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Dialogues in Health 1 (2022) 100057

Contents lists available at ScienceDirect

Dialogues in Health

journal homepage: www.elsevier.com/locate/dialog

Likelihood of COVID-19 reinfection in an urban community cohort in Massachusetts

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Reinfection
Immunity
Healthcare utilization

ABSTRACT

Background: Understanding the association of prior SARS-CoV-2 infection with subsequent reinfection has public health relevance.
Objective: To explore COVID-19 severity and SARS-CoV-2 infection and reinfection rates.
Design: Retrospective cohort study.
Setting: Boston, Massachusetts, during the first COVID-19 surge (01/01/2020–05/31/2020; Period-1) and after the first surge (06/01/2020–02/28/2021; Period-2); Period-2 included the second surge (11/01/2020–02/28/2021).
Participants: Patients in an academic medical center and six community health centers who received a clinical diagnosis of COVID-19 between 01/01/2020 and 05/31/2020 or SARS-CoV-2 testing between 01/01/2020 and 02/28/2021.
Measurements: COVID-19 severity was compared between Period-1 and Period-2. Poisson regression models adjusted for demographic variables, medical comorbidities, and census tract were used to assess reinfection risk among patients with COVID-19 diagnoses or SARS-CoV-2 testing during Period-1 and additional SARS-CoV-2 testing during Period-2.
Results: Among 142,047 individuals receiving SARS-CoV-2 testing or clinical diagnoses during the study period, 15.8% were infected. Among COVID-19 patients, 22.5% visited the emergency department, 13% were hospitalized, and 4% received critical care. Healthcare utilization was higher during Period-1 than Period-2 (22.9% vs. 18.9% emergency department use, 14.7% vs. 9.9% hospitalization, 5.5% vs. 2.5% critical care; $p < 0.001$). Reinfection was assessed among 8961 patients with a SARS-CoV-2 test or COVID-19 diagnosis in Period-1 who underwent additional testing in Period-2. A total of 2.7% ($n = 65/2431$) with SARS-CoV-2 in Period-1 tested positive in Period-2, compared with 12.6% ($n = 821/6530$) of those who initially tested negative (IRR of reinfection = 0.19, 95% CI: 0.15–0.25).
Conclusions: Prior SARS-CoV-2 infection among this observational cohort was associated with an 81% lower reinfection rate.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused approximately 245 million cases and 5 million deaths worldwide as of October 28, 2021 [1]. The United States (U.S.) has recorded over 46 million confirmed cases and 742,000 deaths [2]. Currently available safe and effective vaccines can reduce disease incidence and the severity of disease [3,4]. In the U.S, approximately 66.7% are fully vaccinated against COVID-19 [5]. In addition, the emergence of the SARS-CoV-2 Delta (B.1.617.2) variant has led to increasing numbers of vaccine breakthrough cases [6,7]. Within this context, understanding the role of natural immunity in preventing SARS-CoV-2 reinfection, as well the trajectory of disease severity after implementation of non-pharmaceutical interventions including face coverings, physical distancing, and improved medical treatments is paramount [8–10].

A growing body of evidence indicates that the majority of individuals develop neutralizing antibodies following SARS-CoV-2 infection [11–13], and immune responses can persist for several months [14–17]. In addition, virus-specific memory B- and T-cells have been demonstrated for several months following infections, and cell-mediated immunity and the development of immune memory may mitigate disease severity upon re-exposure [14,18–20]. However, SARS-CoV-2 reinfection is common, antibodies may wane or lose effectiveness against new variants, and immunity may vary by other demographic factors and/or COVID-19 symptom severity [21,22–26].

Massachusetts suffered two major COVID-19 surges during the study observation period. The first surge occurred between 01/01/2020 and

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http://dx.doi.org/10.1016/j.dialog.2022.100057
Received 21 January 2022; Received in revised form 3 October 2022; Accepted 4 October 2022
Available online 08 October 2022

05/31/2020 with the prevalent wild-type SARS-CoV-2 strain (Wuhan-Hu-1) at a time when non-pharmaceutical interventions were lacking, testing was scarce, and medical facilities lacked personal protective equipment and medical expertise to effectively treat patients with COVID-19. COVID-19 confirmed cases and related deaths in Massachusetts peaked near the end of April 2020 with a 7-day average of over 2200 new confirmed cases and 175 deaths daily [27]. Suffolk county, which includes the Greater Boston metropolitan area, bore a large burden of disease during the first surge. Nearly 25% of all cases in Massachusetts occurred in Suffolk county, with a 7-day average of over 500 positive cases, and a 7-day average of 27 deaths daily in April 2020 [28,29].

The Alpha (B.1.1.7) and Gamma (P.1) variants began to circulate in Massachusetts during the second COVID-19 surge (11/01/2020–02/28/2021) [30,31,32]. During this time, face covering and physical distancing mandates were in place, testing was widespread, and hospital treatment protocols were developed [29,33]. Cases during this second surge peaked in January 2021 with a 7-day average of 6234 new confirmed cases and 76 deaths daily [27]. Suffolk county bore a smaller share of total disease in the second surge: the 7-day average of positive cases peaked at 750 and the 7-day average of deaths peaked at 9 in January 2021 [28,29]. Beginning in mid-December 2020, COVID-19 vaccines became available. However, vaccine supplies were limited to frontline healthcare workers and nursing home residents through February 2021 [34–37].

In this retrospective cohort study, we describe rates of SARS-CoV-2 test positivity and clinical COVID-19 diagnoses, as well as emergency department visits, hospital admissions, and critical care requirements among a high-exposure cohort in an academic medical center and outpatient clinic network serving a diverse, urban community in the greater Boston metropolitan area in Massachusetts. We compare these outcomes during the first COVID-19 surge (01/01/2020–05/31/2020) and after the first COVID surge and including the second COVID-19 surge (06/01/2020–02/28/2021) and evaluate the risk of SARS-CoV-2 reinfection.

2. Methods

The Informatics Institute Integrating Biology and the Bedside (i2b2) database, which contains de-identified electronic medical record information including outpatient and inpatient visits to an urban academic medical center and six affiliated community health centers in Massachusetts, was queried for results SARS-CoV-2 Polymerase Chain Reaction (PCR) tests and COVID-19 clinical diagnoses and occurring between 01/01/2020 and 02/28/2021 [38]. We defined Period-1 from 01/01/2020 to 05/31/2020 corresponding to the first surge in COVID-19 cases in Massachusetts. We defined Period-2 from 06/01/2020 to 02/28/2021, corresponding to the time following the first surge and including the second surge. Per i2b2 de-identification protocols, all dates reported were shifted up to +/− 30 days. The shift in reporting dates are constant for each individual participant, meaning that each person's dates are shifted the same amount so temporal relationships remain the same.

The total study cohort included all patients with either a SARS-CoV-2 PCR test with a valid result (positive or negative) during the entire study period (01/01/2020 through 02/28/2021) *or* a documented COVID-19 clinical diagnosis without confirmatory testing during Period-1 (01/01/2020 through 05/31/2020). Inclusion criteria were selected to focus on incident SARS-CoV-2 infections in both time periods. Diagnoses without confirmatory testing were included in Period-1 as many patients with clinical COVID-19 were unable to obtain testing due to limited availability. When testing was more widely available (Period-2), confirmatory testing was required for inclusion in the study cohort. A clinical diagnosis of COVID-19 was assigned when a patient had an ICD-10 diagnosis of COVID-19 during Period-1 and a valid SARS-CoV-2 test result was not available. For simplicity, we will subsequently refer to all patients meeting either testing or diagnostic criteria for COVID-19 as having a SARS-CoV-2 infection. The total study cohort was used to examine infection rates, emergency department use and inpatient hospital admissions within 14 days of infection, and critical care use among hospitalized patients during Period-1 (01/01/2020–05/31/2020) and Period-2 (06/01/2020–02/28/2021). Critical care use included receiving intubation, mechanical ventilation, or critical care monitoring during the hospital stay.

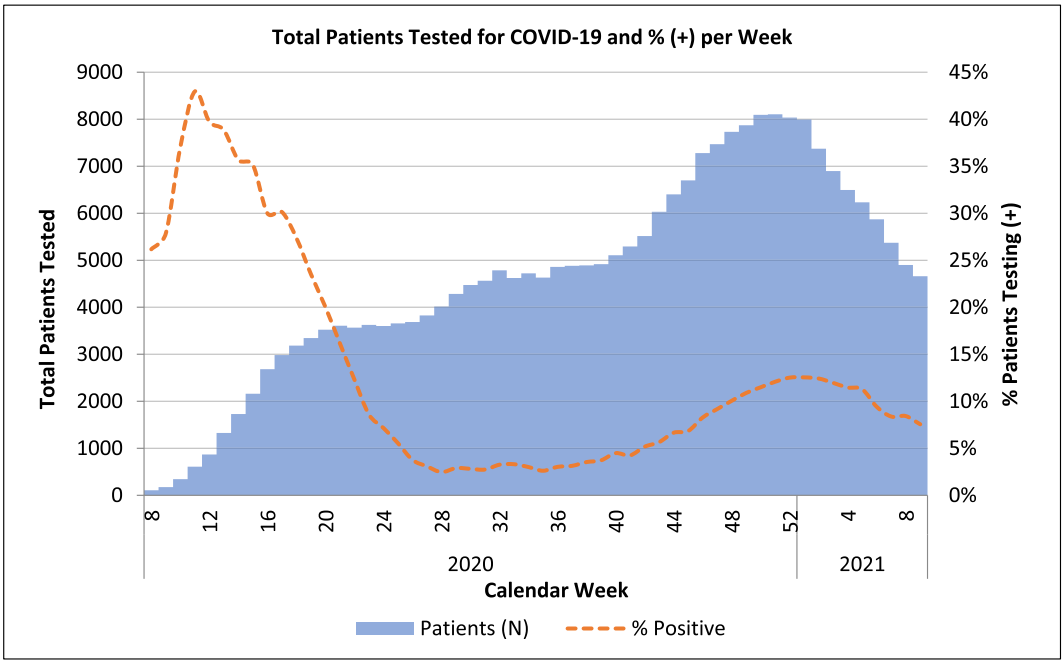
To examine the association of prior SARS-CoV-2 infection with risk of reinfection, we used a cohort of patients that had either a valid SARS-CoV-2 PCR test result or clinical diagnosis of COVID-19 in Period-1 *and* a subsequent valid test result in Period-2, and also had census tract information and were not the only residents in their census tract (Fig. 1). As test availability was higher during Period-2, reinfection was assessed only among patients withs valid test results in Period-2; reinfections were not diagnosed clinically. We compared the likelihood of a positive SARS-CoV-2 test in Period-2 among patients who tested negative for SARS-CoV-2 during Period-1 to the likelihood of a positive test in Period-2 among those who tested positive or received a COVID-19 diagnosis during Period-1. A reinfection was defined as a positive test occurring at least 90 days after the first positive SARS-CoV-2 test or diagnosis [39]. A negative test was not required as guidelines changed from test-based to time- and symptom-based clearance during this time period [40]. We also performed sensitivity analyses to assess whether results were affected by a) removing patients with only clinical diagnoses (no test), b) limiting the sample to patients with documented negative tests in between positive tests at >90 day intervals, and c) removing patients with evidence of COVID vaccination in the electronic medical record. Of note, due to the study timing, COVID vaccine availability was limited to healthcare workers and nursing home residents, and therefore inaccessible to the majority of individuals in this community-based cohort.

We used Poisson regression models of Period-2 infection (0/1) adjusting for patient age, sex, multiple comorbidities (as described in Supplementary Table 1), race/ethnicity, and English as the primary language. We included census tract fixed effects to adjust for systematic differences in exposure risk by neighborhood. As infection risk may vary systematically by area, we used the patient census tract as the area unit and obtained estimates of reinfection risk that adjusted for the clustering at the census tract level (using a fixed effects Poisson regression specification). We estimated the incidence rate ratio (IRR) of Period-2 infection risk associated with each covariate group relative to the reference group. *P*-values were calculated from two-tailed z-tests of the proportion of the population in each category in Period-1 compared to Period-2 (Supplementary Table 1), and based on Period-1 COVID-19 status (Table 1). Statistical significance was assessed at the 5% level; we report 95% confidence interval (CI) associated with each estimate. Statistical analyses were conducted using R Studio version 1.3.1056. This retrospective cohort study conforms to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) [41]. The Boston University School of Medicine institutional review board approved the creation and maintenance of the Informatics for Integrating Biology and the Bedside database (IRB# H- 28835), and the use of the database for this study (IRB# H-41078).

3. Results

3.1. SARS-CoV-2 infection characteristics in the total study cohort

A total of 142,047 patients underwent SARS-CoV-2 testing during the entire study period or were clinically diagnosed with COVID-19 during Period-1. Among this cohort, 139,981 individuals were received ≥1 valid SARS-CoV-2 test result and 5222 received a clinical COVID-19 diagnosis without a positive test during Period-1. Approximately 43.3% of the cohort was male, 33.2% was between 30 and 49 years; 31.2% of individuals were Black, 29.9% were White, 17.7% were Hispanic, 4.9% were Asian, and 16.4% identified as other races/ethnicities or declined to identify their race/ethnicity. Most individuals reported English as their primary language (72.5%). Among the comorbidities assessed in this study, 21.5% of individuals were categorized as obese (BMI ≥ 30 kg/m^2) and 21.7% had hypertension. This overall cohort was further stratified by Period-1 and Period-2 (Supplementary Table 1). Compared to Period-2, patients undergoing testing or who received a COVID-19 diagnosis in Period-1 were more likely to



	Mean	Standard deviation	Minimum	Maximum	Median
Tests	11.7%	10.0%	2.06%	37.92%	8.51%
Patients	13.1%	11.5%	2.47%	42.95%	8.89%

Fig. 1. Test prevalence and test positivity rate by date.

be Black or Hispanic, over age 30, and non-English language speaking; a higher proportion had comorbidities. Overall, 15.8% (n = 22,509) of patients were SARS-CoV-2 infected during the study period. Test positivity rates in Period-1 (31.3%, n = 7966) were higher than in Period-2 (11.7%, n = 14,909; $p < 0.001$).

Among patients who received a positive PCR test *or* a COVID-19 diagnosis (n = 22,509), 22.5% (n = 5074) visited the emergency department and 13% (n = 2935) were hospitalized within 14 days of receiving a positive test result or diagnosis. A total of 917 (31.2%) patients who were hospitalized required critical care. The proportion of emergency department visits, hospitalization, and critical care needs of patients were higher during Period-1 compared to Period-2 (Period-1: 22.9% visited the emergency department, 14.7% were hospitalized, 37.2% required critical care; Period-2: 18.9% visited the emergency department, 9.9% were hospitalized, 24.8% received critical care; $p < 0.001$ for all comparisons).

The number of patients tested for COVID-19 during the study period and the proportion of tests that were positive is shown in Fig. 2. The proportion of patients testing positive for COVID-19 was highest early in the pandemic, peaking at 43.0% positive in March 2020. This corresponded temporally to a high disease burden within the Boston metropolitan area as well as limited SARS-CoV-2 testing availability during this time. SARS-CoV-2 test positivity rates were lowest in July and August 2020 (<5%) and increased to more than 10% during the second wave of COVID-19 infections in December 2020–January 2021 (Fig. 2).

3.2. SARS-CoV-2 reinfection likelihood among patients with data in both Periods-1 and -2

From the overall cohort of 142,047 patients, we excluded patients who did not have either a valid SARS-CoV-2 test result (8.04% of tests overall; Period-1: 10.65%, 7.63% in Period-2) or clinical diagnosis of COVID-19 in Period-1 *and* at least one subsequent valid test PCR result in Period-2. Among the 12,496 patients who fulfilled these criteria, we excluded a further 3535 patients who had no census tract information or were the only resident in their census tract in the sample, as the analysis plan included utilizing census tract fixed effects to account for unobservable differences related to area of residence. The remaining 8961 patients comprised the reinfection assessment cohort for regression analysis (Fig. 2). Factors associated with having a SARS-CoV-2 infection during the study period among the reinfection assessment cohort are described in Table 1. Univariate analyses demonstrated that age ≥ 80 years, Hispanic race/ethnicity, and having obesity, diabetes, or hypertension were associated with higher likelihood of a SARS-CoV-2 infection, while White race, English as a primary language, and medical diagnoses of cancer, HIV/AIDS, liver disease, psychiatric, pulmonary, and substance use disorders were associated with lower infection likelihood.

A total of 10% of patients in the reinfection assessment cohort tested positive for COVID-19 in Period-2 (n = 866/8961). Among patients with SARS-CoV-2 infections in Period-1, 2.7% (n = 65/2431) had a positive test at least 90 days later, indicating reinfection. Among these patients, 38 had a negative test following their initial infection, and then a subsequent positive SARS-CoV-2 test. The mean time from initial SARS-CoV-2 infection to reinfection was 191 days (± SD: 65 days, range: 93–308 days). Among the 2431 patients with SARS-CoV-2 infections in Period-1, the mean number of days until their last negative test in Period-2 was 193 days (± SD: 88.3 days). Among 65 patients with reinfection, we assessed likelihood of visiting the Emergency Department or having an inpatient admission within 14 days of a diagnosis. Emergency Department use was as follows: 31 (47.7%) no visits, 18.5% visit during the first infection only, 9.2% visit during the reinfection only, and 24.6% visit during the both the initial and reinfection. Inpatient hospital admissions were as follows: 41 (63.1%) never hospitalized, 20.0% hospitalized during the first infection only, 7.7% hospitalized during reinfection only, and 9.2% hospitalized during both first and reinfection. Among the cohort of 38 patients with at least two positive COVID tests separated by at least one interceding negative

Table 1
Characteristics of the reinfection assessment cohort (n = 8961).

		COVID-19 Positive			
		Period-1		Period-2	
	Overall[1]	01/2020–05/2020		06/2020–02/2021	
	n = 8961	*n* = 2431 (21.7%)		*n* = 1091 (12.2%)	
	n (%)	n (%)	*p* value[2]	n (%)	p value
Sex					
Male	3695 (41.2)	1043 (28.2)	*ref.*	446 (12.1)	*ref.*
Female	5266 (58.8)	1388 (26.4)		645 (12.2)	
Age (years)					
<1–29	1273 (14.2)	332 (26.1)	*ref.*	159 (12.5)	*ref.*
30–49	3282 (36.6)	898 (24.3)		415 (12.6)	
50–64	2919 (32.6)	779 (26.7)		347 (11.9)	
65–79	1244 (13.9)	335 (26.9)		142 (11.4)	
≥80	243 (2.7)	87 (35.8)	< 0.001	28 (11.5)	
Race/Ethnicity					
White	2329 (26.0)	508 (21.8)	*ref.*	259 (11.1)	*ref.*
Black	3872 (43.2)	1065 (27.5)	< 0.001	390 (10.1)	
Hispanic	1942 (21.7)	631 (32.5)	<0.001	340 (17.5)	<0.001
Asian	191 (2.1)	49 (25.7)		26 (13.6)	
Other race/ethnicity	627 (7.0)	178 (28.4)	<0.001	76 (12.1)	
Primary Language					
English	6262 (69.9)	1447 (23.1)	*ref.*	648 (10.3)	*ref.*
Non-English	2699 (30.1)	984 (36.5)	<0.001	443 (16.4)	<0.001
Comorbidities[3]					
BMI					
Not Obese < 30 kg/m^2	5595 (62.4)	1423 (25.4)	ref.	677 (12.1)	
Obese ≥ 30 kg/m^2	3366 (37.6)	1008 (41.5)	<0.001	414 (12.3)	
Cancer	656 (7.3)	150 (22.9)		72 (11.0)	
Cardiovascular disease	2628 (29.3)	682 (25.9)		316 (12.0)	
Diabetes	2105 (23.5)	678 (32.2)		239 (11.4)	
Hematologic disorder	1414 (15.8)	409 (28.9)		204 (14.4)	
HIV and AIDS	197 (2.2)	41 (20.8)		25 (12.7)	
Homelessness	1707 (19.0)	453 (26.5)		187 (11.0)	
Hypertension	3855 (43.0)	1100 (28.5)		445 (11.5)	
Liver disease	1343 (15.0)	325 (24.2)		178 (13.3)	
Neurologic disorder	932 (10.4)	256 (27.5)		105 (11.3)	
Psychiatric disorder	3496 (39.0)	866 (24.8)		393 (11.2)	
Pulmonary disease	2497 (27.9)	591 (23.7)		292 (11.7)	
Renal disease	1935 (21.6)	569 (29.4)		232 (12.0)	
Substance use disorder	2323 (25.9)	483 (20.8)		210 (9.0)	

COVID-19 = Coronavirus Disease 2019; BMI = body mass index.

[1] The analytic cohort includes patients with SARS-CoV-2 testing or a clinical diagnosis of COVID-19 during Period-1 *and* at least one valid SARS-CoV-2 test result in Period-2. Among the 8961 patients, 8759 were diagnosed by test results and 202 were diagnosed by a clinical diagnosis only. To be defined as COVID-negative, in Period-1 patients had at least one negative test AND no clinical diagnosis of COVID-19. In Period-2, patients had at least one negative test.

[2] P-values obtained from two-tailed z-tests of the proportion of the population in each demographic category being Positive for COVID-19 vs. a reference group within that category.

[3] Comorbidities assessed within the past 2 years included in the Elixhauser comorbidity criteria, categorized by organ system: Cancer: solid tumor without metastasis, metastatic cancer, lymphoma; Cardiovascular disease: valvular disease, cardiac arrhythmias, peripheral vascular disease, congestive heart failure; Diabetes: diabetes with chronic complications, diabetes without chronic complications; Hematologic disorder: coagulation deficiency, deficiency anemias; Hypertension: hypertension complicated, hypertension uncomplicated; Neurologic disorder: neurologic disorders, paralysis; Psychiatric disorder: psychoses, depression; Pulmonary disease: chronic pulmonary disease, pulmonary circulation disorders; Renal disease: fluid and electrolyte disorders, renal failure; Substance use disorder: alcohol abuse, drug abuse. Significance testing for Comorbidities aside from BMI were not performed.

SARS-CoV-2 test, Emergency Department use was as follows: 17 (44.7%) no visits, 23.7% visit during the first infection only, 10.5% visit during the second infection only, and 21.1% visits during both initial and reinfection. Inpatient hospital admissions were as follows: 22 (57.9%) never hospitalized, 23.7% hospitalized during first infection only, 7.9% hospitalized on reinfection only, and 10.5% hospitalized during both first and reinfection.

A total of 8961 patients were included in the reinfection analysis cohort (See Fig. 2 for cohort criteria). Among patients in this cohort who tested negative for SARS-CoV-2 in Period-1, 12.6% (n = 821/6530) subsequently tested positive compared to 2.7% (n = 38/2431) of those with COVID infections in Period-1 (Table 2). We also performed sensitivity analyses, with similar findings (Table 2). First, we excluded 27 patients who did not an intervening negative test between their positive tests separated by at least 90 days. Second, we excluded 202 patients diagnosed clinically (*i.e.,* without a test result in Period-1). Third, we excluded 330 patients with evidence of receiving at least 1 vaccine dose prior to their COVID testing; results remained consistent.

The primary regression analyses were performed on the full reinfection cohort of 8961 patients. Poisson regression estimates indicated an 81% lower risk of infection in Period-2 among those with a SARS-CoV-2 infection Period-1 compared to those with a negative test (IRR = 0.19, 95% CI: 0.15–0.25; Table 3). Other factors associated with lower infection risk included individuals with English as their primary language (IRR 0.77, 95% CI: 0.65–0.91) and a diagnosis of substance use disorder (IRR 0.53, 95% CI: 0.41–0.68). Factors significantly associated with higher Period-2 infection risk were Hispanic race/ethnicity (IRR 1.40, 95% CI: 1.12–1.68), and diagnoses of hematologic disorders (IRR 1.34, 95% CI: 1.10–1.62) or liver disease (IRR 1.32, 95% CI: 1.06–1.63). When the definition of reinfection was limited to those with an intervening negative test, the IRR of Period-2 infection risk among those with a SARS-CoV-2 infection during Period-1 was 0.11 (95% CI: 0.08–0.16). The associations of other

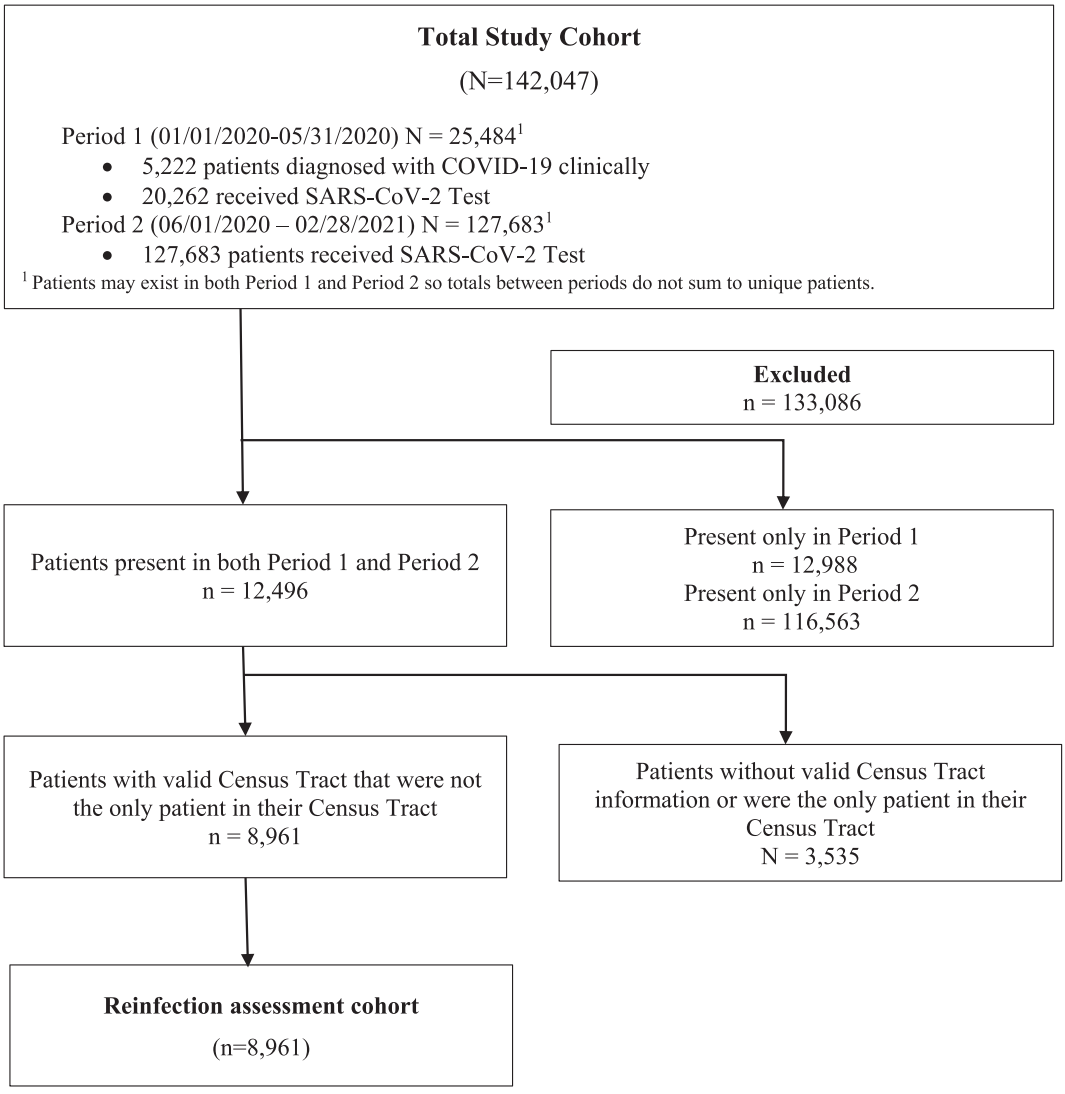


Fig. 2. Flowchart describing selection of the reinfection assessment cohort from the total study cohort.

variables examined remained similar (Table 4), to assess whether reinfection risk was similar by age we estimated regression models including the interaction of age groups with indicators of prior infection; no differences in reinfection by age were noted.

4. Discussion

In this retrospective cohort study, we analyzed data from a multi-racial, urban population in Massachusetts to estimate the risk of SARS-CoV-2

Table 2
COVID-19 Period 2 Reinfection[2] vs Initial Infection by Period 1 COVID-19 Status.

	Period 1 COVID-19 Status[1]	N	Period 2 COVID-19 Status N (%)	p value[5]
All (N = 8961)	Negative	6530	821 (12.5)	*ref.*
	Positive	2431	65 (2.7)	< 0.001
Excluding those without an intervening negative test between first and second infection[3] (*N* = 8934)	Negative	6530	821	*ref.*
	Positive	2431	38	< 0.001
Excluding those with only a clinical diagnosis of COVID (no test result)	Negative	6530	821 (12.5)	*ref.*
(*N* = 8759)	Positive	2229	64 (2.9)	< 0.001
Excluding those who recieved COVID-19 Vaccination[4]	Negative	6272	794 (12.7)	*ref.*
(*N* = 8631)	Positive	2359	65 (2.8)	< 0.001

[1] Negative is defined as at least one negative test without any positive test results. Positive is defined as 1 or more positive test results.
[2] Repeat positive tests were eligible for reinfection analysis when occurring ≥90 days after Period-1 infection.
[3] Repeat positive tests were eligible for reinfection analysis when occurring ≥90 days after Period-1 infection *and* patient had at least one negative test between initial infection and subsequent positive test.
[4] COVID-19 Vaccination status was determined from EHR data only.
[5] P-values obtained from two-tailed z-tests of the proportion of the proportion of those Positive for COVID-19 in Period 1 who were re-infected in Period 2 compared to the proportion Negative in Period 1 with initial infection in Period 2.

Table 3
Association of COVID-19 diagnosis or positive SARS-CoV-2 test in Period 1 with positive SARS-CoV-2 test in Period 2 (total n = 8961, n of COVID-positive 886).

	Poisson Regression	
	Adjusted IRR	95% CI
Period-1 COVID-19 infection status		
Negative	ref	ref
Positive (includes prior diagnosis)	**0.19**	**0.15, 0.25**
Sex - Male	1.05	0.90, 1.23
Age (years)		
< 1–29	ref	ref
30–49	1.07	0.86, 1.33
50–64	0.93	0.73, 1.17
65–79	0.89	0.68, 1.17
≥ 80	0.92	0.54, 1.57
Race/Ethnicity		
Asian	1.01	0.65, 1.57
Black	0.95	0.76, 1.19
Hispanic	**1.40**	**1.12, 1.68**
Other race/ethnicity	0.88	0.67–1.15
White	ref	ref
Primary Language - English	**0.77**	**0.65, 0.91**
Comorbidities[1]		
Obesity (BMI ≥ 30 (kg/m^2))[2]	1.03	0.89, 1.20
Cancer	0.82	0.63, 1.07
Cardiovascular disease	1.15	0.94, 1.41
Diabetes	0.91	0.75, 1.09
Hematologic disorder	**1.34**	**1.10, 1.62**
HIV and AIDS	1.24	0.81, 1.90
Homelessness	1.21	0.95, 1.55
Hypertension	0.99	0.83, 1.18
Liver disease	**1.32**	**1.06, 1.63**
Neurologic disorder	0.94	0.73, 1.21
Psychiatric disorder	0.92	0.78, 1.09
Pulmonary disease	1.10	0.93, 1.30
Renal disease	1.04	0.85, 1.27
Substance use disorder	**0.53**	**0.41, 0.68**

COVID-19 = Coronavirus Disease 2019, IRR = incidence rate ratio, CI = confidence interval, BMI = body mass index.
The analytic cohort includes patients who had SARS-CoV-2 testing or a clinical diagnosis of COVID-19 during Period-1 *and* at least one valid SARS-CoV-2 test in Period-2, and who had census tract information and were not the only resident in their census tract.
For Table 2 analysis, at least 90 days must have passed between the initial diagnosis and subsequent positive test, but negative intervening testing was not required.
[1] Comorbidities assessed included in the Elixhauser comorbidity criteria, categorized by organ system: Cancer: solid tumor without metastasis, metastatic cancer, lymphoma; Cardiovascular disease: valvular disease, cardiac arrhythmias, peripheral vascular disease, congestive heart failure; Diabetes: diabetes with chronic complications, diabetes without chronic complications; Hematologic disorder: coagulation deficiency, deficiency anemias; Hypertension: hypertension complicated, hypertension uncomplicated; Neurologic disorder: neurologic disorders, paralysis; Psychiatric disorder: psychoses, depression; Pulmonary disease: chronic pulmonary disease, pulmonary circulation disorders; Renal disease: fluid and electrolyte disorders, renal failure; Substance use disorder: alcohol abuse, drug abuse. Comorbidity diagnoses were current within past 2 years.
[2] Compared to individuals with a BMI < 30 (kg/m^2).

Table 4
Association of COVID-19 diagnosis or positive SARS-CoV-2 test in Period 1 *followed by a negative SARS-CoV-2 test* with a subsequent positive SARS-CoV-2 test in Period 2 (n = 8961).

	Poisson Regression	
	Adjusted IRR	95% CI
Period-1 COVID-19 infection status		
Negative	ref	ref
Positive (or prior diagnosis)	**0.11**	**0.08, 0.16**
Sex - Male	1.04	0.89, 1.22
Age (years)		
<1–29	ref	ref
30–49	1.10	0.88, 1.38
50–64	0.94	0.74, 1.21
65–79	0.91	0.70, 1.19
≥80	0.94	0.56, 1.57
Race/Ethnicity		
Asian	1.02	0.65, 1.60
Black	0.94	0.74, 1.18
Hispanic	**1.34**	**1.09, 1.64**
Other race/ethnicity	0.85	0.64, 1.12
White	ref	ref
Primary Language - English	**0.77**	**0.65, 0.92**
Comorbidities[1]		
Obese (BMI ≥ 30 (kg/m^2))[2]	1.05	0.90, 1.23
Cancer	0.82	0.63, 1.09
Cardiovascular disease	1.18	0.96, 1.44
Diabetes	0.89	0.74, 1.07
Hematologic disorder	**1.34**	**1.10, 1.62**
HIV and AIDS	1.23	0.79, 1.91
Homelessness	1.19	0.92, 1.53
Hypertension	0.99	0.82, 1.19
Liver disease	**1.33**	**1.08, 1.64**
Neurologic disorder	0.89	0.68, 1.17
Psychiatric disorder	0.92	0.78, 1.09
Pulmonary disease	1.08	0.91, 1.27
Renal disease	1.05	0.86, 1.29
Substance use disorder	**0.53**	**0.41, 0.69**

COVID-19 = Coronavirus Disease 2019, IRR = incidence rate ratio, CI = confidence interval, BMI = body mass index.
The analytic cohort includes patients who had SARS-CoV-2 testing or a clinical diagnosis of COVID-19 during Period-1 *and* at least one valid SARS-CoV-2 test in Period-2, and who had census tract information and were not the only resident in their census tract.
For Table 4 analysis, at least 90 days must have passed between the initial diagnosis and subsequent positive test, and negative intervening testing was required.
[1] Comorbidities assessed included in the Elixhauser comorbidity criteria, categorized by organ system: Cancer: solid tumor without metastasis, metastatic cancer, lymphoma; Cardiovascular disease: valvular disease, cardiac arrhythmias, peripheral vascular disease, congestive heart failure; Diabetes: diabetes with chronic complications, diabetes without chronic complications; Hematologic disorder: coagulation deficiency, deficiency anemias; Hypertension: hypertension complicated, hypertension uncomplicated; Neurologic disorder: neurologic disorders, paralysis; Psychiatric disorder: psychoses, depression; Pulmonary disease: chronic pulmonary disease, pulmonary circulation disorders; Renal disease: fluid and electrolyte disorders, renal failure; Substance use disorder: alcohol abuse, drug abuse. Comorbidity diagnoses were current within past 2 years.
[2] Compared to individuals with a BMI < 30 (kg/m^2).

reinfection. In this cohort, a prior SARS-CoV-2 infection was associated with an 81% decreased risk for subsequent infection during the observation period. These data contribute to the body of literature describing immunity following SARS-CoV-2 infections. Several studies examined risks of reinfection among individuals with and without SARS-CoV-2 antibodies, and found that the presence of antibodies decreased reinfection by 81–95% and also decreased disease severity [13,42,43]. However, as antibody testing is not routine, understanding the role of prior clinically-diagnosed infection is valuable. A population-level study from Denmark found that infection during their first surge was associated with 80.5% lower risk of subsequent reinfection [17]. Interestingly, our study found similar reductions in reinfection rates despite substantially higher overall prevalence of SARS-CoV-2 infection: 2% in Denmark compared to 15.8% in our cohort. Emerging data indicate that prior infection may be protective against illness with viral variants [44–46], and although genetic sequencing was not performed in this study, the Alpha (B.1.1.7) and Gamma (P.1) variants were circulating in Massachusetts during the second COVID-19 surge (11/01/2020–02/28/2021) [30–32].

We also evaluated emergency department visits, hospitalizations, and critical care needs between January 2020 and February 2021, and found that acute care requirements were somewhat lower among those diagnosed with COVID-19 after June 1st, 2020. Several factors may contribute to apparent decreased COVID-19 severity [47–49]. During Period-2, a relatively higher proportion of diagnosed SARS-CoV-2 infections were among

younger patients, greater test availability allowed diagnosis of milder cases, implementation of non-pharmaceutical interventions including face coverings and physical distancing may have decreased disease severity by lowering the viral inoculum exposure, and medical treatment protocols were developed. Both COVID-19 severity and the likelihood of poor outcomes may be influenced by a variety of factors, including the availability of adequate hospital staffing and supplies [50], and the emergence of more transmissible and virulent variants [51,52].

The COVID-19 pandemic continues to evolve rapidly, and many questions remain. However, it remains clear that Immunity through vaccination is infinitely preferable to immunity through infection, as SARS-CoV-2 infections have substantial risks of mortality as well as short- and long-term morbidity while vaccination is both safe and effective [1,3,4,64]. As our understanding of the long-term health consequences of COVID-19 continues to evolve, both the short- and long-term sequelae of infection have emerged a serious public health concerns [53,54]. However, susceptibility to reinfection increases over time following both infection and from immunization [3,4,17,55]. More research is needed to understand the dynamics of immunity from infection and vaccination [56–58]. Furthermore, millions of individuals received vaccination after a SARS-CoV-2 infection, and breakthrough infections are producing a growing cohort of individuals who become infected with SARS-CoV-2 after vaccination [7,59]. Data indicate lower risks of reinfection among those who received vaccination after infection [60]. Moreover, several studies have investigated antibody titers among individuals with and without a previous SARS-CoV-2 infection following one dose of an mRNA COVID-19 vaccine. Those with SARS-CoV-2 antibodies prior to vaccination had higher antibody titers after a single dose than antibody-negative vaccinees after two doses [61,62,63]. As SARS-CoV-2 becomes endemic throughout the world, understanding the mechanisms of immune control and the interactions between repeated viral exposures, past infections, original vaccine series and booster doses on immune memory responses are critical areas for future research [65].

In addition, the association between age and reinfection would benefit from additional research. Our study found no difference in reinfection risk by age, other studies have shown inconsistent relationships between age and reinfection [17]. The lack of association noted in our cohort may be in part attributable to societal factors. Boston experienced its first surge of COVID-19 when little was known about disease transmission and non-pharmaceutical interventions were not in place. By Period-2, public health measures had been implemented to protect older adults, including restrictions on nursing home and hospital visitation and public encouragement not to visit elderly relatives or restrict visits to outdoors with masks. These measures may have reduced exposures among older adults compared to younger adults who were often working, caring for children, and may have had more public interactions.

This study has several limitations. First, due to limited SARS-CoV-2 testing availability in Period-1, PCR testing during this time was restricted to moderately to severely ill individuals meeting strict criteria and their close contacts. Individuals with asymptomatic and mild infections are likely underrepresented in Period-1 data. Further, patients diagnosed with COVID-19 during the first surge may have been sicker overall, a factor which could potentially affect the apparent protection against reinfection associated with natural immunity. Several studies indicate that more severe disease may lead to higher antibody titers soon after recovery, although the association between disease severity and antibody titers appears to decrease over time [22,64,66]. As many patients with mild or asymptomatic disease likely were not diagnosed in Period-1, the magnitude of association between prior infection and reinfection might differ if all cases of disease were included. Misclassification is possible if patients were tested outside of the hospital system, tested within the hospital system but presented to outside facilities for emergency care or hospitalization, or presented to the emergency department or required hospitalization within 14 days of a SARS-CoV-2 infection, but for reasons unrelated to COVID-19. Next, the database did not report reasons for SARS-CoV-2 testing for individuals in this cohort, which might include COVID-19 symptoms, close contact with an infected person, requirements for work, school, or travel, or testing required for medical procedures. Similarly, we could not evaluate correlations between severity of initial COVID-19 symptoms and protection against subsequent reinfection. Our ability to determine illness characteristics as well as compare severity by Period or prior infection status are limited by the database characteristics and small numbers of patients requiring hospitalization. The database also does not contain information on deaths, so we could not assess this outcome. While we did perform sensitivity analyses excluding patients with evidence of vaccination, it is possible that additional patients received vaccinations that were not documented in the electronic medical record. Lastly, due to unavailability of SARS-CoV-2 genome sequencing, we were unable to assess the associations between SARS-CoV-2 variants and reinfection. Future prospective studies should evaluate protection against repeat SARS-CoV-2 infections in the setting of additional SARS-CoV-2 variants.

In conclusion, results from this large cohort study indicate that prior SARS-CoV-2 infection is associated with an approximately 80% lower risk of subsequent infection over an average of 6 months of follow-up. Future research is needed to understand long-term durability of natural immunity, immunity in individuals with both vaccination and infection, and the impacts of emerging SARS-CoV-2 variants.

Funding

This work was funded by Boston Medical Center via a Seed grant from the Obstetrics and Gynecology Department.

Declaration of Competing Interest

No authors have conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dialog.2022.100057.

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