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INFECTIOUS DISEASES,
2021; VOL. 0,
NO. 0, 1–7

https://doi.org/10.1080/23744235.2021.1905174

REVIEW ARTICLE

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Reinfection of SARS-CoV-2 – analysis of 23 cases from the literature

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ABSTRACT

Introduction: The duration of immunity after infection from SARS-CoV-2 conferring protection from subsequent COVID-19 episodes is not yet fully understood. We reviewed the literature for cases of documented reinfection.

Materials and methods: A comprehensive computerized search in PubMed, through 15 December 2020, using the following terms in combination: *COVID-19, SARS-CoV-2, reinfection, reactivation, recurrence*. To exclude cases due to prolonged viral shedding or protracted infection, only cases occurring at least 12 weeks apart or confirmed as being sustained by genetically different viruses by viral genome analysis were included.

Results: We identified 23 cases globally, for which viral genome analysis was performed in 10 cases and serology in 19 cases. The mean interval between the two episodes was 15 weeks. Mean age of cases was 44.5 years, and 10 (43.5%) were women. In 17/23 cases, no comorbidity was observed. In 10 cases, the first episode was more severe than the ensuing episode, whereas in seven cases the ensuing episode was more severe. In four cases, there was no difference in severity and in two cases both episodes were asymptomatic.

Conclusions: From this sample of 23 cases, a clear pattern of the second episode being less or more severe did not emerge. A better understanding of immunity to SARS-CoV-2, necessary to assess the probability of a second infection and the durability of protection conferred by vaccination, is warranted.

KEYWORDS
COVID-19
SARS-CoV-2
reinfection
reactivation
recurrence
serology
immunity

ARTICLE HISTORY
Received 23 December 2020
Revised 24 February 2021
Accepted 14 March 2021

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Introduction

At the time of writing (10 January 2021), there have been over 88 million confirmed cases of COVID-19 globally (https://covid19.who.int), and many countries are starting vaccination programs. However, the debate is still open regarding the strength and the persistence of immunity induced by SARS-CoV-2. Unfortunately, the protective immunity after infections due to the known seasonal coronaviruses is short-lasting, with frequent reinfections occurring at 12 months [1]. How long the adaptive immunity triggered by SARS-CoV-2 can last is of crucial relevance in assessing the probability of a second infection and the long-term efficacy of vaccination programs; neutralizing antibody activities and memory T cells against SARS-CoV-2 can remain stable for up to 6–7 months [2].

To date, reports of persons presenting more than one clinical episode attributed to COVID-19 are increasingly being published. Understanding why some patients are predisposed to a second infection is crucial. The time lapse reported in literature between clinical episodes is variable. In a study of 11 patients presenting symptoms compatible with COVID-19 after a symptom-free interval from a previously documented infection, and then confirmed as such by another positive SARS-CoV-2 RT-PCR test, the shortest interval described was 25 days and the longest 49 days [3]. Other authors [4] have suggested that reinfection be defined as PCR positivity at least 28 days after a previous PCR-positive COVID-19 episode that was followed by clinical recovery and at least one negative PCR. Arafkas et al. [5] sustained that any observed COVID-19 relapse within 90 days might be a protracted infection, and that a positive SARS-CoV-2 testing and recurrent clinical symptoms occurring outside this time frame should be required to diagnose true reinfection.

In this brief review, we investigated cases of documented reinfections reported globally. Although viral shedding reaches a minimum by day 28 after an initial acute SARS-CoV-2 infection [6], to reduce the risk of including cases due to prolonged viral shedding or persistent low level infection, viral reactivation, or previously false-negative laboratory results, we concentrated only on cases occurring at least 12 weeks apart, with the exception of cases in which genomic analysis was performed on viral samples and genetically significant differences emerged between the causative agents of each episode.

Materials and methods

A comprehensive computerized search was performed using PubMed, through 15 December 2020, involving both Medical Subject Headings (MeSH) terminology and relevant keywords for search strings. The following terms were searched in combination: *COVID-19, SARS-CoV-2, reinfection, reactivation, recurrence*. References in retrieved articles were manually searched to ensure identification of studies not found in the initial literature search. The selection was limited to publications written in English. After de-duplication, all authors independently screened titles and abstracts, and finally full texts, to identify all potentially relevant studies, resolving discrepancies through discussion and consultation between them.

Results

We identified 23 cases from 13 different countries (Belgium, Brazil, Ecuador, France, Hong Kong, Israel, Italy, Qatar, South Korea, Spain, Turkey, UK and USA) [4,7–25]. Mean age (±standard deviation) of cases was 44.5 (±7.3) years, and 10 (43.5%) were women. In 17/23 cases (73.9%), no comorbidity was observed. Nine were healthcare workers. Mean interval between the two episodes was 15.0 ± 5.6 weeks. For all cases, except three, each episode was confirmed by a positive PCR test on nasopharyngeal swab: for the three cases in which a swab was not performed or resulted negative the diagnosis was based on clinical manifestations and serology [14,17,22]. For 19 cases (82.6%), serology was reported [4,7–13,15–22,24]: more than half of these (10/19 cases) were recorded as IgG positive following the first infection [4,8,11,12,14–17,24]. In 10 cases [9–11,13,16,18–20,25], viral genomic material was isolated at each of the two episodes and was sequenced: significant differences in the nucleotide sequences emerged, and in six cases phylogenetic analysis showed that the viruses responsible for the two episodes belonged to different clades [9–11,13,16,19].

Regarding clinical differences between the two episodes, in 10 cases the first episode was more severe than the ensuing episode, whereas in seven cases the ensuing episode was more severe. In four cases, there was no difference in severity and in two cases both episodes were asymptomatic.

Table 1 shows the main characteristics of the cases and of the different episodes of SARS-CoV-2 infection.

Discussion

Since antibody titre has been proved to be significantly lower in asymptomatic/pauci-symptomatic persons

Table 1. Cases from literature source undergoing SARS-CoV-2 reinfection.

Ref.	Country	Patient (sex, age)	Comorbidities	Hospital admission (episode)	Symptoms during first infection	Symptoms during second infection	More severe episode	Time between episodes (weeks)	Nasopharyngeal swab PCR test	Serology (Ig anti-SARS-CoV-2)	Viral genome analysis
[7]	Turkey	F, 23[a]	None reported	None	Fever (39 °C), chills, fatigue, cough, headache, sore throat, muscle and joint pain	Fever (38.7 °C), chills, fatigue, loss of appetite, anosmia and ageusia, muscle and joint pain	Similar	16	Positive at each episode, two intermediate negative swabs.	Serology following 1st episode not available. IgG positive on day 25 from 2nd episode.	Not performed
[8]	Italy	M, 69	Smoker	Both	Bilateral pneumonia. During hospitalization diagnosis of Hodgkin lymphoma	Pneumonia (patient had started chemotherapy)	Similar	16	Positive at each episode, two intermediate negative swabs.	IgG positive on day 50 from 1st episode.	Not performed
[9]	South Korea	F, 21	Allergic rhinitis	Both	Sore throat, cough	Cough with sputum	Similar	4	Positive at each episode, four intermediate negative swabs.	The antibody levels increased 10 days after onset of reinfection (about 5 weeks from the 1st episode).	Different clades of the virus isolate in the two episodes (clade V and clade G, respectively)
[4]	UK	M, 82	Atrial fibrillation, congestive cardiac failure, aortic stenosis, abdominal aortic aneurysm, diabetes, lung cancer	Not specified	Cough, fever, sore throat, dyspnoea, hypoxia, haemoptysis	Fever, cough, dyspnoea	Similar	12	Positive at each episode, five intermediate negative swabs.	IgG positive at the beginning of the 2nd episode	Not performed
		F, 62[a]	None	Not specified	Cough, fever, dyspnoea	Asymptomatic	1st	12	Positive at each episode, one intermediate negative swab.	IgG positive 9 weeks after the onset of the 1st episode and 1 week after the 2nd one	Not performed
[10]	Hong Kong	M, 33	None	Both	Fever, headache, cough for 3 days	Asymptomatic	1st	20	Positive at each episode, two intermediate negative swabs.	IgG negative after the onset of the 1st episode and at the onset of the 2nd. IgG positive 5 days after the 2nd episode.	Different clades of the virus isolate in the two episodes (clade V and clade G, respectively)
[11]	Belgium	F, 51	Asthma	None	Fever, myalgia, coughing, chest pain, dyspnoea, anosmia	Similar symptoms to first episode, but milder and shorter lasting	1st	12	Positive at each episode.	IgG positive at the onset of the 2nd episode (not performed before).	Different clades of the virus isolate in the two episodes (lineage B and lineage A)
[12]	Israel	F, 20	None	None	Mild fever and cough	None	1st	15	Positive at each episode, two intermediate negative swabs.	IgG positive at the onset of 2nd episode (not performed before).	Not performed
[13]	USA	M, 60 s	Emphysema, hypertension, atrial fibrillation	Both	Severe pneumonia with respiratory failure	Pneumonia	1st	20	Positive at each episode, two intermediate negative swabs.	IgG positive the first weeks after the 2nd episode (not performed before).	Different clades of the virus isolate in the two episodes (lineage B and lineage A respectively)
[14]	France	M, 42	Not reported	None	Dyspnoea, fever, headache, diarrhoea, abdominal pain, ageusia, anosmia	Fever, nasal burning, anosmia and ageusia	1st	20	Not performed.	IgG weakly positive 2 months after the 1st episode. IgG highly positive 1 month after the 2nd episode (not witnessed by a positive nasal swab for SARS-CoV2).	Not performed

(*continued*)

Table 1. Continued.

Ref.	Country	Patient (sex, age)	Comorbidities	Hospital admission (episode)	Symptoms during first infection	Symptoms during second infection	More severe episode	Time between episodes (weeks)	Nasopharyngeal swab PCR test	Serology (Ig anti-SARS-CoV-2)	Viral genome analysis
	Spain	F, 38[a]	Not reported	1st	Dyspnoea, fever, headache and diarrhoea	Fever, headache, anosmia and ageusia	1st	23	Positive at each episode, one intermediate negative swab.	Not performed.	Not performed
[15]	Italy	F, 48[a]	None	None	Dry cough and mild fever	None	1st	15	Positive at each episode, four intermediate negative swabs.	IgG positive at the end of the 1st episode and after 1 month. IgG highly positive 3 weeks after the 2nd episode.	Not performed
[16]	France	M, 70	Dementia	Not specified	Fever and cough	Asymptomatic	1st	17	Positive at each episode, three intermediate negative swabs.	IgG negative 2 weeks after the 1st episode but positive 2 weeks later.	Different clades of the virus isolate in the two episodes (Nextrain clade 20A and Marseille 4 lineage, respectively)
[17]	UK	M, 25[a]	None	None	Fever and headaches for 3 days, severe fatigue for 3 weeks	Coryzal symptoms	1st	25	Negative at first episode, positive at second.	IgG positive 1 month after the 1st episode.	Not performed
[18]	USA	M, 25	None	2nd	Sore throat, cough, headache, nausea and diarrhoea	Pneumonia with respiratory failure	2nd	8	Positive at each episode, one intermediate negative swab.	IgM and IgG positive 6 days after the onset of the 2nd episode (never performed before).	Genetically significant differences between the two variants of the same Nexstrain clade 20°C with different mutations in each episode of infection.
[19]	Ecuador	M, 46	None	None	Headache and drowsiness	Odynophagia, nasal congestion, fever of 38.5 °C, strong back pain, productive cough, dyspnoea	2nd	9	Positive at each episode, one intermediate negative swab.	IgM positive and IgG negative 4 days after the onset of the 1st episode. IgM and IgG positive 1 month after the 2nd episode.	Different clades of the virus isolate in the two episodes (clade A and clade B, respectively)
[20]	USA	M, 42[a]	None	None	Cough, fever, myalgias	Pneumonia, fever, cough, shortness of breath and gastrointestinal symptoms	2nd	8	Positive at each episode.	IgG positive about two weeks from the onset of the 2nd episode (not performed before).	Both specimens belonged to the 20 °C clade, but presented different single nucleotide variants
[21]	Rhode Island, USA	M, 70s	Obesity, chronic low back pain, neuropathy, asthma, OSAS, hypertension	2nd	Dyspnoea ($SO2 > 90\%$)	Fever and pneumonia with respiratory failure	2nd	28	Positive at each episode.	IgG negative at the onset of the 2nd episode.	Not performed
[22]	Brazil	F, 36[a]	None	2nd	Rhinorrhoea, sore throat, low fever, diarrhoea, asthenia and mild headache; erythematous vesicles	Pneumonia Ageusia and anosmia	2nd	12	Positive at the 1st episode, then repeatedly negative.	IgG negative 3 weeks after the onset of the 1st episode. IgM and IgG positive 3 weeks after the 2nd episode and still positive after 5 weeks.	Not performed
[23]	Qatar	F, 46	Asthma	None	Sore throat	Sore throat, fever and body pain	2nd	12	Positive at each episode, one intermediate negative swab.	Not performed.	Not performed

(*continued*)

Table 1. Continued.

Ref.	Country	Patient (sex, age)	Comorbidities	Hospital admission (episode)	Symptoms during first infection	Symptoms during second infection	More severe episode	Time between episodes (weeks)	Nasopharyngeal swab PCR test	Serology (Ig anti-SARS-CoV-2)	Viral genome analysis
[24]	Qatar	M, 57	Diabetes	2nd	Asymptomatic	Fever, myalgia, headache, productive cough	2nd	12	Positive at each episode, two intermediate negative swabs.	IgM and IgG positive at the onset of the 2nd episode.	Not performed
[25]	India	M, 25[a]	None	None	Asymptomatic	Asymptomatic	Similar	14	Positive at each episode, one intermediate negative swab.	Not performed.	Analysis of the two genomes revealed 9 unique variant differences between the virus isolates from the two episodes
		F, 28[a]	None	None	Asymptomatic	Asymptomatic	Similar	15	Positive at each episode, one intermediate negative swab.	Not performed.	Analysis of the two genomes revealed 10 unique variant differences between the virus isolates from the two episodes

[a]Healthcare worker.

compared to patients who developed critical illness [26], it has been hypothesized that patients experiencing only mild symptoms during the first episode may develop a weaker immune response which might explain predisposition to the reinfection. However, antibodies are only one marker for immunity, which is also influenced by T cell-mediated immunity. Tan et al. [2] showed that all the patients they investigated, including those with mild symptoms, developed a cellular immune response to SARS-CoV-2 antigens, and this is promising in terms of protection from reinfections. On the other hand, other authors [20] have suggested possible mechanisms to explain a more severe second infection, including immune enhancement, acquisition of a more pathogenic strain, and a greater viral inoculum load. Some people who have experienced a first infection might have immune cells that are primed to respond in a disproportionate way again the second time, and antibodies could be implicated in the so-called phenomenon of antibody-dependent enhancement [21].

From our analysis conducted on a total sample of 23 cases with documented reinfections retrieved from literature, a clear pattern of the second episode being less severe (due to acquired immunity) or more severe (due to immune enhancement) did not emerge. Most of the persons described were immunocompetent, and most did not present any comorbidity at all. Of the cases where serology was available, most cases had developed antibodies following a first infection, a confirmation that effective immunity depends not on antibodies alone. Healthcare workers are heavily represented in this sample (nine out of 23 cases), probably due to a selection bias, as healthcare workers tend to be subjected to PCR testing more frequently than the general population; however, the 12-week time lapse and confirmation by viral genome analysis criteria suggest they represent cases of real reinfections, rather than cases of prolonged viral shedding. There is no clear evidence from the analysis of these few patients indicating that they had low-degree immune response, even if in one case IgG was negative 3 weeks after the onset of the first episode [22]. It should be observed that immunocompetent persons are in the majority, thereby statistically more likely to be exposed; in the case of healthcare workers especially, immunocompromised individuals often have significantly reduced exposure from shielding measures which could account for their absence in reinfection cases.

Iwasaki underlined that it is not known how frequently reinfections really occur, since asymptomatic

cases can only be picked up by routine testing, and the phenomenon of asymptomatic reinfections is probably severely underestimated [27]. Our data, in which two retrieved cases were asymptomatic at both episodes, support the existence of multiple asymptomatic episodes, and therefore the probable underestimation of their prevalence.

Despite the uncertainty around the real rate of reinfection, it is perhaps reassuring to have a relatively small sample of confirmed reinfections worldwide given the scale of total infections: if reinfection was likely to occur in an individual case of COVID-19 (within a time period of months) one might expect a much larger sample of proven reinfection cases to already exist in the literature.

In the 10 cases in which genome analysis of the viruses was performed, significant differences emerged, indeed in most cases membership to different clades. This raises the worrying question of what degree of cross-immunity exists to viruses belonging to different clades.

Further studies are warranted as many questions still need to be answered [28]. Issues needing to be addressed include how a first infection by SARS-CoV-2 impacts on the predisposition to and the severity of the disease occurring with subsequent reinfections, how often they occur, and the reasons why; finally, as vaccination programs are ongoing and patients with known history of SARS-CoV-2 infection were excluded from clinical trials [29,30], when should persons who have already been infected by SARS-CoV-2 be vaccinated.

Disclosure statement

The authors report no conflict of interest.

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