



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](#)



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



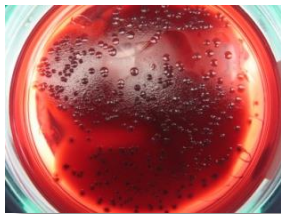
Oxford Challenge Model



Mrs Quiailes

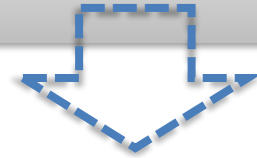
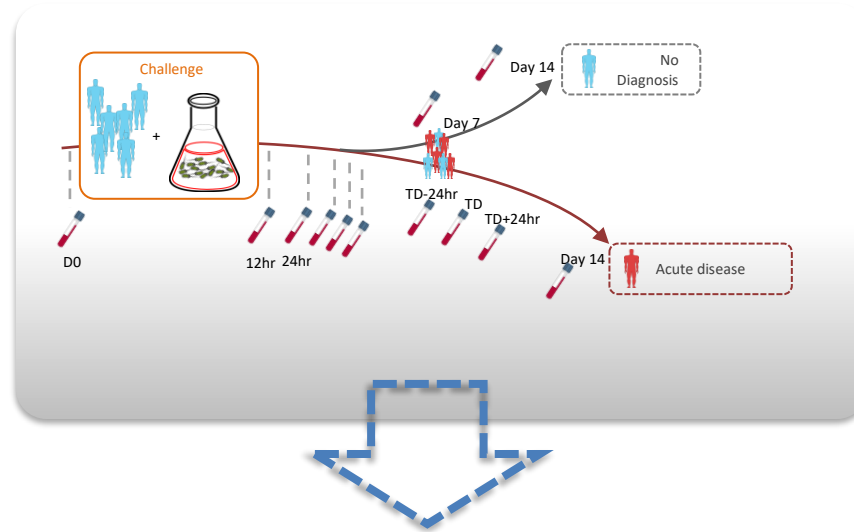


S.typhi Quiailes strain
B.N. ASS/VPU/2010/002
Oral Administration 1×10^5 cfu/ml
Volume: 1ml Vial Number: 678.
D.o.M. 12 AUG 10
Store: -65°C to -80°C
A.Pollard Tel: 01865 234226
FOR CLINICAL TRIAL USE ONLY

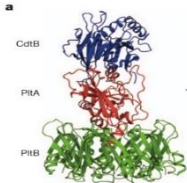


wellcometrust

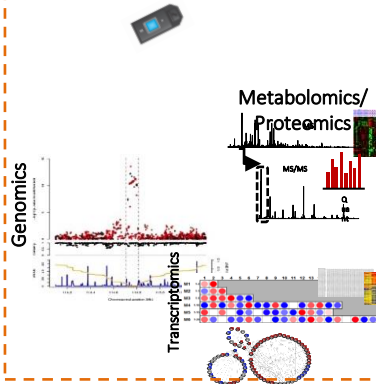
Using CHIM to Accelerate Discovery



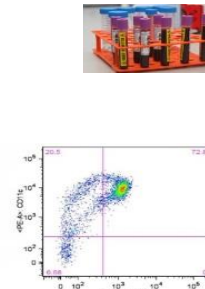
Pathogenesis



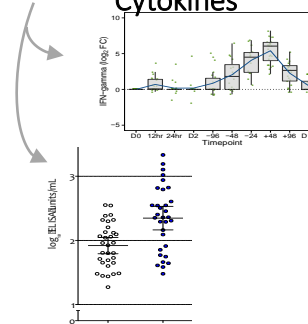
Omics



CMI



Serology & Cytokines

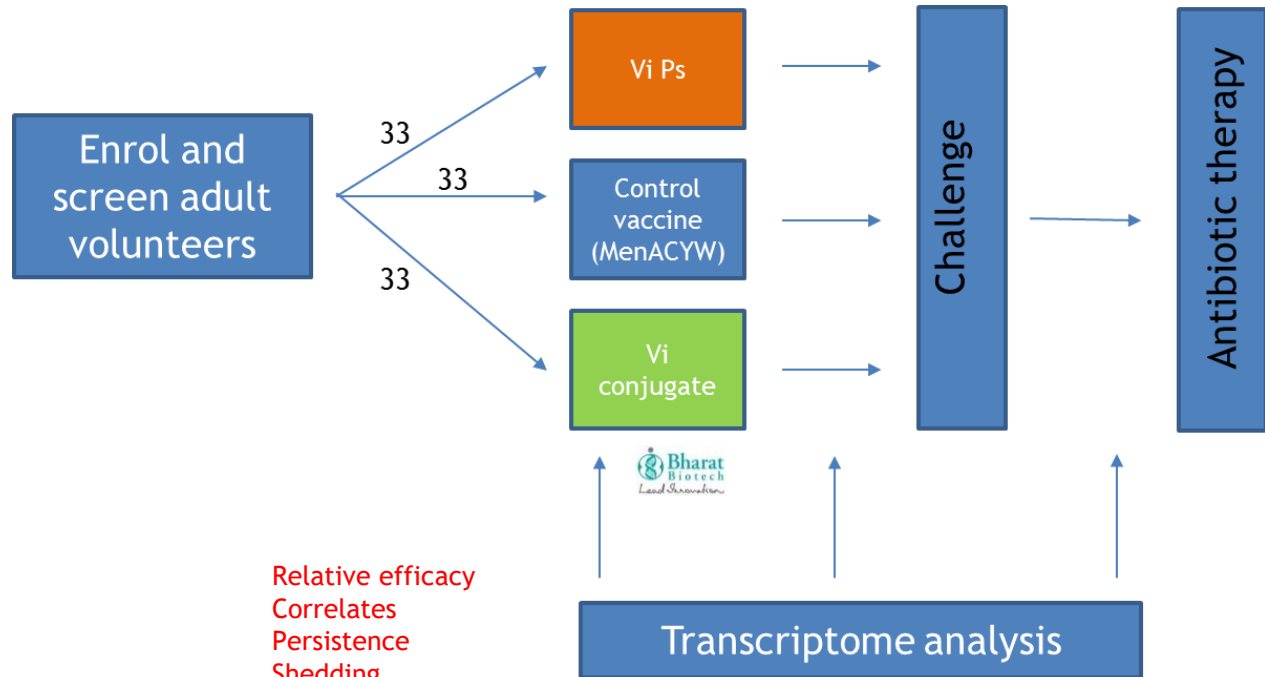


Vaccines

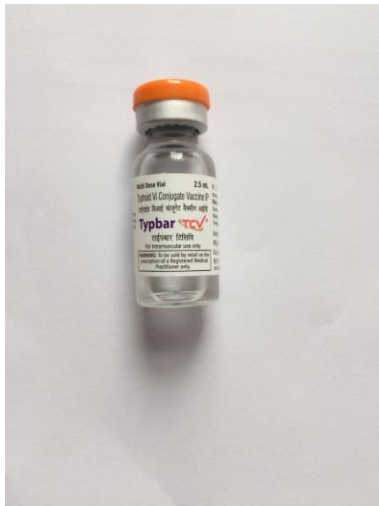


Slide courtesy of C. Blohmke

New Vi conjugate vaccine



Relative efficacy
Correlates
Persistence
Shedding
B cell repertoire

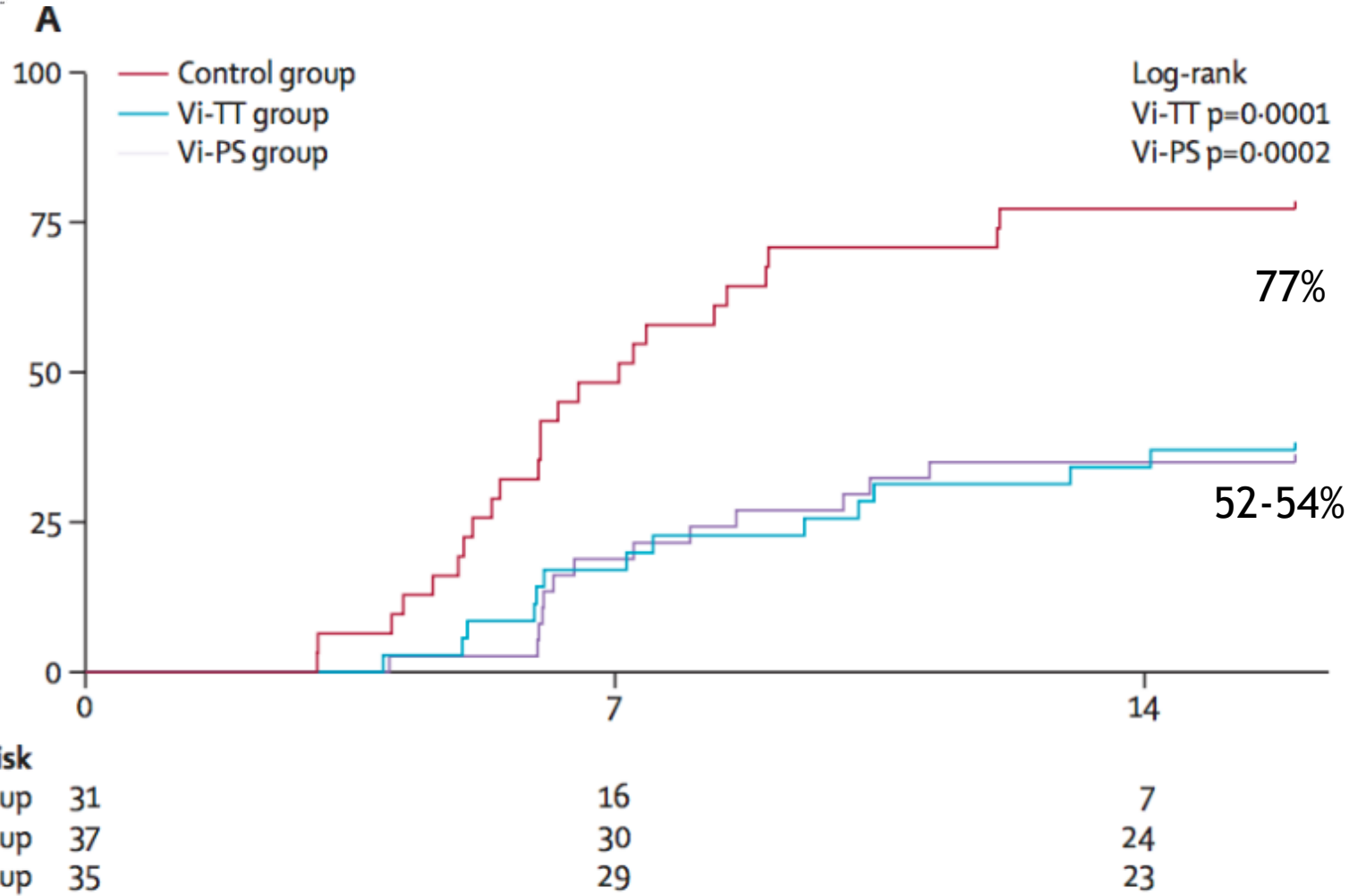


Celina Jin

BILL & MELINDA
GATES foundation

Summary
 Background *Salmonella enterica* serovar Typhi (Typhi) is responsible for an estimated 30 million infections and 200 000 deaths each year in resource-poor regions of the world. Despite its global health impact, conjugate vaccines for Typhi are not available in resource-poor regions and the only available vaccine is not available in resource-poor regions. We assessed the efficacy of a novel conjugate vaccine using an established human infection model of Typhi.
Methods In this multicentre, randomised controlled, phase 2b study, using an established conjugate-based human infection model, we compared the efficacy of a novel conjugate vaccine (Vi-TT) with a control vaccine (Vi-PS) in preventing typhoid fever infection in a typhoid-endemic region. Participants were randomised 1:1 to receive a single dose of conjugate Vi-TT, Vi-PS or placebo. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period.
Results Between Aug 18, 2015, and Nov 4, 2016, 102 participants were enrolled and randomised to the control group (37 in the Vi-PS group and 37 in the Vi-TT group) and 30 participants completed challenge (16 in the control group, 15 in the Vi-TT group and 10 in the Vi-PS group) in the controlled human infection model. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period. The primary endpoint was the proportion of participants who were infected with *S. Typhi* during the study period.
Conclusions Vi-TT is a highly immunogenic vaccine that significantly reduces typhoid fever cases when assessed using a rigorous controlled model of typhoid infection. Vi-TT can be the vaccine to protect the burden of typhoid fever and associated health impacts.
 Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

VE in CHIM



Effcacy 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

Chitra Jha, Rajibul M Ghani, Nishi Akter, Mdona E Saif, Elizabeth Jones, James Mahony, Victoria Parry, Jonathan Godwin, Anna Molybdeus, Simon A Karimaj, Jonathan Hill, Indira Tharmadason, Christoph Jahnke, Lyellia Yu, Brian Angus, Andrew J Valleron

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-germinal 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 40 years, with no previous history of typhoid vaccination, infection, or prodromal symptoms in a typhoid endemic region. Participants were randomised assigned (1:1) to receive a single dose of Vi conjugate (Vi-TT), Vi polysaccharide (Vi-PS), or control meningococcal vaccine with a contemporaneous randomisation schedule (block size 4). Investigators and participants were masked to treatment allocation, and an unmasked team of nurses administered the vaccines. Following oral ingestion of S Typhi, participants were assessed with daily blood cultures 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 presence of fever $\geq 38.0^{\circ}\text{C}$ higher for 12 h or 3 Typhi bacteremia, 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 NCT01870771, and is ongoing.

Findings: Between Aug 18, 2014, and Nov 4, 2016, 112 participants were enrolled and randomly assigned: 34 in 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 34 (77%) of 44 participants in the control group, 13 (35%) of 37 participants in the Vi-TT group, and 12 (29%) of 41 participants in the Vi-PS group to give vaccine efficacies of 64.4% (95% CI 36.8–77.1) for Vi-TT and 52.9% (33.2–70.4) for Vi-PS. Seroprevalence was 100% in Vi-TT and 85.4% 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 also 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 (AMITIC).

Copyright: © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction
Salmonella enterica subsp. *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, particularly in south Asia and sub-Saharan Africa. Children are especially susceptible to infection and have a high burden of illness. Mortality is estimated at 1% and about 3% of

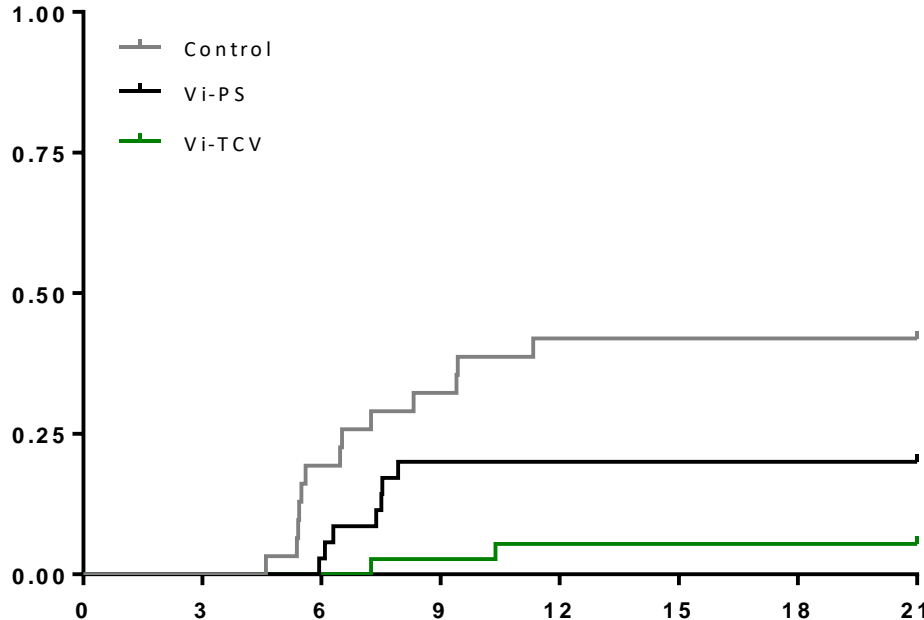
individuals become chronic carriers.¹⁰ The large burden of febrile illness associated with typhoid fever in some affected populations—eg, 17% of children with fever attending a health-care facility in Nepal during one rainy season¹¹—arises widespread, over-the-counter, and prescription antibiotic use.¹² Antimicrobial resistance (AMR) is increasingly reported among S Typhi lineages spreading from south Asia to Africa, with resistance to first-line

VE in CHIM

VE 54-87%

Fever $\geq 38.0^{\circ}\text{C}$ followed by positive *S. Typhi* blood culture

Cumulative proportion of participants with fever $\geq 38.0^{\circ}\text{C}$ followed by positive *S. Typhi* culture



Control Attack Rate = 42%

Vi-PS Attack Rate = 20%
Vaccine Efficacy = 52.3% (-4.2% , 78.2%)

Vi-TT Attack Rate = 5%
Vaccine Efficacy = 87.1% (47.2% , 96.9%)

Time after Challenge (days)

correlates of protection

Vaccination



Vi-TT



Vi-PS

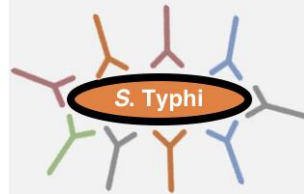
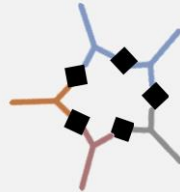
Polyclonal Antibody Production

IgG1 IgG2 IgG3 IgG4



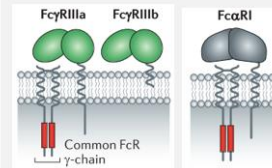
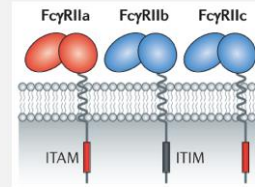
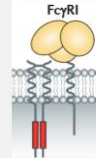
Dependent on Antigen Type
(T-dependent versus T-independent)

Immune Complex Formation/Opsonisation



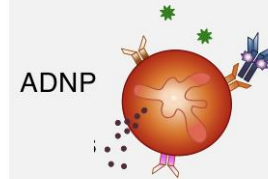
Dependent on Avidity

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)

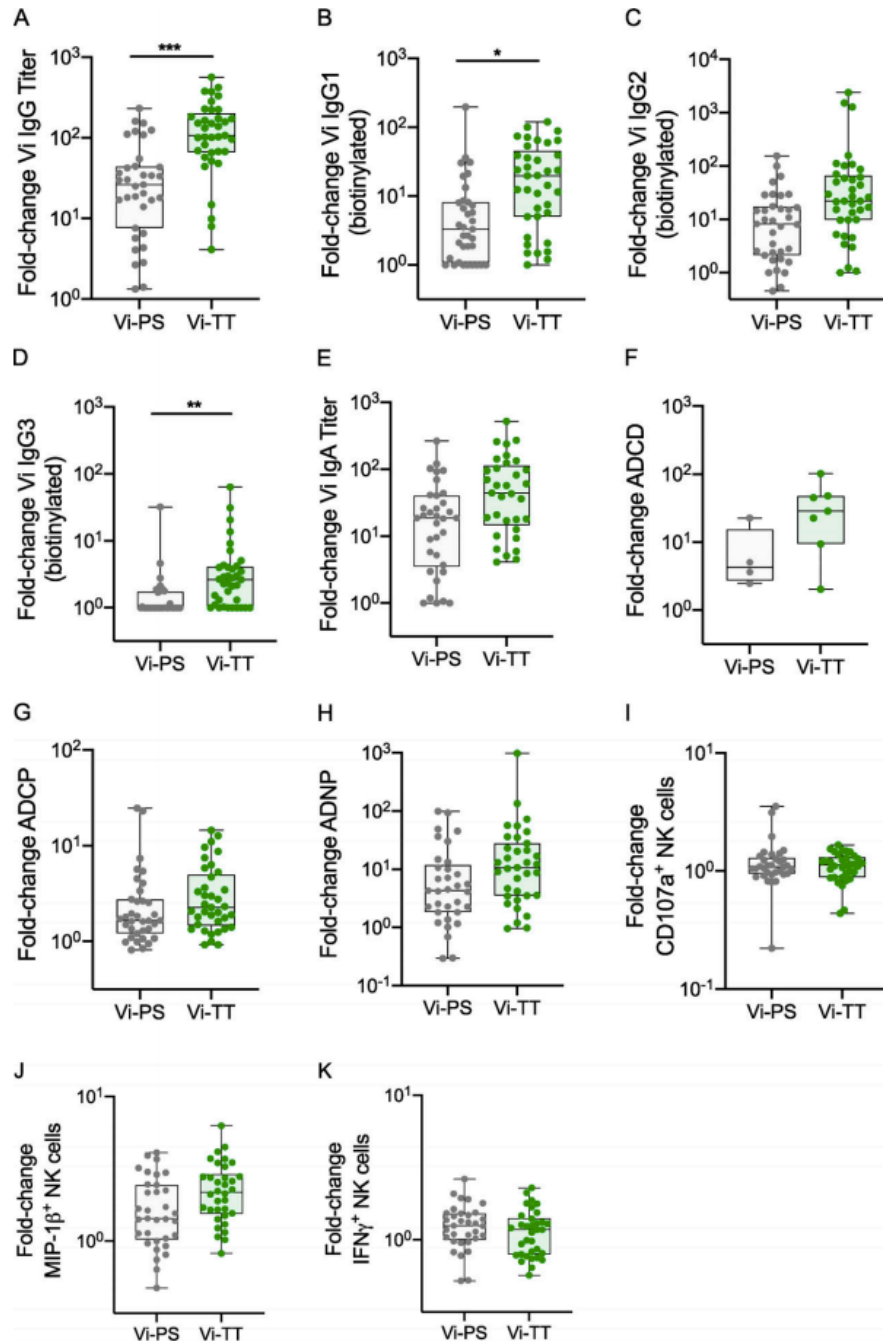
Clinical Protection



Protected

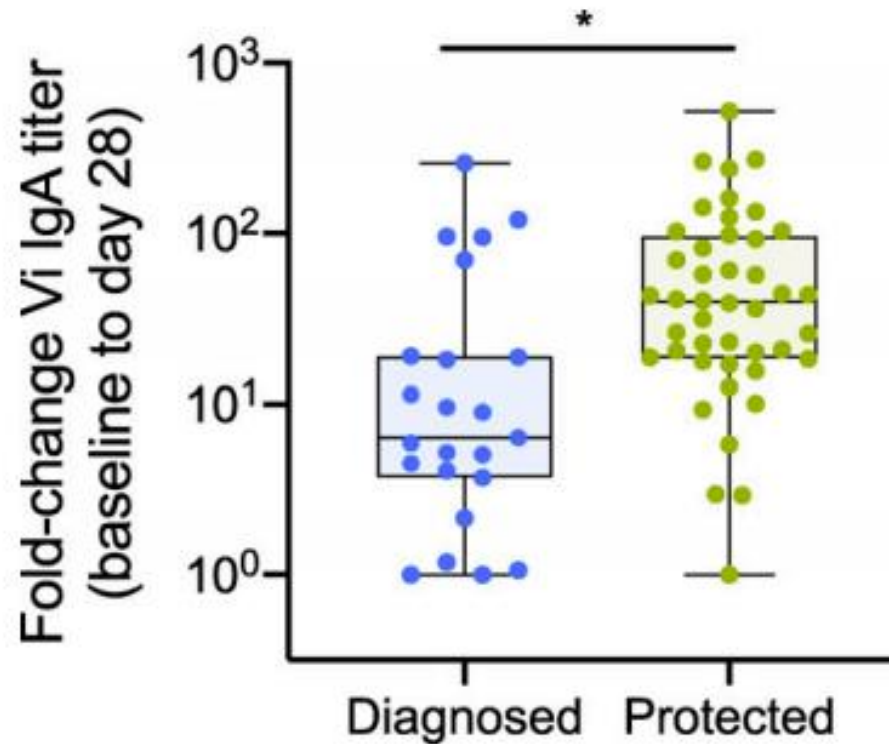


Diagnosed



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

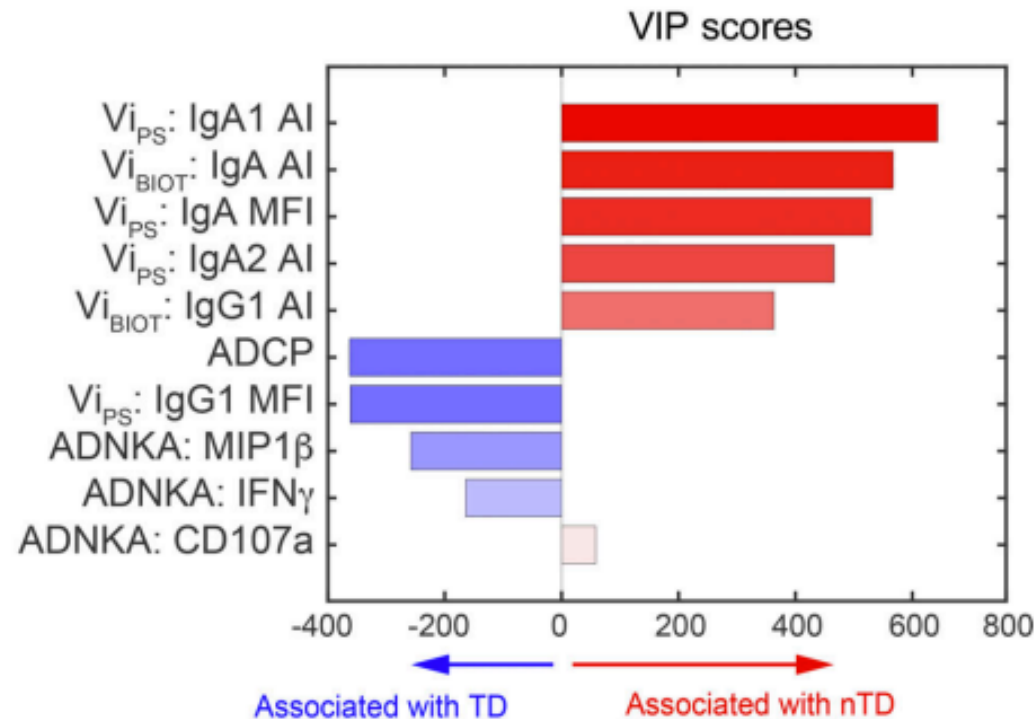
IgA and protection



Jin et al, JEM 2020

ADNP and IgA predict protection within Vi-TT

B

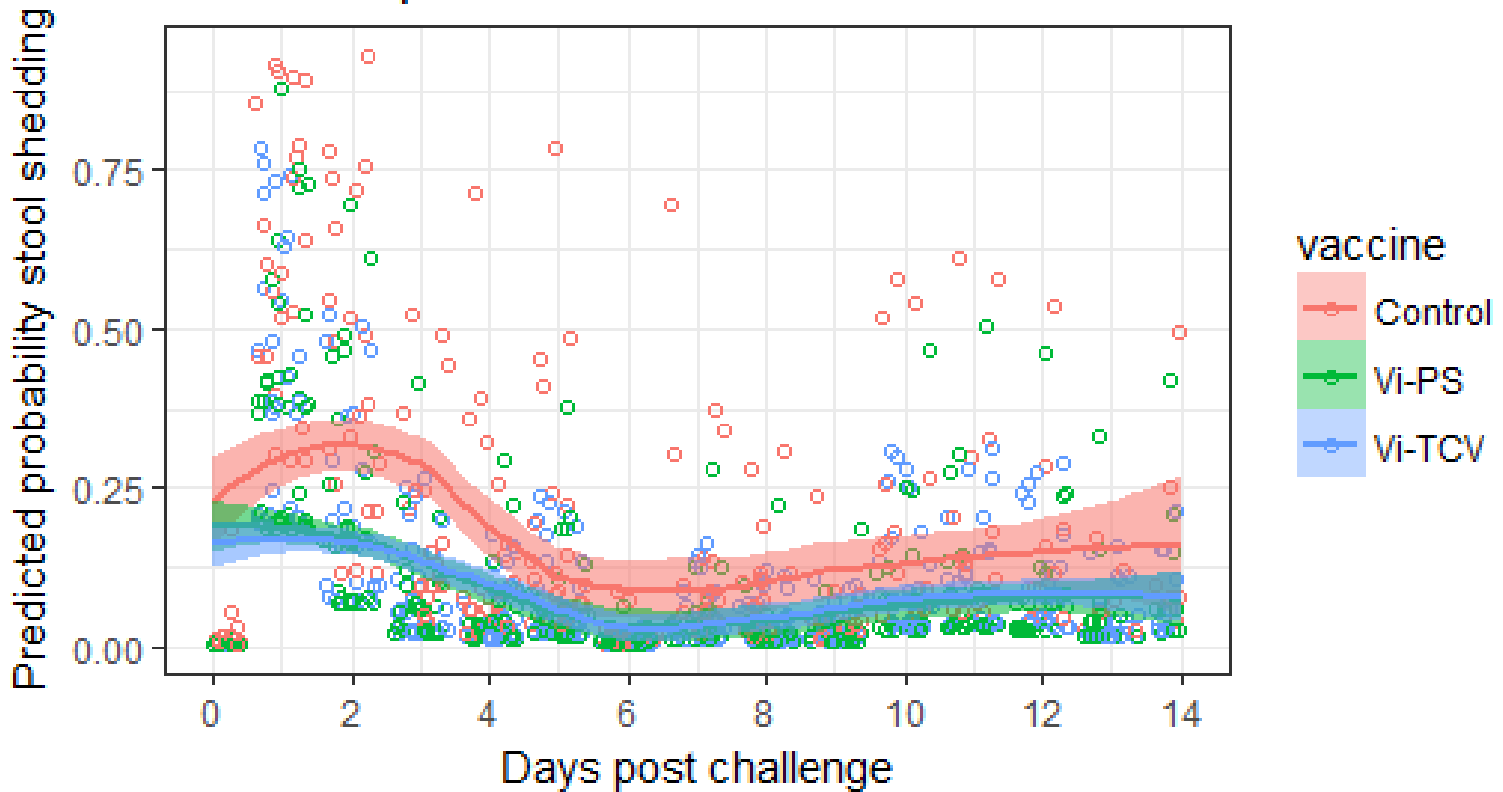


Wen-Han Yu

 **Ragon Institute**
of MGH, MIT and Harvard

Shedding

Stool samples from VAST



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



Essential medicines and health products

Typhoid vaccine prequalified

3 JANUARY 2018 - WHO has prequalified the first conjugate vaccine to prevent typhoid fever called Typbar-TCV® developed by Indian pharmaceutical company Bharat Biotech.

The vaccine has long-lasting immunity, requires only one dose and can be given to children as young as 6 months through routine childhood immunization programmes. Other Typhoid vaccines are recommended for children over 2 years of age.

Prequalification by WHO means that the vaccine meets standards of quality, safety and efficacy, thus making it eligible for procurement by United Nations agencies, such as the United Nations Children's Fund.

A conjugate vaccine is one that is composed of a polysaccharide antigen that is fused to a carrier molecule.

In October 2017, the Strategic Advisory Group of Experts (SAGE) on immunization, which advises WHO, recommended typhoid conjugate vaccine for routine use in children over six months of age in typhoid endemic countries.

Related links

- More information
- See WHO's full list of prequalified vaccines
- Press release pdf, 85kb

The screenshot shows the 'Take on Typhoid' website. The header includes the slogan 'Together We Can Take on Typhoid' and a search bar. The navigation menu lists: HOME, WHY TYPHOID?, POLICY & ADVOCACY, PREVENT & TREAT, BLOG, CONFERENCES, ABOUT US. The main content area features a photograph of a woman and a young girl. Below the photo is the article title 'Gavi: Millions of children set to be protected against typhoid', posted on November 30, 2017. The article text states: 'Press Release from Gavi, the Vaccine Alliance: Gavi Board approves US\$ 85 million funding window for 2019-2020 to support the introduction of typhoid conjugate vaccine in developing countries'. A related article is also visible at the bottom right: '10 years after typhoid sequenced - what is control typhoid fever?'



UNIVERSITY OF OXFORD



TyVac

UOXF, UMB

UOXF UMB

Nepal Bangladesh Malawi

20,000

>58,000

28,000

Buddha Basnyat
Shrijana Shrestha

John Clemens
Firdausi Qadri

Melita Gordon



BILL & MELINDA GATES foundation

Interim analysis

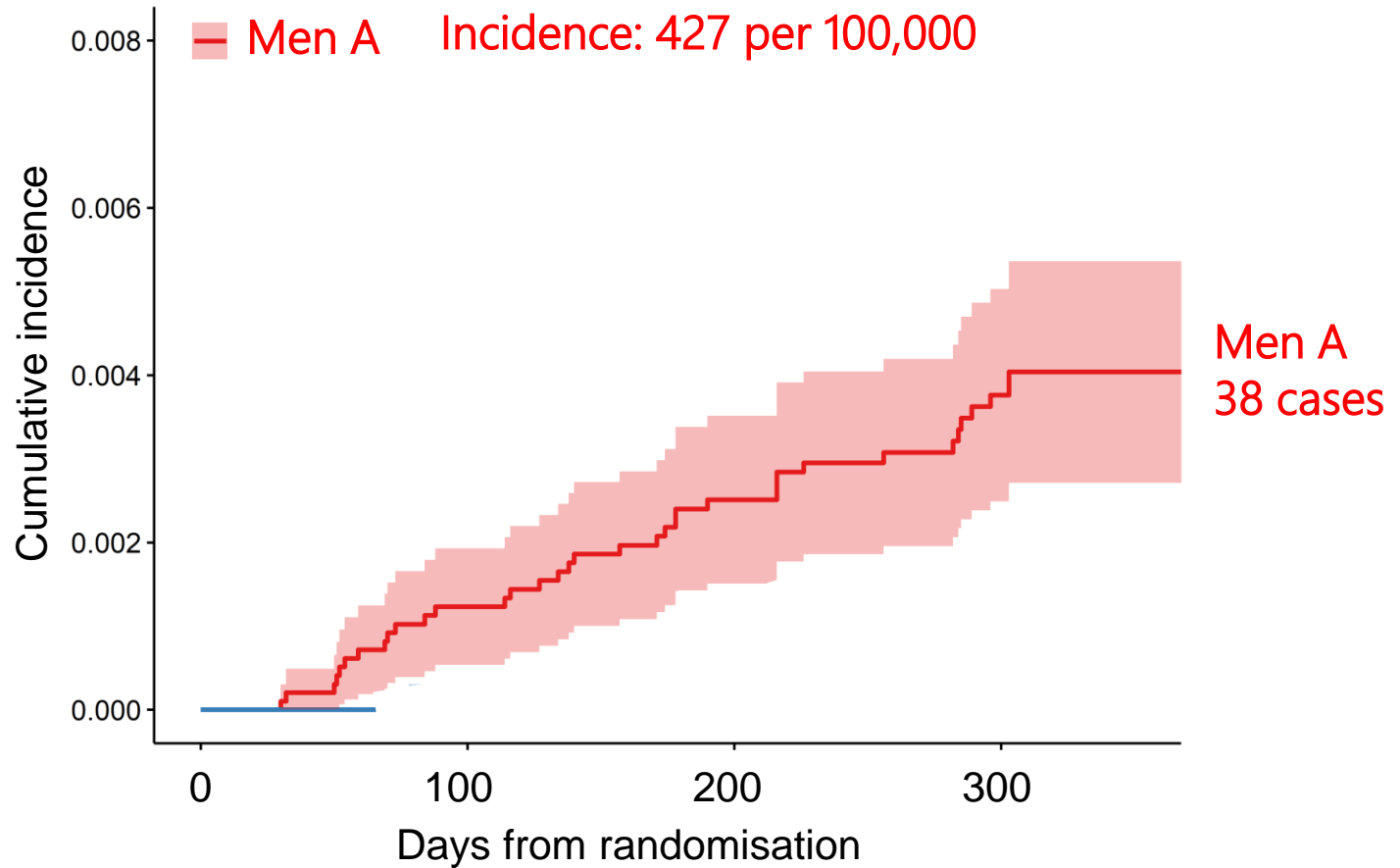


www.ovg.ox.ac.uk

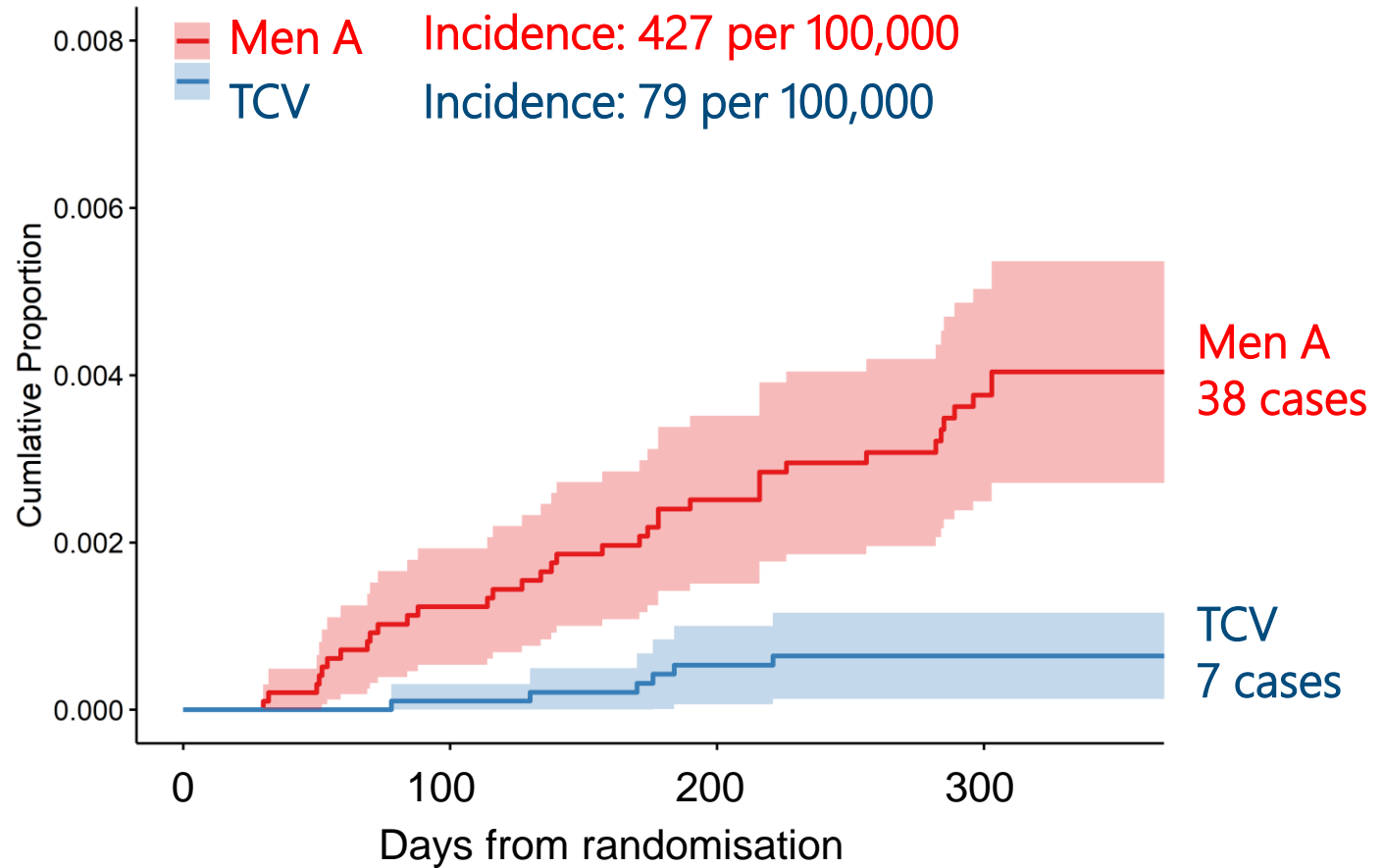
Oxford Biomedical Research Centre
Enabling translational research through partnership

NHS
National Institute for Health Research

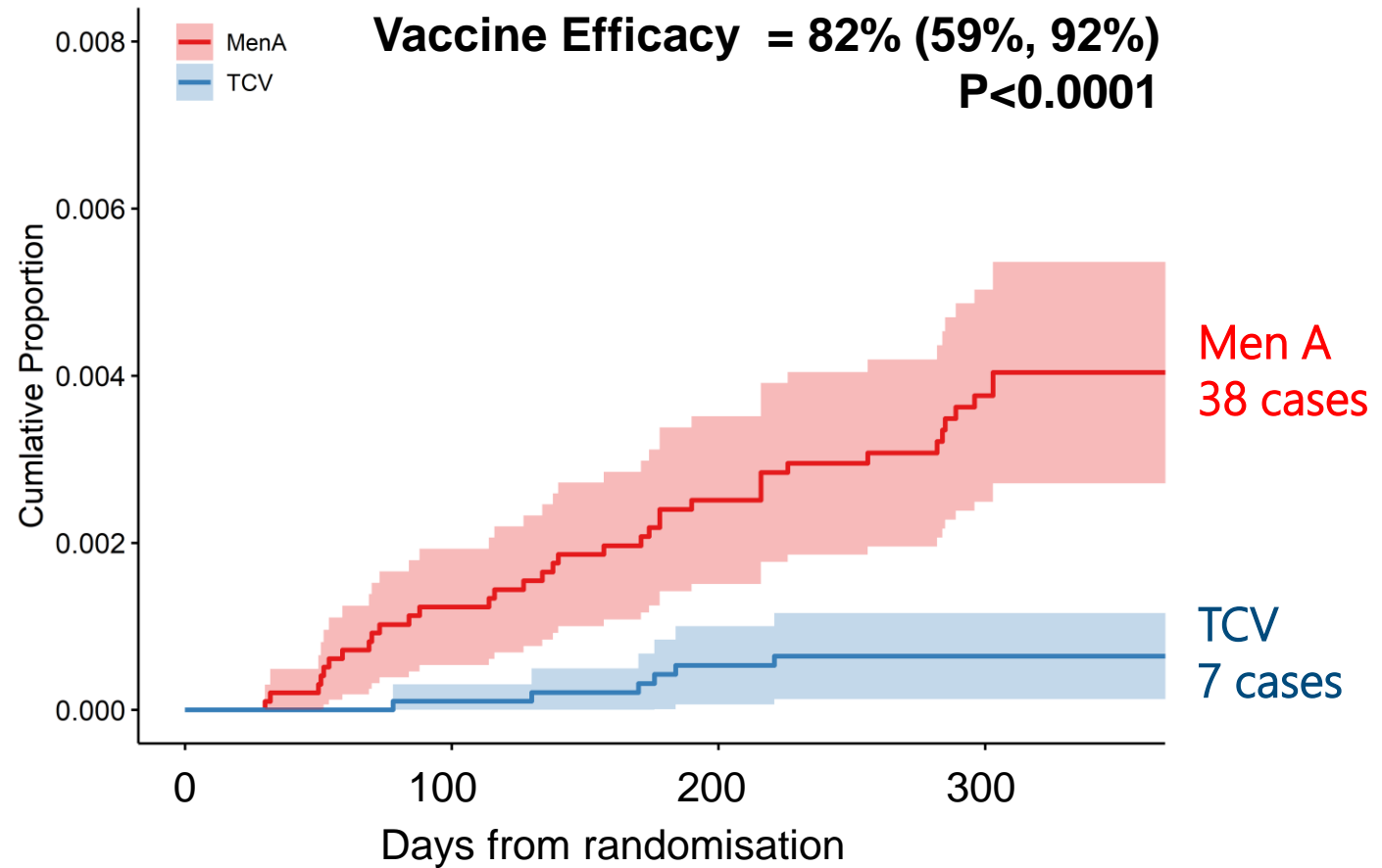
Incidence in Control Group



Incidence in TCV Group



Vaccine efficacy



Typhoid and Paratyphoid combined

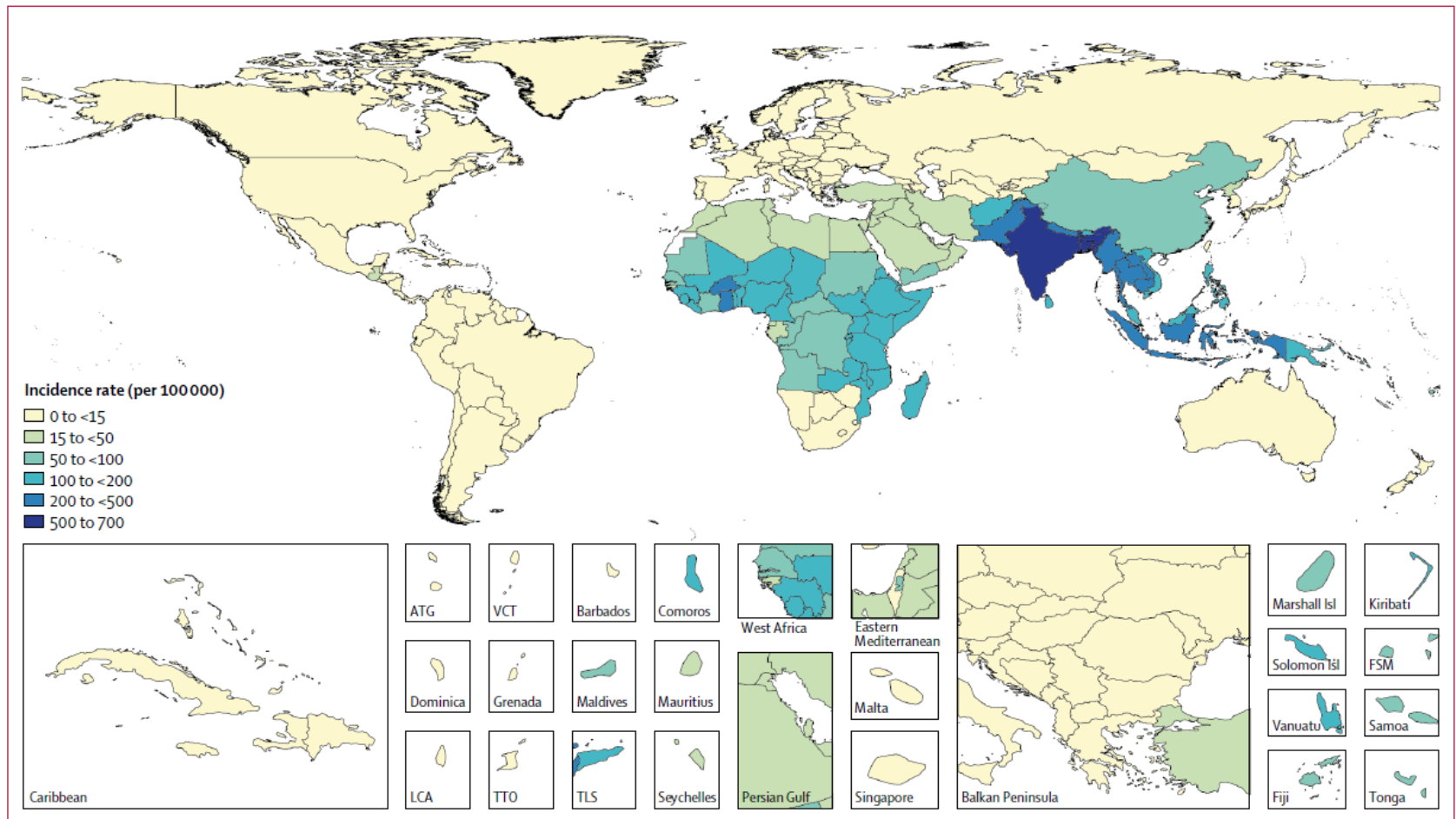
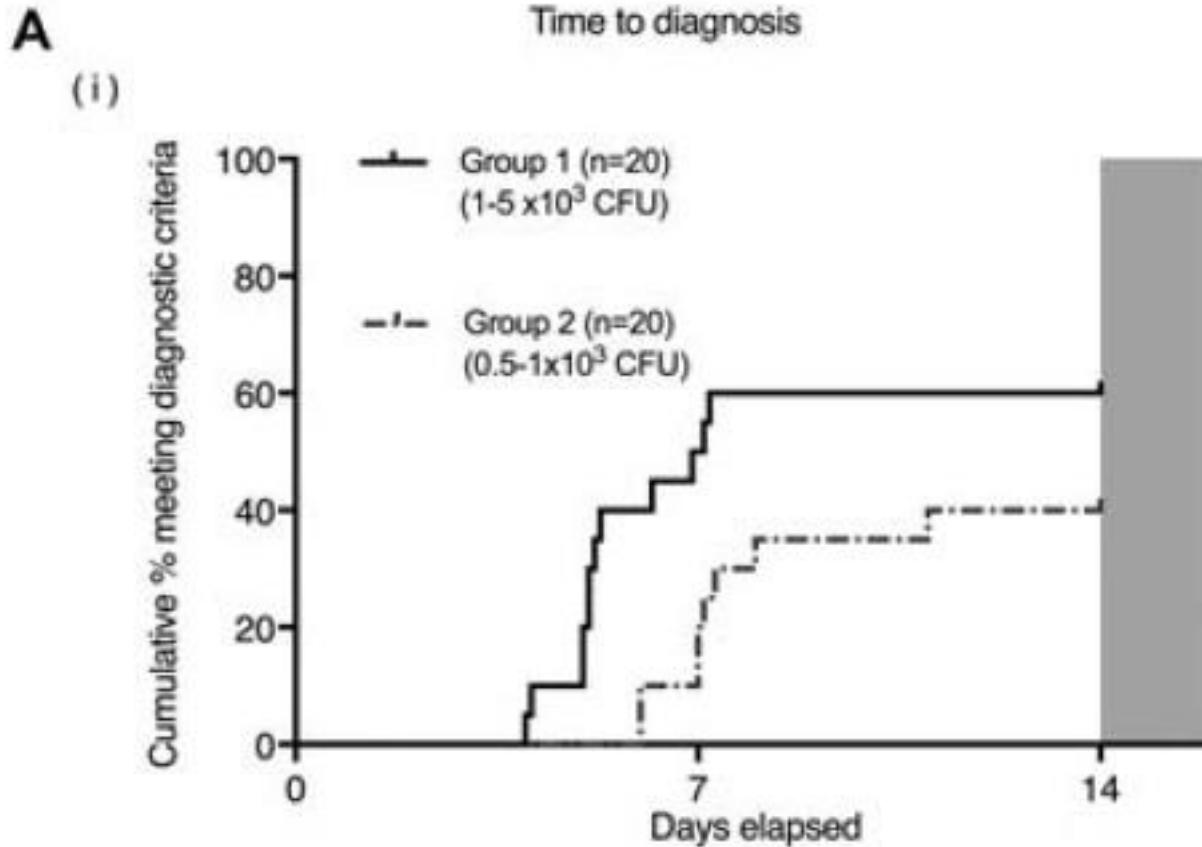


Figure 1: Incidence rates (per 100 000) of typhoid and paratyphoid fevers, by country, in 2017

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.

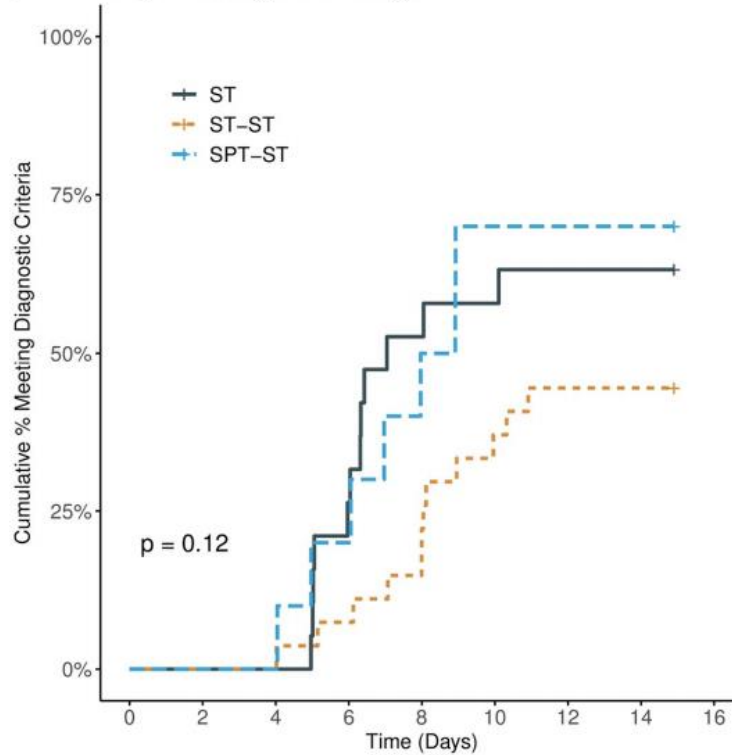
Paratyphoid attack rates

Composite diagnosis

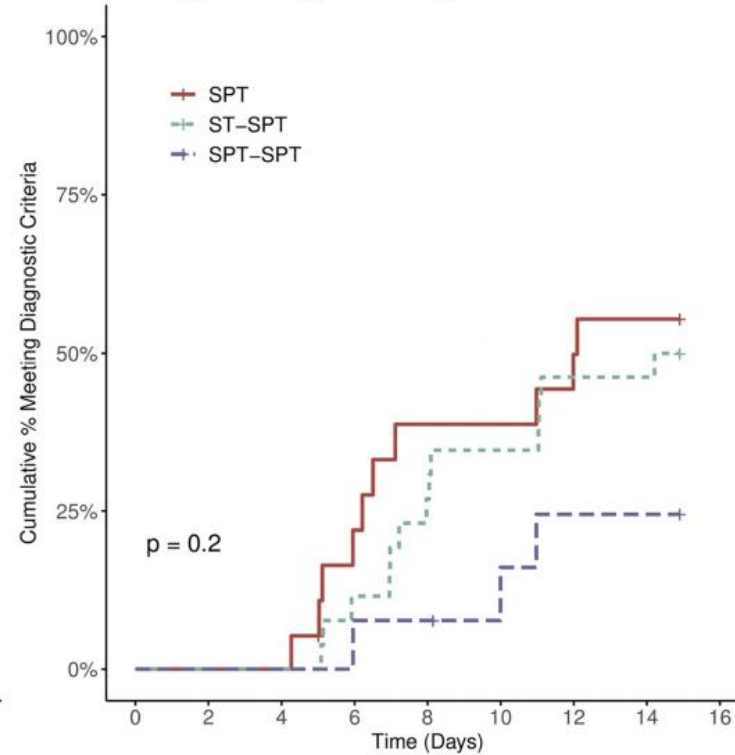


Dobinson et al, 2017

a *S. Typhi* challenge/re-challenge



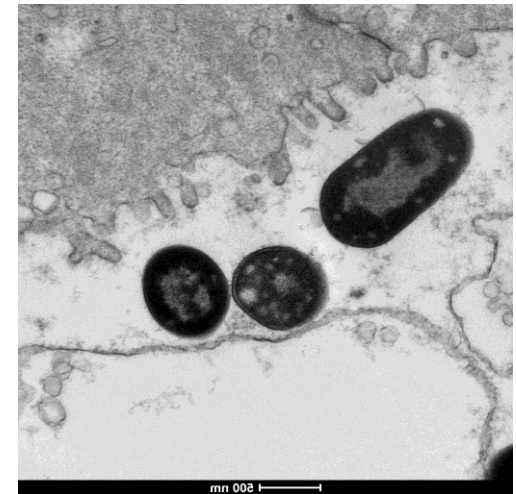
b *S. Paratyphi* challenge/re-challenge



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



EUROPEAN VACCINE INITIATIVE



Kathmandu
April 2018

wellcome trust

BILL & MELINDA
GATES foundation



www.ovg.ox.ac.uk

Oxford Biomedical Research Centre
Enabling translational research through partnership

NHS
National Institute for Health Research