Controlled human infection models as a tool for malaria and schistosomiasis vaccine research

Langenberg, M.C.C.

III

Improvement of controlled human infection models

CHAPTER 8

Are placebo controls necessary in controlled human infection trials for vaccines?

Marijke C. C. Langenberg,
Olaf M. Dekkers, Meta Roestenberg

The Lancet Infectious Diseases 2020 Apr;20(4):e69-e74

Abstract

Controlled human infection trials, whereby a small group of healthy participants is deliberately exposed to a pathogen under controlled circumstances, can provide preliminary data for vaccine efficacy and for the selection of the most promising candidate vaccines for field trials. Because of the potential harm to participants through the deliberate exposure to a pathogen, the use of smaller groups minimises the cumulative risk. As such, a control group that receives a placebo vaccine followed by controlled exposure to a pathogen should be scientifically well justified. As these types of trials are designed to generate consistent infection rates and thus comparable outcomes across populations and trial sites, data from past studies (historical data) could be used as a valid alternative to placebo groups. In this Personal View, we review this option and highlight the considerations for choosing historical data as a suitable control. For the widespread application of this method, responsibility for the centralisation and sharing of data from controlled human infection trials lies with the scientific community.

Introduction

Between 2001 and 2003, eight women with type 1 diabetes were enrolled in a trial to assess the safety of a single-donor islet transplantation and all achieved insulin independence in the first year after the procedure.[1] Even though this study was not designed as a randomised controlled trial with a placebo group, the outcome was convincing because the treatment effect was clearly evident. The clinical course of type 1 diabetes in the absence of islet transplantation is known with certainty: patients will continue to need exogenous insulin. Although health-care professionals are often wary of evidence from sources other than randomised controlled trials to infer treatment effects, there are multiple examples of convincing results without this randomised design. Examples in the field of infectious diseases include treatment with phototherapy for skin tuberculosis in the 1890s[2–4] and treatment with streptomycin for tuberculous meningitis in the 1940s.[5] Both studies had a large effect size (eg, an 80% reduction in deaths using sulphamidochrysoidin for puerperal sepsis),[6] showing that treatment effectiveness can sometimes be measured reliably even in the absence of a control group.

In controlled human infection trials, susceptibility to infection after vaccination or clearance of the infection after taking a drug are tested in healthy individuals by exposing them to pathogenic microorganisms. In this Personal View, we will focus only on the design of vaccine trials. Most of these studies are done as randomised controlled trials in which participants are randomly assigned to either a vaccine or placebo group. The treatment allocation is commonly blinded to both the investigators and participants, and individuals in both the vaccine and placebo group are challenged with the infectious agent to compare the attack rates (figure 1A). Less frequently, an infectivity control group is used in an open-label design to establish if the pathogen is infectious during the procedure, rather than to measure the infection rate (figure 1B). In the historical control approach, data are based on results from a placebo or non-intervention group from previous controlled human infection studies (figure 1C).

Controlled human infection trials to test the efficacy of new interventions have increased in number from 15 studies in the 1950s to 140 studies from 2011 to 2017.[7] The advantages are that they require small sample sizes (10 to 50 participants) and are designed to detect large effects in an homogeneous population with 100% exposure. By contrast, clinical trials in endemic areas are large (hundreds to thousands of participants) and have heterogeneity in pre-exposure, infection dose, exposure timing, and incidence of exposure, resulting in lower rates of infection and decreased power. Controlled human infection trials can also select for products with the highest potential for efficacy in field studies.[7,8] As a result, they will lower overall costs by reducing the number of products progressing to field studies. Additionally, this type of trial allows multiple products to be evaluated in parallel and reduces unnecessary exposure of participants in field trials to ineffective products. As such, controlled human infection trials are generally accepted as a tool to minimise the risk of late clinical failure.[7]

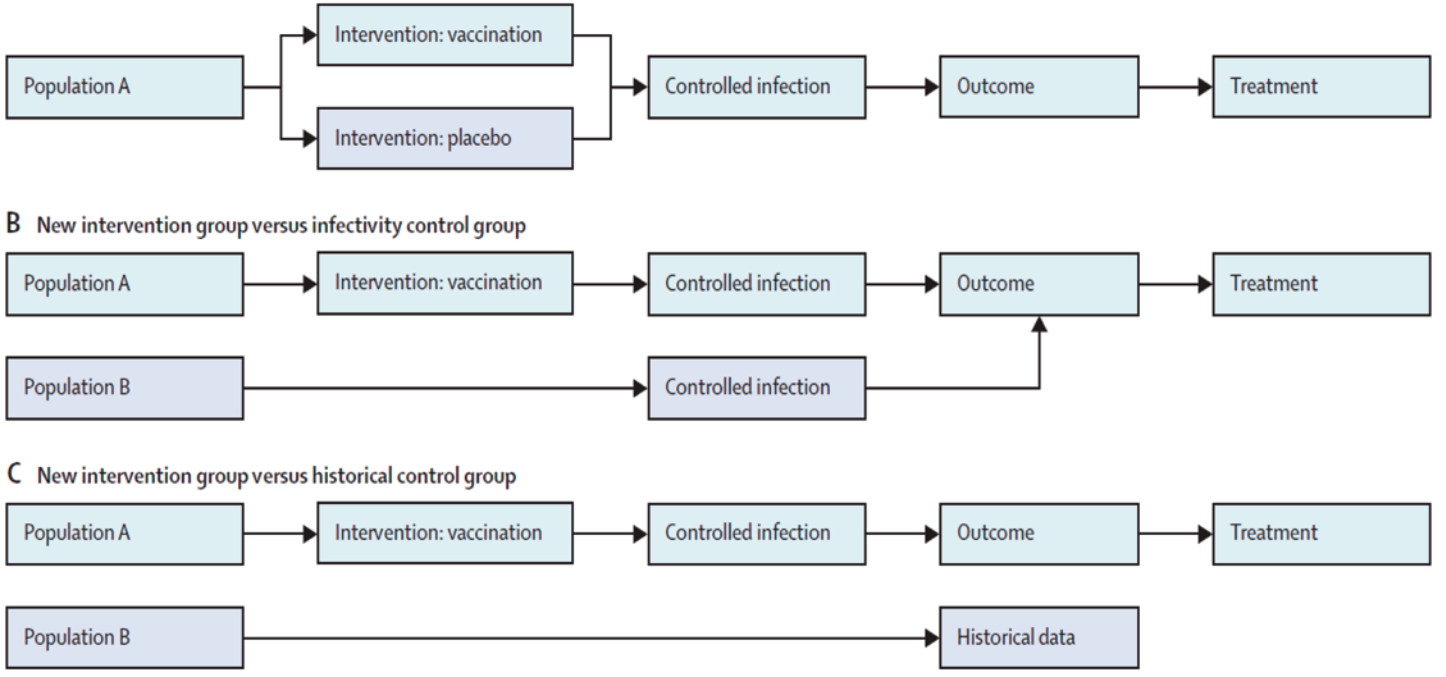

Figure 1. Controlled human infection trial designs in vaccine research. Rows show different trial designs using a placebo control group, infectivity control group, and historical control group. (A) In a randomised controlled trial, participants are given an inactive intervention (placebo) or the vaccine. Both groups are subsequently exposed to an infectious agent during the controlled infection. (B) In an open-label trial, participants in the infectivity control group do not receive the vaccine or placebo, but are exposed to an infectious agent during the controlled infection. (C) Historical data from previous human infection studies can be used as a control group. Columns represent the different trial stages. (1) Population: volunteers are screened and selected to participate in a controlled human infection trial. (2) Intervention: participants are given a vaccine or placebo, or are left untreated. (3) Controlled infection: after a predefined period, participants are deliberately exposed to a pathogen. (4) Outcome: volunteers are monitored to see if they have reached the infection endpoint; at this stage historical data can serve as a control group. (5) Treatment: all volunteers receive pathogen specific treatment.

Similarly to phase 1 trials (dose-finding studies in healthy participants), controlled human infection studies are subject to ethical debate as they seemingly breach the so-called do no harm principle by exposing healthy people to risks (ie, a pathogen), with no direct benefit to the individual.[8] Participants might be subjected to symptomatic infection, a high frequency of blood, urine, or stool sampling, or invasive procedures, such as bronchoscopy. Moreover, periods of quarantine might be required, and, in the case of a transmissible agent, there might be potential for third-party exposure. Although the risks to volunteers are very small, serious events have occurred previously.[9–12] As such, the total sum of risks and the burden on participants and third parties should be carefully weighed against the value of science and the expected benefits to society.[13] This concept is especially important for high risk or high burden studies, where the number of individuals exposed to a pathogen should be minimised. A framework has been proposed to ensure proper ethical justification for the inclusion of healthy volunteers;[8,13,14] risk and burden should be reduced as much as possible and the scientific rationale should be carefully articulated.[15] Importantly, we will argue that placebo control groups might not be necessary to obtain valid study results in some controlled human infection models and their inclusion should therefore be scientifically scrutinised and ethically justified.

Healthy volunteer controls

A healthy volunteer control group can be scientifically justified in four different scenarios: first, to show that the infection procedure was successful; second, if one of the secondary outcome measurements (eg, immunological response) is unknown and these data add indispensable scientific value; third, the infection rate (primary outcome measure) is unknown; and finally, differences between an intervention group testing a new vaccine and a placebo control group are expected to be small.

In the first scenario, infectivity controls provide information on the quality and procedure of infection. For example, clinical malaria trials used between four and six volunteers in the infectivity control group to prove that the exposure procedure resulted in infection.[16–18] In these situations, the size of the control group depends on the expected infection rate, requiring information based on previous studies. The goal is to show that at least one healthy volunteer can be successfully infected. As such, the infectivity control group is usually smaller than the placebo control group, which will also determine the frequency of infections.

In the second scenario, when the expected infection rate (the primary outcome) is known from historical data, the use of a placebo control group can still be essential to determine secondary outcomes. For instance, to compare immune responses between people that are colonised and non-colonised with pneumococcus, along with vaccine efficacy, placebo control samples might be needed.[19] In this case, previously obtained specific samples (eg, freshly processed samples) or data might be absent and the size of the placebo group should then be based on the sample size calculation of the secondary endpoint.

In the third scenario, when the infection rate is unknown, there is no other way to determine the efficacy of a vaccine other than to include a placebo control group. However, in established infection models, the procedures are typically standardised and the expected infection rate for placebo control groups is well known. Because of this consistency, an historical control

group could serve as a benchmark. As an example, over 2650 volunteers worldwide have been experimentally exposed to malaria in controlled human infection trials, with more than 99% of participants developing patent parasitaemia after five bites from mosquitoes infected with *Plasmodium falciparum*.[20–22] As the number of successful infections is consistent between trials, these data can be used for comparison as a historical control group.

In the final scenario, when the expected efficacy of a vaccine, which is often based on animal studies or target-product profiles, is low, the uncertainty of historical data is generally too large and a placebo group is needed to act as a comparator.[23] This control is also required in human infection trials where the magnitude or precision of the treatment effect needs to be established with certainty. However, the group sizes are often too small to reliably determine the treatment effect size, and the purpose of these trials is to instead search for signals of vaccine efficacy.

Historical controls

To examine the suitability and validity of historical data for a specific controlled human infection model it is important that the data are based on comparable populations, the method is comparable, the infection rate from previous studies is reproducible, and that there are suitable data to provide a reliable outcome estimate.[24] Although these models are designed to mimic naturally occurring infections, data from non-controlled epidemiological studies are generally unsuitable to use as historical controls because of differences and uncertainties in infection dose, route of infection, and population. These criteria are equivalent for the selection of historical data for non-controlled human infection trials.[25]

Population

The first variable to consider is the study population. Immunological responses to a specific pathogen might vary according to race, age, health status, and previous exposure. For consistent data and comparisons, the differences in demographics should have no effect on the infection rate between the historical control group and the intervention group. Demographic variation is often already reduced as controlled human infection studies generally have strict inclusion criteria, selecting for only healthy participants. Population differences were clearly shown in a controlled human malaria infection study in which semi-immune African participants showed a reduced infection rate of 64% compared with nonimmune European participants (100%),[26] underlining the need for similar population characteristics when used for comparison.

Methods

When the population is considered similar, variations in method that could influence the infection rate should be examined. For controlled human infection models, differences between species can affect outcome measures. For example, about 65% of volunteers were infected when given *Salmonella enterica* serovar Typhi at a dose of 1×10^4 colony forming units (CFU) but for

Salmonella enterica serovar Paratyphi a dose of 1×10^3 CFU was needed.[27,28] However, with the *Cryptosporidium* model, infection with 1×10^5 *Cryptosporidium muris* oocysts or 1×10^5 *Cryptosporidium meleagridis* oocysts resulted in the same infection rate (100%).[29,30] Differences in strains can also be important; for instance, *Neisseria gonorrhoeae* MS11mkC is more infectious than the FA1090 strain, with the estimated dose needed for 50% infection being $1{\cdot}8 \times 10^3$ CFU (MS11mkC) and $1{\cdot}0 \times 10^5$ CFU (FA1090).[31] Other models use one strain only, such as for *Haemophilus ducreyi*.[32]

Centre clustering (eg, controlled human infection studies for one pathogen that are all done in one centre), between centre differences (eg, related to variations in protocols between study centres), seasonal variation, batch-to-batch variability, and operator effects (eg, variation in adverse event registration by operators) can all result in inconsistent outcomes. For controlled human infections of *Necator americanus* (hookworm), the percentage of infected volunteers was similar (90–100%) after controlled exposure to the same hookworm dose, but substantial differences in egg counts were observed (125 eggs per g *vs* 2400 eggs per g) and depended on the batch, study centre, or operator effects.[33,34] In the influenza A model, infection with 1×10^7 of the A/Kawasaki/8/86 H1N1 strain resulted in variable proportions of viral shedding from 70–100%.[35,36] This variety could be due to seasonal variation, but might also be related to the amount of pre-exposure among volunteers (population). These factors should be taken into account when a study is done in another geographical region or during a different season.

The infection dose is directly related to the primary study outcome. For example, increasing the dose of *S.* Typhi from 1×10^5 to 1×10^9 CFU raised the percentage of infected volunteers from 28% to 95%.[37] For many models, the pathogen dose has been standardised and is generally based on an initial dose-escalation study whereby infection rates, and the risks and burden to the participants, are carefully balanced.

The route of infection also affects the study outcome, as each method requires a specific dose to obtain 100% infection rates. For example, *the Plasmodium falciparum* model uses controlled exposure through mosquito bites, intramuscular or intradermal injections, or by direct venous inoculation.[38–40] Only one route of infection is used in most models, such as with the dengue virus, respiratory syncytial virus, rhinovirus, and influenza virus.[41–44]

The infection rate can be based on microbiological (infection model) or clinical parameters (disease model). Both can be used as historical data as long as the criteria to determine infection rate between studies are similar. A well-described disease model for *Vibrio cholerae* states that participants producing more than 3 L of diarrhoea are considered positive for cholera;[45] however, if this cut-off point varies between studies it will affect the measured infection rate. This difference can be seen in the enterotoxigenic *Escherichia coli* model, where diarrhoea is listed as three watery stools per 24 h or one to two loose stools in 24–48 h.[46] Distinct microbiological outcome measures might also lead to variation, such as with the influenza model that uses titration on canine kidney cells, PCR, or the inoculation of embryonated eggs followed by the haemagglutination inhibition assay.[44] However, if the sensitivity of these tests are similar they can be pooled together to generate historical data.

Outcome consistency

In addition to population and methods, the infection rates should be compared and must be comparable between studies. A model with consistent outcomes was shown in the *S.* Typhi

model with 65%–67% of volunteers developing infection according to predefined criteria.[47–49] This finding contrasts with the enterotoxigenic *E.coli* model which resulted in infection rates of between 50% and 100% when the same infection dose is being used.[46] Consistent outcomes with low variability are suitable data for historical controls.

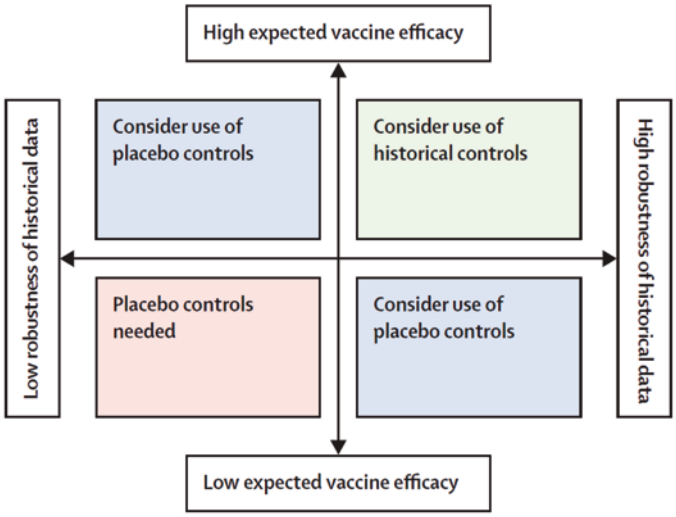

Figure 2. Considerations for choosing the control group in controlled human infection trials.

Suitable data

The variability of the data should be offset by the size of the dataset, and large numbers of participants, such as with the rhinovirus model (5760 individuals),[7] are more likely to generate suitable historical evidence than models that have recently been established (eg, *Schistosoma* spp infections with only 17 participants).[50,51]

As with any sample size calculation, the estimated group size needed depends on the expected efficacy of the vaccine and the variability in infection rates between vaccinated and control groups. Historical controls will probably have a high variability in infection rates because of the heterogeneous nature of the data. Therefore, for studies that are testing a vaccine with a low expected efficacy, the use of a placebo control group (with a lower variability in infection rates) is likely to lead to more robust results. In general, historical data are suitable to use when they are robust and the expected vaccine efficacy is high (figure 2). Realising that historical controls have uncertainties and cannot be used as fixed-effect estimators is important.[52,53] However, there are sophisticated modelling techniques that can analyse different datasets separately and together to better assess the effects of data pooling and corresponding sample size calculations to more accurately estimate infection rates and the variability around these estimates.[53] Although caution should be taken when pooling historical data—for example, if there is variability in the outcome between centres—one could envision selecting historical data from the trial site where the intervention was performed, instead of pooling all available data.

In conclusion, the use of historical data needs to be carefully considered and must take into account the population, method, outcome, and the amount of available data. The suitability to use historical data depends on the controlled human infection model and the design of the study. All of these factors should be evaluated before the start of a new controlled human infection trial.

Future directions

Given the public and research community's perception regarding the deliberate infection of healthy volunteers,[8,13] participants should be included with the utmost care and through solid scientific justification. The design of controlled human infection studies should be scrutinised so that the output is scientifically impactful, yet minimises the cumulative risk with proper justification of placebo controls.

Controlled human infection studies are designed to generate uniform outcomes (eg, infection rates). When these data are sufficiently consistent, they can be used to generate an historical control group as an alternative to a placebo control, reducing the number of participants exposed to a pathogen. To facilitate data pooling, study designs should be harmonised between centres. Agreement on the route and dose of infection, the use of similar inclusion and exclusion criteria to reduce the variability of study populations, harmonisation of endpoints by using similar microbiological techniques or clinical criteria, and optimisation of pathogen production according to good manufacturing practice guidelines are likely to optimise controlled human infection models, generating better quality historical data in the future. Such efforts have been undertaken for the malaria model, resulting in guidelines for the "Standardization and conduct of *P. falciparum* sporozoite controlled human malaria infection trials".[54] This could also be done for other controlled human infection models by establishing consensus groups that will outline methods aimed to harmonise between centres.

Moreover, several open access data repositories are available, such as ImmPort (https://immport.niaid.nih.gov/home) from the National Institutes of Health and Zenodo (https://zenodo.org/) from OpenAIRE, where controlled human infection trial data can be deposited.[55,56] These repositories improve access to trial results, making it easier to pool historical data, analyse variability, and ultimately work with larger and more exhaustive datasets. In addition, a newly established digital platform funded by the Wellcome Trust (https://tghn.org/) aims to promote sharing of protocols and data, complementing the existing network from the Bill and Melinda Gates Foundation (see https://chimstudies.org). As these initiatives show, funders can actively promote and support open data sharing, creating opportunities for data pooling, data reuse, and the identification of consistent endpoints.

Whether the use of historical controls will be considered acceptable to the regulators for licensure depends on the balance between the risk of controls, whether alternative investment is required, and the position of the trial in the development pathway. The considerations presented here are meant to ignite and guide the discussion around the use of historical controls in controlled human infection studies.

Are placebo controls necessary in controlled human infection trials for vaccines? The answer depends on the pathogen-specific model, the expected vaccine efficacy, and the quality of the

available historical data. In our opinion, each researcher has the moral obligation to consider alternatives to the randomised controlled study design. Alternative approaches, such as the use of an historical control group, should be explored and prespecified. If the use of a placebo group is deemed absolutely necessary, this decision should be justified in the protocol, trial register, and in the research paper.

References

1. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. JAMA 2005; 293: 830–35.

2. Grzybowski A, Sak J, Pawlikowski J. A brief report on the history of phototherapy. Clin Dermatol 2016; 34: 532–37.

3. Finsen NR. Om anvendelse i medicinen af koncentrerede kemiske lysstraaler. Copenhagen: Gyldendalske Boghandels Forlag, 1896.

4. Finsen NR. Om anvendelse i medicinen af koncentrerede kemiske lysstraaler, fortsatte meddelelser. Copenhagen: Gyldendalske Boghandels Forlag, 1902.

5. Cooke RE, Dunphy DL, Blake FG. Streptomycin in tuberculous meningitis; a report of its use in a one-year-old infant. Yale J Biol Med 1946; 18: 221–26.

6. Dunn PM. Dr Leonard Colebrook, FRS (1883–1967) and the chemotherapeutic conquest of puerperal infection. Arch Dis Child Fetal Neonatal Ed 2008; 93: F246–48.

7. Roestenberg M, Hoogerwerf MA, Ferreira DM, Mordmüller B, Yazdanbakhsh M. Experimental infection of human volunteers. Lancet Infect Dis 2018; 18: e312–22.

8. Bambery B, Selgelid M, Weijer C, Savulescu J, Pollard AJ. Ethical criteria for human challenge studies in infectious diseases. Public Health Ethics 2016; 9: 92–103.

9. Keitel WA, Couch RB, Cate TR, Six HR, Baxter BD. Cold recombinant influenza B/Texas/1/84 vaccine virus (CRB 87): attenuation, immunogenicity, and efficacy against homotypic challenge. J Infect Dis 1990; 161: 22–26.

10. Barroso L, Treanor J, Gubareva L, Hayden FG. Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. Antivir Ther 2005; 10: 901–10.

11. Nieman AE, de Mast Q, Roestenberg M, et al. Cardiac complication after experimental human malaria infection: a case report. Malar J 2009; 8: 277.

12. van Meer MP, Bastiaens GJ, Boulaksil M, et al. Idiopathic acute myocarditis during treatment for controlled human malaria infection: a case report. Malar J 2014; 13: 38.

13. Hope T, McMillan J. Challenge studies of human volunteers: ethical issues. J Med Ethics 2004; 30: 110–16.

14. Miller FG, Grady C. The ethical challenge of infection-inducing challenge experiments. Clin Infect Dis 2001; 33: 1028–33.

15. Evers DL, Fowler CB, Mason JT, Mimnall RK. Deliberate microbial infection research reveals limitations to current safety protections of healthy human subjects. Sci Eng Ethics 2015; 21: 1049–64.

16. Roestenberg M, Teirlinck AC, McCall MBB, et al. Long-term protection against malaria after experimental sporozoite inoculation: an open-label follow-up study. Lancet 2011; 377: 1770–76.

17. Schats R, Bijker EM, van Gemert GJ, et al. Heterologous protection against malaria after immunization with *Plasmodium falciparum* sporozoites. PLoS One 2015; 10: e0124243.

18. Epstein JE, Paolino KM, Richie TL, et al. Protection against *Plasmodium falciparum* malaria by PfSPZ vaccine. JCI Insight 2017; 2: e89154.

19. Ferreira DM, Jambo KC, Gordon SB. Experimental human pneumococcal carriage models for vaccine research. Trends Microbiol 2011; 19: 464–70.

20. Langenberg MCC, Wammes LJ, McCall MBB, et al. Controlled human malaria infection with graded numbers of *Plasmodium falciparum* NF135.C10- or NF166.C8-infected mosquitoes. Am J Trop Med Hyg 2018; 99: 709–12.

21. Sauerwein RW, Roestenberg M, Moorthy VS. Experimental human challenge infections can accelerate clinical malaria vaccine development. Nat Rev Immunol 2011; 11: 57–64.

22. Epstein JE, Rao S, Williams F, et al. Safety and clinical outcome of experimental challenge of human volunteers with *Plasmodium falciparum*-infected mosquitoes: an update. J Infect Dis 2007; 196: 145–54.

23. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007; 334: 349–51.

24. Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials. Pharm Stat 2014; 13: 41–54.

25. European Medicines Agency. Choice of control group in clinical trials (ICH topic E 10). Amsterdam: European Medicines Agency, 2001. https://www.ema.europa.eu/en/documents/scientificguideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf (accessed July 22, 2019).

26. Lell B, Mordmüller B, Dejon Agobe JC, et al. Impact of sickle cell trait and naturally acquired immunity on uncomplicated malaria after controlled human malaria infection in adults in Gabon. Am J Trop Med Hyg 2018; 98: 508–15.

27. Gibani MM, Voysey M, Jin C, et al. The impact of vaccination and prior exposure on stool shedding of *Salmonella Typhi* and *Salmonella Paratyphi* in 6 controlled human infection studies. Clin Infect Dis 2019; 68: 1265–73.

28. Gibani MM, Jin C, Thomaides-Brears H, et al. Investigating systemic immunity to typhoid and paratyphoid fever: characterising the response to re-challenge in a controlled human infection model. Open Forum Infect Dis 2017; 4(Suppl 1): S227–28.

29 Chappell CL, Okhuysen PC, Langer-Curry RC, Akiyoshi DE, Widmer G, Tzipori S. *Cryptosporidium meleagridis*: infectivity in healthy adult volunteers. Am J Trop Med Hyg 2011; 85: 238–42.

30. Chappell CL, Okhuysen PC, Langer-Curry RC, Lupo PJ, Widmer G, Tzipori S. *Cryptosporidium muris*: infectivity and illness in healthy adult volunteers. Am J Trop Med Hyg 2015; 92: 50–55.

31. Hobbs MM, Sparling PF, Cohen MS, Shafer WM, Deal CD, Jerse AE. Experimental gonococcal infection in male volunteers: cumulative experience with *Neisseria gonorrhoeae* strains FA1090 and MS11mkC. Front Microbiol 2011; 2: 123.

32. Janowicz DM, Ofner S, Katz BP, Spinola SM. Experimental infection of human volunteers with *Haemophilus ducreyi*: fifteen years of clinical data and experience. J Infect Dis 2009; 199: 1671–79.

33. Diemert D, Campbell D, Brelsford J, et al. Controlled human hookworm infection: accelerating human hookworm vaccine development. Open Forum Infect Dis 2018; 5: ofy083.

34. Hoogerwerf MA, Coffeng LE, Brienen EAT, et al. New insights into the kinetics and variability of egg excretion in controlled human hookworm infections. J Infect Dis 2019; 220: 1044–48.

35. Hayden FG, Tunkel AR, Treanor JJ, Betts RF, Allerheiligen S, Harris J. Oral LY217896 for prevention of experimental influenza A virus infection and illness in humans. Antimicrob Agents Chemother 1994; 38: 1178–81.

36. Youngner JS, Treanor JJ, Betts RF, Whitaker-Dowling P. Effect of simultaneous administration of cold-adapted and wild-type influenza A viruses on experimental wild-type influenza infection in humans. J Clin Microbiol 1994; 32: 750–54.

37. Waddington CS, Darton TC, Woodward WE, Angus B, Levine MM, Pollard AJ. Advancing the management and control of typhoid fever: a review of the historical role of human challenge studies. J Infect 2014; 68: 405–18.

38. McCall MBB, Wammes LJ, Langenberg MCC, et al. Infectivity of *Plasmodium falciparum* sporozoites determines emerging parasitemia in infected volunteers. Sci Transl Med 2017; 9: eaag2490.

39. Gómez-Pérez GP, Legarda A, Muñoz J, et al. Controlled human malaria infection by intramuscular and direct venous inoculation of cryopreserved *Plasmodium falciparum* sporozoites in malaria-naïve volunteers: effect of injection volume and dose on infectivity rates. Malar J 2015; 14: 306.

40. Lyke KE, Laurens MB, Strauss K, et al. Optimizing intradermal administration of cryopreserved *Plasmodium falciparum* sporozoites in controlled human malaria infection. Am J Trop Med Hyg 2015; 93: 1274–84.

41. Larsen CP, Whitehead SS, Durbin AP. Dengue human infection models to advance dengue vaccine development. Vaccine 2015; 33: 7075–82.

42. Habibi MS, Chiu C. Controlled human infection with RSV: the opportunities of experimental challenge. Vaccine 2017; 35: 489–95.

43. Del Vecchio AM, Branigan PJ, Barnathan ES, Flavin SK, Silkoff PE, Turner RB. Utility of animal and *in vivo* experimental infection of humans with rhinoviruses in the development of therapeutic agents for viral exacerbations of asthma and chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2015; 30: 32–43.

44. Balasingam S, Wilder-Smith A. Randomized controlled trials for influenza drugs and vaccines: a review of controlled human infection studies. Int J Infect Dis 2016; 49: 18–29.

45. Shirley DA, McArthur MA. The utility of human challenge studies in vaccine development: lessons learned from cholera. Vaccine (Auckl) 2011; 2011: 3–13.

46. Porter CK, Riddle MS, Tribble DR, et al. A systematic review of experimental infections with enterotoxigenic *Escherichia coli* (ETEC). Vaccine 2011; 29: 5869–85.

47. Darton TC, Zhou L, Blohmke CJ, et al. Blood culture-PCR to optimise typhoid fever diagnosis after controlled human infection identifies frequent asymptomatic cases and evidence of primary bacteraemia. J Infect 2017; 74: 358–66.

48. Waddington CS, Darton TC, Jones C, et al. An outpatient, ambulant-design, controlled human infection model using escalating doses of *Salmonella typhi* challenge delivered in sodium bicarbonate solution. Clin Infect Dis 2014; 58: 1230–40.

49. Darton TC, Jones C, Blohmke CJ, et al. Using a human challenge model of infection to measure vaccine efficacy: a randomised, controlled trial comparing the typhoid vaccines M01ZH09 with placebo and Ty21a. PLoS Negl Trop Dis 2016; 10: e0004926.

50. Janse JJ, Langenberg MCC, Kos-Van Oosterhoud J, et al. Establishing the production of male *Schistosoma mansoni* cercariae for a controlled human infection model. J Infect Dis 2018; 218: 1142–46.

51. Langenberg MCC, Hoogerwerf MA, Koopman JPR et al. A controlled human *Schistosoma mansoni* infection model to advance novel drugs , vaccines and diagnostics. Nat Med 2020; published online Feb 24. DOI:10.1038/s41591-020-0759-x.

52. Schoenfeld DA, Finkelstein DM, Macklin E, et al. Design and analysis of a clinical trial using previous trials as historical control. Clin Trials 2019; 16: 531–38.

53. Berliner LM. International encyclopaedia of the social and behavioural sciences, second addition (spatial statistical methods). London: Elsevier, 2015.

54. Targett GAT, Moorthy VS, Brown GV. Malaria vaccine research and development: the role of the WHO MALVAC committee. Malar J 2013; 12: 362.

55. Trans-NIH BioMedical Informatics Coordinating Committee. NIH data sharing repositories. https://www.nlm.nih.gov/NIHbmic/nih_data_sharing_repositories.html (accessed December 5, 2018).

56. Nederlandse Organisatie voor Wetenschappelijk Onderzoek. Data management section. https://www.nwo.nl/beleid/open+science/datamanagementparagraaf (accessed December 5, 2018).