



March 11, 2021

COVID-19 Variants: Vaccines, Diagnostics, and Therapeutics

Introduction

As SARS-CoV-2, the virus that causes COVID-19, has spread widely over time, a number of new variants have been identified globally. According to the Centers for Disease Control and Prevention (CDC), “a new virus variant has one or more mutations that differentiate it from the wild-type or predominant virus variants already circulating among the general population.” Genetic variation in circulating viruses is expected, especially with RNA viruses (e.g., influenza virus), which have high rates of mutation generally. When a virus infects its host, it uses the host cell machinery to replicate itself. This replication process is error prone and offers chances to introduce changes to the virus’s genetic code. Many of these changes are inconsequential, but a few improve the fitness of the virus, providing a selective advantage and establishing new strains of the virus, which would be expected to increase in prevalence over time. Although they may occur in any part of the viral genome, changes in the genetic code for the virus part (known as the “spike protein”) that locks onto the host cell, have been noted in the SARS-CoV-2 variants of concern. These changes appear to strengthen viral attachment to the host cell, which can result in more efficient viral transmission (increased infectiousness). This type of change does not have to correlate with a change in the clinical severity of infection (virulence), although it may.

To date, several COVID-19 variants of concern have been identified globally, including B.1.1.7 (identified by the United Kingdom, UK); B.1.351 (emerged in South Africa); and P.1 (emerged in Brazil). Each of these variants have been found in the United States as of January 2021. Recent evidence indicates that additional variants have emerged and are circulating in parts of the United States as well. The variants pose potential challenges to the effectiveness of existing countermeasures—vaccines, diagnostics, and therapeutics—and the development of new ones. Efforts have increased nationally to track the emergence and spread of new variants, primarily through increasing genomic and other surveillance.

Given these concerns, Congress, in the American Rescue Plan Act of 2021 (H.R. 1319), appropriated \$1.75 billion to CDC specifically for SARS-CoV-2 genomic sequencing and surveillance; other funding in the bill, such as for data modernization and forecasting, may also aid with variant tracking, as well as with coordination of such efforts at the federal level. CDC has also used appropriations from several prior coronavirus supplemental appropriations acts to expand such efforts. H.R. 1319 further provided funding to the Food and Drug Administration (FDA) to support, among other things, the continued evaluation of COVID-19

countermeasures, including with respect to emerging variants.

Identifying and Tracking Variants

Identifying and tracking virus variants primarily relies on genomic surveillance. Genomic surveillance—ongoing and systematic genomic sequencing of virus samples collected from patients—is relatively new to the public health field, though some countries (e.g., the UK) have more robust systems than others. Genomic surveillance capabilities are uneven across U.S. public health agencies, and the United States currently sequences less than 1% of its COVID-19 samples. Even with new investment, it is uncertain if genomic surveillance can be scaled before variants spread widely. Genomic surveillance is complex, involving not only sequencing viral genomes, but also developing capabilities to process and analyze large volumes of data. Such efforts involve specialized equipment, software, personnel, bioinformatics expertise, and systems to share, harmonize, and analyze data. Genome sequences collected through surveillance and other sequencing efforts are shared to public repositories, such as GenBank or GISAID (global initiative on sharing avian influenza data), by public health, academic, or other research institutions. These efforts support better understanding of global patterns of transmission, identify outbreaks potentially driven by new variants, and guide mitigation measures, among other things.

CDC leads national variant tracking through various efforts. First, CDC conducts national SARS-CoV-2 strain surveillance, which combines genomic surveillance with characterization of biological features of the strains (e.g., virulence or transmissibility). CDC ramped up collection of specimens from state and jurisdictional health departments through its National SARS-CoV-2 Strain Surveillance (NS3) starting in November 2020. CDC also supports genomic surveillance capacity at state and other public health agencies through its Advanced Molecular Detection (AMD) program. Guidance for recent Epidemiology and Laboratory Capacity grant awards to jurisdictions made with funding from the Consolidated Appropriations Act, 2021 (P.L. 116-260) provides that recipients are to increase both samples sent to CDC and genomic surveillance capabilities within the jurisdiction using AMD. In addition, CDC partners with academic, commercial, and public health laboratories to collect genomic sequence data. In mid-February 2021, the CDC Director announced further investment of \$200 million for genomic surveillance, with the goal of increasing sequencing to 25,000 samples per week. CDC had already increased weekly specimens processed from 750 in January 2021 to 7,000 in February 2021. Both CDC and some commentators note that even this level of sequencing may not be adequate to track

variants nationwide, with many experts recommending sequencing at least 5% of test samples.

Variants and Vaccines

To date, FDA has granted emergency use authorization (EUA) to three COVID-19 vaccines, based on analyses of data from Phase 3 clinical trials evaluating each vaccine's safety and effectiveness in tens of thousands of participants. The vaccines available under EUA thus far, as well as many of the vaccines that are under investigation in clinical trials, are designed to elicit a protective immune response to the SARS-CoV-2 spike protein. SARS-CoV-2 variants with mutations in the spike protein raise concerns that currently authorized vaccines may provide reduced protection against these variants. While FDA indicates that currently available vaccines remain effective against circulating strains of the virus, some evidence suggests reduced effectiveness against certain variants (e.g., the B.1.351 [South African] variant). As such, researchers have begun assessing the effectiveness of EUA-authorized vaccines against the SARS-CoV-2 variants and exploring modifications to the vaccines.

Any changes to the currently authorized vaccines, including any change in composition, dose, or dosing schedule, would have to be reviewed and approved by FDA. To assist vaccine developers with generating data to support modifications to authorized vaccines, FDA has updated its guidance, *Emergency Use Authorization for Vaccines to Prevent COVID-19*, outlining what data and information are needed to support an EUA amendment. With respect to clinical data, FDA does not expect vaccine developers to conduct the same large-scale clinical trials that were required for EUA issuance. Instead, the effectiveness of a modified COVID-19 vaccine may be demonstrated by conducting immunogenicity studies comparing the immune response induced by the modified vaccine against the SARS-CoV-2 variant(s) with the immune response induced by the EUA-authorized vaccine against the SARS-CoV-2 virus upon which the vaccine was originally based. The guidance provides recommendations for conducting immunogenicity studies assessing the effectiveness of a modified COVID-19 vaccine as part of the primary vaccine series and as a booster dose.

Variants and Diagnostics

The performance of COVID-19 tests, including molecular, antigen, and serology tests, may be affected by the emergence of new variants. FDA has released guidance—*Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests*—to provide test developers with recommendations on evaluating the impact of new viral genetic mutations on their tests' designs and performance over time as new variants emerge. Molecular tests, such as polymerase chain reaction (PCR) tests, identify the virus by recognizing specific snippets of the viral genome, and have generally been developed based on the same reference sequences. If a test's viral targets are altered in a variant, then the diagnostic may not detect them, generating a false negative result. This may be mitigated through the use of multiple targets in a molecular test; most EUA-authorized PCR tests do have multiple targets, often in different parts of the viral genome. Separately, antigen test performance may be affected if a viral genetic mutation affects the

eventual structure of viral proteins that are targeted by the tests, and serology tests—tests that detect antibodies to the virus—can be affected if the structure of the viral protein that elicits an antibody response to the virus is altered. In both cases, these changes may lead to false negative results.

FDA notes that the agency has been “routinely monitoring publicly available databases and has coordinated efforts to evaluate the impact of new virus variants on tests that have received . . . EUA.” FDA uses reports in the peer-reviewed literature on variants of clinical significance, as well as identification of mutations appearing with increasing frequency in public sequence repositories, to identify potential mutations or variants of concern. Test components are routinely compared against these mutations to determine the effect, if any, on test performance. FDA released a safety communication in January 2021 based on this work to alert the diagnostics community about potential impacts on specific EUA tests. To date, the agency has focused its efforts on monitoring the effects of genetic changes on molecular tests, but FDA is currently also considering approaches to monitoring for possible effects of changes on antigen and serology tests.

Variants and Therapeutics

Several therapeutics are now available for the treatment of COVID-19, and they differ with respect to their intended use (e.g., treatment of mild to moderate or severe disease) and mechanism of action (e.g., whether they target the virus itself or the body's inflammatory response). To date, FDA has approved one drug, the antiviral Veklury (remdesivir), which is intended for treatment of patients hospitalized with COVID-19. It works by stopping viral replication, thereby reducing the time it takes for symptoms to improve. FDA also has granted EUA to several monoclonal antibody (mAb) products, which are intended for the treatment of mild to moderate COVID-19 in patients who are at high risk for progressing to severe disease. mAbs are designed to bind to the spike protein that allows the virus to infect the host cell in order to stop infection.

The emergence of SARS-CoV-2 variants has raised concerns about the effectiveness of existing therapeutics. FDA has indicated that it is aware that some authorized mAb products are less active against some of the SARS-CoV-2 variants that have emerged. As such, FDA has issued a new guidance, *Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency*, which provides recommendations for design of mAb development programs and considerations for emerging variants. FDA recommends that individual mAb products be developed with the expectation that they will be combined with other antibody products that can bind to different parts of the viral protein. FDA also updated its guidance, *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention*, to include recommendations for conducting drug resistance analyses (e.g., characterizing a drug's antiviral activity against SARS-CoV-2 variants).

Amanda K. Sarata, Specialist in Health Policy
Agata Bodie, Analyst in Health Policy

Kavya Sekar, Analyst in Health Policy

Disclaimer

This document was prepared by the Congressional Research Service (CRS). CRS serves as nonpartisan shared staff to congressional committees and Members of Congress. It operates solely at the behest of and under the direction of Congress. Information in a CRS Report should not be relied upon for purposes other than public understanding of information that has been provided by CRS to Members of Congress in connection with CRS's institutional role. CRS Reports, as a work of the United States Government, are not subject to copyright protection in the United States. Any CRS Report may be reproduced and distributed in its entirety without permission from CRS. However, as a CRS Report may include copyrighted images or material from a third party, you may need to obtain the permission of the copyright holder if you wish to copy or otherwise use copyrighted material.