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BRIEF REPORT

Risk of Symptomatic Infection During a Second Coronavirus Disease 2019 Wave in Severe Acute Respiratory Syndrome Coronavirus 2–Seropositive Individuals

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We analyzed 221 coronavirus disease 2019 cases identified between June 2020 and January 2021 in 6074 individuals screened for immunoglobulin G antibodies in May 2020, representing 77% of residents of 5 Italian municipalities. The relative risk of developing symptomatic infection in seropositive participants was 0.055 (95% confidence interval, .014–.220).

Keywords. serological screening; COVID-19; SARS-CoV-2; natural immunity; reinfection risk.

Infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is expected to provide temporary protective immunity against subsequent reinfection or against the risk of disease following reinfection episodes [1, 2]. Published evidence indicates that more than 90% of individuals develop immunoglobulin G (IgG) and neutralizing antibodies following primary infection, but that antibody titers may wane rapidly over time, particularly in mild and asymptomatic patients [2, 3]. Sporadic episodes of SARS-CoV-2 reinfection have been documented [2, 4-7]. However, to what extent and for how long natural infection provides protective immunity from SARS-CoV-2 are still debated.

Recent estimates suggest 80%–85% protection from reinfection [8, 9] and 99% protection against symptomatic disease [10] up to 6 months after the first infection. However, follow-up studies comparing infections in recovered individuals with well-matched naive individuals are still lacking [2]. Cohort studies conducted to date mainly relied on the comparison of infection rates among individuals who had a previous polymerase chain reaction (PCR) result. Due to the limited testing of asymptomatic and paucisymptomatic individuals, this approach may underestimate the number of individuals who have already experienced the infection in the past. Combining surveillance data with extensive serological screening applied to the general population could help reduce biases in the assessment of the risk of reinfection.

METHODS

Patients and Analyses

We analyzed 5 Italian municipalities within the Autonomous Province of Trento, Italy, where an IgG serological screening aimed at covering the entire adult resident population was conducted between 5 May 2020 and 15 May 2020. These municipalities were selected as those showing the highest cumulative case incidence in the province during the first coronavirus disease 2019 (COVID-19) wave [11] (ranging from 18.7 to 27.6 per 1000 individuals). For purposes of this study, the Azienda Provinciale per i Servizi Sanitari, Department of Prevention, sent a letter of invitation to all residents in the 5 municipalities who were aged ≥10 years. Individuals residing in nursing homes were excluded as their exposure to the infection might have been markedly different compared with the general population. All other residents were invited to take part in the serological screening. However, participation among severe cases might have been hindered by their clinical status during the conducted survey. IgG results were communicated to tested participants. More details on the study design can be found in [11].

In autumn 2020, the Italian government progressively increased restrictions to counter the observed increase in COVID-19 cases. Applied measures included a curfew between 10 PM and 5 AM, limitations to retail and service activities, restrictions on interregional mobility, and reinforced distance learning in schools [12]. COVID-19 vaccination of the general population started in February 2021 [13]. In Italy, notification to health authorities at the first signs of COVID-19 symptoms is mandatory for the entire population, and monitoring for respiratory symptoms and fever is performed at school and at work [14, 15]. Close contacts of cases are regularly identified through standardized epidemiological investigations of positive cases. Case contacts are quarantined and tested against SARS-CoV-2 infection. The analyzed surveillance records consist of

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laboratory-confirmed infections identified by health authorities through surveillance or contact tracing operations between June 2020 and January 2021. Symptomatic cases were defined as positive individuals having fever and either cough or at least 2 of the following symptoms: widespread myalgia, headache, dyspnea, pharyngodynia, diarrhea, nausea/vomiting, anosmia/ageusia, or asthenia. Infections that occurred in residents who did not participate in the serological screening were excluded from the analysis.

Laboratory Tests

Serological tests were performed using Abbott SARS-CoV-2 IgG chemiluminescent assays and analyzed on the Abbott Architect i2000SR automated analyzer (Abbott Diagnostics, Chicago, IL) [11]. The assay detects IgG directed against the SARS-CoV-2 nucleocapsid protein, measured as a relative light unit (RLU), which is considered a proxy of the concentration of IgG antibodies to SARS-CoV-2 in the sample. Serological results are provided as the ratio between sample RLU and the calibrator mean chemiluminescent signal from 3 calibrator replicates. Results are interpreted as positive when this ratio is ≥1.4 and negative when <1.4 [11]. Positive cases that occurred after June 2020 were determined using either the RealTime SARS-CoV-2 assay on naso-oropharyngeal swabs (PCR, detectability per milliliter of Universal Transport Medium buffer 250 copies) or the rapid antigenic test (sensitivity >90%, specificity >97%).

Statistical Methods

We estimated the relative risk of developing a symptomatic infection for participants who tested positive for IgG antibodies in May 2020 compared with those who were IgG-negative to SARS-CoV-2 infection. To do this, we applied a generalized linear mixed model (GLMM) with logit link, defining the dependent variable as the confirmation of a symptomatic infection that occurred between 1 June 2020 and 31 January 2021 and using the participant age and IgG binary result obtained in May 2020 (positive vs negative) as independent variables. In the GLMM, age was standardized by subtracting the mean and dividing by the standard deviation to help interpret the estimated intercept, which refers to average-aged individuals, and to facilitate model convergence when exploring rare events (notably, reinfections). The municipality of residence was considered a random effect to account for possible heterogeneity in exposure to SARS-CoV-2 across different geographical areas.

Informed consent for blood collection was obtained from all the participants. The study was approved by the Ethics Committee of the Instituto Superiore di Sanitâ (Prot. PRE BIO CE n. 15997, 04.05.2020).

RESULTS

The serological screening involved 6074 individuals (median age, 50; interquartile range, 32–63), representing 77.1% of the resident population (Table 1). Of these, 1402 (23.1%) resulted positive for IgG antibodies. At the provincial level, between 1 June 2020 and 31 January 2021, surveillance activities identified 22 767 SARS-CoV-2–positive individuals; 36% of them were determined via contact tracing operations (9% symptomatic and 27% asymptomatic). Of the residual 64% identified infections, 71% developed symptoms. In the 8 months of follow-up, 276 infections were identified in the study area. Of these, 55 did not participate in the serological screening and were excluded from the analysis. Of the 221 positive participants, 99 were confirmed by PCR tests and 124 were symptomatic (Table 1). Four cases were identified among participants who tested positive to IgG in May 2020; 2 of them were symptomatic. Both of these cases were males, determined in December 2020, who requested to be tested after symptom onset. The older patient (88 years) was admitted to a hospital but did not require mechanical ventilation or admission to an intensive care unit. The younger patient (52 years) was a mild case who was isolated and treated at home. The cumulative incidence of identified symptomatic infections over the observation period was 2.60% (95% confidence interval [CI], 2.08%–3.26%) in the IgG-negative group and 0.14% (95% CI, .04%–.57%) in the IgG-positive group. The adjusted relative risk of being confirmed as a symptomatic SARS-CoV-2 infection in IgG-positive compared with IgG-negative participants was 0.055 (95% CI, .014–.220; see the Supplementary Materials). The number of infections identified over time in the study area is shown in the Supplementary Materials, where a comparison of the age distributions of infections determined during the IgG screening and in the follow-up is also provided.

DISCUSSION

Our analysis confirms the hypothesis that the likelihood of experiencing SARS-CoV-2 symptomatic infection is greatly reduced in individuals who had already been infected in the previous 8–10 months [11]. In line with what has been observed elsewhere [7–9, 16, 17], our findings suggest that the relative risk of symptomatic infection for individuals who previously tested positive to IgG antibodies compared with seronegative individuals is less than 6%.

Our results should be interpreted in light of the following limitations. First, the study design is not suitable to determine if previous infection from historical lineages of SARS-CoV-2 provides protection against asymptomatic reinfection. In fact, reinfection episodes were identified through the surveillance system, which is prone to underestimate asymptomatic infections. For instance, the serological screening conducted in May 2020 identified 3.4 times more infections than those determined through PCR during the first epidemic wave [11]. However, during the entire study period, notification at the first clinical signs or respiratory symptoms was mandatory for the entire population; close monitoring for respiratory symptoms

Table 1. Characteristics of the Population With Prior Seroprevalence Data (from 5 May 2020 through 15 May 2020), Those Under Surveillance (from 1 June 2020 through 31 January 2021) and Individuals With Severe Acute Respiratory Syndrome Coronavirus 2 Infection During Surveillance

Municipality	Resident Population	Number (%) of Persons Tested for SARS-CoV-2 IgG Antibody[a]	Number (%) of Persons Tested for SARS-CoV-2 IgG Antibody Who Were Positive	Number (%) of Persons Tested for SARS-CoV-2 IgG Antibody Who Were Negative	Average Age (Min–Max)[b] of Surveillance Participants by SARS-CoV-2 IgG Antibody Status, Years		Number (%) of SARS-CoV-2 Infections Detected by Polymerase Chain Reaction or Antigen Testing During Surveillance[c]		Average Age (Min–Max) of SARS-CoV-2–Infected Individuals During Surveillance,[b] Years		Number (%) of Symptomatic SARS-CoV-2 Infections During Surveillance[c]		Average Age (Min–Max) of Those With Symptomatic SARS-CoV-2 Infections During Surveillance,[b] Years	
					IgG Positive	IgG Negative	IgG Positive	IgG Negative	IgG Positive	IgG Negative	IgG Positive	IgG Negative	IgG Positive	IgG Negative
Borgo Chiese	2006	1357 (67.6)	284 (20.9)	1073 (79.1)	47 (9–94)	48 (9–93)	1 (0.1)	53 (3.9)	67 (...)	51 (9–92)	0 (0.0)	22 (1.6)	...	56 (13–83)
Campitello	715	592 (82.8)	147 (24.8)	445 (75.2)	46 (9–88)	49 (10–93)	2 (0.3)	22 (3.7)	70 (53–88)	37 (16–70)	1 (0.2)	17 (2.9)	88 (...)	38 (16–70)
Canazei	1898	1511 (79.6)	419 (27.7)	1092 (72.3)	45 (9–86)	47 (9–96)	1 (0.1)	46 (3.0)	51 (...)	47 (10–85)	1 (0.1)	34 (2.3)	51 (...)	49 (10–85)
Pieve Di Bono	1435	1123 (78.3)	200 (17.8)	923 (82.2)	46 (8–93)	49 (10–98)	0 (0.0)	60 (5.3)	...	45 (10–98)	0 (0.0)	27 (2.4)	...	49 (18–98)
Vermiglio	1824	1491 (81.7)	352 (23.6)	1139 (76.4)	45 (10–91)	47 (8–93)	0 (0.0)	36 (2.4)	...	51 (10–84)	0 (0.0)	22 (1.5)	...	56 (22–84)
Overall	7879	6074 (77.1)	1402 (23.1)	4672 (76.9)	46 (8–94)	48 (8–98)	4 (0.1)	217 (3.6)	64 (51–88)	47 (9–98)	2 (0.0)	122 (2.0)	70 (51–88)	50 (10–98)

Abbreviations: Ig, immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]From 5 May 2020 through 15 May 2020.

[b]Unstandardized age.

[c]From 1 June 2020 through 31 January 2021.

and fever at schools and at workplaces was required by Italian regulation as well [14, 15]. Therefore, the underreporting of symptomatic infections, which represents the target outcome of this analysis, was likely negligible. Second, the observed reinfection events depend not only on the duration and amount of protection against reinfection but also the individual number of contacts and temporal changes in the prevalence of infection in the general population. The perceived protection provided by previous infection episodes might have resulted in different behaviors and contact patterns between seropositive and seronegative participants. Consequently, seropositive participants may have been exposed to a larger risk of infection, leading us to overestimate the risk of symptomatic reinfection from SARS-CoV-2. Moreover, the lower viral circulation during the summer months may have resulted in an overestimation of the duration of protection against the disease. It is also possible that we underestimated the number of reinfection episodes due to potential IgG negative results from previously infected individuals. Finally, the analyzed data do not provide any information about the potential presence of SARS-CoV-2 lineages that have emerged in recent months. Therefore, estimates obtained here may not apply to SARS-CoV-2 variants that are quickly replacing historical lineages that circulated in 2020 [2].

The major strength of the proposed analysis is that study participants cover 77% of residents of 5 municipalities, providing a comprehensive view of infection risks in the general population. In addition, individuals who were previously exposed to SARS-CoV-2 were identified via IgG serological testing, therefore, reducing biases caused by underestimation of infection episodes in asymptomatic and mild disease cases. Additional studies are needed to quantify sterilizing immunity against SARS-CoV-2 and its duration, to explore whether immune responses mounted following initial infection can prevent possible onward transmission, and to investigate cross-protection across different SARS-CoV-2 lineages.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. P. P., S. M., and A. F. conceived and designed the study. M. M. performed the analysis. S. P., G. Gi., M. G. Z., P. P. B., and A. F. collected data. M. M. and P. P. wrote the first draft. All authors contributed to data interpretation, critical revision of the manuscript, and approval of the final version of the manuscript.

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