Controlled human infection models

Andrew J Pollard FMedSci
Smallpox & variolation

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

Lady Mary Montagu
Jenner & vaccination

Sarah Nelmes

Edward Jenner vaccinating James Phipps, 1796

www.ovg.ox.ac.uk
The Cow-Pock — or — the Wonderful Effects of the New Invasion! — Vive... the Publication of the Vaccine Society.
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

- 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.
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

Experimental infection of human volunteers

A

- Other
- Plasmodium falciparum
- Influenza
- Rhinovirus

Number of clinical trials

Year

<1900
1900-10
1911-20
1921-30
1931-40
1941-50
1951-60
1961-70
1971-80
1981-90
1991-2000
2001-19
2011-17

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Number of volunteers per trial

Experimental infection of human volunteers

Meta Roestenberg, Marie-Astrid Hoogewerf, Daniela M Ferreira, Benjamin Mordmüller, Maria Yazdanbakhsh
22,257 and counting

Total=22 257 Volunteers
ETHICAL, LEGAL AND SAFETY CONSIDERATIONS
Informed consent
Minimise risk

Controlled Human Infection Model Studies
Summary of a workshop held on 6 February 2018

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

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ROLE IN VACCINE DEVELOPMENT
Vaccine development pathway

Discovery

Pre-clinical
Safe?
Pre-clinical immune response? Protect?

Phase I
Safe?
Immune response?

Phase II
Best dose?
Safe?
Immune response?

Phase III*
Does it work?

licensure

Post approval studies (Phase IV)

Identification of possible candidates

Identification of endpoints & diagnostics

Identification of CORRELATES

Identification of CORRELATES?

Direct measure of protective efficacy

nb. participant selection

Cross protection

Which
• Candidate?
• Dose?
• Formulation?

* Or bridging/Phase IIb studies

nb. participant selection

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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," Nita 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 U.S."

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.
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

No efficacy data
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

University of Oxford Centre for Clinical Vaccinology and Tropical Medicine
Typhoid attack rates

Challenge dose

- $10^3$ CFU
- $10^4$ CFU

Cumulative percentage with typhoid diagnosis (any method)

Waddington, Clin Infect Dis, 2014
Study Recruitment

Recruitment period
August 2015 to November 2016

Unblinding
5th January 2017

- Invitation letter sent (n=124,718)
  - Did not respond (n=120,750)
  - Return to sender (n=1431)
  - Declined participation (n=1051)
- Yes responses (n=1486)
  - Not eligible (n=639)
  - Declined further participation (n=640)
- Medical screening (n=207)
  - Excluded at screening (n=73)
  - Declined further participation (n=22)
- Enrolled and Randomised (n=112)
  - Vi-TT (n=41)
    - Withdrew (n=4)
      - Challenged (n=37)
        - Completed Challenge (n=37)
  - Vi-PS (n=37)
    - Withdrew (n=2)
      - Challenged (n=35)
        - Completed Challenge (n=35)
  - Control (n=34)
    - Withdrew (n=2)
      - Challenged (n=32)
        - Excluded (n=1)
        - Completed Challenge (n=31)
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

Celia Jin, Malick M Gibson, Maria Moore, Helene D Joel, Elizabeth Jones, James Meling, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kendig, Jennifer Hill, Helen Thomas-Mayr, Christoph J Bohmker, Lyn-Maree Yu, Brian Angus, Andrea J Poillard

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-poly saccharide-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 residence in a typhoid-endemic region. Participants were randomly assigned (1:1) to receive a single dose of Vi-conjugate (Vi-TT), Vi-poly saccharide (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 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 NCT02524751, and is ongoing.

Findings Between Aug 15, 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 disease diagnosis was met in 24 (77%) of 31 participants in the control group, 13 (35%) of 37 participants in the Vi-PS group, and 13 (35%) of 37 participants in the Vi-TT group to give vaccine efficacies of 54–66% (95% CI 26.8–71.8%) for Vi-TT and 52–90% (23–72–70%) 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 vaccinated. 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 had the potential to reduce both the burden of typhoid fever and associated health inequality.

Funding The Bill & Melinda Gates Foundation and the European Commission FPs7 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 12.3–20.6 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. 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—drives widespread over-the-counter, and prescription antibiotic use. Antimicrobial resistance (AMR) is increasingly recognised among S Typhi lineages spreading from south Asia to Africa, with resistance to first-line antibiotics
Anti-Vi-TT higher than anti-Vi-PS
Persistence of antibody good for 7 months

Log$_{10}$ anti-Vi IgG (ELISA units/ml) vs Time post-vaccination (months)

- Control
- Vi-PS
- Vi-TT

Challenge timing?
Herd immunity?

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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Comparator</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Vi-PS</td>
<td>3.28 (1.31, 8.19)</td>
<td>0.0111</td>
</tr>
<tr>
<td>Control</td>
<td>Vi-TCV</td>
<td>2.88 (1.18, 7.06)</td>
<td>0.0208</td>
</tr>
<tr>
<td>Vi-PS</td>
<td>Vi-TCV</td>
<td>0.88 (0.37, 2.11)</td>
<td>0.7729</td>
</tr>
</tbody>
</table>
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‡

0.6–1.2 µg/ml

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*, Keith P. Klugmanb, Steven Hunta

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, CA, USA

1.4–2.0 µg/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.
Probability of typhoid infection

Probability of typhoid diagnosis

Anti-Vi IgG Day 0

Vaccine:
- Control
- Vi-PS
- Vi-TCV
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 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.
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).
Neelam Adhikari, Shrijana Shrestha, Imran Ansari, Meera Gurung, Stephen Thorson, Buddha Basnyat, Mila Shakya and many more....

(Para)Typhoid team

Oxford

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U.K. Typhoid vaccine consortium
TyVAC
Typhoid Vaccine Acceleration Consortium

TyVAC
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