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The unprecedented speed of delivery of SARS-CoV-2 pandemic vaccines has redefined the limits for all vaccine development. Beyond the aspirational 100-day timeline for tomorrow's hypothetical pandemic vaccines, there is a sense of optimism that development of other high priority vaccines can be accelerated. Early in the COVID-19 pandemic, an intense and polarised academic and public discourse arose concerning the role of human challenge trials for vaccine development. A case was made for human challenge trials as a powerful tool to establish early proof-of-concept of vaccine efficacy in humans, inform vaccine down selection, and address crucial knowledge gaps regarding transmission, pathogenesis, and immune protection. We review the track record of human challenge trials contributing to the development of vaccines for 19 different pathogens and discuss relevant limitations, barriers, and pitfalls. This Review also highlights opportunities for efforts to broaden the scope and boost the effects of human challenge trials, to accelerate all vaccine development.

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Introduction

Human challenge studies model an encounter between human hosts and pathogens by deliberately exposing selected volunteers to a well characterised pathogen, or representative surrogate challenge agent under controlled conditions. There has been increasing use of human challenge studies to explore pathogenesis and protection, and to evaluate vaccines and therapeutics. Since 1980, more than 15 000 people have participated in human challenge studies for at least 30 pathogen models, including SARS-CoV-2.[1–4]

Intentional human infection has a long history in medicine. Famously, protective immunity following deliberate inoculation with smallpox heralded the successful development of the smallpox vaccine by Edward Jenner, who showed the efficacy of experimental inoculation of vaccinia virus (cowpox) as protection against repeated smallpox exposure in a child (James Phipps).[5] Unfortunately, looming large over human challenge research is the spectre of infamous dehumanising abuses perpetrated in the name of medical science, some involving deliberate human infection.[6] However, modern human challenge research is characterised by high standards of research accountability, ethical and regulatory scrutiny, and public engagement.

The ethical principles and safety considerations of human challenge research can be likened to non-oncological phase 1 trials whereby volunteers are exposed to an experimental intervention with known and unknown risks, without direct benefit. Early phase trials of live-attenuated vaccines present an interesting borderline instance, whereby vaccine-strain pathogen transmission and attenuated disease might occur in participants and also third parties.[7] There have been multiple recent reviews of ethical frameworks guiding human challenge research, all finding that the degree of acceptable risk should be balanced against potential public health benefits (or social value).[6–8] The safety record of contemporary human challenge trials has been reassuring. A systematic review of 187 studies between 1980 and 2021 identified only 23 challenge-related serious adverse events (eg, hospitalisation) in more than 10 000 participants, with no deaths or permanent impairment.[9]

Vaccines have been spectacularly effective in advancing public health, especially in preventing death and morbidity in early childhood. Before the COVID-19 pandemic, the pace of modern vaccine development had slowed,[10] with several high priority vaccine projects impeded by scientific, technical, regulatory, and commercial barriers. Achieving a successful outcome in resource intensive pivotal efficacy studies has been a particularly difficult goal, with a modest probability of success.[10] The resurgence in popularity[3] of human challenge research in recent years is motivated, in part, by hope that this approach might accelerate vaccine development by improving efficiency in navigating these

Key messages

- Human challenge models appeal as a platform for learning more about human infectious diseases and efficiently evaluating interventions for their prevention, diagnosis, and treatment
- Human challenge trials might accelerate development of new vaccines by providing an early indicator of efficacy and important insights regarding immune correlates of protection
- We reviewed more than 80 trials evaluating vaccines in 19 human challenge models and the subsequent development trajectory of the vaccines
- The contribution of human challenge trials to vaccine development depends on pathogen-specific and product-specific factors that should be explicitly considered when designing models and trials
- There is untapped potential for human challenge trials to have a greater effect on accelerating development of vaccines against high priority pathogens in pandemic and non-pandemic settings

	Examples	Mitigation and comments
Strain diversity and selection		
The selected challenge strain might not be representative of naturally circulating strain or evolving seasonal variants, so that VE against the challenge strain cannot be reliably extrapolated.	For some pathogens (eg, *Vibrio cholerae*) there is limited diversity among strains principally responsible for human disease. More extensive strain diversity is most relevant when it affects the vaccine antigen—for example, the *Streptococcus pneumoniae* capsular polysaccharide targeted by successive generations of multivalent vaccines.	Challenge strains should be selected according to a pathogen-specific and product-specific rationale, considering molecular epidemiology (vaccine antigens and virulence factors). Multiple strains might be introduced to broaden a model's scope and to evaluate homologous and heterologous protection (as for cholera, malaria, *Shigella*, and enterotoxigenic *Escherichia coli*). Platform manufacturing technology could expedite production of seasonal variants of challenge strains.
Syndrome, severity, and clinical endpoint alignment		
Findings emerging from a challenge model of one non-severe clinical syndrome might not apply to other syndromes and severe disease caused by the same pathogen (for safety reasons the human challenge is planned such that clinical outcomes would be muted). If challenge trials do not use clinically relevant endpoints fit for use in late-stage field trials, comparison (and correlation) of results is difficult.	Some pathogens induce a restricted spectrum of disease, such as cholera and typhoid. For other pathogens (eg, influenza virus and RSV) the use of different endpoints led to considerably different VE results between human challenge and field trials.	Challenge models should be relevant, with clinical, microbiological, and immunological outputs that contribute meaningfully to development of vaccines against a particular pathogen. Reasonable efforts should be made to identify endpoints that can be consistently applied across clinical trials. In some cases, consensus endpoints could follow from challenge trial findings.
Sample size and attack rate		
A high and reproducible attack rate is key to delivering early and efficient proof-of-concept for VE. However, if a too-high inoculum or a too-invasive challenge procedure is used to obtain the desired attack rate, vaccine-induced protection could be overwhelmed.	Exposure to a *Plasmodium falciparum* sporozoite challenge causes infection in 100% of unimmunised controls and does not overwhelm vaccine-induced protection. Low attack rates in the placebo arms of trials have affected efficacy results from trials of live-attenuated *Shigella sonnei* vaccine (using the same strain as previous trials) and a *Helicobacter pylori* vaccine trial (different strain from previous studies).	Challenge strains should be standardised across trials; guidelines have been developed for manufacturing and maintaining stability of challenge stocks. The inoculum and method of inoculation (challenge procedure) can be studied in an initial dose-ranging trial to establish the model. Although a high attack rate is important, the most desirable attack rate for a model will depend on the specific pathogen and clinical syndrome.
Susceptibility (pre-existing immunity, age, and setting)		
Volunteers in human challenge vaccine trials might differ from the target population regarding comorbidities, immunity, age, immunogenetics, and microbiome, all of which could influence VE.	Cholera VE differed in participants in endemic *vs* non-endemic settings, resulting in specific licensure of CVD 103-HgR as a travel vaccine. Human challenge trials of PfSPZ malaria vaccine and Ty21a live-attenuated typhoid vaccines in adults showed higher efficacy than in later phase trials in children, particularly infants, whereas human challenge trials of the intranasal live-attenuated influenza vaccine showed lower efficacy among adult participants compared with field trials in children. Conversely, oral killed cholera vaccine, typhoid conjugate vaccines, RTS,S malaria vaccine, and the MVA85A BCG-booster vaccine candidate all showed similar VE in adult human challenge vaccine trials compared with paediatric phase 2 and 3 trials. RSV vaccine performance was similar in human challenge trials in young healthy adults and field trials in adults older than 60 years.	There are increasing efforts to promote human challenge development in endemic settings. Human challenge vaccine trials have been performed in endemic settings for *Shigella*, *P falciparum*, and *P vivax*. A single-sex *Schistosoma mansoni* human challenge model is being established in Uganda, and experimental human pneumococcal carriage has been established in Malawi. Vaccine performance across age groups is dependent on multiple factors, including pathogen-specific and vaccine-specific characteristics. Human challenge has been usefully applied to assess vaccines targeting children and older people. Correlates of protection from human challenge can also be applied to phase 3 trials. RSV human challenge has also been safely performed in older, more susceptible populations. Traditional vaccine trial selection criteria also do not address all of these variables.
Selecting out an effective vaccine candidate		
Developers might be concerned that human challenge trials will inadvertently down select vaccines that would have been successful in the field against natural exposure.	The available examples suggest this concern might be overstated. For vaccines that have ultimately not progressed, when human challenge trials and field trials were run simultaneously, rather than sequentially, VE results were similar (tuberculosis, malaria blood stage vaccine AMA-1/AS01B, and killed oral typhoid vaccine [Taboral]). In other cases, vaccine candidates with only moderate VE in human challenge trials have still progressed to licensure (eg, the RTS,S malaria vaccine).	Human challenge vaccine trials (and model development) should be planned with a clear view of how the factors listed in this table apply to the specific pathogen and disease. Human challenge trials will usually not be a true go or no go stage gate for vaccine development. Early involvement of regulators and industry might help boost the impact of human challenge vaccine trials, ensuring that the model is fit for purpose.

CVD=Center for Vaccine Development. RSV=respiratory syncytial virus. VE=vaccine efficacy.

Table 1: **The five S's—limitations of human challenge vaccine trials**

barriers. The hope of accelerating vaccine development has been expressed in a series of claims expounding the transformational potential of human challenge research. The discourse surrounding these claims was especially heated early in the COVID-19 pandemic, with a vigorous debate occurring in the popular and scientific media, whereas careful stepwise ethical and regulatory processes gradually moved COVID-19 human challenge research towards study completion.[11,12]

This cautious approach was overtaken by the rapid development of COVID-19 vaccines that used a traditional vaccine development pathway turbocharged by pandemic contingencies, especially the large populations eligible and available for pivotal efficacy study, suitable trial sites with high levels of viral transmission, and unprecedented public support to expedite regulatory and commercial barriers. The success of rapid pandemic vaccine development has been juxtaposed with the slower

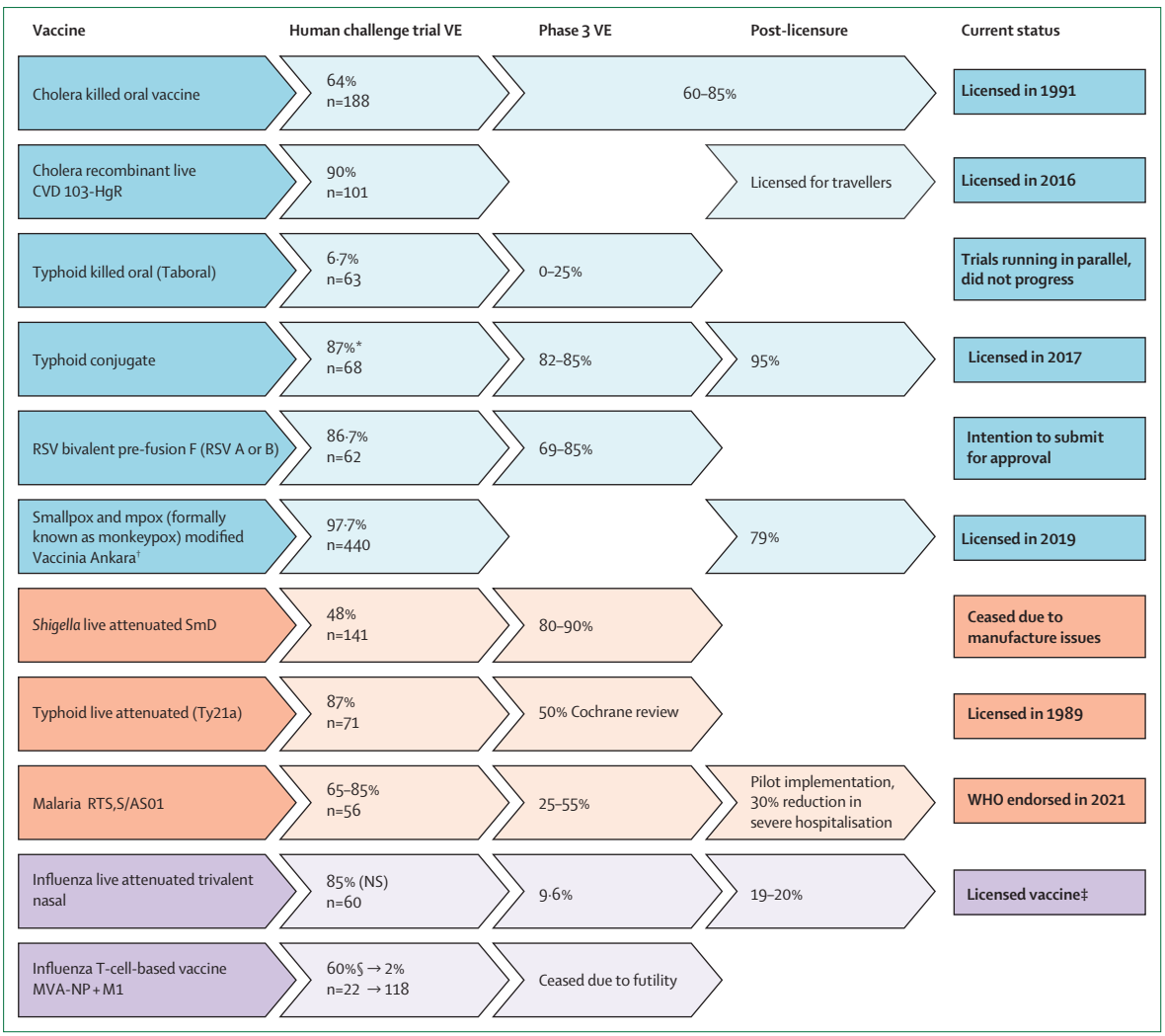

Figure: **Vaccine efficacy in human challenge trials compared with phase 3/4 results**
Blue=concordant human challenge trial and further phase trial results. Orange=higher or lower human challenge trial *vs* further phase trial results. Purple=markedly higher human challenge trial *vs* further phase trial results. CVD=Center for Vaccine Development. n=number of participants. NS=not significant. RSV=respiratory syncytial virus. SmD=streptomycin-dependent. VE=vaccine efficacy. *Post-hoc analysis. †Challenge using replicating-vaccinia smallpox vaccine ACAM2000 with VE measured against attenuation of major cutaneous reaction, and labelled a phase 3 trial. ‡Efficacy demonstrated in children before adult human challenge trial. §Initial influenza T-cell-based vaccine human challenge trial that might be underpowered; subsequent challenge study occurred after the phase 3 trial. Further details of the trials are in the appendix (p 2).

See Online for appendix

deliberative approach taken towards COVID-19 human challenge research—the first trial results were published in March, 2022,[13]—raising questions regarding the usefulness of human challenge research for vaccine development.

Arguably, the most commonly quoted benefit of human challenge vaccine trials are that they provide rapid early proof-of-concept for vaccine efficacy (VE), particularly for pathogens without known correlates of protection, at reduced cost, and requiring only a small group of volunteers.[3,7,11,14,15] Human challenge vaccine trials have also been proposed to down select vaccine candidates with unsatisfactory efficacy early in the development pipeline. These vaccine candidates might also provide important surrogate immunological data to optimise vaccine development, measure post-vaccination (asymptomatic) infection, and characterise correlates of protection. Measurement of colonisation, shedding, and other microbiological outcomes beyond binary infection and disease outcomes in human challenge trials might assess proxies for transmission potential. Human challenge vaccine trials do not depend on naturally occurring community transmission of a disease as in traditional phase 2 or 3 efficacy trials, which is difficult to predict and always involves less than universal exposure. This difference alone necessitates a large sample size in these field trials, increasing the number of people exposed to the risk of receiving an investigational product (active

	Human challenge trial VE	Current status
Malaria		
Live-attenuated *Plasmodium falciparum* sporozoite (pyrimethamine prophylaxis)[18]	87·5%	Entering phase 3 in Bioko Island
R21 in matrix-mTM adjuvant[19]	81·8%	VE 80% high dose adjuvant; n=409 children aged 5–17 months in Burkina Faso;[20] further phase 3 underway (NCT4704830)
Dengue		
TV003 live-attenuated tetravalent[21]	100%	Phase 3 trial in participants aged 2–59 years in Brazil underway (NCT02406729)
RSV		
Recombinant Ad26.FSV.preF[22]	45·8%	Phase 2 field trial 80%[23]
MVA-BN-RSV modified vaccinia Ankara vector genetically engineered to encode the RSV F, G(A), G(B), N, and M2-1 proteins[24]	88·5%	Phase 3 commenced (NCT05238025)
Norovirus		
Bivalent GI.1/GII.4/alum TAK214[25]	100% (severe disease)	Phase 2 field trial; n=2357; VE 61·8% moderate to severe disease;[26] phase 2 dose-finding completed in children[27]
Rotavirus		
Monovalent P2-VP8-P[8][28]	52% (reduction in shedding*)	A trivalent version of this vaccine is currently being developed[29]
Shigella		
Flexyn2a conjugate[30]	52% (severe disease)	Phase 1/2 field trials of multivalent candidate in Kenya underway (NCT04056117)
Human challenge vaccine trials in progress		
Hookworm recombinant subunit vaccine Na-GST-1 (NCT03172975)	..	..
Paratyphoid fever live-attenuated oral vaccine CVD1902 (ISRCTN15485902)	..	..
Norovirus vaccine VXA-G1.1-NN (NCT05212168)	..	..
Pneumococcal conjugate vaccine-13 (PACTR202008503507113)	..	..

RSV=respiratory syncytial virus. VE=vaccine efficacy. *Using live-attenuated vaccine as challenge agent.

Table 2: **Vaccines tested in human challenge trials with field trials planned or in progress**

group), or the risk of exposure without the protection of a potentially efficacious intervention (placebo group).[15,16] It has been argued that human challenge vaccine trials might obviate the requirement for phase 3 trials (alongside expanded phase 2 field trials).[12,17]

The facts

To describe the effect of human challenge research on vaccine development to date, a literature search was performed to identify and link human challenge trials evaluating vaccines with the subsequent development trajectory for each vaccine product and to address facts versus fantasy regarding the contribution of human challenge to vaccine development. We first assessed the comparative vaccine efficacy across human challenge and further phase trials by pathogen, then the contribution of human challenge to down selection and identification of correlates of protection.

The findings from this descriptive overview cannot be simply applied to predict the future success of human challenge models for accelerating the development of vaccine products under any circumstances (eg, pandemic contingencies *vs* less urgent scenarios). The aim of this Review was to explore general and study-specific factors that make human challenge trials useful for vaccine development, thus addressing the intrinsic limitations. Broadly, these limitations relate to generalisability concerns that can be organised under the headings: strain diversity and selection; syndrome, severity, and clinical endpoint alignment; sample size and attack rate; susceptibility (pre-existing immunity, age, and setting); and selecting-out effective vaccines (table 1).

We identified human challenge trials evaluating vaccine candidates for 19 pathogens. Human challenge trials of vaccine candidates targeting seven pathogens have been trialled in phase 3/4 studies (figure; appendix p 2). Other vaccine candidates have recently been tested in human challenge trials and further phase trials are currently in progress (table 2). Further vaccine candidates have been down selected after human challenge (table 3).

Efficacy in human challenge versus field trials

Cholera

Human challenge research has a long history in cholera vaccine development.[62] The killed whole-cell recombinant B-subunit cholera vaccine (Dukoral) was tested in a human challenge trial in 1986, showing 64% VE against diarrhoea, which was similar to several subsequent phase 3 and 4 studies (VE 58–75%; figure; appendix p 2).[63–69] Dukoral is one of five currently licensed

inactivated cholera vaccines that is registered in more than 60 countries.[70] Use of killed oral vaccines is a key component of the Global Task Force on Cholera Control's strategy to control endemic cholera under non-emergency conditions.[71]

Recombinant live oral cholera vaccines have been evaluated in human challenge trials since 1988. In the first trial, the Center for Vaccine Development (CVD) 103-HgR vaccine showed a VE of 62%.[72] Several further human challenge vaccine trials were performed, including a 1992 study showing a VE of 91% against moderate to severe diarrhoea.[73] The safety, immunogenicity, and effect on patterns of *Vibrio cholerae* excretion and transmissibility for CVD 103-HgR were subsequently studied in placebo-controlled trials in endemic populations (6000 participants aged 12 months to 65 years).[74] These studies revealed that higher vaccine doses were required for seroconversion of participants in countries affected by endemic or epidemic cholera.[74] Subsequent field trials of higher dose CVD 103-HgR had mixed results, with a VE of only 14% in a phase 3 trial in Indonesia that captured a few cholera cases,[75,76] in contrast to 79·2% (95% CI 71·9–84·6) crude vaccine effectiveness in a retrospective study of a mass vaccination campaign during a Micronesian cholera outbreak in 2000.[77]

Reinvigorated development of CVD 103-HgR (now VaxChora, Emergent BioSolutions) was supported by a

	Human challenge trial result		Phase 2 field trial (if applicable) and comment
	Vaccine efficacy	Vaccine *vs* control (outcome n/total n)	
***Salmonella enterica* serovar Typhi**			
M01ZH09[31]	13%	18/31 *vs* 20/30	..
Shigella			
E coli–Shigella flexneri 2a hybrid vaccine EcSfa-1 and EcSfa-2[32]	36% (any disease, three doses); 27% (four lower doses)	9/30 *vs* 10/21; 10/16 *vs* 12/14	Study of 1398 military recruits could not evaluate efficacy as there were no cases over 2·5–7 months' follow-up[33]
Live-attenuated *S flexneri* 2a (SC602)[34]	100% (severe syndromes)	0/7 *vs* 6/7	Vaccine induced fever in 20% of participants; field immunogenicity trials did not match immunogenicity results in *Shigella*-naive human challenge trial participants[35]
Live-attenuated *S sonnei* (WRSS1)[36]	40% (any disease)	3/10 *vs* 5/10	Further attenuating mutations were introduced to address the reactogenicity resulting in the WRSS2 and WRSS3 candidate vaccines
GMMA-based *S sonnei* vaccine (1790GAHB)[37]	−9·8%	15/33 *vs* 12/29	A next-generation quadrivalent vaccine, altSonflex1-2-3 (*S flexneri* 1b, 2a, 3a, and *S. sonnei*) with higher O-antigen is currently being tested in a phase 1/2 clinical trial (NCT05073003)
Enterotoxigenic *Escherichia coli* (ETEC)			
Type 1 somatic pili[38]	67% (1800/1800 µg)	2/6 *vs* 7/7	Unacceptable reactogenicity (1800/1800 µg), unacceptable purging in several participants (1800/900 µg); no VE shown with lower challenge inoculum or against heterologous challenge strain that expressed antigenically identical type 1 somatic pili
	43% (1800/900 µg)	3/6 *vs* 7/8	
CFA/II fimbriae			
Oral purified[38]	No efficacy (strain H10407 and H1765)	5/6 *vs* 5/6 5/6 *vs* 5/6	..
Polymer microspheres and purified CFA/II fimbriae[39]	30%	7/10 *vs* 10/10	..
Inactivated fimbriated whole-cell vaccines[40]	78% (homologous challenge); no efficacy (heterologous strains)	2/10 *vs* 8/9	..
Formalin inactivated whole-cell fimbriated ETEC[38]	33%	2/5 *vs* 6/10	Underpowered study
Live fimbriated, toxin-negative ETEC (prototype live oral vaccine E1392-75-2A)[38]	75% (heterologous strain)	3/12 *vs* 6/6	Prototype further developed
Multivalent ETEC vaccine ACE527[41]	26·6% (any disease); 41% (severe diarrhoea)	15/29 *vs* 19/27	Adjuvanted
ACE527 with double mutant heat labile toxin adjuvant[42]	65·9% (severe diarrhoea)	3/13 *vs* 21/31	Did not progress due to lack of funding
Helicobacter pylori			
Recombinant *H pylori* antigens (VacA, CagA, NAP)/alum[43]	22%	6/19 *vs* 6/15	..
Recombinant Ty21a vaccine expressing *H pylori* antigens (Ty21a[pUreA/B])[44]	33%	6/9 *vs* 4/4 (pilot)	..
HP0231 (Ty21a[pHP0231])[44]	No efficacy	12/12 *vs* 20/21	..

(Table 3 continues on next page)

	Human challenge trial result		Phase 2 field trial (if applicable) and comment
	Vaccine efficacy	Vaccine *vs* control (outcome n/total n)	
(Continued from previous page)			
Malaria			
Plasmodium falciparum			
AMA-1/AS02A or AS01B[45]	0%	16/16 *vs* 6/6	Phase 2 natural infection in Malian children 7·6% (not significant) at between ages 24 months and 6 years*[44]
FMP21/AS01 (apical membrane 1 ag)[46]	0%; no effect on PMR	12/12 *vs* 15/15	..
AMA1-C1/ Alhydrogel + CPG.7909[47]	0%; no difference in PMR	5 *vs* 3; 16-fold *vs* 17-fold reduction in PMR	..
PEV3A alone, or PEV3A+FFM ME-TRAP[48]	No sterile immunity and lower rates of parasite growth	..	..
Plasmodium vivax			
Soluble recombinant protein VMP001/AS01B[49]	0%	27/27 *vs* 6/6	..
BCG and tuberculosis			
MVA85A BCG-booster vaccine[50]	No efficacy (against mycobacterial load on skin biopsy)	13 *vs* 11 (BCG naive); 12 *vs* 13 (BCG exposed)	17% QuantiFERON Tb Gold Test conversion 32/1399 *vs* 39/1395 of children aged 4–6 months in Cape Town;*[51] 32·8% of 650 adults living with HIV given two doses*[52]
Influenza			
Recombinant protein influenza A vaccine (D protein)[53]	41·6%	7/15 *vs* 12/15	No further studies found
PMED influenza DNA vaccine[54]	41% (any illness with or without fever); 53% (upper respiratory tract infection)	10/27 *vs* 17/27 7/27 *vs* 15/27	No further studies found
Inactivated trivalent proteosome[55]	100% and 85% febrile illness with seroconversion; 66% and 43% against any illness (two regimens of 15 µg and 30 µg)	0/19 *vs* 0/38 *vs* 9/45	No further studies found
FLU-v peptide vaccine[56]	40·6% with one dose; 33% with two doses	13/40 (FLU-v, one dose) *vs* 15/40 (FLU-v, two doses) *vs* 23/42	No further studies found
VXA.A1.1 adenovirus vectored tablet vaccine[57]	39·5% against influenza positive illness	17/58 *vs* 15/31	No further studies found
Streptococcus pneumoniae			
Recombinant protein subunit vaccine with three recombinant T-cell antigens GEN-004	Entered human challenge trial in 2014 (NCT02116998)	Trial did not meet primary endpoint of efficacy (personal communication Daniela Ferreira)	..
Rickettsia rickettsii			
Formalin inactivated[58]	25%	12/16 *vs* 6/6	..

Further enterotoxigenic *Escherichia coli*[38] and controlled human malaria infection[59,60,61] have been reviewed. PMR=parasite multiplication rate. *Field trials were underway before human challenge trial.

Table 3: **Vaccine efficacy in human challenge trials leading to down selection or not immediately progressed to further development**

further human challenge trial, designed in consultation with the Food and Drug Administration (FDA), that included 101 non-infected adult US volunteers. VE was 90·3% (95% CI 61·7–100%) 10 days after vaccination and 79·5% at 3 months (95% CI 49–100%).[76,78] In 2016, the FDA approved CVD 103-HgR for travellers aged 16 to 64 years, which was the first time the FDA had approved a vaccine on the basis of human challenge trial results, although Canadian, Swiss, and Australian regulators had licensed the previous CVD 103-HgR product because of the earlier human challenge trial results. Positive safety and immunogenicity results from further clinical trials have extended the licensure of VaxChora to include children from age 2 years.[71] Licensure of the CVD-103-HgR cholera vaccine for people travelling to cholera endemic countries, on the basis of human challenge trials results, can be considered as an ideal use-case for human challenge in vaccine development.

Typhoid

Three different typhoid vaccines have been tested in both human challenge and phase 3 or 4 trials. First, oral killed typhoid vaccine (Taboral) did not show protection in a 1971 human challenge trial (VE 6·7% after six doses and 29% after 12 doses).[79] Two phase 3 trials of oral killed typhoid vaccines in Delhi between 1968 and 1971 showed similar disappointing efficacy (VE 25% and 0%, respectively).[80]

Second, live-attenuated oral Ty21a VE was 87% in an initial human challenge trial.[81] Live oral typhoid vaccines were licensed in 1989 in the US, after a large successful study whereby 1·4 million vaccine doses were administered.[82] Although VE in an endemic setting was lower than in human challenge trials (cumulative VE of 50% at 2·5 to 3 years from four field trials including 235 239 adults and children),[82–84] the challenge trials supported efforts towards licensure of a vaccine for children aged over 5 years.

Third, efficacy results from the human challenge trial of a typhoid conjugate vaccine (TCV) informed WHO recommendation for TCV in children aged 6 months and older in endemic countries.[85] Safety and durable immunogenicity (lasting at least 2 years) across age groups of Typbar TCV was shown in a large phase 3 trial in 2015;[86] in parallel, TCV efficacy was shown in a human challenge trial.[87] Celina Jin and colleagues showed a 54·6% (95% CI 26·8–71·8) VE against persistent fever or bacteraemia in a human challenge trial of 68 healthy typhoid-naive adults. Post-hoc analysis of alternative diagnostic criteria of fever greater than 38·0°C preceding *Salmonella typhi* bacteraemia showed a VE estimate of 87·1%.[87] Phase 3 trials of TCV among children aged 9 months to 16 years in Nepal, Malawi, and Bangladesh showed a VE ranging from 79% to 85% against blood culture-confirmed infection.[88–91] TCV has been introduced in Pakistan, Liberia, and Zimbabwe.[88] In a cohort of 23 407 children during a typhoid outbreak in Hyderabad, TCV effectiveness was 95%.[92]

Shigella

Vaccines have been tested in *Shigella sonnei* and *S flexneri* human challenge trials since 1946.[93] One candidate completed phase 3, and one is currently being tested in a phase 2 field trial (NCT04056117). Most human challenge trials have led to down selection of vaccine candidates with poor efficacy or unacceptable reactogenicity (table 3).

A historical *Shigella* human challenge vaccine trial provides an example of lower VE than in subsequent field trials, related to stringent human challenge clinical endpoint definitions. The lyophilised streptomycin-dependent live-attenuated *S flexneri* vaccine had a VE of 48% against disease (oral temperature ≥100°F and ≥four watery stools per 24 hours) in a human challenge trial including 118 prisoners.[32] In comparison, a field trial in 737 soldiers showed 100% VE against homologuous strain dysentry (defined as diarrhoea with two or more soft or liquid stools within 12 hours or a stool containing blood, pus, or mucous).[94] Furthermore, a multi-strain streptomycin-dependent vaccine showed high VE in 7281 children aged 2 to 8 years (*S flexneri* 1 and *S flexneri* 2a vaccine VE 91·% against disease with homologous strains, and *S flexneri 3* and *S sonnei* vaccine VE 82%; endpoint was culture positive diarrhoea defined as one or more bowel movements with liquid stool).[95] Manufacturing difficulties prevented streptomycin-dependent vaccines from progressing to licensure.[96]

In 2017, experts convened to develop a uniform procedure to conduct *Shigella* human challenge studies[93] including clinical and immunological endpoints. These endpoint definitions allow for a broader definition of shigellosis and were used for the Flexyn2a conjugate vaccine human challenge study[30] that has progressed to a phase 2 field trial in Kenya (NCT04056117; table 2).

Malaria

Controlled human malaria infection (CHMI) is arguably the most mature human challenge system, with human challenge trials an accepted component of the clinical development pathway of antimalarial drugs and vaccines. There is ample evidence of reproducibility and safety, especially against the most important species *Plasmodium falciparum,*[97] and there has been development of a *Plasmodium vivax* model.[98]

Sporozoite challenge by mosquito bite or, more recently, cryopreserved sporozoites, has been pivotal to the development of three vaccines targeting the pre-erythrocytic stage of the parasite lifecycle, one of which has been registered and two others in advanced clinical development. The first, RTS,S/AS01 (GSK Mosquirix) consists of a portion of *P falciparum* circumsporozoite protein fused to hepatitis B virus surface antigen, assembled into virus-like particles and formulated with the AS01 adjuvant. In 2015, RTS,S/AS01 was recommended for use outside the EU[99] and in 2021, WHO recommended the large-scale use of RTS,S/A01 for children living in areas with moderate to high malaria transmission.[100] Human challenge trials evaluated different doses, schedules, and adjuvants to find a VE of 12·5% to 86% in malaria-naive adults (appendix p 9). Phase 2 field trials that included infants and children in malaria endemic settings showed a VE of 30% to 66%.[101–104] VE in phase 3 trials were 26% (infants aged 6 to 12 weeks) and 36% to 55% (infants aged 5 to 17 months).[105] Pilot implementation studies are underway in Ghana, Kenya, and Malawi.[106]

Other advanced candidates have been tested in human challenge, but there are no comparative phase 3 results yet (table 2).[20,107] For the three most advanced vaccines, human challenge trials have informed adjuvant selection, vaccine schedule design, and route of immunisation. Consistently, VE for malaria-naive adult CHMI participants in non-endemic settings has been higher than in endemic populations (appendix p 9), suggesting immune imprinting from previous exposure affects vaccine responses, which is being addressed by conducting CHMI in endemic settings.

Influenza

Following the 2009 H1N1 influenza pandemic, the US National Institutes of Health validated a new influenza human challenge model after safety concerns had

previously halted human challenge trials.[108] A phase 2 human challenge trial with 60 participants reported a VE of 85% for a trivalent cold-adapted live-attenuated vaccine.[109] Volunteers in this trial were pre-screened for serum haemagglutination-inhibition antibody titres of 1:8 or less against vaccine strains. In the subsequent phase 3 trial without pre-screening antibody tests and with different endpoints, VE was 9·6%.[110] Post-licensure studies in approximately 1 million US military personnel from 2004 to 2007 found 10·7% (95% CI 2·7–18·1) to 20·8% (95% CI 12·3–28·5) effectiveness for pneumonia or influenza endpoints.[111] These divergent results highlight the difficulties in interpreting findings when trial endpoints are not aligned, and point to an original antigenic sin phenomenon with pre-existing immunity affecting vaccine responses. Results in children, with comparably less pre-existing immunity, are consistent with this observation: in a meta-analysis of five studies including children aged 6 months to 7 years, the pooled VE was 83%.[112]

MVA-NP+M1, a universal influenza vaccine candidate that produces potent and persistent T-cell responses, had 60% VE against symptomatic influenza and viral shedding in a seemingly underpowered human challenge trial (22 participants, no confidence interval reported).[113] The authors concluded that the trial warranted further clinical development and along with multiple immunogenicity studies, propelled phase 2 and 3 trials, which showed no efficacy in 2998 participants (NCT03880474).[114] A subsequent human challenge trial (NCT03883113) of the vaccine showed concordant poor efficacy of 2%, which might have rightly led to caution in progressing to field trials, highlighting the need to properly power human challenge trials.

The influenza human challenge model has been used to evaluate numerous other vaccine candidates, none of which progressed to further development (table 3). The 2021 Research and Development Roadmap for influenza vaccines outlines four milestones to optimise use of the model.[115] All milestones can be applied to human challenge use in vaccine development more broadly, as discussed later.

Respiratory syncytial virus

A bivalent respiratory syncytial virus (RSV) prefusion F subunit (RSVpreF) vaccine was evaluated in a phase 2a double-blind randomised placebo-controlled RSV-A human challenge trial that recruited non-infected adults aged 18 to 50 years. Participants were pre-screened for RSV A–neutralising antibody activity to enrich for increased RSV susceptibility. Vaccine efficacy was 86·7% (95% CI 53·8–96·5) against symptomatic RSV infection (at least one symptom from two categories or one grade 2 symptom from any category), with a marked reduction also in viral shedding.[116] The ongoing RENOIR phase 3 trial has reported an interim result of 85·7% VE (95% CI 32·0–98·7) against RSV-associated lower respiratory tract illness with at least three signs or symptoms in older adults across one RSV season, leading to the US FDA Biologics License Application priority review for this indication in December, 2022.[117] Separately, the phase 3 MATernal Immunization Study for Safety and Efficacy (MATISSE) ceased enrolling participants after meeting one of two primary endpoints, with a VE of 81·8% (95% CI 40·6–96·3) against severe medically attended lower respiratory tract infection in infants in the first 90 days of life and 69·4% (95% CI 44·3–84·1) up to age 6 months.[118]

Smallpox and mpox (formerly known as monkeypox)

Licensed live-attenuated vaccines have been used as a surrogate for some pathogens when a direct challenge is unsafe or impractical. For example, in a phase 3 trial of modified vaccinia Ankara (MVA) non-replicating smallpox vaccine, the licensed and highly successful live-attenuated replication-competent vaccinia smallpox vaccine (ACAM2000) served both as a comparator vaccine and as a human challenge agent to evaluate efficacy of the investigational MVA product.[119] Two doses of MVA had 97·9% efficacy (95% CI 96·6–98·3) against cutaneous reaction to subsequent ACAM2000 vaccination (ie, localised vaccinia infection) compared with ACAM2000 only. Median cutaneous lesion area was 0 mm² in the MVA group and 76·0 mm² in the ACAM2000-only group. Geometric mean titre of neutralising antibodies was also equivalent at day 14 in the ACAM2000-only group compared with the MVA group.

MVA (JYNNEOS) was approved in 2019 for prevention of smallpox or mpox infection, and has been effective in combating the 2022 mpox outbreak: as of October, 2022, estimated incidence of mpox in 43 USA jurisdictions was ten times higher among unvaccinated people compared with fully vaccinated people.[120] An earlier study in 1970 people found 79% vaccine effectiveness (95% CI 24–94%).[121] Curiously, the phase 3 trial publication does not refer to the ACAM2000 challenge following MVA vaccination as a human challenge trial (or similar term), and FDA documentation does not refer to the human vaccine efficacy signal, instead preferring the immunogenicity data and efficacy in animal challenge studies.[122]

Down selection

Human challenge trials have helped to down select vaccine candidates for cholera, malaria, typhoid, *Shigella*, tuberculosis, *Streptococcus pneumoniae*, enterotoxigenic *Escherichia coli* (ETEC), and *Helicobacter pylori* (table 3). Early down selection limits the financial and opportunity costs associated with large field efficacy trials and the number of volunteers exposed to investigational products. Poor performance in a human challenge trial has also informed efforts to improve vaccine products: no ETEC vaccine candidates tested in human challenge trials have progressed beyond phase 2, but challenge trial results

have influenced the development of next-generation vaccines.[38,61] Human challenge malaria studies have also fulfilled a crucial role in vaccine development by down selecting antigens that show insufficient protection in CHMI studies to merit further development.[46,123]

The potential benefits of human challenge trials for down selection are well illustrated by a live oral hybrid *Shigella* vaccine candidate that performed badly in two human challenge trials: a VE of 36% against any illness when administering three doses (n=51) and 27% with four doses (n=21).[124,125] Simultaneously, a field trial of 1398 military recruits delivered no useful efficacy data because there were no cases of shigellosis during follow-up of up to 7 months.[33] Likewise, a BCG-booster vaccine—modified vaccinia virus Ankara vector expressing antigen 85A of *Mycobacterium tuberculosis* (MVA85A)—was tested in a human challenge trial with intradermal BCG as a surrogate challenge agent for tuberculosis. In a human challenge trial of 49 adults, MVA85A vaccination was not associated with additional reduction in skin biopsy mycobacterial load compared with repeat BCG.[50] MVA85A also had limited efficacy in field trials that conceivably might not have proceeded if human challenge trial results were already known.[51,52]

Correlates of protection

Immunological correlates of protection (CoP) can be helpful for vaccine development, allowing for comparisons between products and the prediction of efficacy (from immunogenicity) in new populations.[126] Post-vaccination samples from phase 3 trials might be used to identify CoP, but intensive sampling from participants in large field trials is not always feasible.[126] Human challenge trials are an ideal setting to explore CoP in great depth, although the broad generalisability of potential correlates emerging from challenge trials usually requires validation in a more natural field setting.

Considering enteric pathogens, in cholera human challenge trials, a four-fold or greater rise in vibriocidal antibody was observed to confer protection against subsequent infection. Seroconversion following vaccination (or infection) correlates with long-lasting protection against disease, although waning of the serum response suggests that the mechanistic correlate is mucosal.[127] In a typhoid fever human challenge trial, Vi IgA quantity and avidity after vaccination with Vi-tetanus toxoid conjugate or unconjugated Vi-polysaccharide vaccines correlated with protection from infection with *Salmonella* Typhi, and Vi IgG responses were associated with reduced disease severity.[128] Protection and disease severity after *Shigella* bioconjugate vaccination was associated with the lipopolysaccharide-specific serum IgG response.[30] Multidimensional principal component analyses of recent *Shigella* human challenge trials have highlighted that protective immune responses to *S sonnei* were predominantly mucosal compared with *S flexneri*, which induced balanced mucosal and serological responses.[129] In norovirus challenge trials, serum IgA, memory B-cell responses, and serum histo-blood group antigen blocking titres have been described as potential correlates of protection, although high post-vaccination histo-blood group antigen blocking titres in a more recent field trial of TAK-214 vaccine did not prevent all norovirus gastroenteritis.[26] Although there are no known CoP for ETEC, human challenge trials studying post-vaccination immune responses compared with challenge and homologous re-challenge have exposed a broader repertoire of immune responses beyond classic antigens.[130] In trials of pre-erythrocytic malaria vaccines, the level of circumsporozoite protein-specific antibodies is the key CoP,[131] whereas multifunctional T cells and γδ T cells are potentially important CoP.[132–34] The titre of haemagglutinin inhibition antibody was a predictor of efficacy for inactivated influenza vaccines tested in human challenge.[135] However, in human challenge trials evaluating alternative approaches to influenza vaccine design, protection does not correlate with haemagglutinin antibody response.[136,137]

Discussion

Towards a pathogen-specific and product-specific human challenge use case

The example of CVD-103-HgR cholera vaccine licensure as a travel vaccine can be considered an ideal human challenge research use-case: a restricted clinical spectrum of disease affecting groups matching the trial population, limited strain diversity with well characterised and conserved virulence factors, little pre-existing immunity in potential trial participants, an established immune correlate of protection, and an existing effective comparator vaccine. We have also highlighted human challenge trials that have successfully contributed to advancement of vaccines under less ideal conditions and show the importance of a focused pathogen-specific and product-specific rationale that eschews simplistic claims and explicitly engages with the limitations of human challenge research (table 1). In each case, these potential limitations should be assessed against limitations of alternative approaches to VE evaluation: in vitro and in silico studies, small and large animal studies, and phase 2/3 trials in naturally exposed populations.[138,139]

Warp speed human challenge trials to accelerate vaccine development

Comparison of fast-tracked COVID-19 pandemic vaccine development with the traditional slow vaccine development path, with or without incorporation of human challenge studies, are false dichotomies. Compared with COVID-19, virtually all priority diseases face potential barriers to development of new vaccines including the absence of decisive public investment made available during the COVID-19 pandemic and a highly motivated pathogen-naive population available for study recruitment.[10]

However, pandemic contingencies have led to reconsideration of established conservative vaccine development paradigms and have fostered debate over which transformative innovations can be implemented.[10,140] The role of human challenge research in accelerating vaccine development will depend on the feasibility and utility of the specific challenge model. The authors of a 2022 article entitled, *Delivering Pandemic Vaccines in 100 Days—What Will It Take?*, by the Coalition for Epidemic Preparedness Innovations, answered their rhetorical question without once referring to human challenge research, preferring to state the "use of early markers of immunity or in-vitro or computer-generated models to provide efficacy indications".[140] Separately, researchers have been working to identify and negotiate barriers to realising the full potential of human challenge as a scientific and strategic tool for all vaccine development.[141]

Harmonised and streamlined approaches for human challenge research might help to increase its effects. Regulatory oversights for human challenge strain manufacture and dose ranging clinical trials vary across jurisdictions. Oversight does not fall under national regulatory authorities in all countries and a lack of clear oversight mechanisms might be a barrier to model development, particularly in low-income and middle-income countries. Manufacturing challenge agents might not be possible in Good Manufacturing Practice facilities (eg, in cases where use of an intermediate vector for growth is required)[2] but the same principles of safe high-quality manufacture apply, as do Good Clinical Practice provisions in the conduct of human challenge trials to maximise participant safety and study results. Ideally, national regulatory authorities should provide standardised oversight and regulatory guidance on the manufacture and conduct of clinical trials for human challenge models, to streamline this process. The FDA recently published regulatory considerations for human challenge models to support vaccine development.[142] A consortium of global experts in human challenge including global regulators and representatives from Africa, Asia, the USA, and the EU have developed a document to guide manufacture of challenge agents for use in human challenge.[143] Among other improvements, the use of available technologies should be optimised—for example, metagenomic sequencing and other molecular approaches to test for adventitious agents and purity of the challenge agent. Platform manufacturing technology experience has also been highlighted to expedite production of variants of challenge agents (including evolving seasonal variants).[144] Accelerated dose-escalation schedules for establishing new challenge models could be used, similar to the first SARS-CoV-2 human challenge trial compared with previous schedules (eg, typhoid).[145] A study design incorporating challenge by natural exposure (to an infected person) has also been proposed as a means of obviating the need for dose-escalation studies and to address strain diversity, selection, and manufacturing timeline concerns.[12]

Further aspects that could enhance human challenge vaccine trial capability relate to infrastructure, investment in long-term programmes (rather than single studies), ethics, and public engagement. A biorepository of diverse, accessible, and well characterised challenge agents should be generated and made available to investigators in challenge centres that are ready to go with appropriate experience and biosafety capability. There should also be harmonised protocols that can be operationalised in multisite studies to shorten and maximise recruitment, ideally coordinating with vaccine manufacturers to design multi-arm trials, or composite phase 1–2 trials whereby participants go onto challenge after satisfactory safety assessment.[146] For models with 100% attack rates, challenge control groups might not always be required.[147] Rapid data collection, dissemination, and sharing is also important and would permit aggregation of results across trials.[115] Long-term programmes of families of pathogens with epidemic or pandemic potential, similar to the UK Common Cold Unit that operated from 1946 to 1989 (and completed key studies of coronaviruses), would enable rapid commencement of vaccine trials in an emergency. Guidance for early and effective public engagement with ethics committee members should also be developed. Continuing capacity building for ethical review of human challenge trials is a priority. Centralised credentialled ethics committees with specific expertise might even be established to expedite review in exceptional circumstances, such as a pandemic. Early and regular meetings between industry, research sponsors, and regulators will be necessary to realise this potential. Many of these steps to improve human challenge research would also boost its effects for the development of therapeutics, diagnostics, and non-pharmacological interventions.

Conclusion

Human challenge trials have evaluated vaccines against a wide range of pathogens, and their use is increasing. Well designed human challenge trials have already proven to be valuable: VE results in non-infected adult participants have translated well to phase 3 field trials, with notable exceptions (eg, live-attenuated influenza vaccine) that have emphasised the importance of standardising human models. Furthermore, down selection via fast and early failure of vaccines in human challenge trials has prevented major financial costs associated with unsuccessful late phase development, delivered important new knowledge to improve vaccines, and enabled focused resources on products that are more likely to succeed. Human challenge research is not a one size fits all proposition. Well considered pathogen-specific and product-specific human challenge use cases will only rarely permit dispensing with phase 3 field trials. Even then, human challenge research can reduce

Search strategy and selection criteria

References for this Review were retrieved through searches of OVID MEDLINE and PubMed up to April, 2022, using search terms to identify vaccine trials, AND "controlled human infection*" OR "experimental-infection*" OR "challenge*" OR "infection-model*" OR "volunteer*" OR "rechallenge*" (appendix p 29), combined with the names of pathogens known to have established challenge agents. Targeted searches were then performed to find further phase trials for vaccines tested in a human challenge trial. Clinical trials registries were searched to identify trials underway or with unpublished results. Relevant references cited in identified articles were also reviewed, as were references in the authors' personal files. Trials of prophylactic drugs (eg, monoclonal antibodies) and articles in languages other than English were excluded.

uncertainty early in vaccine development to decisively advance clinical development. The extent to which human challenge research can help to reimagine and transform vaccine development, as envisioned during the COVID-19 pandemic, will ultimately depend on whether the same optimistic spirit of innovation applied to deliver pandemic vaccines can also be applied to improve human challenge research in pandemics and non-pandemic circumstances alike.

Contributors

Y-NA and JO were responsible for the concept and study design. Y-NA performed the literature search, data collection and analysis, and prepared the initial draft. All authors contributed to the data interpretation and review, editing, and manuscript revisions. All authors are responsible for reported content and approve the manuscript as submitted.

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