

TITLE PAGE

Title: What defines an efficacious COVID-19 Vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

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SUMMARY

The novel coronavirus SARS-CoV-2 has been responsible for more than 800,000 deaths in the first six months of the pandemic as well as huge economic and social upheaval internationally. An efficacious vaccine is essential to prevent further morbidity and mortality. Although some countries may deploy COVID-19 vaccines on the strength of safety and immunogenicity data alone, the goal of vaccine development remains to gain direct evidence of vaccine efficacy in protecting humans against SARS-CoV-2 infection and/or disease so that manufacture of those with proven efficacy can be selectively upscaled. A candidate vaccine against SARS-CoV-2 may act against infection, disease or transmission, and a vaccine capable of reducing any of these elements may play a role in disease control. However, the most significant efficacy endpoint, protection against severe disease and death, is difficult to assess in Phase III clinical trials. In this review, we explore the challenges in assessing the efficacy of candidate COVID-19 vaccines, the caveats needed to interpret reported efficacy endpoints and provide insight into answering the seemingly simple question, 'Does this COVID-19 vaccine work?'

INTRODUCTION

The novel coronavirus SARS-CoV-2 has been responsible for more than 800,000 deaths in the first six months of the pandemic(1) as well as huge economic and social upheaval internationally.(2) An efficacious vaccine is considered essential to prevent further morbidity and mortality.(3) To date, 34 candidate COVID-19 vaccines are in clinical assessment and 142 are in pre-clinical development utilising a range of vaccine platforms.(4) In this unprecedented pandemic, vaccine development is time critical and considerable collaborative efforts are being expended to expedite pre-clinical and clinical assessment of candidate vaccines.(5) The cost to manufacture and internationally deploy an efficacious COVID vaccine will be vast and the process at risk of politicisation.(3) Although some countries may deploy COVID-19 vaccines on the strength of safety and immunogenicity data alone, the goal of vaccine development remains to gain direct evidence of vaccine efficacy in protecting humans against SARS-COV-2 infection and/or disease(6) so that manufacture of those with proven efficacy can be selectively upscaled.

In their Target Product Profile for COVID vaccines, the WHO suggested that a “*clear demonstration of efficacy (on a population basis) ideally with ~ 50% point estimate*” should be a minimum criterion for any acceptable COVID vaccine, and that efficacy may be assessed against, ‘*disease, severe disease, and/or shedding/transmission*’ endpoints.(7) This definition is necessarily non-specific and reflects the complexities of assessing the clinical efficacy of candidate vaccines in the context of a novel pathogen. Indeed, a COVID-19 vaccine capable of reducing any of these elements might play a role in disease control where there are no proven prophylactic medications and few treatments.(8) The US Food and Drug Administration (FDA) recently suggested efficacy against COVID-19 disease or SARS-CoV-2 infection are appropriate primary endpoints for vaccine efficacy studies, with an

endpoint estimate of at least 50% for placebo-controlled efficacy trials.(6) However, protection against severe disease and death is extremely difficult to assess in Phase III clinical trials due to the unfeasibly large numbers of participants required. Instead, data to address this endpoint may only be available from large Phase IV trials or epidemiological studies conducted after widespread deployment of a vaccine.

In this review, we explore the challenges in assessing the efficacy of candidate SARS-CoV-2 vaccines, the caveats needed to interpret reported efficacy endpoints and provide insight into answering the seemingly simple question, ‘Does this COVID-19 vaccine work?’

DEFINING VACCINE EFFICACY

Many different endpoints are used in vaccine research to define efficacy depending on the pathogen, consequences of infection and transmission dynamics. Commonly, outcome data from randomised controlled trials (RCTs) is presented as a proportional reduction in disease between vaccinated and control subjects to calculate a vaccine-attributable reduction.(9) Outcomes may include reduction in infection (assessing sterilising immunity), severity of resultant clinical disease (assessing disease modifying immunity)(9) or duration of infectivity(10). Such RCTs represent ‘best case scenarios’ of vaccine efficacy under idealised conditions in particular populations and provide key data necessary for vaccine licensure. However, vaccine efficacy does not always predict vaccine effectiveness – the protection attributable to a vaccine administered non-randomly under field conditions.(11) For example, the effectiveness of rotavirus vaccines in children in low- and middle-income settings was lower than the efficacy observed in children in high-income countries.(12) RCTs may not predict protection gained indirectly from herd protection (sometimes called ‘herd immunity’) following widespread vaccine deployment. Equally,

RCTs conducted in a particular age group or geographical setting may not predict effectiveness if more widely deployed. It is possible that alternative vaccine platforms or the addition of adjuvants are required for adequate immunogenicity in older age groups, as for influenza vaccines.(13) For this reason, prospective studies of vaccine effectiveness in 'real-world' scenarios post-licensure are routinely needed.

In the case of SARS-CoV-2, an efficacious vaccine may prevent infection, disease or transmission (Figure 1). The outcome of SARS-CoV-2 infection in individuals is heterogenous and dependent on multiple variables including age, sex, ethnicity and co-morbidities.(14) On an individual level, the consequence of infection can range from pauci-symptomatic states to hospital admission, requirement for respiratory support and death.(14) Transmission dynamics of SARS-CoV-2 are not yet fully understood but the ability of infected individuals to transmit infection when asymptomatic or in a pre-symptomatic period means that if infection control strategies focus solely on preventing transmission from symptomatic individuals, this will be insufficient alone to interrupt transmission of SARS-CoV-2.(15)

The impact of an efficacious vaccine on the course of the SARS-CoV-2 pandemic is complex and there are many potential scenarios post-deployment. The ability of a vaccine to protect against severe disease and mortality is the most important efficacy endpoint as hospital and critical care admissions place the greatest burden on health care systems. However, the beneficial effects of such a vaccine on a population may only be observed if the vaccine is efficacious in older adults and wide-spread distribution of the vaccine, including those most vulnerable to disease, is achieved. High coverage amongst these risk groups would have the greatest impact against disease endpoints. Alternatively, vaccines

that do not impact on clinical course but reduce the transmissibility of SARS-CoV-2 could still be valuable interventions on a population level.

STUDY DESIGN OF SARS-CoV-2 VACCINE EFFICACY TRIALS

Provided SARS-CoV-2 is circulating, comparison of clinical endpoints between vaccinated participants and an unvaccinated comparator group in a RCT is the most efficient study design to demonstrate vaccine efficacy.⁽⁶⁾ While vaccines candidates may be assessed in isolation,⁽⁴⁾ the WHO and US FDA suggest an adaptive trial design, evaluating multiple vaccine candidates in parallel against a single placebo group, may be an acceptable method to increase efficiency, provided the trials are sufficiently powered.^(6, 16)

Studies that rely on natural exposure to SARS-CoV-2 are vulnerable to multiple variables that influence whether a vaccinee is exposed to SARS-CoV-2 and then whether exposure leads to infection (Figure 2). For example, older participants may be more likely to avoid social gatherings or use public transport, reducing their likelihood of exposure to SARS-CoV-2. However, health-care workers (HCWs) may not only be more likely to be exposed to SARS-CoV-2, but may also receive higher infecting doses than other participants in the study. Alternatively, by virtue of their recognised 'high-risk' occupations, HCWs may have better access to protective strategies such as personal protective equipment (PPE) than other participants, reducing the likelihood of infection following exposure. These complex, and difficult-to-control behavioural variables are such that blinded randomisation of participants between vaccine and comparator groups is important to ensure reliable assessment of efficacy outcomes.

Efficacy studies must be adequately powered to meet efficacy endpoints and multiple variables inform these calculations, including local transmission rates and

participant characteristics. For example, severity of COVID-19 disease and mortality rates vary according to age, sex and ethnicity with higher rates of hospitalisation, critical care admissions and death in older individuals, men and individuals of Black, Asian and minority ethnic groups.(14) For illustrative purposes, if a Phase III efficacy study only enrolled participants aged 20-29 years, the low expected mortality rate in this population would require an unfeasibly large sample size to adequately power the study to assess mortality as an endpoint, and is reliant on a high level of transmission to meet other efficacy endpoints (Table 1). Selection of older participants with higher rates of mortality, for example those >80 years old could reduce this number (Table 1). However, given that such participants, especially those with comorbidities, are more likely to socially ‘shield,’ they may be less likely to be exposed to SARS-CoV-2 and so a mortality efficacy endpoint may still not be met. Indeed, recruitment of older participants in vaccine trials has historically been challenging;(17, 18) recent Cochrane reviews of Influenza vaccine studies listed 52 RCTs in healthy adults with participants predominately aged 16-65 years, but only 8 RCTs in adults >65 years old,(19, 20) despite the higher burden of disease in older adults. Given mortality from SARS-CoV-2 disproportionately affects older adults, it is important that enrolment of older participants in COVID-19 vaccine trials is actively pursued via targeted engagement, minimizing inconvenience to participants and proactive sharing of study results.(21, 22)

Dedicated trials will be needed to assess COVID-19 vaccines in individuals < 18 years old as trial data in adults may not be predictive of vaccine safety and efficacy in this age group. However, since children are relatively less affected by COVID-19 disease, substantial safety data must be collected from adults, and greater understanding of the biology of Paediatric Multisystem Inflammatory Syndrome temporarily associated with SARS-CoV-2 infection acquired, before paediatric vaccine studies are initiated.(23)

Incidence of SARS-CoV-2 infection varies hugely, with hot spots and surges occurring in an unpredictable fashion.(1) This has a considerable impact on study sample sizes for efficacy endpoints (Table 1), especially as infection rates are highly likely to change over the study follow-up period. For these reasons, assessment of vaccine efficacy against mortality is non-viable in current Phase III clinical trials. However, as the pandemic spreads internationally and other variables such as poverty and restricted hospital care contribute to higher rates of severe disease in certain populations, clinical trials with smaller numbers of participants may be able to provide some measure of efficacy. Alternatively, pooling of data from multiple trials that were not originally configured as a network of sites could mean efficacy endpoints are met earlier, and conclusions about the efficacy of candidate vaccines reached sooner.(24) This assumes trial protocols can be sufficiently aligned and may come at the expense of loss of statistical power if heterogeneity exists between trials.(25)

Whilst SARS-CoV-2 vaccine efficacy against mortality may not be measured directly in clinical trials, it may be deduced from other endpoints. For example, an RCT efficacy study of a live rotavirus vaccine including more than 69,000 participants, mostly in high-income countries, demonstrated 95% efficacy against severe disease in vaccinees(26) (of note this sample size was chosen for safety rather than efficacy endpoints). Whilst this study and others did not provide direct data on vaccine efficacy against mortality,(27) this could be conjectured, and following a WHO recommendation for the widespread introduction of rotavirus vaccination,(28) significant declines in mortality from diarrhoeal illness were seen.(29)

Asymptomatic SARS-CoV-2 infection is a less important endpoint clinically. However, if prevention of asymptomatic infection were shown to be a surrogate endpoint for efficacy against clinical disease or transmission, this could allow earlier estimation of the clinically

relevant efficacy of a vaccine using a reduced sample size. Indeed, such an approach is already utilised for the assessment of pneumococcal vaccines, where the ability of a vaccine to prevent colonisation with vaccine serotypes is increasingly used as a surrogate measure of efficacy of vaccines against pneumococcal disease.(30)

As the incidence of SARS-CoV-2 falls, the time required to meet efficacy endpoints increases. This can be countered by increasing the size of the study (Table 1), however such a strategy increases the number of individuals exposed to the risks of receiving an investigational product pre-licensure. When the incidence is low, data on vaccine efficacy against infection and mild disease may still be collected in outbreak situations. For example, a 'ring vaccination' study design may be employed, which relies on tracing and vaccinating contacts, and contacts of contacts, of a confirmed case. Vaccination may be performed immediately or after 21 days and can provide a rapid efficacy measure if appropriately powered.(31) This study design was used to demonstrate the efficacy of an rVSV vectored Ebola vaccine (rVSV-ZEBO) during the Ebola outbreak in Guinea, when no cases were confirmed among contacts vaccinated immediately compared to 16 cases in the delayed vaccination group.(32) However, for this study design to successfully assess SARS-CoV-2 vaccine efficacy, robust diagnostic and contact tracing pathways as well as rapid inducement of protective immunity post-vaccination would be needed. Given the respiratory route of transmission and the short incubation period of SARS-CoV-2, it is unlikely this study design would be a feasible means of assessing SARS-CoV-2 vaccine efficacy.

It is claimed that there is a relatively slow rate of mutation and phylogenetic diversification of SARS-CoV-2.(33) This, combined with the selection of conserved antigens for the majority of COVID-19 vaccine candidates,(4) means that vaccine efficacy detected

against a particular circulating variant of SARS-CoV-2 in one region is likely to predict efficacy in other parts of the world.(34) However, to prove this expectation, and because an efficacious vaccine may itself provide a selective pressure for SARS-CoV-2 mutation, sera from vaccinees in efficacy studies should be tested for neutralisation against a range of viral lineages.(35) On-going surveillance for viral escape from vaccine-induced and monoclonal antibody-mediated immunity will also be important.

EFFICACY ENDPOINTS

In order to allow comparison of efficacy between vaccine candidates and within differing populations, it is essential that standardised, quantifiable endpoints are applied routinely to clinical trials of COVID-19 vaccines, and that their limitations and potential for bias are understood.

(i) COVID-19 Disease Severity and Mortality

The COVID-19 Clinical Working Group of the Coalition for Epidemic Preparedness Innovations (CEPI) has published guidance suggesting that the primary efficacy endpoint for assessment of efficacy should be virologically confirmed COVID-19 disease.(36) As understanding of COVID-19 disease grows, so does appreciation of the heterogeneity of the symptoms and signs associated with SARS-CoV-2 infection.(14, 37) The clinical criteria chosen to prompt diagnostic testing needs to carefully balance sensitivity, to ensure all cases are identified, with specificity.(36) Symptoms which should prompt contact with the clinical trial team need to be communicated carefully to trial participants since this diagnostic testing is reliant on ad hoc presentation with symptoms and requires significant

engagement and motivation on the part of the participant. As new information accrues, recognition of additional specific symptoms may require a change to diagnostic criteria.

Given not all cases meeting the clinical criteria will be infected with SARS-CoV-2, diagnostic testing to confirm the causative pathogen is important. However, the sensitivity of RT-qPCR, the current gold standard assay for diagnosis of SARS-CoV-2, is imperfect and influenced by variables such as viral load, sample type and timing (Box 1).(38) In clinical settings, a significant proportion of patients continue to be managed as presumed COVID-19 disease despite repeated negative tests RT-qPCR tests, potentially reflecting current limitations in diagnostic assays and growing understanding of the clinical presentation and course of SARS-CoV-2 infection. RT-PCR assay specificity is an even more important consideration, especially if the incidence of infection is low and efficacy analysis is powered by a relatively small number of cases.(39)

BOX 1: Key considerations in utilising SARS-CoV-2 RT-qPCR assays as an efficacy endpoint

- **Sensitivity and specificity of any RT-qPCR assay for SARS-CoV-2 disease is unknown given the lack of validated gold standard for diagnosis.(40)**
- **Numerous RT-qPCR methods using different SARS-CoV-2 genomic targets (including Orf1a/b, nucleocapsid genes, spike protein genes) have been validated with varying reported sensitivity and specificity.(41)**
- **Reported assay sensitivity is influenced by multiple factors including; assay type, time-point of infection, sample choice and duration in transit.(38)**
- **The dynamics of viral shedding in pre-symptomatic, symptomatic and recovering infection varies and remains incompletely understood, so timing of sampling is important.(42)**

- **Most RT-qPCR assays in use fail to distinguish between RNA from live, transmissible virus and non-infectious RNA persisting post-infection.(43) For this reason, both symptoms and PCR positivity are recommended as a primary outcome by CEPI.(36)**

An efficacious COVID vaccine could reduce the severity of disease resulting from SARS-CoV-2 infection. To assess this, careful data collection is required to evaluate markers of severe disease. Numerous methods of scoring the severity of COVID-19 disease exist and few are validated (see Appendix; Proposed severity grading scores for SARS-CoV-2 disease). Classical measures of disease severity, such as hospitalisation, requirement for respiratory support or intensive care admission, represent the clinical phenotypes which place the most burden on healthcare systems and are important endpoints.(36) However, these may represent only a proportion of those with disease.(37)

It is currently unclear if prior exposure to SARS-CoV-2 provides protection against subsequent infection. Some studies to date have excluded participants who are seropositive for SARS-CoV-2. However, the US FDA recommends participants in vaccine efficacy studies are not screened or excluded if they have a history or laboratory evidence of prior SARS-CoV-2 infection, as pre-vaccination screening is unlikely to occur in practice with deployment of a licensed COVID-19 vaccine.(6) Stratification analysis will therefore be important to determine the effect of pre-existing immunity on efficacy outputs.

A syndrome of 'vaccine-associated enhanced respiratory disease' (VAERD) has been reported in pre-clinical studies of certain viral vaccines, where immunised animals demonstrated increased likelihood of infection or severe disease when subsequently challenged with the target pathogen. Murine, ferret and non-human primate animal data of

candidate SARS-CoV-1 and Middle East Respiratory Syndrome (MERS) vaccines have demonstrated this phenomenon, which is thought to be mediated by non-neutralising antibodies or Th2 skewed immune responses.(44)

There is a risk of SARS-CoV-2 vaccine-associated ERD.(6) It is currently unknown how VAERD might manifest in humans. If VAERD were to increase the likelihood of severe disease, the relative risk (RR) of VAERD could be calculated by comparing incidence of severe disease and mortality between vaccinees and recipients of a comparator vaccine. However, if detection of VAERD is dependent on the occurrence of disease this would provide a null-biased estimate of the RR of VAERD. Regular screening of study participants for asymptomatic infections post-vaccination as well as testing of symptomatic participants allows calculation of the true incidence of infection in groups. This denominator allows accurate calculation of the relative and absolute risk of VAERD, which is important safety data of public interest.

Clinical trials may not be sufficiently powered to detect VAERD or vaccine related serious adverse events if these are uncommon. Indeed, the US FDA recommend that follow-up of study participants should continue as long as feasible, ideally for at least one to two years, to assess duration of protection and potential for VAERD as immune response to the vaccine wanes.(6) Given COVID-19 vaccines may be deployed in the early post-marketing period to large populations over a relatively short timeframe, it will be important that robust, ongoing pharmacovigilance is in place post-licensure to identify safety signals that large scale RCTs may not capture.(6)

(ii) SARS-CoV-2 Infection

SARS-CoV-2 infection may result in only mild, non-specific symptoms in many individuals that do not result in contact with a healthcare professional.(14) Asymptomatic infections are well recognised(45) but difficult to capture. Serial sampling of vaccinees, for example via weekly diagnostic testing could ensure all infected individuals are identified, regardless of symptoms, and give an indication of the duration of infectivity. Ideally, vaccinees would be informed of their test results in real-time to allow appropriate isolation. However, it is worth considering that such a system may introduce an unavoidable bias towards clinical endpoints, as participants may be more likely to report symptoms meeting clinical criteria for COVID-19 disease if they know they are infected. This monitoring strategy requires a considerable commitment from vaccinees over a prolonged period, likely to result in an ever-reducing number of samples collected. Asking vaccinees to 'self-sample' by, for example, posting weekly self-collected oronasal swabs for RT-qPCR testing, could help increase the number of samples obtained; however, this may be logistically difficult to implement, with considerable costs and a likely ever reducing return rate.

Following infection with SARS-CoV-2, antibody responses are formed against key viral antigens including the nucleoprotein (N) and spike (S) protein, typically peaking 14-21 days post onset of symptoms.(46) Most SARS-CoV-2 vaccine candidates seek to induce neutralising anti-S antibodies(47) and several assays have been described as methods of assessing evidence of infection.(38) Vaccine efficacy studies that screen and exclude participants seropositive for SARS-CoV-2 could use seroconversion of vaccinees post-vaccination as a surrogate for infection (Figure; Appendix), provided the antibody assayed is specific to infection and not induced by the candidate vaccine.(48) Seroconversion may allow detection of ongoing or recovered infection in vaccinees with minimal symptoms who do not present for RT-qPCR testing(48) and increase the likelihood of diagnosis when

combined with RT-qPCR testing.(49) Furthermore, given that the duration of seropositivity exceeds that for which RNA may be detected, serological testing offers a significant operational advantage over RT-qPCR, with a larger time window to capture the end-point (Figure; Appendix).(38) However, recent US FDA guidance that participants in vaccine efficacy studies should not be excluded if they have a history or laboratory evidence of prior SARS-CoV-2,(6) means this endpoint is of limited value, particularly in populations with high baseline seropositivity to SARS-CoV-2. In addition, key caveats further limit the use of seroconversion as an efficacy endpoint (Box 2).

BOX 2: Key considerations when using serological markers of infection as a vaccine efficacy endpoint

- **Sensitivity and specificity of any serological assay for SARS-CoV-2 disease is unknown given the lack of a validated gold standard for diagnosis.(40)**
- **Reported sensitivity and specificity of antibody tests for SARS-CoV-2 vary widely(50) and are likely influenced by timing of sampling in relation to timing of infection.(46, 49, 50)**
- **Need to be able to distinguish antibodies induced by infection from those induced by vaccination.**
- **The kinetics of antibody responses post-infection are incompletely described and may wane significantly within months.(51)**
- **Individuals may be seronegative for antibodies post-infection as evidenced by the detection of memory T cell responses to SARS-CoV-2 in the absence of antibodies.(52)**

(iii) **Transmission:**

SARS-CoV-2 is readily transmitted between individuals, predominantly via droplet transmission. However, aerosol and faeco-oral routes of transmission may also take place.(53) Individuals are also known to transmit virus in the asymptomatic and 'pre-symptomatic' period.(45) During convalescence, patients can shed viral RNA for many weeks,(54, 55) and even longer if immunosuppressed.(56) However, there is an unclear association between detectable RNA by RT-qPCR and the ability to culture SARS-CoV-2 *in-vitro*.(57)

It is possible that a SARS-CoV-2 vaccine could reduce severity of disease but lead to a prolonged shedding of infectious virus, which could have important public health consequences if this resulted in increased transmission. It may therefore be important for investigators to consider not only the duration of RNA positivity in regularly collected samples, but whether these samples include replication competent live virus. Nested RT-qPCR targeting sub-genomic RNA encoding conserved structural proteins has been suggested as a marker of active SARS-CoV-2 replication.(57) As the transcription of these RNAs is reliant on translation of the Orf1 gene within the host cell and the subsequent assembly of an RNA-dependent RNA polymerase, the detection of sub-genomic RNAs can help identify replication competent and therefore transmissible virus.(58) However, emerging evidence suggests sub-genomic RNAs may be more stable than previously purported and so may be detectable for a period beyond the disappearance of actively replicating virus.(59)

SURROGATE ENDPOINTS

If an immunological correlate of protection is known, the protective efficacy of a vaccine can be assessed by measuring the proportion of vaccinees who generate a particular immune response, without having to measure clinical outcomes.(60) This facilitates the rapid screening and deselection of candidate vaccines. A potential surrogate endpoint for a SARS-CoV-2 vaccine would likely depend on the characteristics of the vaccine including; antigen structure, mode of delivery and antigen processing and presentation in vaccines.(6)

Not all individuals exposed to SARS-CoV-2 become infected(61) and heterogeneity is seen in clinical outcomes.(14) However, the immunological mechanisms underlying protection or susceptibility to natural infection remain unknown. Seroconversion of antibodies against SARS-CoV-2 is a marker of exposure, but it remains unclear whether the presence of neutralising antibodies is sufficient to provide protection against subsequent infection or disease.(46) Moreover, if these antibodies are sufficient, we do not know the titre needed for protection or the diverse range of innate immune effector functions that may be relied upon for antibody action, such as antibody-dependent complement deposition and antibody-dependent neutrophil phagocytosis.(62) Cellular immune responses have also been described in response to infection and are likely to be an important component of a protective adaptive immune response.(63) Indeed, seronegative individuals with T cell responses to SARS-CoV-2 spike protein have been described.(52) However, the particular 'cellular signature' required for protection is currently unknown and it is unclear if 'protective' T cells can be measured in peripheral blood samples. Additionally, an efficacious SARS-CoV-2 vaccine may provide protection by a mechanism distinct from that induced following natural infection. Distinguishing immunological markers of infection from mechanistic correlates of protection is difficult but important to inform rational vaccine design.

If a SARS-CoV-2 vaccine were to demonstrate efficacy, a priority would be to identify an *in-vitro* correlate or surrogate of protection.(64) Other vaccine candidates could then be deemed efficacious and licensed if they induced similar levels of immune responses in non-inferiority studies, which would circumvent the need for large efficacy studies. Confirmation of effectiveness against disease would be needed in post-licensure studies, however this approach could markedly accelerate development of multiple SARS-CoV-2 vaccines. This approach relies on collaboration and standardisation of *in-vitro* assays to allow meaningful comparison of immunological outputs from different laboratories.(65)

In the absence of human data, animal studies can help identify potential correlates of protection. Indeed, non-human primate studies are being widely used to understand SARS-CoV-2.(66) Protection against re-infection with SARS-CoV-2 has been observed in rhesus monkeys who formed neutralising antibodies on initial exposure,(67) and a minimum neutralising antibody titre has been proposed.(68) However, since SARS-CoV-2 is a novel pathogen any surrogate endpoints identified in animal studies would ideally need validation in clinical trials to ensure they adequately predict efficacy in humans.

When human efficacy studies are unethical or unfeasible, marketing approval may be granted on the basis of “*well controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans*” (the ‘Animal Rule’).(69) For example, recently the European Medicines Agency recommended marketing approval for an Ebola vaccine (Ad26.ZEBOV + MVA-BN-Filo administered in a prime-boost regimen) on the basis of efficacy data extrapolated to humans from animal and immunobridging studies.(70) If it is impossible to collect human efficacy data, it may be that SARS-COV-2 vaccines are licensed on the basis of the ‘Animal Rule,’ with effectiveness data collected post vaccine roll-out. However currently, the absence of accepted surrogate

endpoints in humans or animals that are reasonably likely to predict clinical benefit of a SARS-CoV-2 vaccine mean investigators continue to pursue clinical evidence of vaccine efficacy in human studies.(6)

CONTROLLED HUMAN INFECTION MODEL (CHIM)

CHIM studies, where human volunteers are exposed to infectious agents (known as challenge agents), are an important component of pathology, immunology and vaccine research. Microbial challenge studies are useful for providing proof-of-concept for therapeutic interventions and can significantly reduce the time needed to reach Phase III studies, as has been demonstrated for malaria and typhoid vaccine development.(71-73)

Administration of a known dose of SARS-CoV-2 in a carefully controlled setting, has been suggested as a model to allow rapid initial assessment of vaccine efficacy, and early deselection of vaccine candidates.(74) A COVID-19 CHIM model has several advantages over studies reliant on naturally occurring, community transmission which is difficult to predict and dependant on changes in behaviour and public health interventions (Table 2).

COVID-19 vaccine development has proceeded at an unprecedented rate to date, with some candidates beginning Phase III studies within 4 months of the start of vaccine development.(4) If performed, SARS-CoV-2 CHIM studies are likely to include carefully selected young volunteers at low risk of severe disease, who are exposed to low doses of SARS-CoV-2 with the aim of establishing asymptomatic or mild infection only. It is unclear if efficacy demonstrated in such a model will predict the key efficacy measure of protection against severe disease and death in the target older, at-risk population. (75)

CHIM studies could provide valuable immunological insights. For example, re-exposing individuals to SARS-CoV-2 who have recovered from 'naturally' acquired infection

could identify a surrogate marker of protection which would inform vaccine design.

Provided CHIM studies can be performed safely, the information gained can be viewed as complementary to traditional RCTs, both to guide resources for large scale Phase III studies and in the efficacy evaluation of existing vaccines.

CHIM studies require controlled delivery of a standardised inoculum, ideally manufactured to Good Manufacturing Practice, as well as meticulous care to prevent community transmission of the challenge strain (Appendix: Obstacles to the use of SARS-CoV-2 CHIM studies to assess vaccine efficacy).(76) They can be logistically difficult to conduct and costly per participant, though the number of participants is far fewer than large Phase 3 studies. Whilst there are challenges to setting up a CHIM of SARS-CoV-2, there may also be significant value in doing so, even in the context of a licensed product. Use of this ethically complex and controversial approach for vaccine assessment will require multidisciplinary, international oversight to ensure outputs are rigorous and justify the potential risks to participants and their communities.(75, 76)

CONCLUSION

Assessment of the efficacy of a vaccine is complex for many diseases but particularly so in the case of SARS-CoV-2 where our fundamental understanding of the pathogen is evolving. Multiple vaccines are currently being tested worldwide in early phase studies and some vaccine candidates are already in Phase III studies assessing efficacy.(4) It is likely there will be no single vaccine winner; diverse platforms and technologies may offer different strengths and be relevant in distinct epidemiological contexts. It is also likely that there will be insufficient supply, at least initially, of a single vaccine. However, collaboration and standardised approaches for assessing different efficacy endpoints will be important to

allow meaningful comparison and ensure the most effective candidates are deployed.

Following deployment, well supported pharmacovigilance studies must be established to ensure the ongoing evaluation of the vaccine safety.

Capacity to measure vaccine efficacy in field studies is reliant on on-going SARS-CoV-2 transmission, which is rightly at odds with public health interventions. In the absence of a surrogate of protection, CHIM trials may provide the only means of rapidly assessing vaccine efficacy, however the relationship between efficacy data from CHIM studies in young individuals and population level protection is unclear. CHIM studies may help in the identification of a surrogate of protection. It is likely that any evidence for efficacy against severe disease and mortality in at-risk populations will only be garnered post-licensure via large epidemiological studies.

Finally, the development of SARS-CoV-2 vaccines is under great political and media scrutiny. In keeping with the development of any novel medical intervention, but particularly so in this context, it is imperative that efficacy outcomes for a SARS-CoV-2 vaccine are critically appraised with scientific rigor to understand their generalisability and significance.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through searches of PubMed for articles published from 1971 to July 2021 by use of the terms “COVID-19,” and “SARS-CoV-2.” Other relevant references were identified from key online sources (e.g. WHO) and authors’ personal files. Only articles published in English were included.

FIGURE LEGENDS

Figure 1: An efficacious COVID-19 vaccine may reduce; (i) Likelihood of infection of an individual; (ii) Severity of disease in an individual or; (iii) Degree of transmission within a population.

Figure 2: Key variables that determine the likelihood that an individual is exposed to, and then infected with, SARS-CoV-2, as well as the likelihood that they experience a poor outcome.

TABLE LEGEND

Table 1: Illustrative sample size calculations for a randomised controlled trial to assess

efficacy of a SARS-CoV-2 vaccine candidate. Calculations assume no clustering, 1:1

randomisation of participants (SARS-COV-2: comparator or placebo), with 80% power to

detect 70% vaccine efficacy within 6 months of follow-up, with 5% significance, for various

primary efficacy endpoints. Calculations assume that incidence remains unchanged over the

follow-up period, that there is no difference in rates of infection on exposure according to

age and that 60% of infected individuals become symptomatic.⁽⁷⁷⁾ Age related

hospitalisation rates and infection fatality ratio are taken from *Verity et al.*⁽⁷⁸⁾ *Incidence of

SARS-COV-2 infection at peak of transmission in UK (April 2020; derived from UK Office of

National Statistics (ONS) data reporting 4,793 RT-PCR positive cases per day which are

presumed to only include symptomatic cases). **Incidence of SARS-COV-2 infection post

peak in UK (July 2020; derived from UK ONS data reporting 512 RT-PCR positive cases per

day which are presumed to only include symptomatic cases). ^Each illustrative scenario

presumes only participants aged either 20-29 years or > 80 years are enrolled in the vaccine

efficacy trial.

Table 2: A comparison of the key factors for clinical trials reliant upon natural exposure

to, or a direct challenge with, SARS-CoV-2. *The risk of infection in a CHIM trial could be

lower than naturally acquired infection as low risk individuals can be selected (e.g. age 18-

25 years old), the minimum dose of virus needed to acquire infection can be administered,

individuals can be carefully monitored and rescue therapies can be given if needed.

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CONTRIBUTORS

Conceived and wrote manuscript: SHH, KM, GM, KE, AJP.

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Performed statistical calculations: VH.

Reviewed publication: SHH, KM, GM, VH, KE, AJP.

CONFLICTS OF INTEREST

SHH, KM, GM, KE have worked or are currently working on the UK clinical trials of the SARS-CoV-2 candidate vaccine; ChAdOx-1 nCoV-19. AJP is the Chief Investigator of these clinical trials. This work is funded by UK Research and Innovation (MC_PC_19055), Coalition for Epidemic Preparedness Innovations (CEPI), the National Institute for Health Research (NIHR) and the NIHR Oxford Biomedical Research Centre. The University of Oxford has entered into a partnership with AstraZeneca on vaccine development.

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SHH is a NIHR Academic Clinical Lecturer in Infection at the University of Oxford.

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