The risk of symptomatic infection during a second COVID-19 wave, in SARS-CoV-2 seropositive individuals

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Abstract

We analyzed 221 COVID-19 cases identified between June 2020 and January 2021 in 6,074 individuals screened for IgG antibodies in May 2020, representing 77% of residents of five Italian municipalities. The adjusted relative risk of developing symptomatic infection in SARS-COV-2 seropositive participants was 0.055 (95%CI: 0.014 - 0.220)

Introduction

Infection from 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 indicate that more than 90% of individuals develop 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 is still debated.

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

Methods

Subjects and Ascertainment We analyzed five 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 May 5 and 15, 2020. These municipalities were selected as those showing the highest cumulative case incidence in the province during the first COVID-19 wave [11] (ranging between 18.7 and 27.6 per 1,000 individuals). To the purpose of the study, the Azienda Provinciale per i Servizi Sanitari (APSS), Department of Prevention, sent a letter of invitation to all

citizens resident in the five municipalities who were at least 10 years old. Individuals residing in nursing homes were excluded as their exposure to the infection might have been markedly different compared to the general population. All the other residents were invited to take part of 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 of COVID-19 cases. Applied measures included a curfew between 10pm and 5am, limitations to retail and service activities, restrictions on inter-regional 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 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 two of the following symptoms: widespread myalgia, headache, dyspnoea, pharyngodynia, diarrhea, nausea/vomiting, anosmia/ageusia, asthenia. Infections 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, USA) [11]. The employed assay detects IgG directed against the SARS-CoV-2 nucleocapsid protein, measured as a Relative Light Unit (RLU), which is considered as 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 three calibrator replicates. Results are interpreted as positive when this ratio is ≥1.4 and negative when <1.4 [11]. Positive cases occurred after June 2020 were ascertained by using either RealTime SARS-CoV-2 assay on naso-oropharyngeal swabs (PCR, detectability per ml of UTM buffer 250 copies) or 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 to those who resulted 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 occurred between June 1, 2020 and January 31, 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 standard deviation to help interpreting 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 as a random effect to account for possible heterogeneity in exposure to SARS-CoV-2 across different geographical areas.

Results

The serological screening involved 6,074 individuals (median age 50; IQR: 32-63), representing 77.1% of the resident population (Table 1). Of these, 1,402 (23.1%) resulted positive for IgG antibodies. At the provincial level, between June 1, 2020 and January 31, 2021, surveillance activities identified 22,767 SARS-CoV-2 positive individuals; 36% of them were ascertained 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. Out 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; two of them were symptomatic. Both these cases were males ascertained in December 2020, who requested to be tested after symptoms 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%CI: 2.08% – 3.26%) in the IgG negative group and 0.14% (95%CI: 0.04% – 0.57%) in the IgG positive group. The adjusted relative risk of being confirmed as a symptomatic SARS-CoV-2 infection in IgG positive compared to IgG negative participants was 0.055 (95%CI: 0.014-0.220, see Supplementary Data). The number of infections identified over time in the study area is shown in Supplementary Data, where a comparison of the age distributions of infections ascertained during the IgG screening and in the follow-up is also provided.

Discussion

The conducted analysis confirms the hypothesis that the likelihood of experiencing SARS-CoV-2 symptomatic infection is greatly reduced in individuals already infected in the previous 8-10 months[11]. In line with what 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 to seronegative subjects is less than 6%.

Our results should be interpreted in light of the following limitations. First, the study design is not suitable to assess 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 under ascertain asymptomatic infections. For instance, the serological screening conducted in May 2020 identified 3.4 more infections than those ascertained through PCR during the first epidemic wave [11]. However, during the entire study period, the notification at the first clinical signs or respiratory symptoms was mandatory for the entire population; close monitoring for respiratory symptoms and fever at schools and at workplaces was required by Italian regulation as well [14,15]. Therefore, the underreporting of symptomatic infections, which represent 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 from 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 emerged in recent months. Therefore, estimates obtained here may not apply to SARS-CoV-2 variants that are quickly replacing historical lineages circulating 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 under ascertainment of infection episodes in asymptomatic and mild disease cases**.** Further 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 onwards transmission, and to investigate cross-protection across different SARS-Cov-2 lineages.

NOTES

Author contributions

PP,SM,AF conceived and designed the study. MM performed the analysis. SP,GGi,MGZ,PPB,AF collected data. MM,PP wrote the first draft. All authors contributed to data interpretation, critical revision of the manuscript and approved the final version of the manuscript.

Ethical statement

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

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Competing interests

MA has received research funding/consulting fees/travel support related to influenza vaccination in Italy from Seqirus. The funding is not related to COVID-19.

All other authors declare no conflict of interest.

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Table 1 Characteristics of the Population with Prior Seroprevalence Data[a], Those Under Surveillance[b] and Individuals with SARS-CoV-2 Infection During Surveillance

Municipality	Resident population	Number (%) of Persons Tested for SARS-CoV-2 IgG Antibody	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 in Years (min-max) [c] of Surveillance Participants by SARS-CoV-2 IgG Antibody Status		Number (%) of SARS-CoV-2 Infections Detected by PCR or Antigen Testing During Surveillance [b]		Average Age in Years (min-max) [c] of SARS-CoV-2 Infected Individuals During Surveillance		Number (%) of Symptomatic SARS-CoV-2 Infections During Surveillance [b]		Average age in years (min-max) [c] of Symptomatic SARS-CoV-2 Infections During Surveillance	
					IgG positive	IgG negative	IgG positive	IgG negative	IgG positive	IgG negative	IgG positive	IgG negative	IgG positive	IgG negative
Borgo Chiese	2,006	1,357 (67.6)	284 (20.9)	1,073 (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	1,898	1,511 (79.6)	419 (27.7)	1,092 (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	1,435	1,123 (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	1,824	1,491 (81.7)	352 (23.6)	1,139 (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	**7,879**	**6,074 (77.1)**	**1,402 (23.1)**	**4,672 (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)**

[a] May 5 through May 15, 2020; [b] June 1,202 through January 31, 2021; [c] Unstandardized age.