

What reinfections mean for COVID-19

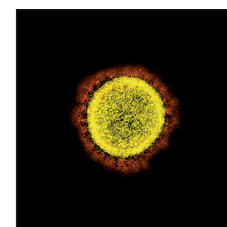


Figure 1: SARS-CoV-2

One of the key questions in predicting the course of the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is how well and how long the immune responses protect the host from reinfection. For some viruses, the first infection can provide lifelong immunity; for seasonal coronaviruses, protective immunity is short-lived.¹

In *The Lancet Infectious Diseases*, Richard L Tillett and colleagues describe the first confirmed case of SARS-CoV-2 reinfection in the USA.² A 25-year-old man from the US state of Nevada, who had no known immune disorders, had PCR-confirmed SARS-CoV-2 infection in April, 2020 (cycle threshold [Ct] value 35.24; specimen A). He recovered in quarantine, testing negative by RT-PCR at two consecutive timepoints thereafter. However, 48 days after the initial test, the patient tested positive again by RT-PCR (Ct value 35.31; specimen B). Viral genome sequencing showed that both specimens A and B belonged to clade 20C, a predominant clade seen in northern Nevada. However, the genome sequences of isolates from the first infection (specimen A) and reinfection (specimen B) differed significantly, making the chance of the virus being from the same infection small. What is worrisome is that SARS-CoV-2 reinfection resulted in worse disease than did the first infection, requiring oxygen support and hospitalisation. The patient had positive antibodies after the reinfection, but whether he had pre-existing antibody after the first infection is unknown (table).

This case report adds to rapidly growing evidence of COVID-19 reinfection, in which viral genomic sequences were used to confirm infections by distinct isolates of SARS-CoV-2. What do reinfection cases mean for public health and vaccination endeavors to stop the COVID-19 pandemic?

Do reinfections occur because of a scant antibody response after first infection? Of the four reinfection cases reported to date, none of the individuals had known immune deficiencies. Currently, only two individuals had serological data from the first infection and one had pre-existing antibody (IgM) against SARS-CoV-2. Because of the wide range of serological testing platforms used across the globe, it is impossible to compare results from one assay to another. For example, antibody reactivity to nucleocapsid protein indicates previous exposure to SARS-CoV-2 but not whether antibodies that can block infection (anti-spike) are present. Also, antibody levels are highly dependent on the timing after exposure. The key goal for the future is to ascertain the level and specificity of antibody to spike protein at the time of reinfection, to determine immune correlate of protection.

Does immunity protect an individual from disease on reinfection? The answer is not necessarily, because patients from Nevada and Ecuador had worse disease outcomes at reinfection than at first infection. It is important to keep in mind that the reinfection cases in general are being picked up because of symptoms and are biased towards detection of symptomatic cases. Due to the paucity of broad testing and surveillance, we do not know how frequently reinfection occurs among individuals who recovered from their first infection. Asymptomatic reinfection cases can only be picked up by routine community testing or at an airport, for example,³ and we are probably severely underestimating the number of asymptomatic reinfections. Why do some reinfections result in milder disease,^{3,4} whereas others are more severe?^{2,5} Further investigation is needed of pre-existing immune responses before second exposure, and viral inoculum load.

Lancet Infect Dis 2020

Published Online
October 12, 2020
[https://doi.org/10.1016/S1473-3099\(20\)30783-0](https://doi.org/10.1016/S1473-3099(20)30783-0)
See Online/Articles
[https://doi.org/10.1016/S1473-3099\(20\)30764-7](https://doi.org/10.1016/S1473-3099(20)30764-7)

	Sex	Age (years)	First infection (Ct)	Second infection (Ct)	Intervening period (days)	Antibody after first infection	Antibody after reinfection
Hong Kong ³	Male	33	Mild (N/A)	Asymptomatic (27)	142	Negative	IgG+
Nevada, USA ²	Male	25	Mild (35)	Hospitalised (35)	48	N/A	IgM+ and IgG+
Belgium ⁴	Female	51	Mild (26–27)	Milder (33)	93	N/A	IgG+
Ecuador ⁵	Male	46	Mild (37)	Worse (N/A)	63	IgM– and IgG–	IgM+ and IgG+

Data were obtained Sept 14, 2020, for reinfection cases confirmed by viral genome sequences. Ct=cycle threshold. N/A=not available. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table: Characteristics associated with reinfection with SARS-CoV-2

Does infection by different viral isolates mean we need a vaccine for each type? While differences in the viral genome sequence of the various isolates are a great way to know if an individual is reinfected (ruling out reactivation of lingering virus infection), it does not indicate that the second infection was due to immune evasion. There is currently no evidence that a SARS-CoV-2 variant has emerged as a result of immune evasion. For now, one vaccine will be sufficient to confer protection against all circulating variants.⁶ Furthermore, reinfection by a distinct viral variant from the original virus does not imply immune escape.

Does immunity prevent transmission from those who are reinfected? The Ct value of PCR correlates with viral load, and low Ct values (high viral load) might indicate infectiousness of the individual. Although Ct values can vary substantially between various tests and laboratories, in one study, samples with Ct values greater than 35 were only 8% positive for cultivable virus.⁷ A good proxy for infectiousness can be obtained through viral plaque assays that measure the infectious virus. However, these assays require biosafety level 3 facilities and are labour intensive, and the assays are not routinely done in clinical laboratories. Since some reinfection cases had Ct values less than 35,^{3,4} infectious virus might have been harboured in the nasal cavity. Thus, reinfection cases tell us that we cannot rely on immunity acquired by natural infection to confer herd immunity; not only is this strategy lethal for many but also it is not effective. Herd immunity requires

safe and effective vaccines and robust vaccination implementation.

As more cases of reinfection surface, the scientific community will have the opportunity to understand better the correlates of protection and how frequently natural infections with SARS-CoV-2 induce that level of immunity. This information is key to understanding which vaccines are capable of crossing that threshold to confer individual and herd immunity.

I declare no competing interests.

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