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## Short Communication

## Effect of vaccination on SARS-CoV-2 reinfection risk: a case–control study in the Republic of Cyprus

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## ABSTRACT

**Objectives:** We explored the effectiveness of COVID-19 vaccines in preventing reinfection in the Republic of Cyprus.

**Study design:** This was a matched case–control study (1:2).

**Methods:** Cases were adults with a first episode of SARS-CoV-2 infection in 2020 and a second episode (i.e. reinfection) between June and August 2021. Controls were adults with only one infection episode in 2020 (i.e. not reinfected). Matching was performed by age, gender, and week of diagnosis for the first episode. The reinfection date of a case was applied to the matched controls for estimating full or partial vaccination status. Cases and controls were classified as unvaccinated, partially vaccinated (i.e. vaccination series not completed or final dose received  $\leq 14$  days before the reinfection date), or fully vaccinated (i.e. final dose received  $> 14$  days before the reinfection date). Conditional logistic regression was performed to calculate odds ratios and 95% confidence intervals for full or partial vaccination, against no vaccination, between controls and cases.

**Results:** This study showed that controls were more likely to be vaccinated (odds ratio for full vaccination: 5.51, 95% confidence interval: 2.43–12.49) than cases.

**Conclusions:** This finding answers a pressing question of the public and supports the offer of vaccination to people with previous SARS-CoV-2 infection.

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## Background

Reinfection rates after the initial acquisition of SARS-CoV-2, the virus that causes COVID-19, seem to be low.<sup>1</sup> This could be

explained, at least partly, by the establishment of immunological memory after SARS-CoV-2 infection,<sup>2</sup> although questions are still lingering regarding the long-lasting protection from clinical disease. Vaccines have further shielded human populations because of their high effectiveness against COVID-19 infection, hospitalization, and death.<sup>3</sup> The emergence of variants, the predominance of the more infectious Delta SARS-CoV-2 variant of concern (1.617.2), and waning humoral immunity pose significant challenges on the level of vaccination coverage that is needed to impede viral spread.

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Nevertheless, vaccines continue to offer, at the moment, high-level protection from hospitalization and death.<sup>4</sup>

As the pandemic progresses and transmission continues to occur, the likelihood of reinfection increases. We have previously reported a reinfection rate of 0.08% among COVID-19 cases diagnosed in Cyprus until February 2021, within a median period of 7 months after the first infection.<sup>5</sup> Public Health England reported a cumulative 1.2% reinfection rate between April and June 2021, with higher risk of reinfection >6 months after the first episode due to the Delta variant.<sup>6</sup> More recently, a reinfection rate around 1%, due to Delta variant, has been confirmed in the United Kingdom by the Scientific Advisory Group for Emergencies (<https://www.gov.uk/government/publications/sage-99-minutes-coronavirus-covid-19-response-16-december-2021>).

Given the above, we sought to explore the effectiveness of vaccines in preventing reinfection in the Republic of Cyprus.

### Methods

During the COVID-19 pandemic, the Unit for Surveillance and Control of Communicable Diseases, within the Department of Medical and Public Health Services of the Ministry of Health, is responsible for surveillance and public health interventions. A Scientific Advisory Committee consisting of national experts provides scientific advice and recommends data analyses.

From the national COVID-19 surveillance system, all persons aged ≥18 years diagnosed with SARS-CoV-2 infection either by real-time polymerase chain reaction (PCR) or rapid antigen test (RAT) within the period March–December 2020 were eligible for inclusion. A suspected COVID-19 reinfection (hereafter defined as reinfection) was defined as one with positive PCR or RAT on a sample collected ≥60 days after previous positive: (1) PCR or (2) RAT or (3) serology (anti-spike IgG Ab).

For this analysis, a case was defined as a person aged ≥18 years with a first episode of SARS-CoV-2 infection between March and December 2020 and a second episode (i.e. reinfection) between June and August 2021. The period for reinfection was selected based on the following two reasons: (1) all persons aged ≥18 years in Cyprus were offered, during that period, the choice of vaccination and thus were considered eligible for vaccination; and (2) the Delta variant predominated in Cyprus between June and August 2021. A control was defined as a person aged ≥18 years with only one episode of SARS-CoV-2 infection that occurred between March and December 2020 (i.e. not reinfected). Cases were randomly matched to controls at 1:2 ratio based on age group (5-year age bands), gender, and International Organization for Standardization (ISO) week of diagnosis for the first episode (i.e. March to December 2020).

Vaccination status of cases and controls was determined using data from the national vaccination registry. The reinfection date of a case was applied to the matched control for estimating full or partial vaccination status. Cases and controls were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of any other vaccine administered in Cyprus (Pfizer-BioNTech, Moderna, or Astrazeneca) had been received >14 days before the reinfection date. Partial vaccination was defined when either the vaccination series was not completed or the final dose was received ≤14 days before the reinfection date.

Conditional logistic regression was performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for full vaccination or partial vaccination (against no vaccination) in controls vs. cases. Furthermore, stratified analysis was performed by vaccine brands (Pfizer-BioNTech, which was delivered to the majority of the population, and all other brands combined). For all analyses, Stata v.16 was used.

**Table 1**  
Characteristics of people with (cases) and without (controls) SARS-CoV-2 reinfection, Republic of Cyprus (government-controlled area), June to August 2021.

| Characteristics                   |                      | Controls (n = 186) |      | Cases (reinfections; n = 93) |      | OR <sup>a</sup> | 95% CI     |
|-----------------------------------|----------------------|--------------------|------|------------------------------|------|-----------------|------------|
|                                   |                      | n                  | %    | n                            | %    |                 |            |
| Sex                               | Males                | 94                 | 50.5 | 47                           | 50.5 |                 |            |
|                                   | Females              | 92                 | 49.5 | 46                           | 49.5 |                 |            |
| Age group (years)                 | 18–29                | 96                 | 52.2 | 52                           | 55.9 |                 |            |
|                                   | 30–39                | 51                 | 27.4 | 19                           | 20.4 |                 |            |
|                                   | 40–49                | 22                 | 11.8 | 15                           | 16.1 |                 |            |
|                                   | 50–59                | 13                 | 7.0  | 5                            | 5.4  |                 |            |
|                                   | 60–69                |                    | 0.0  |                              | 0.0  |                 |            |
|                                   | 70–79                | 3                  | 1.6  | 1                            | 1.1  |                 |            |
|                                   | 80+                  | 1                  | 0.5  | 1                            | 1.1  |                 |            |
| Month of initial infection (2020) | March                | 8                  | 4.3  | 3                            | 3.2  |                 |            |
|                                   | April                | 13                 | 7.0  | 8                            | 8.6  |                 |            |
|                                   | May                  | 3                  | 1.6  | 1                            | 1.1  |                 |            |
|                                   | June                 | 1                  | 0.5  | 0                            | 0.0  |                 |            |
|                                   | July                 | 3                  | 1.6  | 2                            | 2.2  |                 |            |
|                                   | August               | 10                 | 5.4  | 5                            | 5.4  |                 |            |
|                                   | September            | 0                  | 0    | 0                            | 0    |                 |            |
|                                   | October              | 37                 | 19.9 | 18                           | 19.4 |                 |            |
|                                   | November             | 49                 | 26.3 | 26                           | 28.0 |                 |            |
|                                   | December             | 62                 | 33.3 | 30                           | 32.3 |                 |            |
| Vaccination status <sup>b</sup>   | Fully vaccinated     | 61                 | 32.8 | 8                            | 8.6  | 5.51            | 2.43–12.49 |
|                                   | Partially vaccinated | 24                 | 12.9 | 7                            | 7.5  | 2.60            | 1.04–6.47  |
|                                   | Unvaccinated         | 101                | 54.3 | 78                           | 83.9 | Ref             |            |

<sup>a</sup> Odds ratios (OR) and their 95% confidence intervals (CI), from conditional regression, refer to odds of full or partial vaccination (against no vaccination) in controls (without reinfection from SARS-CoV-2) vs. cases (with reinfection).

<sup>b</sup> Cases were considered fully vaccinated if a complete COVID-19 vaccine series was received >14 days before the cases' reinfection date. Cases were considered partially vaccinated if ≥1 dose of vaccine was received, but the vaccination series was either not completed or the final dose was received ≤14 days before their reinfection date. For control participants, the same criteria were applied using the matched case's reinfection date.

## Results

During the study period (June to August 2021), 44,227 laboratory-confirmed infections with SARS-CoV-2 were diagnosed in Cyprus. Among them, 93 (0.2%) were reinfections (cases), which were matched to 186 people diagnosed with only one episode of SARS-CoV-2 infection (controls). The population included in the analysis ( $n = 279$ ) had a similar proportion of males and females, mainly comprised individuals aged <40 years (78.1%), and 222 people (79.6%) were initially infected during October to December 2020 (Table 1).

Among cases, 7.5% and 8.6% were partially vaccinated and fully vaccinated, respectively, compared with 12.9% and 32.8% of controls. A total of nine individuals were admitted to hospitals during the study period; eight patients were from the control group and one from the cases group (4.3% vs. 1.1%;  $P = 0.151$ ).

Considering all vaccine brands, the odds of full vaccination were 4.5 times greater in controls than in cases ( $n = 233$ ; OR = 5.51; 95% CI = 2.43–12.49). Similarly, partial vaccination was almost twice as likely in controls than in cases ( $n = 193$ , OR = 2.60; 95% CI = 1.04–6.47; Table 1).

From subgroup analysis for Pfizer-BioNTech, the odds of full vaccination were six times greater in controls than in cases ( $n = 209$ ; OR = 7.06; 95% CI = 2.46–20.30). However, the odds of partial vaccination were barely not significant between cases and controls ( $n = 185$ , OR = 2.62; 95% CI = 0.96–7.17). Furthermore, subgroup analysis for all other vaccine brands combined did not reach nominal statistical significance at 5%, although the direction of association was always positive (odds of full vaccination,  $n = 166$ ; OR = 3.00; 95% CI = 0.84–10.75; and odds of partial vaccination,  $n = 151$ ; OR = 2.50; 95% CI = 0.29–21.40).

## Discussion

Vaccination decreases the likelihood of infection and offers high-level protection from severe disease; thus, increasing vaccination coverage has allowed societies to resume activity. The spread of the Delta variant has altered the course of the pandemic, leading to a significant surge in many settings in the summer of 2021, including Cyprus, and increasing the necessary level of population immunity to limit viral spread. The dynamics of long-term protection through natural immunity remain largely unknown; despite evidence for the establishment of immune memory,<sup>2</sup> waning of neutralizing antibody levels raise the potential for reinfection. Moreover, although vaccine effectiveness against severe disease is preserved, protection against infection wanes through time.<sup>4</sup>

Estimation of vaccine effectiveness was not among the aims of our study; we sought to evaluate the effectiveness of vaccination on the risk of breakthrough infection among people with a first episode of SARS-CoV-2 infection by comparing it with the effectiveness of previous infection alone on preventing reinfection. To this end, we showed that the odds of vaccination were greater in people without reinfection than in those who had been reinfected, thus supporting findings of previous epidemiological research on additional protective effect of vaccination compared with natural immunity.<sup>7</sup> The pattern of association was observed both for the Pfizer-BioNTech vaccine, which was primarily used in Cyprus, and for the other vaccines combined, although statistical significance was not reached in the latter case, probably because of the smaller sample size. Of interest, in our analysis, the estimated reinfection risk for the unvaccinated was higher. A recent study from the basic sciences field also showed that the neutralization capacity of antibodies of vaccinated individuals with previous SARS-CoV-2 infection was better than that of people who got the vaccine without previous exposure to the virus.<sup>8</sup> The Delta variant is considered an immune evasive

variant with an increased risk of reinfection. Hence, our findings are even more timely, given the fact that the reinfections in this study were observed during the surge of the Delta wave in Cyprus. It is likely that the synergy of natural and vaccine-generated immunity provides stronger and broader immune responses than what is expected including against multiple variants.<sup>9</sup>

The interpretation of our results is subject to certain limitations. Possible bias could be present because of inconsistencies in the matching variables between the different registries of vaccination and surveillance. Lack of genomic sequencing data did not allow the confirmation of suspected reinfections. In addition, small numbers precluded the risk analysis for hospitalization. Furthermore, although Cyprus has a high testing rate per population, as of 10 May 2021, testing became thereafter a requirement for unvaccinated persons to resume certain activities;<sup>10</sup> this may have led to sampling bias, thus overestimating the ORs in our analyses.

In conclusion, our findings support the benefit of vaccination for persons previously infected with SARS-CoV-2. Although access to vaccination has increased, public health actions should be directed toward maximizing protection among vaccine-eligible individuals.

## Author statements

### Ethical approval

The study was approved by the Cyprus Bioethics Committee (approval number EEBK EII 2021.01.197, 7 October, 2021).

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None declared.

### Competing interests

None declared.

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