Wen-Han Yu

Ragon Institute of MGH, MIT and Harvard

# Shedding


Stool samples from VAST
Predicted probability stool shedding
0.00
0.25
0.50
0.75
0
2
4
6
8
10
12
14
Days post challenge
vaccine
Control
Vi-PS
Vi-TCV

**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.

WHO prequalification

WHO SAGE recommendations

Gavi funding


# TyVac

UOXF, UMB

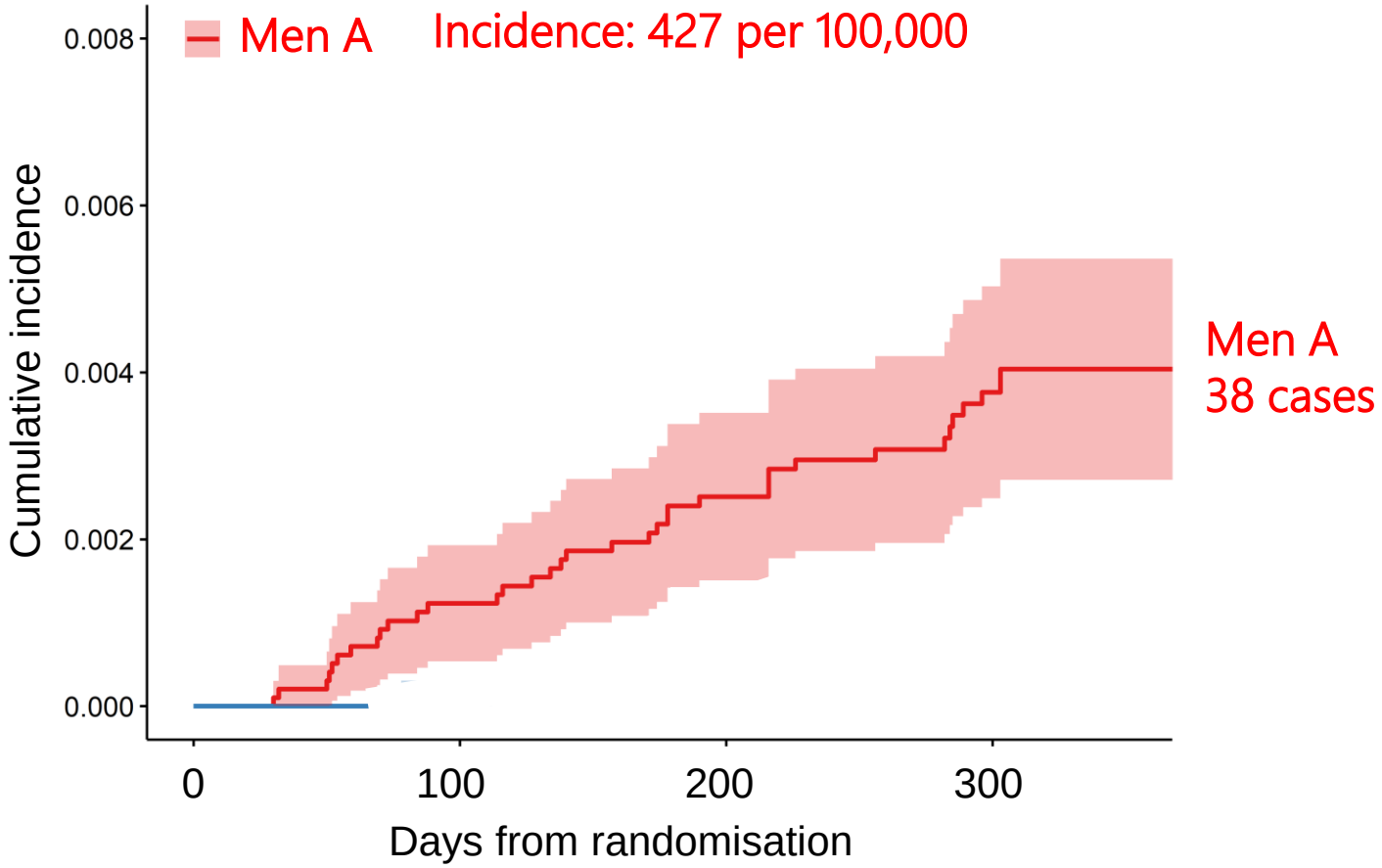
UOXF | UMB

| Nepal | Banglades h | Malawi |
|---|---|---|
| 20,000 | >58,000 | 28,000 |
| Buddha Basnyat Shrijana Shrestha | John Clemens Firdausi Qadri | Melita Gordon |

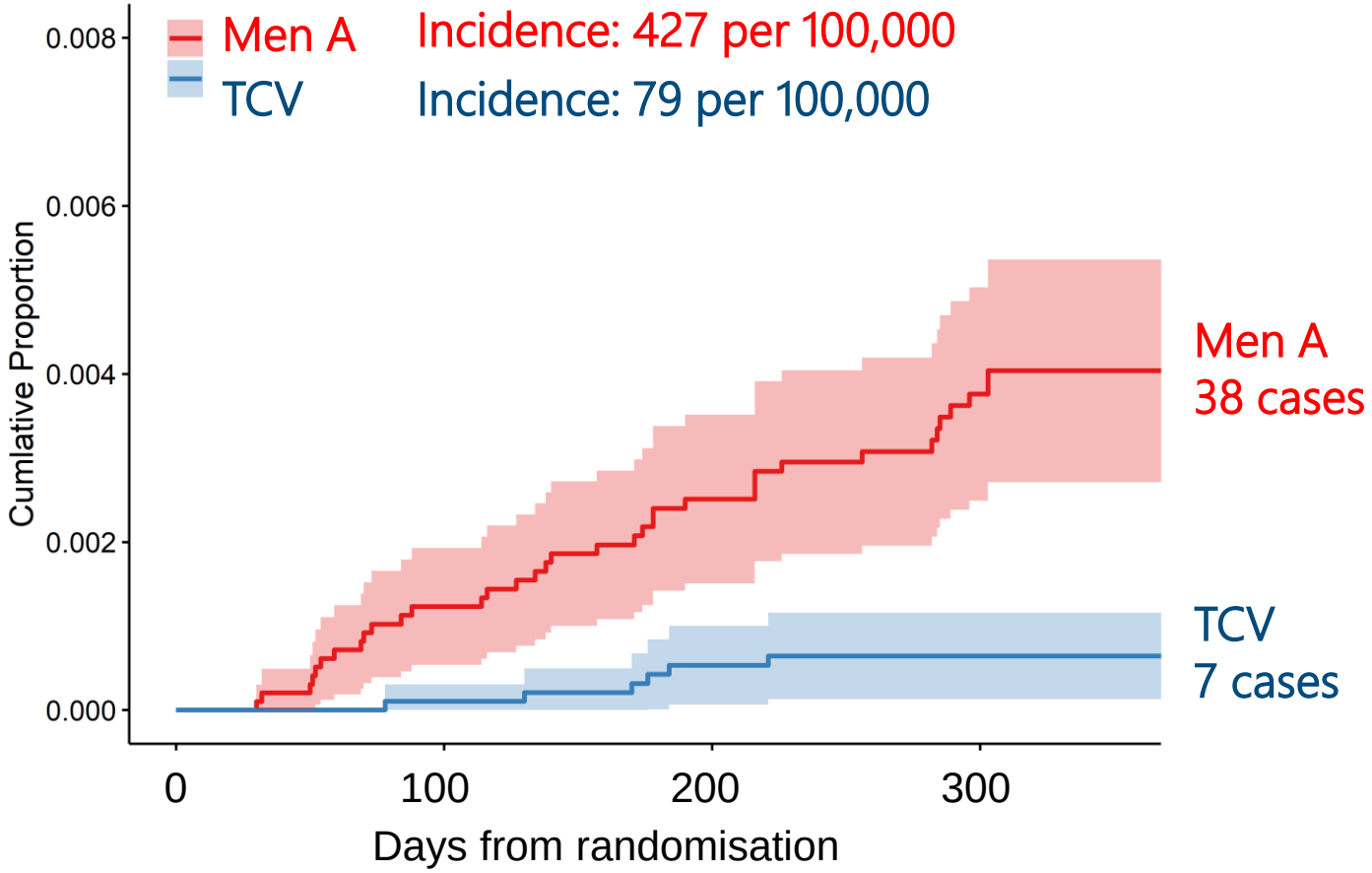
BILL & MELINDA GATES foundation

## Interim analysis

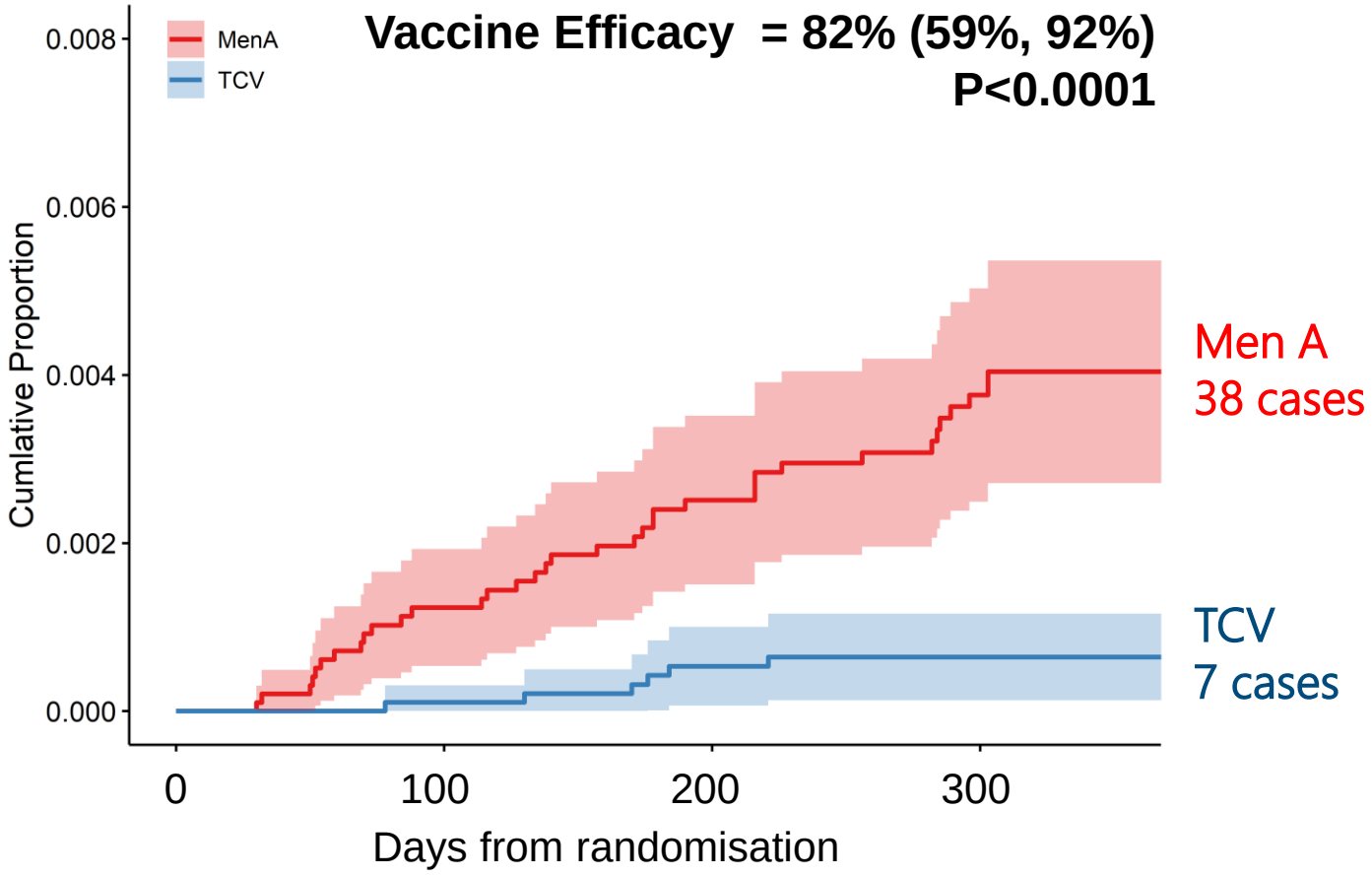
# Incidence in Control Group



# Incidence in TCV Group



# Vaccine efficacy



# Typhoid and Paratyphoid combined

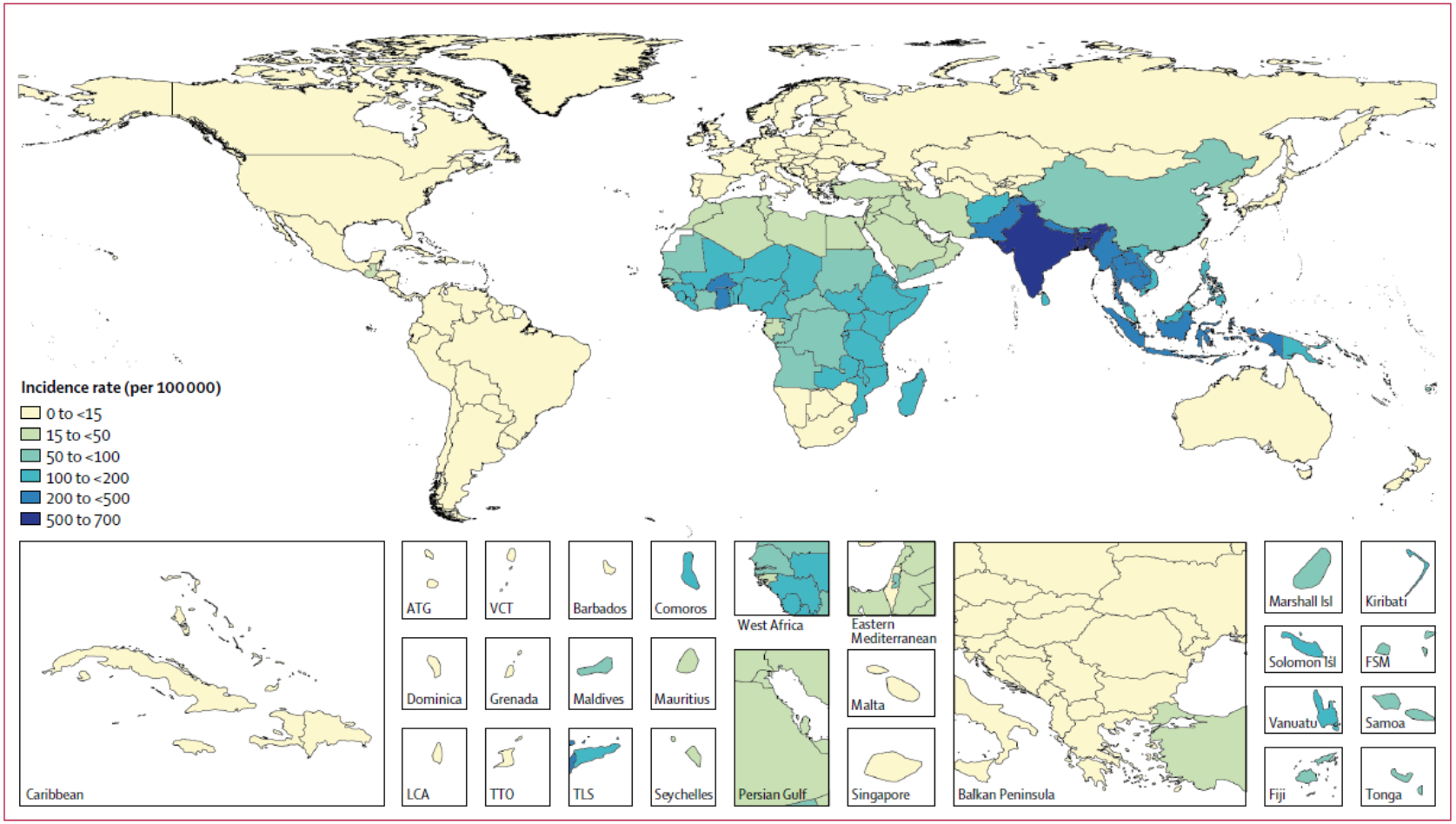
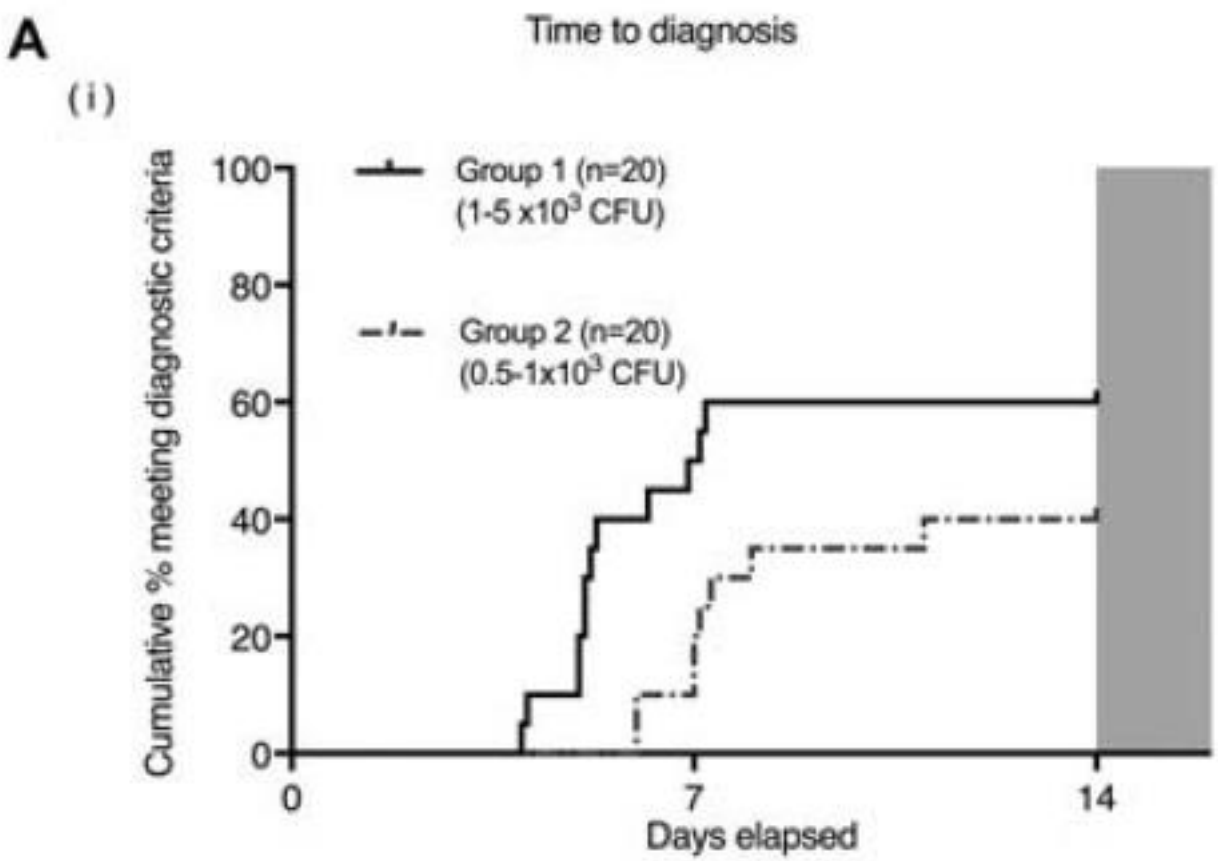



*Figure 1:* **Incidence rates (per 100 000) of typhoid and paratyphoid fevers, by country, in 2017**
Unfilled locations are those for which GBD does not produce estimates. The inset maps detail smaller locations. ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. Isl=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines.

# Paratyphoid attack rates

## Composite diagnosis

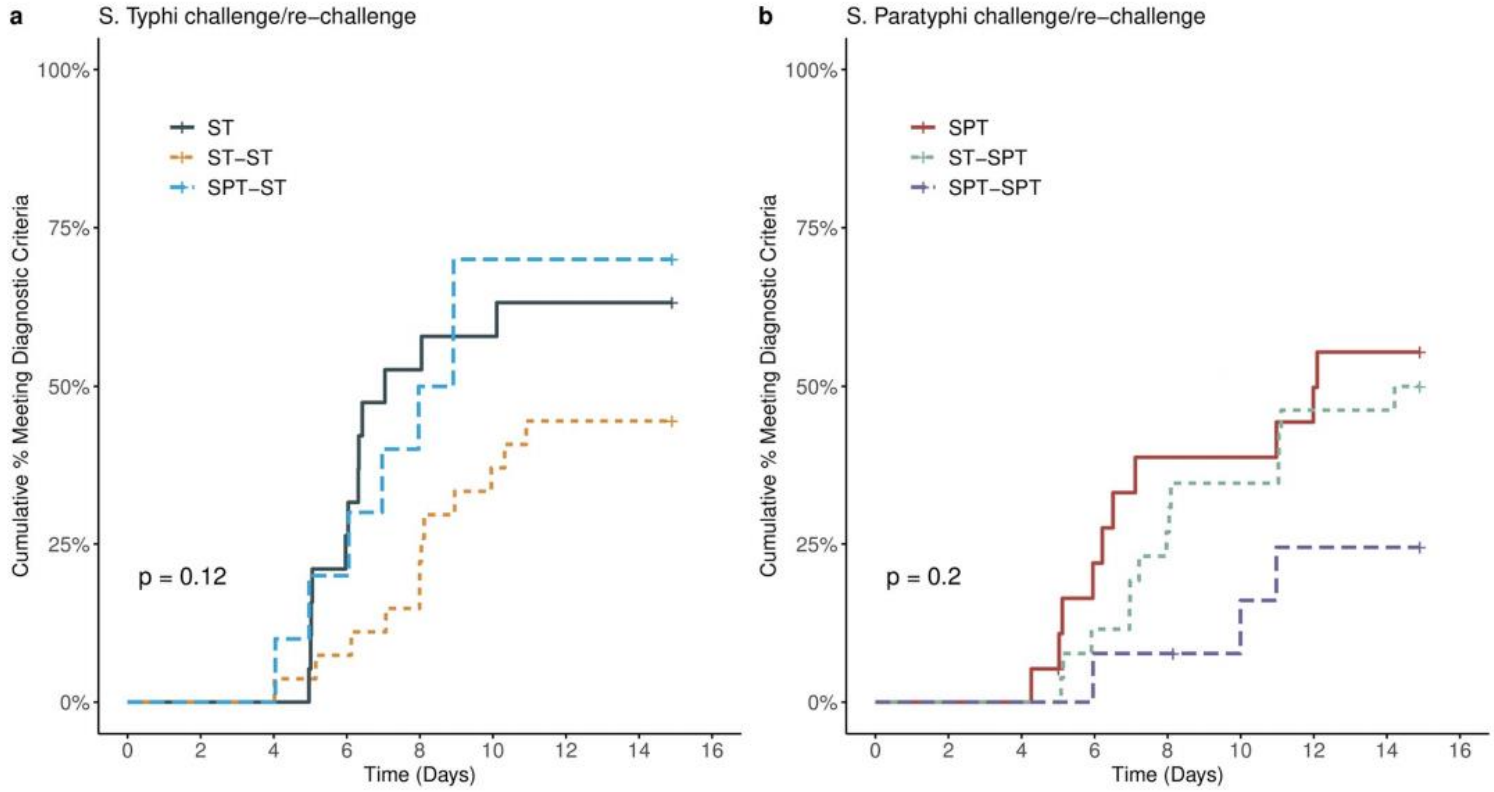



Dobinson et al, 2017

# Time to Diagnosis after naïve *S.* Paratyphi challenge and Re-challenge.

PLOS NEGLECTED TROPICAL DISEASES

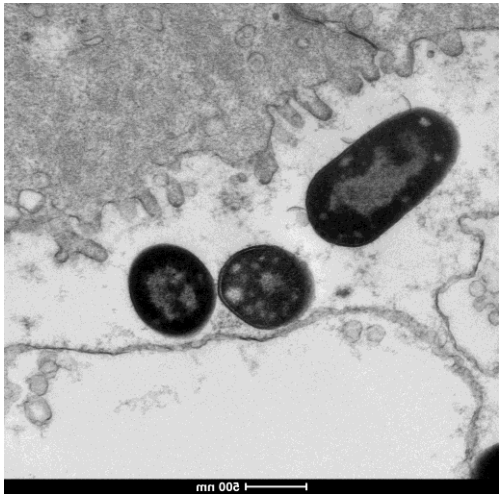
Typhoid and paratyphoid re-challenge




Gibani et al, 2020

# Paratyphoid Vaccine approaches

- Live attenuated strain – CHIM 2021(UMB/Bharat), Prokarium
- Bivalent – Vi-conjugate + LPS conjugate (Bio-E)
- Paratyphoid efficacy trials probably not feasible
  - 100,000-250,000
  - supporting data for paratyphoid component from CHIM



*S.* Paratyphi A (NVGH308)

# Acknowledgements

## Volunteers


www.ovg.ox.ac.uk

Oxford Biomedical Research Centre
Enabling translational research through partnership