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COVID-19 Outpatient Treatment Recommendations—Maine, 2022

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COVID-19 Outpatient Treatment Recommendations—Maine, 2022

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Abstract

COVID-19 Outpatient Treatment Recommendations—Maine, 2022

By Isaac Benowitz

Background

Risk factors for severe COVID-19 include older age, certain medical conditions and social behaviors, and inadequate COVID-19 vaccination. Two oral antiviral drugs first became available in 2021 and are highly effective at preventing progression to hospitalization or death in persons at higher risk for severe disease. Clinicians initially received limited guidance on who to treat in outpatient settings. CDC did not provide clinical treatment guidelines for outpatient treatment, including information on age- and vaccination-related risks, until June 2022. Federal allocation of limited supplies of monoclonal antibody and oral antiviral medications to each U.S. state led to clinician concerns about an inadequate supply for all eligible patients. Several health systems in Maine relied on the NIH prioritization tiers to establish who to treat. We sought to identify risk factors for hospitalization or death in COVID-19 patients in Maine in late 2021, develop clinical recommendations for outpatient COVID-19 treatment using antiviral drugs, and estimate the deaths potentially averted by using these local recommendations instead of NIH guidelines.

Methods

We described characteristics of COVID-19 cases reported to Maine CDC during the Delta wave period (October 3 to December 18, 2021). We defined categories by vaccination status, age, and comorbid medical conditions, aligning with the NIH prioritization groups. We used logistic regression to compare a model predicting severe disease from vaccination status, age, and comorbidities against a reduced model predicting severe disease from age alone. We used state-specific risk information to develop clinical treatment recommendations for prioritizing outpatient treatment and communicating severe disease risk. We incorporated information obtained informally from several groups of clinicians in the state. We calculated total COVID-19 cases leading to severe disease during the Delta wave in Maine that would have been treated with outpatient antivirals by following Maine's top tier category had been treated.

Results

During the Delta wave period, there were 50,860 cases of COVID-19 reported to Maine CDC, including 12,733 cases with complete investigation records. We found an elevated risk of severe disease for some unvaccinated persons and some vaccinated persons, particularly in persons with comorbid conditions. The largest proportion of overall cases with severe disease were among unvaccinated persons age 75+ years old with 1+ risk factors and among fully-vaccinated persons age 75+ years old with 1+ risk factors. The full model statistics suggest the full model has a better fit. We created guidelines for COVID-19 treatment in outpatient settings. These were similar to the NIH tier groups but include some vaccinated persons in higher groups. Early versions of Maine guidelines used numbered tiers and specified which drugs a patient should have access to. Later, after it became clearer that there was a sufficient supply of antiviral medications to offer any available treatment to all eligible patients, Maine revised these guidelines, describing patients at high, higher, and highest risk for severe disease, supporting clinicians' education to patients at risk. Using Maine Tier 1 would have treated 134% more people than using NIH Tier 1.

Discussion

We found notable levels of severe disease for older persons, including older vaccinated persons. We used case investigation data to develop recommendations for COVID-19 treatment that were more timely and relevant than NIH guidelines that relied on data collected prior to the widespread availability of vaccines. These recommendations supported clinicians in their treatment decisions and provided valuable insights into the risk for severe disease and provided a rational way for the state to encourage a uniform approach to COVID-19 treatment decisions in outpatient settings. There is an ongoing need to support clinicians who educate patients about risk factors for severe disease and make treatment recommendations.

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Chapter 1: Background Literature Review

COVID-19 is a severe respiratory illness caused by infection with the SARS-CoV-2 virus. It was first recognized in late 2019 and early 2020 after an outbreak in China led to characterization of this novel coronavirus.[1] COVID-19 can present as an asymptomatic infection, mild respiratory illness, or severe illness characterized by multi-system involvement leading to hospitalization and death. COVID-19 was a leading cause of death in the U.S. in 2020–2022.[2,3] Infection can lead to an array of chronic conditions, referred to as Post-COVID Conditions or Long COVID, which represent a substantial population burden of chronic disease.[4] Reinfection can occur with variable severity.[5] The SARS-CoV-2 virus has continued to evolve with regularity. Emerging variants may be associated with decreased effectiveness of vaccines and therapeutics, and with decreased protection afforded by prior infection with the same strain or with different strains. The initial predominant circulating strain was designated the Wuhan and was followed by the Alpha, Beta, and Delta strains predominated through late 2021. The Omicron variant first appeared in late 2021 and became the predominant circulating strain in the U.S. around mid-December 2021.[6,7,8,9]

By January 1, 2022, there were 3.7 million hospitalizations and 848,852 deaths in the U.S. attributed to COVID-19.[10] Initial descriptions of COVID-19 highlighted high morbidity and mortality in older adults (median age 56 years) and a male predominance (75%).[11] Early observational studies found a case fatality rate of 2.3%; 81% of patients had mild illness, 14% had severe illness, and 5% had critical illness; and most patients were between 30–79 years old.[12] Commonly-described risk factors for severe disease including age (older adults, infants, and young children), immunocompromising conditions, hypertension, cardiovascular disease, diabetes, chronic kidney disease, chronic liver disease, autoimmune conditions, obesity, psychiatric conditions, substance abuse, smoking, and other chronic conditions.

Several large-scale studies examined risk factors for severe disease using data from the Premier Healthcare Database. Pennington et al. used data from 181,813 hospitalized adults diagnosed with

COVID-19 during March–September 2020 and found older age associated with an increased risk for poor outcomes among hospitalized patients, and identified increased clinical severity in certain racial/ethnic minority groups: compared with non-Hispanic White patients, risk of death was lower for non-Hispanic Black patients and higher for Hispanic/Latino patients, non-Hispanic Asian patients, and patients of other racial and ethnic groups. Risk of intensive care unit (ICU) admission and invasive mechanical ventilation (IMV) were elevated in some racial and ethnic groups.[13] Kompaniyets et al. conducted a cross-sectional study of 540,667 adult hospitalized patients with COVID-19, using data from >800 hospitals to describe risk factors for severe disease in patients aged 18 years or older hospitalized with COVID-19 from March 2020 through March 2021 and found that 94.1% of hospitalized patients with COVID-19 had at least one underlying condition (Figure 1), with risk of hospitalization or death rising with additional conditions (Figure 2). Hypertension and disorders of lipid metabolism were the most common; obesity, diabetes with complication, anxiety disorders, and total conditions were the strongest risk factors for severe illness.[14]

COVID-19 vaccines are the mainstay of prevention of severe COVID-19. In the United States, the Food and Drug Administration (FDA) granted emergency use authorization to vaccines from Pfizer-BioNTech, Moderna, Janssen, and Novovax, and later granted full approval to vaccines from Pfizer-BioNTech and Moderna.[15,16,17,18,19] All four vaccines were initially authorized for use in adults; the Pfizer-BioNTech and Moderna vaccines were later authorized for use in teenagers and younger children following additional studies, and CDC now recommends that everyone age 6 months and older get the COVID-19 vaccine.[20] National equity strategies for vaccine distribution at the national level focused on health care personnel and residents of long-term care facilities, two groups at high risk of COVID-19; further recommendations focused on persons age 75 years and older, non-health care frontline essential workers, persons aged 65–74 years, persons aged 16–64 years with certain conditions, and all other essential worker groups.[21,22]

The Centers for Disease Control and Prevention (CDC) conducted public health surveillance to determine vaccine effectiveness, developed recommendations for use these vaccines, and measured disparities in

access to and receipt of vaccines. COVID-19 vaccines are highly effective across age groups, yet some people who have been vaccinated remain at risk for severe outcomes, including persons age 65 years and older, people with immunocompromising conditions, and persons with certain underlying conditions (e.g., overweight/obesity, diabetes mellitus, chronic kidney disease, chronic neurologic disease, chronic cardiac disease, chronic pulmonary disease, and chronic liver disease), with risk increasing with multiple conditions (Figure 3).[23] Persons with immunocompromising conditions typically have lower vaccine effectiveness after each dose and can get additional vaccine doses on an alternative schedule. The initial COVID-19 vaccination schedule involved a primary series, then added booster doses after studies found an increase in infections; later studies found that the risk of severe disease increased with time since the most recent vaccine dose.[24] Many race/ethnicity groups experienced lower rates of vaccination, largely attributed to misinformation and decreased access to vaccines.[25,26]

Several therapies have been identified or developed for treating COVID-19 in inpatient and outpatient settings. Clinicians and scientists investigated several antiviral and other medications for effectiveness against COVID-19. Several of the earliest treatments, such as baloxavir marboxil, lopinavir/ritonavir, ruxolitinib, chloroquine, hydroxychloroquine, interferon β-1a, and colchicine, proved ineffective or harmful and are no longer used in the U.S.[27] Early efforts sought to identify treatment options for patients hospitalized with moderate to severe illness and for patients with COVID-19 in the outpatient setting who had not been hospitalized. In late 2021, key inpatient therapies included antivirals (Veklury [remdesivir]), steroids (dexamethasone), and biologicals (tocilizumab, baricitinib, and sarilumab).

Outpatient treatment options included monoclonal antibodies (bamlanivimab, etesevimab, casirivimab, imdevimab, and sotrovimab) and antiviral medications (Paxlovid, Lagevrio, and Veklury).[28,29] The monoclonal antibodies were the first highly-effective outpatient treatments. Several monoclonal antibody products were available at different times, with FDA authorizing new monoclonals and de-authorizing those that did not work against the COVID-19 variants circulating at the time. All monoclonal antibodies

were authorized for treatment and some were also authorized for use as post-exposure prophylaxis.[30]

Veklury, an antiviral and a key inpatient treatment for COVID-19 in U.S. hospital settings, gained recognition as an option for outpatient use in late 2021 following a study that found a three-day course of intravenous (IV) Veklury resulted in an 87% decreased risk of hospitalization or death compared with placebo.[31] However, the dosing regimen for Veklury, once daily for three days via IV infusion, proved highly challenging in the outpatient setting in the real world, particularly at a time of heavily constrained health care resources, limiting the availability of outpatient Veklury in most parts of the country.

The first two widely-available antivirals for outpatients were Paxlovid (ritonavir-boosted nirmatrelvir) and Lagevrio (molnupiravir), both initially authorized for use in late December 2021. FDA emergency use authorization of these two antiviral drugs provided eligibility for any person age 12 years or older, weighing at least 40 kilograms, who has mild or moderate COVID-19 symptoms, a positive test (e.g., rapid antigen test or polymerase chain reaction [PCR] test), and is within 5 days of symptom onset at the start of treatment. Both studies were conducted entirely among unvaccinated persons due to their timing.

Paxlovid was studied in two trials among high-risk and standard-risk patients. EPIC-HR was a Phase 2/3, randomized, double-blind, placebo-controlled trial in non-hospitalized symptomatic adult subjects with laboratory-confirmed SARS-CoV-2 infection. Eligible subjects were 18 years of age and older with at least 1 risk factor for progression to severe disease: diabetes mellitus, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, malignancy, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, medically-related technological dependence, or age 60 years or older regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were included in the study and randomized 1:1 to get Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. Individuals with a prior COVID-19 infection or vaccination, or on medication with

significant drug interactions with Paxlovid, were excluded. A total of 1/490 (0.2%) Paxlovid recipients versus 8/479 (1.7%) placebo recipients met the primary endpoint of COVID-19 related hospitalization or death from any cause through Day 28. A second trial, in unvaccinated subjects without a risk factor for progression to severe COVID-19, or fully vaccinated against COVID-19 with at least one factor for progression to severe COVID-19, did not meet its endpoints.[32,33]

Lagevrio was studied in a phase 3, double-blind, randomized, placebo-controlled trial of 1,433 non-hospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19 and at least one risk factor for severe COVID-19 illness, that found Lagevrio reduced the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19. Participants were randomly assigned to get 800mg of Lagevrio or placebo twice daily for 5 days. The primary endpoint was hospitalization or death at day 29. A total of 716 participants got Lagevrio and 717 participants got a placebo. The risk of hospitalization for any cause or death through day 29 was lower with Lagevrio, 28/385 (7.3%), than with placebo, 53/377 (14.1%) (P = 0.001). The proportion participants who were hospitalized or died through day 29 was lower in the Lagevrio group, 48/709 (6.8%), than in the placebo group, 68/699 (9.7%); (95% CI, -5.9 to -0.1). One death was reported in the Lagevrio group and 9 were reported in the placebo group through day 29.[34]

Several groups developed extensive clinical information to help guide treatment decisions. The National Institutes of Health (NIH) convened a panel to review treatments and make recommendations for clinical management of hospitalized and non-hospitalized patients.[35] In early 2022, these recommendations refer to Paxlovid, Lagevrio, Veklury, and sotrovimab (a monoclonal antibody) "for patients who are at high risk of progressing to severe COVID-19" without further guidance on who to treat.[36] The accompanying *COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19*, indicates that "these [antiviral and monoclonal] anti-SARS-CoV-2 therapeutics, which were evaluated initially in unvaccinated individuals, provide the greatest benefit for nonhospitalized patients who have risk factors for progression to severe COVID-19," adding that "risks

for progression are substantially higher for those who are not vaccinated or those who are vaccinated but who are not expected to mount an adequate immune response to the vaccine."[37] Both documents cite the Panel's *Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints*, which uses the same framing, then asserts that in the period of increased cases of COVID-19 and the emergence of the Omicron variant, triage might be necessary due to logistical or supply constraints. The statement provides a framework for prioritization of groups of people who "might receive the greatest benefit" from outpatient treatment:

- "Treatment of COVID-19 over post-exposure prophylaxis (PEP) of SARS-CoV-2 infection.
- Treatment of COVID-19 in unvaccinated or incompletely vaccinated individuals with clinical risk factors for severe illness and vaccinated individuals who are not expected to mount an adequate immune response…
- Use of [pre-exposure prophylaxis (PrEP)] for severely immunocompromised individuals over moderately immunocompromised individuals…"

The NIH panel statement recommends "that clinicians prioritize their use for patients at *highest risk of clinical progression*" (emphasis added) and then provides risk groups based on age, vaccination status, immune status, and clinical risk factors, with four groups in descending order of priority, and referring back to CDC for details of risk factors to consider (Figure 4). The Panel statement also refers back to the FDA's EUA documents for a list of medical conditions or other factors for use of these treatments.[38]

The Infectious Diseases Society of America (IDSA), a leading professional organization of infectious disease physicians, developed their *COVID-19 Treatment and Management Guidelines* starting in April 2020. These guidelines include the use of Paxlovid and Lagevrio in the outpatient setting: the entry for Paxlovid refers to patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease, and notes that "patients who will most likely benefit from antivirals are those with risk factors for progression to severe disease (e.g., elderly, those with high-risk comorbidities, incomplete vaccination

status, or immunocompromised)."[39] No specific treatment criteria are cited in these IDSA guidelines. As of early 2022, NIH and IDSA had continued to update these recommendations on a regular basis.

CDC and other U.S. government agencies had conducted extensive planning and preparations for an influenza pandemic, and much of the initial response activities during the COVID-19 pandemic followed these pandemic plans for influenza given similarities in responding to an emerging respiratory pathogen. CDC had indicated that, in the event of a pandemic, the agency would provide interim clinical recommendations for the treatment of influenza.[40] CDC first provided interim clinical considerations for the treatment of COVID-19 on June 15, 2021. These clinical considerations encouraged clinicians to "consider COVID-19 treatment in non-hospitalized patients who meet all of the following:

- "Test positive for SARS-CoV-2 (with PCR or antigen test, including at-home tests)
- Have symptoms consistent with mild-to-moderate COVID-19. People with mild COVID-19 experience symptoms such as fever, sore throat, cough, or headache that do not affect the lungs and breathing. People with moderate illness have symptoms that affect the lungs like shortness of breath or difficulty breathing.
- Are within 5 days of symptom onset for Paxlovid or 7 days of symptom onset for Veklury
- Have one or more risk factors for severe COVID-19"

The CDC recommendations describe risk factors for severe COVID-19:

- "Age over 50 years, with risk increasing substantially at age ≥ 65 years
- Being unvaccinated or not being up to date on COVID-19 vaccinations
- Specific medical conditions and behaviors

In addition to these criteria, CDC notes that "some people from racial and ethnic minority groups are at risk of being disproportionately affected by COVID-19 from many factors, including limited access to vaccines and healthcare. Healthcare providers can consider these factors when evaluating the risk for severe COVID-19 and use of outpatient therapeutics."[41]

With the release of CDC's clinical considerations for treatment of COVID-19, clinicians finally had clear information on which patients to treat. However, prior to this time, clinicians largely relied on the NIH treatment guidelines that put four prioritization tiers out front as the clearest pronouncement of who was at highest risk for severe disease; IDSA guidelines did not provide further clarity, and the FDA EUA documents referred to CDC information regarding who is at high risk, yet those CDC documents did not specify who should get treated until June 2022. In the absence of more specific clinical recommendations, and at a time when it was unclear whether there was sufficient antiviral supply to treat all patients seeking to get treated, clinicians and health care systems often looked to the NIH prioritization guidelines, which were primarily intended to help manage shortages and were not intended to determine who to treat.

Who should clinicians treat for COVID-19 in the outpatient (non-hospitalized) setting? Can public health case investigation data help guide clinical recommendations that will improve population outcomes for COVID-19 infection? We used public health COVID-19 case investigation data from Maine to determine who was at the highest risk of severe disease by vaccination, age group, and comorbidities; we developed simple recommendations to guide clinicians in treating COVID-19 patients to reduce hospitalizations and deaths; and we estimated the number of people who would get treated by using these recommendations in place of the NIH prioritization guidelines before CDC treatment recommendations arrived in June 2022.

Student Contribution

Study Design

Data Analysis

Writing

Figures and Tables

Chapter 2: Journal Article

Abstract

Background

Risk factors for severe COVID-19 include older age, certain medical conditions and social behaviors, and inadequate COVID-19 vaccination. Two oral antiviral drugs first became available in 2021 and are highly effective at preventing progression to hospitalization or death in persons at higher risk for severe disease. Clinicians initially received limited guidance on who to treat in outpatient settings. CDC did not provide clinical treatment guidelines for outpatient treatment, including information on age- and vaccination-related risks, until June 2022. Federal allocation of limited supplies of monoclonal antibody and oral antiviral medications to each U.S. state led to clinician concerns about an inadequate supply for all eligible patients. Several health systems in Maine relied on the NIH prioritization tiers to establish who to treat. We sought to identify risk factors for hospitalization or death in COVID-19 patients in Maine in late 2021, develop clinical recommendations for outpatient COVID-19 treatment using antiviral drugs, and estimate the deaths potentially averted by using these local recommendations instead of NIH guidelines.

Methods

We described characteristics of COVID-19 cases reported to Maine CDC during the Delta wave period (October 3 to December 18, 2021). We defined categories by vaccination status, age, and comorbid medical conditions, aligning with the NIH prioritization groups. We used logistic regression to compare a model predicting severe disease from vaccination status, age, and comorbidities against a reduced model predicting severe disease from age alone. We used state-specific risk information to develop clinical treatment recommendations for prioritizing outpatient treatment and communicating severe disease risk. We incorporated information obtained informally from several groups of clinicians in the state. We calculated total COVID-19 cases leading to severe disease during the Delta wave in Maine that would have been treated with outpatient antivirals by following Maine's top tier category had been treated.

Results

During the Delta wave period, there were 50,860 cases of COVID-19 reported to Maine CDC, including 12,733 cases with complete investigation records. We found an elevated risk of severe disease for some unvaccinated persons and some vaccinated persons, particularly in persons with comorbid conditions. The largest proportion of overall cases with severe disease were among unvaccinated persons age 75+ years old with 1+ risk factors and among fully-vaccinated persons age 75+ years old with 1+ risk factors. The full model statistics suggest the full model has a better fit. We created guidelines for COVID-19 treatment in outpatient settings. These were similar to the NIH tier groups but include some vaccinated persons in higher groups. Early versions of Maine guidelines used numbered tiers and specified which drugs a patient should have access to. Later, after it became clearer that there was a sufficient supply of antiviral medications to offer any available treatment to all eligible patients, Maine revised these guidelines, describing patients at high, higher, and highest risk for severe disease, supporting clinicians' education to patients at risk. Using Maine Tier 1 would have treated 134% more people than using NIH Tier 1.

Discussion

We found notable levels of severe disease for older persons, including older vaccinated persons. We used case investigation data to develop recommendations for COVID-19 treatment that were more timely and relevant than NIH guidelines that relied on data collected prior to the widespread availability of vaccines. These recommendations supported clinicians in their treatment decisions and provided valuable insights into the risk for severe disease and provided a rational way for the state to encourage a uniform approach to COVID-19 treatment decisions in outpatient settings. There is an ongoing need to support clinicians who educate patients about risk factors for severe disease and make treatment recommendations.

Background

COVID-19 is a severe respiratory illness caused by infection with the SARS-CoV-2 virus, which can present with asymptomatic infection or with mild to severe illness, including hospitalization and death.[42] Risk factors for severe COVID-19 include older age, certain medical conditions and social behaviors (such as smoking and substance abuse), and inadequate COVID-19 vaccination.[43] In 2020–2022, COVID-19 was a leading cause of death in the United States.[44,45]

Severe COVID-19 illness can be prevented through vaccination and through treatment after illness onset. COVID-19 vaccines first became available in late 2020 for adults; the Centers for Disease Control and Prevention (CDC) later recommended vaccination for everyone age 6 months and older.[46,47] Outpatient treatment for COVID-19 first became available in 2020 with COVID-19 monoclonal antibodies for treatment or post-exposure prophylaxis.[48] Veklury, an intravenous (IV) antiviral drug used for severe COVID-19 in hospitalized patients, has also been used for outpatient COVID-19 treatment since late 2021, however it is not widely available in the outpatient setting in most parts of the U.S. due to the logistical challenges of outpatient IV administration.[49] Two oral antiviral drugs, Paxlovid (ritonavir-nirmatrelvir) and Lagevrio (molnupiravir), first became available in 2021 and are highly effective at preventing progression to hospitalization or death in persons at higher risk for severe disease.[50,51]

Clinicians initially received limited guidance on who to treat in outpatient settings using monoclonal antibody and antiviral medications. The U.S. Food and Drug Administration (FDA) emergency use authorization (EUA) for Paxlovid and Lagevrio allowed the treatment of non-hospitalized persons with mild to moderate COVID-19, a positive COVID-19 test, and risk factors for severe disease, within 5 days of symptom onset, pointing to CDC for information on risk factors for severe disease.[52,53] CDC studied and described risk factors for severe disease, however CDC did not provide clinical treatment guidelines for outpatient treatment, including information on age- and vaccination-related risks, until June 2022.[54,55]

The National Institutes of Health (NIH) developed treatment guidelines that recommended prioritizing access to outpatient treatment in the event of shortage (Figure 4).[56] These recommendations prioritized persons with moderate to severe immunocompromise, and unvaccinated persons with certain age- and comorbidity-based criteria, over vaccinated persons with similar age- and comorbidity-based criteria, and were based on COVID-19 mortality data collected prior to the availability of COVID-19 vaccines.[57,58]

Federal allocation of limited supplies of monoclonal antibody and oral antiviral medications to each U.S. state led to clinician concerns about an inadequate supply for all eligible patients. Several health systems in Maine relied on the NIH prioritization tiers to establish who to treat, and did not have access to information about drug supply that would allow them to expand eligibility to other patients described in the FDA EUA documents. In Maine in 2022, limited information on oral antiviral supplies led clinicians to use the NIH prioritization tiers for some treatment decisions. Public health case investigation data and discussions with clinicians suggested age remained a crucial factor contributing to risk of hospitalization and death from COVID-19, and this suggested reliance on NIH prioritization guidelines could lead to undertreatment of COVID-19 in persons at risk for severe disease, particularly older vaccinated adults.

COVID-19 infection is a reportable condition in Maine. Clinicians and laboratories are required to report positive polymerase chain reaction (PCR) and antigen-based test results to the Maine Center for Disease Control and Prevention (Maine CDC). Maine CDC then investigated these COVID-19 cases, with a focus on investigating cases with hospitalization, death, outbreaks, and in other patients and groups of interest.

We sought to identify risk factors for hospitalization or death in COVID-19 patients in Maine in late 2021, develop clinical recommendations for outpatient COVID-19 treatment using antiviral drugs, and estimate the deaths potentially averted by using these local recommendations instead of NIH guidelines.

Methods

COVID-19 case investigation records contain demographic data, identification of priority groups (e.g., healthcare workers, marginalized groups, very young, and very old), and review of hospitalization and death records and linkage to vaccination data. Maine CDC investigated cases during the isolation period in use at the time. Records lacked information on who received treatment in the outpatient setting. Staff attempted to obtain full investigation information on all hospitalized patients and on all deceased persons, relying on calls to patients or health care facilities, as well as drawing on vital records, vaccination data from the state's vaccination registry, and medical records in a centralized health information exchange, which included information from all hospitals in the state except for Veterans Affairs hospitals.

Maine CDC initially investigated all COVID-19 cases reported by healthcare facilities and other testing entities in the state, including symptomatic close contacts in public health investigations. In late 2020, Maine CDC stopped investigating symptomatic close contacts and implemented a surge classification system to prioritize investigations based on staffing capacity and the number of pending investigations that week. This system determined which cases had full investigations and the extent of follow-up to initiate or complete an investigation, with different selections by week. Some investigation records included only limited demographic data collected at testing.

We analyzed COVID-19 case investigation records for cases reported to Maine CDC during the Delta wave period (October 3 to December 18, 2021). We used SAS 9.4 (Cary, NC). This study was determined to be public health surveillance and exempt from Emory University IRB review.

We described characteristics of COVID-19 cases reported to Maine CDC during the Delta wave period and the cases for which we had complete records (vaccination status, age, comorbidities, hospitalization, and death). We described rates of 1+ comorbid condition and commonly-identified conditions (Table 1).

For investigation records with complete information, we defined categories by vaccination status, age, and 0 versus 1+ comorbid medical conditions, aligning with the NIH prioritization groups. We calculated total persons hospitalized or deceased, and risk of hospitalization or death for each group, and compared risk of severe disease (hospitalization or death) between these groups to determine relative risk (Table 2).

We used logistic regression to compare a model predicting severe disease from vaccination status, age, and comorbidities against a reduced model predicting severe disease from age alone to determine whether to keep all variables in the final model, assessing fit by several criteria including the Akaike Information Criterion (AIC), Schwarz Criterion (SC), -2 Log Likelihood, and Likelihood Ratio (Table 3).

We used state-specific risk information to develop clinical treatment recommendations for prioritizing outpatient treatment and communicating severe disease risk. We also incorporated information obtained informally from several groups of clinicians in the state, and discussion with colleagues at other public health agencies, in our final determinations of which groups to include. We described groups in two ways: as tiered groups (Figure 5) and patients at high, higher, and highest risk for severe disease (Figure 6).

To compare the real-world impact of making clinical treatment decisions using local information instead of relying on national information, we calculated total COVID-19 cases leading to severe disease during the Delta wave in Maine that would have been treated with outpatient antivirals by following Maine's top tier category had been treated, and we compared this with the total number of cases that would have been treated if all of the patients in the top tier of the NIH prioritization recommendations (Table 4).

Results

During the Delta wave period, there were 50,860 cases of COVID-19 reported to Maine CDC, including 1,051 with severe disease (899 hospitalizations and 553 deaths). There were 12,733 cases with complete investigation records. The most commonly-identified comorbid conditions included chronic lung disease,

hypertension, cardiovascular disease, and diabetes (Table 1).

Among the 12,733 COVID-19 cases in Maine during the Delta wave period for which we had complete records, 2,435 persons (19.1%) were fully-vaccinated (i.e., they had received two doses of the Pfizer/BioNTech or Moderna mRNA vaccine, or received one dose of the Janssen or Novovax vaccine, at least 2 weeks earlier). We found an elevated risk of severe disease for some unvaccinated persons and for some vaccinated persons, particularly among persons with 1+ comorbid conditions. The largest proportion of overall cases with severe disease were among unvaccinated persons age 75+ years old with 1+ risk factors and among fully-vaccinated persons age 75+ years old with 1+ risk factors (Table 2).

The full model has a lower AIC, SC, and -2LL, and the LRT and Wald Chi-Square tests for the full model predictors are all significant, indicating each variable contributes to the model (Table 3). These measures collectively suggest the full model has a better fit; we retained the full model.

We created state-specific guidelines for COVID-19 treatment in outpatient settings. These were similar to the NIH tier groups but include some vaccinated persons in higher groups. The Maine groups also include immunocompromised persons, pregnant persons, and persons residing in a congregate facility, based on clinician and other external input, even though we did not have sufficient information in our investigation data to calculate total persons with severe disease, or proportions with those outcomes (Figure 5).

Early versions of Maine guidelines used numbered tiers and specified which drugs a patient should have access to. Later, after it became clearer that there was a sufficient supply of antiviral medications to offer any available treatment to all eligible patients, Maine revised these guidelines, describing patients at high, higher, and highest risk for severe disease, supporting clinicians' education to patients at risk (Figure 3).

In June 2022, when CDC released clinical recommendations for COVID-19 treatment, Maine

discontinued updating this local information, instead pointing to CDC's recommendations.

Treating using Maine Tier 1 would have treated 453 cases of severe disease, an increase of 134% over using NIH Tier 1, which would have treated only 194 cases of severe disease (Table 4).

Discussion

The complete records included a larger proportion with 1+ comorbid condition (20% vs 5%), lower mean age, and a greater proportion of persons age <50 years old compared with all case investigation records, likely reflecting more complete investigations among schoolchildren and school-based outbreaks. There were far fewer fully-vaccinated persons (19% vs 36%) and more persons with severe COVID-19 (5.4% vs 2.1%), reflecting prioritization of investigations for persons with more severe disease.

We found notable levels of severe disease for older persons, including older vaccinated persons. COVID-19 vaccination remains protective across all ages, but even after vaccination some groups have higher risk for severe disease compared to other age groups: CDC continues to offer or recommend additional doses of COVID-19 vaccines, on an alternate schedule, for people age 65 years and older and for people who have immunocompromising conditions who still face these elevated risks of severe disease.

Comparison of the full model and a reduced model led to retention of the full model, reinforced the value of using age, vaccination status, and comorbidities in treatment decisions. The full model's significantly better fit compared with the reduced model, and the statistical significance of all predictors, underscore the multifaceted nature of disease severity. Our analysis supports the inclusion of age, vaccination status, and comorbidities to predict the severity of COVID-19 outcomes. Our findings suggest that considering multiple risk factors supports managing and mitigating severe outcomes in COVID-19 cases.

We used state-specific case investigation data to develop recommendations for COVID-19 treatment that

were more timely and relevant than NIH guidelines that relied on data collected prior to the widespread availability of vaccines. These local recommendations supported clinicians in their treatment decisions.

The Maine tiers provided valuable insights to clinicians and patients into the risk for severe disease based on local information that included period when vaccination was available, and provided a rational way for the state to encourage a uniform approach to COVID-19 treatment decisions in outpatient settings when different health systems were approaching this matter using an array of alternative inputs and approaches.

We considered additional factors in our recommendations that went beyond our case investigation data, based on discussions within the health department and with clinicians in hospital and community settings, allowing us to consider other populations that were not adequately reflected in public health investigation data. Population-level public health surveillance supports development of clinical recommendations that can improve population health through clearer information on treatment of COVID-19.

The substantially higher number of persons who would be treated using the Maine guidelines, compared to the NIH guidelines, indicates the potential for substantial real-world impact from treatment. Paxlovid, the most commonly used antiviral, was shown to be 90% effective in preventing severe disease.

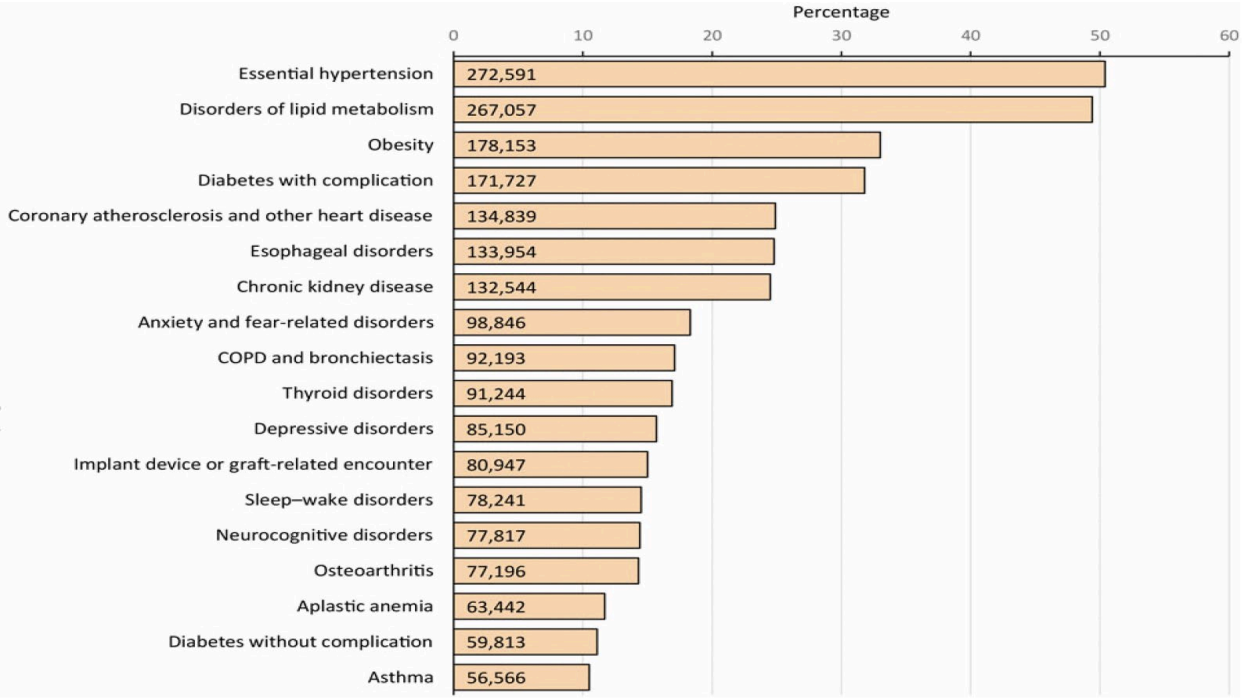
Our findings are subject to limitations. Reported COVID-19 cases represent an unknown proportion of all SARS-CoV-2 infections because not all infections cause symptomatic disease, not all persons with either asymptomatic or symptomatic infection get tested, not all results get reported to public health, and public health does not investigate every reported case. Our data here are skewed by investigation priorities that varied by week, oversampled for persons with severe illness, and cannot be used to compare all persons who had severe disease with all persons who did not have severe disease. Disproportionate investigation of one or more age groups could lead to overestimation or underestimation of the true proportion of cases involving severe disease in that group. We compensated for this by considering total cases with severe

disease in addition to the relative proportions. We lacked information on prior COVID-19 infection or treatment. However, the data allowed us to create information on severe disease that was widely accepted by the clinical community and adopted prior to the release of CDC's clinical treatment guidelines.

Prevention of severe COVID-19 disease remains a public health priority. There is an ongoing need to support clinicians who educate patients about risk factors for severe disease and make treatment recommendations. Risk factors for severe disease might vary for certain populations, for new variants, and with changes in immunity from vaccination or prior infection. Maine's experiences described here brought substantial value to the clinical community during a time when there was extensive COVID-19 case surveillance and a lack of national guidance on which patients to treat in the outpatient setting. It is unlikely that COVID-19 cases will remain reportable in most states, limiting the availability of source data for similar studies in the future. However, such studies could still be conducted on COVID-19 case investigation data in public health research networks (e.g., CDC's Emerging Infections Program, or large health care systems such as Kaiser Permanente) and would provide valuable information to clinicians.

Tables and Figures

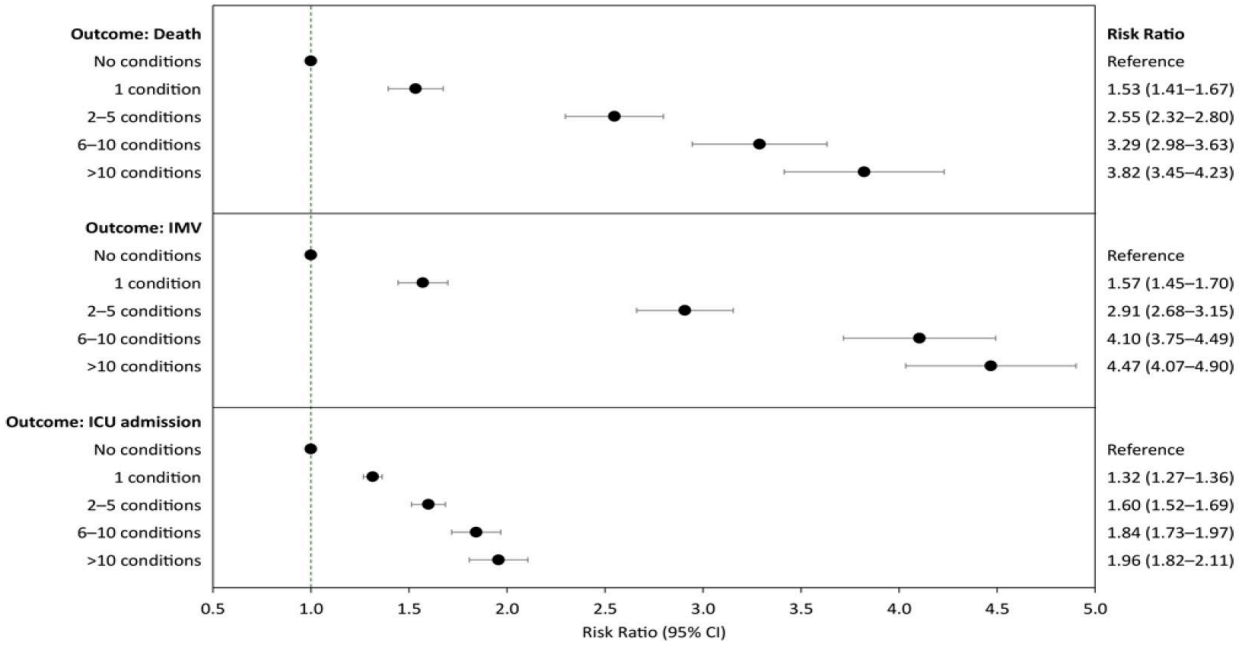
Figure 1. Prevalence of the most frequent underlying medical conditions in a sample of adults hospitalized with COVID-19 in Premier Healthcare Database Special COVID-19 Release.



COPD, chronic obstructive pulmonary disease

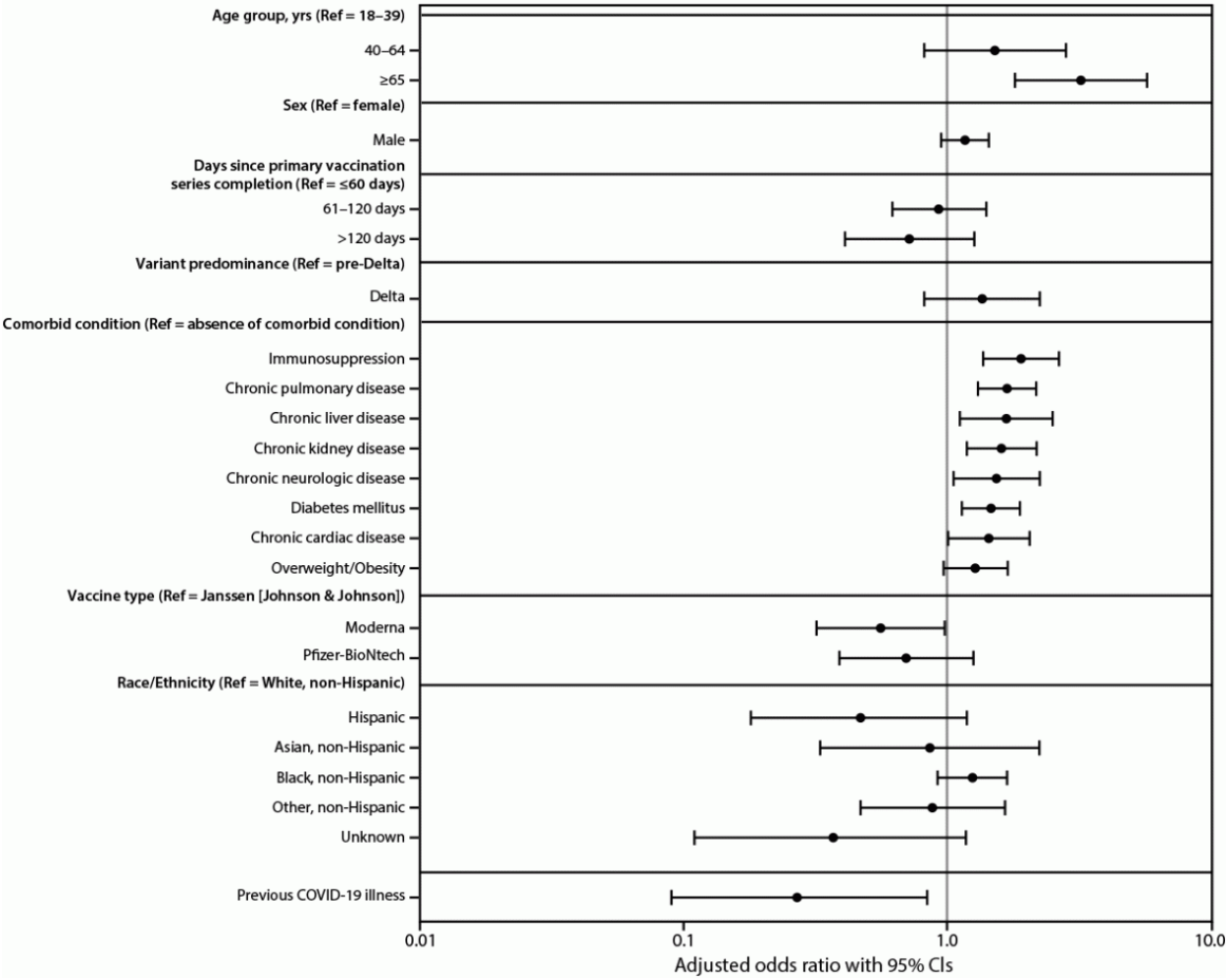
Source: Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, Chevinsky JR, Schieber LZ, Summers AD, Lavery AM, Preston LE, Danielson ML, Cui Z, Namulanda G, Yusuf H, Mac Kenzie WR, Wong KK, Baggs J, Boehmer TK, Gundlapalli AV. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020-March 2021. Prev Chronic Dis. 2021 Jul 1;18:E66. doi: 10.5888/pcd18.210123. PMID: 34197283; PMCID: PMC8269743.

Figure 2. Risk ratio (95% CI) of death, invasive mechanical ventilation (IMV), and admission to intensive care unit (ICU), by the number of underlying medical conditions among adults hospitalized with COVID-19 in the Premier Healthcare Database Special COVID-19 Release. Each panel contains the results of a single generalized linear model with Poisson distribution and log link function, adjusted for age group, sex, race/ethnicity, payer type, hospital urbanicity, US Census region of hospital, admission month, and admission month squared as controls. Patients who died without ICU care or IMV were excluded from the sample when estimating the model with the outcome of ICU care or IMV, respectively.



Source: Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, Chevinsky JR, Schieber LZ, Summers AD, Lavery AM, Preston LE, Danielson ML, Cui Z, Namulanda G, Yusuf H, Mac Kenzie WR, Wong KK, Baggs J, Boehmer TK, Gundlapalli AV. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020-March 2021. Prev Chronic Dis. 2021 Jul 1;18:E66. doi: 10.5888/pcd18.210123. PMID: 34197283; PMCID: PMC8269743.

Figure 3. Risk factors for severe COVID-19 among persons who completed a primary COVID-19 vaccination series — 465 health care facilities, United States, December 2020–October 2021.



Source: Yek C, Warner S, Wiltz JL, Sun J, Adjei S, Mancera A, Silk BJ, Gundlapalli AV, Harris AM, Boehmer TK, Kadri SS. Risk Factors for Severe COVID-19 Outcomes Among Persons Aged ≥18 Years Who Completed a Primary COVID-19 Vaccination Series - 465 Health Care Facilities, United States, December 2020-October 2021. MMWR Morb Mortal Wkly Rep. 2022 Jan 7;71(1):19-25.

Figure 4. National Institutes of Health: Patient Prioritization for Treatment, March 2022.

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.

Source: National Institutes of Health. 2022. Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints.

Table 1. COVID-19 cases, Maine, October 3 to December 18, 2021 (Delta wave period)

	All cases (N=50,860)	**Complete records (N=12,733)**
Male (%)	24,544 (48.3%)	6,271 (49.3%)
Age (median, range)	36.5 (<1–109)	19.6 (<1–104)
<50 years old	35,724 (70.2%)	11,207 (88.0%)
50 to <65 years old	9,097 (17.9%)	512 (4.0%)
65 to <75 years old	3,388 (6.7%)	322 (2.5%)
75+ years old	2,651 (5.2%)	692 (5.4%)
White non-Hispanic (%)	50,330 (99.0%)	12,416 (97.5%)
1+ comorbid conditions* (%)	2,547 (5.0%)	2,541 (20.0%)
Chronic lung disease		1,173 (9%)
Hypertension		685 (5%)
Cardiovascular disease		509 (4%)
Diabetes Mellitus		456 (4%)
Neurological disability		282 (2%)
Chronic kidney disease		210 (2%)
Chronic liver disease		51 (<1%)
Autoimmune disease		116 (1%)
Obesity		270 (2%)
Other chronic condition		855 (7%)
Substance abuse		78 (1%)
Former smoker		682 (5%)
Current smoker		291 (2%)
Psychiatric condition		586 (5%)
Other underlying condition		80 (1%)
Fully-vaccinated (%)	18,029 (35.5%)	2,435 (19.1%)

Severe COVID-19 (%)	1,051 (2.1%)	688 (5.4%)
Hospitalized (%)	899 (1.8%)	656 (5.2%)
Deceased (%)	553 (1.2%)	280 (2.2%)

Table 2. COVID-19 patients who were hospitalized or died, Delta wave, Maine

	Total cases in group	**Hospitalized (N=656)**	**Died (N=280)**	**Any severe disease* (N=688)**
Unvaccinated				
Age 75+, 1+ risk factors	144	54 (38%)	99 (69%)	**107 (74%)**
Age 75+, 0 risk factors	34	2 (6%)	10 (29%)	**10 (29%)**
Age 65–74, 1+ risk factors	95	44 (46%)	75 (79%)	**77 (81%)**
Age 65–74, 0 risk factors	25	3 (12%)	9 (36%)	**9 (36%)**
Age 50–65, 1+ risk factors	131	44 (34%)	80 (61%)	**91 (69%)**
Age 50–65, 0 risk factors	70	4 (6%)	24 (34%)	**24 (34%)**
Fully-vaccinated**				
Age 75+, 1+ risk factors	394	74 (19%)	146 (37%)	**163 (41%)**
Age 75+, 0 risk factors	120	1 (1%)	5 (4%)	5 (4%)
Age 65–74, 1+ risk factors	147	20 (14%)	52 (35%)	**54 (37%)**
Age 65–74, 0 risk factors	55	0 (0%)	1 (2%)	1 (2%)
Age 50–65, 1+ risk factors	172	13 (8%)	35 (20%)	**35 (20%)**
Age 50–65, 0 risk factors	139	0 (0%)	3 (2%)	3 (2%)

**Severe disease refers to hospitalization or death*

***Fully-vaccinated is defined as 2 doses of the original COVID-19 vaccine*

Table 3. Comparison of full model (3 variables) versus reduced model (only age group)

Model	***Full Model (age group, vaccination status, and 1+ comorbidities)***	***Reduced Model (age group)***
Akaike Information Criterion (AIC)	2640.506	3238.523
Schwarz Criterion (SC)	2685.217	3268.331
-2 Log Likelihood (-2LL)	2628.506	3230.523
Likelihood Ratio Tests (LRT)	Not applicable	2725.0244
Wald Chi-Square Test	1439.7945 (age group)	801.7054 (age group) 192.8690 (vaccinated) 320.1361 (comorbidities)

Figure 5. COVID-19 Treatment Guidelines by Tier, Maine (March 11, 2022)

Tier	Risk Group
1	• **Moderately/Severely Immunocompromised*** • **Unvaccinated** or Vaccinated**, 75+ years** • **Unvaccinated**, 50+ years, 1+ clinical risk factors***** • **Unvaccinated**, Pregnant**[+]
2	• **Unvaccinated**, 65+ years** • **Vaccinated**, 65+ years, 1+ clinical risk factors***** • **Unvaccinated** or Vaccinated**, 2+ clinical risk factors***** • **Residing in a congregate facility**[++]
3	• **All other patients per EUA or prescriber information**

***Immunocompromising conditions:** Moderately or Severely Immunocompromised People include people who have been receiving active cancer treatment for tumors or cancers of the blood, received an organ transplant and are taking medicine to suppress the immune system, received a stem cell transplant within the last 2 years or taking medicine to suppress the immune system, moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome), advanced or untreated HIV infection, or active treatment with high-dose corticosteroids or other drugs that suppress the immune response.*

***Unvaccinated** refers to a person who has not received 2 doses of an mRNA vaccine or 1 dose of J&J vaccine. **Vaccinated** refers to a person who received 2 doses of an mRNA vaccine or 1 dose of the J&J vaccine. Vaccinated persons who have not received a vaccine booster dose are likely at higher risk for severe disease than those persons who are boosted, and providers may choose to prioritize such persons for treatment.*

****Clinical risk factors:** some of the most important Underlying Medical Conditions Associated with High Risk for Severe COVID-19 include cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt or immunosuppressive medications, obesity (BMI ≥30), pregnancy, sickle cell disease.*

[+]***Pregnant:** Treat all pregnant COVID-19 patients who are unvaccinated. Also consider treatment in the postpartum period. Consider treating vaccinated persons with other risk factors. Avoid use of antivirals if other drugs are available.*

[++]***Congregate facility:** Includes persons living in nursing homes, assisted living facilities, jails, prisons, and homeless shelters who do not meet higher-level criteria.*

Figure 6. Patients at High, Higher, and Highest Risk, Maine (March 29, 2022)

Category	Risk Group
Highest **Risk for COVID-19 Severe Disease**	• **Moderately/Severely Immunocompromised*** • **Unvaccinated** or Vaccinated**, 75+ years** • **Unvaccinated**, 50+ years, 1+ clinical risk factors***** • **Unvaccinated**, Pregnant**[+]
Higher **Risk for COVID-19 Severe Disease**	• **Unvaccinated**, 65+ years** • **Vaccinated**, 65+ years, 1+ clinical risk factors***** • **Unvaccinated** or Vaccinated**, 2+ clinical risk factors***** • **Residing in a congregate facility**[++]
High **Risk for COVID-19 Severe Disease**	• **All other patients per EUA or prescriber information**

***Immunocompromising conditions:** Moderately or Severely Immunocompromised People include people who have been receiving active cancer treatment for tumors or cancers of the blood, received an organ transplant and are taking medicine to suppress the immune system, received a stem cell transplant within the last 2 years or taking medicine to suppress the immune system, moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome), advanced or untreated HIV infection, or active treatment with high-dose corticosteroids or other drugs that suppress the immune response.

****Unvaccinated** refers to a person who has not received 2 doses of an mRNA vaccine or 1 dose of J&J vaccine. ***Vaccinated** refers to a person who received 2 doses of an mRNA vaccine or 1 dose of the J&J vaccine. Vaccinated persons who have not received a vaccine booster dose are likely at higher risk for severe disease than those persons who are boosted, and providers may choose to prioritize such persons for treatment.*

*****Clinical risk factors:** some of the most important Underlying Medical Conditions Associated with High Risk for Severe COVID-19 include cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt or immunosuppressive medications, obesity (BMI ≥30), pregnancy, sickle cell disease.*

[+]***Pregnant:** Treat all pregnant COVID-19 patients who are unvaccinated. Also consider treatment in the postpartum period. Consider treating vaccinated persons with other risk factors. Avoid use of antivirals if other drugs are available.*

[++]***Congregate facility:** Includes persons living in nursing homes, assisted living facilities, jails, prisons, and homeless shelters who do not meet higher-level criteria.*

Table 4. Cases of severe disease potentially treated using Maine versus NIH guidelines, Delta wave

	Patients in the study population	**Patients with severe disease**	**Cases of severe disease treated in Tier 1 *NIH guidelines***	**Cases of severe disease treated in Tier 1 *Maine guidelines***
Immunocompromised	N/A	N/A	—	—
Pregnant	N/A	N/A	—	—
Residing in a congregate facility	N/A	N/A	—	—
Unvaccinated				
Age 75+, 1+ risk factors	144	107	107	107
Age 75+, 0 risk factors	34	10	10	10
Age 65–74, 1+ risk factors	95	77	77	77
Age 65–74, 0 risk factors	25	9	—	—
Age 50–65, 1+ risk factors	131	91	—	91
Age 50–65, 0 risk factors	70	24	—	—
Fully-vaccinated				
Age 75+, 1+ risk factors	394	163	—	163
Age 75+, 0 risk factors	120	5	—	5
Age 65–74, 1+ risk factors	147	54	—	—
Age 65–74, 0 risk factors	55	1	—	—
Age 50–65, 1+ risk factors	172	35	—	—
Age 50–65, 0 risk factors	139	3	—	—
Total			194	453

N/A, Not Available (this category was not quantified in our analysis)

Chapter 3: Future Directions/Public Health Implications

This study provides valuable information for clinicians seeking to treat patients with COVID-19 in the outpatient setting and provides an approach for continued updates based on the most recently-reported cases. Once CDC released interim clinical considerations for COVID-19 treatment, Maine supported those recommendations and stopped promoting this as independent clinical guidance to reduce confusion for clinicians. Later iterations of this information, framed in terms of patients at high risk, higher risk, and highest risk, provided a pathway to continue offering timely, local information to Maine clinicians that supported their clinical decisions and patient education regarding risk for severe COVID-19.

In early 2024, COVID-19 is still a reportable condition in Maine, and Maine continues to conduct limited case investigations for all reported cases. This is not sustainable with current public health funding and resource levels. If Maine and other states stop requiring reporting all cases or stop investigating all of these cases, we would not be able to perform this level of analysis. Similar analyses might still be feasible in states that obtain additional funding for special surveillance activities (e.g., CDC Emerging Infections Program) and in larger health systems, particularly those that are able to leverage electronic health records to conduct population health studies (e.g., the Kaiser Permanente health systems in California).

The U.S. government supported extensive discussions around vaccine equity during the period of initial vaccine rollout. There was no similar national effort for COVID-19 treatment: public health authorities who collected extensive data on who was getting vaccinated did not collect any similar data on who was getting treated, limiting the ability of public health authorities to assess disparities in access to treatment. In general, the same groups of people who derived the greatest benefit from COVID-19 vaccination also derived the greatest benefit from COVID-19 treatment. Studies supporting treatment recommendations can contribute to equity that complement vaccine strategies and ensure that vulnerable populations derive maximum benefit from all components of the public health response.

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