Human Challenge Trials: A Tool in the Fight Against Infectious Diseases

In the wake of the COVID-19 pandemic, research into infectious diseases remains an integral and growing avenue of clinical research. What benefits can Human Challenge Trials have for clinicians exploring such diseases?

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The SARS-CoV-2 pandemic created an unprecedented health crisis on a global scale. Pandemic diseases (epidemic diseases that spread over a wide region) are not new and have repeatedly swept through human populations for millennia. Well-known examples include the bubonic plague, also known as the Black Death, that killed between 25 and 75 million people in Europe in the 1300s and the 'Spanish flu' during 1918-19, an influenza pandemic that killed an estimated 40-70 million people worldwide. More recently, the 2014-2016 Ebola outbreak in West Africa caused over 28,000 cases and 11,000 deaths.

Other, less severe, pandemic influenzas emerged in 1957-58, 1968, and 2009. In the latter three cases, researchers developed influenza vaccines targeted specifically to the circulating virus, although experts debate how effectively the vaccines reduced disease spread.

Vaccines and antivirals play a critical role in the prevention and treatment of infectious diseases, however developing them is a challenging, lengthy, and expensive process, with a high attrition (1).

Human Challenge Trials

In human challenge studies (HCT) or Controlled Human Infection Models (CHIM), healthy volunteers are administered a well-charactersied pathogenic or virulent strain of a challenge agent, which can be a virus (e.g., influenza), bacteria (e.g., cholera), or a parasite (e.g., malaria). In a historical context, the concept of challenge studies is not new. The experiments conducted by Louis Pasteur in the 19th Century can be seen as a type of challenge study, where chickens were challenged with a weakened bacterium – causing chicken cholera – and immunised from further chicken cholera infection. Human Challenge Trials have been performed in the UK since 1946 when the Medical Research Council established the Common Cold Unit (CCU) (also known as the Common Cold Research Unit [CCRU]) in Salisbury, Wiltshire. The aim was to undertake laboratory and epidemiological research on common colds with the aim of reducing human and economic costs (2, 3).

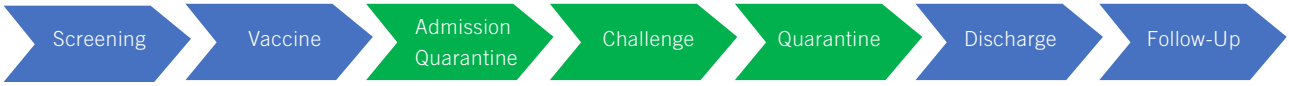

Figure 2: Schematic overview HCT with vaccine (green: quarantine phase / blue: outpatient phase)

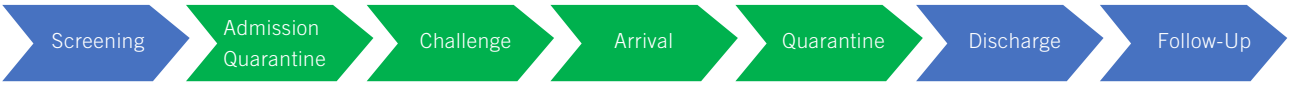

Figure 3: Schematic overview HCT with antiviral (green: quarantine phase / blue: outpatient phase)

Since the 1990s, these types of studies have been used to provide early performance data through proof-of-concept (PoC) and mode-of-action (MoA) studies to accelerate the clinical development of vaccines. Governmental and commercial organisations are developing challenge models to accelerate vaccine development programmes – e.g., for small interfering RNA (siRNA) and monoclonal antibody (mAB) trials in respiratory tract infections (influenza and RSV), and to gain a better understanding of the underlying pathological processes that drive immune responses. Such exploratory models started gaining favour in regulated clinical trials in the early 1990s and were first mentioned in regulatory guidance in 2010.

Challenge trials have been performed in a great variety of infectious diseases as illustrated in **Figure 1**, including a recent COVID-19 challenge model (4).

In a CHIM trial involving a vaccine or antiviral, the well-characterised strain of an infectious agent is given to carefully selected, healthy adult volunteers after they have been vaccinated, or before they receive the antiviral. They follow a traditional double-blind design with an active treatment group and a placebo group.

These trials are performed in specialised quarantine units, where the inoculated volunteers are monitored under 24/7 medical supervision. A schematic overview of human challenge trials involving a vaccine and an antiviral can be found in **Figures 2** and **3**.

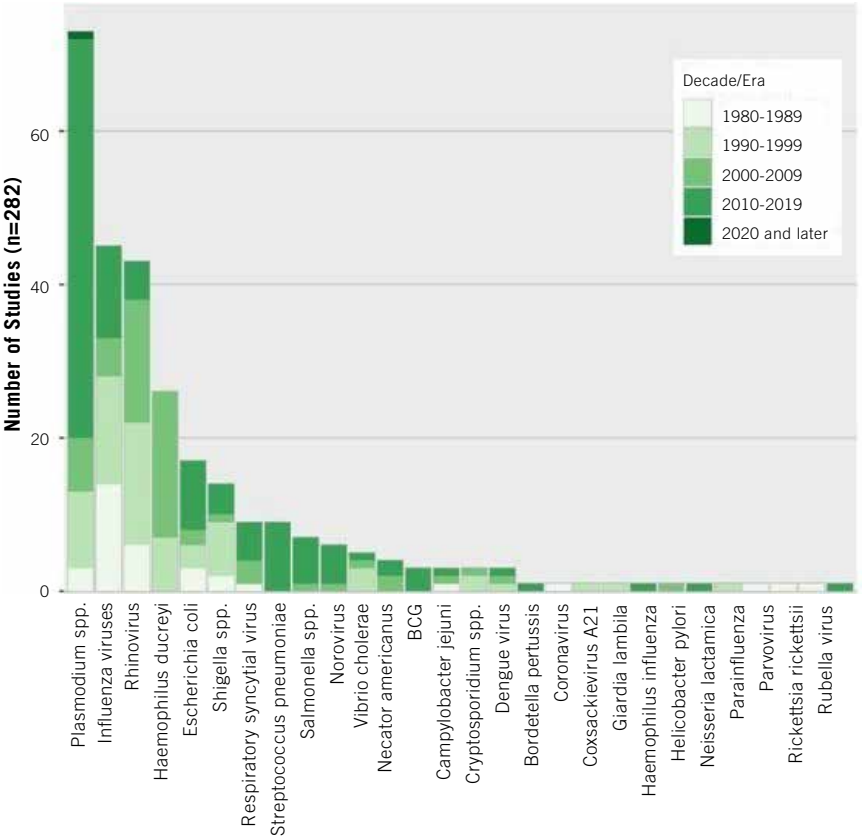

Figure 1: Overview of Human Challenge Trials per Pathogen (15)

In current drug and vaccine development, human challenge trials can be utilised in a variety of ways – like dose-finding studies – in preparation of field trials, but the most common use is that challenge trials are used as proof-of-concept (PoC) studies. Due to the reduced number of subjects needed for a challenge trial, (40-60 subjects) compared to a classic 'field' PoC trial (180-600 subjects), Human Challenge Trials form a cheaper alternative. In addition, their shorter duration allows for a quicker availability of efficacy data.

These proof-of-concept trials are designed to provide early evidence about efficacy and if a drug is likely to be successful in later clinical trial phases. Hence, PoC studies can guide drug developers to make smarter 'go or no-go' decisions if proceeding with larger, more expensive studies in the next stage of drug development.

The results of PoC studies are critically pivotal for strategic decisions in early drug clinical trial development and help the design of later stage field trials (5, 6).

Regulatory Acceptance

Regulatory-wise, data from CHIM trials have been accepted by regulators as supportive for the following:

- As PoC studies for influenza and other upper respiratory tract infections. In such early phase studies, protective (vaccine) or curative (vaccine/drug) efficacy is being assessed. There are

currently no specific guidelines regarding efficacy markers (correlates of protection) for PoC in CHIM studies, although the FDA guideline on influenza studies mentions haemagglutination and tissue culture infective dose 50% (TCID50)
- As a method for determining optimal dosage (to identify the correct individual dose, dose range, or schedule for field studies)
- 'Preliminary clinical evidence' in the framework of Fast Track and Breakthrough designation by the FDA
- Acceptance as a pivotal efficacy trial: The Vaxchora vaccine – aimed at preventing cholera in travellers – received marketing authorisation approval based on a pivotal efficacy part. Vaxchora received marketing authorisation valid throughout the EU in April 2020 and was approved by the FDA in June 2016. In the US, the marketing authorisation holder is PaXVax; in Europe, it is Emergent BioSolutions. The challenge trial was supported by a large safety immunogenicity trial. The main reason for both the FDA and the EMA to have agreed with a CHIM trial as a pivotal efficacy trial is that it would have been extremely difficult to perform a meaningful Phase III trial that would give conclusive results in this indication (7, 8)

WHO has published guidance on the use of challenge trials in vaccine development (9-12). The guidance also specifies that if they are performed, human challenge trials may be of particular use:

- When there is no appropriate nonclinical model (e.g., when a candidate vaccine is intended to protect against an infectious disease that is confined to humans)
- When there is no known immune correlate of protection (ICP)
- When vaccine efficacy field trials are not feasible

Human challenge trials may help to resolve at least some of the issues faced in the development of vaccine in a future pandemic, like the recent SARS-CoV-2 pandemic. Firstly, fewer subjects are needed for a CHIM than for a classic clinical trial, between 80 and 120, and the inclusion criteria for the study group can be limited to subjects at the lowest possible risk (i.e., 18- to 25-year-olds). Secondly, challenge trials can be used to determine the infectious dose of the disease-causing agent, starting from a very low dose and up titrating.

Additionally, CHIMs can be used to compare vaccines side by side, limiting the need for placebo controls, and therefore reducing potential ethical burden. Challenge studies could determine correlates of protection, which could be used in Phase III studies.

Finally, if the CHIM results are favourable, such a trial can help in obtaining emergency use authorisation for a vaccine to be used, for example, in high-risk populations (13, 14). Early interaction with regulators via a Scientific Advice meeting or a pre-IND meeting is strongly recommended to discuss the implementation of a Human Challenge Trial in a development programme.

Performing Human Challenge Trial

Another important issue is the regulatory and operational aspect of running a human challenge study itself. It is extremely important to avoid cross-contamination between the patients infected with the virus and the staff conducting the study. This is to avoid contaminated study staff infecting patients, jeopardising the study results by infecting placebo patients, and to avoid the virus from being spread to the 'outside world'.

Before enrolling into a Human Challenge Trial, volunteers undergo a series of screening tests, including a serosuitability test to ensure potential volunteers do not already have antibodies against the challenge agent being used.

Participants will need to be isolated in a specifically designed quarantine unit and will be treated according to the principle of 'reversed-barrier nursing.' This method is comparable to barrier nursing used in an intensive care unit (ICU) setting, where the aim is to keep pathogens away from the ICU patients by creating a barrier between the outside world and the inside of a patient room through using gloves, masks, gowns, and disinfectants. With reversed-barrier nursing, the objective is to keep the challenging agents confined in the facility using the same principles. Depending on the challenge agent used, subjects can remain in quarantine for up to 14 days.

Conclusion

Human challenge trials play a significant and supportive role in both our understanding of disease and the testing of novel antivirals and vaccines. Animal models for many diseases are a poor approximation of disease pathogenesis, especially for human host restricted diseases. Properly designed and ethically conducted CHIM studies have tremendous potential to improve our understanding of pathogenesis, help design better vaccine candidates, and reduce the costs and timelines of vaccine and/or drug development.

As the Vaxchora case shows, human challenge trials could form an alternative to 'traditional field trials' and be the basis of a regulatory pathway for accelerated approval in specific cases. They also have their place in the development of any future pandemic vaccines.

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Before joining hVIVO, Bruno had a variety of roles at SGS Life Sciences, where in his last position he managed the global regulatory consultancy and modelling & simulation teams.

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