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COMMENTARY



# Vaccine safety – is the SARS-CoV-2 vaccine any different?

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**ABSTRACT**

Vaccines have changed modern medicine, and are a mainstay in reducing morbidity and mortality from infections. Our research group recently published a study in which we found that vaccines approved by the US Food and Drugs Administration were safe with few clinically important post-approval adverse effects. The current COVID-19 pandemic presents regulators with the unprecedented challenge of balancing a public demand for the rapid development and approval of a safe and effective SARS-CoV-2 vaccine without compromising the strict pre-marketing requirements used for previous vaccines. Here, we review the approval process and safety profiles of FDA approved vaccines and discuss some of the challenges currently facing the FDA regarding the SARS-CoV-2 vaccine approval.

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## Introduction

Vaccines are among the most important advances in modern medicine. Few other medical developments have reduced child morbidity and mortality from infectious diseases such as mumps, measles, rubella, and poliomyelitis.[1–3] Recent years have shown several outbreaks of vaccine-preventable diseases, mostly in unvaccinated individuals due to guardian hesitancy.[4,5] Moreover, vaccination rates have dropped even further during the current ongoing COVID-19 pandemic, which might in turn result in even larger outbreaks of those vaccine-preventable diseases.[6] Public trust in vaccine safety has become a cornerstone of public health measures, and as such, the US National Institutes of Health and Centers for Disease Control (CDC) have put major efforts in communicating vaccine safety to the public, both by sharing information regarding the rigorous vaccine approval studies and by constantly assessing emerging post-approval safety data.[7]

Following the 1986 National Childhood Vaccine Injury Act,[8] the US Food and Drugs Administration (FDA) and CDC have initiated the Vaccine Adverse Event Reporting System (VAERS) program, designed to facilitate post-marketing safety monitoring of FDA-approved vaccines.[9,10] The FDA receives more than 30,000 annual VAERS reports, and these are scrutinized for any unexpected adverse events patterns. VAERS reports, alongside with clinical trials and collaboration with databases such as the Clinical Immunization Safety Assessment Project,[11] enable the FDA to rapidly detect rare or long-term vaccine safety issues undetected in the initial approval studies. Importantly, these measures can also serve as a tool to increase public trust in vaccines.[12]

## Are vaccines really safe?

A recent study published by our research group reported on the post-approval safety modifications of FDA-approved vaccines over a 20-year period (1996–2015).[13] We have also described data sources triggering these label modifications.

During the study period, 57 vaccines were approved by the FDA, including vaccines for seasonal influenza (n = 21, 37%), and several vaccine combinations for tetanus, diphtheria, poliomyelitis, pertussis, Haemophilus influenzae type b, hepatitis A and B (n = 16, 28%). Most vaccine approvals (n = 52, 93%) were supported by randomized controlled trials (RCTs) which included a median of 4,161 persons (IQR, 2,204 to 8,634). Median safety follow-up was 1.5 months.

A total of 58 post-approval safety-related label changes were identified, comprising 49 warnings and precautions, 8 contraindications, and 1 safety-related withdrawal. Most of these were not clinically important. The most common issue which triggered safety profile modifications was expansion of population restrictions (n = 21, 36%), including immunocompromised patients, patients with specific preexisting medical conditions, pregnant women, and premature infants. There were also 13 (22%) safety modifications related to allergies, mostly due to changes in latex-containing packaging. Twelve (21%) post-marketing safety-related label changes involved risk of post-vaccination syncope episodes. The single safety-related vaccine withdrawal (RotaShield; Wyeth Laboratories) occurred within a year of initial marketing approval and was triggered by safety signals of an increased risk of less than 0.05% for bowel intussusception identified through VAERS shortly following marketing approval.[14,15]

The excellent safety profile of FDA-approved vaccines underlines both the high-quality vaccine approval process

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which relies on high-quality, large-scale RCTs to identify any potential safety issues prior to vaccine approval, and the robustness of VAERS and similar post-marketing vaccine safety surveillance programs. The rare safety issue leading to the single identified vaccine withdrawal was swiftly identified by the existing post-market surveillance program. The safety profile of FDA approve vaccines compares favorably to that of FDA approved drugs.[16]

## SARS-CoV-2 and COVID-19

COVID-19 was declared a pandemic by the World Health Organization (WHO) in March 11, 2020, less than 3 months after receiving initial signals of a new type of viral pneumonia in Wuhan, China. More than 30 million people have been diagnosed with an infection caused by the novel coronavirus SARS-CoV-2, resulting in more than one million deaths.[17] Recently, it was reported that COVID-19 has become the number 3 cause of death in the US.[18] The current pandemic has proven to be more than just a global medical crisis, and the past few months have seen a global economic recession and a staggering social burden caused by prolonged closures and social distancing.[19–21] These ongoing events have had an even larger effect on vulnerable sectors, such as the elderly and some racial minorities.[22,23]

## SARS-CoV-2 vaccine development – business as usual?

The development of the SARS-CoV-2 vaccine is underway in an unprecedented rate. The virus' genetic sequence became publicly available within 2 weeks of initial recognition of the novel clinical entity.[24] A protocol for detection of SARS-CoV-2 using reverse transcription–polymerase chain reaction was published a few days later.[25] As of September 3, 2020, at least 176 vaccine candidates were being studied, and 34 of these were already in various stages of clinical assessment, some already enrolling patients to large RCTs.[26,27] Some of these candidates use tried-and-tested technologies (e.g. protein subunit or an inactivated virus), while others utilize new techniques which have yet to be used in large-scale human vaccine production (e.g. viral vectors, mRNA, or DNA based).[28] The pace of vaccine development, driven by the urgent, unmet clinical need and large financial incentives is even more impressive when compared to the average pace of vaccine development, which lasts 10 to 15 years from pre-clinical studies to full marketing approval.[29,30]

This unprecedented development and testing schedule might raise concerns regarding the thoroughness and quality of testing the efficacy and safety of the SARS-CoV-2 vaccine candidates.

### *Should the same high safety threshold be used for the COVID-19 vaccine?*

The FDA has published a guidance document to industry regarding the development of vaccines for COVID-19.[31] In the document, the FDA states that "The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases." In response to the guidance, two phase III studies have recently began patient recruitment, with an accrual goal of 30,000 patients each, a number reflecting the fact that there are no previously approved COVID-19 vaccines for efficacy and safety comparison.[32,33] Meanwhile, as these trials are ongoing, news of successful development of a viral-vector vaccine (Sputnik V) emerged from the Gamaleya Research Institute of Epidemiology and Microbiology in Russia.[34] No results were published for the vaccine's phase I and II trials, and Russian authorities stated that phase III trials will be ongoing during vaccine production and dissemination.[35]

These two different approaches to vaccine development in the face of the SARS-CoV-2 pandemic reflect different priorities regarding the preferred balance between rapid vaccine approval with incomplete safety data versus slower approval following the assessment of mature data from large RCTs. The choice between these approaches raises issues extending far beyond the scope of pure medical research.

Large-scale phase III RCTs will provide the best safety and efficacy data for vaccine candidates and will likely result in a vaccine with few, if any, unexpected post-marketing safety issues, as shown by the FDA's impressive track record. These studies are also likely to serve as an important tool in improving public trust in the upcoming vaccines, a trust level which is currently wanting.[36–38] Vaccine-skepticism might be further amplified if the Sputnik V vaccine proves to have a less-than-optimal safety record, and may in turn result in a significant number of people choosing not to get vaccinated by any COVID-19 vaccine, thereby perpetuating the current pandemic. This potential increase in vaccine hesitancy might also affect rates of non-COVID vaccination. From this perspective, The FDA should approve a new vaccine only following the successful completion of large phase III RCTs, with ample safety follow-up periods. The main limitation of this approach is the relatively long timeframes required for the recruitment, follow-up, and data analysis of these trials, and the potential price in human lives, social distancing, and economic havoc increasing with every day without an approved vaccine. The FDA is faced with a hard choice, weighing safety and public trust against rapid approval and dissemination of a potentially lifesaving vaccine. Previous experience with similar regulatory dilemmas is limited to few examples, including the case of the rapid H1N1 vaccine development in 2009, resulting in unexpected side effects.[39,40]

During the current pandemic, the FDA approved various treatments for COVID-19 through the Emergency Use Authorization (EUA) framework, in order to rapidly authorize several novel treatments with insufficient evidence for regular approval.[41] On a recent interview, FDA commissioner Dr. Stephen Hahn revealed that the FDA is considering giving an EUA status to upcoming vaccine candidates.[42] Granting a SARS-CoV-2 vaccine EUA status will represent a huge gamble for the FDA. Should the vaccine prove to be safe and effective, the benefits to vulnerable populations and to society will be considerable and the FDA will be lauded as a flexible, nimble, focused and effective organization, able to rapidly adjust to new conditions and make informed choices in the face of uncertainty. However, if the new vaccine will

prove to be less effective than anticipated, or if it will be associated with a less favorable safety profile than reflected by the limited pre-approval data, the damage to the FDA's reputation and to the perceived safety profile of vaccines might be unprecedented.

The COVID-19 crisis extends far beyond the realm of a purely medical event, and carries vast social, financial, regulatory, and political implications. Policies and priorities involved in the development and approval of the COVID-19 vaccine should not be discussed only among medical professionals and administrators, and should not remain in the territory of medical regulators. Although political involvement in the medical sphere is usually undesired, the current situation demands a new way of thinking. Just as the tools used to curb the pandemic are not restricted to the medical domain (e.g. social distancing, bans on international travel, large-scale quarantines, mandatory face masking), the decisions regarding the best method of achieving control over the pandemic should not be left only in the hands of physicians and medical authorities. Shared decision-making regarding the acceptable safety margins and efficacy thresholds for upcoming vaccines may be the best way forward. Transparent discussions between vaccine experts, regulators, financial and political leaders, and public representatives can increase the trust in the decision process and its results.

## Conclusions

Vaccines are remarkably safe, with few clinically significant post-approval adverse events and a robust post marketing surveillance program. Using the same strict approval standards for the SARS-CoV-2 vaccine will lead to a delayed approval of a safer vaccine compared to an approval based on incomplete, preliminary data. Weighing these alternatives and choosing a path forward is matter of an already overdue public discussion.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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