Use of human infection studies in vaccine development

Report of a meeting held at Wellcome, London, UK

Human Investigations & Challenge Team
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Executive summary

Human infection studies, deliberate infection of volunteers in closely monitored settings, can provide important insights into the mechanisms of disease and responses to infection. There are also hopes that such studies could accelerate the development of new interventions, particularly vaccines, by enabling efficacy studies to be carried out rapidly on a limited number of participants after a suitably sized phase I safety study.

In order for human infection studies to influence licensing decision-making, the data they generate must be acceptable to regulatory authorities. To stimulate discussion on the use of such data in vaccine development and product licensing, in July 2022 Wellcome organised a multidisciplinary workshop at which academic researchers working on human infection studies, vaccine developers and representatives from regulatory agencies came together to review past use of human infection study data and the prospects for greater use in the future. Discussions highlighted several important issues:

1. **There are a range of 'niches' in vaccine development where human infection studies are of value:**
   Human infection studies have multiple applications, for example in enhancing understanding of disease mechanisms and host responses, identifying correlates of protection, providing evidence of efficacy to support further investment in clinical development, and potentially in providing an alternative to costly and time-consuming phase III efficacy studies in the field.
2. **Application of human infection studies should be considered on a case-by-case basis:**
   Where human infection studies could be applied in vaccine development will depend on a range of factors, including the nature of the target pathogen, target populations and type of vaccine. It is therefore difficult to identify specific points in a product development cycle at which they could routinely be applied. Rather, it is important to identify key evidence gaps and to consider whether human infection studies are best placed to close those gaps.
3. **It is currently unlikely that human infection studies will be a frequently used alternative to phase III efficacy trials:**
   The cholera vaccine Vaxchora was licensed by the US Food and Drug Administration (FDA) primarily on the basis of efficacy data generated in human infection studies. However, this example is likely to be an exception rather than a model for future regulatory practice, for a range of reasons: it would have been difficult to conduct a phase III trial in the target population (travellers), a wealth of data was already available on the product, and it had been previously licensed without controversy in five other countries. Regulators would need strong evidence that a phase III efficacy trial was not feasible for epidemiological or operational reasons before a human infection study would be considered as an alternative source of data.
4. **Given the variety of uses of human infection studies, it is difficult for regulatory agencies to provide general guidance on their application:**
   While regulators are willing to consider inclusion of human infection study data in licensing applications, the appropriateness of such data needs to be considered on a case-by-case basis according to pathogen, populations targeted and anticipated use scenarios. Early engagement with regulators is encouraged to discuss data requirements.
5. **Standardisation of models and assays, plus sample banking and sharing, could ensure that the best possible use is made of each human infection study project:**
   Data comparability and synthesis will be facilitated by use of common models and standardised assays. Sample banking and sharing could ensure that the maximum amount of data is obtained from each study.

In summary, human infection studies have the potential to accelerate new vaccine development. However, human infection studies are a flexible tool that can be applied in multiple ways in product development pathways. Their application needs to be considered on a case-by-case basis to identify where they are best placed to add value, with early engagement with regulators to agree an overarching approach to data collection for licensing submissions.

Introduction

Recent years have seen renewed interest in human infection studies, to gain new insights into disease processes and host responses to infection and to accelerate the development of interventions, particularly vaccines. As well as high-income countries, there is a growing trend for such studies to be conducted in endemic settings, when vaccines are designed primarily to be used in low- and middle-income countries (LMICs). Wellcome has funded multiple human infection studies in endemic countries (Box 1).

Ultimately, the use of new vaccines (or other interventions) in national control programmes is dependent on regulatory approval. It is therefore important to consider at an early stage how regulatory authorities view data generated through human infection studies and how they might inform licensing decision-making. Key regulatory decision-makers include those in high-income countries, particularly the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), but also national regulatory authorities (NRAs) in endemic countries, which will make the ultimate decision on approval at the national level.

In July 2022, Wellcome organised an international multi-stakeholder meeting to consider how human infection study data can contribute to regulatory processes. Participants included academic researchers working on human infection studies in the UK and endemic settings, vaccine developers and representatives of regulatory agencies including the FDA, EMA and NRAs in endemic countries. The workshop aimed to discuss use of human infection study data in regulatory decision-making, obstacles to their consideration, and ways these obstacles might be overcome.

The meeting had a particular focus on Vaxchora (Box 2), a cholera vaccine licensed by the FDA for use in travellers, which received approval based largely on efficacy data generated by human infection studies. A key question is therefore whether the regulatory processes applied to Vaxchora are more generally applicable and could accelerate the development of other vaccines.

Key themes

Presentations and discussions at the workshop identified a range of key themes:

1. **There are a range of 'niches' in vaccine development where human infection studies are of value**
2. **Application of human infection studies should be considered on a case-by-case basis**
3. **It is currently unlikely that human infection studies will be a frequently used alternative to phase III efficacy trials**
4. **Given the variety of uses of human infection studies, it is difficult for regulatory agencies to provide general guidance on their application**
5. **Standardisation of models and assays, plus sample banking and sharing, could ensure that the best possible use is made of each human infection study project**

1. There are a range of 'niches' in vaccine development where human infection studies are of value:

One key message to emerge from the workshop is that human infection studies are a flexible tool that can be applied to a range of scientific and product-development challenges.

For example, they can provide **novel insights into disease mechanisms and host responses to infection.** The key advantages of human infection studies include a known point of infection, so the kinetics of pathogen reproduction and host responses can be tracked, a high probability of infection, so limited numbers of participants can generate abundant data, and the opportunity to profile participants before infection, so that associations with pre-existing markers can be evaluated.

These kinds of studies can provide insights into **correlates of protection**[1] – immune or other markers showing a statistical association with protection against infection or disease[2]. These may or may not be mechanistically linked to protection, but either way provide a valuable tool for assessing the efficacy of interventions without the need for clinical efficacy data. Use of correlates of protection can generate rapid insight into the likely efficacy of candidate vaccines and in extending the use of licensed vaccines to new populations without the need for large-scale efficacy trials.

Other possible applications include use of human infection studies to establish **optimal doses for phase III trials,** which conventionally requires a phase II trial. For example, this approach was used during the development of an antiviral drug for mild to moderate flu. After successful phase I studies, a dose-finding study was required in advance of a pivotal phase III study, but a limited flu season made a phase II study impractical. The EMA recommended a dose-finding human infection study as an appropriate alternative.

Also in the sphere of therapy development, human infection studies have been used as a stepping stone to the testing of an antiviral medication in hospitalised flu patients. Positive phase I data had been obtained but, in the absence of a reliable animal model, a study in such a vulnerable population would have been a major step. The FDA recommended instead that a phase II human infection study should be carried out in non-hospitalised patients, to provide evidence of efficacy before a phase III trial in hospitalised patients.

These examples illustrate the potential of human infection studies to **de-risk intervention** development. In terms of vaccine development, a key role of such studies could be to de-risk phase III trials, for example by demonstrating efficacy in endemic populations, which can be considered a step closer to target populations compared with participants in high-income countries.

However, for vaccines designed for use in children, **pre-existing immunity** may be an important complicating factor. Past exposure to pathogens may mean that adults already have high levels of protection, making it less easy to demonstrate efficacy. This raises the risk that a human infection study to assess efficacy might generate unfavourable results even for a vaccine that would be effective in the target population.

In the planned Wellcome-funded Kenya human infection project, seroprevalence studies are being carried out to identify pre-existing levels of immunity and to inform the development of thresholds for inclusion in the human infection study, which aims to achieve an infection rate of 60% or higher[3].

One of the most important applications of human infection studies is down-selection of vaccine candidates through comparative studies. This is one aim of the *Shigella* human infection studies being established in Kenya. Several *Shigella* vaccines are in various stages of development but there is limited capacity for phase III trials in endemic settings[4,5]. The Kenya programme plans to assess multiple vaccine candidates in order to prioritise interventions for phase III efficacy studies[3].

Down-selection of vaccine candidates is also a potential application of the **COVID-19 infection model** established at Imperial College, in collaboration with the Royal Free Hospital and hVIVO[6]. Although multiple COVID-19 vaccines have been approved, more than 100 are still in development. COVID-19 human infection studies could also be used evaluate vaccines with unconventional mechanisms of action, for example simulating T-cell immunity, or modes of administration, such as intranasal administration. In these cases, conventional correlates of protection (neutralising antibody levels) would not be appropriate for vaccine evaluation. Human infection studies could provide insight into the effects of vaccines on viral load to generate data on likely protective efficacy.

The initial rationale for COVID-19 human infection studies was to compare first-generation vaccine candidates. When these turned out to be surprisingly efficacious, alternative uses of the platform were prioritised, with proof-of-concept studies providing important insights into viral kinetics and the evolution of symptoms[6]. As time of infection was well defined, the platform also provided an opportunity to assess diagnostic test performance at different stages.

Follow-on studies at the University of Oxford are using a dose-escalation approach to explore reinfection of seropositive participants, to identify factors associated with breakthrough infections and thereby gain more insights into correlates of protection[7]. These studies are using the original Wuhan challenge strain. Meanwhile, a GMP-quality delta challenge has recently been developed and will be studied at both Imperial and Oxford[8].

2. Application of human infection studies should be considered on a case-by-case basis:

Although developers might prefer to see human infection studies as a specific stage in the product-development pathway, this is unlikely to be the case. Their applicability depends on several factors, including type of pathogen, nature of disease course, vaccine type, target populations and setting (e.g. endemic versus pandemic), making it difficult to draw up hard and fast rules on when they should be used.

Rather, there is a need to consider **key evidence gaps** and whether human infection studies are best placed to close them. The decision to use human infection studies needs to consider the specific strengths and weaknesses of individual platforms and their suitability for generating the evidence required to support further development or licensing.

For example, there are important constraints associated with the use of human infection studies. Development of GMP-standard challenge strains, for example, takes several months, limiting their use in fast-moving pandemic situations in which variants are constantly arising. In addition, a limited number of challenge strains are likely to be available for particular pathogens, and these are not necessarily the epidemiologically most significant in endemic settings. For *Shigella,* for example, the most common strains in Kenya are *S. flexneri* followed by *S. sonnei.* Human infection studies will focus on *S. sonnei* as a well-characterised challenge agent is available and results obtained in Kenya will be comparable with those generated in previous US studies.

A further important consideration is the **validity of the human infection study platform** – a further advantage for Vaxchora, as the cholera human infection study was already well-established[9,10]. The validity of a platform covers factors such as routes of administration and infectious doses, recapitulation of natural disease course, and relevance of endpoints. It is important to consider what the key outcome measure is for a vaccine (e.g. prevention of any disease, or severe disease, or transmission), how this can be reliably measured, and how it relates to clinical efficacy in the field.

Choice of endpoint is therefore critical: an endpoint needs to be practical for use in human infection studies but also relevant to clinical disease in the field. In COVID-19 human infection studies, viral load is used as a key outcome measure, given its correlation with symptoms[4]. For *Shigella,* some studies have used a composite disease score[11].

No platform is ever fully equivalent to infection in the field, so each needs to be assessed to determine the kind of evidence it can generate and how this might inform decision-making on clinical development and licensing.

3. It is unlikely that human infection studies will be a frequently used alternative to phase III efficacy trials:

One important application could be the use of human infection studies as an alternative to phase III trials, the cost of which is a major obstacle to the development of interventions designed specifically for low-resource settings and where limited trial capacity may exist. A phase III trial may not be feasible for epidemiological or operational reasons. Possible alternatives include a human infection efficacy study followed by a confirmatory post-licensing effectiveness study.

However, despite the Vaxchora example, the consensus at the meeting was that, if they are feasible, phase III efficacy studies in endemic settings will always be preferred.

It was recognised that the **Vaxchora experience was an exception** and not a model of future regulatory practice[7]. For Vaxchora, it would have been difficult to carry out a phase III trial in the target population, travellers. In addition, extensive additional clinical data had already been generated on Vaxchora – although data from a previous licensing application was not part of the formal submission, it was available to assessors. The fact that the product had already been licensed in five other countries may also have provided assessors with additional confidence.

4. Given the variety of uses of human infection studies, it is difficult for regulatory agencies to provide guidance on their specific application:

Although developers would like clear indications on how human infection study data fit into regulatory decision-making, regulators are unwilling to go beyond principles, important considerations or general guidance[12], such as the need for GMP-standard challenge strains.

As the Vaxchora case illustrates, regulators have shown a willingness to consider data generated through human infection studies and may be more open to consideration of such data than in the past. The COVID-19 pandemic may also have led to increased flexibility in decision-making and encouraged greater convergence in regulatory activities globally. However, the use of human infection studies to support licensing applications needs to be considered on a case-by-case basis, dependent on the pathogen, target populations, use scenarios and feasibility of other approaches for generating data. Regulators recommended early dialogue to discuss options and the design of studies.

5. Standardisation of models and assays, plus sample banking and sharing, could ensure that the best possible use is made of each human infection study:

Standardisation of platforms, including challenge strains and choice of endpoints, can provide important quality assurance and also ensure the comparability of findings and facilitate data meta-analyses. Greater standardisation of assays would deliver similar benefits. However, limiting production of challenge agents to single sites could create supply vulnerabilities. Wellcome has developed guidelines on challenge strain development to ensure consistency and promote quality assurance[13]. Wellcome has also developed a community of practice for human infection studies on The Global Health Network (TGHN) website, which could be used to share information and documents such as standard operating procedures (SOPs) to enable harmonisation of these studies[14].

Although it may be impractical to mandate specific analyses, sample banking and sharing could be recommended to allow for the application of newly developed analytical technologies, as well as analyses by laboratories specialising in particular techniques. It could be considered an ethical responsibility to gain as much knowledge as possible from each study. Wellcome and the Bill and Melinda Gates Foundation (BMGF) are working to establish a set of 'funders' principles' to guide funders of human infection studies, to ensure that studies are aligned and develop best practices, that volunteers are treated well and have a high-quality experience regardless of the location of study, and most importantly that there is a shared commitment to volunteer safety.

However, the **practicalities and expense of biobanking** would need to be considered, as well as the need for equity in access given that researchers in LMICs may be less able to mobilise resources for studies on local samples. The need for **access mechanisms** would also need to be addressed. **Informed consent** procedures could also be an obstacle to sample sharing – consent may not have been obtained to allow additional analysis of existing samples and open-ended consent for any analysis on collection of new samples would be problematic.

Human infection study programmes in endemic settings have placed a high priority on **community engagement** and securing the approval of local populations for human infection studies. Embedded **social research** is also generating valuable insights into community attitudes and practices to inform the design of studies[15].

Community engagement has been used to inform the conduct of studies and has covered key issues such as participants' expenses. The issues raised at community discussion events are typically similar to those highlighted in high-income countries. There is now a consensus on what is considered good practice in community engagement, and it was recognised that deep engagement needs to be maintained as studies can only proceed on the basis of a trusting relationship between researchers and local communities.

The sites involved in human infection studies have had **little difficulty in recruiting participants,** despite the lack of incentives. In low-resource settings, the comprehensive health check given to participants is seen as a benefit, while the limited expenses provided is an incentive to some. In Kilifi, a significant financial reward for participation was not seen as desirable as it could imply a trade-off for exposure to a high level of risk.

Across multiple sites, **altruism** is seen to be a common motivator, with potential participants acutely aware of the impact of the diseases under study on local communities. In high-income countries, COVID-19 has encouraged more members of professional groups to volunteer, driven by a desire to contribute to the battle against the pandemic. In some cases, potential participants may be attracted by possible financial gain but become committed to a project when they learn more about it, illustrating that motivation may evolve over time[16].

Conclusions

The workshop heard how human infection studies can make a valuable contribution to vaccine R&D, potentially at multiple stages of development. Over the last 2–5 years, there have been significant advances in the field of human infection studies, spurred on by advances in technology such as transcriptomics, and there has also been an expansion of these studies in endemic settings. Nevertheless, it is difficult to make general statements on how they can routinely be applied in vaccine-development pathways.

Human infection studies have a number of advantages but also constraints. Their most appropriate use during vaccine development will depend on multiple factors, including the nature of the pathogen under study, course of disease, availability of validated correlates of protection, the feasibility of phase III efficacy studies in endemic settings, and underlying context (such as endemic or pandemic disease).

This implies that the use of human infection studies will be dependent on an evaluation of key evidence gaps and whether such studies are best placed to close these gaps. Their potential use should be discussed early with regulators, who are generally willing to consider human infection study data in licensing applications and can offer advice on how such data could be included in a wider data package for a licensing application.

With the growing interest in human infection studies, there will be a need for further engagement with stakeholders to highlight the opportunities they offer, where they are likely to add most value, and how human infection study data can contribute to licensing decision-making.

Box 1

Wellcome-funded human infection study programmes

In endemic countries:

- Thailand: Plasmodium vivax[17]
- Malawi: Pneumococcus[18]
- India: Typhoid (not started)
- Vietnam: Dengue (exploratory study to assess possible future use)
- Brazil: Hookworm[19]
- Kenya: *Shigella*[20]
- Uganda: Schistosomiasis[21]
- India: Cholera (on hold)

In the UK:

- COVID-19: Dose-escalation study in seropositive individuals (University of Oxford)[7]
- COVID-19: SARS-CoV-2 delta characterisation (Imperial)[8]

Box 2

Development of Vaxchora

In the 1980s, a human infection study platform for cholera was established at the University of Maryland, Baltimore (UMB). This generated important data on host responses to infection and virulence factors, such as cholera toxin. Deletion mutants were produced to generate attenuated strains suitable for investigation as vaccine candidates[22].

The most promising of these, CVD-103-HgR, was licensed in five high-income countries for use in travellers. However, while accepting that human infection study data could be considered in licensing applications, the US FDA's advisory committee declined to approve CVD-103-HgR, arguing that data from double-blinded randomised controlled trials using a validated platform were required.

A standardised human infection study platform was established at three US sites and generated consistent data demonstrating the efficacy of CVD-103-HgR. However, the manufacturers, Berna Biotech, were unwilling to upgrade facilities to meet FDA requirements and global production was later halted for business reasons. Berna Biotech was acquired by Crucell, which subsequently acquired the manufacturers of the oral cholera vaccine Dukoral[23].

CVD-103-HgR intellectual property reverted to UMB and in 2009 an exclusive licensing agreement was signed with PaxVax Inc. to develop the product, renamed Vaxchora. In discussions with the FDA, it was agreed that efficacy data from a phase II human infection study could be used in the licensing application given the difficulty in organising a phase III trial in the intended target population, travellers. In 2016, Vaxchora received FDA licensing approval for use in the US travellers market[13,24].

Annex 1: Meeting attendees

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Endnotes:

1. Talaat KR, Alaimo C, Martin P et al. Human challenge study with a Shigella bioconjugate vaccine: Analyses of clinical efficacy and correlate of protection. EBioMedicine. 2021;66:103310. doi: 10.1016/j.ebiom.2021.103310.
2. Wilkinson T, Li C, Chui C. et al. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. Nat Med. 2012;18:274–280. https://doi.org/10.1038/nm.2612
3. Clarkson KA, Porter CK, Talaat KR et al. Shigella-Controlled Human Infection Models: Current and Future Perspectives. Curr Top Microbiol Immunol. 2022. doi: 10.1007/82_2021_248. Online ahead of print.
4. ClinicalTrials.gov. A Study to Determine If a New Shigella Vaccine is Safe, Induces Immunity and The Best Dose Among Kenyan Infants – Full Text View. Available at: https://clinicaltrials.gov/ct2/show/NCT04056117
5. Obiero CW, Ndiaye AGW, Sciré AS et al. A Phase 2a Randomized Study to Evaluate the Safety and Immunogenicity of the 1790GAHB Generalized Modules for Membrane Antigen Vaccine against Shigella sonnei Administered Intramuscularly to Adults from a Shigellosis-Endemic Country. Front Immunol. 2017;8:1884. doi: 10.3389/fimmu.2017.01884.
6. Killingley B, Mann AJ, Kalinova M et al. Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. Nat Med. 2022;28(5):1031-1041. doi: 10.1038/s41591-022-01780-9.
7. University of Oxford. Volunteers needed for human challenge trial to study immune response to Covid-19. 2022. https://www.ox.ac.uk/news/2022-01-27-volunteers-needed-human-challenge-trial-study-immune-response-covid-19
8. Osman D. UK Researchers Exposed 36 People to COVID in Human Challenge Trial. insider.com. 2022. https://www.insider.com/uk-human-challenge-covid-19-trial-2022-2
9. Sack DA, Tacket CO, Cohen MB et al. Validation of a volunteer model of cholera with frozen bacteria as the challenge. Infect Immun. 1998;66(5):1968-72. doi: 10.1128/IAI.66.5.1968-1972.1998.
10. Chen WH, Cohen MB, Kirkpatrick BD et al. Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With Vibrio cholerae O1 El Tor. Clin Infect Dis. 2016;62(11):1329-1335. doi: 10.1093/cid/ciw145.
11. MacLennan CA, Riddle MS, Chen WH et al. Consensus Report on Shigella Controlled Human Infection Model: Clinical Endpoints. Clin Infect Dis. 2019;69(Suppl 8):S591-S595. doi: 10.1093/cid/ciz891.
12. Ramanathan R, Stibitz S, Pratt D, Roberts J. Use of controlled human infection models (CHIMs) to support vaccine development: US regulatory considerations. Vaccine. 2019;37(31):4256-4261. doi: 10.1016/j.vaccine.2019.06.009.
13. Balasingam S, Meillon S, Chui C et al. Human infection studies: Key considerations for challenge agent development and production. Wellcome Open Res. 2022;7:140. doi: 10.12688/wellcomeopenres.17869.1.
14. The Global Health Network. Human Infection Studies. https://humaninfectionstudies.tghn.org/
15. Mtunthama Toto N, Gooding K, Kapumba BM et al. "At first, I was very afraid"—a qualitative description of participants' views and experiences in the first Human Infection Study in Malawi [version 2; peer review: 2 approved]. Wellcome Open Res. 2021;6:89. https://doi.org/10.12688/wellcomeopenres.16587.2
16. Oxford JS, Catchpole A, Mann A et al. A Brief History of Human Challenge Studies (1900-2021) Emphasising the Virology, Regulatory and Ethical Requirements, Raison D'etre, Ethnography, Selection of Volunteers and Unit Design. Curr Top Microbiol Immunol. 2022. doi: 10.1007/82_2022_253. Epub ahead of print.
17. ClinicalTrials.gov. A Controlled Human Vivax Malaria Infection Study Through Inoculation of Infected Erythrocytes – Full Text View. https://clinicaltrials.gov/ct2/show/NCT05071079
18. Morton B, Burr S, Chikaonda T et al. A feasibility study of controlled human infection with Streptococcus pneumoniae in Malawi. EBioMedicine. 2021;72:103579. doi: 10.1016/j.ebiom.2021.103579.
19. George Washington University. Vaccine Researchers Testing Human Hookworm Vaccines in Brazil. 2020. https://microbiology.smhs.gwu.edu/news/vaccine-researchers-testing-human-hookworm-vaccines-brazil
20. Wellcome Trust. The future of vaccines: human infection studies are helping us to develop better vaccines, faster. 2020. https://www.youtube.com/watch?v=Tm1pO_DcXXE
21. London School of Hygiene and Tropical Medicine. Human Infection Studies for Schistosoma mansoni (CHI-S) in Uganda. https://www.lshtm.ac.uk/research/centres-projects-groups/chi-s
22. Levine MM, Kaper JB, Herrington D et al. Volunteer studies of deletion mutants of Vibrio cholerae O1 prepared by recombinant techniques. Infect Immun. 1988;56(1):161-7. doi: 10.1128/iai.56.1.161-167.1988.
23. Herzog C. Successful comeback of the single-dose live oral cholera vaccine CVD 103-HgR. Travel Med. Infect. Dis. 2016;14:373-377
24. US Food and Drug Administration. FDA approves vaccine to prevent cholera for travelers. 2016. https://www.fda.gov/news-events/press-announcements/fda-approves-vaccine-prevent-cholera-travelers

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