Controlled human infection models

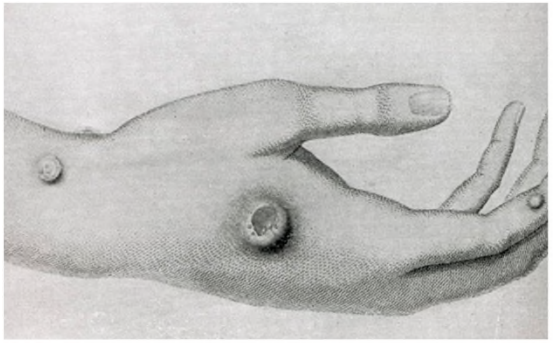
Andrew J Pollard FMedSci

Smallpox & variolation

Lady Mary Montagu

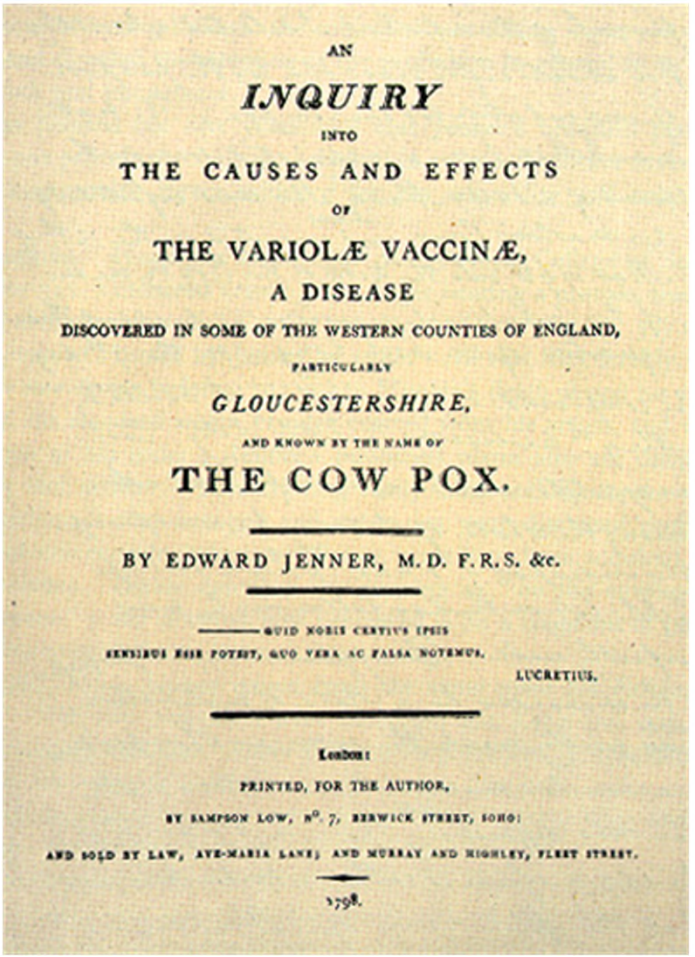
- Variolation of 6 prisoners in exchange for pardon (England, 1722)
- Variolation of orphans to assess safety in children (London, 1722)

Jenner & vaccination



Sarah Nelmes

Edward Jenner vaccinating James Phipps, 1796



AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

——— QUID NOBIS CERTIUS IPSIS
SENSIBUS HOC POTEST, QUO VERA AC FALSA NOTEMUS.
LUCRETIUS.

London:

PRINTED, FOR THE AUTHOR,

BY SAMPSON LOW, N°. 7, BERWICK STREET, SOHO:

AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.

1802

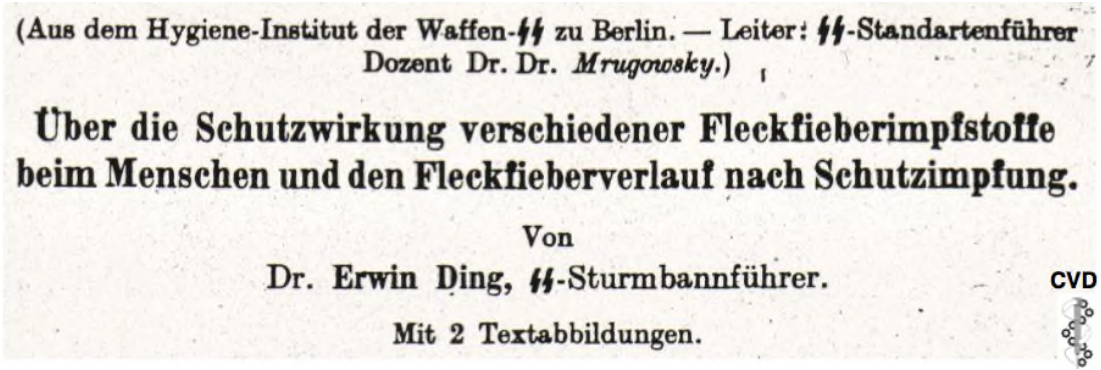

The Cow-Pock — or — the Wonderful Effects of the New Inoculation!

Wolfgang Casper: gonococcal vaccine

- Rudolf Virchow Hospital, Berlin (1930)
- 5 vaccinees & 5 controls
- ‘exposed’ to a commercial sex worker on a hospital ward
- Attack rates: 0/5 in vaccinees vs. 4/5 in controls

Unethical studies during WWII

- Studies performed by Nazi Waffen-SS doctors in concentration camps



(Aus dem Hygiene-Institut der Waffen-SS zu Berlin. — Leiter: SS-Standartenführer Dozent Dr. Dr. *Mrugowsky*.)

Über die Schutzwirkung verschiedener Fleckfieberimpfstoffe beim Menschen und den Fleckfieberverlauf nach Schutzimpfung.

Von

Dr. Erwin Ding, SS-Sturmbannführer.

Mit 2 Textabbildungen.

CVD

- Spotted fever, also yellow fever, smallpox, cholera, tuberculosis etc.
- High lethality in control subjects (+/-1000 died at Buchenwald)

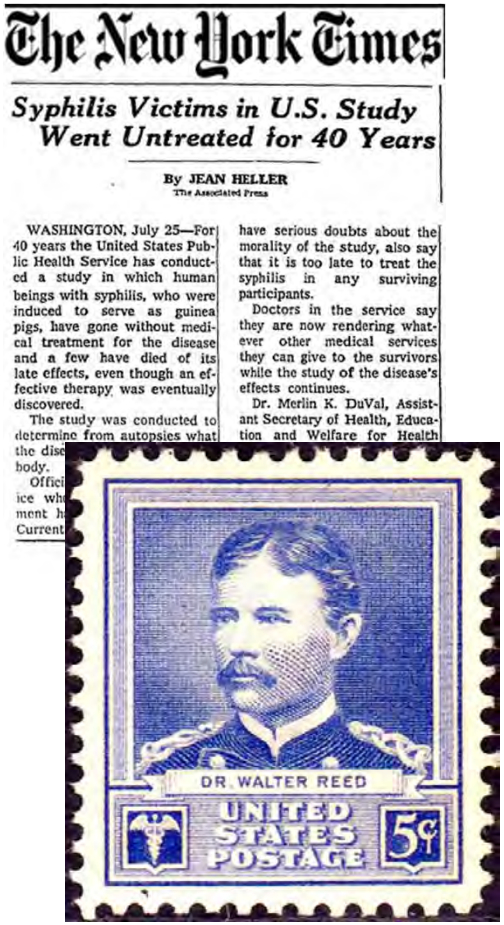
The Nuremburg Code

- The Doctors' Trial
- USA vs. Karl Brandt and others – *US Military Tribunal Nuremburg, 19 July 1947*
- Based on 6 initial points used to define legitimate medical research – a further 4 were added by Nuremburg Trial verdict

 # 1. The voluntary consent of the human subject is absolutely essential

Other infamous cases

- Japanese, Unit 731 (1937 – 1945)
  - Experimentation with infectious agents
  - Infants, elderly and pregnant women
  - Syphilis, gonorrhoea, plague, cholera, smallpox, botulism, typhoid, TB
- Willowbrook State School – Hepatitis A studies (mid 1950s – early 1970s).
  - Deliberate infection of children with hepatitis A to study spread
- Syphilis studies in Tuskegee (1932-1972)
  - Natural history of syphilis in 622 Africa-Americans…naturally infected and not treated. Followed for 40 years, and not given penicillin even after it became routine treatment.



The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the dise
body.
Offici
ice wh
ment h
Current

have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health

Other challenge studies, 1950s - 1974

- Many experimental challenge studies performed using incarcerated prisoners
  - Malaria, typhoid, shigella, influenza, diarrhoeal *E. coli*, viral gastroenteritis, tularaemia

Common Cold Unit

- 1946 -1990, Salisbury (UK)
- Rhinovirus & coronavirus
- >20,000 volunteers

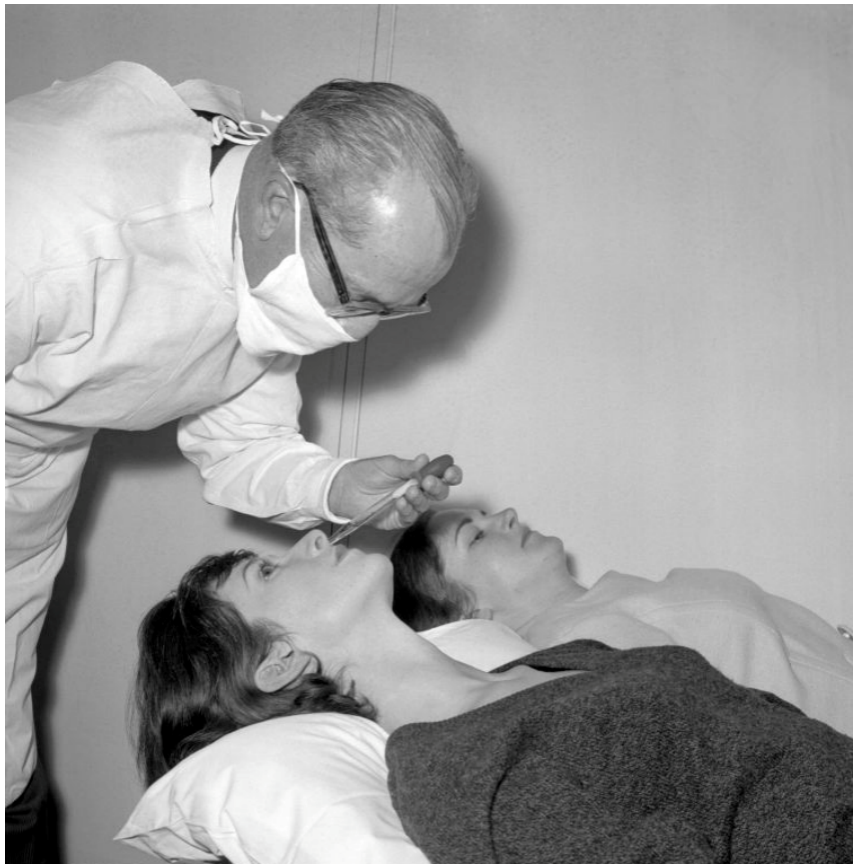
RESEARCH INTO COMMON COLDS AND INFLUENZA

10 DAYS HOLIDAY - FREE!

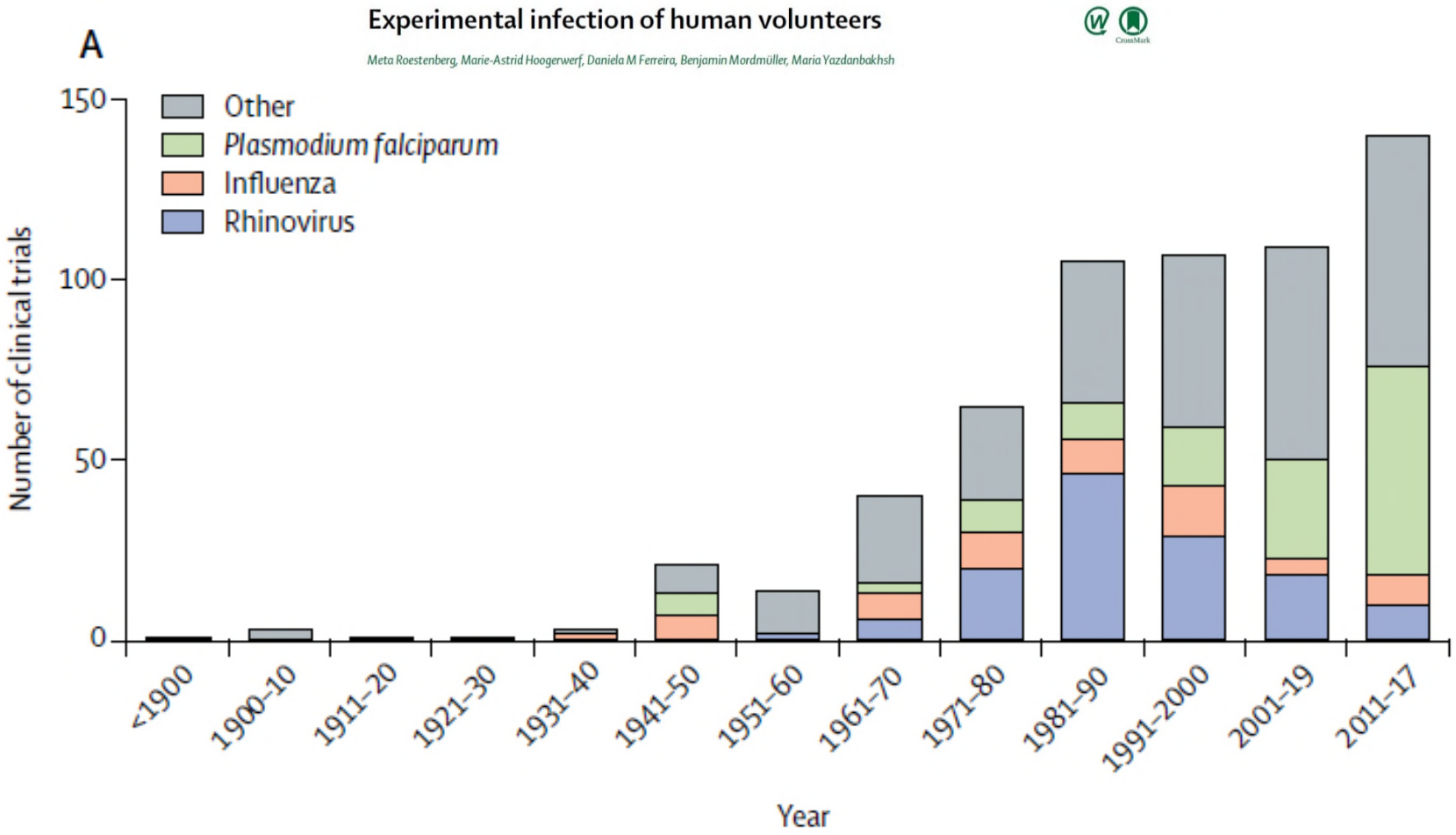
How would you like a cheap and comfortable holiday, everything free and no expense, and even 35p a day pocket money?

We have so much sunshine in summer that we have to warn visitors about getting burnt. Even in winter there are lots of dry sunny days, and anyway there are always warmth and comfort indoors.

It is true there is a one in three risk of catching a cold but in a very good cause, and our infections are usually minor and brief.

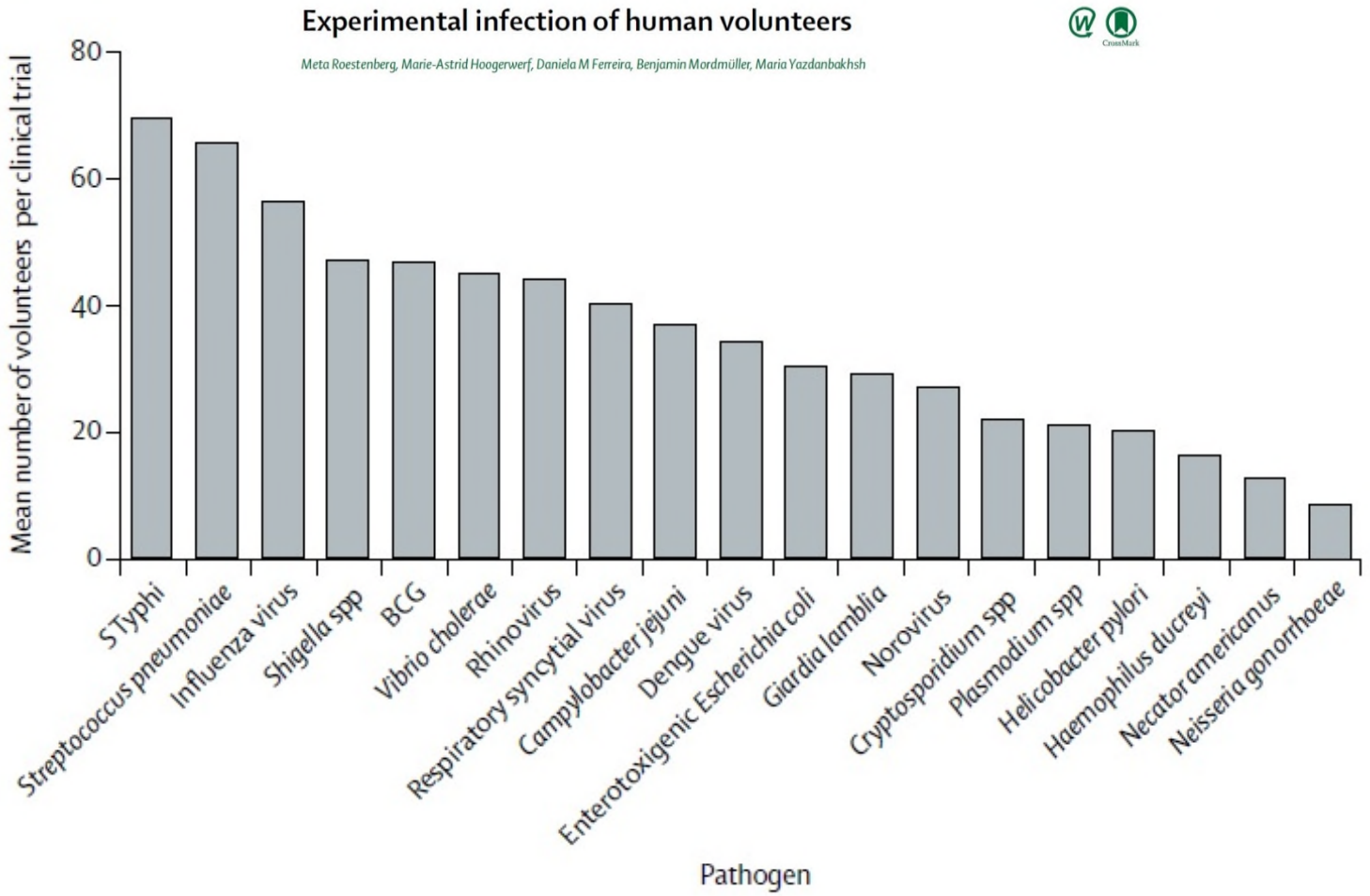


Number of trials



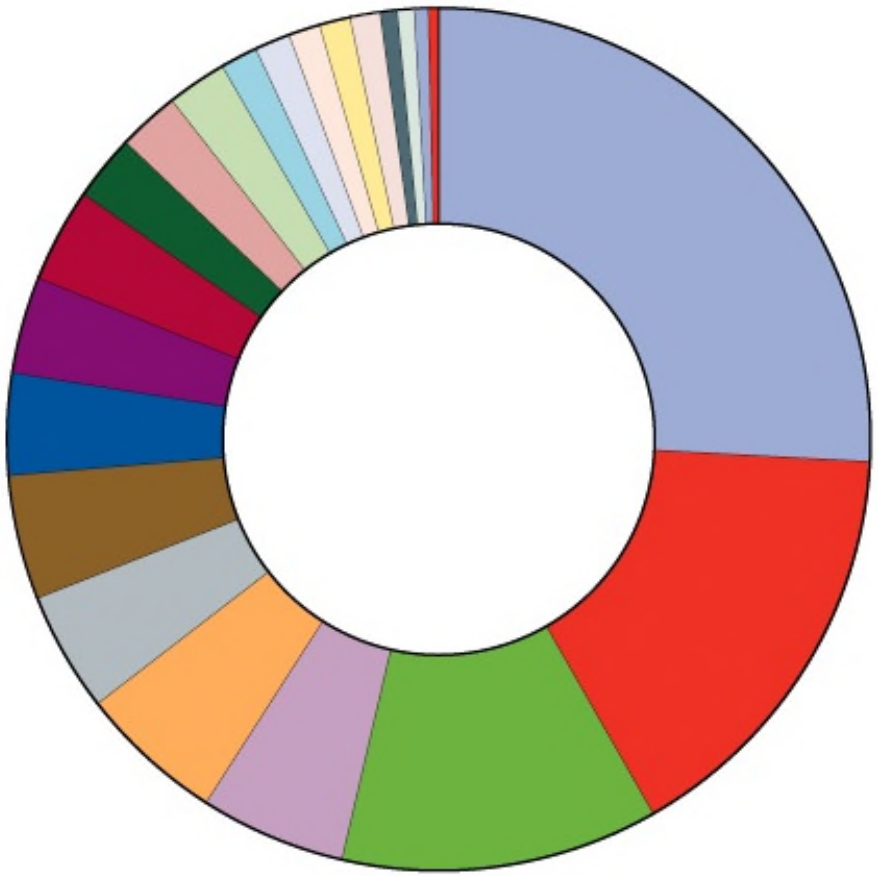
www.thelancet.com/infection Published online June 8, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30177-4

Number of volunteers per trial



www.thelancet.com/infection Published online June 8, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30177-4

22,257 and counting



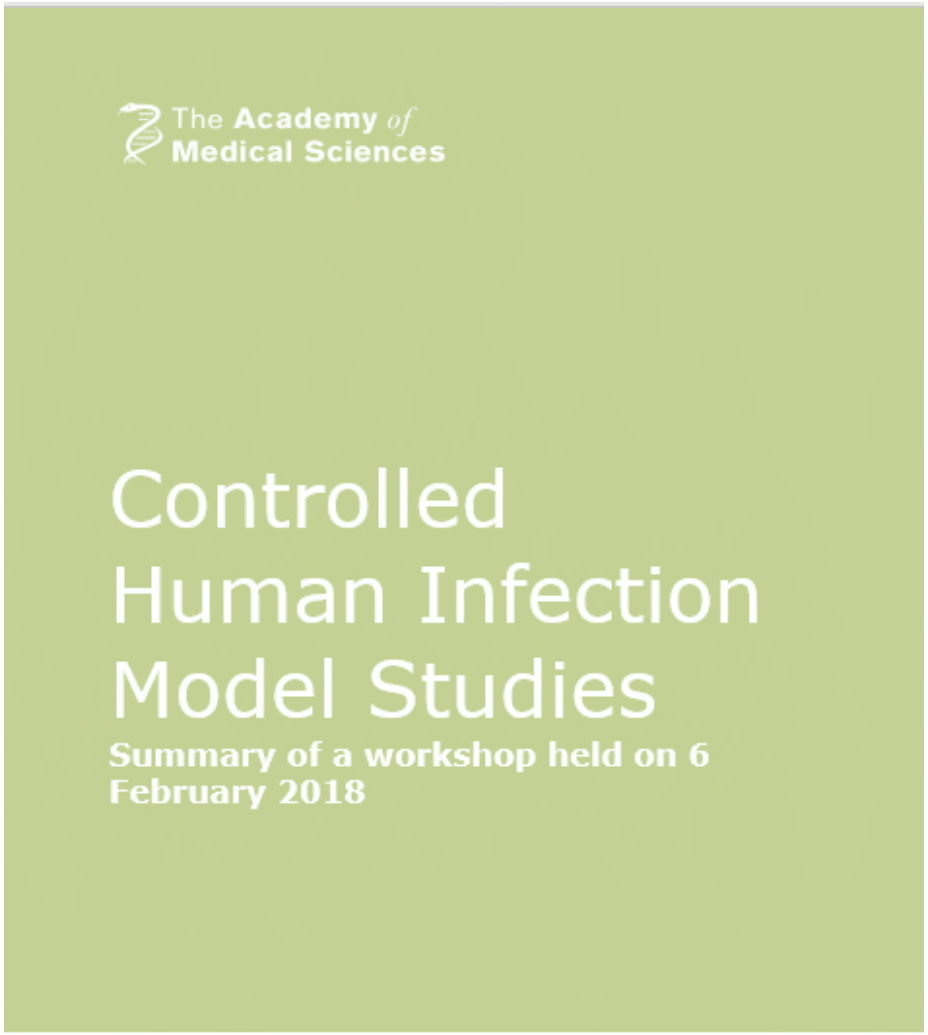
Total=22 257 Volunteers

- Rhinovirus
- Influenza virus
- *Plasmodium spp*
- Enterotoxigenic *Escherichia coli*
- *Vibrio cholerae*
- Respiratory syncytial virus
- *Salmonella enterica*
- *Shigella spp*
- Norovirus
- *Streptococcus pneumoniae*
- *Haemophilus ducreyi*
- Dengue virus
- *Francisella tularensis*
- *Neisseria lactamica*
- *Plasmodium vax*
- *Cryptosporidium spp*
- *Campylobacter jejuni*
- *Necator americanus*
- *Neisseria gonorrhoeae*
- BCG
- *Giardia lamblia*
- *Helicobacter pylori*

www.thelancet.com/infection Published online June 8, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30177-4

ETHICAL, LEGAL AND SAFETY CONSIDERATIONS

Informed consent
Minimise risk



https://acmedsci.ac.uk/policy/policy-projects/controlled-human-infection-models

Ethical approval

PUBLIC HEALTH ETHICS VOLUME 9 • NUMBER 1 • 2016 • 92–103

Ethical Criteria for Human Challenge Studies in Infectious Diseases

Ben Bambery*, Monash University
Michael Selgelid, Monash University
Charles Weijer, Western University
Julian Savulescu, University of Oxford
Andrew J. Pollard, University of Oxford

*Corresponding author: Ben Bambery, Faculty of Medicine, Nursing and Health Sciences, Monash University, Victoria 3800, Australia. Email: ben.bambery@gmail.com

Purposeful infection of healthy volunteers with a microbial pathogen seems at odds with acceptable ethical standards, but is an important contemporary research avenue used to study infectious diseases and their treatments. Generally termed 'controlled human infection studies', this research is particularly useful for fast tracking the development of candidate vaccines and may provide unique insight into disease pathogenesis otherwise unavailable. However, scarce bioethical literature is currently available to assist researchers and research ethics committees in negotiating the distinct issues raised by research involving purposefully infecting healthy volun-

"Challenge studies should not be considered ethically unacceptable. To the contrary, they may sometimes be ethically required. "

Dr Hugh Davies, Ethics committee chair

http://www.reviewingresearch.com/human-challenge-studies/

Regulatory considerations

- Quality – GMP
- Trial protocol
- Regulation in UK?
- Environmental and Public Safety (DEFRA)
- Pathway to licensure
  - Timing of challenge after immunisation
  - Strain selection/number of strains
  - Geographic location of volunteers
  - Dose of challenge strain

World Health Organization

POST ECBS Version
ENGLISH ONLY

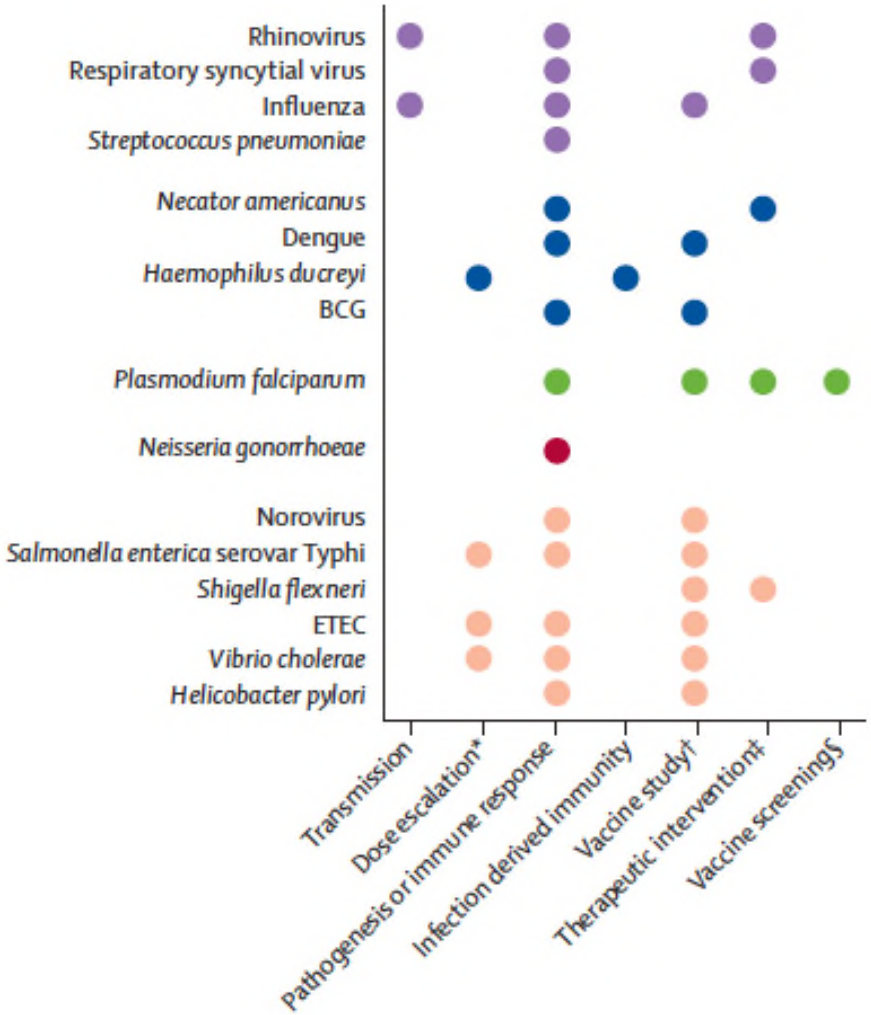
EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2016

Human Challenge Trials for Vaccine Development: regulatory considerations

Regulatory confusion

- FDA
- EMA
- WHO
- EU directive for national regulators
  - Different interpretations
  - MHRA
- EU regulations coming, but still not clear

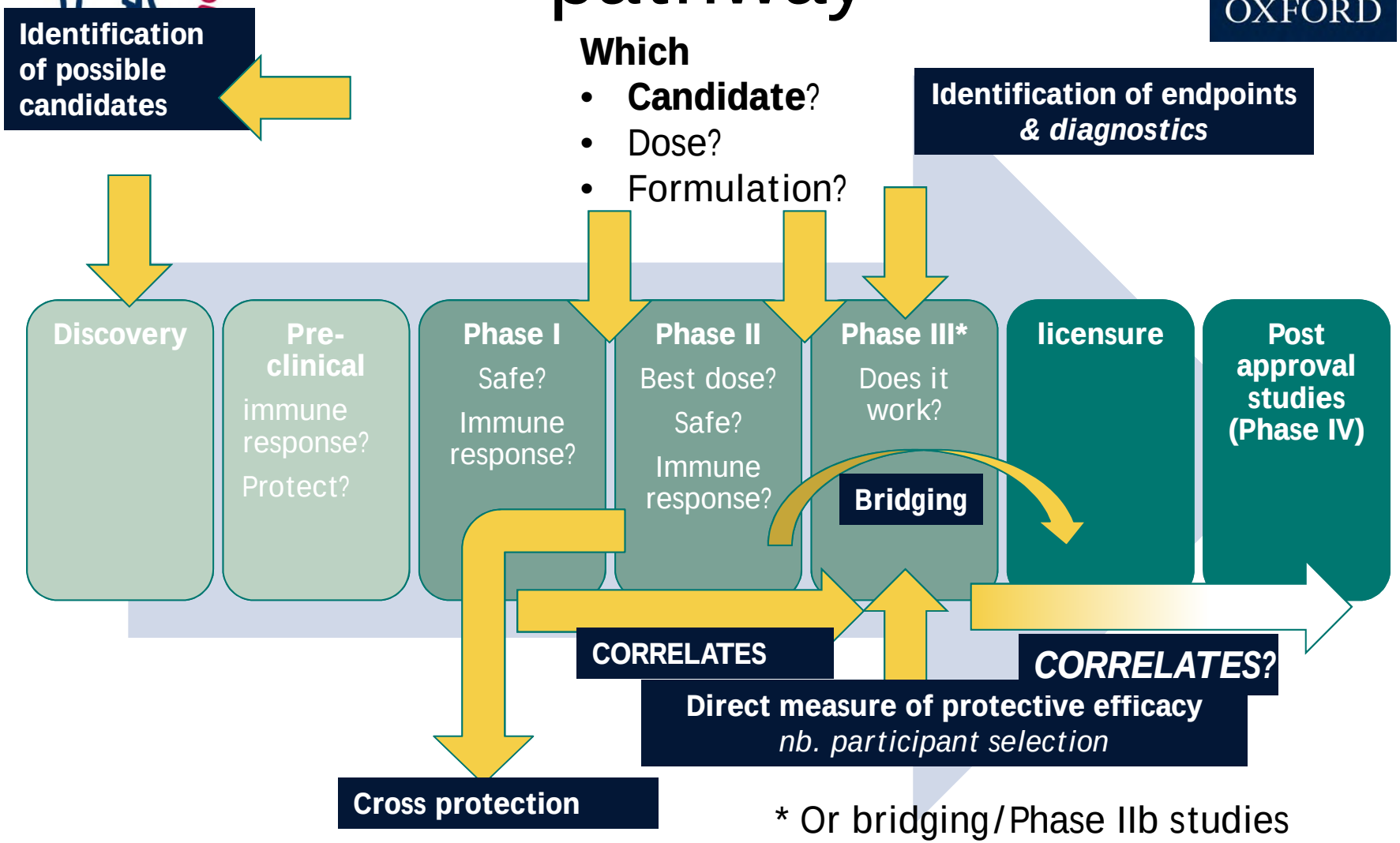
Use and development stage of some current challenge studies



Darton, 2015

ROLE IN VACCINE DEVELOPMENT

Vaccine development pathway



* Or bridging/Phase IIb studies

Regulatory issues

- Don't get hung up….it is just a model
- Is it the right target population
- Naïve or immune
- Dose/Route of challenge agent
- Manufacturing quality: To GMP or not to GMP?
- Wild-type or attenuated strain
- Which strain and how many strains?
- What endpoints are relevant?

Children

- Scientific justification
- Ethical justification
- Regulatory justification
- It is just a model
- Never say never?

Licensure pathway

- Considerable attention to licensure
- Perhaps greater role envisaged
  - Supporting data for licensure
  - Confidence to move forwards
  - Down selection
  - correlates

Up to 90% efficacy

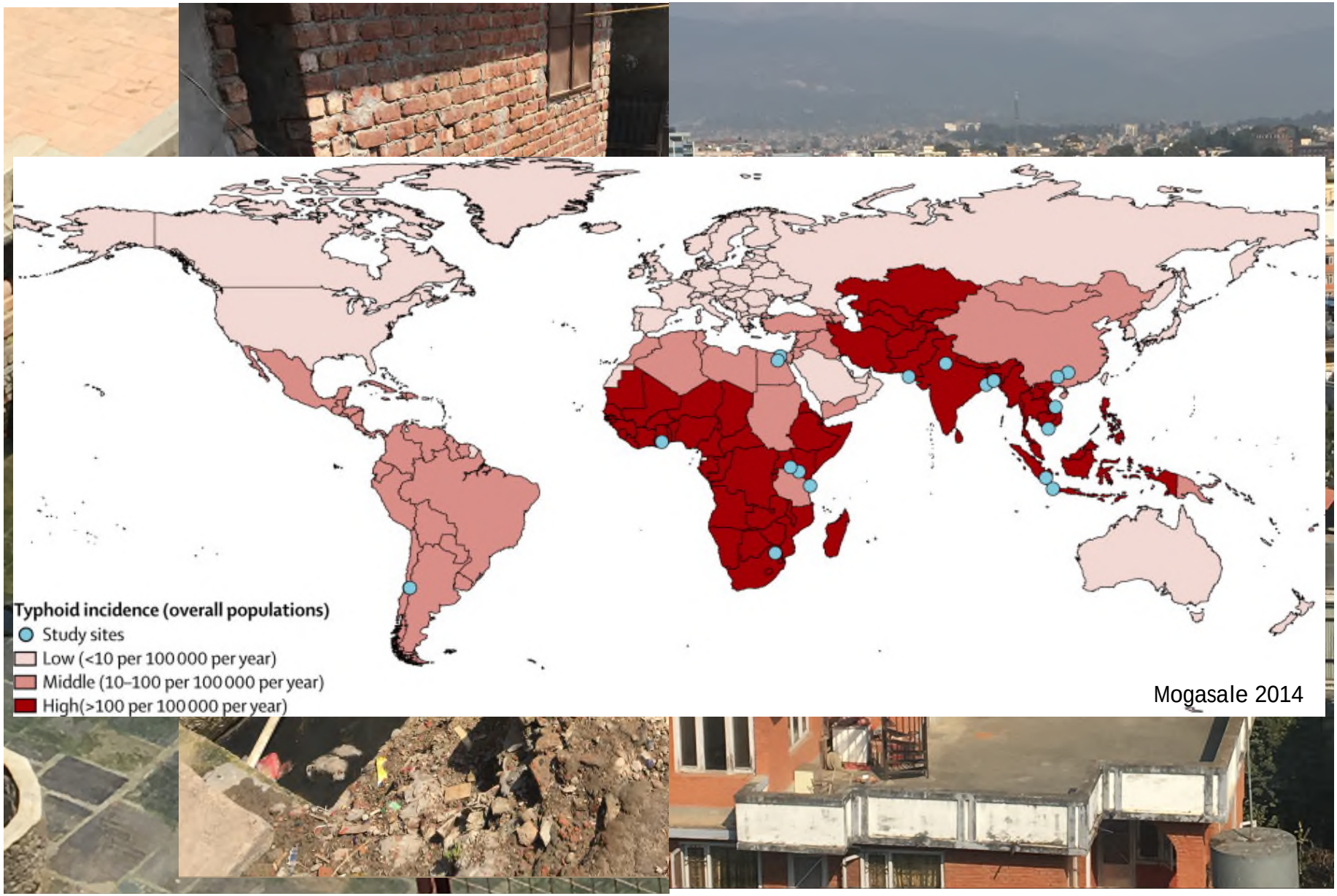
The vaccine's efficacy was demonstrated in a randomized, placebo-controlled human challenge study of 197 US volunteers 18 to 45 years of age, the agency reported. Of the 197 volunteers, 68 Vaxchora recipients and 66 placebo recipients were challenged by oral ingestion of *V cholerae*. Vaccine efficacy was 90% among those challenged 10 days after vaccination and 80% in those challenged 3 months after vaccination.

In immunogenicity trials in the United States and Australia, at least 90% of adults who received the vaccine developed antibodies indicating protection against cholera, the FDA said.

"FDA approval of a new vaccine for a disease for which there has been no vaccine available is an extremely rare event," Nima Farzan, MBA, chief executive officer and president of PaxVax, said in a company press release. "We are proud to provide the only vaccine against cholera available in the US."

Vaxchora's effectiveness has not been established in people living in cholera-affected areas or in those who have pre-existing immunity because of previous exposure to *V cholerae* or receipt of a cholera vaccine, the company said. Also, the vaccine has not been shown to protect against disease caused by non-O1 serogroups.

PaxVax is based in Redwood city, Calif., and the vaccine is made in Hamilton, Bermuda.



Mogasale 2014

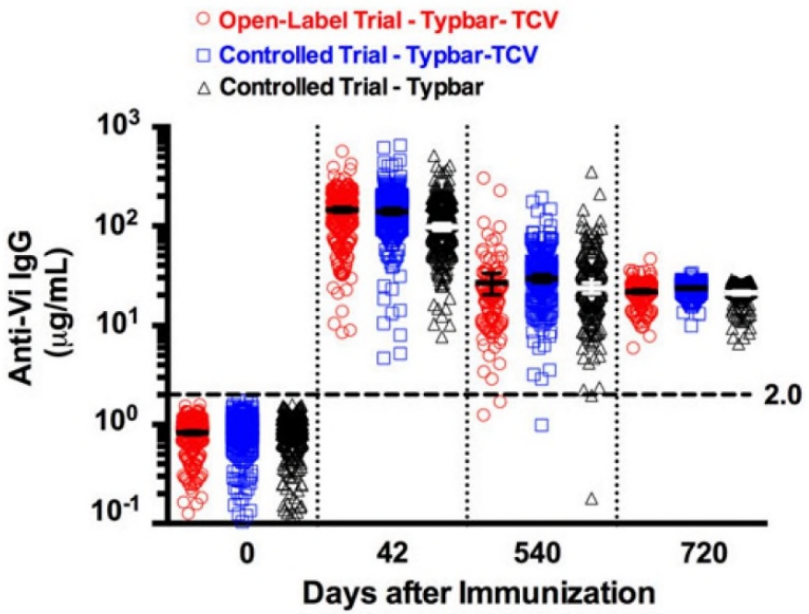
Clinical Infectious Diseases Advance Access published May 7, 2015

MAJOR ARTICLE

Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study

Vadrevu Krishna Mohan,[1] Vineeth Varanasi,[1] Anit Singh,[1] Marcela F. Pasetti,[2] Myron M. Levine,[2] Ramasamy Venkatesan,[1] and Krishna M. Ella[1]

[1]Bharat Biotech International Limited, Hyderabad, Telangana, India; and [2]Centre for Vaccine Development, University of Maryland School of Medicine, Baltimore



No efficacy data

World Health Organization

FINAL
ENGLISH ONLY

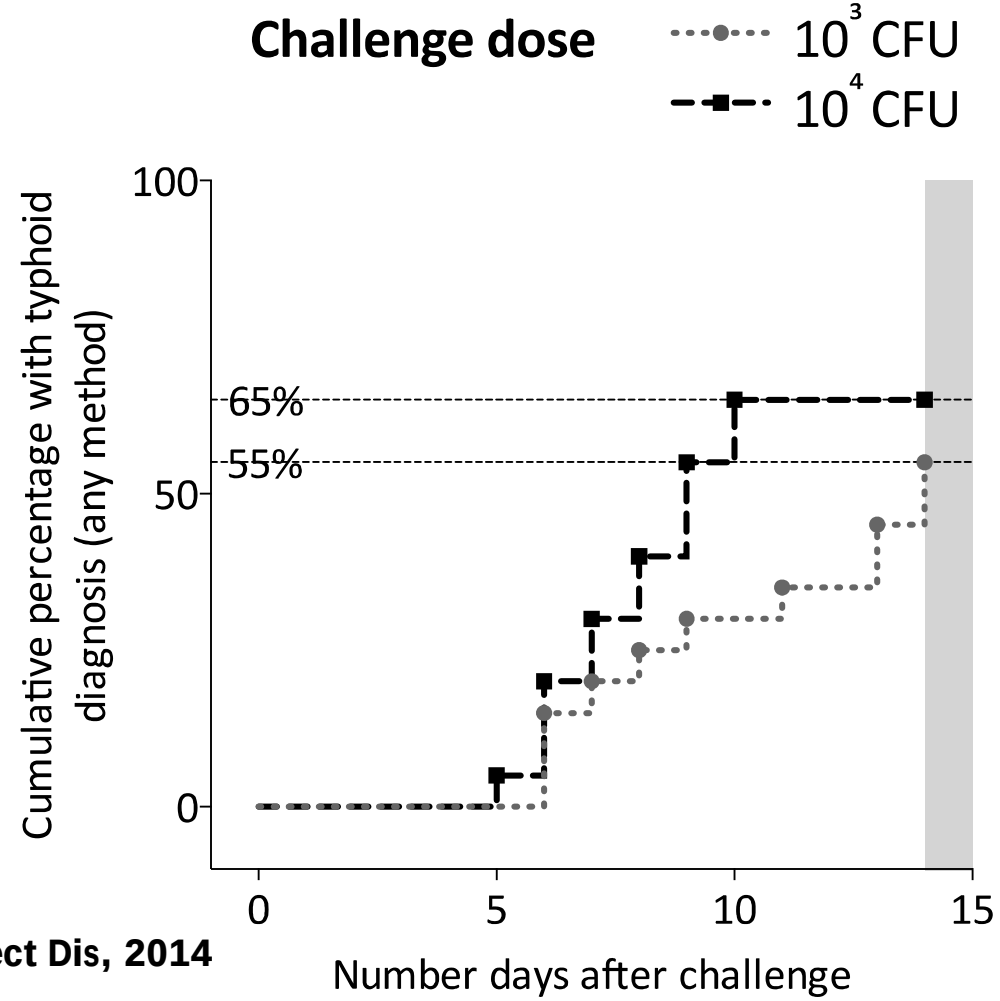
Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines:

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

A controlled human infection model in Oxford established 2011

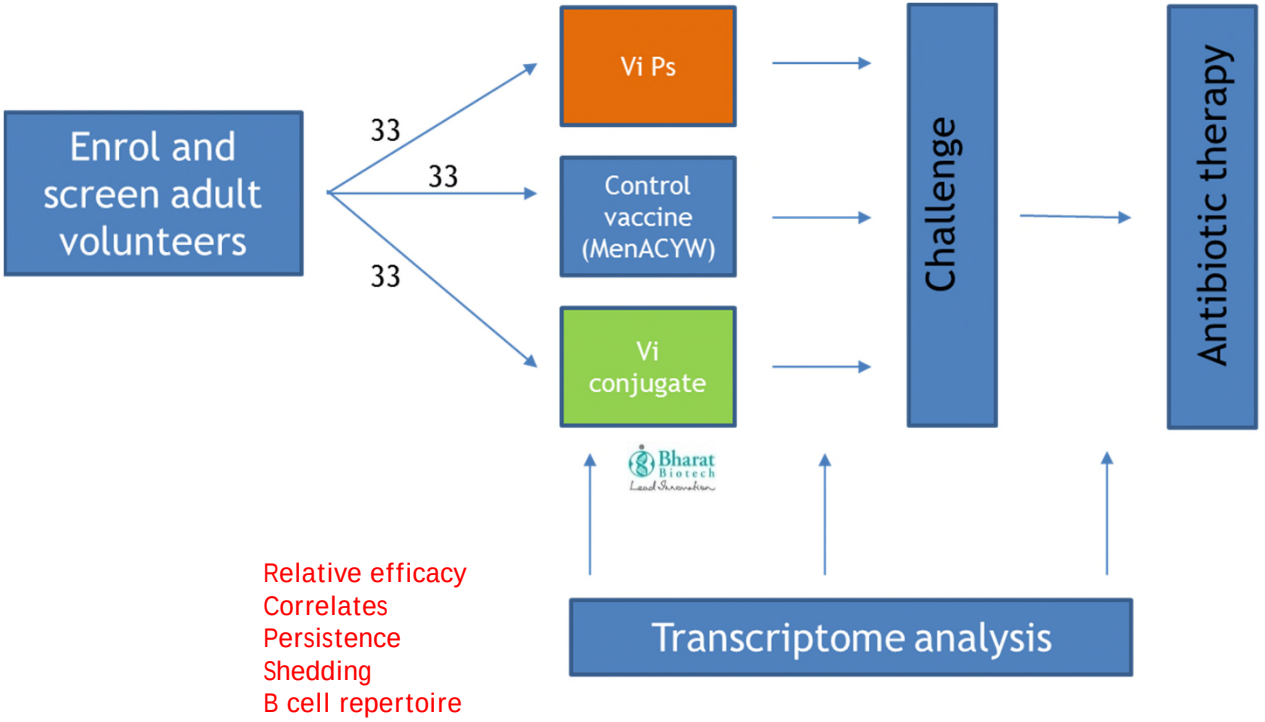
Funded by wellcome trust

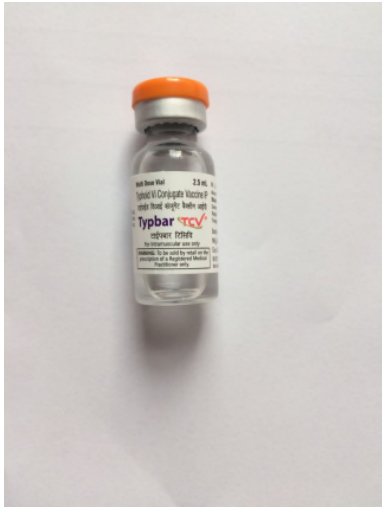
Typhoid attack rates



Waddington, Clin Infect Dis, 2014

Vi conjugate vaccine



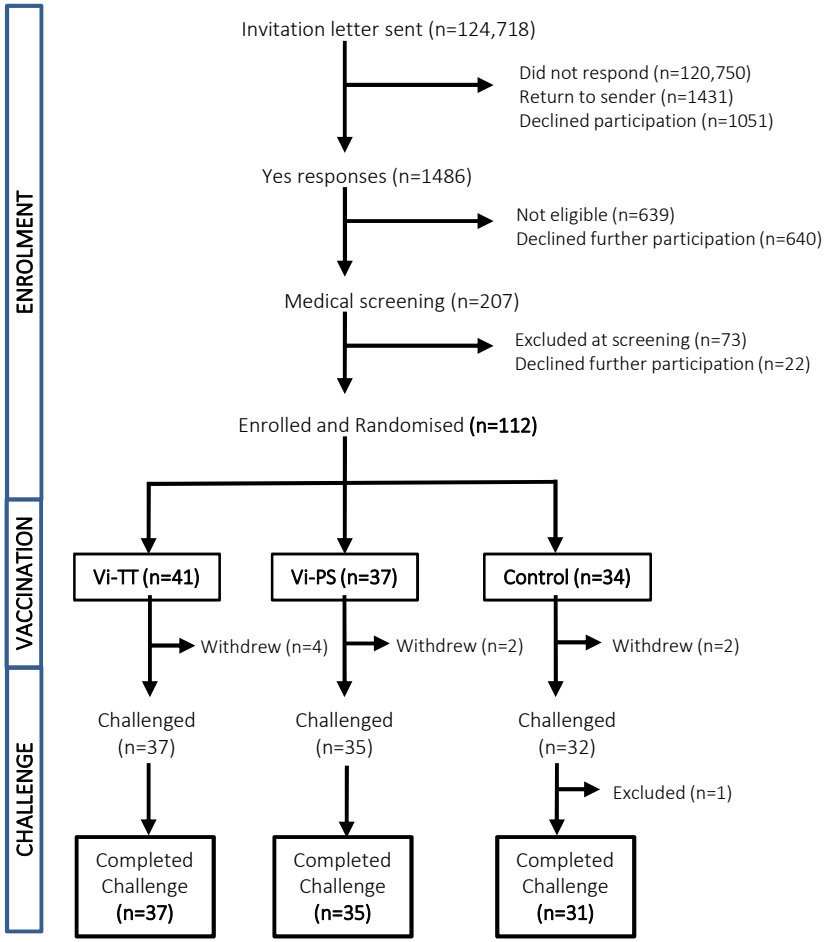


Celina Jin

Study Recruitment

Recruitment period
August 2015
to November 2016

Unblinding
5th January 2017



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

Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, Brian Angus, Andrew J Pollard

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 *S* Typhi, participants were assessed with daily blood culture over a 2-week period and diagnosed with typhoid infection when meeting predefined 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 *S* 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 26·8–71·8) for Vi-TT and 52·0% (23·2–70·0) 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).

Published Online September 28, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32149-9

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32407-8

Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, UK (C Jin MBBS, M M Gibani MRCP, M Moore BA, H B Juel PhD, E Jones BMedSc, J Meiring MBChB, J Gardner BNurs, A Nebykova, S A Kerridge MSc, J Hill PhD, H Thomaides-Brears DPhil, C J Blohmke PhD, A J Pollard FMedSci); **Nuffield Department of Primary Care Health Sciences, University of Oxford, UK** (V Harris PhD, L-M Yu DPhil); **and Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK** (B Angus FRCP)

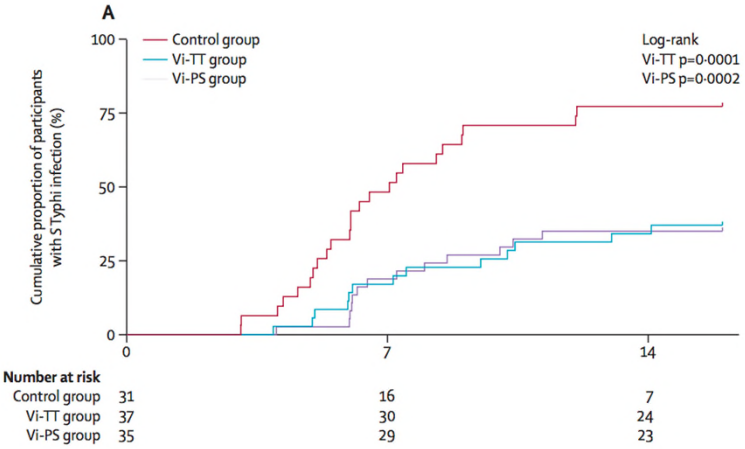
Correspondence to: Dr Celina Jin, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Headington, Oxford OX3 7LE, UK celina.jin@paediatrics.ox.ac.uk

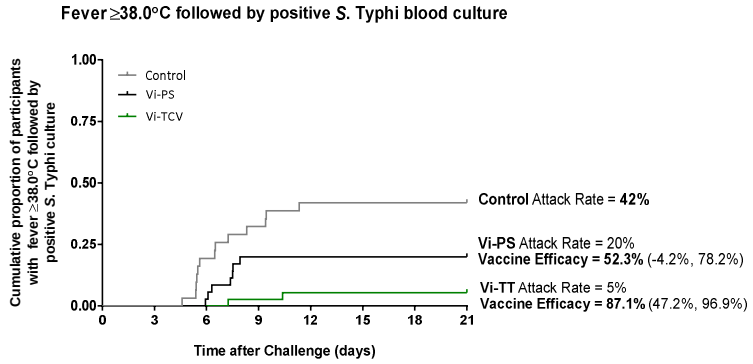
Introduction

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,[1,2] particularly in south Asia and sub-Saharan Africa. Children are especially susceptible to infection and have a high burden of illness.[3] Mortality is estimated at 1% and about 3% of individuals become chronic carriers.[4,5] The large burden of febrile illness associated with typhoid fever in some affected populations—eg, 15% of children with fever attending a health-care facility in Nepal during one rainy season,[6] drives widespread over-the-counter, and prescription 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 54-87%

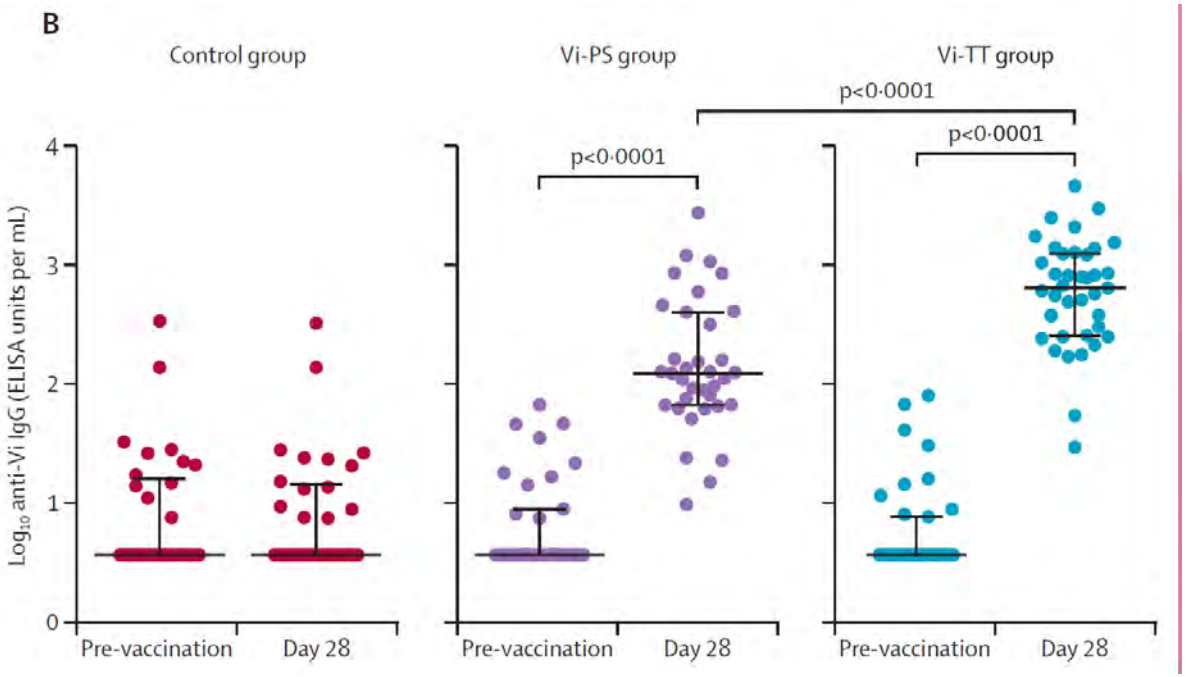
UNIVERSITY OF OXFORD



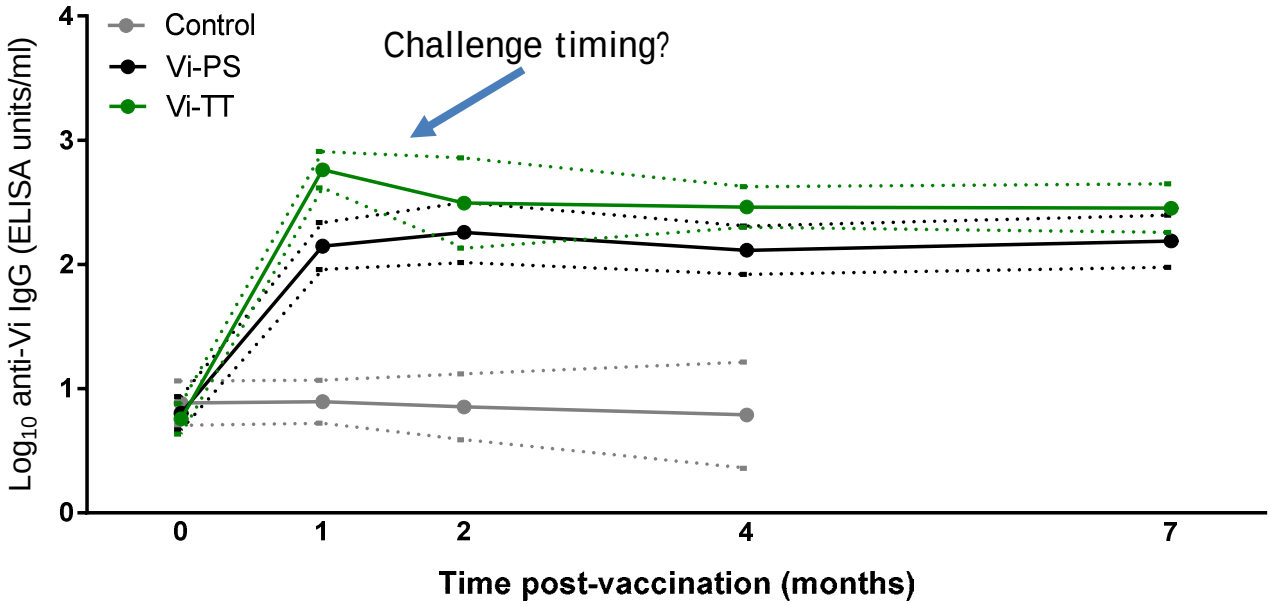


Oxford University Hospitals NHS
NHS Trust

Anti-Vi-TT higher than anti-Vi-PS



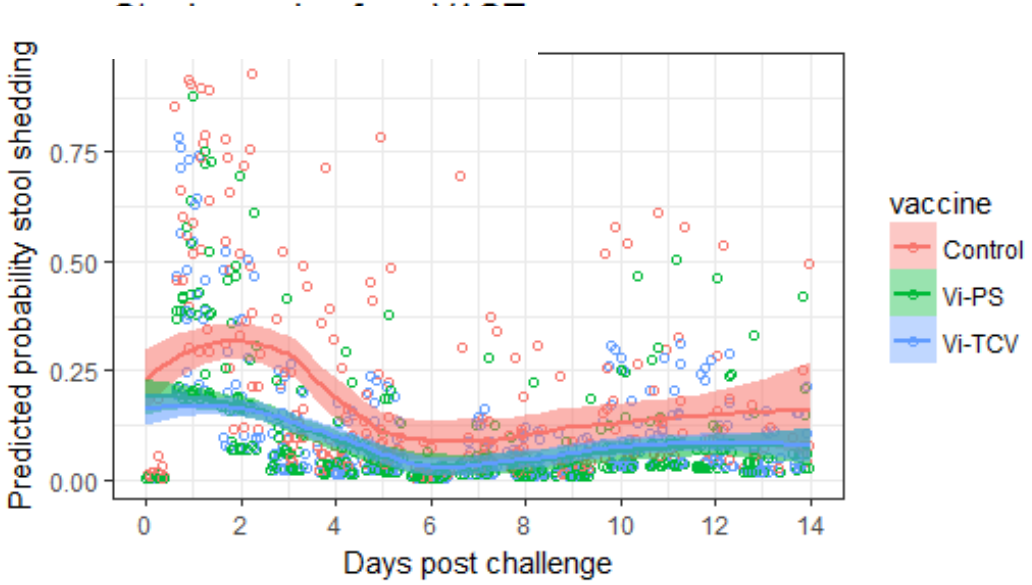
Persistence of antibody good for 7 months



Herd immunity?

Odds of shedding overall are 3 times higher if unvaccinated (averaged across all 14 days)

Vaccine	Comparator	OR (95% CI)	P
Control	Vi-PS	3.28 (1.31, 8.19)	0.0111
Control	Vi-TCV	2.88 (1.18, 7.06)	0.0208
Vi-PS	Vi-TCV	0.88 (0.37, 2.11)	0.7729



Pre-existing estimates of correlates of protection for Vi-vaccines exist, but are difficult to reproduce

Immunogenicity, efficacy and serological correlate of protection of *Salmonella typhi* Vi capsular polysaccharide vaccine three years after immunization

Vaccine, 1996

Keith P. Klugman*§, Hendrik J. Koornhof*, John B. Robbins† and Nancy N. Le Cam‡

0.6– 1.2µg/ml

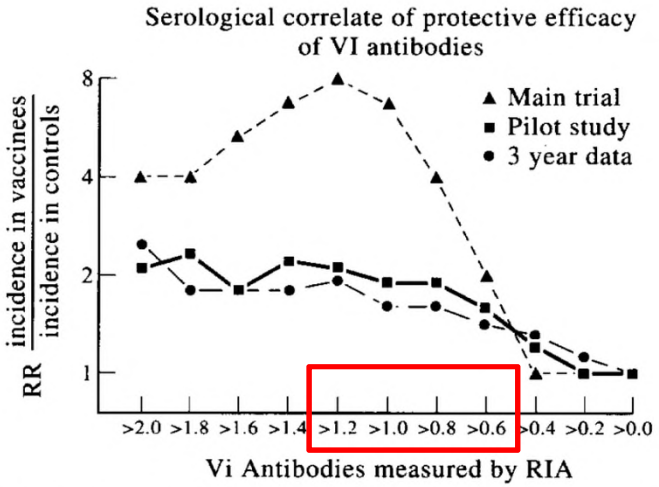


Figure 1 Serological correlate of the protective efficacy of Vi antibodies. The graphs represent the Antibody Relative Ratio (RR), i.e. the incidence of antibodies in Vi vaccinates/incidence in controls for each set of matched data

Re-examination of immune response and estimation of anti-Vi IgG protective threshold against typhoid fever-based on the efficacy trial of Vi conjugate in young children

Vaccine, 2014

Shousun C. Szu[a,*], Keith P. Klugman[b], Steven Hunt[a]

[a] National Institute of Child Health & Human Development, National Institutes of Health, Bethesda, MD, USA
[b] Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

1.4– 2.0µg/ml

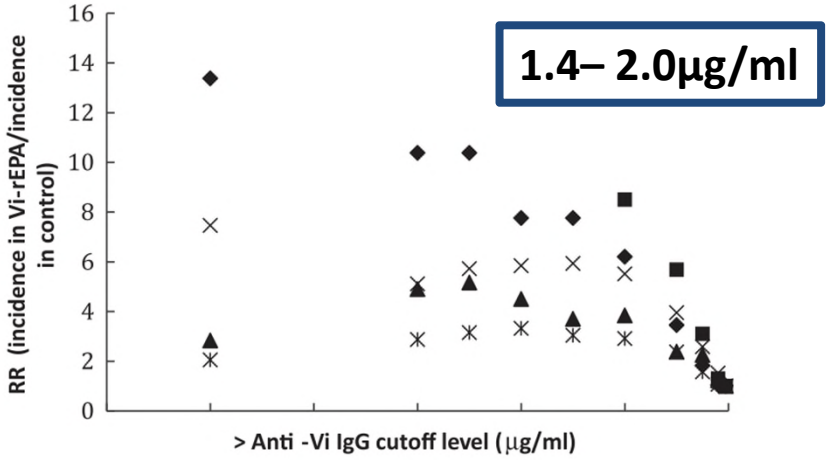
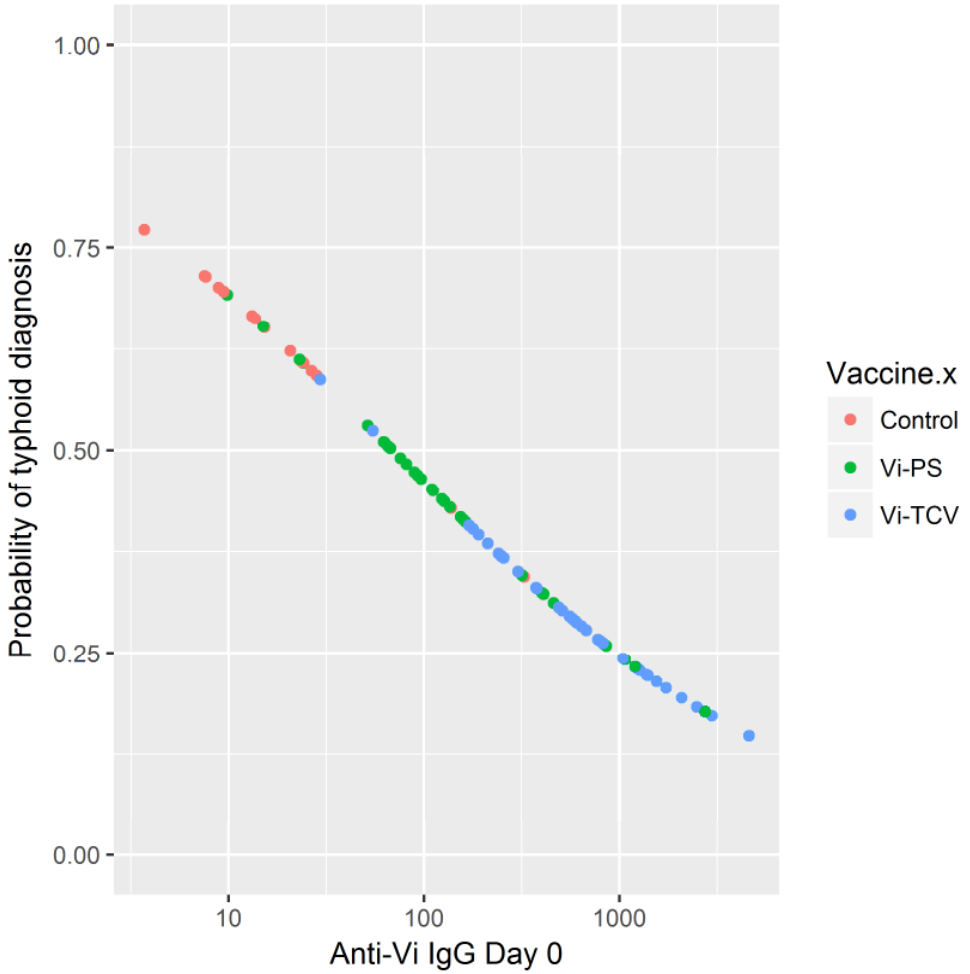


Fig. 1. Incidence relative ratio (RR) of anti-Vi IgG from Vi-rEPA conjugate efficacy trial in 2–5 years old children. The relative antibody ratio (RR) of anti-Vi IgG in children receiving Vi-rEPA or saline at different time periods after the first injection: ♦ 6 months, ■ 12 months, × 24 months, ▲ 30 months, * 42 months. The X-axis indicates the cutoff anti-Vi IgG in µg/ml. The *Y*-axis indicates the relative ratio of incidence between the vaccine group and the control group having the anti-Vi IgG level higher than the cutoff point *X* µg/ml.

Probability of typhoid infection



Bivalent

- Typhoid (Vi) –Paratyphoid (LPS)
- Efficacy trials for paratyphoid bordering on unlikely to be feasible
- Licensure on typhoid component with supporting data on paratyphoid component?

Summary of the October 2017 meeting of the Strategic Advisory Group of Experts on Immunization

The Strategic Advisory Group of Experts (SAGE) on Immunization[1] met on 17-19 October 2017 in Geneva, Switzerland.

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.

oxford vaccine group

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Gavi: Millions of children set to be protected against typhoid

Posted on ***November 30, 2017*** *by* ***admin***

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

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).

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