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EDITORIAL COMMENTARY

Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2: What Goes Around May Come Back Around

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread around the world, causing the coronavirus disease 2019 (COVID-19) pandemic. In less than a year since its emergence in December 2019, >32 million cases have been detected worldwide and, as of this writing, COVID-19 has resulted in >1 000 000 deaths [1]. Multitudes have recovered from COVID-19, but it has been uncertain whether they are immune to being reinfected with SARS-CoV-2 or, if not, whether the disease course during a second episode would be mitigated, similar, or worse than the first infection. As reports of reinfection begin to appear [2–5], including a person in South Korea described by Lee and colleagues in this issue of *Clinical Infectious Diseases* [6], and other individuals around the world (Table 1), what are the implications for our understanding of immunity to SARS-CoV-2 and the prospects for a COVID-19 vaccine?

Reinfection has been described for other respiratory and nonrespiratory RNA viruses, both after natural infection and after vaccination. For example, people who have recovered from parainfluenza may be susceptible to symptomatic disease, even if reinfected with the same strain, likely due to waning of immunity from the prior infection [7]. Viral diversity can result in escape from memory responses that may not recognize new strains, as demonstrated in more diverse viruses such as influenza and hepatitis C virus (HCV). Even for HCV, in which reinfection occurs commonly in certain high-risk populations, protective immunity that ameliorates its subsequent disease course has been described [8], highlighting the complex interplay between the immune response and viral factors that may determine the outcome of reinfections. Similarly, some vaccines (including influenza and pertussis) may not fully prevent infection but may reduce the likelihood of severe disease [9, 10]. These examples from natural infection and from vaccination illustrate the spectrum of immunity and potential outcomes: sterilizing immunity that fully protects against infection; partial or protective immunity that reduces the incidence, severity of disease, and/or contagiousness; no immunity; or even enhancing immunity that actually contributes to worse disease severity (Figure 1).

For coronaviruses other than SARS-CoV-2, what do we know about the type of immune responses and the extent and durability of immunity to reinfection? Typically, after infection with other coronaviruses, virus-specific antibodies appear approximately 7–14 days after symptom onset and eventually wane. For the seasonal coronaviruses, reinfection is associated with a rise in strain-specific antibodies and may occur as soon as 6–12 months after initial infection, as documented in prospective cohorts and viral challenge experiments [11]. Reassuringly, after experimental rechallenge with a common cold human coronavirus, 229E, participants were reinfected but the period of viral shedding was shorter and no participants developed cold symptoms—an example of partial and disease-ameliorating immunity [12]. In a study in Kenya, a subset of participants with repeat infection with the endemic human coronavirus NL63 had higher viral levels during their second infection, but the frequency of upper respiratory symptoms diminished with repeat infections [13]. In patients who have recovered from the severe acute respiratory syndrome or Middle East respiratory syndrome coronaviruses, antibodies remain detectable up to 1–3 years after infection; it is not known, however, whether individuals are protected from reinfection because reexposures were improbable [11]. For SARS-CoV-2, macaques rechallenged after infection had brief periods of detectable virus in the

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Table 1. Reported Reinfections in Published and Preprint Reports, Available as of 28 September 2020[a]

Citation	Location	Age, y/Sex	Interval Between Episodes	Stage[b] (First Episode)	Stage (Second Episode)	Ct Values (First/Second Episodes)		Epidemiology for First Case	Epidemiology for Second Case
To et al [2]	Hong Kong	33/M	17.5 wk	Mild	No symptoms	NR	26.69	NR	Travel to Europe
Tillett et al (unpublished data)	Nevada, USA	25/M	4.5 wk	Mild	Severe (hospitalized, required O_2)	35.24	35.31	NR	Confirmed household exposure
Larson et al [3]	Virginia, USA	42/M	7 wk	Mild	Severe (O_2 saturation 92%–94% on room air)	NR	NR	Occupational exposure	Confirmed household exposure
Gupta et al [4][c]	North India	25/M	14 wk	No symptoms	No symptoms	36	16.6	NR	NR
	North India	28/F	14 wk	No symptoms	No symptoms	28.16	16.92	NR	NR
Van Elslande et al [5]	Belgium	51/F	13 wk	Mild	Mild, lesser magnitude of symptoms	25.6 (N1) & 27.2 (N2)	32.6 (N1) & 33.2 (N2)	NR	NR
Shastri et al (unpublished data)[c]	India	24/F	8 wk	Mild	Mild	32 (N)	25 (N)	NR	NR
	India	27/M	8 wk	No symptoms	Mild	33 (N)	36 (N)	NR	NR
	India	31/M	3 wk	No symptoms	Mild	36 (N)	21 (N)	NR	NR
	India	27/M	7 wk	Mild	Mild	32 (N)	17 (N)	NR	NR
Goldman et al (unpublished data)	Washington, USA	60s	12 wk	Severe	Severe (O_2 requirement lower when compared to first hospitalization)	22.8 (E) & 26.5 (RdRP)	43.3 (E) & 39.6 (N2)	Exposure in skilled nursing facility	Exposure in another skilled nursing facility
Prado-Viva et al (unpublished data)	Ecuador	46/M	7 wk	Mild	Moderate	NR	NR	Household	Family contact (different than first)
Lee et al [6]	South Korea	21/F	4 wk	Mild	Mild	22.34 (E) & 22.75 (RdRP)	32.36 (E) & 32.79 (RdRP)	NR	NR

Abbreviations: Ct, cycle threshold; E, envelope; F, female; M, male; N1, nucleocapsid 1; N2, nucleocapsid 2; NR, not reported; O_2, oxygen; RdRP, RNA-dependent RNA polymerase; USA, United States.

[a]Other cases have been reported online but are not yet available in preprint/manuscript form.

[b]Staging was determined or inferred by review of the report and classification into categories as defined by National Institutes of Health guidelines found at: https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/.

[c]Cases from these reports were presumed to be occupational in these healthcare workers; it is unclear if community exposures were also ruled out.

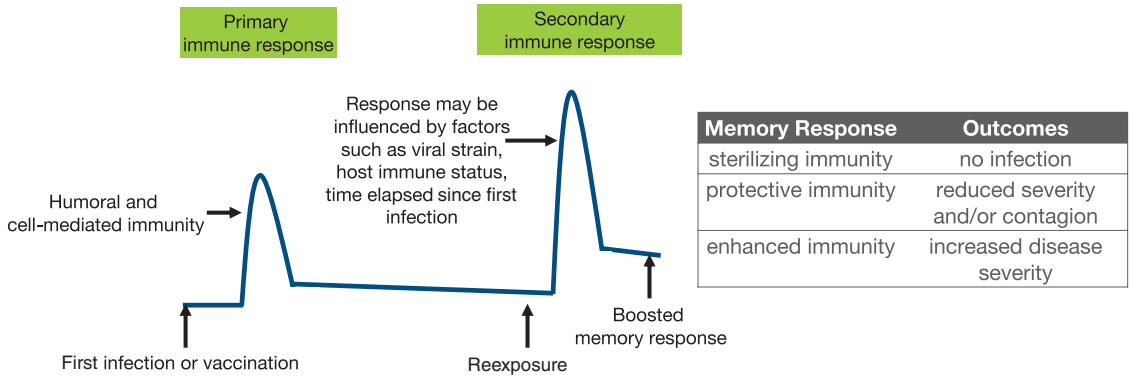

Figure 1. Immunity after rechallenge; reinfections may have variable success and outcomes. Protective immunity could affect the incidence, severity, and/or infectiousness of disease. Thus far, enhanced immunopathology to severe acute respiratory syndrome coronavirus 2 has not been described.

nasopharynx but did not suffer from prolonged infection and/or severe disease [14]. Based on what we know about other coronaviruses and protective immunity, the recent reports of SARS-CoV-2 reinfection should not surprise us but highlight the importance of determining whether partial or protective immunity will affect the likelihood or disease course of the second infection.

In all but 1 of the reinfection reports to date, including the report by Lee and colleagues [6], the first episode of COVID-19 was asymptomatic or mild and reinfection occurred between 3–17 weeks after the initial infection (Table 1). Why has reinfection rarely been reported in those who initially had severe disease? One likely explanation is that, because most COVID-19 is mild, a far greater proportion of recovered individuals have had mild rather than severe disease. Another potential explanation is that the greater magnitude of antibody responses or T-cell responses generated during severe COVID-19 may confer more robust and/or long-lasting protection. Correlates of protection may not only include the severity of the original illness but may also be influenced by viral escape mutations and/or viral inoculum at the time of reexposure. Complete protection against SARS-CoV-2 infection (or reinfection) likely requires multifaceted and coordinated immune responses (humoral and cell-mediated) deployed at the right place (mucosal immunity) in an expeditious fashion (eg, anamnestic response).

What are the implications of the reported reinfection cases for public health surveillance? First, it is critical to define what we mean by reinfection. It is notable that these reports are occurring in a context where jurisdictions have deployed an unprecedented level of surveillance and testing, using very sensitive polymerase chain reaction (PCR)–based tests. This high sensitivity resulted in early "false alarms," as it was appreciated early on during the pandemic that patients would frequently test positive on PCR assays, then negative, then positive again even without clinical or epidemiologic concerns for reinfection. Subsequent studies suggested that the vast majority of these individuals had prolonged and/or intermittent PCR positivity after the original infection, and, when tested, viral genomic data revealed persistent detection of the same isolate rather than reinfection. Fortunately, intermittent PCR positivity was not associated with culturable infectious virus nor with disease or transmission [15]. While mass testing resulted in these false alarms, it also allowed examination of sequence data to detect reinfections. A strict definition of reinfection requires sequence data from both detections, separated in time, to distinguish that there are 2 distinct viral isolates, which distinguishes reinfection from intermittent shedding of the original viral isolate. Suspected reinfection warranting investigation may, in the absence of detailed sequence data, include criteria such as clinical features, epidemiologic evidence for reexposure, laboratory data such as PCR cycle threshold and/or rise in antibody titers, and—importantly—lack of an alternative diagnosis. One of the most critical tasks for the field is to develop consensus case definitions for reinfection that can be used for surveillance and diagnosis.

In addition to developing clear-cut case definitions, another imminent need is for public health authorities to provide the laboratory support to store specimens and sequence virus. Notably, proving reinfection required retrieval of viral genomic material from the initial episode, which is not always available, as well as access to a laboratory with sequencing capabilities beyond detection. In addition, it is critical to determine whether patients who are reinfected remain likely to infect others; samples from people with molecular evidence of reinfection should be cultured in specialized laboratories for infectious virus, and rigorous contact tracing studies must be performed.

What do the reinfection cases tell us about how to think about people who have had COVID-19? At this point, not enough. Given the millions of people who have recovered from COVID-19, so far reinfection seems to be uncommon. Case reports of reinfection are useful to establish that these individuals are not completely protected from SARS-CoV-2

reinfection, but they are unable to tell us much more due to the lack of systematic collection and the likelihood of bias in who receives repeat testing. In addition, although a subset of individuals with reinfection had more symptoms or greater disease severity the second time around, raising the possibility of immune enhancement (as may occur with dengue or the coronavirus that causes feline infectious peritonitis), there are other potential explanations for these observations. Because individuals who exhibit symptoms are more likely to be tested again, we are much less likely to detect those who are reinfected but asymptomatic, such as the patient who returned from Europe to Hong Kong and was found to have reinfection only because of travel-related screening [2]. We also cannot control for ascertainment or recall biases, nor for other potential factors, such as a higher viral inoculum during the second infection. Most reported cases are in young and healthy individuals, and thus we do not yet know the natural history of reinfection in older or immunocompromised patients. Prospective cohorts that test regularly and systematically in regions of ongoing transmission are critical to define the true incidence and natural history of reinfection, to assess the dynamics of serologic and T-cell responses, and to determine how preexisting or infection-induced immune responses affect outcomes when people are reexposed to SARS-CoV-2.

Until we know more, patients who have recovered from COVID-19 should continue preventive measures, such as social distancing and mask-wearing. Once a safe and efficacious vaccine is available, it should be offered to those who have had previous COVID-19. As clinicians, we need to not only counsel our patients regarding measures to avoid reinfection but to be prepared to make these diagnoses, and to potentially treat such patients. The provider considering a reinfection diagnosis for a patient with development of recurrent symptoms after recovery from COVID-19 should take a detailed history, including for potential reexposures; consider alternate diagnoses; and work with research and public health laboratories to evaluate whether a viral isolate distinct from the original one is present.

For now, the implications of the recently described SARS-CoV-2 reinfection cases are uncertain. What is indisputable, however, is that we will only make progress in understanding these cases if clinicians, public health experts, basic and translational science researchers, and vaccinologists work together to determine the incidence of reinfection, why some people are susceptible and others are not, the immune and virologic correlates of disease severity when reinfection occurs, and the longevity of infection- and vaccine-induced immune responses against SARS-CoV-2. Establishing effective and durable protective immunity through vaccination that reliably reduces COVID-19 disease may alter SARS-CoV-2 to "only" another seasonal coronavirus, a better situation than the one we are currently facing. The challenges are immense but so are the opportunities to apply the lessons from what we learn from reinfections to developing an effective and durable vaccine against SARS-CoV-2.

Notes

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References

1. World Health Organization. World Health Organization COVID-19 dashboard. Available at: https://covid19.who.int/. Accessed 30 September 2020.
2. To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1275.
3. Larson D, Brodniak SL, Voegtly LJ, et al. A case of early re-infection with SARS-CoV-2. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1436.
4. Gupta V, Bhoyar RC, Jain A, et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1451.
5. Van Elslande J, Vermeersch P, Vandervoort K, et al. Symptomatic SARS-CoV-2 reinfection by a phylogenetically distinct strain. Clin Infect Dis **2020**; doi:10.1093/cid/ciaa1330.
6. Lee JS, Kim SY, Kim TS, et al. Evidence of SARS-CoV-2 reinfection after recovery from mild COVID-19. Clin Infect Dis **2020**. In press.
7. Branche AR, Falsey AR. Parainfluenza virus infection. Semin Respir Crit Care Med **2016**; 37:538–54.
8. Osburn WO, Fisher BE, Dowd KA, et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Gastroenterology **2010**; 138:315–24.
9. Godoy P, Romero A, Soldevila N, et al. Influenza vaccine effectiveness in reducing severe outcomes over six influenza seasons, a case-case analysis, Spain, 2010/11 to 2015/16. Euro Surveill **2018**; 23:1700732.
10. Préziosi MP, Halloran ME. Effects of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. Clin Infect Dis **2003**; 37:772–9.
11. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun **2020**; 11:4704.
12. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect **1990**; 105:435–46.
13. Kiyuka PK, Agoti CN, Munywoki PK, et al. Human coronavirus NL63 molecular epidemiology and evolutionary patterns in rural coastal Kenya. J Infect Dis **2018**; 217:1728–39.
14. Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science **2020**; 369:812–7.
15. Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis **2020**; 71:799–806.