



Keeping COVID-19 variants in-check under The Big Sky

Summary

- COVID-19 variants of concern are spreading throughout Montana
- FYR is using an innovative approach to perform variant tracking in western Montana, successfully tracking an outbreak of the Alpha variant in Ravalli County
- With the Delta variant now the predominate variant in Montana, variant tracking is critical from both an epidemiological and clinical standpoint
- Having variant information would help better track outbreaks and allow for care providers to adapt accordingly
- FYR proposes to continue to provide variant tracking information, and help facilitate the dissemination of the variant data to health care providers

Introduction

As of July 2021, the COVID-19 pandemic has resulted in 33.6 million cases and 603,000 deaths occurring in the US, with 114,000 cases and 1,661 deaths in Montana, where COVID-19 was the third leading cause of death in 2020 after heart disease and cancer. Several vaccines were approved under emergency use authorization and have been effective at bringing cases of COVID-19 down across the country, however the state is currently at a higher 7-day average case number than a year ago before vaccines were available. Additionally, vaccination rates have been plateauing in some areas, including Montana, where the vaccination rate is under the country-wide average by several percentage points.

The stagnating rate of vaccinations is troubling, as new variants of SARS-CoV-2 have emerged that may be more infectious or deadly and may potentially reduce vaccine or treatment efficacy. Prioritizing which variants to monitor is paramount to enacting effective public health measures, therefore the CDC has characterized and identified several Variants of Concern (VOCs) and Variants of Interest (VOIs) with a high potential for impacting global health outcomes, including showing demonstrable changes in transmissibility, virulence, disease severity (increased hospitalizations or deaths), reduced effectiveness of treatments and vaccines, or diagnostic detection failures (Table 1). Some include the 'Alpha' variant (first identified in the UK as B.1.1.7), the 'Beta' variant (first identified in South Africa as B.1.351), the 'Gamma' variant (first identified in Brazil as P.1), and the 'Delta' variant (first identified in India as B.1.617.2).

Table 1. Variants of Concern (VOCs)

WHO classification	Pango Lineage	Earliest documentation	Date of VOC Designation	Attributes
Alpha	B.1.1.7	UK, Sept 2020	Dec 18 th 2020	• 50% increased transmission • Potential increase in disease severity • Reduced neutralization by convalescent and post-vaccination sera
Beta	B.1.351	South Africa, May 2020	Dec 18 th 2020	• 50% increased transmission • Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment • Reduced neutralization by convalescent and post-vaccination sera
Epsilon	B.1.427/ B.1.429	US (California), Jan 2021	Mar 16 th 2021	• 20% increased transmission • Modest decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment • Reduced neutralization by convalescent and post-vaccination sera
Gamma	P.1	Brazil, Nov 2020	Jan 11 th 2021	• Increased transmissibility • Potential reduction in neutralization by some EUA monoclonal antibody treatments • Potential reduction in neutralization by post-vaccination sera
Delta	B.1.617.2	India, Oct 2020	May 11 th 2021	• Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment • Reduced neutralization by convalescent and post-vaccination sera

Information adapted from: SARS-CoV-2 Variant Classifications and Definitions, CDC, Updated June 23, 2021; (<https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>)

FYR's contribution to variant tracking in Montana

During the pandemic, FYR built a state-of-the-art high-throughput automation-enabled clinical testing lab and partnered with the state health department to offer COVID-19 testing to clinics and health care providers in Missoula and the surrounding counties. Soon after the CDC started to designate VOCs and VOIs, FYR decided to implement a plan to track these variants in positives samples identified at FYR using a system that would be compatible with our current testing infrastructure. Next-Generation Sequencing (NGS) is the definitive method required by the CDC to confirm the presence of variants, however, there is currently a bottleneck for the sequencing of COVID-19 samples. FYR's ability to rapidly and precisely identify presumptive COVID-19 variants to prioritize for sequencing allows for the more efficient use of scarce sequencing resources.

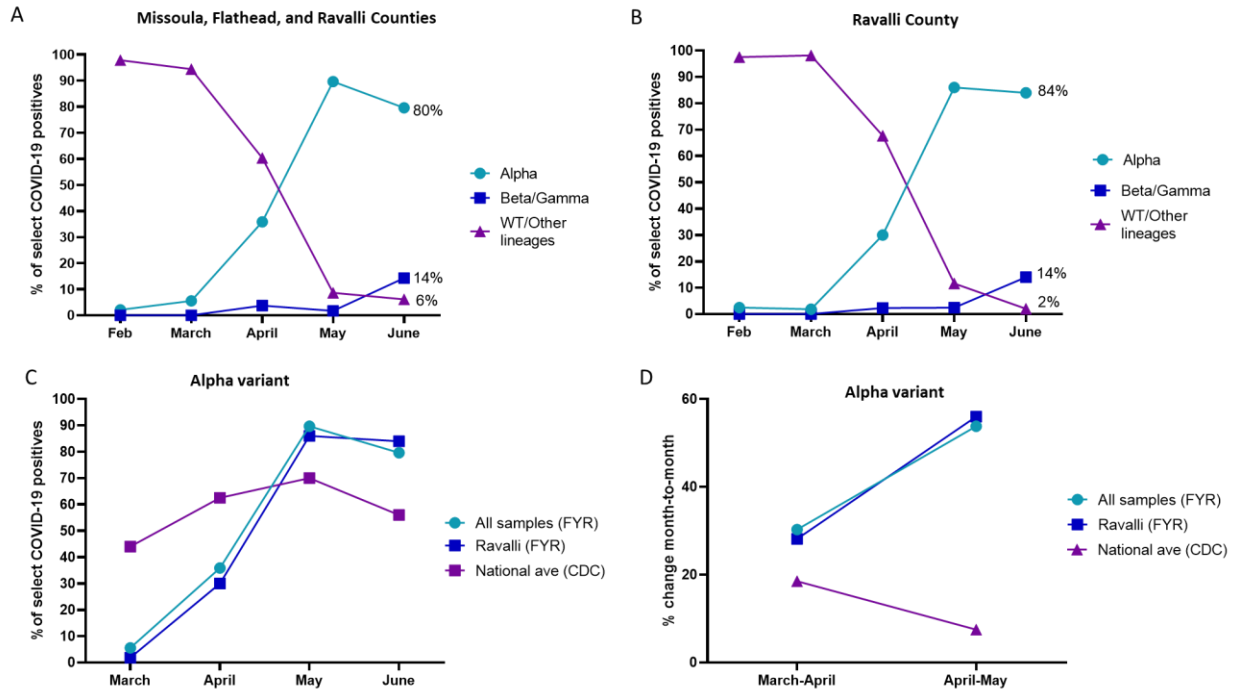
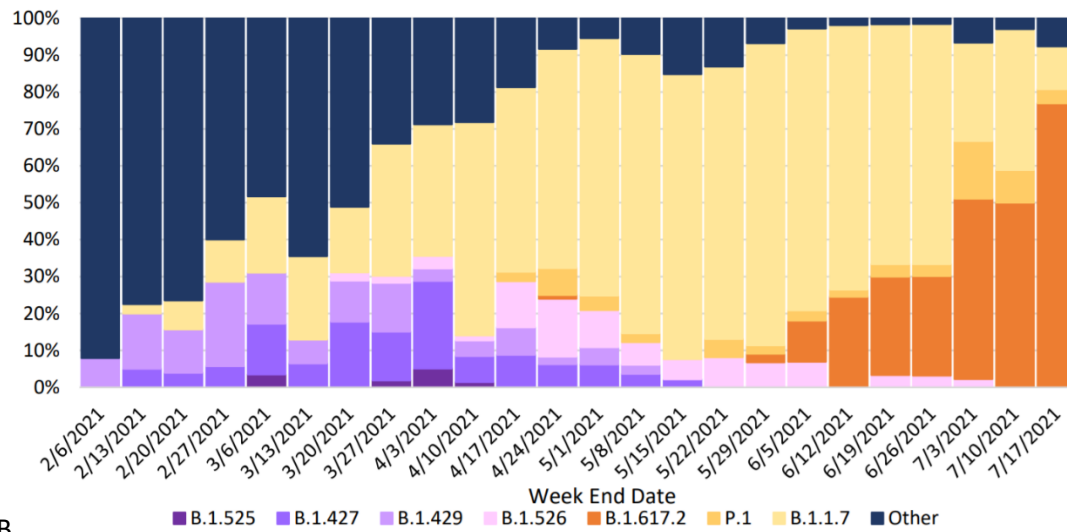


Figure 1: FYR's tracking of Variants in Missoula, Flathead, and Ravalli Counties. (A) Percentage of variants from COVID-19 positives from Missoula, Flathead and Ravalli counties combined from February to June. (B) Percentage of variants from COVID-19 positives from Ravalli counties from February to June. (C) Percent of Alpha variant between March and June, also including national averages from the CDC. (D) Month-to-month change in the Alpha variant including national averages from the CDC.

Through a combination of a custom rapid RT-PCR test to identify presumptive variants and NGS, FYR has been monitoring the presence of variants since February 2021 and has observed an above normal increase in the presence of the alpha variant over time compared to the national average (Figure 1. A,C). Furthermore, Ravalli County is the major contributor of variants we identified, which we observed to have the greatest number of variant cases and the most rapid increase in the presence of the alpha variant, which was also significantly higher and faster than the national averages reported by the CDC (Figure 1. B,C). Between March and May, the month-to-month change in Alpha variant proportion increased in the samples we tested, including those from Ravalli County compared to the national average (Figure 1D). In fact, in May, the highest percentage of Alpha variants in a single state was Tennessee at 86.1%, the same as the percentage of Alpha variants in Ravalli County during that time [1]. Furthermore, because FYR was doing the majority of testing for Ravalli County, if it was not for the variant monitoring plan FYR had in place, this surge would probably not have been discovered. And while this data was being relayed to public health authorities, there was an inability for the providers in Ravalli County to access the variant data at a provider or institutional level. Unfortunately, during the height of the alpha variant surge, Ravalli County recorded an all-time high number of single-day COVID-19 deaths, with 12 deaths on May 8th, 2021, with no knowledge of the surge in variants taking place.

Since these events, the Delta variant has now taken a foothold in Montana and has displaced Alpha as the most common SARS-CoV-2 variant present in the state (Figure 2A). Accordingly, the 7-day average of new cases have now increased in Montana to the highest in the last few months (Figure 2B).

A



B

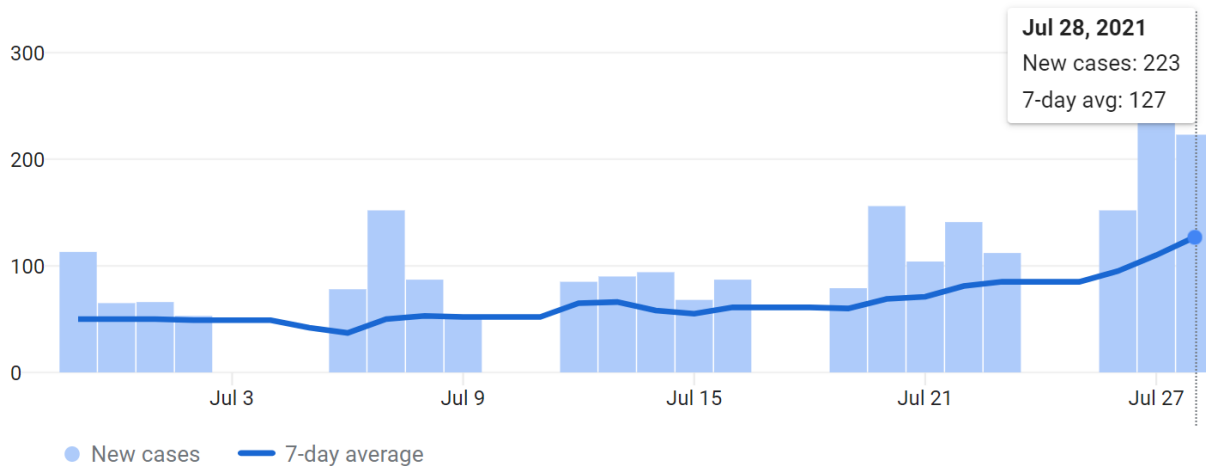


Figure 2: Current snapshot of COVID-19 cases in Montana (as of July 28th, 2021). (A) Percent of SARS-CoV-2 variants in sequenced samples by collection date (taken from DPHHS website: <https://montana.maps.arcgis.com/apps/MapSeries/index.html?appid=7c34f3412536439491adcc2103421d4b>). (B) Increase in COVID-19 cases in July 2021, as Delta becomes the predominate variant (taken from NY Times website: <https://www.nytimes.com/interactive/2021/us/montana-covid-cases.html>).

Delta is associated with the current surge in cases seen in unvaccinated individuals, and breakthrough cases seen in fully vaccinated individuals. Because of the seriousness of the variant, it is imperative that the tracking of longitudinal variant data for the State also be done at the County level and ensure that providers have access to some form of institutional level data. While Delta now will make up the majority of cases across counties in Montana, there are other VOIs that are emerging that could become VOCs at some point, potentially leading to new outbreaks in Montana.

The recommended path moving forward

Our RT-PCR based screening process for variant identification is meant to be a rapid easy bridge to sequencing, which is the definite method to classify VOCs/VOIs. We have been lucky to have external sequencing resources available during most of the screening process, however, at several points during

the pandemic we have hit sequencing capacity limits as available sequencing resources in-state is a huge bottleneck in Montana, and as a result samples are often sent out-of-state to be sequenced.

To circumvent this issue, FYR has implemented our own sequencing infrastructure that allows for selected positive samples (including presumptive variant samples) to be sequenced in-house. This data will be shared with the CDC and the State health department for epidemiological and surveillance purposes. To assist in this further, FYR has also joined the CDC's consortium on COVID-19 sequencing called SPHERES (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance).

While this data is very useful for the surveillance of outbreaks, there has been a critical disconnect on getting this data at an institutional level to healthcare providers, where variant information could be supremely beneficial in tracking variant presence with mortality data and allow for clinics, hospitals, long-term care facilities, and other providers to adapt as needed. As seen in the surveillance data produced by FYR's efforts, the increase in the presence of variants can occur extremely rapidly. Thus, for the variant surveillance to provide utility to healthcare providers during these sudden changes, this data needs to be produced immediately after COVID-19 variant cases have been identified and that data needs to be quickly accessible by healthcare providers. FYR's screening and sequencing infrastructure enables rapid testing and surveillance monitoring that can provide same week results of variant data after the initial COVID positive sample is identified. This will provide the most real-time up-to-date information for providers to utilize once a system is in place.

What could more data about the variants tell us?

The data generated through sequencing efforts have been essential in enabling further characterization of variants to determine the role the variants have on vaccine efficacy, health outcomes (e.g. mortality), transmission rates, and the efficacy of treatment options. Some specific areas that benefit from this data include:

- **Identifying Breakthrough cases:** Determination of a causal relationship between certain variants or mutations and cases of infection following historical infection events or vaccination may be an indication of viral evolution driven by immune escape. For example, several of the variants have reduced neutralization by convalescent and post-vaccination sera including the Alpha, Beta and Delta variants (Table 1), and a recent study has shown that the Alpha and Beta variants are associated with increased breakthrough cases [2].
- **Selective pressures driven by therapies and vaccines:** As our arsenal of therapeutic tools to combat SARS-CoV-2 grows, it is important to understand if any of these therapies apply selective pressure on the virus favoring the proliferation of existing VOCs or the generation of new VOCs.

The data has also been used to demonstrate the effect of mutations on therapeutics and what the long-term health outcomes might be. It should be important to note that at this time sequencing data, including variant level lineage information, is currently considered for research use only (i.e. for epidemiological purposes), and is not regulated by CLIA or CMS to be used for individual patient level healthcare decisions, nor is the data to be disseminated to patients, providers, or institutions at the patient level. While there is strong evidence showing the value of VOC data on therapeutics treatment options or symptomology, this data was generated at a research study level, and there is no current guidance on making health care decisions based on these VOCs. However, once there is proper regulation and guidance, the data would be pertinent to health care providers who could use VOC information to

guide treatment options, or to understand symptomology. More specifically when eventually permitted the data could be used in addressing the following areas of concern:

- **Impact on therapeutics or treatment regimens:** There is already evidence of reduced efficacy of certain therapeutics such as bamlanivimab/etesevimab or convalescent antibodies against certain variants (Table 1). Data on regional prevalence of these variants will be critical in informing care providers on the use of affected therapies in patient care settings.
- **Monitoring trends regarding long COVID patients, or those with unique symptomatology:** By pairing variant data with those patients with unique or characteristic symptoms (e.g. long COVID), insight can be gained into understanding the full impact of variants on these clinical observations. For example, if a given variant is associated with longer or more severe hospitalizations, this would allow for hospital administrators to plan accordingly for a surge if there is an outbreak of that variant. A preliminary study out of the UK suggests that symptomology for the Delta variant might be different from other variants [3], thus easily monitoring the presence of this variant in the COVID-19 positive population alongside the symptomology is of extreme importance.

The current surveillance systems that have been established are a key step in curbing this pandemic. However, there remains a scarcity of genomic data for many locations, despite high or rising case numbers. This is problematic in that there are likely to be many more SARS-CoV-2 variants circulating globally than are currently characterized. Only those locales with routine genomic surveillance are likely to detect them.

What do we need to continue moving forward?

We have implemented our sequencing infrastructure to operate at capacity to sequence any positive samples that come through FYR and handle excess COVID-19 sequencing that other state sequencing resources cannot handle, thus drastically increasing the sequencing capacity of the state. To have maximal impact on the health care of Montanans there needs to be an integrated way to inform the providers when relevant variants are discovered that could inform general patient treatments and health outcomes. A faster turnaround time for samples to be sequenced and data provided would enable early detection and lead to an earlier course of action. Currently, due to the way variant screening or sequencing is performed, and the data is being utilized, the data is restricted to epidemiological and surveillance purposes, and providers and patients have limited access to reporting of variant data. Even if reporting of variant information cannot be disseminated at the patient level, finding a way to bridge the variant surveillance data with the health care providers would be beneficial.

Currently, there is an urgent need for longitudinal county-level data to see how variant rates are changing in comparison to total positive cases. In order to accomplish this, FYR proposes one of two solutions to be implemented. 1) FYR can tap into the already existing reporting system that is linked to hospital systems and healthcare providers around the state. FYR is already integrated with the DPHHS electronic reporting system, which enables secured bidirectional HL7 messaging. FYR could pool the information that DPHHS and other entities are reporting through DPHHS and combine it with the data produced by FYR, then push relevant updates and information on variant rates to each healthcare provider system. 2) FYR could alternatively build an online database that combines all the variant surveillance data from DPHHS, other entities, and FYR and makes it accessible to healthcare providers at an institutional level in real-time as the data is produced. This would enable healthcare providers to login and see the updated positive COVID

rates and variant rates over time for their specific location, which allows them to have rapid easy access to this essential information.

In either deployment scenario, once FYR has access to all the COVID testing data and variant surveillance data, FYR could also couple this information with other relevant information, such as location-based vaccine distribution numbers or location-based mortality numbers and produce important reports and graphs in real-time that provide comparisons between all of this data for the ultimate view of relevant information. This platform will have real-time data and can be setup to enable production of custom graphs and reports depending on what the end user (e.g. healthcare providers) would like to view. In addition, FYR can provide links and easy access to relevant guidelines and information from the CDC, FDA, WHO, and other health agencies relevant to the variants that are of interest based on the data produced.

Having a seamless strategy to exchange variant surveillance data with providers is essential for the health of Montanans, especially as a significant proportion of the population remains unvaccinated and additional VOCs emerge.

References

- [1] COVID Data Tracker, CDC, Updated June 05, 2021; <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>
- [2] Kustin, T., Harel, N., Finkel, U. et al. *Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals*. Nat Med (2021). <https://doi.org/10.1038/s41591-021-01413-7>
- [3] ZOE COVID Symptom Study, Updated February 2021: <https://covid.joinzoe.com>