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EDITORIAL

COVID-19 Re-Infections: More Common with the Omicron Variant / COVID-19 Pandemic: Is There Light at the End of the Tunnel?

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Abstract

A recent surge of COVID-19 reinfections has been ascribed to new variants of concern (VOCs) with increased transmissibility, such as the Omicron variant, but also to laxity in compliance with measures of prophylaxis, incomplete or lack of vaccination, the Peltzman effect where people tend to increase their risky behavior when safety measures are mandated, weaker antibody responses after booster immunization in some individuals and/or immunocompromised patients, and increased antigen variability in VOCs. The latter impairs humoral and cellular immunity post-infection rendering COVID-19 convalescents more vulnerable and at risk of re-infection with VOCs. Unfortunately, COVID-19 disease is here to stay demanding observance of measures of prophylaxis, expansion of vaccination programs and continued vigilance; there is still a dire need for the development of durably effective vaccines against SARS-CoV-2 but also against its emerging variants. ***Rhythmos 2022;17(3): 46-52***.

Key Words: COVID-19; SARS-CoV-2; reinfections; COVID-19 vaccines; variants of concern; Omicron variant

Abbreviations: COVID-19 = corona virus disease 2019; PCR = polymerase chain reaction; WHO = World Health Organization

Introduction

In an early retrospective cohort study of 75,149 predominantly (66%) Hispanic individuals (53% females; 1.3% immunocompromised), 315 suspected reinfections were identified, with a cumulative incidence at 270 days of 0.8%.[1] These were individuals with PCR-positive COVID-19 infection between March and October 2020 followed through electronic health records for subsequent positive SARS-CoV-2 tests (suspected reinfection) ≥90 days after initial infection, through the end of January 2021. Hospitalization was more common at suspected reinfection (11.4%) than initial infection (45.4%). Suspected reinfection rates were higher in females (1% vs 0.7%, p = 0.002) and immunocompromised patients (2.1% vs 0.8%, p = 0.004), and lower in children than adults (0.2% vs 0.9%, p 0.023). Patients hospitalized at initial infection were more likely to have suspected reinfection (1.2% vs 0.8%, p = 0.030). In an adjusted Cox proportional

hazards model, being female (hazard ratio - HR) 1.44), adult (age 18-39, HR 2.71, age 40-59 HR 2.22, age ≥60 HR 2.52, vs <18 years), immunocompromised (HR 2.48), hospitalized (HR 1.60), and initially infected later in 2020 (HR 2.26, September-October vs March-May) were significant independent predictors of suspected reinfection. The authors suggested a need for continued precautions and vaccination in patients with COVID-19 to prevent reinfection.

A nationwide retrospective cohort study analyzed 99,993 confirmed cases of COVID-19.[2] The overall risk of reinfection (≥28 elapsed days after the initial infection) was 0.21% (incidence density, 2.5 reinfections per 100,000 person-days) and older subjects and those with the mild primary disease were at reduced risk of the event. Healthcare workers and immunosuppressed or renal patients had at greater risk of SARS-COV-2 reinfection.

In a national cohort of 353,326 persons with polymerase-chain-reaction (PCR)–confirmed infection between February 28, 2020, and April 28, 2021, 1304 reinfections were identified, 413 (31.7%) were caused by the B.1.351 variant, 57 (4.4%) by the B.1.1.7 variant, 213 (16.3%) by "wild-type" virus, and 621 (47.6%) were of unknown status.[3] For reinfected persons, the median time between first infection and reinfection was 277 days. The odds of severe disease at reinfection were 0.12 times that at primary infection. There were no cases of critical disease at reinfection vs 28 cases at primary infection (odds ratio – OR of 0.00). There were no cases of death from Covid-19 at reinfection vs 7 cases at primary infection (OR 0.00). The odds of the composite outcome of severe, critical, or fatal disease at reinfection were 0.10 times that at primary infection. Thus, reinfections had 90% lower odds of resulting in hospitalization or death than primary infections. Four reinfections were severe enough to lead to acute care hospitalization. None led to hospitalization in an ICU, and none ended in death. The authors concluded that reinfections were rare and were generally mild, perhaps because of the primed immune system after primary infection.

However, since the reports of these studies, several re-infections have occurred. Although the majority of adult patients with COVID-19 reinfection have been reported to be unvaccinated,[4] a lot of re-infections occur in vaccinated people, as well. The latter phenomenon has been attributed to several factors, among which a rapid (within 2 months from the peak response) decline of the boosted neutralization titers, particularly to the Omicron variant, which has recently become the dominant virus variant, seems to account for the majority of re-infections due to a dramatic decrease in the protection against reinfection.[5, 6] This is in contrast to the boosted titers against the initial prototypic D614G variant.

Variants of Concern

Breakthrough infections (BTIs) in individuals who have completed a primary COVID-19 vaccination series have been reported to be more common among variants of concern (VOC) of which initially Delta accounted for the largest number of BTIs (96%). [7] Interestingly, 90% of patients with BTIs recovered, 11.6% were hospitalized with mechanical ventilation, and 0.6% resulted in mortality. BTIs were more common in healthcare workers (HCWs) and immunodeficient individuals with a small percentage found in fully vaccinated healthy individuals. VOC mutations were the primary cause of BTIs. Continued mitigation approaches (e.g., wearing masks and social distancing) are warranted even in fully vaccinated individuals to prevent transmission.

Decreases in protection against reinfection, seemed primarily to be driven by viral evolution. SARS-CoV-2 infection provided patients with a high level of sustained protection against reinfection, comparable with that offered by vaccines, but decreased with the introduction of new main virus variants.

According to a retrospective population-based matched observational study, amongst individuals testing positive by PCR during follow-up, reinfection cases had 77% lower odds of symptoms at the second episode (adjusted OR 0.23) and 45% lower odds of dying in the 28 days after reinfection (adjusted OR 0.55).[8] Prior SARS-CoV-2 infection offered protection against reinfection in this population. There was evidence that reinfections increased with the new variants compared to the wild-type SARS-CoV-2 variant highlighting the importance of continued monitoring as new variants emerge.

Increased antigen variability in VOCs impairs humoral and spike-specific T cell immunity post-infection, strongly suggesting that COVID-19 convalescents are vulnerable and at risk of re-infection with VOCs.[9]

The Omicron vs the Other Variants

The reinfection rates have increased with the appearance and spread of the Omicron variant. Reinfection has been reported about 30 times more frequent in the Omicron variant than in the Alpha variant and 10 times more frequent than the Delta variant.[10]

The Omicron variant has new mutations in its spike protein, most of which are in its receptor binding site; these mutations increase its transmissibility and reduce its antibody and vaccine response.[11]

A more dramatic decrease in protection has been noted since the Omicron variant appeared. Protection has been lower among the elderly but appears more pronounced following symptomatic compared to asymptomatic infections. The level of estimated protection against serious disease is somewhat higher than that against

infection and possibly longer lasting. According to a cohort study, data from a Danish register indicated that the estimated protection against reinfection was 83.4%, albeit lower for the 65+ year-olds (72.2%).[6] Moderately higher estimates were found for protection against symptomatic disease, 88.3% overall. First-time cases who reported no symptoms were more likely to have a reinfection (odds ratio-OR 1.48). By autumn 2021, when infections were almost exclusively caused by the Delta variant, the estimated protection after a recent first infection was 91.3% vs 71.4% after a first infection over a year earlier. With Omicron, a first infection with an earlier variant in the past 3-6 months provided an estimated 51% protection, whereas a first infection longer than 1 year earlier gave only 19% protection. Protection by an earlier variant-infection against hospitalisation due to a new infection was estimated at: 86.6% for Alpha, 97.2% for Delta, and 69.8% for the Omicron variant.

Children and adolescents have also been reported to show some loss of cross-neutralization against all viral variants, with the most pronounced loss noted against Omicron.[12]

Waning Immunity and Re-infection

A recent study reported that uptake of vaccination in previously infected individuals is relatively low.[13] Importantly, previously infected females were more likely to receive vaccination than previously infected males. Similarly, differences in vaccination uptake exist between age groups. When examining the interval between the last vaccine dose and infection, the most significant breakthrough infection rate was noted among individuals aged 20-59 years.

Data contributed by 21 universities on 1378 student athletes who tested positive for SARS-CoV-2 (1-11/2021; pre-Omicron) showed that among the 1378 student athletes positive for SARS-CoV-2, 1070 (77.6%) were infected when unvaccinated and 22.4% (n = 308) were infected after full vaccination.[14] There was a significant difference by race, between Black (14.7%, n = 40) and White (23.9%, n = 168) student athletes who experienced a COVID-19 infection after being fully vaccinated ($p < 0.01$), but not by gender ($p = 0.06$). Thus, the level of infections among fully vaccinated student athletes indicates the need for maintaining precautions to prevent infection.

In the pre-Omicron era, when the B.1.617.2 (delta) variant was predominant, a study was performed on all persons who had been previously infected with SARS-CoV-2 or who had received COVID-19 vaccine.[15] The number of cases of SARS-CoV-2 infection per 100,000 person-days at risk (adjusted rate) increased with the time that had elapsed since vaccination or since previous infection. Among unvaccinated persons who had recovered from infection, this rate increased from 10.5 among those who had been infected 4 -6 months previously to 30.2 among those who had been infected $\geq$ 1 year previously. Among persons who had received a single dose of vaccine after previous infection, the adjusted rate was low (3.7) among those who had been vaccinated < 2 months previously but increased to 11.6 among those who had been vaccinated at least 6 months previously. Among previously uninfected persons who had received two doses of vaccine, the adjusted rate increased from 21.1 among those who had been vaccinated <2 months previously to 88.9 among those who had been vaccinated at least 6 months previously. The authors concluded that among persons who had been previously infected with SARS-CoV-2 (regardless of whether they had received any dose of vaccine or whether they had received one dose before or after infection), protection against reinfection decreased as the time increased since the last immunity-conferring event; however, this protection was higher than that conferred after the same time had elapsed since receipt of a second dose of vaccine among previously uninfected persons. A single dose of vaccine after infection reinforced protection against reinfection.

In the Omicron era, an observational study from India on 11,474 health care workers (HCWs) (aged 36·2±10·7 years; 83% fully vaccinated) showed that the incidence density of all infections and reinfection during the omicron transmission period was 34.8 and 45.6 per 10000 person days respectively.[16] The infection was milder as compared to previous periods. Vaccine effectiveness was 52.5% ($p = 0.036$) for those who were tested within 14-60 days of receiving second dose and beyond this period (61-180 days), modest effect was observed. The authors concluded that almost one-fifth of HCWs were infected with COVID-19 during the omicron transmission period, with predominant mild spectrum of COVID-19 disease. Waning effects of vaccine protection were noted with increase in time intervals since vaccination.

The Peltzman Effect

The Peltzman Effect, named for Sam Peltzman's postulation about mandating the use of seatbelts in automobiles, describes the concept of 'Risk Compensation', theorizing **that people are more likely to engage in risky behavior when security measures have been mandated**.[17]

In this context, COVID-19 vaccination seems to be triggering Peltzman effect.[17] An analysis of Peltzman effect reveals 4 factors involved in risk compensation, all of which seem to be present in this COVID-19 pandemic. First, COVID-19 vaccines do decrease the number of infections, motivating people to possibly increase their risky behaviour, in this pandemic, these two factors seem

to explain 'pandemic fatigue' leading to decreasing adherence to risk reduction strategies of social distancing, face coverings and hand washing in the population. Such attitudes seem to put in danger the global public health efforts to control the pandemic.[17] Finally, the overall *effectiveness* of the vaccine intervention is being increasingly acknowledged worldwide; however, on the other hand, this high efficacy seems to reduce adherence to other safety precautions. People's complacency and a false sense of increased security following vaccination may explain why people seem to abandon protective and preventive behavioural strategies.

Furthermore, mutant strains, like the *Omicron* variant, have been reported to increase the virulence of COVID-19. The new resurgence or wave of infections seems to be the result of more transmissible mutant strains, a fall in 'herd immunity' and a spread of Peltzman effect leading people to forego wearing face coverings and observe social distancing principles.

*Thus, strategies to counter the Peltzman effec*t, with clear health messages, information, education and communication activities to the public by the government, medical personnel and health authorities are direly needed to reinforce the principles of infection control strategies. Prioritizing mask wearing regardless of vaccination status would be helpful; social distancing must be maintained, and; vaccine hesitancy must be addressed. The pandemic is far from over; the battle is yet ongoing![17]

As mentioned, there are specific populations subgroups, e.g., males 20-59 years old, that may serve as reservoirs of viral spread, as these individuals experience a false sense of security and acquired immunity, resulting in low levels of vaccine uptake and non-compliance with protective behaviours.[13] Targeted messaging in such groups should reemphasise the need for continued protective behaviours.

The Omicron Variant and Sub-Variants

As mentioned, the Omicron variant is new 'Variant of Concern' (VOC) of SARS-CoV-2, rapidly evolving into new sub-variants or sub-lineages (BA.1, BA.2 etc.). These sub-variants have higher transmissibility, decreased vaccine effectiveness and increased risk of reinfection. [18] The Omicron variant involves new mutations in the spike protein, most of which are in its receptor binding site, and increase its transmissibility and decrease its antibody and vaccine response.[11, 19] Although sequence proven reinfections have increased with the Omicron variant, fortunately such reinfections generally cause mild disease.[20]

As also mentioned, in the era of the Omicron pandemic wave, continued mitigation approaches by wearing masks and observing social distancing are still warranted even in fully vaccinated individuals to prevent transmission.[7]

Risk Factors

An Italian study exploring the risk factors associated with SARS-CoV-2 reinfections indicated that regardless of the prevalent virus variant, being unvaccinated was the most relevant risk factor for reinfection.[21] The risk of reinfection was almost 18-fold higher following emergence of the Omicron variant compared with the Delta variant. A severe first SARS-CoV-2 infection and age >60 years were significant risk factors for severe reinfection. In keeping with these results, a retrospective cohort study following 1,293,941 Italian persons from the beginning of the pandemic to the current emergence of the Omicron variant (2/2022), indicated that after an average of 277 days, 729 reinfections were recorded among 119,266 previously infected persons (overall rate: 6.1‰), there were 8 COVID-19-related hospitalizations (7/100,000), and two deaths.[22] The risk of reinfection was significantly higher among females, unvaccinated individuals, and during the Omicron wave.

Also, individuals with weaker antibody responses after booster immunization are prone to Omicron breakthrough infections. Among 1391 healthcare workers. The risk of developing an Omicron breakthrough infection was independent of vaccination scheme, sex, body mass index, smoking status or pre-existing conditions. In participants with low pre-infection anti-spike antibodies (≤ 2641.0 BAU/ml) and weaker neutralization capacity (≤ 65.9%) against Omicron one month after the booster vaccination, the risk for developing an Omicron infection was 10-fold increased (P= 0.001). [23]

As mentioned, the highest reinfection rate was observed in the Omicron variant with a 30-fold reinfection risk in the Omicron variant than in the Alpha variant and a 10-fold higher risk than the Delta variant. [10]

Table 1. **Risk Factors for COVID-19 Reinfection**

- Variants of concern (e.g., Omicron) / Omicron wave
- Weaker antibody responses after booster immunization
- Unvaccinated individuals
- Hospitalized at initial infection
- Severe primary/first SARS-CoV-2 infection
- Females
- Age >60 years
- Adults > children
- Immunocompromised patients
- Recent infection
- Health care workers
- The Peltzman effect

Protection Against Reinfection

Findings of a case-control evaluation of the association between vaccination and SARS-CoV-2 reinfection among persons previously infected with SARS-CoV-2 indicated that persons who were not vaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated (odds ratio - OR 2.34).[24] Thus, full vaccination seems to provide added protection against reinfection and should be offered to all eligible persons, even if they have been previously infected with SARS-CoV-2.

It has been suggested that receiving a booster vaccination cycle is more effective and less variable than natural immunity in terms of afforded protection against SARS-CoV-2 infections. [25] It was reported that a previous SARS-CoV-2 infection (irrespective of its timing) offers 85% and 36% protection against being reinfected by Delta and Omicron, respectively.[25] It was also estimated that the third dose was more effective in both periods and had a minor proportional loss of effectiveness due to the rise of the Omicron variant, with an afforded effectiveness against SARS-CoV-2 Delta and Omicron infection of 97% and 47%, respectively.

Nevertheless, the antibody response after SARS-CoV-2 infection or vaccination in the general population is quite variable and heterogeneous. A study characterized the anti-spike IgG titers in 13,971 participants included in a French multicohort population-based serological survey on COVID-19.[26] The anti-spike titer was lower in adults with no vaccination even in case of infection or reinfection, while it was higher in adults with infection followed by vaccination. The anti-spike titer was negatively correlated with age in vaccinated but uninfected adults, whereas it was positively correlated with age in unvaccinated but infected adults. The decrease in anti-spike titer was much more rapid in vaccinated than in infected subjects. These results indicate a strong heterogeneity of the antibody response against SARS-CoV-2 in the general population depending on previous infection and vaccination.

A systematic review indicated that the pooled estimation of reinfection, recurrence, and hospital readmission among recovered COVID-19 patients was 3, 133, and 75 per 1000 patients, respectively.[27] The overall estimation of reinfection was greater in males vs females; however, the prevalence of recurrence was more common in females vs males. Hospital readmission between men and women was the same. The authors pointed out that with mass vaccination of people and using the measures of prevention and appropriate management of the disease, frequent occurrence of the disease can be controlled.

A recent review of 18 studies with data on protection against reinfection after SARS-CoV-2 infection indicated that the reinfection risk ranged from 0% to 2.2%.[28] In persons with recent SARS-CoV-2 infection compared with unvaccinated, previously uninfected individuals, 80% to 98% of symptomatic infections with wild-type or Alpha variants were prevented. In the meta-analysis, previous infection reduced risk for reinfection by 87%, in several settings (general population, health care workers and in care facilities). Protection remained >80% for at least 7 months, but no study followed patients after the emergence of the Delta or Omicron variant. Thus, the durability of protection in the setting of the Delta and Omicron variants could not be determined.

Recent data indicate that naturally infected populations are less likely to be reinfected by SARS-CoV-2 than the infection-naïve and vaccinated individuals.[29] Importantly, reinfected persons do not seem to suffer severe disease, however, a significant proportion of naturally infected or vaccinated individuals seem to be (re)-infected by the emerging variants. In keeping with these findings, other data indicate that prior SARS-CoV-2 infection confers lower odds of dying, and both prior infection and immunization yield a protective effect against severe disease in selected populations.[30] Older age, sex and underlying comorbidities appear to be important risk factors for illness severity at reinfection. In a similar context, a recent study in health care workers (HCW) indicated that hybrid immunity (from natural infection and vaccination) resulted in the strongest humoral immune response; antibodies induced by natural infection decreased more slowly than after vaccination, resulting in higher antibody levels at 10 months compared to vaccinated HCWs without prior infection.[31]

As mentioned, receiving booster vaccination is more effective and less variable than natural immunity in terms of afforded protection against SARS-CoV-2 infections. [25] In the end, the combination of a previous COVID-19 infection and a vaccination for COVID (hybrid immunity) seems to confer the greatest protection against COVID infections and re-infections.[31-33] As shown in a cohort study of 4943 health care workers (HCWs), COVID-19 vaccination further decreases the risk of reinfection more markedly among seropositive; the rate of reinfection among seropositive individuals was 81% lower for those who were symptomatic compared with those who were asymptomatic (incidence rate and ratio-IRR of 0.19; p = 0.003). [34]

Due to Omicron's current prevalence, and in view of a lessened effect of the vaccination on symptomatic disease, albeit with lower occurrence of fever and loss of smell or taste upon reinfection, and/or other serious complications, irrespective of pre-existing immunity, systemic vaccination and mask-wearing should still be continued in high-risk groups (e.g., among HCWs) and places (e.g., indoors, public transport, etc.), as well as social distancing, when possible. [35]

Finally, as mentioned, data indicate that increased antigen variability in VOCs impairs humoral and spike-specific T cell immunity post-infection, strongly suggesting that COVID-19 convalescents are vulnerable and at risk of re-infection with VOCs, thus stressing the importance of vaccination programs and measures of prophylaxis.[9] More durably effective vaccines to encompass the emerging VOCs are direly needed.[36]

Table 2. **Protection Against COVID-19 Reinfection**

- Full vaccination / Booster vaccination / Durable protection
- Measures of prevention (mask wearing, social distancing, etc.), especially for high-risk groups (e.g., health care workers) and places (e.g., indoors, public transport, etc.)
- *Strategies to counter the Peltzman effec*t:
  - Clear health messages, information, education and communication activities to the public by the government, medical personnel and health authorities
  - Reinforcing the principles of infection control strategies
  - Prioritizing mask wearing regardless of vaccination status
  - Maintaining social distancing
  - Addressing vaccine hesitancy
- Proper disease management
- Stronger hybrid immunity protection (natural infection plus vaccination)

Conclusion

COVID-19 reinfection rates have recently increased for various reasons, including new variants of concern (VOCs) with increased transmissibility, e.g., the Omicron variant, laxity in implementation and observance of measures of prophylaxis, people who are still unvaccinated, the Peltzman effect where people tend to increase their risky behavior when safety measures are mandated or implemented, weaker antibody responses after booster immunization in some individuals and/or immunocompromised patients, and increased antigen variability in VOCs which impairs humoral and cellular immunity post-infection, rendering COVID-19 convalescents more vulnerable and at risk of re-infection with VOCs. Unfortunately, COVID-19 disease is here to stay and everybody should remain vigilant. Expanding vaccination programs to achieve herd immunity and developing more durably effective vaccines against the emerging new variants remain of paramount importance.

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