Factors influencing participation in controlled human infection models: a pooled analysis from six enteric fever studies [version 1; peer review: awaiting peer review]

Blanche Oguti 1, Malick Gibani 1,2, Christopher Darlow 1, Claire S Waddington 1,3, Celina Jin 1, Emma Plested 1, Danielle Campbell 1, Claire Jones 1, Tom C Darton 1,4, Andrew J Pollard 1

1Deptment of Paediatrics, University of Oxford, Oxford, UK
2Division of Infectious Diseases, Imperial College London, London, UK
3Department of Medicine, University of Cambridge, Cambridge, UK
4Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

Abstract

Background: Enteric fever is an acute febrile-illness caused by infection with the human-restricted Salmonella serovars Typhi and Paratyphi. Controlled human infection models (CHIM) of S. Typhi and Paratyphi infection are used to accelerate vaccine development and to better understand host-pathogen interactions. The primary motivations for participants to take part in these studies are unknown. We studied participant motivations, attitudes and the factors influencing CHIM study participation.

Methods: Participant surveys were nested in six enteric fever CHIM studies conducted at a single centre in Oxford, UK, between 2011 and 2017. All eligible participants received one invitation to complete an anonymous, self-administered paper or online survey on either day 28 or 60 after challenge. A descriptive analysis was performed on these pooled data. All studies were included, to minimize selection bias.

Results: Survey response rates varied from 33.0%-86.1%, yielding 201 participants. In the cohort, 113/198 (57.0%) were educated to bachelor’s level, 61.6% were employed, 30.3% were students and 4.6% were unemployed. The most commonly cited motivations for CHIM study participation were a desire to contribute to the progression of medicine (170/201; 84.6%); the prospect of financial reimbursement (166/201; 82.6%) and curiosity about clinical trials (117/201; 57.2%). The majority of respondents (139/197; 70.6%) reported that most people advised them against participation.

Conclusion: Motivation to participate in a CHIM study was multi-factorial and heavily influenced by internal drivers beyond monetary reimbursement alone. High educational attainment and employment may be protective.
factors against financial inducement; however, further research is needed, particularly with CHIM studies expanding to low-income and middle-income countries.

**Keywords**
Typhoid, Paratyphoid, Volunteer, Trial, Challenge, Human, Infection

**Corresponding author:** Blanche Oguti (blanche.oguti@paediatrics.ox.ac.uk)

**Author roles:** Oguti B: Conceptualization, Formal Analysis, Methodology, Writing – Original Draft Preparation; Gibani M: Funding Acquisition, Investigation, Software, Visualization, Writing – Review & Editing; Darlow C: Writing – Review & Editing; Waddington CS: Conceptualization, Funding Acquisition, Investigation, Methodology, Writing – Review & Editing; Jin C: Funding Acquisition, Investigation, Writing – Review & Editing; Pleased E: Project Administration, Writing – Review & Editing; Campbell D: Investigation, Writing – Review & Editing; Jones C: Data Curation, Project Administration, Writing – Review & Editing; Darton TC: Funding Acquisition, Investigation, Writing – Review & Editing; Pollard AJ: Funding Acquisition, Investigation, Resources, Supervision, Validation, Writing – Review & Editing

**Competing interests:** AJP is Chair of UK Dept. Health Social Care’s (DHSC) Joint Committee on Vaccination & Immunisation (JCVI) & the European Medicine Agency (EMA) scientific advisory group on vaccines and is a member of the WHO’s Strategic Advisory Group of Experts. The views expressed in this article do not necessarily represent the views of DHSC, JCVI or WHO. AJP is an NIHR senior investigator. The views expressed in this article do not necessarily represent the views of NIHR.

**Grant information:** This work was supported by multiple sources. The Wellcome Trust Strategic Translational Award [092661] and Emergent BioSolutions supported OVG2009/10 and OVG2011/12. Study OVG2011/12 was also supported by the NIHR Oxford Biomedical Research Centre; the Jenner Institute; the Oxford Martin School; the National Institute of Allergy and Infectious Diseases and National Institutes of Health [R01 AI-036525, U19 AI-082655]. Studies OVG2013/07, OVG2014/08 and OVG2016/03 were supported by the Bill & Melinda Gates Foundation [OPP1084259, OPP1126235]. Study OVG2013/07 was also supported by the European Vaccine Initiative. Study OVG2014/01 was funded by the UK Medical Research Council [MR/K021222/1]. Study OVG2014/08 was also supported by the European Commission FP7 grant for Advanced Immunization Technologies. M.M.G is supported in part by the NIHR Imperial Biomedical Research Centre.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Copyright:** © 2019 Oguti B et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Oguti B, Gibani M, Darlow C et al. Factors influencing participation in controlled human infection models: a pooled analysis from six enteric fever studies [version 1; peer review: awaiting peer review] Wellcome Open Research 2019, 4:153 (https://doi.org/10.12688/wellcomeopenres.15469.1)

**First published:** 11 Oct 2019, 4:153 (https://doi.org/10.12688/wellcomeopenres.15469.1)
Introduction

Enteric fever is an infection caused by *Salmonella enterica* subspecies *enterica* serovars Typhi and Paratyphi. It remains a considerable global health challenge, causing an estimated 14.3 million (12.5–16.3) infections and 136 000 deaths annually\(^1\). Until recently\(^2\), licensed vaccines for S. Typhi were only moderately efficacious\(^3\) and could not be used in young children. There are currently no licensed vaccines for S. Paratyphi\(^1\). Both serovars are human host-specific pathogens, and animal models have limited utility to screen candidate vaccines in a biologically relevant system\(^4\).

Controlled human infection models (CHIM) of typhoid or paratyphoid infection could represent a solution to this problem. Such models of typhoid infection have been in existence for several decades, first established by the University of Maryland in 1952 and used for a series of studies until 1974\(^5\). Six S. Typhi and Paratyphi controlled human infection model studies have since been conducted at the University of Oxford (UK) between 2011 and 2017 (Extended data, Supplementary Table 1\(^6\)). The use of these, and similar, models is projected to increase\(^7\). An improved understanding of the factors motivating individuals to volunteer for challenge studies could help to expand their use, to optimise the extent and detail of study information imparted, and to refine the consent procedures used.

Participant motivation and personal experiences are important considerations in the design and delivery of CHIM studies. Identification and recruitment of willing volunteers for such studies can pose distinct challenges—in a recent study 120,000 potential recruits were contacted to recruit 112 participants\(^8\). One study on the experiences and perceptions of participants in a malaria challenge study in Kenya focussed on ethical considerations appropriate to a malaria endemic setting\(^9\). There is otherwise a paucity of research on factors motivating participants to enrol in human challenge studies. In particular, it is unclear as to whether financial considerations are the main driver and whether level of education should be an important inclusion criterion when recruiting volunteers to challenge studies\(^10\). An improved understanding of participant experience could help optimise the design and conduct of future challenge studies. We conducted a quantitative survey of the participants in enteric fever challenge studies, with the aim of exploring the motivations, attitudes and factors influencing participation in human challenge research.

Methods

The survey

A survey on participant motivation and experience was included in every enteric fever CHIM study conducted at the Centre for Clinical Vaccinology and Tropical Medicine in Oxford. The survey population consisted of healthy adults, aged 18–65 years, enrolled in one of the six studies performed during the time period chosen (Extended data, Supplementary Table 1\(^6\)).

Data collected from nested surveys in six separate trials were combined to obtain a more representative overview of motivating factors and attitudes towards participation. All parent trials were conducted at a single site and used comparable inclusion and exclusion criteria\(^11\). The different trial sizes resulted in a variable contribution of survey participants; however, the identical eligibility criteria and catchment area ensured comparable study populations. Non-probability sampling of the trial participants occurred as survey participation relied on voluntary response.

Participants were provided with a 48-question semi-structured survey at follow-up appointments pre-specified in the trial protocol (either day 28 or day 60 after challenge). The time-point was chosen opportunistically to capture experiences immediately after completing the challenge period. The protocol specified study investigators should invite participants to complete the survey on one occasion. Participants provided written consent at enrolment and additional verbal consent prior to completion. The questionnaire was self-administered and returned anonymously.

The bespoke questionnaire (available as Extended data\(^7\)) was developed in-house, based on a published study exploring the attitudes and experiences of healthy volunteers in phase one trials\(^12\). Demographic information on occupational status, income level, education and social support were collected using a multiple-choice format with pre-defined categories. Demographic characteristics of the participants in each study are described elsewhere\(^13\). No identifying information was included on the questionnaire to ensure anonymity. Where appropriate, questions on motivation and attitudes utilised the Likert scale\(^14\) a four- or five-point scale with pre-defined responses, allowing the respondent to express how much they agree or disagree with a given statement.

The survey tool was electronic in two trials (with the option of a paper version if preferred) and exclusively paper in four studies. Emails prompting participants to fill out the electronic survey was sent out in two studies. Participants could choose to complete the questionnaire in the waiting room after a study visit or to return it at a later date. Questionnaires were returned in a blank, sealed envelope and deposited in a collection box at the reception.

The data were transcribed into an electronic spreadsheet and collated by non-study investigators. A descriptive data analysis was performed using Microsoft Excel 16.0 and R 3.5.1 statistical software.

The CHIM studies

The specific aims, trial design and results of the included studies are described elsewhere\(^13\). All studies were advertised by several modalities, including poster advertising, targeted mail drops and social media. The adults were required to initiate contact with study staff at the Oxford Vaccine Group (OVG), at which point they were provided with written information and telephone screened. Extensive pre-study counselling was then performed for interested individuals, consisting of a structured 90-minute consultation with a study physician. To confirm agreement with study participation, individuals provided written informed consent.
Screening for study inclusion/exclusion criteria included a medical history, physical examination, blood screening, electrocardiogram and an ultrasound examination of the gallbladder. Eligible candidates were assessed seven days prior to receiving the challenge agent, to re-explain the trial if required, re-assess eligibility and reconfirm consent.

Challenge study procedures and safety measures are detailed elsewhere. The participants were reviewed daily for 14-days following challenge, which involved a clinical evaluation plus blood and stool sampling.

**Participant reimbursement**
Participants were reimbursed for participation using a standardised template, including: £15 (17 EUR, 19 USD) per visit for travel expenses; £10 (11 EUR, 13 USD) per donation for inconvenience of blood tests; £20 (23 EUR, 25 USD) per visit for time required for visit; £100 (114 EUR, 127 USD) for endoscopy (study OVG2014/01; *Extended data, Supplementary Table 1*); £150 (171 EUR, 191 USD) reimbursement per day for 10 days of potential time off work. The maximum reimbursement was £3275 (3729 EUR, 4164 USD) for study 1, £3350 (3815 EUR, 4259 USD) for study 2, £3305 (3763 EUR, 4202 USD) for study 3, £2930 (3337 EUR, 3725 USD) for study 4, £3655 (4165 EUR, 4647 USD) for study 5 and £2750 (3125 EUR, 3496 USD) for study 6. The amount of financial reimbursement was determined following consultation with local Research Ethics Committees. The aim was to compensate adequately for the time and inconvenience involved, including potential loss of earnings and travel expenses.

**Ethical approval**
All trials were conducted in accordance with the relevant clinical trial protocols, the principles of the Declaration of Helsinki, and the International Conference on Harmonization (ICH) Good Clinical Practice standards. Ethical approval for all six Oxford CHIM studies was provided by the South Central, Oxfordshire Research Ethics Committee A (*Extended data, Supplementary Table 1*). The data were anonymized.

**Results**
Studies were conducted between November 2011 and August 2017. Our pooled analysis included 201 individuals from six nested surveys which were offered to 421 individuals giving an overall response rate of 47.7%. The individual studies had different sample sizes (Table 1) and response rates varied from 33–86% of total participants (Figure 1). One survey was excluded due to insufficient data. The denominators for each question are variable; not every question was answered by every respondent. There was <5% missing data per question. Individual participant responses are available as *Underlying data*; summary statistics are available as *Extended data*.

**Demographics: all participants**
The median age of participants from all studies was 27 years (interquartile range 23–38), Figure 1A. In the cohort, 113 of 198 participants (57.0%) were educated to bachelor’s level or higher, 122 (61.6%) of the 198 respondents were in employment or self-employed, 60 (30.3%) were students and 9 (4.6%) were unemployed (Figure 1D). The modal annual income was <£10,000, reported by 56 (28.6%) of the 196 participants (Figure 1F). Overall, 91 (46.2%) of the 197 respondents felt that they could receive social support from a partner they lived with. A breakdown of these data by study is provided in Table 2. To encourage candour in responses and for the purposes of anonymisation, patient specific details were de-linked from individual questionnaires. Consequently, we are unable to analyse the demographics of participants who responded to the questionnaire as compared with those who did not.

**Descriptive analysis**
Knowledge of typhoid or paratyphoid infection prior to participation was low, with 177 (88.5%) of 200 respondents reporting “little” or “no” knowledge of enteric fever. In total, 84 (42.0%) of 200 respondents reported that they knew “little” of clinical trials before participating and 14 (7.0%) had never heard about clinical trials before. Specifically, 117 (58.8%) of the 199 participants reported little or no prior knowledge of human challenge studies.

In response to the statement that “financial reimbursement was a motivation for joining this study”, 166 (82.6%) of 201 respondents agreed or strongly agreed (Figure 2A). If there had been no financial reimbursement offered, 129/197 (65.5%) participants stated that they would not have taken part in the study. With reference to reimbursement levels, 129/198 (65.2%) participants felt that the amount received was “fair” amount and 65/198 (32.8%) thought that the compensation was “generous”. The modal bracket of minimum financial reimbursement that participants would accept for taking part in a similar study in the future was £2,000 – £2,500, as indicated by 46 (23.3%) of 198 respondents.

The opportunity to participate in a clinical trial was a motivating factor for many of the respondents, with 139 (69.2%) agreeing or strongly agreeing with this statement (Figure 2A).

---

**Table 1. Survey participants for the included studies.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Survey Respondents</th>
<th>Total Survey Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVG2009/10</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>OVG2011/02</td>
<td>30</td>
<td>91</td>
</tr>
<tr>
<td>OVG2013/07</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>OVG2014/08</td>
<td>35</td>
<td>103</td>
</tr>
<tr>
<td>OVG2014/01</td>
<td>53</td>
<td>113</td>
</tr>
<tr>
<td>OVG2016/03</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Overall</td>
<td>201</td>
<td>421</td>
</tr>
</tbody>
</table>
progress of medicine was a motivating factor”, 170 (84.6%) “agreed” or “strongly agreed”. The motivation to join the study to “learn more about one’s own health” ranked lowest low, with 109 (54.2%) participants agreeing or strongly agreeing with this statement.

The majority of those surveyed (166/199; 83.4%), were “very satisfied” with the information provided before the study. All 199 respondents felt that the information in the study booklet was not difficult to understand; 52 (22.9%) reported that it was “easy” to understand and 147 (77.1%) felt that it was “very easy” to understand. Similarly, they answered that the verbal information given during the screening visit was not difficult to understand, with 177 (88.9%) feeling that it was “very easy” to understand.

Less than 5.0% of the participants were “very concerned” about possible study-related risks such as hospitalisation or complications from enteric fever infection (Figure 2B). Before deciding to take part in the study, 46 (23.2%) of 198 participants thought that the study was “not risky at all” and 91 (46.0%) perceived that it held a “slight risk”. Overall, 137 (68.5%) of 200 respondents asked someone else’s opinion before enrolling in the trial. Many participants approached more than one person; 62 (31.0%) of the study population conferred with a relative, 64 (32.0%) with their partner and 69 (34.5%) with a friend. Only 13 (6.5%) asked their GP for advice before the study.

When asked about the reaction of other people during discussions about participation in the study, 64 (33.3%) of 192 respondents indicated that, “some said that it was a good idea, and some said it was a bad idea”. A further third, 64 (33.3%), indicated that “almost all of them said that taking part in the study was a bad idea”. The majority, 139 (70.6%), of 197 respondents reported that most people advised them against joining the study because of the potential risk to the participant and 53 (27.0%) reported that the deterrent was the perceived risk of transmitting the infection to others (Figure 2B).

For 110 (55.6%) of 198 survey respondents, the challenge study was their first participation in a clinical trial. Approximately
Table 2. Demographics of survey participants (by study and overall). Missing data from non-response, not included in denominators.

<table>
<thead>
<tr>
<th></th>
<th>OVG2009/10 N (%)</th>
<th>OVG2011/02 N (%)</th>
<th>OVG2013/07 N (%)</th>
<th>OVG2014/01 N (%)</th>
<th>OVG2014/08 N (%)</th>
<th>OVG2016/03 N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>4 (13.8)</td>
<td>7 (24.1)</td>
<td>4 (13.3)</td>
<td>9 (17.3)</td>
<td>5 (14.3)</td>
<td>2 (9.1)</td>
<td>31 (15.7)</td>
</tr>
<tr>
<td>A Level</td>
<td>4 (13.8)</td>
<td>8 (37.9)</td>
<td>7 (23.3)</td>
<td>9 (17.3)</td>
<td>12 (34.3)</td>
<td>10 (45.5)</td>
<td>53 (27.0)</td>
</tr>
<tr>
<td>Bachelor’s</td>
<td>14 (48.3)</td>
<td>11 (27.6)</td>
<td>10 (33.3)</td>
<td>21 (40.4)</td>
<td>13 (37.1)</td>
<td>3 (13.6)</td>
<td>69 (35.0)</td>
</tr>
<tr>
<td>Higher Degree</td>
<td>7 (24.1)</td>
<td>3 (10.3)</td>
<td>9 (30.0)</td>
<td>13 (25.0)</td>
<td>5 (14.3)</td>
<td>7 (31.8)</td>
<td>44 (22.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>29 (100.0)</td>
<td>29 (100.0)</td>
<td>30 (100.0)</td>
<td>52 (100.0)</td>
<td>35 (100.0)</td>
<td>22 (100.0)</td>
<td>197 (100.0)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>8 (26.7)</td>
<td>3 (10.3)</td>
<td>14 (46.7)</td>
<td>16 (30.8)</td>
<td>12 (34.3)</td>
<td>7 (31.8)</td>
<td>60 (30.3)</td>
</tr>
<tr>
<td>Employed</td>
<td>16 (53.3)</td>
<td>15 (51.7)</td>
<td>12 (40.0)</td>
<td>26 (50.0)</td>
<td>15 (42.9)</td>
<td>10 (45.5)</td>
<td>94 (47.5)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>3 (10.0)</td>
<td>8 (27.6)</td>
<td>1 (3.3)</td>
<td>7 (13.5)</td>
<td>6 (17.1)</td>
<td>3 (13.6)</td>
<td>28 (14.1)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2 (6.7)</td>
<td>1 (3.5)</td>
<td>3 (10.0)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>2 (9.1)</td>
<td>9 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
<td>2 (6.9)</td>
<td>0 (0.0)</td>
<td>2 (3.9)</td>
<td>2 (5.7)</td>
<td>0 (0.0)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30 (100.0)</td>
<td>29 (100.0)</td>
<td>30 (100.0)</td>
<td>52 (100.0)</td>
<td>35 (100.0)</td>
<td>22 (100.0)</td>
<td>198 (100.0)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Annual Income</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; £10,000</td>
<td>8 (26.7)</td>
<td>5 (17.2)</td>
<td>13 (43.3)</td>
<td>13 (25.5)</td>
<td>11 (32.4)</td>
<td>6 (27.3)</td>
<td>56 (28.6)</td>
</tr>
<tr>
<td>£10,000 – £20,000</td>
<td>7 (23.3)</td>
<td>8 (27.6)</td>
<td>7 (23.3)</td>
<td>14 (27.5)</td>
<td>13 (38.2)</td>
<td>3 (13.6)</td>
<td>52 (26.5)</td>
</tr>
<tr>
<td>£20,000 – £30,000</td>
<td>9 (30.0)</td>
<td>9 (31.0)</td>
<td>6 (20.0)</td>
<td>13 (25.5)</td>
<td>5 (14.7)</td>
<td>8 (36.4)</td>
<td>50 (25.5)</td>
</tr>
<tr>
<td>£30,000 – £40,000</td>
<td>5 (16.7)</td>
<td>4 (13.8)</td>
<td>1 (3.3)</td>
<td>9 (17.7)</td>
<td>4 (11.8)</td>
<td>2 (9.1)</td>
<td>25 (12.8)</td>
</tr>
<tr>
<td>&gt; £40,000</td>
<td>1 (3.3)</td>
<td>3 (10.3)</td>
<td>3 (10.0)</td>
<td>2 (3.9)</td>
<td>1 (2.9)</td>
<td>3 (13.6)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30 (100.0)</td>
<td>29 (100.0)</td>
<td>30 (100.0)</td>
<td>51 (100.0)</td>
<td>34 (100.0)</td>
<td>22 (100.0)</td>
<td>196 (100.0)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td><strong>Social Support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-one</td>
<td>6 (20.0)</td>
<td>3 (10.3)</td>
<td>3 (10.0)</td>
<td>14 (26.9)</td>
<td>11 (32.4)</td>
<td>2 (9.1)</td>
<td>39 (19.8)</td>
</tr>
<tr>
<td>Friends</td>
<td>6 (20.0)</td>
<td>4 (13.8)</td>
<td>10 (33.3)</td>
<td>12 (23.1)</td>
<td>7 (20.6)</td>
<td>3 (13.6)</td>
<td>42 (21.3)</td>
</tr>
<tr>
<td>Partner</td>
<td>12 (40.0)</td>
<td>19 (65.5)</td>
<td>13 (43.3)</td>
<td>20 (38.5)</td>
<td>13 (38.2)</td>
<td>14 (63.6)</td>
<td>91 (46.2)</td>
</tr>
<tr>
<td>Relative</td>
<td>1 (3.3)</td>
<td>3 (10.3)</td>
<td>6 (20.0)</td>
<td>9 (17.3)</td>
<td>3 (8.8)</td>
<td>4 (18.2)</td>
<td>26 (13.2)</td>
</tr>
<tr>
<td>Acquaintance</td>
<td>5 (16.7)</td>
<td>2 (6.9)</td>
<td>2 (6.7)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>1 (4.6)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30 (100.0)</td>
<td>29 (100.0)</td>
<td>30 (100.0)</td>
<td>52 (100.0)</td>
<td>34 (100.0)</td>
<td>22 (100.0)</td>
<td>197 (100.0)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Half, 105/198 (53.0%), of the survey respondents reported developing either typhoid or paratyphoid infection during the challenge studies. Overall, 73 (69.5%) of these felt that the experience of enteric fever infection was “as expected as or better than expected” (Figure 2C) and 32 (30.5%) felt that it was somewhat “worse” than they expected. Of the 196 participants that responded to questions about time off work, 103 (52.6%) did not take any days off work during the study; 52 (26.5%) took <2 days off work, 25 (12.8%) took 3–4 days and 16 (8.2%) needed >4 days of sick leave.
When asked to indicate the level of satisfaction they had with the care they received from the staff during the study, 184 (94.2%) of the 199 respondents were “very satisfied”. A high proportion of respondents would take part in the study again, with 177 (90.3%) of 196 respondents indicating “yes”. To the question, “would you recommend participation in a challenge study to a friend or relative?” the modal response was “probably” from 155 (79.1%) of 196 respondents.

**Discussion**

This survey represents the first comprehensive analysis of participant motivations for, and experiences of, participating in typhoid and paratyphoid CHIM studies. These data suggest that participants were motivated by a range of factors, with a desire to contribute to the progress of medicine was the most frequently cited motivator for participation. The offer of financial reimbursement was the most important additional driver for attracting participation to this type of research and, for many, was a necessary pre-requisite. Generally, participants perceived the risks of participation to be low, in contrast to their close household contacts and relatives. These data provide valuable information to investigators conducting challenge studies in high-income, non-disease-endemic settings.

Participants in the survey reported that the chance to contribute to science and curiosity about clinical trials were strong motivating factors, combined with financial reimbursement. Similar to other healthy-volunteer studies, most participants reported that they would not have taken part without reimbursement. An unexpected finding was that a substantial proportion of our survey participants (35%) would have taken part with just their basic expenses met. Some studies have suggested that volunteers in early-phase trials may have an objective financial need but they leverage their emotions as the rationale for participation, whereas other studies have suggested that participation is seldom altruistic and primarily driven by financial compensation. In keeping with this study, one systematic review suggested that motivation to participate in clinical trials is driven by a combination of financial and humanitarian reasons. These data are indicating that the decision to participate in challenge studies was likely to be multifactorial and one can speculate that these are influenced by a variety of economic and socio-demographic factors not captured by this survey.

These data show that most of the respondents perceived the risk of participating in a challenge study to be low. A recent survey of the motivations of 1,200 healthy volunteers in phase I clinical trials, conducted in three high-income countries, found that most participants rated the consideration of risks as even more important to their enrolment decisions than the amount of money offered. Ultimately, the participants enrolled anyway, having assessed the risk themselves; a phenomenon that has been previously described in a study exploring the personality characteristics of healthy volunteers. It is notable that most of the responders who were diagnosed with enteric fever, an adverse experience, still felt positive about their participation in the study.

**Figure 2. Survey responses.** (A) Distribution of strength of agreement with statements on motivation for participants joining the study. N =201. (B) Level of concern in response to statements regarding potential risks in participation. (C) Participants comparing experience of (para)typhoid infection with prior expectation.
Remarkably, a third of the survey participants revealed that their contacts thought that enrolling in a challenge study was a bad idea. A significant proportion of contacts who advised the participants against study enrolment were concerned about the potential for them to transmit typhoid to others. This raises the question as to whether close-contacts should be consented for third party risk, and whether this would justify forfeiting a participants’ right to anonymity.

There was no strong evidence of financial inducement detected in this study. Most participants were in paid employment, with only 4.6% describing themselves as unemployed. The modal income was less than £10,000 a year; however, a third of the cohort were students, comparable to 23% of Oxford’s adult population\(^\text{20}\), who may have relatively lower living expenses. In response to this potential risk, the exact remuneration for participation in CHIM studies were carefully considered and required justification as part of the ethical approval process. The financial reimbursement was decided based on several factors including travel expenses, multiple clinic visits, the inconvenience of each study procedure and the potential for lost earnings due to sickness. It has been suggested that it is a participant’s perception of their economic circumstances—rather than the absolute amount reimbursed—that primarily influences their decision to participate in a clinical trial\(^\text{20}\). Previous studies have demonstrated an inverse correlation between education and financial reward as a motivator and education, suggesting that highly educated people may be less likely to need the money or less susceptible to financial inducement\(^\text{18}\). As these studies were set in a high-income context the survey results may not be generalizable to low-income countries where (at present) ~7% of challenge studies are conducted\(^\text{8}\) and the ethics of financial benefits may need a higher level of scrutiny\(^\text{19}\).

The limitations to the survey approach are acknowledged. The survey relied on voluntary participation and yielded varying response rates from the six included CHIM studies. The low response rate from some of the studies may have introduced some selection bias\(^\text{18}\). Though the demographic data were similar across the CHIM studies, the study with an 86% response rate had a higher proportion of participants with a higher degree, compared to the two studies with the lowest response rates. It is possible that the CHIM participants with a higher educational attainment were more likely to respond to the survey than those with a lower attainment. Although we present the age distribution of the parent studies, we did not capture the age and gender of the survey respondents, which may have hidden disparities in attitudes; a previous study on the motivations of healthy volunteers observed that the younger participants were motivated by financial gain, whereas the older participants were attracted by a free medical screening or contributing to the benefit of others\(^\text{19}\). Difference in responses based on the demographic strata would provide more in-depth interpretation and understanding of the data and will be included in future studies.

These data may only be applicable to challenge models associated with the development of clinical disease, rather than a model designed to assess carriage or other surrogate measures of infection\(^\text{16}\). Self-reported data, which can introduce a systematic error in the measurement of opinions, as positive responses tend to be favoured in surveys\(^\text{17}\). Using a self-administered survey may have introduced some random measurement error, as it was not possible to ensure that the questions were understood in the same way. In-depth interviews could be applied in future studies to explore the issues raised in greater depth.

In conclusion, although financial compensation is a very important factor considered by CHIM study participants, it forms part of a multifactorial decision-making process and does not negate the consideration of risk. Although there was no clear evidence of financial inducement to participate in the CHIM studies, we cannot definitively conclude that it did not occur. These data describe a cohort with a relatively high socioeconomic status and may not be generalizable to low-resource settings. These findings can be used to optimize participant experience and are useful as the design of challenge studies continues to evolve. Further studies are needed to determine whether education and employment are causally associated with financial inducement, particularly if CHIM studies are to increase in low and middle-income countries.

**Data availability**

**Underlying data**


This project contains the following underlying data:

- Day_26_append (Participant questionnaire raw data from typhoid/paratyphoid challenge studies; TYGER, PATCH, VAST).

**Extended data**


This project contains the following extended data:

- Paper summary typhoid (summary statistics from survey data).
- Questionnaire text (Questionnaire tool used in this study).
- Supplementary Table 1 (Description of parent challenge studies).

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Acknowledgements**

The authors acknowledge the support of the NIHR Oxford Biomedical Research Centre and the NIHR Thames Valley and South Midlands Clinical Research Network.
References


