Journal of Infection and Public Health 16 (2023) 1137–1141

Contents lists available at ScienceDirect

Journal of Infection and Public Health

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

Original article

Natural and vaccine-induced immunity are equivalent for the protection against SARS-CoV-2 infection

Matteo Franchi [a,b,*], Giacomo Pellegrini [a,c], Danilo Cereda [d], Francesco Bortolan [d], Olivia Leoni [d], Giovanni Pavesi [d], Massimo Galli [e,f], Giuseppina Valenti [d], Giovanni Corrao [a,b,d]

[a] National Centre for Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy
[b] Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[c] ASST Sette Laghi, Ospedale di Circolo, Varese, Italy
[d] Directorate General for Health, Lombardy Region, Milan, Italy
[e] Infectious Diseases Unit, Luigi Sacco Hospital, Milan, Italy
[f] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

ARTICLE INFO

Article history:
Received 2 November 2022
Received in revised form 11 April 2023
Accepted 15 May 2023

Keywords:
SARS-CoV-2
COVID-19
Immunity
Protective effect
COVID-19 vaccines

ABSTRACT

Objectives: To compare the long-term cumulative risk of SARS-CoV-2 infection associated with natural and vaccine-induced immunity.
Methods: Retrospective population-based cohort study based on registry of COVID-19 vaccinations and SARS-CoV-2 infections among 9.1 million citizens of Lombardy, Italy, eligible for vaccination on 27th December 2020. Those who developed SARS-CoV-2 infection from 24th May to 14th September 2021, provided they did not yet receive the COVID-19 vaccine when infection was confirmed, and those who received the second mRNA vaccine dose, provided they had not yet developed the infection, were selected to be 1:1 matched for sex, age and index date. The latter corresponded to 90 days after confirmed infection or 14 days after vaccine administration. A control cohort including citizens who, on the index date, had neither developed infection nor received vaccination was also selected. Kaplan–Meier curves were used for comparing the cumulative incidence of new SARS-CoV-2 infection from the index date until 22nd June 2022.
Results: Overall, 19,418 1:1:1 risk-sets were included. After 9 months of follow-up, the cumulative risk of new SARS-CoV-2 infection was 21.8%, 22.0%, and 25.9%, respectively, among exposed to natural immunity, vaccine-induced immunity and unexposed.
Conclusions: Equivalent potential for protecting against new SARS-CoV-2 infection was observed.

Introduction

Real-life evidence has consistently shown that both natural immunity acquired after SARS-CoV-2 infection [1–4] and induced immunity acquired by anti-COVID-19 vaccines [5] have protective action against SARS-CoV-2 infection. Nevertheless, few studies have directly compared the protection given by natural and induced immunity, generating inconsistent findings [6–9]. This population-based study compared the risk of SARS-CoV-2 infection associated with natural and vaccine-induced immunity.

Methods

The vaccine integrated platform of Lombardy, an Italian region accounting for about 11 million inhabitants, was used. Briefly, the platform includes the vaccine registry collecting individual data on the date, type, and dose of the dispensed vaccine; the registry of patients with a confirmed diagnosis of SARS-CoV-2 infection; the health registry, including updated data on vital status, sex, and age of all beneficiaries of the Regional Health Service (RHS). A unique anonymized individual identification code was used to link each database with each other. Details of the platform and its use in the setting of regional mass vaccination are reported elsewhere [10,11].

* Correspondence to: Dipartimento di Statistica e Metodi Quantitativi, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy.
E-mail address: matteo.franchi@unimib.it (M. Franchi).

https://doi.org/10.1016/j.jiph.2023.05.018

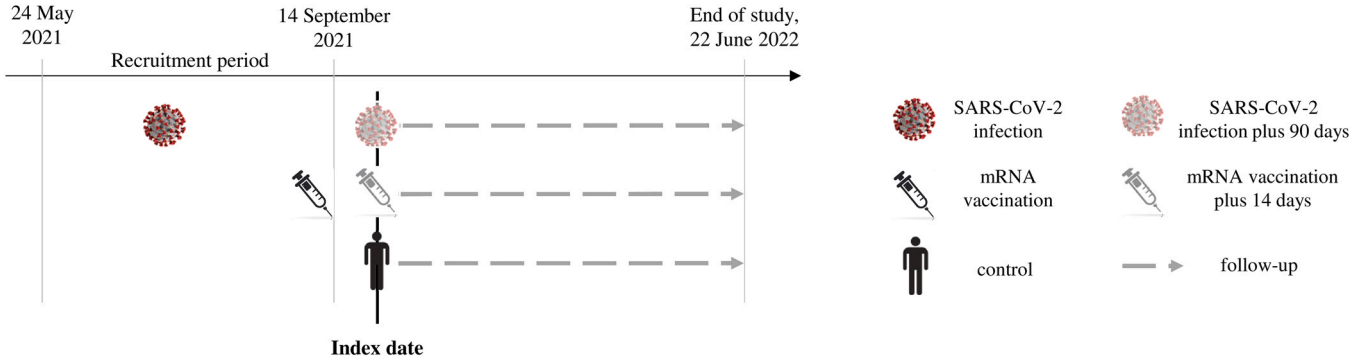

Fig. 1. Graphical representation of the study cohort selection.

Starting from the cohort of 9.1 million RHS beneficiaries eligible for vaccination on 27 December 2020 (target population), those who developed SARS-CoV-2 infection for the first time, confirmed by molecular testing of nasopharyngeal swabs, from 24 May to 14 September 2021 were identified. To select citizens exposed for the first time to natural immunity only, those vaccinated before the date of infection were excluded. Because a citizen must be considered at risk of reinfection starting from 90 days after complete resolution of the first infection, according to the U.S. Center for Disease Control and Prevention guidelines [12], we labelled the date corresponding to the first infection plus 90 days as the "index date.".

For each cohort member exposed to natural infection, a citizen belonging to the target population was randomly selected to be 1:1 matched based on age and sex, provided that he/she received the second-dose mRNA vaccine (Pfizer-BioNTech or Moderna) 14 days prior to the index date (under the assumption that immunity is achieved 2 weeks after receiving vaccination [13]). To select citizens exposed to vaccine-induced immunity only, those who developed SARS-CoV-2 infection prior to receiving the complete vaccine dose were excluded. In addition, because differences in conferring protection was noticed for mRNA and adenovirus-based vaccines [11], citizens who received adenovirus-based vaccines (Oxford-AstraZeneca or Janssen) were excluded from our study. Finally, for each matched pair of beneficiaries who had natural or induced exposure, a citizen belonging to the target population was randomly selected to be matched based on age and sex, provided that they were neither infected nor vaccinated on the index date (Fig. 1).

Each cohort member of the 1:1:1 risk sets accumulated person-years of follow-up from the index date until the outcome onset (i.e., SARS-CoV-2 infection established by positive PCR test to the SARS-CoV-2 virus in any clinical setting regardless, of the presence of symptoms) or censoring (i.e., death for any cause, migration from Lombardy, administration of the first or the booster vaccine dose, or the end date 22 June 2022), whichever came first. The cumulative risk of infection was estimated using the Kaplan–Meier method. The log-rank test was used to test homogeneity between groups. The analyses were also stratified among strata of age. With the aim of maximizing the study power, we decided to use the median age as the cut-off to classify age.

Moreover, with the aim of assessing the protection of natural and vaccine-induced immunity against Delta and Omicron variant, two case-control studies were nested into the study cohort. In the first one, each cohort member experiencing SARS-CoV-2 infection (case) before 01 December 2021, thus likely caused by Delta variant [14], was 1:1 matched based on index date, age and sex to one cohort member (controls) randomly chosen among cohort members still on study and who did not experience SARS-CoV-2 infection at the date of SARS-CoV-2 occurrence of the case. In the second one, each cohort member experiencing SARS-CoV-2 infection (case) after 01 December 2021, thus likely caused by Omicron variant [14], was 1:1 matched based on index date, age and sex to one cohort member (controls) randomly chosen among cohort members still on study and who did not experience SARS-CoV-2 infection at the date of SARS-CoV-2 occurrence of the case. In both nested case-control studies, each individual was classified as belonging to one of the following three mutually exclusive categories of previous exposure: exposure to natural immunity, exposure to vaccine-induced immunity, no exposure to neither natural or vaccine-induced immunity. The association between exposure to natural or vaccine-induced immunity, as compared to not exposure, was assessed by a conditional logistic regression model and was expressed in terms of Odds Ratios (OR) and 95% Confidence Intervals (CI).

The SAS statistical package was used for all statistical analyses (SAS, version 9.4).

Results

The study cohort included 22,471 citizens exposed to natural immunity. Among them, 19,418 contributed to form as many 1:1:1 sets of citizens who had experienced natural exposure, vaccine-induced exposure, and no exposure. The mean age of the cohort was 32.6 years (standard deviation: 15.9 years) and 51.9% were male.

During a median follow-up of 4.9 months, 9738 new infections occurred. The cumulative risk of developing a new infection is shown in Fig. 2. The risk was similar between infected and vaccinated subjects, but it was considerably higher among controls ($p < 0.001$). Among the latter, the risk steadily increased over time, reaching a value of 25.9% at the end of follow-up. Conversely, the trend of the cumulative risk among infected and vaccinated individuals was very similar, being negligible after the first month of follow-up and increasing afterward, reaching values of 21.8% and 22.0%, respectively, at the end of follow-up. Similar patterns were observed among the 9352 sets of citizens aged less than 30 years and among the 10,066 sets of citizens aged 30 years or older (Fig. 3).

The association between natural and vaccine-induce immunity and the risk of experiencing SARS-CoV-2 infection likely due to delta or omicron variant is shown in Table 1. During the period in which the delta variant was dominant, exposure to natural and vaccine-induced immunity were associated with a reduction of the risk of SARS-CoV-2 infection of 0.79 (95% CI 0.62–0.89) and 0.81 (95% CI 0.65–0.89), respectively (p-value of homogeneity of odds ratios < 0.001). During the period in which the omicron variant was

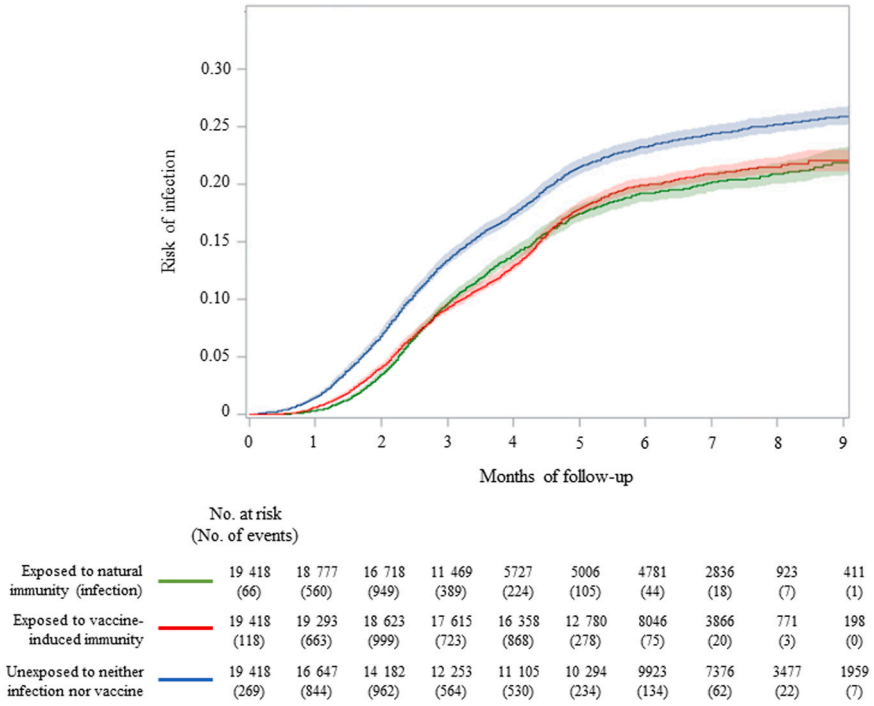

Fig. 2. Cumulative risk of developing a new SARS-CoV-2 infection by exposure status.

dominant, the corresponding risk reductions were 0.17 (95% CI 0.11–0.23) and 0.18 (95% CI 0.13–0.23), respectively, (p-value of homogeneity of odds ratios < 0.001).

Discussion

Our study did not offer evidence that immunity due to SARS-CoV-2 infection and that induced by complete (two-dose) anti-COVID-19 vaccination act differently in conferring protection against the risk of new SARS-CoV-2 infection. Conversely, both natural and induced immunity offer significant protection when compared to individuals who did not have COVID-19 immunity. These results are consistent with a systematic review and pooled analysis, showing equivalence of protection from natural immunity in COVID-19 recovered versus fully vaccinated individuals [15]. Similarly, a population-based study conducted in Israel showed similar protection conferred by previous SARS-CoV-2 infection and by the Pfizer-BioNTech vaccine. However, these findings are limited by the short follow-up period (three months), restricted to the first trimester of 2021, thus not including the spread of the most recent variants [8]. Conversely, a retrospective cohort study conducted in Israel showed that individuals vaccinated with Pfizer-BioNTech had a 13-fold increased risk of infection with the Delta variant, as compared to unvaccinated previously infected individuals [7]. Even in this case, the period of ascertainment of the study outcome was limited to three months.

Although the observed cumulative risk of infection was relatively high among citizens exposed to natural and induced immunization (about 20% within 9 months of follow-up), it should be noted that the study period included the emergence of the Omicron variant, which is known for having numerous mutations with the potential to increase transmissibility and partially escape natural or vaccine-induced immunity [16]. Indeed, our results showed that the protection conferred to natural and vaccine-induced immunity was lower during the period in which Omicron was the dominant variant, as compared to the period in which Delta was the dominant variant. This result may be due, at least in part, to the higher median time elapsed from 2 weeks after vaccination until SARS-CoV-2 infection occurred during the Omicron period (94 days) as compared to the Delta period (51 days), and, consequently, a higher waning of vaccine effectiveness among cases occurred during the Omicron period. Nevertheless, our results are consistent with those reported in two large test-negative case control studies comparing vaccine effectiveness against Delta and Omicron variants, showing a vaccine effectiveness lower than 20% against Omicron variant starting from the third months after vaccination with the second dose [17,18]. Finally, consistently with the main analysis, an equivalent protection conferred by natural and vaccine-induced immunity against infection was observed during both periods during which Delta or Omicron were the dominant variants.

This population-based study had the advantage of using prospectively collected information on vaccination and SARS-CoV-2 infection for the entire Lombardy population, potentially eliminating selection bias. Moreover, the long follow-up period (up to 9 months) allowed to evaluate the long-term protection of both natural and vaccine induced immunity, taking into account the waning of protection over time. Finally, to our knowledge, this is the first population-based study which directly compared the cumulative risk (over time) of SARS-CoV-2 infection associated with natural and vaccine-induced immunity.

The main limitation is that reinfection was first registered in Italy starting August 24, 2021 [19]. Thus, we could not evaluate reinfections before that date. Moreover, in this study the number of new SARS-CoV-2 infections may have been underreported, because not all individuals in whom the infection occurred were tracked. However, it is unlikely that the underreporting rate was different between previously infected and vaccinated citizens, as well as between controls.

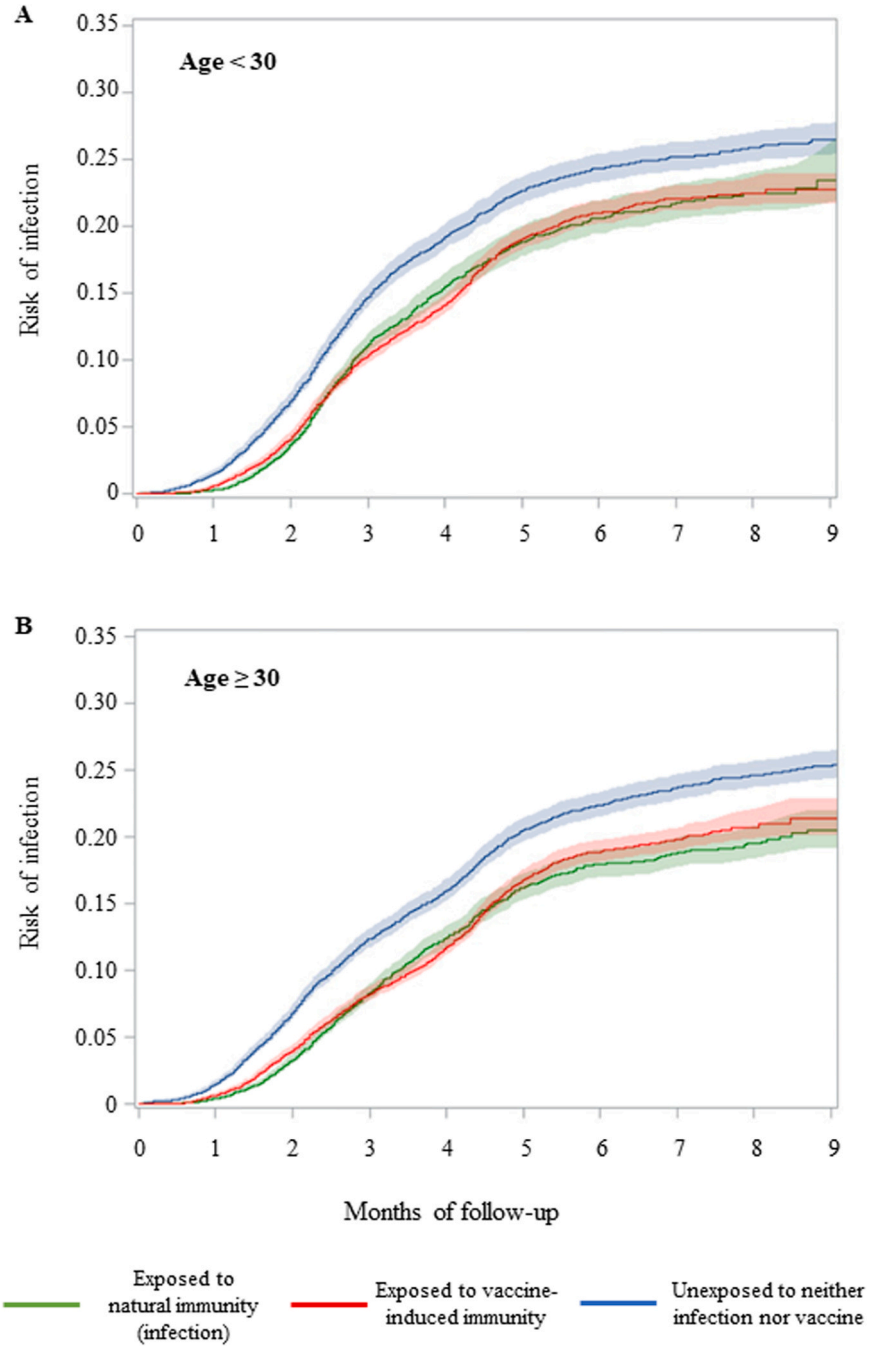

Fig. 3. Cumulative risk of developing a new SARS-CoV-2 infection by exposure status, in individuals aged less than 30 years (panel A) and 30 years or more (panel B).

Table 1
Main effects of natural (previous infection) and vaccine-induced immunity on the Odds Ratio (OR), with corresponding 95% confidence interval, of a new SARS-CoV-2 infection likely caused by Delta (cases occurred before December 2021) or Omicron (cases occurred after December 2021) variant.

	Controls N = 167	Delta cases N = 167		Controls N = 9168	Omicron cases N = 9168	
	N (%)	N (%)	OR	N (%)	N (%)	OR
Unexposed to neither infection nor vaccine	39 (23.4)	115 (68.9)	1 (Reference)	2899 (31.6)	3377 (36.8)	1 (Reference)
Exposed to natural immunity (infection)	56 (33.5)	21 (12.6)	0.21 (0.11–0.38)	2460 (26.8)	2305 (25.1)	0.83 (0.77–0.89)
Exposed to vaccine-induce immunity	72 (43.1)	31 (18.6)	0.19 (0.11–0.35)	3810 (41.6)	3487 (38.0)	0.82 (0.77–0.87)

Declaration of Competing Interest

We have a competing interest to declare Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drugs (AIFA) and the Italian Ministry for University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of the advisory board to Roche.

References

[1] Hanrath AT, Payne BAI, Duncan CJA. Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection. J Infect 2021;82:e29–30.

[2] Leidi A, Koegler F, Dumont R, et al. SEROCoV-POP study group. Risk of reinfection after seroconversion to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a population-based propensity-score matched Cohort study. Clin Infect Dis 2022;74:622–9.

[3] Lumley SF, O'Donnell D, Stoesser NE, et al. Oxford University Hospitals staff testing group. Antibody Status and Incidence of SARS-CoV-2 infection in health care workers. N Engl J Med 2021;384:533–40.

[4] Vitale J, Mumoli N, Clerici P, et al. Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy. JAMA Intern Med 2021;181. 1407-8.

[5] Zheng C, Shao W, Chen X, et al. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int J Infect Dis 2022;114. 252-60.

[6] Lumley SF, Rodger G, Constantinides B, et al. An observational Cohort study on the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. Clin Infect Dis 2022;74:1208–19.

[7] Gazit S., Shlezinger R., Perez G., et al. SARS-CoV-2 Naturally Acquired Immunity vs. Vaccine-induced Immunity, Reinfections versus Breakthrough Infections: a Retrospective Cohort Study. Clin Infect Dis 2022;ciac262.

[8] Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: a three-month nationwide experience from Israel. Am J Epidemiol 2022:30.

[9] Satwik R, Satwik A, Katoch S, Saluja S. ChAdOx1 nCoV-19 effectiveness during an unprecedented surge in SARS COV-2 infections. Eur J Intern Med 2021;93. 112-3.

[10] Corrao G, Bertolaso G, Pavesi G, Moratti L. Eight good reasons for careful monitoring and evaluation of the vaccine campaign against COVID-19: lessons learned through the lombardy experience for dealing with next challenges. Int J Environ Res Public Health 2022;19:1073.

[11] Corrao G, Franchi M, Cereda D, et al. Persistence of protection against SARS-CoV-2 clinical outcomes up to 9 months since vaccine completion: a retrospective observational analysis in Lombardy, Italy. Lancet Infect Dis 2022;22:649–56.

[12] CDC. Science brief: Omicron (B.1.1.529) variant. Atlanta, GA: US Department of Health and Human Services, CDC; 2021https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html. Accessed October 26, 2022.

[13] Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384. 1412–23.

[14] Stefanelli P, Trentini F, Petrone D, et al. Tracking the progressive spread of the SARS-CoV-2 Omicron variant in Italy, December 2021 to January 2022. Eur Surveill 2022;27:2200125.

[15] Shenai MB, Rahme R, Noorchashm H. Equivalency of protection from natural immunity in COVID-19 recovered versus fully vaccinated persons: a systematic review and pooled analysis. Cureus 2021;13:e19102.

[16] European Center for Disease Prevention and Control (ECDC): Contact tracing: public health management of persons, including healthcare workers, who have had contact with COVID-19 cases in the European Union – third update. ⟨https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-contact-tracing-public-health-management-third-update.pdf⟩. Accessed October 26, 2022.

[17] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) Variant. N Engl J Med 2022;386:1532–46.

[18] Buchan SA, Chung H, Brown KA. Estimated effectiveness of COVID-19 vaccines against omicron or delta symptomatic infection and severe outcomes. JAMA Netw Open 2022;5:e2232760.

[19] Italian Ministry of Health. Nota ministeriale n. 0037911 del 20/08/2021 con oggetto "Flusso dati aggregati Ministero della Salute/Protezione Civile: aggiornamento sulla possibilità di inserimento delle reinfezioni da SARS-CoV-2". Accessed October 26, 2022.