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10.12688/wellcomeopenres.15469.1

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RESEARCH ARTICLE

Factors influencing participation in controlled human infection models: a pooled analysis from six enteric fever studies [version 1; peer review: 3 approved with reservations]

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v1 **First published:** 11 Oct 2019, **4**:153 (https://doi.org/10.12688/wellcomeopenres.15469.1)
Latest published: 11 Oct 2019, **4**:153 (https://doi.org/10.12688/wellcomeopenres.15469.1)

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

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factors against financial inducement; however, further research is needed, particularly with CHIM studies expanding to low-income and middle-income countries.

Keywords
Typhoid, Parathyphoid, Volunteer, Trial, Challenge, Human, Infection

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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.

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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: 3 approved with reservations]** 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[4]. Both serovars are human host-specific pathogens, and animal models have limited utility to screen candidate vaccines in a biologically relevant system[5].

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[6]. 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[7]). The use of these, and similar, models are projected to increase[8]. 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[9,10]. 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[11]. 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[11]. 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[7]).

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[10,12–14]. 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 timepoint 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[15]. 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[10,12–15]. No identifying information was included on the questionnaire to ensure anonymity. Where appropriate, questions on motivation and attitudes utilised the Likert scale[16] 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[10,12–14,17]. 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[10,12–14]. 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[7]); £150 (171EUR, 191USD) 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[7]). 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*[18]; summary statistics are available as *Extended data*[7].

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.

Table 1. Survey participants for the included studies.

Study	Survey Respondents	Total Survey Population
OVG2009/10	31	36
OVG2011/02	30	91
OVG2013/07	30	40
OVG2014/08	35	103
OVG2014/01	53	113
OVG2016/03	22	38
Overall	201	421

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). In response to the statement that wanting to "contribute to the

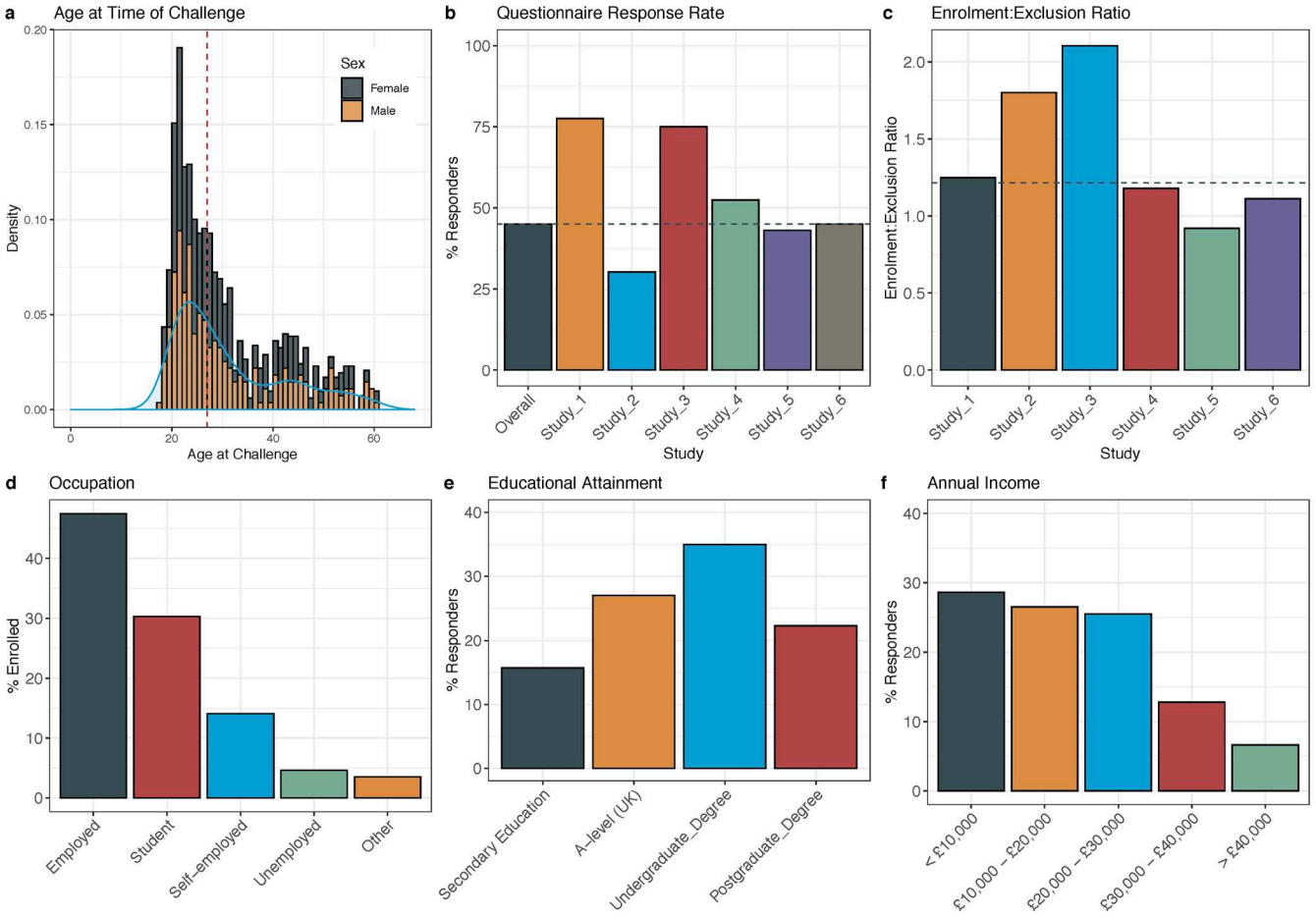

Figure 1. Demographic Characteristics of Participants. (**A**) Age at Time of Challenge for all enteric fever CHIM studies, divided by sex (**B**) Questionnaire response rate per study. Dotted line represents median response rate; (**C**) Enrolment: Exclusion ratio per study; (**D**) Occupational status at time of challenge; (**E**) Educational attainment; (**F**) Annual income.

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.

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

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.

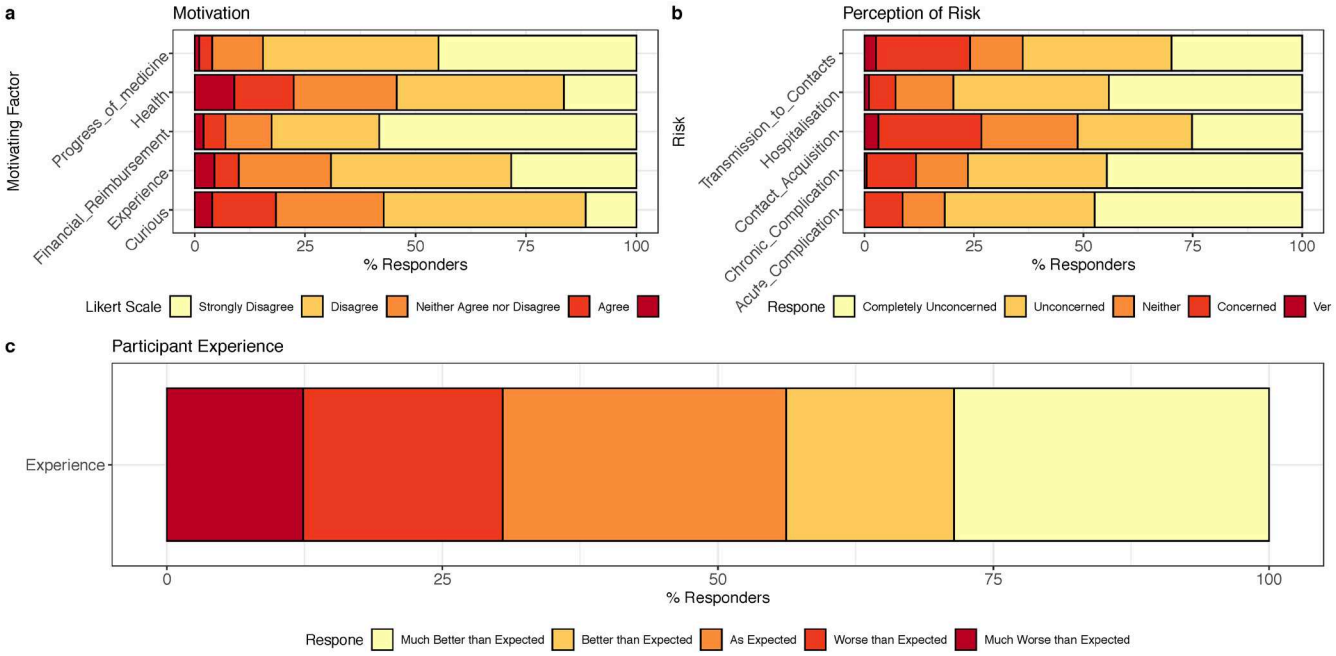

Figure 2. Survey responses. (**A**) Distribution of strength of agreement with statements on motivation for participants joining the study. N =201. (**B**) Level of concern in response to statements regarding potential risks in participation. (**C**) Participants comparing experience of (para)typhoid infection with prior expectation.

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[19], 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[20], whereas other studies have suggested that participation is seldom altruistic and primarily driven by financial compensation[21]. 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[22]. 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[23]. 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[15]. 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.

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[24], 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[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[15]. 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[8] and the ethics of financial benefits may need a higher level of scrutiny[11].

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[25]. 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[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 model designed to assess carriage or other surrogate measures of infection[26]. Self-reported data, which can introduce a systematic error in the measurement of opinions, as positive responses tend to be favoured in surveys[27]. 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 socio-economic 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

Figshare: Enteric Fever Challenge Participant Survey Data. https://doi.org/10.6084/m9.figshare.9901421[18].

This project contains the following underlying data:

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

Extended data

Figshare Repository: Enteric Fever Survey Extended Data. https://doi.org/10.6084/m9.figshare.9902174.v1[7].

This project contains the following extended data:

- Paper summary typhoid (summary statistics from survey data).
- Questionnairetext (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.

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Current Peer Review Status: ? ? ?

Version 1

Reviewer Report 25 November 2019

https://doi.org/10.21956/wellcomeopenres.16918.r36801

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Kawsar R. Talaat
Center for Immunization Research, Department of International Health, Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD, USA

In this manuscript, the authors describe an ancillary survey study that accompanied each of the 6 enteric fever challenge studies performed at the University of Oxford. Controlled human infection models are useful and important tools to evaluate vaccines and therapeutics for which a field trial may be difficult to do. A better understanding of why volunteers participate in these studies will help the field tremendously. This study helps in the elucidation of why some people volunteered for the enteric fever CHIM at their center. The manuscript is well written and easy to read.

Questions for the authors:

Why is the survey offered at 28 OR 60 days after challenge? For which studies was it 28 days? For which 60? and is there a reason that one was chosen over the other?

The studies are listed by name in the first table, but then are listed as "study 1, 2, 3" in the subsequent figure- is there a way to connect them?

Are the demographics of the survey participants similar to the demographics of the original studies? Or are there differences between the original study participants and the ones who chose to participate in the survey study? The authors suggest that the survey participants may be of higher educational level than the general challenge study participants, but don't give any data.

The authors suggest that the responses to the survey may vary by the demographic differences of the respondents, but they do not show the data in a stratified manner by income or education level.

Does the typhoid or paratyphoid attack rate in the participants differ from that of the volunteers of the parent studies? I.e. were people more or less likely to participate in the survey if they became ill in the challenge study?

The authors suggest consenting close contacts to the study; I have several concerns about this, as they

are not participating in the trial, and it would require study participants to notify contacts of their participation. If the authors are concerned about transmission of the infection, there are better ways to ensure lack of transmission without consenting non-participants.

Minor comments: in the Introduction, references 9 and 10 are used to support that claim that 120,000 individuals were contacted to recruit 112 participants. Reference 9 (Bambery et al, does not seem to discuss numbers or recruitment challenges). Reference 10 is likely appropriate, but the manuscript lists the numbers prescreened at 1486 and does not mention 120,000 contacts.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am an infectious disease doctor who conducts early phase vaccine studies, as well as controlled human challenge studies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 12 November 2019

https://doi.org/10.21956/wellcomeopenres.16918.r36758

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David R. Tribble
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Controlled human infection models (CHIM) are an important component in the clinical research development strategy needed to advance preventive means to mitigate high priority public health threats. These studies are very unique compared to other studies of safety, immunogenicity, and efficacy of vaccine candidates presenting major challenges in how best to successfully inform interested individuals who may choose to consent as research subjects. In addition, the ethics are a foremost consideration given the requirement to expose otherwise healthy people to potential adverse health consequences. The submitted work by the authors is of high priority due to the need to systematically investigate the motivations for subject participation in order to best address future CHIM application to assure subject understanding and decisions are most appropriately addressed and an informed consent process is achieved without undue influence.

Major comment
The stated objective of this analysis is to ‘explore the motivations, attitudes, and factors influencing participation in human challenge research’. The analysis that is presented is descriptive in nature and is limited to frequencies of various survey questions. This is definitely interesting and an important component of this report; however, it is not adequate to meet the objective as stated. There needs to be a more robust analysis of the survey responses that explores the relative differences between responses rather than only reporting response frequencies separately. For example, a critical question is among the subset that is employed (not the other large subset of students) what are their responses to motivating factors and where do they stand in relation to income. What is it for students? By only looking at responses separately it is difficult to draw appropriate interpretations. In addition, the relative level on the Likert scale should be assessed at least as bivariate analyses to assess within-subject how one response relates to another. This holds across the board for factors included in Figure 1/Table 1 (various demographics) against the survey responses related to motivation, risk perception, and participant experience. Also, the interplay between the ‘outcomes (motivation, risk perception, and participant experience) should be assessed within individuals since it is highly unlikely that any of these are independent and not influential on a related response.

Additional comments:

1. The data presented does support the multifactorial nature of subject motivation to participate. It would be helpful, along with the analysis discussed above, to also include a question in future surveys incorporating a rank order of motivating factors. The discussion should include future steps to take this line of investigation forward.

2. Would be helpful to add context to the reported income levels by providing information on how these subjects' income ranges fall within the UK with consideration of similar age, gender, racial, and locale. Certainly true that the setting here is clearly distinct from a LMIC; however, do these subjects represent a low income segment of the general population?

3. The perception of risk of a CHIM study clearly differed from the subjects to their family and friends. This is not surprising given the self-selected aspect of who would agree to volunteer. The finding that the majority (almost 70%) of respondents stated that participation was 'not risky at all' or 'slight risk' is worrisome and should be cause for concern that monetary drivers are influencing the subjects' appreciation of the real risks. The obvious expertise and risk mitigation of the study team are clearly exceptional but this should not lead a subject to understate or fail to appreciate that

there are risks. Given that over half of the respondents were participating in their first clinical trial, as a CHIM study no less, there is a substantial learning curve to overcome as they are trying to understand what it means to volunteer for a greater than minimal risk clinical trial. The authors should address this in the discussion.

4. Were there differences in the survey findings between completion at 28 versus 60 days post challenge?

5. Figure 2a appears to have the legend reversed.

6. The surprising finding of 35% reporting they would have participated without compensation requires more analysis to better understand more about the demographics of these subjects (similar to overall comment above). What are their demographics, employment status, income level, past experience in clinical research participation, and experience during the study (did they get enteric fever?).

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease clinical research to include the development and execution of controlled human infection models.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 25 October 2019

https://doi.org/10.21956/wellcomeopenres.16918.r36809

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Chad K. Porter
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Oguti et al. describe the factors associated with participation in Salmonella Typhi/Paratyphi controlled human infection model (CHIM) studies at a clinical site in Oxford, UK. While an important contribution to the literature and to researchers conducting CHIM studies, some modifications are needed.

These are outlined below:
It is unclear if the questionnaire utilized was validated in any way. This should be commented on by the authors.

The authors do not present any bivariable analyses that could have added additional support to their conclusions and/or discussions. These could have included comparisons by gender, income level (or may of the other demographic parameters obtained as part of the survey). The authors should also access the influence of subjects self-reporting 'infection' by their assessment of their experience. On page 7, the authors state '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." However, it is unclear where these data are located in the manuscript and the statement highlights the need for the bivariable comparisons noted above.
There is a potential for bias in the timing of the questionnaire being administered (day 28 vs day 60). Was this evaluated and, if so, were any differences in either the populations and/or the responses noted?

It is unclear if there were any inclusion/exclusion criteria for subjects to participate in completing the questionnaire. How was informed consent assessed (presumed to be based on questionnaire completion; however, this is not explicitly stated).

In a similar vein, it is not stated if there was compensation provide for completing this survey. It is presumed that there was not, but it should be stated.

Figure 1 and Tables 1 & 2 present duplicative information. I recommend removing the figure (based on the rationale below) and including all the data in a single table. Figure 1 refers to studies as 'Study 1', 'Study 2', etc while the tables use a study identifier. In the first paragraph under results, the stated response rate is 33-86%; however, figure 1b shows no response rate >~75%. The studies are represented by different colored bars in figure 1b and 1c.

Results paragraph 2, it is unclear how the 'patient specific details were de-linked from the individual questionnaires'. Please clarify.

The authors report (results, descriptive analysis section, paragraph 4) on the subjects' assessment of the material and its ability to be understood; however, it is unclear if a knowledge assessment was performed to ensure an adequate understanding of the procedures. Please clarify.

The authors describe (results, descriptive analysis section, paragraph 5) that most respondents indicated

people advised them against participating in the study; however, there is little that can be inferred from this given the lack of including non-participants in the clinical trial. It may be that the rate of this feedback of others is higher in that population.

Results, descriptive analysis section, paragraph 5: please clarify whether subjects were asked about developing an 'infection' or an 'illness'.

Results, descriptive analysis section, paragraph 5: is information available for why subjects took 'sick leave'? Was this to comply with the study schedule or because of illness?

Figure 2a and 2b, the text describing the highest level on the likert scale has been cut off.
In the discussion (paragraph 2) the authors indicate that data indicate decision making processes among participants. While accurate, it is unclear if these responses are different from non-participants as those subjects were not surveyed.

In the discussion (paragraph 2) the authors describe consenting close contacts; however, it is unclear how the authors made that leap. A person's sense of risk does not require informed consent (if there is no risk). This would be a determination (I presume) by the regulatory and/or ethical review bodies.

Minor edits:
Change the use of the word 'deliver' ('…design and deliver of CHIM') in paragraph 2 of the introduction as CHIM aren't "delivered".

In paragraph 2 of the introduction section regarding the statement of whether education should be an important inclusion criterion, the authors should note the role of country income in this description. The authors would only be able to extrapolate their findings to high income countries (and not those that are low-middle income).

In paragraph 5 of the Methods section, modify sentence to state 'Emails…were sent'.
Results, descriptive analysis section, paragraph 3, unclear use of the term 'lowest low'
Discussion, 1st sentence, correct the use of the word 'was'.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: epidemiology; clinical trials; human subjects' research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.