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COVID-19 Literature Review Group

Prepared by The Ohio State University

COVID-19 Outbreak and Reinfection, Reinfection with SARS-CoV-2, Vaccine Sensitivity to Variants, Vaccine & Clotting Disorder, and Immune Thrombocytopenia

ODH Literature Review Group
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COVID-19 Literature Review

Prepared by Eliana Burlotos, The Ohio State University

April 16, 2021

Topic: COVID-19 Outbreak and Reinfection

Title: Community Transmission of SARS-CoV-2 Associated with a Local Bar Opening Event – Illinois, February 2021

Source: *MMWR*

Publication Date: April 5, 2021

Link: https://www.cdc.gov/mmwr/volumes/70/wr/mm7014e3.htm?s_cid=mm7014e3_w

Study Period: February 2021

Study Location: Illinois Bar

Sample Size: 100 persons

Summary: This article discusses COVID-19 cases that were linked to an indoor bar opening event in a rural Illinois county in February 2021. Event cases included one hospitalization and one school closure affecting 650 students. The bar accommodated approximately 100 persons. There were 46 overall COVID-19 cases linked to the event, including 26 patrons and 3 staff members who attended the event and 17 secondary cases. 4 persons with cases had COVID-19-like symptoms on the same day that they attended the event. These findings emphasize that as businesses began to reopen, the risk of community transmission of SARS-CoV-2 increases. Furthermore, SARS-CoV-2 transmission originating in businesses not only affects the patrons and employees but can also affect an entire community.

Key Findings Relevant to Ohio's Response: As businesses reopen, as does the risk for community transmission of SARS-CoV-2. It is crucial for businesses to consider additional prevention measures like limiting building occupancy levels and improving ventilation.

Title: Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study

Source: NCBI

Publication Date: March 15, 2021

Link: <https://www.ncbi.nlm.nih.gov.proxy.lib.ohio-state.edu/pmc/articles/PMC7989568/>

Study Period: March 12, 2020 - February 24, 2021

Study Location: Cleveland, Ohio

Sample Size: 150,325 patients tested for COVID-19 infection

Summary: This study article discusses results from a retrospective cohort study of a multi-hospital health system. 150,325 patients were tested for COVID-19 infection via PCR from March 12, 2020 to August 30, 2020. Testing of these patients performed up to February 24, 2021 was included in the analysis. Reinfection, defined as infection \geq 90 days after initial testing, was looked for. Of the 150,325 patients, 5.9% tested positive and 94.1% tested negative prior to August 30. 14.4% of the positive patients were retested after 90 days, and 4.85% (62) of those had possible reinfection. Of those possible reinfections, 50% were symptomatic. Protection offered from prior infection was 81.8% (95% confidence interval 76.6 to 85.8), and against symptomatic infection was 84.5% (95% confidence interval 77.9 to 89.1). In conclusion, prior infection in patients with COVID-19 was highly protective against reinfection and symptomatic disease. This protection increased over time, which suggests viral shedding or ongoing immune response may last beyond 90 days and may not represent true reinfection.

Key Findings Relevant to Ohio's Response: As vaccine rollout continues, it is important to give vaccines to the most vulnerable populations. Perhaps patients with known history of COVID-19 could delay early vaccination to allow for more vulnerable populations to be vaccinated.

COVID-19 Literature Review

Prepared by Elena McGoey, The Ohio State University

April 16, 2021

Topic: Reinfection with SARS-CoV-2

Title: Reactivation of SARS-CoV-2 infection following recovery from COVID-19

Source: LitCovid

Publication: April 14, 2021

Link: <https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/33848891>

Study Period: January 18, 2020 to April 23, 2020

Study Location: Beijing, China

Sample Size: 109

Summary: 27% (29 patients) of the 109 patients who previously had COVID-19 experienced reactivation. 24% (7 patients) of those who had reactivation of SARS-CoV-2 experienced symptomatic COVID-19. Those who experienced reactivation were younger and more likely to experience two or fewer symptoms or low lymphocyte count during their initial SARS-CoV-2 infection, when compared to patients who did not experience relapse.

Key findings most relevant to Ohio's response: The relatively high relapse rate should be considered during implementation of preventive measures. Active surveillance should be continued for those who have recovered from SARS-CoV-2 infection, particularly in groups that have a difficult time maintaining social distancing measures (for example, healthcare workers) and in those with risk factors for SARS-CoV-2 relapse (two or fewer symptoms and/or low lymphocyte count when initially infected).

Title: Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study

Source: *The Lancet Public Health*

Publication: April 12, 2021

Link: [https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667\(21\)00055-4/fulltext](https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00055-4/fulltext)

Study Period: September 28, 2020 to December 27, 2020

Study Location: U.K.

Sample Size: 36,920

Summary: The B.1.1.7 variant was not associated with any changes in reported COVID-19 symptoms or duration. Additionally, the B.1.1.7 variant was not associated with an increase in reinfections by SARS-CoV-2. Relapse cases were more positively correlated to regional rise in cases than to regional increases in the proportion of cases with the B.1.1.7 variant.

Key findings most relevant to Ohio's response: Existing procedures for COVID-19 testing do not need to be changed for the presence of the B.1.1.7 variant. Since reinfection is not more likely due to the presence of the B.1.1.7 variant, this suggests that immunity from previous infection with other SARS-CoV-2 variants will likely protect against the B.1.1.7 variant as well. This data also suggests that current SARS-CoV-2 vaccines for the original variant will be effective for the B.1.1.7 variant.

COVID-19 Literature Review

Prepared by Anjali Prabhakaran, The Ohio State University

April 18, 2021

COVID-19 Literature Review

Title	Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine
Source	American Journal of Hematology
Publication Date	01/21/2021
Link	https://onlinelibrary-wiley-com.proxy.lib.ohio-state.edu/doi/10.1002/ajh.26106
Study Period	n/a
Study Location	Milwaukee, Wisconsin
Sample Size	1
Summary	<p>This study is a case report of a 22-year-old male with immune thrombocytopenia after receiving a Pfizer-BioNTech mRNA SARS-CoV-2 vaccine. The individual was current on his vaccines and had no history of infection, and no personal or family history of bleeding or autoimmune disease. While vital signs, white-cell count, and hemoglobin were normal, lab tests revealed severe thrombocytopenia with a platelet count of $2 \times 10^9/L$. On day 3 post vaccination, Sjogren's Syndrome A antibody (2.8) was elevated. On day six post-vaccination, petechiae and oral bleeding decreased, and the patient was discharged with a platelet count of $28 \times 10^9/L$. At a follow-up on day 11, the patient's platelet count normalized to $173 \times 10^9/L$, and the Sjogren's Syndrome A decreased from 2.8 to 1.5.</p>
Key Findings Relevant to Ohio's Response	<p>Case reports on post-vaccine complications will be incredibly important to monitor post-vaccine complications. Previous studies report only mild or moderate adverse events following the Covid-19 vaccine, and this article marks the first case published in the medical literature experiencing ITP after receiving the Pfizer-BioNTech vaccine with no other cause or associated illness identified. This article will be useful for healthcare professionals to educate themselves on other possible side effects of COVID-19 vaccines.</p>

Title	COVID-19 re-infection
Source	European Journal of Clinical Investigation
Publication Date	03/06/2021
Link	https://onlinelibrary-wiley-com.proxy.lib.ohio-state.edu/doi/10.1111/eci.13537
Study Period	February 2020 to January 2021
Study Location	Marseille, France
Sample Size	232,195
Summary	This study describes cases of re-infection with different SARS-CoV-2 genotypes in patients served in Marseille, France. Patients with confirmed COVID-19 were given a clinical evaluation at day 1, and genome sequencing was performed to identify the SARS-CoV-2 strain. Among the 90, 602 patients tested in the first wave, 31 (0.47%) were diagnosed with re-infection. The mean time that elapsed between the first and second infection was 173 days, mean age was 50 +/- 22 years old, and 51.2% had no comorbidities. Additionally, significantly more patients were classified as having a sever/critical infection than the first infection (p=0.044).
Key Findings Relevant to Ohio's Response	Though re-infections of COVID-19 are rare, it is important to continue to monitor cases of re-infection to understand how COVID-19 immunity functions. Understanding this will be critical to calculating how and when herd immunity can be achieved. However, more research is necessary to determine the mechanisms of re-infection to determine whether re-infection is due to the insufficient efficacy of natural immunity or from its too high specificity regarding SARS-CoV-2 genomic mutations.

COVID 19 Literature Review

Prepared by Amanda Seiffert, The Ohio State University

April 16, 2021

Topic: Vaccine Sensitivity to Variants

Title: Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA Vaccine-Elicited Antibodies

Source: Nature

Publication Date: 03/11/2021

Link: <https://www-nature-com.proxy.lib.ohio-state.edu/articles/s41586-021-03412-7>

Study Period: N/A

Study Location: United Kingdom

Sample Size: 37

Summary: With the emergence of increasingly transmissible variants, namely the B.1.1.7 variant, concerns regarding the effectiveness of Covid-19 vaccines against new strains have arisen. Thus, researchers investigated the immune responses of fully and partially vaccinated individuals to pseudoviruses containing the mutated spike-protein found within the B.1.1.7 variant. After experimentation, researchers found that vaccinated individuals displayed a modest reduction in neutralization against pseudoviruses modeling the B.1.1.7 variant. This reduction was more substantial following the first dose of the Covid-19 vaccine than the second dose. Likewise, recovered patients displayed reduced immunity to the B.1.1.7 variant pseudovirus. The most substantial reduction in neutralization occurred when individuals were exposed to the pseudovirus of a newly discovered variant, known as the VOC 202102/02 variant. Researchers conclude that observed immune responses reflect a threat to the efficacy of mRNA Covid-19 vaccines.

Key Findings Relevant to Ohio's Response: Researchers hold that the reduced efficacy of mRNA vaccines against emerging variants does call for concern. Moreover, they state that next-generation vaccines containing mutated spike sequences and alternative viral antigens are necessary to address the impact of new variants. This suggestion indicates the need to achieve higher vaccine acceptance among the public, as subsequent vaccinations may be necessary to continue combating the Covid-19 pandemic.

Title: Sensitivity of Infectious SARS-CoV-2 B.1.1.7 and B.1.351 Variants to Neutralizing Antibodies

Source: Nature

Publication Date: 03/26/2021

Link: <https://www-nature-com.proxy.lib.ohio-state.edu/articles/s41591-021-01318-5>

Study Period: April 2020

Study Location: France

Sample Size: 77

Summary: In order to investigate immunity against emerging variants, specifically the B.1.1.7 variant and the B.1.351 variant, researchers isolated such strains and tested their sensitivity to antibodies within the sera and nasal swabs of previously infected or vaccinated individuals. They used the D614G strain as a reference virus. Researchers found that convalescent sera neutralized the D614G and B.1.1.7 virus similarly, but there was a mean sixfold reduction in neutralization of the B.1.351 variant. 40% of sera samples did not display any activity against the B.1.351 strain. After second vaccination, a slight increase in neutralization of the B.1.351 strain ensued, but it remained substantially lower than the B.1.1.7 and D614G strains. Moreover, higher antibody levels were associated with higher protection against variants, but the B.1.351 variant was significantly resistant in all scenarios.

Key Findings Relevant to Ohio's Response: This study provides a positive outlook for vaccine efficacy against the B.1.1.7 variant, but a more dire prospect regarding protection against the B.1.351 variant. Overall, it is clear that certain variants reduce immunity to SARS-CoV-2, indicating the need for continued health behaviors, such as mask-wearing, hand-washing, and reduced social gatherings. Even with increased vaccine distribution, the public should be encouraged to continue complying with public health guidelines.

COVID-19 Literature Review

Prepared by Greta Warmbier, The Ohio State University

April 14, 2021

Topic: Vaccine x Clotting Disorder

Title: Hard choices emerge as link between AstraZeneca vaccine and rare clotting disorder becomes clearer

Source: Science Magazine

Publication Date: April 11, 2021

Link: <https://www-sciencemag-org.proxy.lib.ohio-state.edu/news/2021/04/hard-choices-emerge-link-between-astrazeneca-vaccine-and-rare-clotting-disorder-becomes>

Study Period: n/a

Study Location: n/a

Sample Size: n/a

Summary: The AstraZeneca COVID-19 vaccine can, in very rare cases, cause a disorder characterized by dangerous blood clots and low platelet counts. In Europe, at least 222 suspected cases have been reported among 34 million people who have received their first dose of the vaccine. Thirty deaths have been confirmed. On April 7, 2021, The European Medicines Agency (EMA) acknowledged “a probable causal association” between the syndrome and the vaccine. It is possible that the disorder results from a mechanism driven by an errant immune reaction. It is unclear who is vulnerable to this disorder, but some countries have restricted who is receiving the vaccine, limiting it to older age groups. Researchers stress that the vaccine’s benefits outweigh the risks, and the cheap and easy to store vaccine is still the best hope for vaccinating large numbers of people in low- and middle-income countries. Some scientists suggest cutting the vaccine dose in half to reduce risk.

A study in *The New England Journal of Medicine* [describes 11 patients in Germany and Austria](#) and 5 patients in Norway. Results showed that the patients had unusual antibodies that trigger clotting reactions, which use up the body’s platelets and can block blood vessels, leading to potentially deadly strokes or embolisms. The symptoms resemble a rare reaction to the drug heparin, called heparin-induced thrombocytopenia (HIT), in which the immune system makes antibodies to a complex of heparin and a protein called platelet factor 4 (PF4), triggering platelets to form dangerous clots throughout the body. Sickened vaccine recipients also had antibodies to PF4. Researchers are calling the reaction: vaccine-induced immune thrombotic thrombocytopenia (VITT).

The vaccine consists of an adenovirus engineered to infect cells and prompt them to produce the virus’ spike protein. Among the 50 billion or so virus particles in each dose, some may break apart and release their DNA. Like heparin, DNA is negatively charged, which would help bind it to PF4, which has a positive charge. The complex might then trigger the production of antibodies, especially when the immune system is already on high alert because of the vaccine. An immune reaction to extracellular DNA is part of an ancient immune defense triggered by severe infection or injury. Free DNA itself can [signal the body](#) to increase blood coagulation.

Alternatively, the antibodies may already be present in the patients and the vaccine may just boost them. Many healthy people harbor such antibodies against PF4, but they are kept in check by an immune mechanism called peripheral tolerance. Early suggestions that the rare reactions may be the result of a COVID-19 infection before vaccination have not been substantiated. None of the five patients in Norway had been infected, for instance. Others have suggested that antibodies against the virus’ spike protein—which many vaccines seek to elicit—somehow cross-react with PF4. That could spell trouble for nearly all COVID-19 vaccines. But so far, there is no evidence that the messenger RNA–based vaccines are causing similar clotting disorders.

On April 9, 2021, EMA said it was investigating 4 cases of similar clotting seen in U.S. patients who had received the Johnson & Johnson vaccine, which has been used in the United States since early March but has yet to make its debut in Europe. The cases could be coincidence.

Relevance to Ohio’s COVID-19 Response: More common side effects of the vaccine appear less frequently at half a dose. If this is true for more serious side effects, “then what looked like a terrible blow for one of the world’s most important weapons against the pandemic might be good news in disguise: Supplies of the vaccine could vaccinate twice as many people—with fewer side effects.”

Topic: Immune Thrombocytopenia

Title: Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine

Source: American Journal of Hematology

Publication Date: January 21, 2021

Link: <https://onlinelibrary-wiley-com.proxy.lib.ohio-state.edu/doi/10.1002/ajh.26106>

Study Period: n/a

Study Location: n/a

Sample Size: 1

Summary: A 22-year-old healthy male with no medication use received the Pfizer vaccine through his work as an emergency department employee. On day 3, post-vaccination, he experienced widespread petechiae and gum bleeding. He was current on his vaccines, including yearly influenza, with no history of adverse reactions. He denied respiratory and gastrointestinal complaints or a history of infection. He had no personal or family history of bleeding or autoimmune disease. Vital signs and the remainder of his exam were normal. Laboratory tests revealed normal white-cell count, hemoglobin, and severe thrombocytopenia with a platelet count of $2 \times 10^9/L$.

Two months prior to receiving the vaccine, the patient was evaluated at an outpatient clinic for upper respiratory symptoms. His PCR assay returned negative for SARS-CoV-2, and complete blood count was normal. The upper respiratory symptoms resolved within a few days, and the patient had no further complaints. One-week post outpatient evaluation, he was again tested for SARS-CoV-2, which returned negative.

At the emergency department on day 3, post-vaccination, the following labs were normal or negative: prothrombin time, partial thromboplastin time, fibrinogen, BUN, creatine, electrolytes, bilirubin, LDH, alkaline phosphatase, albumin, globulin, total protein, and haptoglobin. The aspartate aminotransferase and alanine aminotransferase were mildly elevated. However, they normalized the next day. He tested negative for HIV, Hepatitis B, Hepatitis C antibody, and Epstein–Barr Virus serology. A nasopharyngeal swab also returned negative for SARS-CoV-2 antigen. The patient was then admitted and given dexamethasone 40 mg daily for 4 days, a platelet transfusion, and intravenous immunoglobulin at 1 g/kg for 2 days.

Immunologic studies performed on day 6 for Rheumatoid factor, antibodies for Cyclic Citrullinated Peptide, Anti Centromere, Chromatin IgG, dsDNA, Jo1, Ribosomal P Protein, Ribonucleoprotein, Scleroderma, Smith, Sjogren's Syndrome B, Sm/Rnp IgG, and Antinuclear Antibody were normal. However, Sjogren's Syndrome A antibody was elevated.

On day 6, post-vaccination, petechiae and oral bleeding decreased, and the patient was discharged. A diagnosis of ITP was made. At follow up, on day 11, the patient's platelet count normalized to $173 \times 10^9/L$, and the patient tested positive for plasma IIb/IIIa and Ia/IIa platelet autoantibodies. Sjogren's Syndrome A antibody returned to normal. Complement C3 was normal, while complement C4 was low.

This is the first case published in the medical literature of an individual, with no other cause identified and no associated illness, experiencing ITP after receiving the Pfizer vaccine. The rapid and severe drop in platelet count to $2 \times 10^9/L$ is reminiscent of the abrupt onset observed in drug-induced thrombocytopenia, which further suggests a recent etiology.

Relevance to Ohio's COVID-19 Response:

The incidence of ITP is about 3.3 per 100,000 adults/year. It is plausible that this patient's diagnosis was purely coincidental. 43,448 participants were included in the Pfizer trial, and no ITP was reported.