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The granting of emergency use designation to COVID-19 candidate vaccines: implications for COVID-19 vaccine trials

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An efficacious COVID-19 vaccine is currently the world's leading research priority. Several nations have indicated that if there is a compelling case for use of a vaccine before it is licensed, they would be prepared to authorise its emergency use or conditional approval on public health grounds. As of Dec 1, 2020, several developers of leading COVID-19 candidate vaccines have indicated that they have applied, or intend to apply, for emergency authorisation for their vaccines. Should candidate vaccines attain emergency use designation and be programmatically deployed before their phase 3 trials conclude, such a strategy could have far reaching consequences for COVID-19 vaccine research and the effective control of the COVID-19 pandemic. These issues merit careful consideration.

Introduction

Vaccines underpin modern public health. Conventionally, conducting double-blind, placebo-controlled randomised trials to assess vaccine efficacy against clinically relevant, predefined endpoints is considered the gold-standard approach to generate evidence for vaccine licensing and policy decisions.¹ As of Dec 1, 2020, at least four COVID-19 vaccine trials have announced very promising interim results.²⁻⁵ Given the urgent need for effective countermeasures against COVID-19, several nations^{6,7} and regions⁸ with stringent regulatory authorities⁹ have indicated that if there is a compelling case for use of a vaccine before it is licensed, they would be prepared to authorise its emergency use or conditional marketing approval on public health grounds. In such instances, the licensing authority might deem that the balance of risk and benefit to patients justifies the temporary supply of the vaccine to designated susceptible populations, pending the issuance of a licence. A favourable benefit–risk determination cannot be made for vaccines that offer only modest benefit, or for those without sufficient data to assess safety profiles.¹⁰ Despite the paucity of publicly accessible data, at least two countries—China and Russia—have commenced programmatic roll-out of homegrown COVID-19 candidate vaccines, and other countries have announced their intent to deploy these candidates imminently, through domestic emergency use regulatory mechanisms or by issuing the candidates full marketing approval. The developers of the leading candidate vaccines that have yielded promising early results have indicated their intent to apply for emergency use authorisation,^{2,4} which could result in vaccine deployment before trial conclusion or the collection of long-term safety data. Such a strategy could have far-reaching consequences for COVID-19 vaccine research and the effective control of the COVID-19 pandemic. These implications merit careful consideration.

The roadmap to accelerated availability of COVID-19 candidate vaccines

Create demand

High-income countries, such as the USA, and the 27 nations forming the EU, have hedged their bets that some promising candidate vaccines will show efficacy

and attain emergency use designation or licensure, and have taken measures to accelerate the development, manufacturing, and deployment of vaccines against COVID-19. To accelerate the development of candidate vaccines, these nations have entered into advanced purchase agreements with vaccine developers and manufacturers.^{11,12} Similarly, China and Russia have aggressively marketed their candidate vaccines to low-income and middle-income countries, resulting in the signing of advanced purchase agreements with several countries.^{13,14} To facilitate the rapid deployment of such candidate vaccines, drug regulatory agencies of various countries have signalled their willingness to make investigational vaccines publicly accessible by use of accelerated regulatory pathways.

Expedite regulatory approval

On Oct 6, 2020, the US Food and Drug Administration (FDA) published a guidance document outlining its receptiveness to issuing an emergency use authorisation to a candidate vaccine on the basis of an interim analysis of a clinical endpoint from a phase 3 efficacy study.⁶ In this document, they state: “To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%”.⁶ Helen Branswell, writing in *Stat*, has suggested that, in the early days of vaccine roll-outs, the FDA should consider making COVID-19 vaccines available through its expanded access mechanism.¹⁵

The European Medicines Agency has reportedly indicated its willingness to approve a candidate COVID-19 vaccine with efficacy of less than 50%,¹⁶ which is less than the threshold set by the FDA for COVID-19 vaccines and the European Medicines Agency's requirement for influenza vaccines.⁸ To facilitate COVID-19 candidate vaccines attaining emergency use designation, the European Medicines Agency has started rolling reviews of leading candidate vaccines, which enable European regulators to quickly analyse results as they become

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available, rather than wait for a full application.⁸ The UK's Medicines and Healthcare products Regulatory Agency has adopted a similar approach.¹⁷

Russia¹⁸ and China^{19–21} have initiated the mass roll-out of state-sponsored domestic candidate vaccines to certain population cohorts on the basis of relatively sparse data. Such abbreviated regulatory pathways and fast-tracked deployments, which are still widely regarded as experimental interventions, in the context of a public health emergency of international concern, are unprecedented. Even before Chinese vaccine developers had applied to Chinese authorities for emergency use authorisation for their vaccines on Nov 25, 2020,²² countries, such as Indonesia,²³ had indicated their intent to initiate widespread programmatic roll-out of Chinese and Russian candidate vaccines based on early interim data from trials in the Middle East and South America. Meanwhile, São Paulo's Health Secretary has announced that he expects Brazil's drug regulator to approve the use of China's candidate vaccine by January, 2021.²⁴ Other countries, such as Venezuela,²⁵ the United Arab Emirates,²⁶ and the Philippines²⁷ have also indicated their intent to commence programmatic deployment of Russian and Chinese vaccine candidates by early 2021. However, production constraints^{28,29} could temper these ambitious aspirations.

As many settings do not have domestic emergency use regulatory mechanisms,³⁰ or the expertise to vet candidate vaccines, or both, to assist WHO member states and UN procurement agencies on decision making regarding the use of products in a public health emergency, WHO has established an emergency use assessment and listing procedure³¹ to expedite the availability of medical products (including vaccines) needed in public health emergencies “based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data”.^{32,33} WHO's evaluation will determine “whether, in light of available WHO/international standards, the submitted data demonstrate a reasonable likelihood that the vaccine quality, safety and efficacy are acceptable and that the benefits outweigh the foreseeable risks and uncertainties” in the context of a public health emergency of international concern.³¹ Such risks and uncertainties are poorly characterised. Although not a regulatory authority, the Pan American Health Organization recommends that national regulatory authorities consider WHO a trusted and reference authority for reliance on pre-qualified products or WHO products on emergency use lists.³⁴ WHO putting candidate COVID-19 vaccines on emergency use lists will probably catalyse the rapid adoption and roll-out of these vaccines in member countries, especially in low-income and middle-income settings that have entered into advanced purchase agreements with vaccine developers through financing schemes with sovereign development banks from the countries that developed the vaccines.

The potential pitfalls of accelerated regulatory pathways: efficacy and safety considerations

Despite influenza vaccination becoming routinely recommended for people aged 65 years or older in the USA, whether it lowers mortality is not certain because randomised trials measuring this outcome have never been done. None of the leading COVID-19 vaccine trials are designed to detect a significant reduction in hospital admissions, admission to intensive care, or death,³⁵ and such data usually only become evident in post-licence evaluations. These inherent limitations of phase 3 COVID-19 vaccine trials might result in similar knowledge gaps by avoiding answering the questions most relevant clinically and most relevant to public health in favour of answering the “easiest question in the least amount of time”.³⁶ In addition, low event rate assumptions on the part of leading vaccine trials have been criticised as “fostering an impression that vaccines are being tested on people at low risk of getting COVID-19—and even lower risk of severe disease—who may be unrepresentative of populations prioritised to receive an approved vaccine”,³⁵ although some major trials are specifically trialling vaccines in people older than 65 years and are making concerted efforts to recruit racially diverse population groups.² A suboptimal vaccine that reduces disease but does not reduce transmission would not decrease disease prevalence if distributed inequitably. Furthermore, deployment of such a vaccine would have little impact if vaccine hesitancy is high in groups at high risk,³⁷ or if immune senescence is evident in the older population.³⁸ The unmasking of participants in COVID-19 vaccine trials on the basis of a candidate vaccine's emergency use designation will compound such knowledge gaps, and could inadvertently facilitate the deployment of a suboptimal candidate vaccine. One leading candidate might owe the impressive higher bound range of its promising early results to a fortuitous dosing error, and the results might be based on a relatively small cohort who were all younger than 55 years.³⁹ These inadvertent protocol violations, coupled with a lack of transparency on the part of sponsors and investigators, highlight how such missteps could undermine trust in candidate vaccines assigned emergency use designation.

Although some vaccine candidates might attain emergency use designation on the basis of an interim analysis, long-term data on vaccine safety are also crucial. A post-hoc analysis of safety and efficacy data of the dengue vaccine found that the cumulative 5-year incidence of hospitalisation for virologically confirmed dengue (VCD) and severe VCD was higher for dengue-seronegative vaccine recipients than for dengue-seronegative controls.⁴⁰ This finding highlights why long-term safety data should not be discounted, and why the ongoing monitoring of safety and effectiveness after issuance of emergency use designation and vaccine deployment will be crucial.

The effect of granting emergency use designation to candidate vaccines being evaluated in ongoing COVID-19 vaccine trials

The granting of emergency use designation to candidate vaccines raises numerous ethical issues, including those in relation to trial unblinding, the potential impact on other COVID-19 vaccine trials, risk reduction behaviour, trial retention, and vaccine confidence.

Trial unblinding

Mass vaccination has been a very successful strategy for preventing the spread of many infectious diseases. Besides providing individual protection, mass vaccination programmes also aim for herd protection: immunisation of a large proportion of the population to protect non-vaccinated, immunologically naive, and immunocompromised individuals by reducing the proportion of susceptible hosts to a level less than the transmission threshold.⁴¹ To achieve population-wide reductions in transmission, a COVID-19 vaccine would need to: (1) show efficacy against infection or transmission and not just against disease, which might only be established in post-licence evaluations, and (2) enjoy wide deployment and uptake.⁴² Accordingly, some countries might be tempted to deploy vaccines with emergency use designation in mass vaccination campaigns in an attempt to counter the severe clinical, public health, social, and economic disruptions precipitated by the COVID-19 pandemic. Although this goal is laudable, a generalised roll-out of a vaccine through emergency use designation, as opposed to a phased deployment initially targeting groups at high risk based on efficacy and safety evidence for these cohorts, could jeopardise ongoing COVID-19 vaccine trials and raises challenging ethical issues. For instance, should investigators unmask trial participants to ensure that those in the placebo group are offered candidate vaccines granted emergency use designation, especially in study settings hosting a phase 3 trial involving that candidate? The deployment of vaccines of suboptimal efficacy could make evaluating high-efficacy vaccines difficult because of the perceived ethical challenges surrounding the use of placebo controls once a vaccine with emergency use designation is deployed or once a licensed vaccine is available. Candidate vaccines are unlikely to be available in sufficient volume to target herd protection for some time, even assuming high demand and acceptance. Therefore, the widespread deployment of candidate vaccines with emergency use designation is not an immediately achievable goal on several levels. When a candidate vaccine granted emergency use designation becomes publicly accessible to study cohorts at high risk of infection (eg, front-line health-care workers and those older than 65 years), and interim evidence suggests that administration of that vaccine is safe and efficacious in these cohorts, some study participants in these cohorts might wish to access the vaccine. In such instances, unmasking might be

deemed ethically permissible on clinical grounds. However, outside such instances, the blanket unmasking of all participants in trials involving candidate vaccines granted emergency use designation should preferably only occur upon analysis of comprehensive or final trial results, or if the trial is prematurely stopped on the grounds of predefined efficacy stopping rules, its data and safety monitoring board recommend offering the vaccine to participants in the placebo group, and the trial sponsor and regulatory authorities concur.

Impact on other COVID-19 vaccine trials

The granting of emergency use designation to candidate vaccines could affect the design of other ongoing or proposed COVID-19 vaccine trials. For instance, if the emergency use designated vaccine is rolled out in a mass vaccination campaign, it could be deemed to have established a standard of prevention in that setting (and possibly elsewhere) for applicable individuals (eg, clinical trial cohorts involving health-care workers and older people), especially if the candidate vaccine were to be subsequently issued with a licence. The uptake of the vaccine by individuals from such cohorts could make them ineligible to participate in future vaccine trials given that being a recipient of a COVID-19 vaccine is an exclusion criterion for current COVID-19 vaccine trials. Such an outcome would considerably reduce the pool of eligible study participants for future COVID-19 vaccine trials. If more than one candidate vaccine is granted emergency use designation, establishing the applicable standard of prevention comparator would become very challenging, more so than the provision of standard of prevention measures for COVID-19 vaccine trials,⁴³ especially if competing vaccine trials have non-uniform endpoints. This dilemma would be compounded if the candidate is awarded a full licence in that setting before the conclusion of its phase 3 trial.

If trials testing other COVID-19 candidate vaccines are forced to recruit cohorts other than those targeted by the trial of the vaccine granted emergency use designation, trial timelines could also be affected. If governing ethics committees require subsequent vaccine trials to make the emergency use vaccine the standard of prevention control, this outcome will also majorly affect trial design. In such instances, later vaccine trials might be forced to shift from superiority designs to non-inferiority designs as they would have to show that new vaccines are not inferior to the vaccine granted emergency use designation, instead of showing that the new vaccines are superior to placebos. As the difference in efficacy between the vaccine granted emergency use designation and another candidate vaccine will be smaller than that between a vaccine and a placebo, subsequent trials might have to become bigger and run for longer to generate a statistically significant finding, notwithstanding that endpoints, levels of efficacy, and non-inferiority margins all involve value-based decisions and are not necessarily informed by objective criteria.

The resulting cost implications could also make some trials unfeasible. Such an outcome would especially affect smaller vaccine developers testing innovative vaccine platforms, which would be counter to the interests of public health and vaccine science by inadvertently deterring or frustrating the development of potentially superior candidate vaccines. Paradoxically, the issuance of an emergency use designation for a COVID-19 vaccine before the completion of its large randomised trial could reduce the ability of that candidate vaccine to show efficacy to support licensure.⁶ Although candidate vaccines are required to achieve pre-specified safety data milestones over a short period to attain emergency use designation, ongoing safety and efficacy monitoring is crucial to informing decision making in regard to licensing. If such data are not possible to collect because trial participants withdraw to access the candidate vaccine programmatically, there could be inadequate data to support licensing that candidate.⁴⁴ Licensing is the first aim of all vaccine developers. If correlates of protection are established by initial trials, bridging studies, defined as studies “performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region”,⁴⁵ should underpin regulatory decision making in regard to COVID-19 vaccine trials. Although such trials are still not ideal, and do not show real efficacy, they could inform the licensing of second-generation vaccines.

The effect of preventive misconception on risk reduction behaviour and trial retention

If a decision is taken not to unmask trial participants, some participants could conceivably withdraw from their trial (in which they have a 50% chance of being administered placebo) and attempt to access the candidate vaccine through programmatic vaccination campaigns (in which individuals would be assured of accessing the vaccine if they meet the qualifying criteria). Masked participants from other COVID-19 vaccine trials could also adopt a similar approach to access the vaccine granted emergency use designation. Both instances could be triggered by preventive misconception, defined as overestimating the probability or level of personal protection afforded by participation in a clinical trial of an unproven intervention, despite incomplete efficacy and preventive data at the time the emergency use designation is issued.⁴⁶ Such a misconception could give recipients a false sense of protection or security, which, in turn, could precipitate risky behaviours, thereby increasing the likelihood that the recipient becomes infected with COVID-19. The release of study findings through media releases instead of peer-reviewed journals could also stoke preventive misconceptions. A case in point is the recent media release by a leading vaccine developer that suggested its

candidate vaccine had shown 90% preventive efficacy, which later turned out to be due to serendipity and based on data from a relatively small cohort who were all younger than 55 years.³⁹ Such misleading communication could make those older than 55 years wrongfully assume that they are likely to gain a high level of protection from the candidate vaccine before data exist to verify so. Moreover, the results of a trial involving a particular candidate vaccine might not necessarily apply to participants in a sister trial testing that same candidate elsewhere. For instance, interim results from a phase 3 trial in one setting (eg, the UK) might not necessarily apply to participants with comorbidities (eg, HIV) in different settings (eg, South Africa). To counter these outcomes, participants should be explicitly informed if interim results apply to them and, further, that later safety and efficacy evidence might result in withdrawal of the emergency use designation by regulatory authorities. Accordingly, participants should be advised to continue to take universal precautions to reduce their chance of contracting COVID-19 and to continue with trial participation where they can be continuously monitored.

The granting of emergency use designation to a candidate vaccine could also severely affect retention and accrual in ongoing COVID-19 vaccine trials, thereby threatening their feasibility. If affected trials end prematurely on the grounds of futility (eg, because of poor accrual or retention), it would represent a considerable opportunity cost for the vaccine trial field. To counter such outcomes, regulators should not unmask participants in ongoing vaccine trials. Although participants have the right to withdraw from a trial at any point, participants in COVID-19 vaccine trials, apart from individuals at high risk in whom administration of a vaccine might be justified on clinical grounds, should be encouraged to remain enrolled until the trial ends or is prematurely terminated on the grounds of efficacy. The framing effect—a cognitive bias that affects decision making on the basis of how options are presented—could have a crucial role in determining whether an individual in a COVID-19 vaccine trial opts to continue participation rather than withdraw and attempt to programmatically access a vaccine candidate granted emergency use designation.⁴⁷ How investigators present potential interim trial result scenarios to trial participants could prove crucial to a participant's decision making. For instance, if a participant is advised during the informed consent process that a vaccine could obtain a temporary emergency use designation and be rolled out programmatically on the basis of interim results, but this status could later be withdrawn if safety and efficacy concerns subsequently emerge, the participant could be more likely to remain in the trial, in which they would receive intensive monitoring beyond what they would probably receive programmatically.

Vaccine confidence

Under both accelerated and traditional approval pathways, there is precedence for drug regulatory authorities basing approval or licensing of drugs and vaccines on surrogate endpoints (eg, laboratory results) rather than the effect on clinical disease.⁴⁸ If COVID-19 candidate vaccines showed enough protection from disease to fulfil the FDA's efficacy threshold, their trials might also reveal correlates of protection. Later candidates might then be given accelerated approvals because of these surrogate markers.⁴⁹ Such a strategy could translate to accelerated approvals but spur vaccine hesitancy. To underscore this concern, some advocacy groups in the USA oppose the granting of emergency use authorisation to a COVID-19 vaccine on the basis that "a faster but riskier EUA pathway will surely be outweighed by the loss in public confidence in the vaccine, accompanied by decreased willingness to be vaccinated".⁵⁰ Emergency use designation also carries potential reputational risks. If a trial were to end prematurely because the candidate vaccine is granted emergency use designation, this termination would represent a lost opportunity to investigate the potential for vaccine-associated enhanced respiratory disease and other potential side-effects that usually only become evident as phase 3 trials unfold. Should many people choose to receive the emergency use vaccine, but later the candidate is found to be potentially harmful (resulting in the withdrawal of its emergency use designation), trust in COVID-19 vaccine research and all candidate vaccines could be irreparably damaged. With WHO having identified vaccine hesitancy as one of the top ten threats to global health in 2019 and the rising prevalence of misinformation, disinformation, and vaccine hesitancy in some settings, this problem is not something the COVID-19 vaccine field can afford.⁵¹ Confidence in any COVID-19 vaccine that is made available under an emergency use designation will depend on the rigour of the clinical criteria, including the duration of follow-up, used to evaluate the candidate.¹⁰ The FDA's issuance of emergency use authorisation to the anti-malaria drug hydroxychloroquine for the treatment of COVID-19 (seemingly because of undue political pressure), and the FDA's later withdrawal of the emergency use authorisation when evidence emerged of hydroxychloroquine's paucity of therapeutic efficacy, undermined public confidence in the drug, which is registered for other uses, and the FDA itself.⁵² Similar concerns have been raised in regard to the FDA's issuance of emergency use authorisation to convalescent plasma for the treatment of COVID-19.⁵³ Perceived political interference in regulatory decision making erodes public trust in regulators and the drug sector, highlighted by a poll in September, 2020, that found that fewer than 10% of 1019 Americans reported having a "great deal of trust" in the FDA or pharmaceutical companies to look out for their interests.⁵⁴ Such lack of confidence in those leading the search for a

COVID-19 vaccine, and those tasked with overseeing the process, underscores the dangers of politicising science and government agencies tasked with overseeing science and protecting the public. Moreover, such sentiments highlight the challenge of addressing vaccine hesitancy.

Hydroxychloroquine and convalescent plasma did not become the standard of care for therapeutic trials and arguably had short-term implications for most recipients. However, the withdrawal of emergency use designation for a candidate vaccine would have long-term implications for vaccine recipients. As noted previously, recipients of vaccines granted emergency use designation could become ineligible to participate in other vaccine trials, at least for a period. The withdrawal of emergency use designation could also affect confidence in other vaccines. A general drop in vaccine uptake could considerably impact global immunisation coverage, which, in turn, could lead to the catastrophic resurgence of preventable diseases. Public engagement will thus be crucial to prospectively communicating the implications of withdrawing an emergency use designation, including that evidence gathered after emergency use designation might indicate a varying risk–benefit for different population groups. Given these factors, candidate vaccines granted emergency use designation should not be deemed to have established a standard of prevention in the settings they are introduced to. Candidate vaccines should only acquire such status upon the issuance of a full licence by stringent regulatory authorities following a careful review of preceding findings from phase 2 and phase 3 trials.

Conclusion

Globally, regulators are under unprecedented public health, economic, and political pressure to facilitate the widespread provision of a COVID-19 candidate vaccine to populations outside clinical trial contexts.⁵⁵ Granting candidate vaccines emergency use designations could meet that objective in the short term, but could inadvertently threaten ongoing vaccine research that is yet to define immunological correlates of protection against COVID-19, which could vary according to the vaccine platform, individual characteristics, age groups, and population subset. Transparency must underpin processes of emergency use designation. With misinformation and disinformation driving vaccine hesitancy in many settings, and COVID-19 infections rising globally, the world cannot afford to make mistakes at this crucial juncture of the pandemic.

Contributors

JAS conceptualised and drafted the first iteration of the manuscript. REGU provided feedback on successive iterations that helped to shape the final version of the manuscript.

Declaration of interests

JAS reports personal fees from WHO, outside the submitted work. JAS and REGU serve as members of the WHO Access to COVID-19 Tools Ethics and Governance Working Group. REGU co-chairs WHO's Working Group on Ethics and COVID-19.

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