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Review

# Human challenge trials in vaccine development

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ABSTRACT

The increasing recent interest in human challenge studies or controlled human infection model studies for accelerating vaccine development has been driven by the recognition of the unique ability of these studies to contribute to the understanding of response to infection and the performance of vaccines. With streamlining of ethical processes, conduct and supervision and the availability of new investigative tools from immunophenotyping to glycobiology, the potential to derive valuable data to inform vaccine testing and development has never been greater. However, issues of availability and standardization of challenge strains, conduct of studies in disease endemic locations and the iteration between clinical and laboratory studies still need to be addressed to gain maximal value for vaccine development.

## 1. Introduction

The use of human challenge studies or controlled human infection model (CHIM) studies for accelerating vaccine development in the context of the ongoing COVID-19 pandemic has been the subject of much global debate and discussion. There is hope that these studies might provide an alternative and shorter route to testing new vaccines under development for COVID-19 [1] and help select those candidates most likely to succeed, but there are issues of uncertain risk. Conversely, there is also considerable interest to volunteer in such studies [2].

Human challenge studies involve the intentional infection of a healthy, adult, consenting volunteers with an infectious agent. The disease agent is well characterized, frequently attenuated, and manufactured under current Good Manufacturing Practice (cGMP) or GMP like conditions [3]. As a research method, human challenge studies are not new. The first widely documented CHIM study was done by Edward Jenner in 1796, who proved the concept of vaccination by challenging James Phipps with smallpox material six weeks after inoculation with cowpox [4].

With improvements in conduct and supervision, CHIM studies are increasingly contributing to better understanding of the biology of disease, identifying host immune response, correlates of protection, microbial pathogenicity and virulence factors and in vaccine and therapeutic development.

## 2. History and current status

While valuable insights were provided by early challenge experiments, especially malaria, cholera and smallpox, this methodology was misused in studies which intentionally infected vulnerable populations, prisoners, sex-workers, institutionalized patients and others [5,6]. This led to a distrust in the methodology and many began to regard intentional infection as an unethical practice. However, with the development of robust ethical frameworks and guidance over the last few decades, and close monitoring and regulatory oversight of clinical research, CHIM has seen a resurgence, proving the methodology as an invaluable tool in infectious disease research.

Over the last 7–8 decades, CHIM studies have been carried out for over 20 different infectious disease pathogens and over 45,000 volunteers have participated in these studies [7,8]. Over 200 CHIM trials have been registered on clinicaltrials.gov and the number continues to increase. These studies have an excellent safety record. For example, in the last 30 years of work by the Walter Reed Army Institute of Research on Controlled Human Malaria Infection (CHMI), not one person has been hospitalized due to adverse events related to the study.

While a majority of these studies have been conducted in high income countries, over the last decade there has been an increasing interest in the conduct of these studies in low- and middle-income countries (LMICs) particularly for endemic diseases, where prior exposure may influence response to subsequent infection or vaccination.

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## 3. Ethics of human challenge studies

The ethics of human challenge have been widely debated, with particular emphasis on the informed consent process and the understanding of risks and benefit [9,10]. Further important aspects are the scientific and social value of these studies, the risk beyond individual participants, environmental risks posed by the challenge agent, risk minimization strategies, compensation and reimbursement, facilities and clinical expertise needed for such studies, rigorous review by institutional ethics committees, safety monitoring and follow up, continuous oversight and the regulatory framework for such studies [11]. Robust public and community engagement are also important especially in LMICs where this methodology is relatively new and research awareness remains low.

In most countries with experience in conducting CHIM studies, there was no or limited normative or ethical guidance for CHIM studies, possibly since they resemble Phase I studies. However, given the increase in the interest in studies in endemic settings, some countries, such as Kenya, have released specific guidance [12]. In addition, the World Health Organisation (WHO) is also working on ethical guidance for human challenge studies which is likely to be released later this year [13], following on recently issued guidance for ethical considerations for those planning human infection studies for SARS-CoV2 [14,15].

## 4. CHIM studies and their use in vaccine development

Vaccines are amongst the most effective public health interventions against infectious diseases, but the time to develop a new vaccine is usually long and the probability of success is low, with an estimated development time of 10.71 years and a market entry probability of 6% [16]. The time taken and the costs associated with the development of new vaccines through the phases of safety, immunogenicity and clinical efficacy are often prohibitive. Well-designed and carefully conducted CHIM studies can provide insights into host-pathogen interactions, determine host factors that contribute to infection, identify immune correlates of protection against infection/disease, and, accelerate the development and testing of vaccines and diagnostics for infectious diseases. CHIM studies can provide information on vaccine efficacy, protection against specific pathogen strains, and resistance in a small number of volunteers [17]. They can therefore facilitate down-selection, with the identification of the most promising vaccine candidates in development which can then be validated for their effectiveness in large scale Phase 3 trials. This reduces both the time and the costs involved in vaccine development and reduces the risk of the vaccine development process. Further, CHIMs have value for diseases where animal models are poor predictors of the disease in humans or when the disease is sporadic, and a phase 3 clinical trial is not feasible. Additional conditions where Phase 3 trials are not suitable include where there is a vaccine but endpoints such as protection from infection, rather than disease, cannot be measured.

Fig. 1 describes how human challenge studies gather information on vaccine efficacy. Volunteers are first rigorously screened based on predefined inclusion and exclusion criteria and enrolled after an informed consent process which frequently includes a test of understanding. The study participants are randomized to receive either the test vaccine or a comparator, and later challenged with the infective pathogen. Careful monitoring throughout the study period, vital signs, and other clinical and laboratory parameters are monitored. Depending on the pathogen, participants may be treated at a defined time (or earlier) based on the development of symptoms.

CHIM studies are conducted at a limited number of mainly academic centres, and a few commercial enterprises, but all such studies require clinical research infrastructure, well trained scientists and protocols with well-defined inclusion and exclusion criteria, rigorous informed consent processes and careful monitoring and governance [17].

CHIM studies have advanced vaccine development for several diseases. Some representative examples are discussed below.

### 4.1. CHIM studies in malaria vaccine development

Controlled Human Malaria Infection (CHMI) studies have used since the 1900s. They were initially used to determine mechanisms of immunity to the malarial parasite and subsequently to determine the efficacy of vaccine and drug candidates [18,19]. In CHMI models, infection is induced either through the use of sporozoites inoculated via direct injection or through bites from infected mosquitoes or plasmodium infected blood [20]. The challenge depends on the stage of infection required by the study objective. For example, sporozoites are used for assessment of the efficacy of pre-erythrocytic vaccine candidates, with the detection of blood stage infection by microscopy and the analysis of parasitemia by qPCR as the end point [21]. For blood stage candidates, on the other hand, infected blood is used and the parasite multiplication rate (PMR) is used to determine vaccine efficacy.

Since 2009, standardization of CHMI models have been emphasized by the WHO and other international organizations such as PATH [22]. Standardized designs for conduct of CHMIs and microscopic methods to

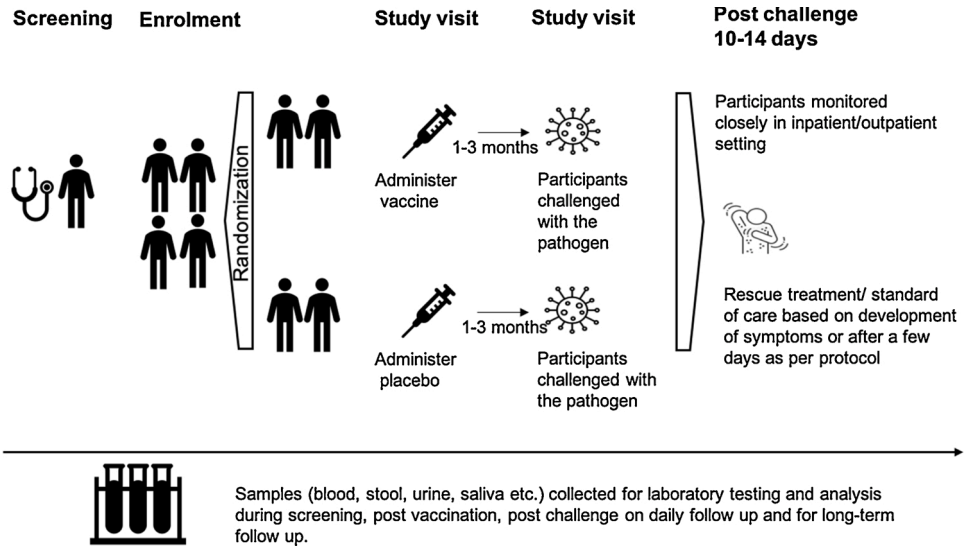


**Fig. 1.** Human challenge studies in vaccine development.

determine endpoints have been developed to support comparison of studies at multiple sites. In the past decade, CHMI models have also benefited from the development of aseptic cryopreserved purified *Plasmodium falciparum* sporozoites which can be injected to cause infection and are manufactured in accordance with regulatory standards [20]. This has allowed the CHMI models to be more widely used, including in endemic regions in Africa [23]. Conducting CHMI studies in endemic settings can help understand the effects of pre-exposure and immunity which is not feasible in non-endemic settings [24].

CHMI studies have been used to down-select malarial vaccine candidates and are now an integral part of the malaria vaccine development cycle [19]. For RTS,S/AS01, a pre-erythrocytic *P. falciparum* vaccine, which is the only licensed malarial vaccine currently being piloted in Africa, volunteers who had been given three doses of the vaccine were challenged 2–3 weeks after the third dose [25]. The vaccine efficacy in the CHMI study was found to be 50 %. This was followed by Phase 3 field trials conducted in over 15,000 infants and young children in Africa [26], resulting in an efficacy in young children (5–17 months of age) of 39 % reduced disease incidence and a 31.5 % reduced incidence of severe disease. Based on the phase 3 vaccine efficacy of RTS,S/AS01, the vaccine was licensed and in 2019 a pilot program supported by WHO has been initiated in Ghana, Kenya and Malawi to vaccinate 360,000 children per year in selected areas in these countries.

Another promising *P. falciparum* vaccine candidate PfSPZ, a live attenuated whole-parasite malaria vaccine has shown the most promising results to date in CHMIs against challenge with both homologous and heterologous strains [27]. The vaccine is currently being tested in larger field trials (Phase 3 studies) in Africa [28].

In addition to *P. falciparum* CHMIs, human challenge models for both sporozoite and blood stage infections have also been developed for *P. vivax* [29,30]. However, these have been more challenging to develop as parasites isolated from *P. vivax* affected individuals are difficult to culture in vitro [30]. Two candidate vaccines have been studied using CHMI studies; a radiation attenuated *P. vivax* sporozoites and VMP001/AS01B [31,32]. The radiation attenuated sporozoite model demonstrated a vaccine efficacy of 42 % with seven immunizations against the end point of parasitemia as measured through thick blood smear microscopy, while the VPM001/AS01B was not found to protective, demonstrating the value of CHIMs in reducing population exposure to ineffective vaccines.

### 4.2. Use of typhoid human challenge studies to support the WHO prequalification of a typhoid vaccine

A killed whole cell vaccine was first developed for typhoid fever in 1896. Since then Vi capsular polysaccharide vaccines, an oral live attenuated vaccine (Ty21a) and typhoid conjugate vaccines have been developed and licensed [33,34]. While all these vaccines with the exception of the killed whole cell vaccine are currently in use, both Ty21a and Vi polysaccharide vaccines were poorly immunogenic in young children and need repeat dosing.

In the past decade, typhoid conjugate vaccines were developed and found to be safe and immunogenic in infants, children and adults. Typbar-TCV, a typhoid conjugate vaccine made in India, was licensed for use based on immunogenicity higher than induced by the Vi-polysaccharide vaccine [35]. No clinical efficacy data was generated pre-licensure. In 2016, the vaccine was tested for efficacy by the Oxford vaccine group in an outpatient human challenge model of typhoid, which built on a similar model previously developed and used by the Center for Vaccine Development at the University of Maryland [36]. In the phase 2b study, healthy adult typhoid naïve volunteers were vaccinated with a single dose of either Typbar TCV, the Vi-polysaccharide vaccine or a control [37]. One month after vaccination, the participants were challenged through oral ingestion of *Salmonella* Typhi Quailes strain and followed up in an out-patient clinic with daily blood cultures for 2 weeks.The end point for typhoid diagnosis was a temperature $\geq$ 38 °C sustained for $\geq$ 12 h and/or blood culture confirmed *S.* Typhi bacteraemia. The vaccine efficacy of Typbar-TCV was found to be 54.6 % (95 % CI 26·8–71·8) for the per-protocol analysis, with 100 % seroconversion and >80 % efficacy with a clinically relevant definition [35]. Based on results from both earlier immunogenicity studies and the data on efficacy from the human challenge study, Typbar-TCV was pre-qualified by WHO in 2017 and recommended for use in endemic areas. Subsequently, this vaccine has been tested in field trials where the initial analysis has revealed a vaccine efficacy of 81.6 % [38].

### 4.3. Use of cholera human challenge studies to support the licensure of an oral cholera vaccine

Human challenge studies in cholera biology have been in use since 1969. The human challenge model for cholera was standardized in 1998 and very well-characterized GMP compliant challenge strain lots are available which give consistent attack rates in challenged volunteers [39]. Several studies using cholera human challenge were conducted in the US over many decades and in Thailand in the 1990s.

In 2013, a human challenge study to determine the vaccine efficacy of Vaxchora (CVD 103-HgR); a live attenuated oral cholera vaccine with diarrhoea as the primary endpoint was initiated at the University of Maryland [40]. The regulators agreed that large field studies were not possible owing to the low disease incidence in the US. Therefore, 197 healthy adult human volunteers ingested the oral cholera vaccine and were challenged with *V. cholerae* O1 El Tor Inaba strain N16961 10 days or 3 months post vaccination. Vaccine efficacy was 90.3 % and 79.5 % at 10 days and 3 months post vaccination. Based on the findings from this efficacy study combined with immunogenicity and safety data, the vaccine was approved for use by the FDA [41].

In general, human challenge studies in vaccine development provide the initial proof of efficacy. Vaccine candidates found to be effective are further evaluated for their effectiveness in real world situations. The efficacy predicted in these studies may be an overestimate (RTS,S/AS01) or an underestimate of the efficacy seen in field studies (Typbar-TCV) owing to multiple factors including participant selection, clinical end points and others.

## 5. Newer challenge models

The examples above discuss infectious diseases for which challenge models have been established and validated over the years. Additionally, there are also many diseases for which challenge models have been more recently established and standardized. These include pathogens such as *Group A Streptococcus* (GAS) which causes scarlet fever, *Schistosoma mansoni* which causes a human helminth infection, *Leishmania* which causes leishmaniasis. Additionally, CHIM have also been developed for colonization studies using *Bordetella pertussis* and *Streptococcus pneumoniae* etc. Similarly, there have been extensive discussions around human challenge studies for Zika virus [42] and more recently for SARS-CoV-2 [1].

GAS causes a significant burden of disease globally [43]. In 1969, in a study where a vaccine developed for GAS was administered to 21 children, two definitive and one probable case of acute rheumatic fever was seen [44]. This unexpected adverse event resulted in very stringent regulations and practically halted the field of GAS vaccine development. In recent years, there has been a resurgence in the vaccine development and a growing recognition of the importance and value of a human challenge model of GAS to test potential vaccine candidates [45]. Very recently, studies to establish a GAS pharyngitis CHIM with an emm 75 (M75) GAS strain have [46,47] have been undertaken. Once the safety and reliability of the challenge model is established it can be used further to test the efficacy of vaccine candidates and downselect the most effective candidates.

Similarly, studies are currently being planned in Africa [48,49] to

use a human challenge model for schistosomiasis which has been developed in the Netherlands [50]. Novel vaccines for schistosomiasis are needed as there is currently only one drug for disease control. Researchers have standardized processes to produce male *S. mansoni* cercaria for human use that meet current regulatory standards. In a recent dose ranging study, to identify a suitable dose for infection), a challenge dose of 20 *S. mansoni* cercariae was found to induce infection in the majority of the volunteers and the safety profile with this dose was acceptable [51]. The model also provided insights into disease biology, with the observation that eggs are not necessary to produce the Katayama syndrome, a syndrome that has symptoms similar to an acute inflammatory response and occurs weeks after infection. This challenge model can now be used to evaluate and downselect effective vaccine candidates in development.

More recently, vials containing the Leishmania parasite have been prepared and these are awaiting quality inspection before they can be used in a challenge study which can then be used to advance therapeutics for Leishmaniasis. Similarly, a challenge model using $10^5$ CFUs of *Bordetella pertussis* has been established which results in asymptomatic colonization of the upper respiratory tract and provides insights into the lifecycle and transmission of *B. pertussis* [52]. Advancements have also been made in understanding pneumococcal colonization in adults aged over 50 years by the expansion of the experimental human pneumococcal colonization model in this age group [53].

There has also considerable discussion on the use of the human challenge methodology to support vaccine development for new and emerging infectious diseases (EIDs). At the time of the Zika epidemic, a panel of experts was constituted to provide advice to the National Institutes of Health on the use of Zika human challenge studies to advance the development of interventions and to better understand the disease [54,55]. The panel recommended that while ethically Zika challenge studies could be justified they were premature to conduct especially given third party risks, since duration of infectivity was unknown at that time. Additionally, since the disease was actively circulating the requirement of challenge studies to accelerate the development of vaccines given the unknown and uncertain risks was not considered beneficial. However, since then, the understanding of Zika biology has evolved and transmission of the disease reduced. Hence, under the current circumstances a Zika human challenge would have considerable value provided all ethical and regulatory concerns are met [42,54]. The risk-benefit analysis and risk management strategies (along with third party) risks require special attention while considering challenge models for emerging infectious diseases.

There has been much deliberation around the use of human challenge studies in young healthy adults, who based on available data represent a low risk group, to fast track the development of COVID-19 vaccine candidates, and, preferentially downselect the more efficacious ones to prioritize their further clinical development. In accordance with these discussions, WHO has released guidance on the ethical aspects of the use of CHIMs for studying SARS-CoV-2 as well as a draft report on the feasibility, value and limitations of COVID-19 CHIMs [56,57].

The key criteria identified for COVID-19 challenge studies include a strong scientific justification, a favourable risk-benefit analysis, consultations and engagement, coordination of research, appropriate site and participant selection, informed consent, expert review, monitoring and oversight. For sites without prior experience, a feasibility report by external experts is helpful for planning.

Given the scale of the pandemic, solutions are urgently needed. Currently, there are efforts ongoing to develop a suitable challenge strain which can then further be considered for use in human challenge model, and, a wide interest from a potential volunteer pool [2]. Once a suitable strain has been developed, dose-escalation studies will need to be conducted, and, a suitable end point defined (such as such as virus replication in the nose, or development of mild symptoms etc) before these studies can be used either to understand disease biology and evaluate vaccines. The view on the need for this methodology however, remains divided. While, many feel that a well-characterized, safe and effective challenge model of SARS-CoV-2 can greatly enhance our basic understanding of several aspects of the disease such as immune responses, correlates of protection, reinfection, transmission, sterilizing versus protective immunity as well as vaccine responses, there are others who feel that given our limited understanding of the disease, the lack of appropriate rescue therapy and the uncertain long-term consequences; that such an undertaking is premature. Similar to the discussions around the Zika human challenge, it is very likely that as our understanding of COVID-19 evolves; a human challenge model with appropriate checks and balances will be a valuable tool in our efforts to develop vaccines and other interventions.

## 6. Global guidance on human challenge studies

With the increase in the human challenge study methodology and with many studies being conducted there have been several global discussions around the need for standardization of methodologies, clinical end points, sharing of reagents, guidance both regulatory and ethical for the use of these studies towards both understanding pathogenesis as well as for their use in the vaccine development pathway.

WHO has published generalized guidance on the use of human challenge studies in vaccine development [58]. Similarly, the US FDA has guidance on the regulatory considerations for use of human challenge studies in vaccine licensure, including a recent guidance on their use in the development of COVID-19 vaccines [59,60].

The International Alliance for Biological Standardization (IABS) has organised consultations regularly since 2014 on aspects of human challenge studies, including two consultations focused specifically on their use in vaccine development [61–64]. The consultations bring together ethicists, researchers, regulators and various other stakeholders with an interest in this methodology to discuss opportunities, pathways and challenges to the use of CHIM studies. Similarly, there have been discussions on having guidance for manufacture of challenge agents so that they adhere to the highest standards of quality, safety, consistency and reproducibility. To facilitate the development of such guidance by regulatory bodies, a manufacturing guidance for challenge agents is currently under preparation with support from the Wellcome Trust and HIC-Vac and is expected to be ready in 2021(13).

Arising from all the regulatory discussions is a consensus that carefully designed CHIM studies are a valuable tool in the vaccine development pathway and provide early proof of efficacy. They are intended to complement, and support information provided to regulatory authorities and are not a replacement for larger field studies.

## 7. Conclusions

As with all research methodologies, human challenge studies are not without their limitations. These studies are a model of infection and hence like all models they are limited in generalizability. Challenge studies have strict inclusion and exclusion criteria and enrol young healthy adults and therefore may not be representative of the population at risk. For instance, in malaria, the primary targets for malarial vaccines are children and young infants whereas CHMI studies are carried out in healthy adults. Similarly, historically most challenge studies, have enrolled participants who have no prior history of exposure to challenge agent, however that is changing with more such studies being carried out in endemic regions and allowing for selection of participants who have had pre-exposure [24]. The route of infection, the dose of the challenge agent use might not appropriately mimic the natural course of infection and hence this might affect the interpretations drawn from such studies [8]. Further the challenge strain itself is chosen for its stability.

However, despite these limitations, human challenge trials play a very important and supportive role in both out understanding of disease

and the development and testing of potential vaccine candidates. 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, assess the safety and efficacy of vaccine candidates and help select the most promising ones, reduce the costs and timelines of vaccine development.

There is interest from researchers and funders for supporting such studies and harmonization of methodologies, reagents and standards will greatly aid the impact of this methodology. Similarly, consensus amongst regulators and ethicists on various aspects of these studies such as study designs, challenge agent requirements and manufacturing, participant selection, compensation etc. will ensure that these studies can provide valuable information and be a safe and effective methodology to design better vaccines in a more cost-effective manner.

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