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Original Article

Estimate of undetected severe acute respiratory coronavirus virus 2 (SARS-CoV-2) infection in acute-care hospital settings using an individual-based microsimulation model

Kasey Jones MS[1], Emily Hadley MS[1], Sandy Preiss MS[1], Eric T. Lofgren PhD[2], Donald P. Rice MD[3], Marie C. D. Stoner PhD[1], Sarah Rhea DVM, PhD[4] and Joëlla W. Adams MPH, PhD[1]

[1]RTI International, Research Triangle, North Carolina, [2]Paul G. Allen School for Global Health, Washington State University, Pullman, Washington, [3]Division of Infectious Disease, Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island and [4]Department of Population Health and Pathobiology, North Carolina State University, Raleigh, North Carolina

Abstract

Objective: Current guidance states that asymptomatic screening for severe acute respiratory coronavirus virus 2 (SARS-CoV-2) prior to admission to an acute-care setting is at the facility's discretion. This study's objective was to estimate the number of undetected cases of SARS-CoV-2 admitted as inpatients under 4 testing approaches and varying assumptions.

Design and setting: Individual-based microsimulation of 104 North Carolina acute-care hospitals

Patients: All simulated inpatient admissions to acute-care hospitals from December 15, 2021, to January 13, 2022 [ie, during the SARS-COV-2 o (omicron) variant surge].

Interventions: We simulated (1) only testing symptomatic patients, (2) 1-stage antigen testing with no confirmatory polymerase chain reaction (PCR) test, (3) 1-stage antigen testing with a confirmatory PCR for negative results, and (4) serial antigen screening (ie, repeat antigen test 2 days after a negative result).

Results: Over 1 month, there were 77,980 admissions: 13.7% for COVID-19, 4.3% with but not for COVID-19, and 82.0% for non–COVID-19 indications without current infection. Without asymptomatic screening, 1,089 (credible interval [CI], 946–1,253) total SARS-CoV-2 infections (7.72%) went undetected. With 1-stage antigen screening, 734 (CI, 638–845) asymptomatic infections (67.4%) were detected, with 1,277 false positives. With combined antigen and PCR screening, 1,007 (CI, 875–1,159) asymptomatic infections (92.5%) were detected, with 5,578 false positives. A serial antigen testing policy detected 973 (CI, 845–1,120) asymptomatic infections (89.4%), with 2,529 false positives.

Conclusions: Serial antigen testing identified >85% of asymptomatic infections and resulted in fewer false positives with less cost per identified infection compared to combined antigen plus PCR testing.

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During the recent surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections attributable to the o (omicron) variant B.1.1.529, increased attention was given to "incidental COVID-19" or hospital admissions with COVID-19 rather than COVID-19 admissions. Due to the substantial number of asymptomatic infections, particularly with newer variants, there is a high risk of admitting patients already infected with SARS-CoV-2 into healthcare settings.[1,2] Therefore, policies and enhanced testing strategies to identify cases prior to inpatient admission may be needed to prevent nosocomial spread. Nosocomial spread of SARS-CoV-2 within US-based acute-care settings is likely significant; however, limited data are available to quantify it. A report from Kaiser Health News using inpatient hospital data from April to September 2020 found that >10,000 patients were diagnosed with SARS-CoV-2 after being admitted for another indication and >20% of those patients died.[3] In the United Kingdom, estimates for the percentage of admitted patients who acquired SARS-CoV-2 as inpatients range from 11% to 25%.[4–6] With >60% of the US population vaccinated with at least 2 doses since the beginning of 2022 and most hospitals implementing universal masking and testing procedures for symptomatic individuals, the risk of nosocomial transmission may be decreased compared to earlier phases of the pandemic.[7,8] However, the high

Author for correspondence: Joëlla W. Adams, E-mail: jadams@rti.org

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transmissibility of the SARS-CoV-2 o (omicron) variant among both vaccinated individuals and those with natural immunity[9] highlights the need to further examine the risk of nosocomial transmission of SARS-CoV-2 in the United States.

As of December 2021, Centers for Disease Control and Prevention (CDC) guidance recommends testing anyone with mild symptoms, regardless of vaccination status, but states that "performance of a preprocedure or preadmission viral testing is at the discretion of the facility."[8] The rationale of this policy is that the number of cases identified through preadmission testing for asymptomatic infection will be low when performed on vaccinated individuals or in areas with low-to-moderate transmission,[8] a conclusion supported by recent research.[10,11] Based on this recommendation, US hospitals vary in their testing policies.

No standard guidance has been established on the appropriate testing strategy for preadmission testing. We used an individual-based model of North Carolina healthcare facilities to simulate the admission of individuals from the community into acute-care hospitals and to estimate the number of undetected cases of SARS-CoV-2 admitted as inpatients under 4 testing approaches during a period of exponential growth in cases within the community.

Methods

Analytic overview

We used the Modeling Infection Diseases in Healthcare Network (MInD-Healthcare), an individual-based microsimulation, to compare hospital testing policies over 1 month. We selected a 1-month time frame to provide insights on how healthcare facilities can prepare for future periods of exponential pandemic growth. We simulated and compared 4 testing policies for patients admitted to acute-care facilities: (1) only testing symptomatic patients (ie, no preadmission screening of asymptomatic admissions); (2) 1-stage antigen testing of asymptomatic admissions; (3) 1-stage antigen testing followed by confirmatory PCR for negative results; and (4) serial antigen testing (ie, repeated antigen test for negative results performed 2 days after the initial test) (Fig. 1). As the main analysis, we ran model scenarios under conditions reflective of conditions in North Carolina from December 15, 2021, to January 13, 2022 (ie, the SARS-CoV-2 o (omicron) [B.1.1.529] variant was dominant). We assumed that the testing policies were implemented uniformly across all hospitals.

Model overview

Originally built to model the natural history of *C. difficile* infection within a regional health system,[13] MInD-Healthcare was adapted in 2020 to forecast hospitalizations for North Carolina during the COVID-19 pandemic. Only North Carolina residents were modeled (ie, patients admitted from other states were not simulated). We used historical reported case counts by county and day from COVID-19 ActNow, which nearly matched case counts reported by the state and were more readily available.[14] The case counts were smoothed using a 10-day rolling average because cases are generally not reported on weekends or holidays. Cases were then multiplied by a case multiplier (8× within the main analysis) to adjust the reported number of cases to reflect actual infections within the community. Measurement bias related to underreporting of positive at-home antigen tests, asymptomatic infection, lack of testing supplies, and other factors have made the use of a case multiplier standard practice in modeling studies. Values range from 4× to 8×.[15,16] We explored the impact of lower case multipliers within a sensitivity analysis.

Bayesian equations were used to assign cases to individuals within the ABM based on age and vaccination status and to determine severity of infection (susceptible or immune, asymptomatic, symptomatic, and recovered). Symptomatic infections were further classified into mild to moderate; severe (requiring an inpatient admission for SARS-CoV-2); and critical (requiring mechanical ventilation). Severity of infection was informed by surveillance data and large population-based cohort studies[17–21] as well as hospitalization data.[22] We focused on asymptomatic screening because we assumed that those with mild and moderate infections would be identified through verbal screening and that those with severe and critical infections would be admitted for COVID-19 treatment.[8]

Testing

Although testing occurs at the discretion of the facility, the current testing algorithm shared by the CDC for screening for asymptomatic infection in congregate settings begins with antigen testing.[23] Although the CDC recommends antigen testing with follow-up polymerase chain reaction (PCR) for anyone with symptoms who tests negative,[23] a follow-up PCR is not recommended for asymptomatic individuals with a negative antigen test. However, the individual is advised to quarantine if they were a close contact of someone with SARS-CoV-2.[23] Serial testing (ie, series of at least 2 antigen tests) for asymptomatic individuals is recommended if the individual has a high likelihood of SARS-CoV-2 infection, is not up-to-date on their vaccines, and has not had a SARS-CoV-2 infection in the prior 90 days.[23] However, retesting strategies will increase the potential for false positives or a positive test result for someone who is not actively infected. In practice, several testing approaches are implemented by hospital systems due to testing availability, cost, and other factors.

Significant heterogeneity in the performance of antigen testing may exist for detecting the SARS-CoV-2 o (omicron) variant,[24] and this variance may be time varying, with decreased sensitivity in the first 1–2 days after exposure.[25] A Canadian government report and several preprint studies report antigen test sensitivity for detecting the SARS-CoV-2 o (omicron) variant as ranging from 37.1 to 97.6%.[26–30] Within the main analysis, we assumed a test sensitivity of 67.4% (the middle of this range) for detecting the SARS-CoV-2 o (omicron) variant in asymptomatic individuals using antigen testing and performed a sensitivity analysis decreasing this number. PCR testing was assumed to have a test sensitivity of 77% for asymptomatic infection.[31,32] We assumed a test specificity of 98%, the negative percentage agreement required for approval by the FDA for both antigen and PCR testing.[26] We additionally assumed that 30% of individuals who had a SARS-CoV-2 infection within the previous 90 days but had since recovered would test positive using PCR testing (ie, persistent positivity) due to persistent viral shedding rather than true reinfection.[33,34] Although we did not conduct a formal cost-effectiveness analysis, we accounted for testing costs based on Centers for Medicare and Medicaid Services (CMS) data ($44 per antigen test and $112 per PCR) to estimate the cost per identified infection and number needed to screen (NNS) to detect 1 infection.

Vaccination

Vaccination was included as a time-invariant agent variable that decreases the likelihood of infection, increases the likelihood

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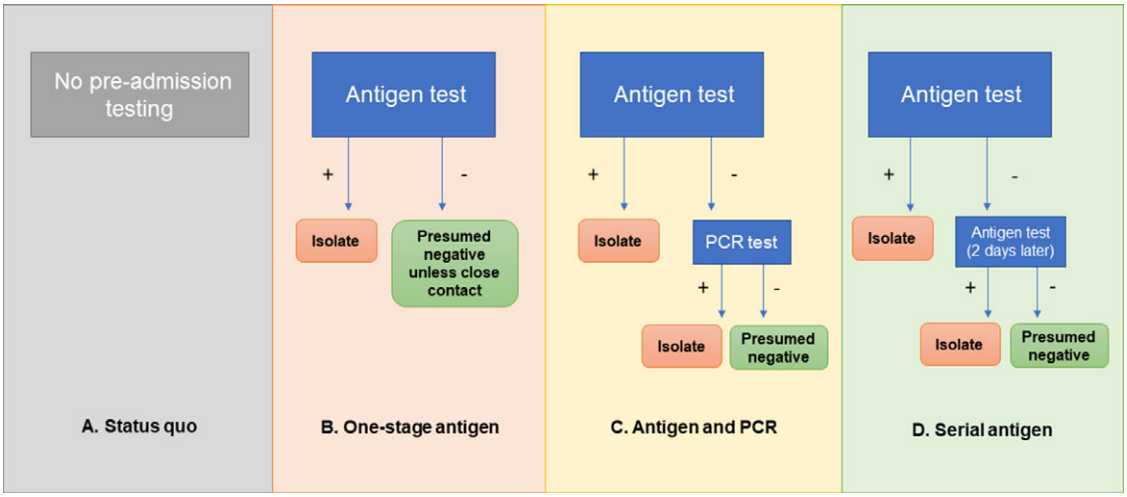

Fig. 1. Simulated policies on preadmission SARS-CoV-2 screening for asymptomatic patients admitted to an acute-care hospital.

of asymptomatic infection,[9,17] and decreases the likelihood of hospitalization.

Recent studies have reported that although receipt of a booster dose confers ~50% vaccine effectiveness against infection with the SARS-CoV-2 o (omicron) variant, marked waning of immunity against infection was seen for those without a booster (ie, not up to date) with, on average, only 7% protection against infection.[35–37] As of January 5, 2022, 37% of the vaccinated population of North Carolina had received a booster dose.[38] Therefore, we implemented a weighted vaccine effectiveness against infection parameter (24%), which accounted for 37% of the vaccinated population having a booster. This calculation resulted in 50% effectiveness against infection and 63% having 7% effectiveness against infection.

Vaccination also increased the likelihood of being asymptomatic if infected.[39] For reported cases, we assumed that 5% of the unvaccinated and 25% of the vaccinated population were asymptomatic. Reported asymptomatic cases would represent cases detected through work-based surveillance or through school- or office-based testing for close contacts. Given the lack of evidence for nonreported cases, we assumed that 25% of the unvaccinated and 50% of the vaccinated population were asymptomatic. Due to uncertainty around this parameter, we increased the proportion of asymptomatic cases by 50% in a sensitivity analysis.

Vaccination decreased the likelihood of developing severe illness and hospitalization. Using data on hospital admissions for COVID-19, which included vaccination status, we replicated historical admissions. Overall, 69% of individuals hospitalized with SARS-CoV-2 were unvaccinated, in line with national trends.

Movement from community into hospital settings

For this analysis, we simulated the movement from the community by agents representing patients into 104 short-term acute-care hospitals over 1 month. At each daily time step, agents had a probability of entering as a patient for COVID-19 or a different primary indication. The probability of hospitalization for a non–COVID-19 indication was informed by the agent's age group, sex, and comorbidities based on statewide hospital discharge data.[22] Parameterizations of length of stay, hospital capacity, rate of transfer, and patient demographic information were informed by statewide hospital discharge data.[22] Key parameters and data sources are summarized in Table 1, and full details are available in the Supplementary Materials.

Sensitivity analyses

We varied the following elements in sensitivity analyses: (1) We changed the case multiplier from 8× to 4× and 6×. (2) We decreased antigen testing sensitivity for asymptomatic infection from 67.4% to 37%. (3) We increased the probability of asymptomatic infection by 50%. (4) We increased vaccine effectiveness against infection from 37% to 75%. And (5) we lowered community COVID-19 incidence from 6,550 to 820 and 200 per 100,000 population weekly.

We ran each model scenario 100 times with 5 million agents. Model output was scaled to represent 10 million agents to represent the population of North Carolina. The MInD-Healthcare model was approved by the RTI International Institutional Review Board and was programmed using Python software. The full model code is available online (https://doi.org/10.5281/zenodo.6141066) and is accompanied by scripts and instructions for recreation of all model results.

Results

Model scenarios initialized with agents representing the population of North Carolina. We modeled 104 acute-care settings with 65% of non-ICU beds and 50% of ICU beds filled at model initialization. Over 1 month within the main analysis (ie, reflecting conditions from December 15, 2021–January 13, 2022), there were 77,980 (credible interval [CI], 75,126–80,875) hospital admissions; 10,724 (13.7%) for COVID-19 (ie, patients with severe or critical SARS-CoV-2 disease status); 3,386 (4.3%) with but not for COVID-19 (ie, had mild or asymptomatic infection); and 63,869 (82.0%) for non–COVID-19 indications and without SARS-COV-2 infection.

Without screening for asymptomatic infection prior to admission, 1,089 (CI, 946–1,253), or 7.72%, of total SARS-CoV-2 infections went undetected (Table 2). In a scenario in which hospitals implemented 1-stage antigen screening, 64,958 tests were performed and 734 (CI, 638–845) total asymptomatic infections (67.4%) were detected, with 1,277 false positives. In a combined

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Table 1. Estimates for Key Model Parameters NC MInD-Healthcare ABM

Parameter	Value, Range/ Distribution	Source
Initializing population		
Sex, %		RTI SynthPop 2017 data set
Male	48.1	
Female	51.9	
Age group, %		RTI SynthPop 2017 data set
<50 y	63.1	
50–65 y	21.0	
≥65 y	15.8	
Counties of residence	100	RTI SynthPop 2017 data set
Presence of comorbidity, %		Medicare Marketscan data, 2016–2017
50–64 years old	23.74	
≥ 65 years old	54.97	
SARS-CoV-2		
Incubation period, d		Ferguson et al[40], Jansen et al[41]
Until Dec 2021	5	
Starting Dec 2021 (omicron dominant)	3	
Period of infectiousness	7 d	Hay et al[42]
Target case count for reported infections[a]	384,868	COVID Act Now (www.covidactnow.org)
Case multiplier (varied in sensitivity analyses)	8	Assumed
Vaccination		
Vaccine effectiveness against infection, %[b]	24	UK Health Security Agency,[35] Buchan et al,[36] preprint: Spensley et al[37]
SARS-CoV-2 asymptomatic status based on vaccination status, % For reported cases (25% of total): Unvaccinated Vaccinated[c] For unreported cases (75% of total): Unvaccinated Vaccinated[c]	5 25 25 50	Fowlkes et al,[17] CDC Case Surveillance data[19]
SARS-CoV-2 severity based on vaccination status[d]	Varies	NC DHHS Report (Nov. 30, 2021)
Statewide vaccination rate as of Jan 15, 2022, %[e]	60	NC DHHS COVID Data Dashboard[38]
Statewide booster rate as of Jan 15, 2022, %	25.6	NC DHHS COVID Data Dashboard[38]
Agent movements		
Community to acute-care setting as patient		NC short-term acute-care hospital discharge data[22]
Length of stay (hospital) Non–COVID-19 admission COVID-19 admission, mean d (SD) [range]	Varied by hospital 3 (5) [1–50]	NC short-term acute-care hospital discharge data[22]
Probability of transfer, hospital to nursing home		NC short-term acute-care hospital discharge data[22]
Acute-care settings		
Short-term acute-care hospitals, no.	104	NC short-term acute-care hospital discharge data[22]
No. of beds by facility	1–1,000+	
Location	100 counties	Centers for Medicare & Medicaid Services data
Non-ICU beds filled at model initiation, %	65	Expert opinion
ICU beds filled at model initiation, %	50	Expert opinion
Testing parameters		
Sensitivity for PCR testing, %	77 for asymptomatic	Butler-Laporte et al,[31] Hellewell et al[32]

(*Continued*)

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Table 1. (*Continued*)

Parameter	Value, Range/ Distribution	Source
Sensitivity for point-of-care antigen testing, %	67.4 for asymptomatic	Ontario COVID-19 Science Advisory Table,[30] preprint: Goodall et al,[27], preprint: Schrom et al,[28] preprint: Michelena et al,[29] Drain[26]
PCR persistent positivity in general hospitalized population (positive test for agents within the "recovered" state), %	30	Landi et al,[33] Aldahaeefi et al[34]
Specificity for PCR and point-of-care antigen testing, %	98	FDA threshold

[a]Actual reported December 15, 2021, through January 13, 2022.
[b]Assumes vaccine effectiveness of 50% with booster and 7% for 2 doses or unvaccinated.
[c]Vaccination is modeled as a time-invariant agent state and does not differ by vaccine manufacturer, number of received doses, or time since last dose.
[d]Varies by age group, informed by hospital inpatient data.
[e]Varied by county.

antigen and PCR testing scenario, 127,631 tests were performed and 1,007 (CI, 875–1,159) total asymptomatic infections (92.5%) were detected. However, in addition to 2,529 false positives, 3,049 patients tested positive with a PCR due to a prior SARS-CoV-2 infection in the previous 90 days (ie, persistent PCR positivity), despite a negative rapid result. In all, 5,587 (CI, 5,374–5,810) total admissions (7.15%) were incorrectly assumed to be currently infectious. A serial antigen testing scenario resulted in 127,631 tests performed and 973 (CI, 845–1,120) total asymptomatic infections (89.4%) were detected, with 2,529 false positives.

In a sensitivity analysis lowering the case multiplier, we found that a lower percentage of admitted patients with SARS-CoV-2 were asymptomatic; therefore, fewer infections were detected with asymptomatic screening. When antigen test sensitivity was decreased from 67.4% to 37%, the number of detected asymptomatic infections decreased to 403 (CI, 350–464) for 1-stage antigen, to 931 (CI, 809–1,071) for combined antigen and PCR, and to 656 (CI, 571–756) for serial antigen testing. A sensitivity analysis increasing the probability of asymptomatic infection by 50% resulted in 1,638 (CI, 1,441–1,811) admitted patients (11.6%) with asymptomatic SARS-CoV-2. The number of asymptomatic infections detected ranged from 1,104 for the one-stage antigen testing to 1,515 for the combined antigen and PCR testing. With increased vaccine effectiveness, 679 (CI, 547–821) patients (6.1%) with SARS-CoV-2 were asymptomatic. A scenario increasing vaccine effectiveness decreased total hospital admissions and averted 2,912 (CI, 2,558–3,093) total admissions (~20%) with SARS-CoV-2 because we assumed that vaccinated individuals had a greater probability of "blocking" SARS-CoV-2 infection. Testing policies did not perform qualitatively different; between 458 (one-stage antigen) and 628 (combined antigen plus PCR) asymptomatic cases were detected. Sensitivity analyses lowering community incidence resulted in fewer admissions with or for COVID-19 and increased the number of tests with a higher ratio of false positives. Overall, the percentage of asymptomatic cases detected ranged from 37% for 1-stage antigen testing with decreased sensitivity to 92.5% for combined antigen plus PCR testing.

When estimating the cost of testing, the lowest cost per identified infection was 1-stage antigen testing at $3,890 (range, $3,488–4,360) followed by serial antigen testing at $5,770 (range, $5,180–6,480) (Table 3). One-stage antigen plus confirmatory PCR testing ($9,810; range, $8,800–11,020) was the most expensive testing policy. The NNS ranged from 89 for 1-stage antigen testing to 131 for serial antigen testing within the main analysis. Community incidence impacted the estimated cost per identified infection and NNS. The NNS for the 3 testing policies ranged from 726 to 1,082 when community incidence was lowered to 820 per 100,000 and from 2,033 to 3,034 at 200 per 100,000. Cost per identified infection ranged from $89,440 to $227,630.

Discussion

In an individual-based microsimulation of acute-care settings in North Carolina, we estimated that nearly 10% of SARS-CoV-2 infections (~1,000 cases) went undetected when no preadmission screening for asymptomatic infection was performed over a month of increased community incidence attributable to the SARS-CoV-2 o (omicron) variant. When asymptomatic screening was implemented with either a combined antigen plus PCR test or serial antigen testing, >85% of asymptomatic infections were detected. However, combined antigen plus PCR testing resulted in a significant number of false positives due to prior SARS-CoV-2 infection among admitted patients and had the highest associated costs. Our modeling results suggest that implementing serial antigen testing during periods of high community transmission may be an effective approach to detecting asymptomatic infection among hospital admissions. Detection of asymptomatic infections and subsequent implementation of appropriate infection prevention measures could reduce SARS-CoV-2 nosocomial transmission risk, along with other infection control measures including screening for symptoms and universal masking.

In a retrospective point-prevalence study of preadmission testing from January to August 2021 during a period of low community incidence, Tande et al[11] reported a low rate of positivity in both asymptomatic vaccinated and unvaccinated patients (0.30% and 1.23%, respectively). Within our analysis, positivity rates were 1.51% and 2.55% for vaccinated and unvaccinated individuals, respectively. The positivity rate during this period was likely higher than our simulated values, but in the absence of comprehensive data in North Carolina, we chose a more conservative approach. Indeed, if the positivity rate had been higher, the modeled testing policies would have been even more efficient in identifying asymptomatic cases. When community incidence is low, preadmission testing may be of limited value;[10] this assertion is supported by sensitivity analyses showing that the NNS and cost per identified infection notably increased at the

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Table 2. Simulated Outcomes for SARS-CoV-2 Testing Policies for Acute-Care Settings

Testing policy	SARS-CoV-2 Total Admitted Inpatients, Mean (Range)	Asymptomatic Testing Performed, Mean (Range)	Asymptomatic Infections Detected, Mean (Range)	Asymptomatic Infections Not Detected, Mean (Range)	No. of False Positive[a] Tests from Asymptomatic Testing, Mean (Range)
Main analyses[b]					
1) Screening for symptomatic patients only	14,111 (12,889–15,183)	0	0	1,089 (946–1,253)	0
2) One-stage antigen testing	14,111 (12,889–15,183)	64,958 (63,183–66,945)	734 (638–845)	355 (308–408)	1,277 (1,245–1,314)
3) One-stage antigen + confirmatory PCR	14,111 (12,889–15,183)	127,631 (124,483–131,731)	1,007 (875–1,159)	82 (71–94)	5,578 (5,374–5,810)
4) Serial antigen testing	14,111 (12,889–15,183)	127,631 (124,483–131,731)	973 (845–1,120)	116 (101–133)	2,529 (2,465–2,601)
Sensitivity analyses					
Screening for symptomatic patients only					
A. Main analysis *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	0	0	1,089 (946–1,253)	0
B. Case multiplier 4× *4,919 cases per 100,000 weekly*	12,517 (11,588–13,529)	0	0	498 (379–617)	0
C. Case multiplier 6× *3,280 cases per 100,000 weekly*	13,336 (12,362–14,453)	0	0	800 (683–931)	0
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	0	0	1,089 (946–1,253)	0
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	14,136 (13,117–15,133)	0	0	1,638 (1,441–1,811)	0
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	11,199 (10,331–12,090)	0	0	679 (547–821)	0
G. Lower community prevalence *820 cases per 100,000 weekly*	3,173 (2,764-3,639)	0	0	138 (91-208)	0
H. CDC threshold for community incidence- low to medium risk *200 cases per 100,000 weekly*	826 (581-1,095)	0	0	49 (19-83)	0
One-stage antigen testing					
A. Main analysis *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	64,958 (63,183–66,945)	734 (638–845)	355 (308–408)	1,277 (1,245–1,314)
B. Case multiplier 4× *4,919 cases per 100,000 weekly*	12,517 (11,588–13,529)	66,018 (64,292–67,847)	336 (255–416)	162 (124–201)	1,310 (1,278–1,345)
C. Case multiplier 6× *3,280 cases per 100,000 weekly*	13,336 (12,362–14,453)	65,514 (63,781–67,174)	539 (460–627)	261 (223–304)	1,294 (1,262–1,325)
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	64,958 (63,183–66,945)	403 (350–464)	686 (596–789)	1,277 (1,245–1,314)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	14,136 (13,117–15,133)	65,538 (63,589–67,333)	1,104 (971–1,221)	534 (470–590)	1,278 (1,243–1,310)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	11,199 (10,331–12,090)	65,391 (63,692–67,055)	458 (369–553)	221 (178–268)	1,294 (1,263–1,325)
G. Lower community prevalence *820 cases per 100,000 weekly*	3,173 (2,764–3,639)	67,435 (65,593–69,051)	93 (61–140)	45 (30–68)	1,345 (1,310–1,377)
H. CDC threshold for community incidence- low to medium risk *200 cases per 100,000 weekly*	826 (581–1,095)	67,696 (66,016–69,698)	33 (13–56)	16 (6–27)	1,353 (1,320–1,392)
One-stage antigen plus confirmatory PCR					
A. Main analysis *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	127,631 (124,483–131,731)	1,007 (875–1,159)	82 (71–94)	5,578 (5,374–5,810)
B. Case multiplier 4× *4,919 cases per 100,000 weekly*	12,517 (11,588–13,529)	130,265 (127,050–133,933)	461 (351–571)	37 (28–46)	5,314 (5,114–5,521)

(*Continued*)

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Table 2. (*Continued*)

Testing policy	SARS-CoV-2 Total Admitted Inpatients, Mean (Range)	Asymptomatic Testing Performed, Mean (Range)	Asymptomatic Infections Detected, Mean (Range)	Asymptomatic Infections Not Detected, Mean (Range)	No. of False Positive[a] Tests from Asymptomatic Testing, Mean (Range)
C. Case multiplier 6× *3,280 cases per 100,000 weekly*	13,336 (12,362–14,453)	128,995 (125,840–132,396)	740 (632–861)	60 (51–70)	5,447 (5,251–5,655)
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	127,631 (124,483–131,731)	931 (809–1,071)	158 (137–182)	5,470 (5,143–5,771)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	14,136 (13,117–15,133)	128,283 (124,964–132,135)	1,515 (1,333–1,675)	123 (108–136)	5,583 (5,498–5,652)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	11,199 (10,331–12,090)	128,859 (125,752–132,232)	628 (506–759)	51 (41–62)	5,415 (5,186–5,635)
G. Lower community prevalence *820 cases per 100,000 weekly*	3,173 (2,764–3,639)	133,396 (129,815–136,585)	127 (84–192)	10 (7–16)	5,130 (4,949–5,333)
H. CDC threshold for community incidence, low-to-medium risk *200 cases per 100,000 weekly*	826 (581–1,095)	133,993 (130,699–137,948)	46 (18–77)	4 (1–6)	5,084 (4,891–5,297)
Serial antigen testing					
A. Main analysis *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	127,631 (124,483–131,731)	973 (845–1,120)	116 (101–133)	2,529 (2,465–2,601)
B. Case multiplier 4× *4,919 cases per 100,000 weekly*	12,517 (11,588–13,529)	130,265 (127,050–133,933)	445 (339–551)	53 (40–66)	2,595 (2,531–2,662)
C. Case multiplier 6× *3,280 cases per 100,000 weekly*	13,336 (12,362–14,453)	128,995 (125,840–132,396)	715 (610–832)	85 (73–99)	2,563 (2,499–2,623)
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	14,111 (12,889–15,183)	127,631 (124,483–131,731)	656 (571–756)	432 (375–497)	2,529 (2,465–2,601)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	14,136 (13,117–15,133)	128,283 (124,964–132,135)	1,464 (1,288–1,619)	174 (153–192)	2,530 (2,461–2,595)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	11,199 (10,331–12,090)	128,859 (125,752–132,232)	607 (489–734)	72 (58–87)	2,563 (2,501–2,623)
G. Lower community prevalence *820 cases per 100,000 weekly*	3,173 (2,764–3,639)	133,396 (129,814–136,584)	123 (81–186)	15 (10–22)	2,665 (2,594–2,726)
H. CDC threshold for community incidence- low to medium risk *200 cases per 100,000 weekly*	826 (581–1,095)	133,993 (130,699–137,947)	44 (17–74)	5 (2–9)	2,679 (2,613–2,757)

[a]PCR is assumed to be falsely positive for 30% of individuals who had a SARS-CoV-2 in the past 90 days but who are no longer within the 7- to 10-day infectious period.
[b]Key parameters for the main analysis: case multiplier (adjustment to reported cases to account for underreporting) = 8x; PCR test sensitivity for asymptomatic cases = 77%; antigen test sensitivity for asymptomatic cases = 67.4%; vaccine effectiveness against infection = 24%; percent asymptomatic for reported cases = 5% if unvaccinated and 25% if vaccinated; percent asymptomatic for unreported cases = 25% if unvaccinated and 50% if vaccinated.

threshold level for CDC community level moving from low to medium risk (200 per 100,000 weekly incidence). Likewise, the ability of tests to ascertain active infection is crucial to the utility of preadmission testing. Persistent positives limit the value of a combined antigen and PCR testing policy.

Within our analysis, serial antigen testing detected the most asymptomatic infections with fewer false positives compared to the combined antigen plus PCR strategy. Ramifications of false positives include unnecessary treatment cancellation or postponement for elective procedures, financial losses related to self-isolation, psychological distress to the patient, and cohorting with actively infected patients.[43] Evidence suggesting that rapid antigen testing will not detect infection with SARS-CoV-2 o (omicron) variant in the first 2 days despite individuals being infectious[25] further supports the need for serial antigen testing.

Although this analysis simulated hospitals in North Carolina, results are likely generalizable to US hospitals. North Carolina has ~10 million residents with diversity across age, race and ethnicity, and socioeconomic status. In addition, urban and rural counties were represented, with wide variance in vaccination rates.[38]

This study had several limitations. Our model simulated entry into the hospital environment based on discharge data and therefore only included inpatient stays. Individuals entering the hospital environment for outpatient or emergency department care or visitation were not modeled. Testing was less likely for these individuals and relies on other mitigation strategies to decrease the risk of nosocomial transmission. We assumed that between 5% (unvaccinated) and 25% (vaccinated) of infected individuals would be asymptomatic. Initial studies of the SARS-CoV-2 o (omicron) variant suggest that the proportion of asymptomatic infection may be much higher, with estimates up to 80%.[2] However, this evidence is still preliminary, and we chose to incorporate a more conservative assumption and to test a higher rate of asymptomatic infection

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Table 3. Estimated Costs and Number Needed to Screen for SARS-CoV-2 Testing Policies for Acute-Care Settings

Testing Policy	Asymptomatic Testing Performed, Mean (Range)	No. Needed to Screen (NNS), Mean (Range)[a]	Estimated Total Cost of Testing Policy Statewide Over 1 Month, Mean (Range)[b]	Estimated Cost per Identified Infection[c]
Main analyses				
1) Screening for symptomatic patients only	0	N/A	$0	$0
2) One-stage antigen testing	64,958 (63,183–66,945)	89 (79–99)	$2,858,000 ($2,780,000–2,945,000)	$3,890 ($3,488–4,360)
3) One-stage antigen + confirmatory PCR	127,631 (124,483–131,731)	127 (114–142)	$9,877,000 ($9,645,000–10,201,000)	$9,810 ($8,800–11,020)
4) Serial antigen testing	127,631 (124,483–131,731)	131 (118–147)	$5,615,800 ($5,477,000–5,796,000)	$5,770 ($5,180–6,480)
Sensitivity analyses				
One-stage antigen testing				
A. Main analysis *6,559 cases per 100,000 weekly*	64,958 (63,183–66,945)	89 (79–99)	$2,858,000 ($2,780,000–2,945,000)	$3,890 ($3,488–4,360)
B. Case multiplier 4x *4,919 cases per 100,000 weekly*	66,018 (64,292–67,847)	197 (163–252)	$2,904,000 ($2,828,000–2,985,000)	$8,650 ($7,180–11,070)
C. Case multiplier 6x *3,280 cases per 100,000 weekly*	65,514 (63,781–67,174)	122 (107–139)	$2,882,000 ($2,806,000–2,955,000)	$5,347 ($4,710–6,100)
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	64,958 (63,183–66,945)	161 (144–181)	$2,858,000 ($2,780,000–2,945,000)	$7,090 ($6,350–7,900)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	65,538 (63,589–67,333)	59 (55–65)	$2,883,678 ($2,797,000–2,962,000)	$2,610 ($2,430–2,880)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	65,391 (63,692–67,055)	143 (121–173)	$2,877,000 ($2,802,000–2,950,000)	$6,280 ($5,330–7,600)
G. Lower community prevalence *820 cases per 100,000 weekly*	67,435 (65,593–69,051)	726 (493–1,069)	$2,967,000 ($2,886,000–3,038,000)	$31,920 ($21,670–47,050)
H. CDC threshold for community incidence, low-to-medium risk *200 cases per 100,000 weekly*	67,696 (66,016–69,698)	2,033 (1,246–5,155)	$2,978,000 ($2,904,000–3,066,000)	$89,440 ($54,820–226,820)
One-stage antigen + confirmatory PCR				
A. Main analysis *6,559 cases per 100,000 weekly*	127,631 (124,483–131,731)	127 (114–142)	$9,877,000 ($9,645,000–10,201,000)	$9,810 ($8,800–11,020)
B. Case multiplier 4x *4,919 cases per 100,000 weekly*	130,265 (127,050–133,933)	283 (235–362)	$10,100,000 ($9,857,000–10,386,000)	$21,930 ($18,200–28,120)
C. Case multiplier 6x *3,280 cases per 100,000 weekly*	128,995 (125,840–132,396)	174 (154–199)	$9,992,000 ($9,756,000–10,260,000)	$13,500 ($11,900–15,440)
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	127,631 (124,483–131,731)	137 (123–254)	$9,886,000 ($9,645,000–10,200,000)	$10,620 ($9,520–11,920)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	128,283 (124,964–132,135)	85 (79–85)	$9,911,000 ($9,671,000–10,220,000)	$6,540 ($6,100–7,260)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	128,859 (125,752–132,232)	205 (174–249)	$9,985,000 ($9,753,000–10,250,000)	$15,890 ($13,500–19,280)
G. Lower community prevalence *820 cases per 100,000 weekly*	133,396 (129,815–136,585)	1,046 (710–1,542)	$10,354,000 ($10,078,000–10,600,000)	$81,180 ($55,100–119,740)
H. CDC threshold for community incidence, low-to-medium risk *200 cases per 100,000 weekly*	133,993 (130,699–137,948)	2,932 (1,797–7,436)	$10,403,000 ($10,149,000–10,710,000)	$227,630 ($139,500–566,500)
Serial antigen testing				
A. Main analysis *6,559 cases per 100,000 weekly*	127,631 (124,483–131,731)	131 (118–147)	$5,615,800 ($5,477,000–5,796,000)	$5,770 ($5,180–6,480)
B. Case multiplier 4x *4,919 cases per 100,000 weekly*	130,265 (127,050–133,933)	293 (243–375)	$5,731,000 ($5,590,000–5,893,000)	$12,880 ($10,690–16,500)
C. Case multiplier 6x *3,280 cases per 100,000 weekly*	128,995 (125,840–132,396)	180 (159–206)	$5,675,000 ($5,536,000–5,825,000)	$7,940 ($7,000–9,070)

(*Continued*)

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Table 3. (*Continued*)

Testing Policy	Asymptomatic Testing Performed, Mean (Range)	No. Needed to Screen (NNS), Mean (Range)[a]	Estimated Total Cost of Testing Policy Statewide Over 1 Month, Mean (Range)[b]	Estimated Cost per Identified Infection[c]
D. Test sensitivity 37% *6,559 cases per 100,000 weekly*	127,631 (124,483–131,731)	194 (174–218)	$5,619,000 ($5,477,000–5,796,000)	$8,560 ($7,670–9,600)
E. Asymptomatic +50% *6,559 cases per 100,000 weekly*	128,283 (124,964–132,135)	88 (82–97)	$5,644,000 ($5,498,000–5,814,000)	$3,900 ($3,590–4,270)
F. Vaccine effectiveness 75% *6,559 cases per 100,000 weekly*	128,859 (125,752–132,232)	212 (174–218)	$5,670,000 ($5,533,000–5,818,000)	$9,340 ($7,930–11,320)
G. Lower community prevalence *820 cases per 100,000 weekly*	133,396 (129,814–136,584)	1,082 (735–1,596)	$5,869,000 ($5,711,000–6,009,000)	$47,630 ($32,330–70,230)
H. CDC threshold for community incidence, low-to-medium risk *200 cases per 100,000 weekly*	133,993 (130,699–137,947)	3,034 (1,860–7,697)	$5,895,000 ($5,750,000–6,069,000)	$133,500 ($81,830–338,670)

Note. N/A, not available.
[a]No. needed to screen (NNS) calculated as no. of asymptomatic tests performed/no. of asymptomatic infections identified.
[b]Estimated total cost of testing policy calculated as (no. of asymptomatic tests performed × cost of test). Cost of rapid antigen test, $45 and PCR, $112. Cost estimates based on Centers for Medicare & Medicaid Services (https://www.cms.gov/files/document/mac-covid-19-test-pricing.pdf).
[c]Estimated cost per identified infection calculated as (estimated total cost of testing policy/# of asymptomatic infections identified).

within a sensitivity analysis. We did not model differing vaccine effectiveness dependent on timing of doses or immunosuppression. In addition, the pediatric population was grouped within the "under 50" age group, even though certain ages were ineligible to receive a vaccine. Lastly, we did not model the transmission of SARS-CoV-2; therefore, we could not simulate cases of SARS-CoV-2 resulting from a nosocomial outbreak.

Patients admitted to an acute-care hospital are likelier to be older, immunocompromised, and frailer than other community members and therefore at higher risk of SARS-CoV-2–related morbidity and mortality. Undetected asymptomatic infection poses a preventable risk within acute-care settings. These model results suggest that serial antigen testing for asymptomatic infection may be the optimal approach for detecting asymptomatic infection in acute-care settings when community levels of transmission are higher.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.174

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