

Strategic and scientific contributions of human challenge trials for vaccine

development: facts versus fantasy

Abo YN^{1,2,3} MBBS, Jamrozik E^{4,5} PhD, McCarthy J^{6,7} PhD, Professor, Roestenberg M⁸ PhD, Professor, Steer AC^{1,2,3} PhD, Professor, Osowicki J^{1,2,3} PhD

1. Tropical Diseases Research Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia
2. Department of Paediatrics, The University of Melbourne, Victoria, Australia
3. Infectious Diseases Unit, Department of General Medicine, Royal Children's Hospital Melbourne, Victoria, Australia
4. Ethox and Pandemic Sciences Institute, Nuffield Department of Population Health, University of Oxford, United Kingdom
5. Monash-WHO Collaborating Centre for Bioethics, Monash University, Victoria, Australia
6. Victorian Infectious Diseases Services, Royal Melbourne Hospital, Victoria, Australia
7. Department of Infectious Diseases, The University of Melbourne, Victoria, Australia
8. Controlled Human Infections Center, Leiden University Medical Center, The Netherlands

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Corresponding author: Dr Yara-Natalie Abo (yara-natalie.abo@rch.org.au)
Tropical Diseases Research Group
Murdoch Children's Research Institute
50 Flemington Rd, Parkville
Victoria, Australia, 3052

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Summary

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 critical knowledge gaps regarding transmission, pathogenesis, and immune protection. We review the track record of human challenge trials contributing to 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 impact of human challenge trials to accelerate vaccine development.

Key Points

- 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 may accelerate development of new vaccines by providing an early signal 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 each vaccine.
- The contribution of human challenge trials to vaccine development depends on pathogen- and product-specific factors that should be explicitly considered in designing models and trials.
- There is untapped potential for human challenge trials to have a greater impact in accelerating development of vaccines against high priority pathogens, in pandemic and non-pandemic settings.

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 subjects have participated in human challenge studies in 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 smallpox vaccination by Edward Jenner, who demonstrated 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-oncology phase I trials in which 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 case, where vaccine-strain pathogen transmission and attenuated disease may 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 (e.g., 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. Prior to 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 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 may accelerate vaccine development by improving efficiency in navigating these barriers. That hope 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, while 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 using a traditional vaccine development pathway turbocharged by pandemic contingencies, especially the very 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 ‘warp speed’ pandemic vaccine development has been juxtaposed with the slower deliberative approach taken towards

COVID-19 human challenge research – the first trial results were published in March 2022¹³ – raising questions regarding the usefulness of human challenge research for vaccine development.

Arguably the most commonly quoted benefit is that human challenge vaccine trials provide rapid early proof-of-concept for vaccine efficacy (VE), particularly for pathogens without known correlates of protection, at reduced cost and using relatively small groups 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. They may 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 may assess proxies for transmission potential. Human challenge vaccine trials do not depend on naturally occurring community transmission of a disease as in traditional phase II or III 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 individuals exposed to the risk of receiving an investigational product (active arm) or the risk of exposure without the protection of a potentially efficacious intervention (placebo arm).^{15 16} Some have also argued that human challenge vaccine trials may obviate the requirement for phase III trials (alongside expanded phase II field trials).^{12 17}

The facts

To describe the impact of human challenge research to vaccine development to date, a literature search was done (Box 1) to identify and link human challenge trials evaluating vaccines with the subsequent development trajectory for each vaccine product, in order to address facts versus fantasy regarding the contribution of human challenge to vaccine development. We first assess 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 or failure of all human challenge models for accelerating the development of all vaccine products in all circumstances (e.g., pandemic contingencies versus less urgent scenarios). The aim was to explore general and study-specific factors that make human challenge trials more or less useful for vaccine development, thus addressing the intrinsic limitations of human challenge research for vaccine development. Broadly, these limitations relate to generalisability concerns that can be organised under the headings: microbiological Strain diversity and selection; Syndrome, severity, and clinical endpoint alignment; Sample size and attack rate; Susceptibility (pre-existing immunity, age, setting); and Selecting-out effective vaccines (the “5 Ss”, Table 1).

We identified human challenge trials evaluating vaccine candidates for 19 pathogens. Human challenge trials of vaccine candidates targeting 7 pathogens have been followed by phase III and/or IV studies (Figure 1, appendix page 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).

Human challenge trial versus phase III/IV vaccine efficacy results by pathogen (Figure 1)

Cholera

Human challenge research has a long history in cholera vaccine development.¹⁸ The killed whole cell recombinant B-subunit cholera vaccine (Dukoral®) was tested in a human challenge trial in 1986, showing 64% VE against diarrhoea, comparable to several subsequent phase III and IV studies (VE 58% to 75%, Figure 1, appendix page 2).^{19 20 21 22 23 24 25 21}

Dukoral® is one of 5 currently licensed inactivated cholera vaccines, registered in more than 60 countries.²⁶ 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.²⁷

Recombinant live oral cholera vaccines have been evaluated in human challenge trials since 1988. In the first trial, the CVD 103-HgR vaccine demonstrated VE of 62%.²⁸ Several further human challenge vaccine trials were performed, including a 1992 study with VE of 91% against moderate-severe diarrhoea.²⁹ The safety, immunogenicity, and impact on patterns of *Vibrio cholerae* excretion and transmissibility for CVD 103-HgR was subsequently studied in placebo-controlled trials in endemic populations (6000 participants aged 12 months to 65 years).³⁰ These studies revealed that higher vaccine doses were required for seroconversion of participants in countries affected by endemic or epidemic cholera.³⁰ Subsequent field trials of higher dose CVD 103-HgR had mixed results, with VE of only 14% in a phase III trial in Indonesia that captured very few cholera cases,^{31 32} 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 2000.³³

Reinvigorated development of CVD 103-HgR (now VaxChora, Emergent BioSolutions[®]) was supported by a further human challenge trial, designed in consultation with the Food and Drug Administration (FDA), that included 101 healthy adult US volunteers. Vaccine efficacy was 90.3% (95% CI 61.7 – 100%) 10 days after vaccination and 79.5% at 3 months (95% CI 49 – 100%).^{32 34} In 2016, the FDA approved CVD 103-HgR for travellers aged 16 to 64 years, the first time the FDA had approved a vaccine based on human challenge trial results - although Canadian, Swiss, and Australian regulators had licensed the previous CVD 103-HgR product based on 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 2 years of age.²⁷ As discussed below, licensure of the CVD-103-HgR cholera vaccine for travellers based on human challenge trial 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 III or IV trials.

First, oral killed typhoid vaccine (Taboral[®]) failed to demonstrate protection in a 1971 human challenge trial (VE 6.7% after 6 doses and 29% after 12 doses).³⁵ Two phase III trials of oral killed typhoid vaccines in Delhi between 1968 and 1971 showed similar disappointing efficacy (VE 25% and 0%).³⁶

Second, live-attenuated oral Ty21a VE was 87% in an initial human challenge trial.³⁷ Live oral typhoid vaccines were licensed in 1989 in the US, after a large successful study where 1.4 million vaccine doses were administered.³⁸ Although VE in an endemic setting was lower

than in human challenge trials (cumulative VE of 50% at 2.5 to 3 years from 4 field trials including 235,239 adults and children),³⁸⁻⁴⁰ the challenge trials supported efforts toward 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 a WHO recommendation for TCV in children 6 months and older in endemic countries.⁴¹ Safety and durable (2 years) immunogenicity across age groups of Typbar TCV[®] was demonstrated in a large phase III trial in 2015⁴²; in parallel, TCV efficacy was demonstrated in a human challenge trial.⁴³ Jin et al demonstrated 54.6% (CI 26.8-71.8) VE against persistent fever or bacteraemia in a human challenge trial of 68 healthy typhoid-naïve adults. Post-hoc analysis using alternative diagnostic criteria of fever $\geq 38.0^{\circ}\text{C}$ preceding *S. typhi* bacteraemia showed a VE estimate of 87.1%.⁴³ Phase III trials of TCV among children aged 9 months to 16 years in Nepal, Malawi and Bangladesh demonstrated VE ranging from 79% to 85% against blood culture-confirmed infection.^{44 45 46 47} TCV has been introduced in Pakistan, Liberia and Zimbabwe.⁴⁴ In a cohort of 23407 children during a typhoid outbreak in Hyderabad, TCV effectiveness was 95%.⁴⁸

Shigella

Vaccines have been tested in *Shigella sonnei* and *flexneri* human challenge trials published since 1946.⁴⁹ One candidate completed phase III, and one is currently being tested in a phase II field trial (NCT04056117). Most of the 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

lyophilized streptomycin-dependent (SmD) live attenuated *S. flexneri* vaccine had VE of 48% against disease (oral temperature ≥ 100 F plus \geq four watery stools per 24 hours) in a human challenge trial including 118 prisoners.⁵⁰ This compared to 100% VE against homologous strain dysentery (defined as diarrhoea with two or more soft or liquid stools within 12 hours or a single soft or liquid stool containing blood, pus, or mucus) in 737 soldiers in the field,⁵¹ and a multi-strain SmD vaccine that also showed high VE in 7,281 children aged 2 to 8 years (*S. flexneri* 1/2a vaccine VE 91.2 % against disease with homologous strains, *S. flexneri* 3/*S. sonnei* vaccine VE 82%; endpoint was culture positive diarrhoea, defined as one or more bowel movements with liquid stool).⁵² Manufacturing difficulties prevented SmD vaccines from proceeding to licensure.⁵³

In 2017, experts convened to develop a uniform procedure to conduct *Shigella* human challenge studies,⁴⁹ including clinical and immunological end-points. These endpoint definitions allow for a broader definition of shigellosis and were used for the Flexyn2a conjugate vaccine human challenge study⁵⁴ that has progressed to a phase II 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 critical pathway for clinical development of antimalarial drugs and vaccines. There is ample evidence of reproducibility and safety, especially against the most important species *Plasmodium falciparum*,⁵⁵ and there has been development of a *Plasmodium vivax* model.⁵⁶

Sporozoite challenge by mosquito bite or, more recently, cryopreserved sporozoites, has been pivotal to development of 3 vaccines targeting the pre-erythrocytic stage of the parasite lifecycle, one of which has been registered and two in advanced clinical development. The first, RTS,S/AS01 (GSK Mosquirix®) consists of a portion of *P. falciparum* circumsporozoite protein (CSP) fused to hepatitis B virus surface antigen, assembled into virus-like particles and formulated with the AS01 adjuvant. In 2015 it received a positive opinion for use outside the European Union⁵⁷ and in 2021, the World Health Organization recommended the large-scale use of RTS,S/A01 for children living in areas with moderate-to-high malaria transmission.⁵⁸ Human challenge trials evaluated different doses, schedules, and adjuvants, finding VE of 12.5% to 86% in malaria-naïve adults (appendix, page 9). Phase II field trials that included infants and children in malaria endemic settings showed VE of 30% to 66%.⁵⁹⁻⁶² Vaccine efficacy in Phase III trials were 26% (infants aged 6- to 12-weeks) and 36% to 55% (infants aged 5- to 17-months).⁶³ Pilot implementation studies are underway in Ghana, Kenya and Malawi.⁶⁴

Other advanced candidates have been tested in human challenge but there are no comparative phase III results yet (Table 2).^{65 66} For the 3 most advanced vaccines, human challenge trials have informed adjuvant selection, vaccine schedule design, and route of immunisation. Consistently, VE for malaria-naïve adult CHMI participants in non-endemic settings has been higher than that observed in endemic populations (appendix page 9), suggesting immune imprinting from previous exposure is affecting vaccine responses. This 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.⁶⁷ A phase II human challenge trial with 60 participants reported VE of 85% for a trivalent cold-adapted live-attenuated vaccine.⁶⁸ Volunteers in this trial were pre-screened for serum hemagglutination-inhibition antibody titres of 1:8 or less against vaccine strains. In the subsequent phase III trial without pre-screening antibody tests and using different endpoints, VE was 9.6%.⁶⁹ Post-licensure studies in approximately 1 million US military personnel from 2004 to 2007 found 10.7% (95% CI, 2.7 to 18.1) to 20.8% (95% CI, 12.3 to 28.5) effectiveness for pneumonia or influenza endpoints.⁷⁰ The divergent findings 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 relatively less pre-existing immunity, are consistent with this observation: in a meta-analysis of 5 studies including children aged 6 months to 7 years, pooled VE was 83%.⁷¹

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 likely underpowered human challenge trial (22 participants, no confidence interval reported).⁷² Authors concluded that the trial supported further clinical development, and along with multiple immunogenicity studies, propelled the phase II and III trials which showed no efficacy in a combined 2998 participants.^{73 74} A subsequent human challenge trial of the candidate showed concordant poor efficacy of 2%,⁷⁵ and this result may 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 a number of other vaccine candidates, none of which has progressed to further development (Table 3). The 2021 Research and Development Roadmap for influenza vaccines outlines 4 milestones to optimise use of the model.⁷⁶ All can be applied to human challenge use in vaccine development more broadly, as discussed below.

Respiratory Syncytial Virus (RSV)

A bivalent RSV prefusion F subunit (RSVpreF) vaccine was evaluated in a phase IIa double-blind randomised placebo-controlled RSV-A human challenge trial that recruited healthy adults aged 18 to 50 years. Participants were pre-screened for RSV A–neutralizing antibody activity to enrich for increased RSV susceptibility. Vaccine efficacy was 86.7% (95% CI, 53.8 to 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.⁷⁷ The ongoing RENOIR phase III trial has reported 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 US FDA Biologics License Application priority review for this indication in December 2022.⁷⁸ Separately, the phase III ‘MATernal Immunization Study for Safety and Efficacy’ (MATISSE) ceased enrolling participants after meeting one of 2 primary endpoints, with 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 6 months of age.⁷⁹

Smallpox and mpox

Licensed live-attenuated vaccines have been used as a surrogate for certain pathogens where a direct challenge is unsafe or impractical. For example, in a phase III 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.⁸⁰ Two doses of MVA had 97.9% efficacy (95% CI, 96.6 to 98.3) against cutaneous reaction to subsequent ACAM2000 vaccination (i.e., localised vaccinia infection) compared to ACAM-2000 only. Median cutaneous lesion area was 0 mm² in the MVA group and 76.0 mm² in the ACAM2000-only group. Geometric mean titer of neutralizing antibodies was also equivalent at day 14 in the ACAM2000 only group and one dose of MVA.

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 U.S. jurisdictions is 10 times higher among unvaccinated compared to fully vaccinated individuals.⁸¹ An earlier study in 1,970 people found 79% vaccine effectiveness (95% CI 24 – 94%)⁸². Curiously, the phase III 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 this human vaccine efficacy signal, instead preferring the immunogenicity data and efficacy in animal challenge studies.⁸³

Down-selection

Human challenge trials have helped to down-select vaccine candidates for cholera, malaria, typhoid, *Shigella*, tuberculosis (TB), *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 II, but challenge trial results have influenced the development of next-generation vaccines.^{84 85} Human challenge malaria studies have also fulfilled a critical role in vaccine development by down-selecting antigens that show insufficient protection in CHMI studies to merit further development.^{86 87}

The potential benefits of human challenge trials for down-selection are well illustrated by the experience with a live oral hybrid *Shigella* vaccine candidate that performed poorly in two human challenge trials: VE of 36% against any illness using 3 doses (51 volunteers) and 27% with 4 doses (21 volunteers).^{88 89} 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.⁹⁰ Likewise, a BCG-booster vaccine - modified vaccinia virus Ankara vector expressing antigen 85A of *M. tuberculosis* (MVA85A) - was tested in a human challenge trial using intradermal BCG as a surrogate challenge agent for TB. In the human challenge trial of 49 adults, MVA85A vaccination was not associated with additional reduction in skin biopsy mycobacterial load compared to repeat BCG.⁹¹ MVA85A also had limited efficacy in field trials that conceivably may not have proceeded if human challenge trial results were already known.^{92 93}

Correlates of protection

Immunological correlates of protection (CoP) can be helpful to vaccine development, allowing comparison between products and prediction of efficacy (from immunogenicity) in new populations.⁹⁴ Post-vaccination samples from phase III trials may be used to determine

CoP, but intensive sampling from participants in large field trials is not always feasible.⁹⁴

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 4-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.⁹⁵ In a typhoid fever human challenge trial, Vi IgA quantity and avidity following 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.⁹⁶ Protection and disease severity after *Shigella* bioconjugate vaccination was associated with the lipopolysaccharide-specific serum IgG response.⁵⁴ Multi-dimensional principal component analyses of recent *Shigella* human challenge trials have highlighted that protective immune responses to *S. sonnei* were predominantly mucosal compared to *S. flexneri* which induced relatively balanced mucosal and serological responses.⁹⁷ 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.⁹⁸ Although there are no known CoP for ETEC, human challenge trials studying post-vaccination immune responses compared with challenge and homologous re-challenge has exposed a broader repertoire of immune responses beyond classical antigens.⁹⁹ In trials of pre-erythrocytic malaria vaccines, the level of circumsporozoite protein-specific

antibodies is the key CoP¹⁰⁰, while multi-functional T cells and $\gamma\delta$ T cells as potentially important CoP.¹⁰¹⁻¹⁰³ The titre of haemagglutinin inhibition antibody was a predictor of efficacy for inactivated influenza vaccines tested in human challenge.¹⁰⁴ However, [in human challenge trials evaluating alternative approaches to influenza vaccine design, protection has not correlated with haemagglutinin antibody responses..](#)^{105 106}

Discussion

Towards a pathogen- 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, to highlight the importance of a focussed pathogen- and product-specific rationale that eschews simplistic claims and explicitly engages with the limitations of human challenge research (see examples in Table 1). In every 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 II/III trials in naturally exposed populations.^{107 108}

‘Warp speed’ human challenge trials to accelerate vaccine development?

The 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. In comparison to COVID-19, virtually all priority diseases

face likely barriers to development of new vaccines including lack of the decisive public investment made available during the COVID-19 pandemic, and a highly motivated pathogen-naïve population available for study recruitment.¹⁰

However, pandemic contingencies have led to reconsideration of established conservative vaccine development paradigms, and have fostered debate over what transformative innovations can be implemented.^{10 109} Although the place of human challenge research in accelerating vaccine development remains uncertain, it will likely 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?’ from the Coalition for Epidemic Preparedness Innovations, answered their rhetorical question without once referring to human challenge research, preferring ‘use of early markers of immunity or in-vitro or computer-generated models to provide efficacy indications...’¹⁰⁹ 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.¹¹⁰

Harmonised and streamlined approaches for human challenge research might help to increase its impact. Regulatory oversight for human challenge strain manufacture and dose ranging clinical trials vary across jurisdictions. Oversight does not fall under national regulatory authorities (NRAs) in every country, and a lack of clear oversight mechanisms may be a barrier to model development, particularly in low- and middle-income countries.

Manufacturing challenge agents may not be possible in Good Manufacturing Practice (GMP) facilities (e.g. 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, NRAs should provide standardised oversight and regulatory guidance on manufacture and conduct of clinical trials for human challenge models to streamline this process. The US FDA recently published regulatory considerations for human challenge models to support vaccine development.¹¹¹ A consortium of global experts in human challenge, including global regulators and representatives from Africa, Asia, USA and the EU, have developed a document to guide manufacture of challenge agents for use in human challenge.¹¹² Among other improvements, use of available technologies should be optimised, for example, metagenomic sequencing and other molecular approaches for testing for adventitious agents and purity of the challenge agent. ‘Platform manufacturing technology experience’ has also been pointed to as a way to expedite production of variants of challenge agents (including evolving seasonal variants).¹¹³ Accelerated dose-escalation schedules for establishing new challenge models could be used, as was done for the first SARS-CoV-2 human challenge trial compared to previous schedules (e.g., typhoid).¹¹⁴ 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 programs (rather than single studies), ethics and public engagement. Ensuring that a biorepository of diverse, accessible, and well-characterised challenge agents is generated and available to investigators in challenge centres that are ready to go with appropriate experience and biosafety capability; harmonised protocols that can be operationalised in multi-site studies to shorten and maximise recruitment, ideally coordinating with vaccine manufacturers to design multi-arm trials, or composite phase I-II trials where participants go onto challenge after satisfactory safety assessment.¹¹⁵ For models with 100% attack rates, challenge control groups may not always

be required.¹¹⁶ Rapid data collection, dissemination, and sharing is also important and would permit aggregation of results across trials.⁷⁶ Long-term programs on 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, including 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 impact for 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: vaccine efficacy results in healthy adult participants have translated well to phase III field trials, with notable exceptions (e.g., live-attenuated influenza vaccine) that have emphasised the importance of standardising human models; 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 focussing resources on products more likely to succeed. Human challenge research is not a ‘one size fits all’ proposition. Well-considered pathogen- and product-specific human challenge use cases will only rarely permit dispensing with phase III field trials. Even then, human challenge research can reduce uncertainty early in vaccine development to decisively advance clinical development. The extent to which human

challenge research can help to re-imagine 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.

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Table 1. The 5 Ss – Limitations of human challenge vaccine trials

Generalisability concerns	Examples	Mitigation/Comment
Strain diversity and selection		
The selected challenge strain/s may not be representative of naturally circulating strains or evolving seasonal variants, so that vaccine efficacy against the challenge strain/s cannot be reliably extrapolated.	For some pathogens (e.g., <i>Vibrio cholerae</i>) there is relatively limited diversity among strains principally responsible for human disease. More extensive strain diversity is most relevant where it affects the vaccine antigen/s, for example, the <i>Streptococcus pneumoniae</i> capsular polysaccharide targeted by successive generations of multivalent vaccines.	Challenge strains should be selected according to a pathogen- and product-specific rationale, considering molecular epidemiology (vaccine antigens, virulence factors). Multiple strains may be introduced to broaden a model's scope and to evaluate homologous and heterologous protection (as done for cholera, malaria, <i>Shigella</i> , ETEC). 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 may 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).	Some pathogens induce a limited spectrum of disease, e.g. cholera and typhoid. For other pathogens (e.g. influenza and RSV) the use of different endpoints led to significantly different vaccine efficacy results between HC and field trials.	Challenge models must be relevant, with clinical, microbiological, and immunological outputs that contribute meaningfully to development of vaccines against a particular pathogen.
If challenge trials do not use clinically relevant endpoints fit for use in late-stage field trials, comparison (and correlation) of results is difficult.		All reasonable efforts should be made to determine endpoints that can be consistently applied across clinical trials. In some cases, consensus endpoints may flow 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 vaccine efficacy. However, if a too-high inoculum or a too-invasive challenge procedure is used to achieve the desired attack rate, vaccine-induced protection may be overwhelmed.	Exposure to a <i>P. falciparum</i> 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 <i>Shigella sonnei</i> vaccine (using same strain as previous trials) and a <i>Helicobacter. pylori</i> 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) may 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, setting)		
Volunteers in HC vaccine trials may differ from the target population with regard to comorbidities, immunity, age, immunogenetics, and microbiome, all of which may influence vaccine efficacy.	Cholera VE differed in participants in endemic vs non-endemic settings, resulting in specific licensure of CVD 103-HgR as a travel vaccine. HC trials of PfSPZ malaria vaccine and Ty21a live attenuated typhoid vaccines in adults demonstrated higher efficacy than in later phase trials in children, particularly infants, while HC trials of the intranasal live attenuated influenza vaccine demonstrated lower efficacy among adult participants compared to field trials in children. Conversely, oral killed cholera vaccine, typhoid conjugate vaccines, RTS,S malaria vaccine and the MVA85A BCG booster vaccine candidate all demonstrated similar VE in adult HC vaccine trials compared to paediatric phase II/III trials. RSV vaccine performance was similar in HC trials in young healthy adults and field trials in adults > 60 years.	There are increasing efforts to promote HC development in endemic settings. HC vaccine trials have been carried out in endemic settings for <i>Shigella</i> , <i>Plasmodium falciparum</i> and <i>P. vivax</i> . A single-sex <i>Schistosoma mansoni</i> HC 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- and vaccine-specific characteristics. HC has been usefully applied to assess vaccines targeting children and older populations. Correlates of protection from human challenge may also be applied to phase III trials. RSV human challenge has also been safely carried out in older susceptible populations. 'Traditional' vaccine trial selection criteria also do not address all of these variables
Selecting out an effective vaccine candidate		

Developers may be concerned that HC trials will inadvertently down-select vaccines that would have been successful in the field against natural exposure.

The available examples suggest this concern may 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 HC trials have still progressed to licensure (e.g. RTS,S malaria vaccine).

HC 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. HC trials will usually not be a true go/no go stage gate for vaccine development. Early involvement of regulators and industry may help boost the impact of HC vaccine trials, ensuring that the model is fit for purpose.

Table 2. Vaccines tested in human challenges trials with field trials planned, or in progress

Pathogen	Human challenge trial vaccine efficacy	Current status
Malaria		
Live attenuated Pf sporozoite (pyrimethamine prophylaxis) ¹¹⁷	87.5%	Entering phase III in Bioko Island
R21 in matrix-mTM adjuvant ¹¹⁸	81.8%	VE 80% high dose adjuvant n = 409 children 5 - 17 months Burkina Faso. ⁶⁵ Further phase III underway NCT4704830
Dengue		
TV003 live attenuated tetravalent ¹¹⁹	100%	Phase III trial in participants aged 2 – 59 years in Brazil underway (NCT02406729)
RSV		
Recombinant Ad26.FSV.preF ¹²⁰	45.8%	Phase II field 80% ¹²¹
MVA-BN-RSV - modified vaccinia Ankara vector genetically engineered to encode the RSV F, G(A), G(B), N, and M2-1 proteins ¹²²	88.5%	Phase III commenced (NCT05238025)
Norovirus		
Bivalent GI.1/GII.4/alum TAK214 ¹²³	100% (severe disease)	Phase II field trial n = 2357, VE 61.8% mod-severe disease ⁹⁸ Phase II dose-finding completed in children ¹²⁴
Rotavirus		
Monovalent P2-VP8-P[8] ¹²⁵	52% (reduction in shedding*)	A trivalent version of this vaccine is under ongoing development ¹²⁶
Shigella		
Flexyn2a conjugate ⁵⁴	52% (severe disease)	Phase I/II field trials of multivalent candidate in Kenya underway (NCT04056117)
Human challenge vaccine trials in progress		
<ul style="list-style-type: none"> 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) 		

*using live-attenuated vaccine as challenge agent

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

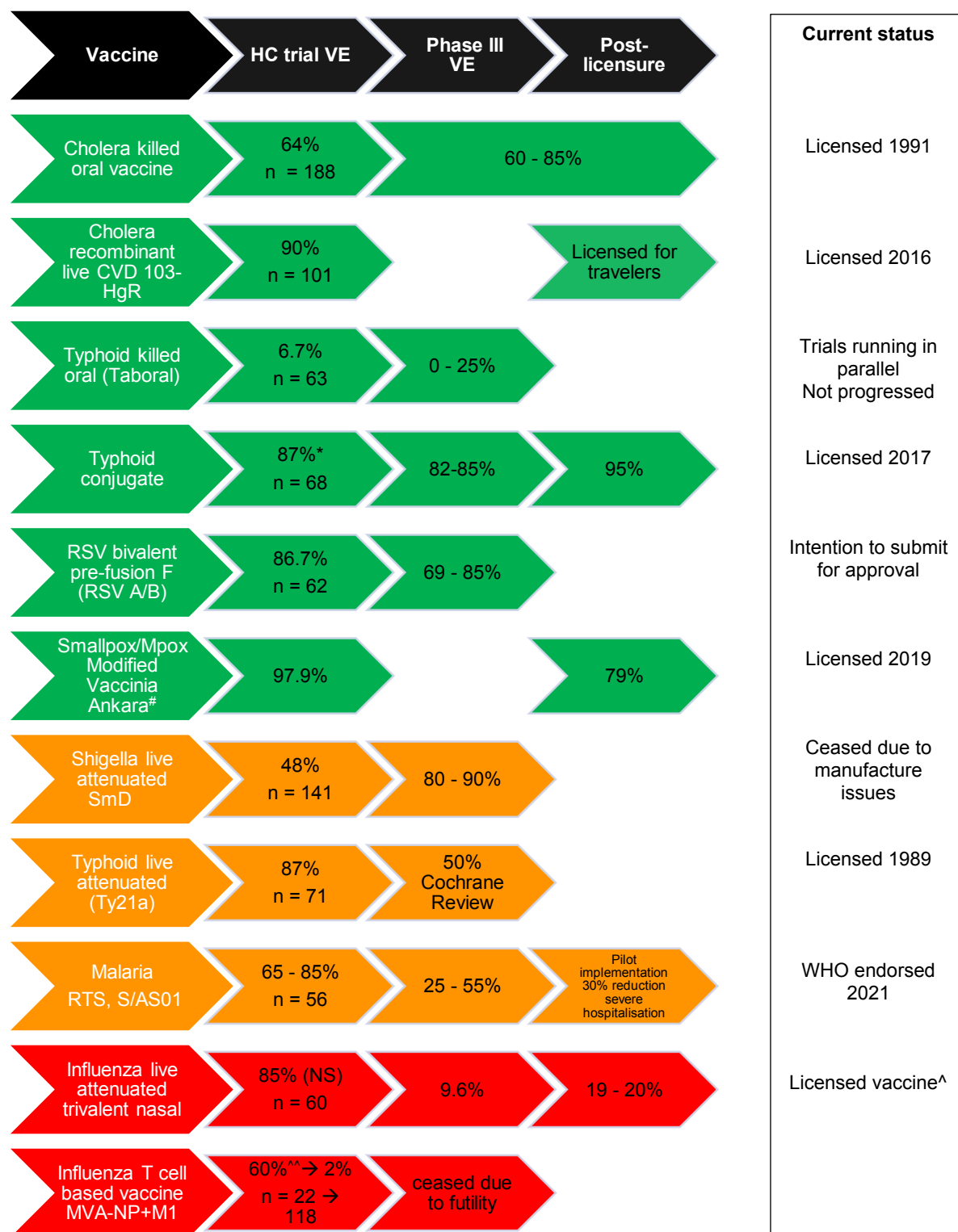
Pathogen and vaccine candidate	Human challenge trial result		Phase II field trial (if applicable) / comment
	vaccine efficacy	vaccine vs control	
<i>Salmonella enterica</i> serovar Typhi			
M01ZH09 (Darton 2016) ¹²⁵	13%	18/31 vs 20/30	N/A
<i>Shigella</i>			
<i>E. coli-Shigella flexneri</i> 2a hybrid vaccine EcSfa-1 and EcSfa-2 (Dupont 1972) ³⁶	36% (any disease, 3 doses)	9/30 vs 10/21	Study in 1398 military recruits could not evaluate efficacy as there were no cases over 2.5-7 months follow up (Mel 1965) ¹²⁶
	27% (4 lower doses)	10/16 vs 12/14	
Live attenuated <i>S. flexneri</i> 2a SC602 (Coster 1999) ¹²⁷	100% (severe syndromes)	0/7 vs 6/7	Vaccine induced fever in 20% of participants. Field immunogenicity trials did not match immunogenicity results in <i>Shigella</i> -naïve HC trial participants (Rahman 2011) ¹²⁸
Live attenuated <i>S. sonnei</i> (WRSS1) (Pitisuttihum 2016) ¹²⁹	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 <i>S. sonnei</i> vaccine (1790GAHB) (Frenck 2021) ¹³⁰	-9.8%	15/33 vs 12/29	A next-generation quadrivalent vaccine, altSonflex1-2-3 (<i>S. flexneri</i> 1b, 2a, 3a, and <i>S. sonnei</i>) with higher O-antigen is currently being tested in a phase 1/2 clinical trial (NCT05073003).
Enterotoxigenic <i>Escherichia coli</i> (ETEC)			
Type 1 somatic pili (Levine 2019) ⁸⁵	67% (1800/1800mcg)	2/6 vs 7/7	Unacceptable reactogenicity (1800/1800mcg), unacceptable purging in several participants (1800/900mcg). No VE demonstrated with lower challenge inoculum or against heterologous challenge strain that expressed antigenically identical type 1 somatic pili
	43% (1800/900mcg)	3/6 vs 7/8	
CFA/II fimbriae			
Oral purified (Levine, 2019) ⁸⁵	No efficacy (strain H10407 and H1765)	5/6 vs 5/6 5/6 vs 5/6	
Polymer microspheres, purified CFA/II fimbriae (Tacket 1994) ¹³¹	30%	7/10 vs 10/10	
Inactivated fimbriated whole cell vaccines (Evans 1988) ¹³²	78% (homologous challenge) no efficacy (heterologous strains)	2/10 vs 8/9	
Formalin inactivated whole-cell fimbriated ETEC (Levine, 2019) ⁸⁵	33%	2/5 vs. 6/10	Underpowered study.
Live fimbriated, toxin-negative ETEC (prototype live oral vaccine E1392-75-2A) (Levine 2019) ⁸⁵	75% (heterologous strain)	3/12 vs 6/6	Prototype further developed below.
Multivalent ETEC vaccine ACE527 (Darsley 2012) ¹³³	26.6% (any disease) 41% (severe diarrhoea)	15/29 vs 19/27	Adjuvanted below.
ACE527 with double mutant heat labile toxin adjuvant (Harro 2019) ¹³⁴	65.9% (severe diarrhoea)	3/13 vs 21/31	Did not progress due to lack of funding.
Further trials reviewed here: Levine, Barry, Chen 2019 ⁸⁵			
<i>Helicobacter pylori</i>			
Recombinant <i>H. pylori</i> antigens	22%	6/19 vs 6/15	N/A

(VacA, CagA, NAP)/alum (Malfertheiner 2018) ¹³⁵			
Recombinant Ty21a vaccineexpressing <i>H pylori</i> antigens (Ty21a(pUreA/B) (Aebischer, 2008) ¹³⁶	33%	6/9 vs 4/4 (pilot)	N/A
HP0231 (Ty21a(pHP0231) (Aebischer, 2008) ¹³⁶	No efficacy	12/12 vs 20/21	N/A
Malaria			
Plasmodium falciparum			
AMA-1/AS02A or AS01B (Spring 2009) ¹³⁷	0%	16/16 vs 6/6	Phase II natural infection in Malian children 7.6% (NS) at 24 months 1-6 year old Malian children (Laurens 2013) ^{*138}
FMP21/AS01 (apical membrane 1 ag) (Payne 2016) ⁸⁷	0% No impact on parasite multiplication rate (PMR)	12/12 vs 15/15	N/A
AMA1-C1/ Alhydrogel + CPG.7909 (Duncan 2011) ¹³⁹	0% - no difference in PMR	5 vs 3 16 fold vs 17 fold reduction in PMR	N/A
PEV3A alone, or PEV3A+FFM ME- TRAP (Thompson 2008) ¹⁴⁰	no sterile immunity lower rates of parasite growth		N/A
Further CHMI trials reviewed by Choy 2022 ⁸⁶ , Shibeshi 2021 ¹⁴¹ and Duffy, Gorres 2020 ¹⁴²			
Plasmodium vivax			
Soluble recombinant protein VMP001/AS01B (Bennet, 2016) ¹⁴³	0%	27/27 vs 6/6	
BCG/TB			
MVA85A BCG-booster vaccine (Harris, 2014) ¹⁴⁴	No efficacy (against mycobacterial load on skin biopsy)	13 vs 11 (BCG naïve) 12 vs 13 (BCG exposed)	17% QFT conversion 32/1399 vs 39/1395 4-6 months old in Cape Town (Tameris 2013) ^{94*}
			32.8% 650 HIV infected adults, 2 doses (Ndiaye 2015) ^{93*}
Influenza			
Recombinant Protein Influenza A vaccine (D protein) (Fries 1993) ¹⁴⁵	41.6%	7/15 vs 12/15	<i>No further studies found</i>
PMED influenza DNA vaccine (Jones 2009) ¹⁴⁶	41% (any illness with or without fever) 53% (Upper respiratory tract infection)	10/27 vs 17/27 7/27 vs 15/27	<i>No further studies found</i>

Inactivated trivalent proteosome (Lambkin-Williams 2016- studies occurred in 2003 and 2004) ¹⁴⁷	100% and 85% febrile illness with seroconversion; 66% and 43% against any illness (15microg x2, 30 microg x2 regimens)	0/19 vs 0/38 vs 9/45	<i>No further studies found</i>
FLU-v peptide vaccine (Pleguezuelos 2020) ¹⁴⁸	40.6% 1 dose 33% 2 dose	13/40 (FLU-v x1) vs 15/40 (FLU-v x2) vs 23/42	<i>No further studies found</i>
VXA.A1.1 adenovirus vectored tablet vaccine (Liebowitz 2020) ¹⁴⁹	39.5% against influenza positive illness	17/58 vs 15/31	<i>No further studies found</i>
<i>Streptococcus pneumoniae</i>			
Recombinant protein subunit vaccine with 3 recombinant T cell antigens GEN-004	Entered HC trial in 2014 (NCT02116998) ¹⁵⁰	<i>Trial did not meet primary endpoint of efficacy (personal communication Daniela Ferreira)</i>	
<i>Rickettsia rickettsii</i>			
Formalin inactivated (Clements, 1983) ¹⁵¹	25%	12/16 vs 6/6	N/A

*Field trials were underway prior to HC challenge trial. CHMI, controlled human malaria infection

Figure 1. Vaccine efficacy in Human Challenge trials compared to Phase III/IV results



HC, human challenge; VE, vaccine efficacy; n, number of participants

Green – concordant HC trial and further phase trial results; orange – higher or lower HC trial vs further phase trial results; red – markedly higher HC trial vs further phase trial results.

*post-hoc analysis.

#Challenge using replicating-vaccinia smallpox vaccine ACAM2000, VE measured against attenuation of major cutaneous reaction, labelled a phase III trial

^efficacy demonstrated in children prior to adult HC trial

^^Initial influenza T cell-based vaccine HC trial likely underpowered, subsequent challenge study occurred after the phase III trial

Further details of trials including references see text and appendix page 2

Box 1. Search strategy

References for this review were retrieved through searches of Ovid Medline and pubmed, from inception to April 2021 using search terms to identify vaccine trials, AND ‘controlled human infection*’ or experimental-infection* or challenge* or infection-model* or volunteer* or rechallenge* (exact search strategy in appendix page 30), combined with pathogens known to have established challenge agents. 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 (e.g. monoclonal antibodies) and articles in languages other than English were excluded.

Appendix - Abo YN, et al. Strategic and scientific contributions of human challenge trials for vaccine development: facts versus fantasy

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Appendix Table 1. Vaccine efficacy in human challenge vaccine trials compared to phase III/IV results

	HCT VE (healthy adults in non-endemic setting unless stated) n (vaccine) vs n (control)	Phase II natural infection VE	Phase III VE (CI) n, population, doses	Post-licensure / real world (e.g. after WHO prequalification (CI) effectiveness
Cholera				
Killed oral cholera vaccines				
killed whole cell vaccine	56% (against diarrhoea), 100% (diarrhoea > 2L) 3/9 vs 6/8 ¹ (Black 1987)		58% (CI 16-79), 52% 3 year cumulative (nil CI) for cases seeking medical care 63498 Bangladeshi children aged 2 - 15 y and women > 15 y, 3 doses (Clemens 1986) ²	
killed whole vibrio-B subunit vaccine	64% (against diarrhoea), 100% (diarrhoea > 2 L) 4/11 vs 7/7 (Black 1987) ¹		85% (CI 62-94), 50% 3 year cumulative 63498 Bangladeshi children aged 2 - 15 y and women > 15 y, 3 doses No immunity children 2 - 5 yr at 3 yr f/up (Clemens 1990) ³	78% (CI 39-92) Mozambique mass vaccination, case control non-pregnant > 2 year olds, 2 doses, 5 month follow up (Lucas 2005) ⁴
			85% (CI 36 - 97) 1563, 18-65y Peruvian military recruits, 6 month f/up, 2 doses (Sanchez 1994) ⁵	
			minus 4% 1 year, 2 doses 60.5% (CI 28-79) 1 year, 3 doses, 72% > 15 yo n = 21,924 2-65y Peruvians (Taylor, 2000) ⁶	79% (CI 47 - 92) Zanzibar mass vaccination, cohort analysis 23921 non-pregnant > 2 year olds, 2 doses, 15 month follow up. Evidence of herd protection. (Khatib 2012) ⁷
Recombinant live oral cholera vaccines				
CVD 103-HgR	62% (against diarrhoea) 2/6 vs 7/8 (Levine 1988) ⁸		14% (lower CL minus 24) at 4 years 67,508 2 - 41 yrs Indonesia, 1 dose Orochol-E Evidence of herd immunity possibly confounding results (Richie, 2000) ⁹	79% (CI 71.9-84.6) Micronesia mass vaccination program during an outbreak, non-pregnant > 2 year olds (Calain 2004) ¹⁰

	100% (against diarrhoea) 0/14 vs 10/15 (Tacket 1992) ¹¹			
	80% (against diarrhoea) 5/28 vs 21/23 (Tacket 1999) ¹²			
	90.3% 10 days (61.7-100), 79.5% 3 months (49-100) (against mod-severe diarrhoea) 2/35 vs 39/66 (Chen, 2016) ¹³			
Salmonella enterica serovar typhi				
Killed oral typhoid vaccine				
Monovalent killed oral typhoid vaccine (Taboral)	6.7%, 6 doses 14/35 vs 12/28 29.7%, 12 doses 8/21 vs 13/24 (NS) (Dupont, 1971) ¹⁴		25% (NS) 100x10 ⁹ dose (x3) (44/6060 vs 60/6248) No efficacy 300x10 ⁹ dose (x3) 52/6136 vs 49/6428 24872 children below 17 yrs in India (Chuttani 1972) ¹⁵	
Live attenuated				
Ty21a	87% 2/28 vaccinees vs. 23/43 controls (Gilman, 1977) ¹⁶		96% at 36 months (77-99) 32000 school children Egypt, 3 doses (Wahdan 1982) ¹⁷	
			67% (CI 47-79) at 3 years 109 000 6 - 21 year olds Chile, 3 doses (Levine, Black, Ferreccio 1987) ¹⁸	
			29% (CI 4-47) at 24 months, single dose 59% (CI 41-71) at 24 months, 2 dose 82543 6 - 21 year olds, Chile ¹⁸	

			42% (CI 23-57) at 30 months, 3 doses weekly (vs 2nd daily as above studies) 20543 3 - 44 year olds Indonesia ¹⁹	
			50% (CI 35 - 61) Cochrane review ²⁰ of cumulative efficacy at 2.5 - 3 years including Wahdan 1980, Levine 1987, Levine 1990, Simunjata 1991	
M01ZH09	13% CI -29 to 41 18/31 vs 20/30 (Darton 2016) ²¹	DOWN-SELECTED		
Typhoid conjugate			Blood culture confirmed typhoid fever	
Vi-TT typhoid conjugate vaccine	54.6% (CI 26·8–71·8) 13/37 vs 24/31 <i>*Post-hoc analyses of alternative diagnostic criteria, of fever of 38·0°C or higher preceding S Typhi bacteraemia resulted in vaccine efficacy estimates of 87·1% (Jin 2017)²²</i>		81.6% (CI 61·9-88·5) at 1 year 79·0% (CI 58.8 to 91.8) at 2 years Nepal, 9 m to <16y individually randomised, n = 20 019 (Shakya, 2019; Shakya, 2021) ^{23 24}	
			83.7% (CI 64.2 to 89.6) at 18-24 months Malawi, individually randomised 9 m to < 13 y, n = 28 052 (Patel, 2021) ²⁵	
			85% (CI 76 to 91) at average 17 months Bangladesh, cluster randomised 9 m to < 16y, n = 67395 (Qadri 2021) ²⁶	
Salmonella enterica serovar paratyphi				
Live attenuated oral				
CVD1902	Phase II commenced May 2022 (ISRCTN15485902)			
Norovirus				

GI.1 intranasal	VE 47% (CI 15-67) 14/38 vs 27/39 Norwalk virus homologous challenge (Atmar 2011) ²⁷		further research was directed to preparing a combination vaccine	
Bivalent GI.1/GII.4/alum intramuscular TAK214	22% against gastroenteritis any severity 13/50 vs 16/48 100% against severe diarrhoea (0/50 vs 4/48, secondary endpoint) Norovirus Cin1 strain (heterologous) (Bernstein 2015) ²⁸	61.8% (CI 20.8-81.6) against moderate to severe norovirus acute gastroenteritis 18-49y Navy recruits, n = 2357, 10 vs 26 cases. Evidence of cross genotype protection (Sherwood 2020) ²⁹		
Shigella				
monovalent lyophilized streptomycin-dependent (SmD) <i>S. flexneri</i> 2a	48% (NS) 16/53 vs 52/88 (Dupont 1972) ³⁰	100% Yugoslavian soldiers, n = 736 (Mel 1965) ³¹		did not progress to licensure for widespread use due to difficulties in large scale manufacture and process control
bivalent lyophilized streptomycin-dependent (SmD) <i>S. flexneri</i> 1 and 2a			91.2% homologous disease 7281 Yugoslavian children 2 - 8 y (Mel 1971) ³²	
bivalent lyophilized streptomycin-dependent (SmD) <i>S. flexneri</i> 3 and <i>S. sonnei</i>			82% homologous disease 7281 Yugoslavian children 2 - 8 y (Mel 1971) ³²	
mutant-hybrid Shigella- <i>E. coli</i> (MH)	25% (NS) 30/68 vs 52/88 (Dupont 1972) ¹⁴	DOWN-SELECTED		
PGAI 42-1-15 hybrid live vector	no efficacy 27/57 vs 20/51 (Levine, Woodward 1977) ³³	DOWN-SELECTED		

E. coli-Shigella flexneri 2a hybrid vaccine EcSfa-1 and EcSfa-2	36% 3 doses, against any illness 9/30 vs 10/21 27% 4 lower doses^ 10/16 vs 12/14 (Kotloff 1995 and 1992) ^{34 35}	No cases Study in military recruits was attempted, however there were no cases of S. flexneri over 2.5-7 months follow up amongst 1398 volunteers so efficacy could not be evaluated (Cohen 1997) ³⁶	Not progressed	
Attenuated S. flexneri 2a SC602	100% against severe fever, dysentery or severe symptoms 0/7 vs 6/7 vaccine induced fever in 20% of participants - narrow safety margin (Coster 1999) ³⁷	Safety and immunogenicity trial - acceptable safety, minimal immunogenicity 88 adults and 79 children 8-10 years in Bangladesh (Rahman et al 2011) ³⁸	No further studies found	
Live attenuated S. sonnei (WRSS1)	40% (nil CI) any disease 3/10 vs 5/10 Thai adults (Pitiisuttihum 2016) ³⁹		No further studies found	
Conjugate vaccine				
Flexyn2a - bioglycoconjugate S. flexneri 2a monovalent	30.2% (CI 15 - 63) against shigellosis 13/30 vs 18/29 51.7% (CI 5.3 to 77.9) against more severe shigellosis 8/30 vs 16/29 (Talaat 2021) ⁴⁰	Phase I/II clinical trial in Kenya (NCT04056117) underway		
Outer membrane particle - Generalized Modules for Membrane Antigens (GMMA)				
GMMA-based S. sonnei vaccine (1790GAHB)	No efficacy minus 9.8 (minus 98 - 33) 15/33 vs 12/29 (Frenck 2021) ⁴¹	no further trials found, likely DOWN-SELECTED		
ETEC – Enterotoxigenic Escherichia coli				
At least 11 vaccine HC trials, all resulting in down-selection and reviewed here: Levine, Barry, Chen 2019 ⁴²				
Type 1 somatic pili				

	67% VE (2/6 vaccinees vs 7/7 controls) with unacceptable reactogenicity 1800/1800mcg; 43% VE (3/6 vaccinees vs 7/8 controls) with unacceptable purging in several participants 1800/900mcg; no VE demonstrated with lower challenge inoculum no VE against heterologous challenge strain that expressed antigenically identical type 1 somatic pili ⁴²	DOWN-SELECTED		
CFA/II fimbriae				
Oral purified	No efficacy H10407 (5/6 vaccinees vs 5/6 controls) strain H1765 (5/6 vaccinees vs 5/6 controls) Levine 2019 ⁴²	DOWN-SELECTED		
Polymer microspheres, purified CFA/II fimbriae	30% 7/10 vaccinees vs 10/10 controls (Tacket 1994) ¹¹	DOWN-SELECTED		
Inactivated fimbriated whole cell vaccines	78% homologous challenge (2/10 vaccinees vs 8/9 controls) no efficacy against heterologous strains (Evans 1988) ⁴³	DOWN-SELECTED		
Formalin inactivated whole-cell fimbriated ETEC	33% underpowered HC trial showing diarrhoea in 2/5 vaccinees vs. 6/10 controls (Levine 2019) ⁴²	DOWN-SELECTED		

Live fimbriated, toxin-negative ETEC (prototype live oral vaccine E1392-75-2A) PROTOTYPE	75% VE against diarrhoea (heterologous strain expressing the same CS1 and CS3 fimbriae as the vaccine; 3/12 vaccinees vs 6/6 controls) (Levine 2019) ⁴²	prototype further developed below		
Multivalent ETEC vaccine ACE527	26.6% (CI -13 – 52) moderate to severe diarrhoea 15/29 vs 19/27 post hoc analysis showing 41% VE against severe diarrhoea measured by volume of grade 3 – 5 stool > 800g (Darsley 2012) ⁴⁴	adjuvanted below		
ACE527 with double mutant heat labile toxin adjuvant	65.9% (3/13 vaccinees vs 21/31 controls, wide CI 5.4 to 87.7) against severe diarrhoea (Harro 2019) ⁴⁵	not currently under further development***		
Rotavirus				
Monovalent P2-VP8-P[8] - live attenuated vaccine challenge	57% reduction in shedding 162 South African infants at 6, 10, and 14 weeks of age. (Chilengi 2020) ⁴⁶	Phase II of a trivalent version - Groome et al 2020, no efficacy data.		
Helicobacter pylori				
Recombinant <i>H. pylori</i> antigens (VacA, CagA, NAP)/alum	22% 6/19 vs 6/15 (Malfertheiner 2018) ⁴⁷	DOWN-SELECTED		
Recombinant Ty21a vaccines expressing <i>H. pylori</i> urease A and B subunits (Ty21a(pUreA/B)) or	Pilot: 33% 6/9 vs 4/4 infection week 6 post vaccination (Aebischer, 2008) ⁴⁸	DOWN-SELECTED		
HP0231 (Ty21a(pHP0231))	No efficacy 12/12 vs 20/21 (Aebischer, 2008) ⁴⁸	DOWN-SELECTED		

Plasmodium falciparum				
Recombinant protein (anti-infection vaccine, pre-erythrocytic)				
RTS,S/alum and RTS,S/alum/MPL	0% and 25% 6/6, 6/8 vs 2/2 controls (Gordan 1995) ⁴⁹			
RTS,S	12.5% vaccine 1 RTS,S/SBAS4 7/8 29% vaccine 2 RTS,S/SBAS3 5/7 86% vaccine 3 RTS,S/SBAS2 1/7 vs 6/6 controls (Stoute 1997) ⁵⁰ minimal protection at 6 m rechallenge (Stoute 1998) ⁵¹	71% (CI 46–85) first 9 weeks follow-up 0% (–52 to 34) in the last 6 weeks 306 men aged 18–45 years in The Gambia 47% (CI 4–71) at 9 week follow-up after fourth dose on year later (n=158) (Bojang 2001) ⁵²		
RTS,S/SBAS2	41% (CI 22%–56%) 41 vaccinees (various doses) vs 23 controls (Kester 2001) ⁵³			
RTS, S /AS01B	50% (CI 32.9-67) 18/36 vs 24/24 (Kester 2009) ⁵⁴			
RTS,S/AS02A	32% (CI 17.6–47.6) 30/44 vs 24/24 (Kester 2009) ⁵⁴	29.9% (CI 11.0–44.8) first clinical episode per protocol, 6 months 57.7% (CI 16.2–80.6) severe malaria Mozambique in 2022 children aged 1–4 years. 3 doses (Alonso, 2004) ⁵⁵		
RTS,S/AS01E		49% (CI 26 to 65) ITT, median 8 months follow up clinical malaria 894 children 5 - 17 months old Kilifi, Kenya, and Korogwe, Tanzania 3 doses (Bejon, 2008) ⁵⁶		

		61.6% (CI 35.6–77.1) 1, 2, 3 month schedule, first malaria episodes 1 year after dose three 63.8% (CI 40.4–78.0) 0, 1, 7 month schedule 511 6-10 week olds Ghana, Tanzania, and Gabon (Asante 2011) ⁵⁷		
		65.9% (CI 42.6-79.8) at 3 month follow up 214 infants less than 18 weeks of age (Aponte, 2007) ⁵⁸		
RTS,S/AS01	65% (CI 29.4–80.1) (6/16) 0, 1, 2 month third fractional dose schedule 87% (CI 66.8–94.6) (4/30) 0, 1, 7 month delayed third fractional dose schedule) (Regules 2016) ⁵⁹		55% (CI 50.5%–59.3%) 5 - 17 months of age, 12 months follow up, 3 doses 36.3% (CI 31.8 – 40.5), 5 – 17 months of age, 48 months follow up, 4 doses 25.9% (CI 19.9-31.5), 6-12 week olds, 38 months follow up, 4 doses 18.3% (11.7-24.4), 3 doses. N=15,459, seven countries in sub-Saharan Africa (RTS,S Clinical Trials Partnership, 2015) ⁶⁰ VE waned over 7 year f/up - 4.4% (CI - 17 – 21.9) (Olotu 2016) ⁶¹	Pilot implementation in endemic countries Ghana, Kenya and Malawi commenced 2019 Reduction of 30% in severe malaria hospital presentations (95% CI 0.55, 1.09), 21% reduction in hospital admissions with positive malaria result (95%CI 7,32%) and results not yet powered to detect a difference in mortality, across the first 2 years of implementation (SAGE report 2021) ⁶²
R21/MM	81.8%; n=11; p=0.0009 sterile efficacy Three doses given 4 weeks apart (Venkatraman 2017 ⁶³ , conference abstract no further details)	71% (95% CI 60 to 78) in the low-dose adjuvant group and 80% (72 to 85) in the high-dose adjuvant group n = 409 children aged 5 - 17 months in Burkina Faso, 2 year follow up (Datoo, 2022) ⁶⁴		

Live attenuated PfSPZ (AIV)				
PfSPZ by mosquito bite with chloroquine prophylaxis	100% 0/10 vs 5/5 (Roestenberg 2009) ⁶⁵			
PfSPZ by IVI and DVI	66% (6/9, 4 doses) vs 3D7 homologous challenge 100% (6/6, 5 doses) vs 3D7 5/6 controls (Seder 2013) ⁶⁶ - lower doses not efficacious, nor against PfNF54 strain)			
	92% (CI 48.0, 99.8) (12/13, 5 doses)-homologous, 70% at 24 weeks 80% (CI 10.4, 99.5) (4/5, 4 doses)-heterologous, 10% at 24 weeks 86.7% (CI 35.9, 98.3) - homologous 22/22 controls (Epstein 2017) ⁶⁷	<u>Phase I/II natural infection in Malian adults</u> 29% (exploratory endpoint) 5 doses 27/41 vs 37/40 (Sissoko 2017) ⁶⁸		
	20% (4/20) at 3 weeks, 5 doses 100% (4/4) at 24 weeks, 5 doses (Jongo 2018) ⁶⁹ Tanzanian males 18 - 35 yrs	<u>Phase II natural infection in Kenyan infants 5 - 12 months old</u> 3 different doses -6.5% at 6 months, highest dose 45.8% against clinical malaria at 3 months (exploratory endpoint), highest dose n= 336 (Oneko 2021) ⁷⁰		
	27% at 15 weeks (5/15 vs 6/7) 3 doses (Jongo 2021) ⁷¹ Equatoguinean adults			

		<u>Phase II natural infection in adults in Burkina Faso (10x dose)</u> 38% at 6 months (P= 0.017) and 15% at 18 months (0.078) (Sirima 2022) ⁷²		
PfSPZ-Cvac (chloroquine prophylaxis)	33 - 67% depending on dosing schedule (Mordmuller 2017) ⁷³		To enter phase III in Bioko Island	
	55% at 14 weeks (8/13 vs 6/7) 3 doses (Jongo 2021) ⁷¹ Equatoguinean adults			
	77% heterologous, 3 doses (increased dose) 3/13 vs 5/5 (Sulyok 2021) ⁷⁴			
	100% (CI 54-100) heterologous (high dose) 0/6 vs 12/12 (Mwakingwe-Omari, 2021) ⁷⁵			
PfSPZ-Cvac (pyrimethamine)	87.5% (CI 42.5-100) homologous (high dose) 78% (CI 29.8-100) heterologous (1/8 and 2/9 vs 12/12) (Mwakingwe-Omari 2021) ⁷⁵			
Blood stage vaccines				
AMA-1/AS01B	0% (16/16 vs 6/6) (Spring 2009)	<u>Phase II natural infection in Malian children</u> 7.6% (NS) at 24 months 1-6 year old Malian children (Laurens 2013)	NOT PROGRESSED**	
FMP21/AS01 (apical membrane 1 ag)	0% 12/12 vs 15/15 No impact on parasite multiplication rate (Payne 2016)			

AMA1-C1/ Alhydrogel + CPG.7909	0% - no difference in parasite multiplication rate 5 vs 3 volunteers (Duncan 2011) P			
Combination B (MSP1/MSP1/RESA)	No difference in parasite growth rate in malaria naïve individuals - clearly stated that this did not preclude possibility of impact of much higher paraistaemia found in people living in endemic regions or that it may boost the pre-existing immunity in these people. (Lawrence 2000)	<u>Phase II natural infection PNG children</u> 62% reduction in parasite densities (CI 13-84) n=120, 5 - 9 yrs 3D7 parasite subtype infections reduced (vaccine variant), no protection against FC27 infections (Genton 2002, Genton 2003)		
ChAd63-MVA Vectored				
ChAd63-MVA CS	6% sterile protection 20% delay in time to treatment 69-79% reduction in liver parasite burden 14/15 vs 6/6 (Hodgson 2014) ⁷⁶	See below		
ChAd63-MVA ME-TRAP	13% sterile protection 33% delay in time to treatment 79-84% reduction in liver parasite burden 13/15 vs 6/6 (Hodgson 2014) ⁷⁶	<u>Phase II natural infection Sengalese adults</u> 8% 12/57 vs 13/58 controls (CI - 100% to 59%) (Mensah 2016) ⁷⁷ (underpowered due to low number of infections, 8 week follow-up)	No further studies found	
	21% sterile protection 11/14 vs 6/6 36% delay in time to patency (Ewer 2013) ⁷⁸	<u>Phase II natural infection Kenyan adults</u> 67% (CI 33 - 83) over 8 weeks f/up 11/61 vs 28/60 n = 121 (Ogwang 2015) ⁷⁹ pooled efficacy Mensah and Ogwang 50%	No further studies found	

		Phase II natural infection children Burkina Faso 13.8% (CI -42.4-47.9) at 6 months, 3.1% by Cox regression (CI -15 to 18) against clinical malaria episode. N = 424, 5- 17 months old (Tiono 2018) ⁸⁰	No further studies found	
PEV3A alone, or PEV3A+FFM ME- TRAP	no sterile immunity lower rates of parasite growth (Thompson 2008) ⁸¹			
Further CHMI trials reviewed by Choy 2022 ⁸² , Shibeshi 2021 ⁸³ and Duffy, Gorres 2020 ⁸⁴				
Plasmodium vivax				
P. vivax radiation attenuated sporozoite				
	42% 7/12 vs 2/2 Duffy-positive , healthy adult Columbians protected (Arévalo-Herrera 2016) ⁸⁵			
Soluble recombinant protein				
VMP001/AS01B	0% 27/27 vs 6/6 (Bennet, 2016) ⁸⁶	DOWN SELECTION	Further trials not found	
Dengue				
TV003	100% 0/21 vs 20/20 (Kirkpatrick 2016) ⁸⁷	phase II trials in children and adults in Bangladesh and Thailand are awaited (NCT02678455 and NCT02332733)	results of the phase III trial of single dose TV003 (selected by Butantan-Merck for further development and manufacture ⁶²) in 2-59 yr olds in Brazil commenced in 2016 (NCT02406729).	
Schistosoma				
CHI exists, not used in vaccine trial to date ⁸⁸				

Hookworm				
Attenuated <i>Necator americanus</i> hookworm larvae	Phase I challenge trial fewer larvae per gram of faeces in vaccine group (median larvae per g 0.8 [IQR 0.00 to 3.91] vs 10.2 [5.1 to 18.1]; p=0.014) (Chapman 2021) ⁸⁹	ongoing development		
	Phase II HC completed recruitment, estimated completion August 2022 NCT 03172975	ongoing development		
Influenza				
Recombinant Protein Influenza A vaccine (D protein)				
Recombinant Protein Influenza A vaccine (D protein)	41.6% (NS) 7/15 vs 12/15 (Fries 1993) ⁹⁰		No further trials found	
Trivalent live cold adapted (CAIV-T)				
	85% (NS) low HA ab titre at baseline 2/29 vs 14/31 (Treanor 1999) ⁹¹		9.6% (against episode of febrile illness, NS) 373/2833 vs 207/1420 17% (against severe febrile illness, 2ndry) Nil efficacy in 50-64 y 4561 healthy adults 18-64 (Nichol 1999) ⁹²	10.7 (95% CI, 2.7 to 18.1) to 20.8 (95% CI, 12.3 to 28.5) ~1 million US military personnel across 2004-2007 influenza seasons against health care encounters resulting in a primary diagnostic code consistent with pneumonia or influenza (non vaccine naive) (Wang 2009) ⁹³
Inactivated trivalent proteosome				
	100% and 85% febrile illness with seroconversion; 66% and 43% gainst any illness (15microg x2, 30 microg x2 regimens) 0/19 vs 0/38 vs 9/45 (Lambkin-Williams 2016) ⁹⁴ although studies occurred in 2003 and 2004)		No further trials found	
DNA vaccine - PMED influenza DNA vaccine				

	41% (CI-1.5, 67.7) for 'Any illness with or without fever' 53% (CI = 8.0, 77) for 'Upper respiratory tract infection' 10/27 vs 17/27 7/27 vs 15/27 (Jones 2009) ⁹⁵		No further trials found	
T-Cell–Based Influenza Vaccine				
MVA-NP+M1	60% (no CI or stats in methods) 'symptoms plus viral shedding' 2/11 vs 5/11 less symptoms and less days of viral shedding (Lillie 2012) ⁹⁶	No efficacy (against moderate to severe symptoms in ILI episodes) underpowered MVA-NP+M1 plus QIV in > 65 yr olds (INVICTUS) Stopped after one season due to change in recommended annual flu vaccine n = 846 participants (Butler 2021) ⁹⁷	Follow up trial below -	
			No efficacy (against lab confirmed flu or ILI) MVA-NP+M1 vs placebo n = 1077 vs 1075, adults 18 and over Stopped due to futility (Unpublished - NCT03880474, results posted April 2021)	
	649.7 vs 726.1 hour*Log10 viral particles/ml degree of nasal shedding by qPCR 43/71 vs 29/47 virologically confirmed ILI (VE 2%, 2ndry outcome) 18-65y (Unpublished, NCT03883113, results posted March 2021)			
Peptide vaccine				

FLU-v (lyophilized vaccine composed of four short peptides; FLU-5 (32aa), FLU-7 (21aa), FLU-8N (20aa), and FLU-10 (24aa))	40.6% 1 dose 33% 2 dose FLU-v x1: 13/40 MMID FLU-v x2: 15/40 vs 23/42 (Pleguezuelos 2020) ⁹⁸		No further trials found	
Monovalent tablet vaccine				
VXA.A1.1 (adenovirus vectored)	39.5% (CI -4 - 65) against influenza positive illness 17/58 vs 15/31 (Leibowitz 2020) ⁹⁹		No further trials found	
<i>Streptococcus pneumoniae</i>				
GEN-004	entered a phase IIa human challenge trial in 2014, completed in 2016; results have not been published (NCT02116998)	DOWN SELECTION - Trial did not meet primary endpoint of efficacy (personal communication Daniela Ferreira)		
Prevenar 13 (post licensure CHIM)	model has been used to demonstrate pneumococcal conjugate vaccine as the gold standard against which to test novel vaccines: 6B pneumococcal colonisation acquisition was reduced by 78% in Prevenar-13 (PCV) vaccinated adults compared with control subjects and those colonised had significantly lower colonisation density (Collins, 2015) ¹⁰⁰	N/A		
RSV				
Recombinant adenovirus vectored - Ad26.FSV.preF Janssen	1o median VL-AUC (area under the curve) qRT-PCR: 0.0 versus 236.0 (nil CI) 2o 45.8% (-1.0, 73.8) against 'liberal illness' (Sadoff 2021) ¹⁰¹	80% (94.2% CI, 52.2–92.9%), 75% (50.1–88.5%), and 69.8% (43.7–84.7%) for case definition 1, 2, and 3 against LRTI N = 5782 older adults > 65 y (Falsey 2023) ¹⁰²	ongoing trials	

MVA-BN-RSV vaccine is based on the modified vaccinia Ankara vector and genetically engineered to encode the RSV F, G(A), G(B), N, and M2-1 proteins	88.5% (CI: 14.8%; 98.5%) (viral culture) 58.7% (CI -17.6 to 85.5%) 4/30 vs 10/31 (Jordan 2022 pre-print) ¹⁰³	Phase III commenced (NCT05238025)		
bivalent prefusion F vaccine (RSV A and B antigens) Pfizer	86.7% (CI 53.8 - 96.5) (PCR confirmed plus at least one symptom from two categories or one grade 2 symptom from any category) viral load: 0 vs 96.7 median VL-AUC n = 2/31 vs 15/31 (Schmoele-Thoma 2022) ¹⁰⁴		85% RENOIR n = 24,966 adults > 60y. Defined by analysis of three or more RSV-associated symptoms (Papi, 2023) ¹⁰⁵ 81.8% MATISSE n = 7,128 maternal immunisation for infants - VE against severe medically attended lower respiratory tract illness due to RSV in infants from birth through the first 90 days of life with high efficacy VE 69.4% through the first six months of life (Kampmann, 2023) ¹⁰⁶	
BCG/TB				
MVA85A BCG-booster vaccine	No efficacy (against mycobacterial load on skin biopsy) (Harris, 2014) ¹⁰⁷	17% QFT conversion 32/1399 vs 39/1395 4-6 months old in Cape Town (Tameris 2013) ¹⁰⁸	Not progressed*	
		32.8% 650 HIV infected adults, 2 doses (Ndiaye 2015) ¹⁰⁹		
Streptococcus pyogenes				
M1 protein + Al(OH) ₃ +RL	89% (CI 23-98) 3 doses 1/19 vs 12/25 (Fox 1973) ¹¹⁰	Further development halted due to safety concerns, later revoked by the FDA		
Aerosol spray mucosal vaccine M1 protein + thimerosal + RL	68% (CI 28-86) 3 doses 5/21 vs 17/23 (Polly 1975) ¹¹¹			

SC (M3 + M12 + AI + RL)	45% 9/20 vs 15/36 (D'Alessandri, 1978) ¹¹²			
Mucosal (M3 + M12 + thimerosal + RL)	21% 6/28 vs 15/36 (D'Alessandri) ¹¹²			
SC M3	21% 6/28 vs 15/36 (D'Alessandri) ¹¹²			
Mucosal M3	25% 3/12 vs 15/36 (D'Alessandri) ¹¹²			
SC M12	46% 6/13 vs 15/36 (D'Alessandri) ¹¹²			
Mucosal M12	19% 3/16 vs 15/36 (D'Alessandri) ¹¹²			
<i>Rickettsia rickettsii</i>				
Formalin-inactivated	25% 12/16 vs 6/6 (Clements, 1983) ¹¹³	DOWN SELECTION		
Smallpox/mpox				
Modified vaccinia ankara	97.9% (attenuation of ACAM2000 cutaneous reaction) (95% CI, 96.6 to 98.3) n= 400 (Pittman 2019) ¹¹⁴			1,970 people found 79% vaccine effectiveness (95% CI 24 – 94%) Arbel et al 2022 ¹¹⁵

*trials running in parallel.

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Appendix 2. Search strategy details

1. exp *Vaccines/im, ae
2. exp *Immunization/
3. (vaccine or vaccines).tw,kf.
4. 1 or 2 or 3
5. Healthy Volunteers/ or Human Experimentation/
6. (experimental-infection* or challenge* or infection-model* or volunteer* or rechallenge* or (controlled-human adj3 infection*)).tw,kf.
7. 5 or 6
8. ((safety or efficacy or infection* or immunity or protection) and (human or humans or child* or paediatric* or pediatric* or boy or boys or girl or girls or adult or adults or man or men or male* or woman or women or female* or volunteer* or student* or subject*)).tw,kf,hw.
9. *safety/ or vaccine efficacy/ or *infections/im
10. ae.fs.
11. 8 or 9 or 10
12. Double-Blind Method/ or clinical trials as topic/ or exp clinical trial/
13. (trial or trials or phase-1 or phase-I or phase-2 or phase-II or phase-3 or phase-III).tw,kf.
14. vaccine development/ or exp drug development/ or drug discovery/
15. 12 or 13 or 14
16. 4 and 7 and 11 and 15
17. (vaccine-efficacy and (human or humans)).tw,kf,hw.
18. 4 and 15 and 17
19. 16 or 18
20. limit 19 to (case reports or editorial or guideline or practice guideline)
21. 19 not 20

22. limit 21 to english language
23. 22 AND [name of pathogen or syndrome of interest known to have an established challenge model]