Position Statement in the Age of COVID-19

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Fast-tracking COVID-19 Vaccine Approval: Rushing to the Finish Line May Result in Tripping and Falling

Review of completed clinical trials is necessary to ensure COVID-19 vaccine safety and effectiveness

As the world contends with the COVID-19 pandemic, developing a safe and effective vaccine as soon as possible remains a top priority. To that end, the U.S. government launched **Operation Warp Speed** (OWS) in May 2020, a public-private partnership intended to develop nine vaccine candidates, with the stated goal of starting distribution by January 2021.

OWS strategy includes streamlining the vaccine approval process while maintaining appropriate safety and effectiveness controls. However, public pressure may push FDA to skip critical data review. On August 30, the **FDA commissioner said** that FDA might grant Emergency Use Authorization (EUA) to COVID-19 vaccines based on *preliminary* phase III trial data if the agency deems it appropriate. In October, FDA also issued **guidance to industry** stating that trial data with a 2-month follow-up might be considered appropriate for EUA. The **Centers for Disease Control and Prevention** (CDC) also requested that states review their supplier licensing requirements to ensure that vaccine distribution could start in November. Among OWS phase III trials, **Pfizer's vaccine** trial has an estimated primary completion of June 2021. **Pfizer's CEO has stated** the company expects its trial data will meet FDA requirements for an EUA by the end of November and plans to apply at that time. **Billions of dollars on the table from presold doses**, **strong backing from capital markets**, and risk reduction from **deregulation and generous government scale-up funds** increase the potential for **conflicts of interest**.

In response, many **medical and scientific experts have warned** that data from unfinished trials may not ensure vaccine safety and effectiveness, while **OWS developers have pledged not to seek EUA** without data from phase III trials. After reviewing the limitations of COVID-19 vaccine testing and the potential harms that vaccines might cause, ECRI recommends that U.S. authorities approve COVID-19 vaccines only after a full review of completed clinical trials that also considers evidence limitations and gaps, and under no circumstances authorize COVID-19 vaccines before 6-month follow-up data from the full trial cohort are reviewed.

COVID-19 vaccine candidates entail old and new risks

Clinical trials first seek to establish safety. FDA-approved vaccines have a long track record of safety, but novel vaccines are not inherently risk-free. Vaccination involves exposing patients to isolated or inactivated antigens to induce protective immune responses against a pathogen. This approach typically results in only transient, localized adverse reactions and mild systemic "flu-like" symptoms. However, in rare cases, inappropriate immune responses, such as **hypersensitivity**, **disease enhancement, cross reactions**, and **Guillain-Barré syndrome**, might also occur and cause serious illness.

During the pandemic, two vaccine technologies emerged that just a year ago were considered novel: mRNA and adenoviral vectors. These vaccines consist of genetic material that directs the patient's cells to produce the viral antigen. They are purported to be safer than conventional vaccines because they contain no pathogen particles and rely less on **additional adjuvants** (e.g., aluminum salts, oil emulsions) to induce immune responses. They are also well-suited for rapid development and production scale-up.

> **ECRI maintains its urgent call for COVID-19 vaccine deployment only after a thorough review of completed phase III trial data, and under no circumstances should FDA authorize vaccines with fewer than six months of follow-up data from the full trial cohort. Doing any less would simply risk too much, and the consequences may be severe.**

mRNA vaccines by **Pfizer** and **Moderna** might be the first to reach the market. mRNA therapeutics are approved for rare diseases, but the technology is unproven for vaccination. **mRNA vaccines** are considered to carry very low risks because mRNA is rapidly cleared from the body and cannot integrate into the patient's DNA.

AstraZeneca and **Johnson & Johnson** are developing adenoviral vector vaccines, which are **genetically modified viruses** that enter host cells and drive antigen expression. Adenoviral vectors yield strong immune responses but carry risks of hypersensitivity or cross-reactivity to the vector's proteins. **Vector genome integration** into the patient's DNA is also a risk factor.

Long-term effectiveness is also an important consideration with novel vaccines. **The World Health Organization (WHO)** recommends that COVID-19 vaccines confer immunity within two weeks and for at least one year; however, factors determining the **duration of immunity conveyed by these investigational vaccines are not fully understood**, and indirect evidence suggests that immunity to COVID-19 might be short-lived. Acquired **immunity to seasonal coronaviruses** can begin to wane as early as three months to one year after infection; **antibody responses in COVID-19 survivors** also suggest transient immunity.

Also, **a new vaccine might be needed every year**, because coronaviruses mutate rapidly. OWS vaccines target the coronavirus Spike protein, the key target for protective antibody responses, and one **likely to mutate in emerging strains**. Incorporating other viral proteins might help improve long-term protection but could also hinder the pace for vaccine development. Adenoviral vaccines may also not be effective year after year due to immunity developed against the vector.

Lack of effectiveness poses a substantial risk of harm

Perhaps the greatest risk with OWS candidates is that deploying a safe but weak COVID-19 vaccine might actually *worsen* the pandemic. In principle, even a partially effective vaccine should help slow down transmission as long as people maintain social distancing, hygiene practices, and personal protective equipment (PPE) use. However, **public response and attitudes** over the past nine months in the United States suggest that **hygiene precautions might relax** as soon as a vaccine is available. Resulting infections may offset the vaccine's impact and end up *increasing* the mortality and morbidity burden.

In step with **WHO recommendations**, FDA will consider only vaccines that show at least 50% effectiveness in clinical trials. However, **this may not be enough** to slow the pandemic if people ease preventive practices or **do not adhere to multiple injection schedules** that might be needed. Furthermore, **FDA guidance to OWS manufacturers** seeking EUA proposes only two-month follow-up data from clinical trials, which is insufficient even for an interim assessment of immunity duration. A vaccine that provides protection for fewer than six months would be of limited utility because readministering it to enough people more than twice a year may not be feasible.

The first rapid COVID-19 vaccine to be deployed must be highly effective. Deploying a weak vaccine would consume resources needed to develop more effective vaccines. Two resources are of critical importance: time, which translates to lives lost to the ongoing pandemic, and public trust, which is already scarce yet necessary for a vaccine to succeed. **According to recent polls**, as many as 2/3 of Americans may wait months to get a vaccine, and 1/3 declare they never will. Lacking widespread trust and use, even effective vaccines will fail, leaving no options but to wait for the pandemic to run its natural course. A weak vaccine that loses public trust could poison the well for epidemic control for **many years**.

Uncertainty is inherent to vaccine testing, more so during a pandemic

To ensure safety and effectiveness, vaccine testing involves several steps. A Biologic License Application **approval by FDA** requires large, multicenter, phase III trials, typically designed as double-blind, randomized, and placebo-controlled, to provide high-quality data.

Nevertheless, trials can still fall short of their aim because trial conditions are highly controlled and may not reflect real-world conditions and outcomes, especially considering that much about COVID-19 is still unknown. Our chief concerns include the following:

- *Sampling may not be representative:* OWS trials rely on community COVID-19 transmission and have prioritized recruitment among highly exposed groups. However, some participants, such as healthcare workers, might actually be at lower risk due to training and access to PPE. **Recruitment among minorities and low-income groups** has also been difficult; however, these groups are most affected by COVID-19. A trial that does not appropriately represent these populations may overestimate the vaccine's effectiveness.
- *Trials may miss critical outcomes:* OWS trials will count symptomatic COVID-19 cases to measure protective effectiveness. However, reducing asymptomatic transmission is also a critical goal because vaccinating the entire population may take many months or may not be feasible. Because vaccinated individuals will likely relax social distancing, the first vaccine recipients may become superspreaders if the vaccine protects from severe disease but not from mild or asymptomatic infection. Only the **AstraZeneca** trial lists asymptomatic infection as a secondary endpoint. The other two trials will assess immune responses in patients, but these do not guarantee protection from asymptomatic infection because immunity may engage different mechanisms in some patients.
- *COVID-19 case counting may not be accurate:* At least one trial (**Pfizer**) will allow for variable follow-up and normalized infection rates (i.e., cases/patient-days). However, normalized data may be misleading because immunity wanes over time. If too many patients in the normalized dataset have short follow-up times, the data may be skewed and make

the vaccine appear more effective than it is. Also, molecular tests are needed to confirm mild COVID-19 cases because symptoms are typically nonspecific; however, available tests are themselves unproven and **false negatives may be common**, which may further skew the data.

- *COVID-19 is a moving target:* Testing accuracy and exposure risks depend on COVID-19 spread, which has varied across regions. Prevalence has also changed dramatically over time. For example, testing the vaccine in areas that are seeing rapid COVID-19 declines because of newly adopted social distancing measures might give the appearance of vaccine effectiveness. Furthermore, how the pandemic will evolve over the next few months is uncertain because of non-COVID-19 factors, such as seasonal behavior patterns, possible co-occurring epidemics (such as influenza), and mounting socioeconomic pressure to relax social distancing. Such factors can have unforeseen effects on how a vaccine might work after deployment compared with how it performed during clinical trials.

Despite these caveats, OWS trials are well-designed and should provide robust data if completed as designed.

Preliminary data are unreliable even in optimal trials

In contrast, preliminary data should be considered at high risk of bias regardless of trial design because what can happen at subsequent time points in the study is unpredictable. OWS trials are even more susceptible because key variables, such as infection risk and immunity, are time-dependent. Moreover, patient demographics at an interim analysis might differ from those in the full study cohort—and from the general population—in unexpected ways; for example, early trial volunteers could be from geographic areas practicing better social distancing than in other areas.

Interim analyses can be useful for determining whether investigators should stop a futile trial or expand a trial that has insufficient statistical power. Interim data may support regulatory action if risks are acceptable, such as for treating rare and fatal diseases or when benefits are dramatic and no serious side effects are expected. However, COVID-19 immunization does not fit such a scenario because immunization is intended for millions of healthy people, has non-negligible risks, and must be effective.

Regulatory action based on preliminary trial data makes for poor evidence-based practice

Vaccines are some of the safest and most effective interventions available, but their benefits should not be taken for granted with rushed timelines and incomplete data. Unexpected events may occur and must be examined, and effectiveness must be ensured to limit disease spread. Streamlining development in response to COVID-19 is reasonable and justified, but not at the expense of valid and thorough evaluation. Considering preliminary trial data for rapid COVID-19 vaccine evaluation might not be justified because the risk of bias is high enough to invalidate the evaluation.

On September 10, **FDA regulators issued a public comment** affirming their commitment to an evidence-based approach; however, the statement falls short of stating what evidence would be needed, at a minimum, to support regulatory action on a COVID-19 vaccine. Thus, ECRI maintains its urgent call for COVID-19 vaccine deployment only after a thorough review of completed phase III trial data, and under no circumstances should FDA authorize vaccines with fewer than six months of follow-up data from the full trial cohort. Doing any less would simply risk too much, and the consequences may be severe.

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