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**ABOUT COVER**

Editorial Board Member of *World Journal of Methodology*, Salvatore Lorenzo Renne, MD, Assistant Professor, Department of Pathology, Anatomic Pathology Unit, Humanitas Research Hospital, Via Manzoni 56, Rozzano, 20089 MI, Italy. [salvatore.renne@hunimed.eu](mailto:salvatore.renne@hunimed.eu)

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## Reinfection, recontamination and revaccination for SARS-CoV-2

Tamás Kullmann, András Drozgyik

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**Tamás Kullmann**, Department of Medical Emergencies, Petz Aladár Hospital, Győr 9024, Hungary

**András Drozgyik**, Department of Surgery, Petz Aladár Hospital, Győr 9024, Hungary

**Corresponding author:** Tamás Kullmann, PhD, Consultant Physician-Scientist, Department of Medical Emergencies, Petz Aladár Hospital, Vasvári Pál u. 2-4, Győr 9024, Hungary.  
[kullmannndoki@gmail.com](mailto:kullmannndoki@gmail.com)

### Abstract

The reports on coronavirus disease 2019 (COVID-19) describe the pandemic in waves. Similar to the ocean's waves, the frequency and amplitude of the number of new cases and the number of deaths were globally quite regular; nevertheless, they showed important regional irregularities and the direction of spread has been generally rather unpredictable for COVID-19. One of the major reasons for the repeated outbreaks is the mutating capacity of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that allows the virus to infect persons who have natural immunity or have been vaccinated. Vaccination began in vast campaigns from the second year of the pandemic that was supposed to decrease the magnitude of the waves. Although it reduced the complications, the expected attenuation of the disease expansion has not yet been met. This paper provides a short overview of the most recent data on the rate of reinfection in vaccinated and non-vaccinated individuals. It points out that testing positive for a second time for SARS-CoV-2 does not necessarily mean a reinfection; it can also be interpreted as recontamination. The symptom free outcome as well as the rapid reconversion of the polymerase chain reaction test may help to determine the difference between reinfection and recontamination. Awareness of this phenomenon may be valuable in times of human resource difficulties. The available evidence may suggest that the protective value of a prior infection could be better considered for vaccine distribution in the future.

**Key Words:** SARS-CoV-2; COVID-19; Polymerase Chain Reaction; Immunisation; Contamination; Vaccination

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**Core Tip:** Reinfection: There is not enough evidence of the protective efficacy of the natural immunity induced by a primary infection with severe acute coronavirus 2 (SARS-CoV-2). Recontamination: Testing positive for a second time for SARS-CoV-2 does not necessarily mean a reinfection; it can also be interpreted as recontamination. Revaccination: The available evidence may suggest that the protective value of a prior infection could be better considered for vaccine distribution in the future.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 400 million people worldwide and caused the death of over 6 million[1]. In the last two years SARS-CoV-2 has become the most common cause of death from a single infectious pathogen, preceding *Mycobacterium tuberculosis*, responsible for an estimated 1.4 million victims in 2019[2] and human immunodeficiency virus and malaria, the mortality of which was below 1 million in the last years[3].

The majority of deceased people were retired Caucasians[1]. The geography of the disease expansion may explain why coronavirus, which was most devastating in North America and Europe, received outstanding media and political attention in comparison to other infections with high mortality even if these infections affect young people as much as the elderly. Reports directly showing patients with respiratory assistance in hospital intensive care units were seen by many people for the first time. Beyond the statistical data these widely diffused images contributed to the shocking experience of the pandemic. Coronavirus disease 2019 (COVID-19) is the first pandemic in history to be broadcast live from the beginning on.

There is no efficacious treatment for COVID-19. Hospitalisation may help in those who require oxygen supplementation and in the care of some complications of the disease. Vaccines of different types have been developed to provide protection against infection. This occasion was a world first for the mRNA vaccines[4,5] and the first adenovirus-based vaccine authorized by the US Food and Drug Administration[6]. To date their efficacy in the prevention of severe complications of COVID-19 is evident but their power to reduce disease spread has not met expectations[1].

## REINFECTION

The first reinfection by a different strain of SARS-CoV-2 was identified in the summer of 2020 with whole genome sequencing and comparative genome analysis in an immunocompetent person with an interval of 142 d between the two episodes[7]. In this case, the primary infection was symptomatic and the reinfection was asymptomatic. A larger analysis of several cases found that the reinfection may be either less severe, or may also have a more severe outcome as compared to the primary infection[8].

When the vaccinations started in spring 2021, follow-up of the protective effect of recovering from a primary infection became problematic, as the promotion of vaccination was so strong in most affected countries, that the majority of the people were vaccinated. Nevertheless, there are some publications available that may help elucidate this issue.

No symptomatic reinfection was detected in 1265 British health care workers who had been followed with positive anti-spike-IgG for 31 wk[9]. In the national, federated database of Qatar there were 350.000 polymerase chain reaction (PCR)-confirmed infections registered between 28 February 2020 and 28 April 2021. Among these cases 1300 reinfections were identified and these cases were matched with primary infections in a 1:5 ratio. The numbers of severe, critical and fatal cases were 158, 28 and 7 for primary infections and 4, 0 and 0 for reinfections, respectively. Vaccinated persons were excluded from the analysis. Severe outcome meant hospitalisation and critical outcome meant hospitalisation in the intensive care unit[10].

These data support the hypothesis that recovering from a primary SARS-CoV-2 infection yields natural immunity that protects from both, potential reinfection and the severe complications of a reinfection. However, vaccinations were declared to provide additional protection.

Breakthrough infections in vaccinated individuals and in those who had a prior infection were compared in the same Qatar database. The PCR cycle threshold is known to inversely correlate with viral load. Or, the cycle threshold value is 1.3 cycles higher for breakthrough infections following the BNT162b2 vaccine, 3.2 cycles higher for breakthrough infections following the mRNA-1273 vaccine, and 4.0 cycles higher for reinfections in unvaccinated individuals than at primary infection. Thus,

unvaccinated persons who recovered from a prior SARS-CoV-2 infection had the lowest viral load during a breakthrough infection as compared to their mRNA vaccinated counterparts[11]. In a Bangladesh cohort including 1644 participants, the naturally infected population was less likely to be reinfected by SARS-CoV-2 than the infection-naïve and vaccinated participants with one of the seven different vaccines authorised in this country[12]. A Danish study of 3.800 blood donors who had SARS-CoV-2 PCR positivity found no evidence of a decline in the proportion of detectable anti-SARS-CoV-2 antibodies over time up to 15 mo[13].

In contrast, in a study of 150.000 patients who had recovered from COVID-19 in Israel, those who were vaccinated had a lower risk of reinfection than those who were not vaccinated. The difference was smaller in the elderly population. The study did not report on the severity of the reinfections. The authors recognise that the lack of assessment of disease severity and hospitalisation is an important limitation of their work[14].

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## RECONTAMINATION

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The second contact with SARS-CoV-2 is not necessarily a second infection and may only be a contamination, which means that some of the pathogen may be present on the body surface or mucus membrane. However, the invasion of adjacent tissues does not follow, as the person's defence system prevents it.

Someone contaminated with SARS-CoV-2 will have a positive test, and may possibly and transitionally transmit the virus but will remain asymptomatic. However, the duration of the positivity of a contaminated individual following primary infection or vaccination will be presumably short. In our experience, the duration of their positivity is around 5 d (unpublished data) as compared to the positivity of healthy individuals who undergo a first infection which is at least 8-20 d.

This is in reality what we may expect from the protective efficacy of vaccinations and natural immunity. They do not inhibit the virus reaching the nasal mucosa when in contact with an infected patient. Nevertheless, they provide a more reactive immunity that helps in preventing the development of the disease within the body.

The possible interpretations of a positive SARS-CoV-2 PCR test are summarised in Table 1. Under the pressure of the pandemic it may be difficult to accept that interpretation of the tests depend on the clinical situation; moreover, if the clinical context is omitted, decisions based exclusively on test results may be harmful. The importance of the correct interpretation of sustained PCR positivity at primary infection has been stressed, particularly in the case of comorbidities needing rapid treatment such as certain malignancies[15]. The authorisation of asymptomatic health care workers to return to work has become routine in many hospitals facing problems of human resources. Some other situations when a positive PCR test may be disturbing are listed in Table 2.

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## REVACCINATION

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Initially, producers affirmed that two doses one month apart provide immunity for SARS-CoV-2, with the exception of Ad26.COV2-S with which one dose is equivalent to two doses of the other products. However, the level of protective antibodies was found to decrease with time; therefore, the potential necessity for a booster dose was discussed. It is important to note, that the waning of immunity was studied in vaccinated populations whereas for naturally immunised populations there are only observations from case series[16].

Currently, in most Western countries a booster is required 6 mo after the first vaccination for official recognition of protection. The suggestion that the booster may or should be different from the primary vaccine adds to the confusion related to the efficacy of each single vaccine. We agree with the WHO's consideration that in view of the shortage of vaccines, assuring booster doses for some populations may increase the possibility that other populations will miss even the primary vaccination[16].

In addition, the above-mentioned results[11,12,13] show that natural immunity may even be stronger and last longer than the effect of vaccination depending on both the severity of the infection and the type of vaccination. The distribution of vaccines to non-infected individuals rather than to naturally immunised individuals would probably have saved more lives and would certainly have been more equitable. This hypothetical redistribution would have concerned hundreds of millions of people.

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## DISCUSSION

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One of the destabilising lessons of the pandemic is that scientific predictions concerning COVID-19's clinical presentation and geographical expansion were rarely correct.

**Table 1 Possible meaning of a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2**

Test result	Meaning
True positive result	Asymptomatic infection with SARS-CoV-2
True positive result	Symptomatic infection with SARS-CoV-2 (COVID-19)
Sustained positive result	Carriage of virus particles after recovering from COVID-19
False positive result	No infection with SARS-CoV-2
Repeatedly positive result	Reinfection with SARS-CoV-2
Repeatedly positive result	Recontamination with SARS-CoV-2

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

**Table 2 Possible situations, when the misinterpretation of contamination with severe acute respiratory syndrome coronavirus 2 may cause unfair disadvantage for the tested individual**

Situations where symptom-free persons can be tested
Being a contact of an infected person
Infection control in a health care or social institution
Starting a new job
Travelling abroad
Participating at a controlled event

Measures seeming reasonable at one point may be completely useless a couple of weeks later and vice versa. For instance, the nationwide testing in Slovakia in the winter of 2020 drew international attention and the identification of a high number of asymptomatic infections gained recognition. It was assumed that containment of the detected individuals would prevent disease spread. Nevertheless, the country could not avoid the explosion of the disease and the burden on its healthcare system. In contrast, Sweden was much criticised for its liberal management of the pandemic and had a relatively high mortality rate in the first months; however, many more restrictive countries had worse outcomes one year later[1].

Decision making and observance of the prevalence are even more unpredictable than the behaviour of the virus. Decision makers are challenged with opposing expectations but miss essential references. They have to solve dilemmas such as protecting the lives of the elderly *vs* the jobs of the young or the equitable distribution of the vaccines *vs* the most rapid care of their own population. On the other hand observance supposes explanations and never meant obedience.

With the arrival of the Omicron strain there is some hope that after more than two years the disease will pass in a more controllable phase.

## CONCLUSION

(1) Differentiation between recontamination and reinfection may be useful for persons testing positive for SARS-COV-2 by PCR; (2) The protective effect of prior infection should be considered before vaccination against COVID-19; and (3) Fairness in vaccine distribution should be respected at the global scale.

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**Country/Territory of origin:** Hungary

**ORCID number:** Tamás Kullmann 0000-0002-8324-1971.

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