

# Can Physical exercise be an effective adjuvant before the potential COVID-19 vaccine? Insights from serological responses and severity of re-infected cases

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## **Systematic Review**

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# Abstract

## Background:

As more than 37 million confirmed cases and 1 million deaths worldwide from COVID-19, we tried to think about supporting immunity. So, there are more than 150 coronavirus vaccines and clinical trials are being developed. The success of those vaccines depends mainly on immunologic memory. People who are at high risk of re-infection with COVID-19 don't show any evidence of having B-cell memory. 10-20% of infected patients don't develop antibody response. randomized controlled trials and cross-sectional studies proved variant results about the effect of chronic exercise on vaccination function.

The aim of this review is to suggest that exercise is an important adjuvant strategy for prevention of re-infection and for development of better protective responses following vaccination.

## Methods:

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as "COVID-19" OR "SARS-CoV-2" AND "Re-infection" for relevant publications up to 1<sup>st</sup> of Nov. 2020. The systematic review was performed using PRISMA protocol.

## Results:

According to inclusion criteria, 6 case reports from search and one case from a press conference were identified. The average age of re-infected patients was 36 years. The average intervening period between initial infection and reinfection was 105 days. 75% of cases who have been tested for antibodies after 1<sup>st</sup> infection were negative, and turned seropositive after second infection. 57% of cases developing re-infection had worse clinical manifestation.

## Conclusion:

Regular moderate intensity exercise not only can enhance the secondary antibody response of B cell memory but also decrease the severity of re-infection and the adverse reactogenicity of potential vaccines under development.

# Background

The COVID-19 pandemic is a critical moment in the 21<sup>st</sup> century. Statistics recorded more than 1 million deaths and more than 54 million confirmed cases worldwide (1)

Concerning this global health emergency that is threatening many lives, Vaccine developers started working out trying to bring a vaccine to the market in a record time to alleviate the global crisis. (2)

Owing to the urgent need to the vaccine, some developers are running the trial phases simultaneously with the clinical process for SARS-CoV-2. Hopefully more than 150 coronavirus vaccines are under development across the world. Hard efforts are being exerted to make finding such a vaccine possible, including the U.S.(3)

Although the current vaccines under development offer great hopes, there is a major concern about the success of these vaccines in providing the desired protective immunity against infection.

Liao and colleagues didn't only explain the uncontrollable activation of immune system and its damaging effect on the lung milieu in severe COVID-19 patients but they also pointed out that there's no evidence in the early recovery period of

B cell memory in the patients with the worst and the most serious outcomes. Therefore, they are more prone to be re-infected with COVID-19 and less likely to develop humoral immunity via antibodies by any possibly made vaccine. (4)

According to Wu and Long et al series, this finding goes in agreement with that 10-20% of infected patients fail to develop antibody responses. On account of the rapid decline of their immune responses 16 days after initial infection, these patients are left at risk of reinfection. That's why the most important factor in predicting the success of any upcoming vaccine is the power of the generated immunologic memory after being infected.(5,6)

Studies show effect of exercise on the immune response after vaccination. Comparing both physically active candidates and those of sedentary life styles in a cross-sectional study, the antibody responses to vaccines are greater in older adults exercising regularly. Another study compares cardiovascular and flexibility trainings for 10 months in previously non-active participants. According to Woods et al., it is shown that cardiovascular exercise done about an hour 3 times each week, leads to increase in neuroprotection evaluated at 6 months after influenza vaccination. Moreover, chronic exercise improves the immune responses to new antigens.(7)

The aim of this article is to report all the re-infection cases, and their characteristics and to explain the pathophysiologic mechanisms involved in improvement of immunologic memory in the elderly with exercise. This might render exercise an important adjuvant strategy for prevention of re-infection and for development of better protective responses following vaccination.

## Methodology

This systematic review has been conducted in agreement with the guidelines of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).<sup>13</sup>

### *>>Data Search*

A computer run has been performed on EMBASE, Medline and the Cochrane Central Register (From 1<sup>st</sup> November 2019 to 1<sup>st</sup> of November 2020). The following terms were included in the search: "COVID-19" OR "SARS-CoV-2" (Severe Acute Respiratory syndrome Coronaviridae 2) AND "Re-infection"

### *>>Study Selection criteria*

Population: No specific age group or sex

Intervention: COVID-19

Comparison: No comparison has been a purpose of the study

Outcome: Re-infection by COVID-19

Observational epidemiological studies and case reports addressing the re-infection with COVID-19 have been considered eligible.

## Results

Literature search has identified 6 cases reported of being re-infected with COVID-19. A seventh case was identified from Melbourne Australia from a press conference of Daniel Andrews, Victoria's premier. (8–13)

Results show that 75 % of cases who have been tested for antibodies after first infection (n=4) were negative, and turned seropositive after second infection. (Table 1, Figure 1)

Results also show that 57% of cases developing re-infection had worse clinical manifestations, and required hospitalization despite mild or asymptomatic first infection (Table 1, Figure 2)

The average intervening period between initial infection and re-infection was 105 days, and the average age of re-infected patients was 36 years.

Data from those reports were scarce, reporting no details about comorbidities or body mass index of re-infected cases

## Discussion

An under trial COVID-19 vaccine, analyzed by Sahin and colleagues, showed evident development of neutralizing antibodies and CD-8 response. However, the mRNA vaccine-induced B-cell response reached its highest two weeks after immunization and then declined afterwards.(14)

The effect of SARS-COV-2 vaccine on the body's immune response was analyzed subsequent to the administration of two doses; the viral-induced antibody concentration seemed to diminish typically around day 43. This finding was in concordance with the results that Wu and Long et al have illustrated in response to the infection, thus clearly providing evidence of the feeble B-cell response to infection as well as vaccination. (5,6)

The memory B cells produced during the primary immune response are specific to the antigen involved during the first exposure; in a secondary response, the memory B cells specific to the antigen or similar antigens will respond. When memory B cells reencounter their specific antigen, they proliferate and differentiate into plasma cells, which then respond to and clear the antigen; such clearance is achieved by what is called the secondary antibody response. It is regarded that that secondary antibody response is the most crucial event that can prevent re-infection with a certain pathogen.(15)

In this context, Kapasi and colleagues tested the secondary antibody response reflective of B cell memory in old vs. young mice in response to bouts of exercise. Secondary antibody response appeared to be exercise dependent, because old mice that received 1 bout of intense exercise demonstrated increased anti-antibody levels compared with old non-exercising mice. Moreover, the old mice that received the booster immunization after undergoing 1 bout of intense exercise, have attained levels of anti-HSA antibodies comparable to those seen in the young mice. In accordance with our findings, Long and colleagues have tested the vaccine responses of two groups of old aged individuals. They have succeeded in showing that antibodies in response to pneumococcal vaccine improved significantly following regular moderate intensity exercise.(16)

Such findings signify that exercise has the ability to not only improve the outcome of infected cases but to prevent re-infection and can improve the response of vaccinated individuals. This should be taken into account during the ongoing trials for a potential COVID-19 vaccine.

Another important concern, during development of the vaccine is the severity of re-infection when compared to the initial infection. As shown in Table 1 as well as Figure 2 that >50% of reported re-infected cases are showing a more severe spectrum of the disease. This should be viewed with extreme caution in conjunction with Sahin et al findings of

augmented systemic adverse reactogenicity after the second dose. Reactogenicity is the series of adverse local or systemic reactions after vaccination. It is usually correlated with baseline serum levels of IL-6. (17)

In spite of reduced vaccine immunogenicity in old age due to insufficient B-cell memory, a number of studies, particularly those of Cowling and associates, illustrated that the local and, to a lesser extent, the systemic reactogenicity of vaccines increased in older adults. This finding could be attributed to the reduction of Soleus Muscle Protein SOCS3 due to lack of exercise and sedentary lifestyle, noting that SOCS3 acts to repurpose IL-6 from a pure pro-inflammatory to a rather regulatory cytokine role.(18)

Thus, exercise not only can improve the immunogenicity of a potential vaccine but can also decrease the severity of re-infection and the adverse reactogenicity of potential vaccines under development.

## Conclusion

In conclusion, we found that not only was exercise important for the overall outcome of an infected patient but also crucial to a healthy memory B cell response. This is especially important after more than half of the documented cases of re-infection were found to have worse clinical manifestations than in their first infection. This raises the possibility that regular cardiovascular exercise might be pivotal for both a stronger immune response and the prevention of a re-infection all together. Exercise might be beneficial as well in preventing the reactogenicity of the potential vaccines under development.

Figure 3 summarizes how regular physical exercise can improve outcome of potential COVID-19 vaccination

## Declarations

### Conflict of interest:

None

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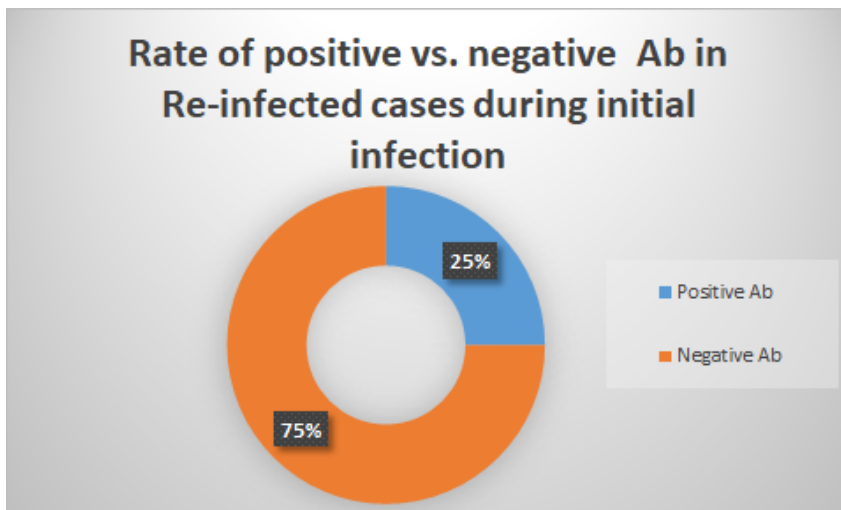
## Table

Table 1: Reported Cases of Re-infection from COVID-19

Country of origin	Age (Years)	Sex	Intervening Period (days)	Antibodies after first infection	Antibodies after re-infection	Manifestations during first infection	Manifestations during second infection
Israel	20	Male	120	N/A	N/A	Mild	Asymptomatic
Brazil	36	Female	120	Negative	Positive (Ig A and IgG)	Mild	Severe
Hong Kong	33	Male	142	Negative	Positive (Ig G)	Mild	Asymptomatic
USA	25	Male	48	Negative	Positive (Ig M and Ig G)	Mild	Severe
Ecuador	46	Male	63	Positive (Ig M)	Positive (Ig M and Ig G)	Mild	Severe
Belgium	51	Female	93	N/A	Positive (Ig G)	Mild	Mild
Australia	42	Male	150	N/A	N/A	Mild	Severe

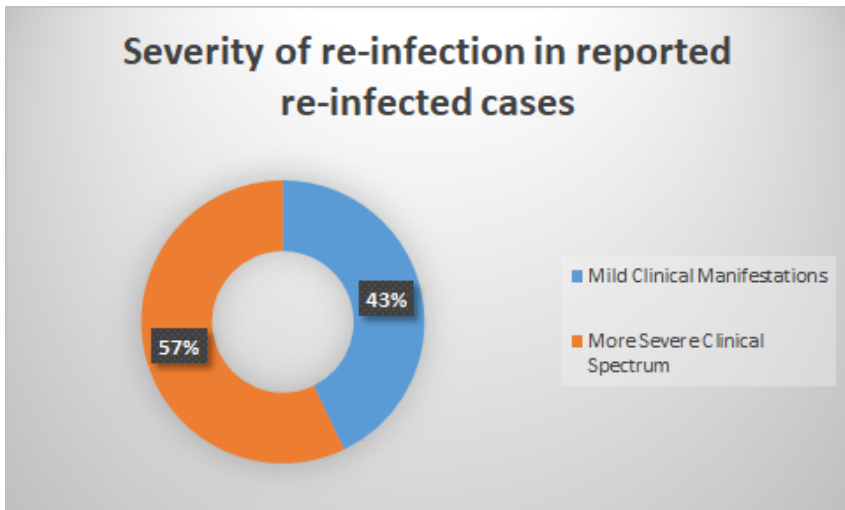
Abbreviations: N/A: Non applicable

## Figures



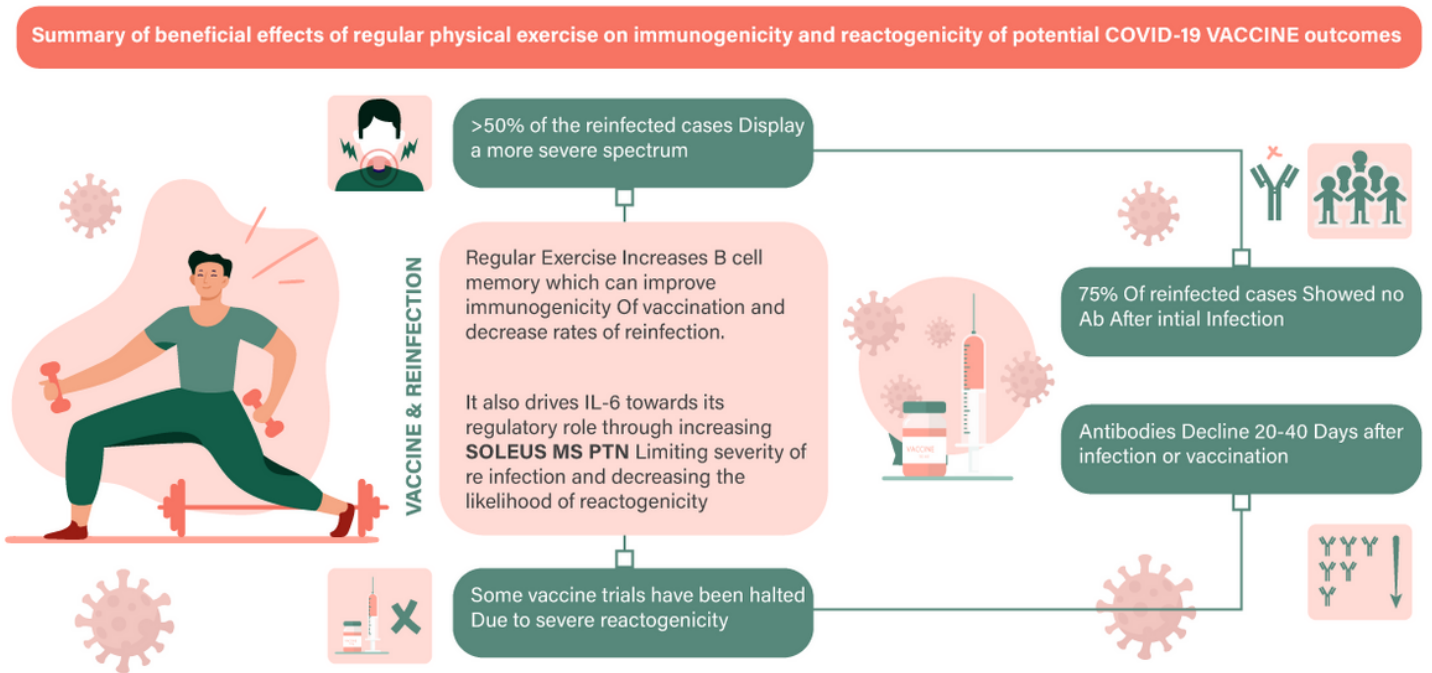
**Figure 1**

Rate of negative vs. positive antibody responses in re-infected cases after initial infection



**Figure 2**

Severity of re-infection in reported re-infected cases



**Figure 3**

Summary of beneficial effects of regular physical exercise on immunogenicity and reactivity of a potential COVID-19 vaccine