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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 like SARS-CoV-2, 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 that locks onto the host cell, known as the "spike protein," have been noted in certain SARS-CoV-2 variants. 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.

Currently, the Delta variant is the predominant variant strain circulating in the United States, according to CDC data. Federal agencies are actively monitoring other variants of possible concern. Certain variants, both existing and potential, may pose possible 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 (ARPA; P.L. 117-2) 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. P.L. 117-2 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.

Tracking and Studying Variants

Identifying, tracking, and studying virus variants primarily relies on two public health functions: (1) genomic surveillance, based on sequencing, and (2) genomic epidemiology, which studies the health effects associated with different variants. Increasing SARS-CoV-2 genomic sequencing to facilitate surveillance in the United States has posed a challenge. Though genomic sequencing capacity exists in the academic and private laboratory sector, these sectors have not been well connected to the public health or health care sectors to readily enable large-scale and coordinated laboratory sample and data sharing for a nationwide virus sequencing effort. CDC has funded efforts and partnerships to increase genomic sequencing and surveillance since fall 2020, including through collecting specimens for sequencing, and by partnering with academic, commercial, and public health laboratories. CDC has also awarded grants to state, local, territorial, and tribal (SLTT) public health agencies to increase their capacity for genomic surveillance. 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). These efforts have boosted U.S. SARS-CoV-2 sequencing by CDC and SLTT labs from about 3,000 sequences per week in early 2021 to a range of 40,000-90,000 sequences per week in September and October.

Boosting genomic epidemiology poses another challenge. Genomic epidemiology can answer questions such as whether certain variants are associated with more severe health outcomes or reduced effectiveness of medical countermeasures, and enable the use of genomic data in outbreak response. Such efforts involve linking genomic surveillance data with other types of health data, such as on patient characteristics, outcomes, or vaccination status. In the United States, siloed health data systems, as well as other legal and institutional barriers, inhibit the data integration that would enable more robust and real-time genomic epidemiology. In addition, SLTT public health agencies have varying capacity for genomic surveillance and epidemiology for a number of reasons, including a lack of technology and trained personnel with bioinformatics expertise, among others. This sector is also already strained by other aspects of the COVID-19 response. The Biden Administration has allocated the ARPA genomic surveillance funds in an effort to address these issues: $1 billion for CDC and SLTT health agencies to expand sequencing, $400 million for new Centers of Excellence in Genomic Epidemiology, and $300 million for a National Bioinformatics Infrastructure. Even with new funding, it may take time to build the infrastructure for robust nationwide genomic surveillance and epidemiology, and some legal and institutional barriers may remain.

Variants and Vaccines

The vaccines available thus far 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 available vaccines may provide reduced protection. Data indicate that vaccines continue to provide strong protection against severe COVID-19 and death in the United States, including against currently circulating variants. To ensure that vaccines continue to provide robust protection against COVID-19, including against emerging variants, FDA has authorized, and CDC has endorsed, booster doses of the available vaccines, including heterologous boosters (i.e., a mix-and-match approach). As new variants emerge, vaccine dosing recommendations may be modified further.

Any changes to the currently approved or authorized vaccines or vaccine regimens must be reviewed and approved by FDA, as explained in the *Emergency Use Authorization* [EUA] *for Vaccines to Prevent COVID-19* guidance. FDA does not expect vaccine developers to conduct the same large clinical trials that were required for initial EUA issuance. Instead, the effectiveness of a modified COVID-19 vaccine may be demonstrated through 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. FDA guidance provides recommendations for conducting 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 released guidance in February 2021—*Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests*—to provide test developers with recommendations for monitoring the impact of variants on their tests' performance and considerations for test design that can mitigate the impact of variants. Molecular tests, such as polymerase chain reaction (PCR) tests, identify the virus by detecting specific pieces of the viral genome, and have generally been developed using the same reference sequence. If a test's viral targets are altered in a variant, then the diagnostic may not detect them, generating a false negative result. This performance issue 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 and serology test performance may be affected if a viral genetic mutation affects the eventual structure of viral proteins (e.g., antigens) that are targeted by, or used as components in, these tests. These changes may also lead to false negative results.

FDA 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 used 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 viral 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 alert for clinical laboratory staff and health care providers in early January 2021 based on this work to alert the community about potential impacts of variants on specific EUA tests. The agency has continued to provide updates on affected tests to the diagnostics community since this time.

In September 2021, FDA issued notice of revisions to the EUAs of certain molecular, antigen, and serological tests, adding new conditions of authorization that must be met by test developers to account for new and emerging variants. Specifically, the conditions include updated labelling requirements to clarify that a test's performance is reflective of the variants circulating at the time of its clinical evaluation. In addition, developers must "evaluate the impact of SARS-CoV-2 viral mutations on your product's performance" on an ongoing basis.

Variants and Therapeutics

Several therapeutics are 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). For example, FDA 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.

The emergence of SARS-CoV-2 variants has raised concern about the effectiveness of existing therapeutics, particularly mAb products, which are designed to bind to the spike protein that allows the virus to infect the host cell in order to stop infection. In April 2021, FDA revoked the EUA for the mAb bamlanivimab, citing a "sustained increase of SARS-CoV-2 viral variants that are resistant to [it] alone resulting in the increased risk for treatment failure." The EUAs for other mAb products remain in effect (e.g., bamlanivimab and etesevimab, when administered together). FDA has further modified EUAs for authorized mAb products to require as a condition of authorization that, among other things, sponsors establish a process for monitoring genomic databases for the emergence of global variants of SARS-CoV-2 and, if requested by FDA, provide an assessment of the authorized products' activity against "any global SARS-CoV-2 variant(s) of interest." Notably, the conditions of authorization for one mAb product (bamlanivimab and etesevimab) limit its use to those states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to it is 5% or less, as determined by FDA based on CDC data. FDA has provided recommendations for design of mAb development programs and considerations for emerging variants in guidance (*Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency*).

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