TITLE:
The impact of vaccination on severity of illness in COVID-19: A multicenter cohort study

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Investigation Protocol

Title:

The impact of vaccination on severity of illness in COVID-19: A multicenter cohort study

Background and Rationale:

With the FDA's emergency use authorization declaration in December of 2020, the Pfizer-BioNtech vaccine became the first of several vaccines to kick off the mass vaccination effort across the United States.[1] Subsequently, Moderna as well as Johnson and Johnson both had their vaccines receive emergency use authorization.[2] While the Pfizer and the Moderna vaccines both utilize novel mRNA technology, Johnson and Johnson's vaccine uses a viral vector that has been used previously in both the European approved Ebola vaccine and a trial vaccine for HIV. However, none of these vaccine types have previously been approved in the United States.[3] While preliminary data from safety and efficacy trials have shown positive results, actual-world data on its effectiveness is still lacking. [4] Several small cohort studies and one large trial from Israel are currently our only insights into the actual rates of infection, hospitalization, and severe illness among vaccinated individuals.[5–7] As COVID-19 variants, with the potential to reduce vaccine efficacy, continue to emerge worldwide, we are in desperate need of more data regarding the real-world effectiveness of our current mass vaccination efforts.[8]

Vaccination efforts in the State of Michigan have been ongoing since December. Given that approximately 33.7% of the state's population is either partially or fully vaccinated, it is unclear why the number of cases has risen so dramatically or if immunization efforts can help the situation.[9]

Given the current situation in the State of Michigan, we aim to evaluate the efficacy of COVID-19 vaccination on rates of severe illness when breakthrough SARS-CoV-2 infection occurs in a region with high incidence of variant strain disease. The research hypothesis is that fully vaccinated patients are at reduced risk for the most severe outcomes.

Specific Aims:

Aim 1: To compare the rate of severe COVID-19 infection among unvaccinated, partially vaccinated, and fully vaccinated patients.

For Aim 1, severe infection is defined as composite ICU admission, mechanical ventilation, and in-hospital mortality.

Aim 2: To compare rate of additional clinical outcomes of COVID-19 infection for hospitalized patients among unvaccinated, partially vaccinated, and fully vaccinated patients.

For Aim 2, relevant clinical outcomes include: Extracorporeal membrane oxygenation (ECMO), new renal replacement therapy (RRT), high flow oxygen, low flow oxygen (non-rebreather or nasal cannula), noninvasive ventilation, and hospital length of stay.

Aim 3: To compare proportions of ED presentations and hospitalizations among unvaccinated, partially vaccinated, and fully vaccinated patients presenting to an emergency department.

For Aim 3, the incidence of ED presentation of partially vaccinated and fully vaccinated populations will be adjusted for the proportion of the local community that is vaccinated based on State of Michigan data.

Aim 4: To compare hospitalization rates among unvaccinated, partially vaccinated, and fully vaccinated patients presenting to an emergency department.

For Aim 4, we will compare the percentage of patients that are admitted from each cohort.

Exploratory Aim 1: To compare three vaccination types for Aim 1 and Aim 2.

For Exploratory Aim 1, outcomes for Aims 1 and 2 will be assessed for fully vaccinated patients receiving Pfizer-BioNtech, Moderna, and Johnson and Johnson vaccinations.

Exploratory Aim 2: To compare predictors of hospitalization among unvaccinated, partially vaccinated, and fully vaccinated patients presenting to an emergency department.

For Exploratory Aim 2, demographic, epidemiological, clinical, and laboratory variables will be assessed to determine risk factors for hospital admission.

Study Design and Eligibility:

Study Design:

We plan to perform a retrospective chart review of all patients who presented to Beaumont health system emergency departments between December 15, 2021 and April 30, 2021 and were diagnosed with COVID-19 ≤ 28 days of ED encounter or prior to discharge. All hospitalized patients will have a designated follow-up date of May 15, 2021. For each individual we will collect epidemiological, demographic, therapeutic, clinical, and outcomes data.

Vaccination data from the state of Michigan will be extracted via the Michigan Care Improvement Registry (MCIR) and therefore capture patients who have been vaccinated outside of the Beaumont Health system. This data includes vaccine type as well as date of administration.

Demographic and epidemiological data includes: age, gender, race, and zip code of residence

Clinical data includes: existing medical conditions (Elixhauser comorbidity score), vital signs (temperature, blood pressure, heart rate, respiratory rate, pulse ox), home medications, chief complaint from emergency provider note, duration of symptoms in days at the time of presentation from emergency provider note, chest x-ray or chest CT results, and laboratory values (WBC, hg, ALT, Cr, lactated, dimer, procalcitonin, CRP, LDH, troponin). Vaccination status including vaccine brand (Pfizer, J&J, Moderna), vaccine administration date(s).

Therapeutic/Outcomes data includes: Hospital admission unit type (regular medical or surgical floor, progressive floor, intensive care unit), ICU length of stay, change in unit type during admission. Oxygen therapy (none, nasal canula, non-rebreather, venturi mask, trach collar, non-invasive ventilation, high flow nasal cannula, mechanical ventilator), days on high flow, days on ventilator, specific inpatient medical therapies (hydroxychloroquine, chloroquine, remdesivir, lopinavir-ritonavir, bamlanivimab, tocilizumab, baricitinib, convalescent plasma, monoclonal antibodies, corticosteroids, vasopressors, anticoagulants), ECMO, RRT, noninvasive ventilation, hospital length of stay, and disposition from hospital (home, rehabilitation unit, death).

Study Definitions:

Patients will be categorized as either unvaccinated, partially vaccinated, or fully vaccinated. Unvaccinated individuals are defined as having positive laboratory COVID-19 testing with no record of immunization against COVID-19 or first-dose vaccination after symptom onset. Partially vaccinated individuals are defined as having positive laboratory COVID-19 testing and symptom onset after a single dose of either mRNA (Pfizer, Moderna) vaccine, or < 14 days after the second dose of either mRNA vaccine (Pfizer, Moderna) or < 14 days after the administration of the single dose of viral vector vaccine (Johnson & Johnson). Fully immunized individuals are defined as having positive laboratory testing for COVID-19 and symptom onset ≥ 14 days since administered of second dose of either mRNA vaccine, or ≥ 14 days since administration of viral vector vaccine (Johnson & Johnson). (Appendix A – Figure represents categorization of study subjects)

Confirmed COVID 19 infection is defined as laboratory confirmed positive result identified by rapid antigen testing or reverse-transcriptase-polymerase-chain-reaction (RT-PCR) by nasopharyngeal swab. Patients are considered lab positive if they had either PCR or antigen testing available in our database. Patients are also considered confirmed COVID 19 if they had clear reference in the medical chart to positive lab testing performed at an outpatient lab ≤ 28 days of ED encounter.

Eligibility:

Inclusion Criteria

All patients presenting to Beaumont health site's emergency departments between December 15, 2020 and April 30th, 2021 who meet our definition of confirmed COVID-19 infection.

Exclusion Criteria

Patients are excluded if:

--Test positive for COVID-19 >28 days prior to ED encounter.

--Identified as COVID-19 by diagnosis or ICD code but have no available lab data and no reference to a positive lab test in the clinical notes.

--There is irregular vaccination data such as duplicate entries or multiple vaccine brands within the MCIR registry.

--Categorized to either vaccine group but no date of symptom onset is evident from the clinical record.

Study Methods:

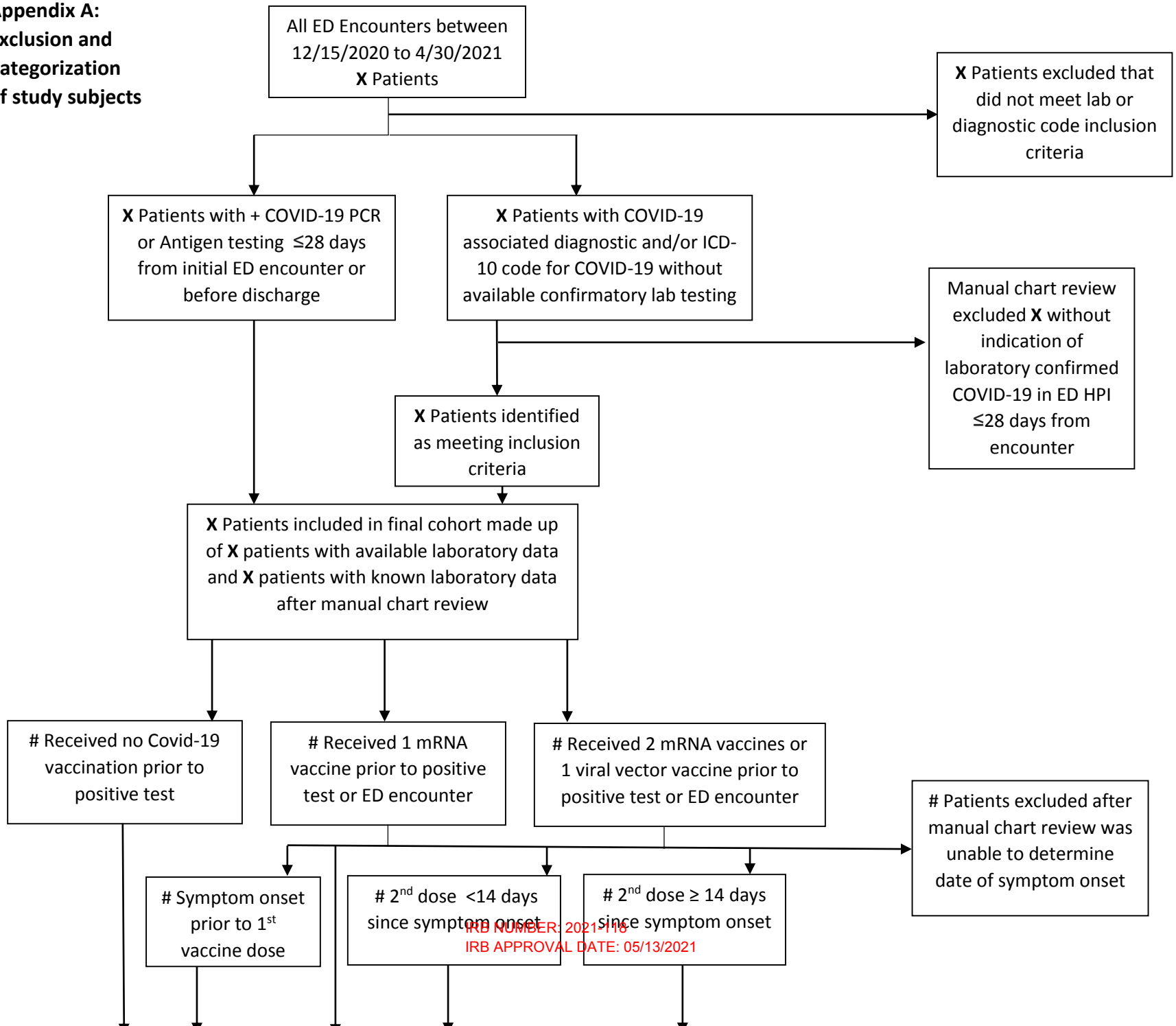
We will review the electronic medical record to identify the study population of interest. See Appendix A for full Inclusion/Exclusion diagram. The query plan includes first identifying all ED encounters to a Beaumont Health ED between 12/15/20 to 4/30/21. From this group, patients with confirmed COVID-19 based on positive PCR or antigen lab value ≤ 28 days from ED encounter date or prior to discharge will be included. A subset of patients with active COVID-19 infection will not have lab results available through the Beaumont medical chart. Many patients have outpatient or urgent care lab testing and only present to the ED when symptoms have worsened. To identify these cases, we will use ICD10 code [U07. 1] for COVID-19 as well as other various diagnostic codes indicating COVID infection. See Appendix B for full list of COVID-19 codes. After identification of these patients, via manual chart review, cases that reference a firm outpatient lab diagnosis ≤ 28 days from initial ED encounter will also be included.

For vaccinated patients, categorization into the correct group is critical. The three groups include: unvaccinated, partially vaccinated, and fully vaccinated. Vaccination data will be extracted from the MCIR registry for all patients. The preliminary partially vaccinated group includes patients who received a single dose of mRNA vaccine prior to positive lab test or ED encounter. The preliminary fully vaccinated group includes patients who received either two doses of an mRNA vaccine or a single dose of the viral vector vaccine prior to positive lab test or ED encounter. These groups will be further refined by manual chart review to determine onset of COVID symptoms. Symptom onset date will then be recorded and compared to date of vaccination to further define these cohorts. Patients in the fully vaccinated group who had <14 days since symptom onset from 2nd vaccine dose will be recategorized into the partially vaccinated cohort. Patients in the partially vaccinated group who had symptom onset prior to vaccine administration will be recategorized into the unvaccinated group.

Statistical Analysis Plan:

v. 5/12/21

Appendix A: Exclusion and Categorization of study subjects



Appendix B – Diagnoses names and IDs

[1494821881] COVID-19
[1495848810] Pneumonia due to Coronavirus disease 2019
[1494821880] COVID-19
[1494811674] Pneumonia due to COVID-19 virus
[1494811646] COVID-19 virus infection
[1495848812] Contact with and (suspected) exposure to covid-19
[1494811626] COVID-19 virus detected
[1608777] Acute hypoxemic respiratory failure due to COVID-19 (CMS/HCC)
[1494826562] Acute respiratory failure due to COVID-19 (CMS/HCC)
[1494811677] Suspected COVID-19 virus infection
[1608670] Lab test positive for detection of COVID-19 virus
[1494811738] Exposure to COVID-19 virus
[1494825072] Encounter for laboratory testing for COVID-19 virus
[1494821577] History of 2019 novel coronavirus disease (COVID-19)
[1494816042] Acute respiratory distress syndrome (ARDS) due to COVID-19 virus (CMS/HCC)
[500934] Pneumonia due to SARS-associated coronavirus
[1494811710] Acute respiratory disease due to COVID-19 virus
[1494811635] Close exposure to COVID-19 virus
[570160] Coronavirus infection, unspecified
[1608808] Hypercoagulable state associated with COVID-19 (CMS/HCC)
[1494811383] 2019 novel coronavirus disease (COVID-19)
[557697] Other coronavirus as the cause of diseases classified elsewhere
[1495848516] Encounter for screening for COVID-19
[379658] Coronavirus infection
[1494826546] Sepsis due to COVID-19 (CMS/HCC)
[1494811642] Gastroenteritis due to COVID-19 virus
[1608956] COVID-19 virus RNA detected
[1494811659] Encephalopathy due to COVID-19 virus
[1494811673] Pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
[1494821713] Lower respiratory tract infection due to COVID-19 virus
[1494828077] COVID-19 affecting pregnancy in second trimester
[1608938] Pulmonary embolism associated with COVID-19 (CMS/HCC)
[1608964] COVID toes
[1494804941] Pneumonia due to 2019 novel coronavirus
[1494811675] Real time reverse transcriptase PCR positive for severe acute respiratory syndrome coronavirus 2 (SARS-C
[1495832946] Multisystem inflammatory syndrome in child (MIS-C) associated with COVID-19
[1495849812] Contact with and (suspected) exposure to covid-19
[1608780] Dyspnea due to COVID-19
[1608813] Stroke associated with COVID-19 (CMS/HCC)
[1494811650] Myocarditis due to COVID-19 virus
[1494816040] Acute respiratory distress syndrome (ARDS) due to severe acute respiratory syndrome coronavirus 2 (SAR

[1494816043] Acute respiratory distress syndrome (ARDS) due to 2019 novel coronavirus (CMS/HCC)
[1494821690] Respiratory tract infection due to COVID-19 virus
[1494821697] Acute bronchitis due to COVID-19 virus
[1494821718] Bronchitis due to COVID-19 virus
[1494826548] Acute respiratory failure due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
[1495849516] Encounter for screening for COVID-19
[21402] Pneumonia due to SARS-associated coronavirus
[1304665] Coronavirus infection, unspecified
[1501417] Confirmed severe acute respiratory syndrome (SARS)
[1608229] Diarrhea due to COVID-19
[1608671] Counseled about COVID-19 virus infection
[1608715] Cardiomyopathy due to COVID-19 virus (CMS/HCC)
[1608732] Acute kidney injury due to COVID-19 (CMS/HCC)
[1608776] Acute hypoxemic respiratory failure due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) di
[1608786] Multisystem inflammatory syndrome associated with COVID-19 in pediatric patient (CMS/HCC)
[1608809] Hypercoagulable state associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infecti
[1494804922] Infection due to 2019 novel coronavirus
[1494811639] Educated about COVID-19 virus infection
[1494811653] Acute respiratory disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
[1494811658] Advice given about COVID-19 virus infection
[1494811680] Upper respiratory tract infection due to COVID-19 virus
[1494823733] Shortness of breath with exposure to COVID-19 virus
[1494826023] COVID-19 with multiple comorbidities
[1494826037] COVID-19 with pulmonary comorbidity
[1494826744] Laboratory confirmed diagnosis of COVID-19
[1494826779] COVID-19 ruled out by clinical criteria
[1494828071] COVID-19 affecting pregnancy in first trimester
[1494828079] COVID-19 affecting pregnancy in third trimester
[1494828083] COVID-19 affecting childbirth
[1494828098] COVID-19 affecting puerperium
[1495849808] Personal history of covid-19
[1495849810] Pneumonia due to Coronavirus disease 2019
[1494805997] Suspected 2019 novel coronavirus infection
[1494823147] Cough with exposure to COVID-19 virus
[1608604] Encounter for screening laboratory testing for COVID-19 virus
[1609291] At increased risk of exposure to COVID-19 virus
[1608961] MIS-C associated with COVID-19 (CMS/HCC)
[285389] SARS-associated coronavirus exposure
[1608799] Rash associated with COVID-19
[1494811390] Close exposure to 2019 novel coronavirus

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