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REVIEW ARTICLE

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COVID-19 reinfection: the role of natural immunity, vaccines, and variants

Bao Y. Sciscent[a], Caroline D. Eisele[a], Lisa Ho[a], Steven D. King[a], Rohit Jain[b] and Reshma R. Golamari[b]

[a]The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania, USA; [b]Department of Hospital Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

ABSTRACT

The COVID-19 pandemic has altered innumerable lives. Although recent mass vaccinations offer a glimmer of hope, the rising death toll and new variants continue to dominate the current scenario. As we begin to understand more about SARS-CoV-2 infections, the territory of reinfections with COVID-19 remains unexplored. In this review, we will discuss several aspects of reinfection: (a) How is COVID-19 reinfection characterized? (b) Does prior literature differentiate between reinfection and reactivation? (c) What SARS-CoV-2 strains do the vaccines target and can they protect against new strains? Larger and longer timeline studies are needed to understand reinfection risks. With the ongoing distribution of the SARS-CoV-2 vaccines to provide protection, the understanding of the possibility for SARS-CoV-2 reinfection remains critical.

Abbreviations CDC: Centers for Disease Control**SARS-CoV-2**: Severe acute respiratory syndrome coronavirus 2**COVID-19**: Coronavirus disease 2019**RT-PCR**: Reverse Transcription Polymerase Chain Reaction**PASC**: Post-Acute Sequelae of SARS-CoV-2 infection

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1. Introduction

The novel coronavirus disease, COVID-19, has presented a multitude of challenges for public health officials and healthcare providers. According to the World Health Organization, there have been over 3 million deaths and the cases multiply as we witness surges worldwide[1]. Still, many questions remain unanswered regarding the virus, SARS-CoV-2. Although we understand more about the concept of SARS-CoV-2 infection and modes of transmission, the notion of reinfection remains relatively unexplored[2]. Reinfection was recently characterized by the Centers for Disease Control (CDC) as infection across two different time periods with established genetic sequencing data[3]. Reinfection has implications for epidemiological modeling and public health with the introduction of vaccines and the various mutations occurring in the genetic sequencing worldwide [4,5]. Reinfection needs to be differentiated from a multifaceted presentation of inflammatory damage and immunologic dysregulation known as Post-Acute Sequelae of SARS-CoV-2 infection (PASC), which has been observed in patients 4 weeks from the onset of acute COVID-19 symptoms[6]. There is a need for additional studies to determine if reinfection is possible, given the implications it has for epidemiological modeling and public health [4,5].

Properties of immunity from a previous infection will help characterize the reinfection potential [7,8]. According to Gomes et al., the duration of immunity matters[7]. In Figure 1 we depict that active immunity, from either infection or a vaccine provides full protection for a limited duration of time, which makes reinfection more likely[7]. In our review, we delve into previous studies and case reports related to reinfection. We must also determine the significance of a positive antibody test, which will deepen our understanding of the concept of reinfection.

2. Definition of reinfection

The definition of reinfection has been interpreted differently across many studies. The Centers for Disease Control defined reinfection as an infection in the same individual across a different time period with evidence of genotypic variance, i.e., infection in an individual with two different viral strains within $\geq$ 45 days in highly suspicious cases of COVID-19 or $\geq$ 90 days in asymptomatic cases or in cases with low suspicion[3]. The above model also takes into consideration cycle threshold values less than or equal to 35[9]. Many other studies define reinfection as two positive SARS-CoV-2 RT-PCR tests with negative tests in between without taking the genotypic variation into account. Hall et al. reported that the prior history of SARS-CoV-2 is associated with an 83% lower risk of reinfection and that the protective

CONTACT Reshma R. Golamari Rgolamari@pennstatehealth.psu.edu; reshma.golamari@gmail.com Department of Hospital Medicine, Penn State Health Milton S Hershey Medical Center, Hershey, Pennsylvania, USA

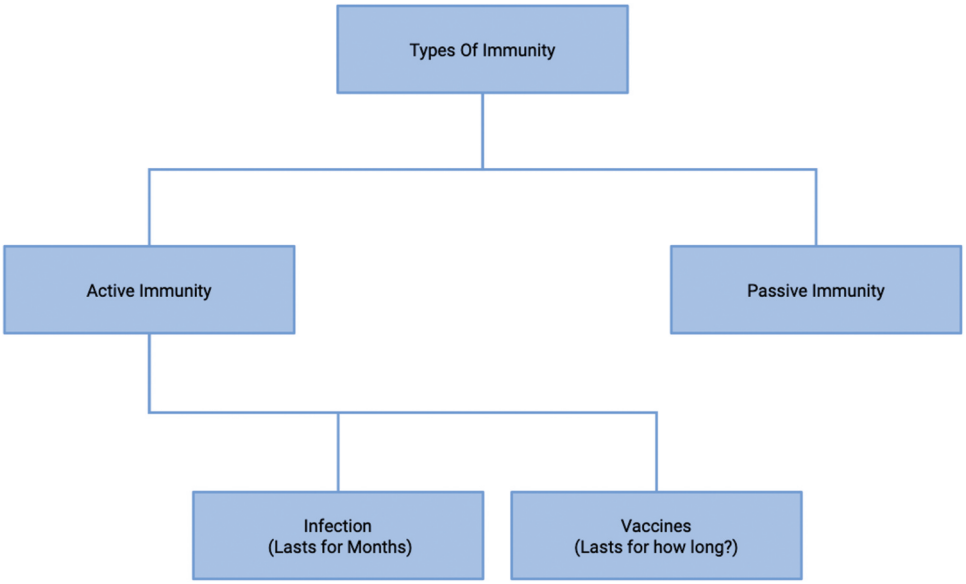

Figure 1. Types of Immunity.

effect may last for 5 months[10]. In a large population study done in Denmark by Hansen et al., protection against repeat infection was deemed to be 80.5% in the general population and 47.1% in patients 65 years or older[11]. However, this study defined reinfection differently. Here, the authors included people who were tested with COVID-19 RT-PCR during the first surge before June 2020 and followed the cohort from September to December 2020 to analyze SARS-CoV-2 contraction[11]. Abu-Raddad et al. studied the efficacy of natural infection against reinfection, which was accounted for by a change in viral genome sequencing. This study found that the rate of reinfection was estimated to be 95.2%[12].

Viral genome sequencing has identified as many as 80 known and identified genotypic variants of SARS-CoV-2 with B.1.1.7 being the most common variant in the USA up to June 2021, when the B.1.617.2, Delta, variant rapidly took over [13–16]. A summary of the previously published literature on SARS-CoV-2 reinfections with a genetically different strain is outlined in Table 1. The first case of

Table 1. Characteristics of patients reinfected with SARS-CoV-2.

Author	RT-PCR	Age in years and Sex	Period between tests	Symptoms	Genomic Strain	Presence of antibodies
Larson et al	NP	42 M	51 days	1st: Mild 2nd: Severe	1st: B.1.26 2nd: B.1.26 but with several mutations	1st: N/A 2nd: N/A
Tillett et al.	NP	25 M	48 days	1st: Mild 2nd: Severe	1st: Clade 20 C 2nd: Clade 20 C With different SNVs	1st: N/A 2nd: (+) IgG (+) IgM
To et al.	OP	33 M	142 days	1st: Mild 2nd: None	1st: Clade 19A 2nd: Clade 20A	1st: (-) IgM (-) IgG 2nd: (+) IgG
Goldman et al.	NP	Between 60–69 Sex unknown	140 days	1st: Severe 2nd: Mild	1st: Clade 19B 2nd: Clade 20A	1st: N/A 2nd: (+) IgG (+) IgM
Elslande et al.	NP	51 F	93 days	1st: Mild 2nd: Mild	1st:Lineage B.1.1 2nd: Lineage A	1st: N/A 2nd: (+) IgG
Selhorst et al.	NP	39 F	185 days	1st: Mild 2nd: Mild	1st: Clade V 2nd: Clade G	1st: (+) IgG 2nd: (+) IgG
Prado-Vivar et al.	OP	46 M	63 days	1st: Mild 2nd: Severe	1st: Clade 20A 2nd: Clade 19B	1st: (+) IgM (-) IgG 2nd: (+) IgM (+) IgG
Shastri et al.	NP	27 M	66 days	1st: Mild 2nd: Mild	1st: B1 2nd: B, 8 SNP mutations	1st: N/A 2nd: No
Shastri et al.	NP	31 M	65 days	1st:Assympto-matic 2nd: Mild	1st: B.1.1 2nd: B, 9 SNP mutations	1st: N/A 2nd: No
Shastri et al.	NP	24 F	55 days	1st: Mild 2nd: Mild	1st: B1.1 2nd: B1.1, 12 SNP mutations	1st: N/A 2nd: No
Marquez et al.	NP	16 F	>90 days	1st: Mild 2nd: Mild	1st: B.1.2 2nd: B.1.1.7	1st: N/A 2nd: (+) IgM (-) IgG
Sevillano et al.	NP	28 M	90 days	1st: Mild 2nd: Mild	1st: B.1.1.29. 2nd: B.1.1.29, 27 SNP mutations	1st: (-) IgM (-) IgG 2nd: (+) IgM (-) IgG

NP = Nasopharyngeal, **OP** = Oropharyngeal, **F** = Female, **M** = Male, **SNV** = Single Nucleotide Variants, **N/A** = Not available.

reinfection in the USA was reported by Tillett et al., which described a 25-year-old man who had two separate nasopharyngeal RT-PCRs taken 2 months apart which showed genetically distinct variants of SARS-CoV-2[17]. At initial diagnosis, the individual presented with mild symptoms, and two subsequent negative tests followed resolution of symptoms. Forty-eight days later, he tested positive for SARS-CoV-2 infection when he presented with similar symptoms as well as shortness of breath. The specimens were analyzed with RT-PCR and genomic sequence analysis showed single nucleotide variants that differed between the specimens and the reference genome. IgG and IgM antibodies were detected a day after the second diagnosis. However, since the patient was not tested for antibodies directly prior to the second encounter, whether he conferred immunity after the first infection is unknown. Similarly, a 42-year-old healthcare worker tested positive with a different strain B.1.126 after 51 days of the initial infection. Unfortunately, no antibody testing was performed after either infection[18].

Other reports of reinfection have also reported that samples taken from each occurrence were found to be phylogenetically distinct [19–26]. In these cases, the patients had two separate positive COVID-19 RT-PCR tests with at least one negative test in between. Goldman et al. reported a patient who tested positive for SARS-CoV-2 twice, 140 days apart[19]. Genomic comparison of the viral RNA from these two occurrences revealed the first infection matched to clade 19B and the second to 20A. To et al. also reported the presence of phylogenetically distinct strains in a case study with the first being from clade 19A and the second from clade 20A.[20] Two similar cases were also reported in Belgium which included a 51-year-old female who tested positive twice with the first sample matching to lineage B.1.1. and the second to lineage A.[21] The other case was of a 39-year-old female who tested positive 185 days apart with the first infection matching to Clade V and the second to Clade G.[22] Similarly in Ecuador, a 46-year-old male tested positive 63 days apart with the first matching to clade 20A and the second to 19B[23]. In the USA, a 16-year-old was first infected by the B.1.2 variant and after resolution was reinfected by the B.1.1.7 variant >90 days later as confirmed by phylogenetic analysis[24]. These case reports show molecular evidence of reinfection in a single patient with variant strains of SARS-CoV -2, as suggested by Kirkcaldy et al [14]. Two cases report reinfection with the same strain, but with significant mutations, as outlined in Table 1. Shastri et al. describe three cases of reinfection after 45 days from the initial infection and similarly, a 28-year-old male in Ecuador was reported to have been first infected by the B.1.1.29 strain and 90 days later by the same strain that differed by 27 nucleotides resulting in 22 mutations [25,26].

One major distinction that must be made is that reinfection is different from reactivation. As the COVID-19 pandemic progresses, we are beginning to better understand SARS-CoV-2 and related immunity. Early on, the temporary nature of immunity and the consequent possibility for reinfection was not clear, so genomic testing was not repeated in studies of subsequent COVID-19 cases. Therefore, some of the reactivation cases, i.e., repeat infections with the same viral strain, were mislabeled as cases of reinfection. SARS-CoV-2 is a virus that mostly causes localized infections. Persistence of viral load in the lower respiratory tract as opposed to upper respiratory tract leads to RNA positivity leading to reactivation[27]. One such study by Ye et al. reported that 9% of patients discharged from the hospital presented with reactivation[28].

3. Post-acute sequelae of SARS-CoV-2 infection

Recent observations of Post-acute sequelae of SARS-CoV-2 infection (PASC), the persistent symptoms and/or complications seen in patients beyond 4 weeks of symptoms, make understanding reinfection a pressing matter. Nalbandian et al. categorizes symptoms to be subacute if present between 4 and 12 weeks and chronic if they persist beyond 12 weeks [6]. While dyspnea and fatigue were found to be the most common symptoms, PASC can be present with manifestations in any organ system[6]. PASC can often be mistaken for reinfection, especially in the chronic phase coupled with persistent viral shedding without genomic testing. It is extremely important to distinguish the two because this may impact management.

With an understanding of the concept of reactivation and PASC, interpretation of reinfection should be made with caution. Careful consideration is warranted while obtaining a sample to obviate the risk of false negatives from insufficient viral material in the specimens, inappropriate timing of sample collection in relation to illness onset, and improper sampling especially from nasopharyngeal swabs [29,30]. Figure 2 illustrates a graphical representation of the timeline of a COVID-19 reinfection.

4. Role of antibodies in reinfection

Some patients infected with SARS-CoV-2 do not develop antibodies, and the reason for this is still unknown [14,31]. For the majority of infected individuals, neutralizing immunoglobulin levels, IgG and IgM, rise within days to weeks of symptom onset[32]. Asymptomatic and mild infections of COVID-19

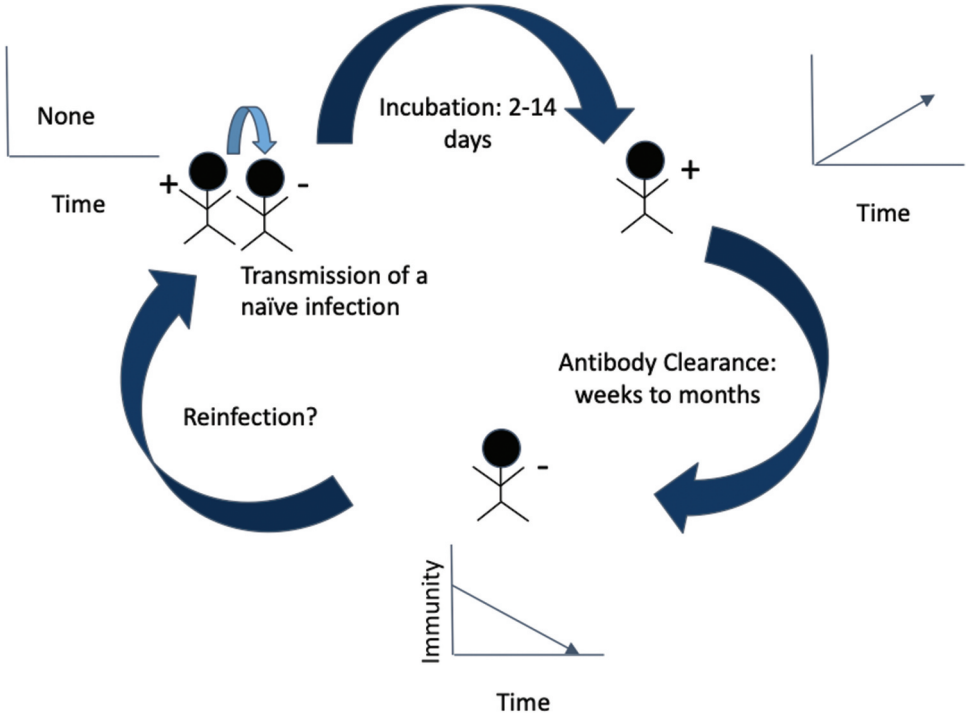

Figure 2. Graphical representation of the cycle and timeline of a COVID-19 infection.

develop a less robust antibody response when compared to severe infections[33]. Exactly how long these antibodies remain detectable following infection varies and depends on the severity of infection[32]. Antibody levels have been shown to fall over the course of several months, between 60 and 90 days from the initial infection [34,35]. Some reports have shown that the immunity lasts until 7–12 months [12,36]. To et al. reported on a case of subsequent COVID-19 in which the patient demonstrated a more robust immune response with IgG neutralizing antibodies and a lack of response from IgM antibodies during the second occurrence of COVID-19. This antibody profile increases the likelihood that the case is caused by reinfection with SARS-CoV-2 rather than reactivation of a previous infection[37].

5. Role of reinfection in vaccination

There are currently several vaccines available all over the world. Some are approved, while some are in the process of being approved. Pfizer/BioNTech, Moderna/NIAID, Johnson & Johnson/Janssen Biotech Inc have been approved by the Food and Drug Administration in the USA, while AstraZeneca/Oxford, Covaxin and Sputnik V have been approved in the rest of the world. Both Pfizer/BioNTech and Moderna/NIAID vaccines are mRNA vaccines that target the spike glycoprotein of SARS-CoV-2, and both confer around 94% efficacy in preventing COVID-19 following receipt of two doses [38]. AstraZeneca/Oxford's vaccine has a 70.4% efficacy and was developed using a modified version of chimpanzee adenovirus as a vector for the SARS-CoV-2 spike glycoprotein, which confers immunity 14 days after the second dose[39]. Johnson and Johnson's Janssen Biotech Inc.'s vaccine is a recombinant adenovirus vaccine which encodes the spike glycoprotein and was 65.5% effective[40]. Covaxin is an inactivated vaccine with an efficacy of 78% and Sputnik V is an adenoviral vector vaccine with an efficacy of 91.6% [41,42]. Considering the different mutations noted, it is uncertain if the vaccine will provide long-lasting immunity. Not only must the vaccines be tested against many of the new mutations, but also more studies are needed to investigate if the vaccine or infection can provide longer-lasting immune protection. There are many other vaccines developed by China which have undergone phase I and phase II trials only. However, one vaccine, CoronaVac (Sinovac Life Sciences, Beijing, China), administered in two doses, is reported to have an efficacy of 50.4–91.25% [43–45]. Sinopharm has also developed two vaccines. One was developed in the Beijing institute with a reported 79% efficacy and the other was developed in Wuhan with a 72.5% efficacy. These vaccines have received many emergency approvals worldwide [43,46,47]. A vaccine developed by Novavax/Novavax, Inc. has undergone phase III clinical trials demonstrating a clinical efficacy of 89.3%. In the Novavax trial, 90% of the isolates were of the South African variant[48]. Similar results were reciprocated in a study done in Israel[49].

Since December 2020, new variants of concern, SARS-CoV-2 B.1.1.7 (Alpha), B.1.351 (Beta), P.1. (Gamma), which have a mutation in N501Y, have

been detected in the UK, South Africa, and Brazil, while variants B.1.427 and B.1.429 have been detected in California[15]. These variants have been shown to exhibit a mutation in the receptor-binding domain of the spike protein, which is known to increase transmission in humans and cause severe disease. In particular, variant B.1.617.2 (variant of concern) has been reported to contain mutations L452R and T478K in the receptor-binding domain. This variant has prompted widespread concern as countries around the world begin to ease restrictions[50]. This variant was studied to be more transmissible and was associated with increased hospitalizations in the younger generations. [51] A few other variants, B.1.525, B.1.526, B.1.617.1, B.1.617.3, P.2, known as variants of interest, have been identified in addition[15].

Additionally, other potential consequences of mutations are the ability to cause more severe diseases in humans, evade detection by specific diagnostic modalities, decrease susceptibility to therapeutic agents, and evade vaccine-induced immunity. Given that the spike protein is the primary target of the majority of the vaccines, vaccine immunity is still unknown against these new and evolving variant strains. The specifics of these vaccines are outlined in Table 2. An in vitro study indicated that the Pfizer/BioNTech vaccine does provide immunity against the N501Y mutation[52]. Pfizer/BioNTech proved an efficacy of 89.5% against the B.1.1.7 variant and 75% efficacy against B.1.351 when tested in Qatar[53]. Bernal et al. reported an 88.0% effectiveness of the Pfizer vaccine and 67.0% of the AstraZeneca vaccine after two doses against the delta variant[54]. However, more studies are still needed to explore if vaccination will result in effective and long-term immunity against this virus.

Case reports represent the majority of studies around reinfection for now, so whether these are a common occurrence or simply rare situations has not been proven yet as surveillance of asymptomatic infection is limited due to lack of routine testing. Larger long-term studies are still needed which should include data on patients' viral load, viral genotype, whether, or not they have antibodies, as well as their immune status. For the time being, public health measures that have been effective at limiting viral spread, such as social distancing and mask wearing, must remain as critical components of the viral mitigation effort.

Table 2. Background on the currently available COVID-19 vaccines.

Vaccine Brand	Type of Vaccine	Number of Doses	Duration between doses	Efficacy
Pfizer/BioNTech	mRNA	Two	21 days	95.0%
Moderna/NIAID	mRNA	Two	28 days	94.1%
Johnson&Johnson/ Janssen	Recombinant adenovirus	One	NA	65.5%
Astra/Zeneca/ Oxford	DNA	Two	28 days	70.4%
Covaxin	Inactivated vaccine	Two	28 days	78%
Sputnik V	Recombinant adenovirus	Two	28 days	91.6%

6. Conclusion

The prevalence of SARS-CoV-2 reinfection is difficult to quantify due to the lack of large-scale studies and the lack of antibody and genomic testing from earlier in the pandemic to confirm a true reinfection. Additionally, immunocompromised patients must be assessed for the likelihood of reactivation as opposed to reinfection.

Immunity to SARS-CoV-2 involves antibody responses, but the variable length of protection permits the possibility of reinfection. Given the limitations of current testing modalities and high false-negative rates, additional tests such as genomic comparisons of viral strains involved in both episodes and testing seroconversion prior to the second episode can be useful testing tools in characterizing reinfection. In the current scenario, vaccinations will play a major role as we are exploring more about the reinfection mutations of the SARS-CoV-2 virus. Thus, the medical community and the general population should stay aware about reinfection at this time in the pandemic.

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ORCID

Reshma R. Golamari http://orcid.org/0000-0002-8842-9762

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