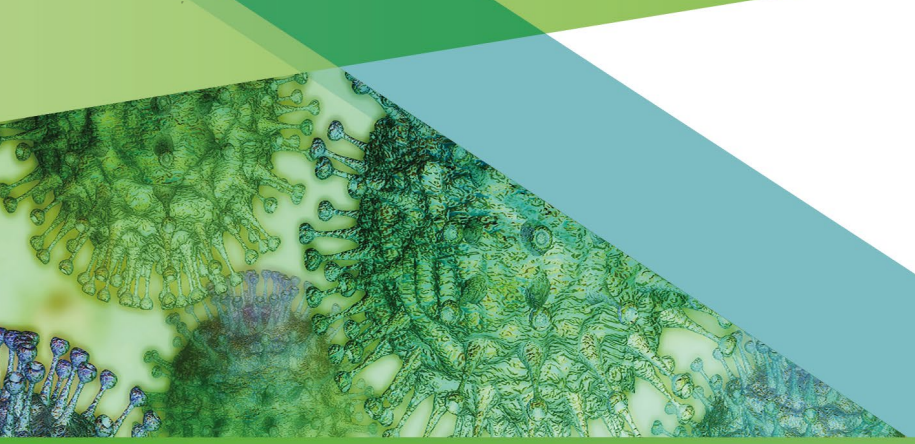


Threat Assessment Brief

Reinfection with SARS-CoV-2: considerations for public health response

21 September 2020

Introduction

Cases with suspected or possible reinfection with SARS-CoV-2 have been recently reported in different countries [1-4]. In many of these cases, it is uncertain if the individual's Polymerase Chain Reaction (PCR) test remained positive for a long period of time following the first episode of infection or whether it represents a true reinfection.

The aim of this Threat Assessment Brief is to elucidate the characteristics and frequency of confirmed SARS-CoV-2 reinfection in the literature, to summarise the findings about SARS-CoV-2 infection and antibody development, and to consider the following questions:

- How can a SARS-CoV-2 reinfection be identified?
- How common are SARS-CoV-2 reinfections?
- What is known about the role of reinfection in onward transmission?
- What do these observations mean for acquired immunity?

Finally, options for public health response are proposed.

Issues to be considered

- Some patients with laboratory-confirmed SARS-CoV-2 infection have been identified to be PCR-positive over prolonged periods of time after infection and clinical recovery [5,6].
- The duration of viral RNA detection (identification of viral RNA through PCR testing in a patient) has been shown to be variable, with the detection of RNA in upper respiratory specimens shown up to 104 days after the onset of symptoms [7-9].
- Of note, patients have also been reported to have intermittent negative PCR tests, especially when the virus concentration in the sampled material becomes low or is around the detection limit of a test [4].
- It is important to note that the identification of SARS-CoV-2 RNA through PCR (i.e. viral RNA shedding) does not equate to the presence of viable, infectious virus within a patient.
- Additional challenges to classifying suspected cases as 'confirmed' reinfections have been the absence of testing results and the lack of genetic sequencing. Confirmation is further complicated because common criteria for the identification of reinfections have not yet been established.
- As described below, additional tests must be run to check for viable virus, and when considering an individual patients' situation, test results must be interpreted in combination with additional epidemiological and clinical characteristics.

Suggested citation: European Centre for Disease Prevention and Control. Reinfection with SARS-CoV: considerations for public health response: ECDC; 2020

Event background

Elucidating the characteristics and frequency of reinfection is crucial, as it could impact on our understanding of acquired immunity after natural infection. This section focuses on recent published or pre-print case reports from Hong Kong, Nevada, USA, Belgium, Ecuador and India that describe reinfections based on genetic sequencing as confirmation of second infections with SARS-CoV-2, following a first confirmed infection [10-14]. There are also media reports of cases in the Netherlands, Spain and several additional cases globally that are under investigation and not yet present in the literature [15-18].

Hong Kong

A publication by To et al [10] reports an episode of SARS-CoV-2 infection detected in mid-August 2020, in Hong Kong, in an immunocompetent 33 year old man during routine airport screening, 142 days after the first positive PCR. The patient presented with symptoms of cough, sore throat, fever and headache for three days during the first episode and was hospitalised for isolation purposes, although his symptoms had mostly resolved upon hospitalisation. The patient was discharged two weeks later after two subsequent negative SARS-CoV-2 PCR assays on nasopharyngeal and throat swabs. During the second infection, the patient was asymptomatic and was reported to have a slightly elevated C-reactive protein, a relatively high viral load which decreased over time, and a seroconversion of SARS-CoV-2-IgG, all suggesting that the second episode was a new acute SARS-CoV-2 infection. The patient's reinfection was differentiated from prolonged PCR positivity after the first infection through whole genome analysis. The two SARS-CoV-2 strains belonged to different clades/lineages with 24 nucleotide differences, which is a high amount given the relatively slow rate of mutation observed for SARS-CoV-2 to date. These clades match the epidemiology of the main clades circulating where the patient was likely infected (i.e. the first strain clustered with viruses from Hong Kong while the second strain clustered with viruses from Spain). Viral culture for the second episode was pending at the time of publication.

Nevada, USA

Tillet et al [11], report a case of a 25 year old immunocompetent male with COVID-19-like symptoms of sore throat, cough, headache and nausea who tested positive for SARS-CoV-2 on 18 April 2020, 24 days post-symptom onset. The patient was isolated and his symptoms resolved nine days after testing. The patient tested negative twice in the weeks following symptom resolution and felt well until 31 May 2020, when the patient sought care for fever, headache, dizziness, cough, nausea and diarrhoea. The patient's symptoms worsened five days later, with hypoxia and shortness of breath leading the patient to be hospitalised and to receive oxygen support. A chest x-ray performed at that time indicated viral or atypical pneumonia and RT-PCR was positive for SARS-CoV-2. Seven days post-symptom onset during the second episode the patient was reactive for IgG/IgM for SARS-CoV-2. Specimens from the first and second episodes were available and whole genome sequencing was performed. SARS-CoV-2 sequences determined from both episodes were found to cluster in the same clade, but with seven nucleotide differences between them. The authors used the substitution rate which calculates the number of mutations over a respective time period and compared the result of the difference between the two viruses, with the expected substitution rate of naturally occurring mutations in SARS-CoV-2 viruses in general over the same time period. The calculations for the difference between episode one and two resulted in a value of 83.6, which by far exceeded the currently observed naturally occurring substitution rate of 23.1, and suggested two independent infections with different viruses. Viral culture and sub-genomic RNA were not performed.

Belgium

Van Elslande et al [12] reported a case of reinfection in a 51 year old woman who presented with headache, fever, myalgia, cough, chest pain, dyspnoea and anosmia to her general practitioner on 9 March 2020. The patient was immunocompetent, but took a daily dose of oral corticosteroids for asthma. A nasopharyngeal swab was positive for SARS-CoV-2 with a Ct value of 25.6. The patient self-isolated at home and reported persistent symptoms for nearly five weeks. Three months (10 June 2020) after her initial symptoms, the patient presented with headache, cough, fatigue and rhinitis. Her nasopharyngeal swab was again positive for SARS-CoV-2 (Ct value 32.6). The symptoms lasted for one week and again resolved without hospitalisation. Neutralising antibodies were assessed six weeks after the second episode's symptom onset and were present at that time (1/320). Full length genome sequencing showed 11 differences between the two episodes' isolates, confirming infection with different strains. Viral culture was not performed, and neutralising antibodies were not assessed between the two episodes.

Ecuador

Prado-Vivar et al [13] report a case of reinfection in a 46 year old immunocompetent male who presented on 12 May 2020 after three days of headache and drowsiness. At 11 days post-symptom onset, an oropharyngeal swab was positive for SARS-CoV-2 with a Ct value of 36.85 (ORF3a gene). The patient's symptoms improved and a repeat PCR on 3 June 2020 was negative. . In July 2020, the patient reported close contact with a relative that was later diagnosed with COVID-19. Two days following this contact, on 20 July 2020, the patient presented with symptoms including headache, fever, cough and shortness of breath. On 22 July 2020, another oropharyngeal sample tested positive for SARS-CoV-2 (no Ct values reported). Although the patient's symptoms during the second episode were more severe than the first episode, hospitalisation was not required. Qualitative IgG/IgM was negative for IgG and positive for IgM on 16 May 2020; a test for antibodies on 18 August during the second episode was positive for IgG and IgM. Genome sequencing and phylogenetic analysis showed that the infection episodes belonged to different clades with nine variant differences. Viral culture was not performed, and neutralising antibodies were not assessed between the two episodes.

India

Gupta et al [14] report two cases of reinfection, both in immunocompetent health workers posted in the COVID-19 unit at a tertiary hospital in India. Patient I1, a 25 year old man, was found PCR positive on 5 May 2020 (Ct: 36) during routine surveillance of health workers. He was asymptomatic but isolated as per institutional policy until he became PCR negative. He continued working thereafter and was found PCR-positive again on 17 August (Ct 16.6). The patient was again isolated and remained asymptomatic throughout the second episode. Antibody testing, neutralising antibodies and viral culture results were not reported. Sequencing of samples from both episodes was performed along with genomic analysis; the first and second episodes revealed nine variant differences.

Patient I2, a 28 year old woman, was found PCR positive on 17 May 2020 (Ct: 28.16), also during routine surveillance of health workers. She was asymptomatic but isolated as per institutional policy until she became PCR negative. She continued working thereafter and was found PCR-positive again on 5 September (Ct 16.92). The patient was again isolated and remained asymptomatic throughout the second episode. Antibody testing, neutralising antibodies and viral culture results were not reported. Sequencing of samples from both episodes was performed along with genomic analysis; the first and second episodes revealed 10 variant differences. A genetic variation 22882T>G (S:N440K) within the receptor-binding domain was detected in the sample from the second episode.

Summary of the results of recent published or pre-print case reports

Commonalities and differences in the six confirmed reinfection cases reported are presented in Figure 1 and Table 1. All six reported reinfections were in relatively young and, according to the information available, generally immunocompetent individuals. Four of the patients reported symptoms during the first episode of their infection while the two asymptomatic cases in India were detected during routine surveillance of health workers. The clinical presentation in the reinfection episode differed across the six cases: three reinfections were likely asymptomatic, one person showed mild symptoms, one showed moderate symptoms and one required hospitalisation with oxygen support. Information on antibody response in the studies remains incomplete. In the Hong Kong [10] and the Ecuadorian case [13], the patients tested negative for IgG after symptom onset of the first episode (at 10 and four days, respectively). Antibody testing was not performed in connection with the first episode for the Belgian or Nevada patients, and was not performed at all for the Indian patients.

Figure 1. Reported cases of reinfection and key information

Location	Age of patient	First episode	Interval	Second episode	Publication
Hong Kong	33 years	Symptomatic	142 days	Asymptomatic	Peer-reviewed
Nevada, USA	25 years	Symptomatic	48 days	Symptomatic with hospitalisation	Pre-print
Belgium	52 years	Symptomatic	93 days	Symptomatic	Peer-reviewed
Ecuador	46 years	Symptomatic	63 days	Symptomatic	Pre-print
India	25 years	Asymptomatic	108 days	Asymptomatic	Pre-print
India	28 years	Asymptomatic	111 days	Asymptomatic	Pre-print

Table 1. Clinical characteristics and laboratory information from COVID-19 reinfection cases

Country (reference)	Age and general health status	Time between episodes (positive PCRs)	Clinical characteristics	Timing of RT-PCR and Ct values	Sequencing	Antibody testing
Hong Kong (To et al) [10]	33 year old male, immunocompetent	142 days	1st episode: fever, cough, headache. 2nd episode: asymptomatic (identified at routine airport screening).	1st episode: positive test three days post symptom onset: Ct 30.5* 2nd episode positive test - days 1-3: Ct 26-28; day 5: Ct 32	First and second viral genomes belonged to different clades/lineages, differing by 24 nucleotides. 1st episode: Nextstrain 19A/GISAID V/Rambout lineage B.2 Clusters with viruses from Hong Kong. 2nd episode Nextstrain 20A/GISAID G/Rambout B.1.79 Clusters with viruses from Spain.	1st episode: IgG negative 10 days post-symptom onset. 2nd episode: IgG negative 1-3 days post-hospitalisation, reactive day 5.
Nevada, USA (Tillett et al) [11]	25 year old individual, immunocompetent	48 days	1st episode: sore throat, cough, headache, diarrhoea. 2nd episode: fever, headache, dizziness, cough→ hypoxia, hospitalisation and oxygen therapy required.	1st episode, positive test day 24 post symptom onset Ct 35.2 2nd episode day six post symptom onset Ct 35.3	First and second viral genomes belonged to the same clade (Nextstrain 20C) differing by seven nucleotides.	1st episode: no antibody testing performed. 2nd episode, seven days post symptom onset: IgG/IgM reactive.
Belgium (Van Elslande et al) [12]	51 year old woman, daily inhaled corticosteroids	93 days	1st episode: headache, fever, myalgia, cough, chest pain, dyspnea. Not hospitalised but some persistent symptoms for five weeks. 2nd episode: headache, cough, fatigue.	1st episode: Ct 25.6 (N1-gene)* 2nd episode: Ct 32.6 (N1-gene)*	First and second viral genomes belonged to different clades, differing by 11 nucleotides. 1st episode: Rambout lineage B.1.1/. 2nd episode: Rambout lineage A.	1st episode: no antibody testing performed. 2nd episode one week post-symptom resolution: IgG reactive with a value of 134 (Roche). 2nd episode, six weeks after symptom onset: neutralising antibodies reactive with a value of 1/320.
Ecuador (Prado-Vivar et al) [13]	46 year old man, immunocompetent	63 days	1st episode: headache, drowsiness. 2nd episode: fever, cough, shortness of breath, sore throat. More severe than first episode although hospitalisation was not required.	1st episode: positive test 11 days post symptom onset, Ct 36.85 (ORF3a gene) 2nd episode: positive test 4 days post-symptom onset	First and second viral genomes belonged to different clades: 1st episode: Nextstrain 20A/GISAID B1.p9 lineage. 2nd episode: Nextstrain 19B/GISAID A.1.1 lineage	1st episode: IgG negative 4 days post-symptom onset. 2nd episode: IgG positive (Ac anti SARS-CoV-2 IgG: 34.1) 30 days post-symptom onset
India, patient I1 (Gupta et al) [14]	25 year old man, immunocompetent*	108 days	Both episodes, asymptomatic (identified through routine screening of health care personnel)	1st episode: positive on diagnosis, Ct 36 2nd episode, positive on diagnosis, Ct 16.6	First and second episodes revealed 9 unique variant differences.	Antibody testing not reported
India, patient I2 (Gupta et al) [14]	28 year old woman, immunocompetent*	111 days	Both episodes, asymptomatic (identified through routine screening of health care personnel)	1st episode: positive on diagnosis, Ct 28.16 2nd episode, positive on diagnosis, Ct 16.92	First and second episodes revealed 10 unique variant differences. Genetic variation 22882T>G (S:N440K) within the receptor-binding domain found in second episode.	Antibody testing not reported

**personal communication with the papers' corresponding author. Ct: Cycle threshold*

SARS-CoV-2 infection and antibody development

The protective role of antibodies or T-cell-induced immunity against SARS-CoV-2 is still not understood. However, antibody identification/antibody titres are usually recognised as a reasonable correlate of antiviral immunity, and anti-receptor-domain antibody levels are known to correspond to plasma viral neutralisation activity [19]. Binding and neutralising antibodies to SARS-CoV-2 have been seen to develop in most individuals sometime between day 10 and day 21 after infection [20-23]. Reviews of the published literature indicate that most patients (>91%) develop IgG seropositivity and neutralising antibodies (>90%) following primary infection with SARS-CoV-2.

The long term longevity of the antibody response to SARS-CoV-2 still needs to be determined, but it is known that antibody levels to other coronaviruses do wane over time, (range: 12–52 weeks from the onset of symptoms) and homologous reinfections have been shown [24]. SARS-CoV-2 antibody levels have been seen to remain up to 94 days [4] after infection, and recent studies depict that the antibody titres peak between 3-4 weeks, and remain relatively stable up to 4 months after diagnosis [25]. Nevertheless, the neutralising activity significantly decreases over time [26-29]. The magnitude and time period of decreasing antibody levels as well as the impact of cellular immunity has not been sufficiently studied on larger population groups over extended periods, adding limitations to the interpretation.

It has been discussed that the magnitude of the antibody response appears to be associated with disease severity [30] and there are indications that antibody-related immunity against SARS-CoV-2 may not be long-lasting in persons that experienced asymptomatic infection or mild illness [28]. Wang et al observed that the antibody response in such mild illness patients was significantly lower, with lower levels of IgM response and lower levels of neutralising antibodies, when compared with severe COVID-19 patients [31].

These results together indicate that most patients do appear to mount an immune response following a first SARS-CoV-2 infection, but that this immunity may wane over time. This appears to be more likely in individuals with a less severe primary infection; which would be the case for the six patients described in the six studies above.

Assessment questions

- How can a SARS-CoV-2 reinfection be identified?
- How common are SARS-CoV-2 reinfections?
- What is known about the role of reinfection in onward transmission?
- What do these observations mean for acquired immunity?

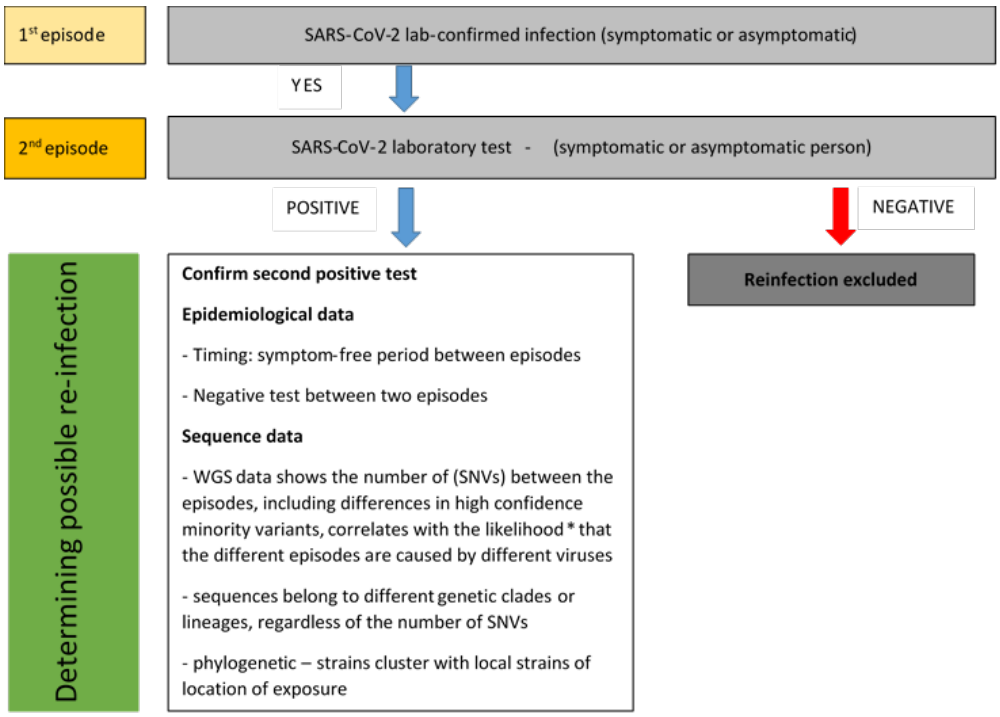
How can a SARS-CoV-2 reinfection be identified?

In order to differentiate cases that are SARS-CoV-2 RNA positive over longer periods of time, possibly with prolonged viral shedding, from cases with a true reinfection, epidemiological and virological information from each infection episode need to be assessed thoroughly.

COVID-19 compatible symptoms in a person that has tested SARS-CoV-2 positive need to be assessed and a swab should be taken for diagnostic analysis. During winter months, other respiratory viruses, such as seasonal influenza cause COVID-19 similar symptoms and should be considered as differential diagnoses. Outlined below are the following main criteria that should be fulfilled to identify a true reinfection in combination with an overall clinical assessment of an individual:

- Laboratory confirmation of two infections by two different strains (minimum distance to be determined or supported by phylogenetic and epidemiological data) with timely separated illness/infection episodes (minimum time period to be estimated), as depicted in Figure 2.

Figure 2. Flow chart for assessing a reinfection in a previously confirmed COVID-19 case



* The virus is expected to mutate by approximately 2 SNVs per month

SNV: single nucleotide variations

WGS: Whole genome sequencing

Additional investigation of suspected or confirmed/probable reinfections, with the aim of further validating that reinfection occurred and documenting the patient and exposure-related features of the two infection episodes can add to our understanding of the determinants of reinfection. Such understanding could further support and guide public health authorities in their actions. These additional investigations could seek to provide the following information:

- Epidemiological information
  - Age, sex
  - Results from investigations of possible exposure.
- Clinical information
  - Presence and severity of symptoms (if any) in both episodes
  - Clinical course of each episode, time-to-detection and recovery time
  - Extent of symptom resolution (if any) between the two episodes
  - Inflammatory parameters that indicate acute infection (e.g. C-reactive protein)
  - Existence of underlying disease/immunosuppressive therapy/immune modulators (diminished immune response)
  - Time elapsed between the first episode and the suspected second episode of infection.
- Information on testing / by test result and specimen
  - Testing methodology
  - Timing of testing
  - Place and reason of testing (e.g. screening border, primary care, hospital emergency, or inpatient hospitalisation)
  - Specimen type (e.g. respiratory, saliva)
  - For RT-PCR results – Ct values.
- Immune assessment tests
  - Duration/persistence, type and titres of antibodies [range]
  - Detection of neutralising antibodies
  - If available: paired serological specimens from both the first (day 0 and 14) and the second infection (day 0 and 7, possibly also day 14)
  - T cell immunity and biomarkers such as CD40L.

- Virus culture from multiple specimen types
- Comparative genomic analyses
  - WGS [32,33] – the number of single nucleotide variations (SNVs) between the episodes, including differences in high confidence minority variants, correlates with the likelihood that the different episodes are caused by different viruses [31]. The virus is expected to mutate by approximately two SNVs per month.
  - Stronger evidence of reinfection if the sequences recovered from the two episodes belong to different genetic clades [34] or lineages [35], regardless of the number of SNVs.

Factors to consider in assessing the evidence for a second SARS-CoV-2 infection.

False positivity: Although the likelihood is small, the possibility of a false positive SARS-CoV-2 RT-PCR test should be considered and ruled out. In low prevalence settings, the positive predictive value of a test may be lower, even in tests with good sensitivity and specificity. Tests can also be false positive due to contamination or human error during sample collection, transport or analysis.

Time period: As listed above, the time period elapsed since the first episode can be supportive information together with the serological analyses, when considering a potential reinfection. A longer time-lapse would relate to waning immunity and lower antibody levels, therefore probably increasing the likelihood of a second infection. If the elapsed time is short between one of these confirmatory negative tests and a subsequent positive PCR test, re-detection of the primary episode is a more likely cause than a true reinfection. More information on reinfections and duration of time periods between episodes is needed to develop time threshold to guide further investigation of suspected reinfections.

Infectious virus identification: Another aspect to consider is that RT-PCR results can remain persistently positive due to the detection of viral RNA fragments, even if viable virus would not be present in the patient/sample. The following tests and information could help to rule out either a persistent infection with viable virus (i.e. RNA from live virus), and that of shedding of non-viable virus remnants (i.e. RNA from none-viable virus) after a primary infection:

- Virus culture can be used to verify whether the prolonged PCR positivity is just a result of non-viable viral RNA shedding (i.e. non-viable virus) or the result of persistent, infectious viral RNA shedding (i.e. viable virus). If the culture is negative for viable virus, then the detected viral RNA from the PCR is a likely result of non-viable viral RNA shedding and thus not an ongoing infection. If viable virus is identified through culture, further investigation is needed to assess whether the viable virus from the second episode is indeed the result of a secondary infection by a different viral strain.
- The quantification of viral load through the cycle threshold (CT) of a PCR could be used as an indirect measure for viable virus as it has been seen to correlate with the detection of viable virus. In a recent pre-published study, authors describe that the probability of isolating infectious SARS-CoV-2 from a patient sample was less than 5% when the viral load, determined though RT PCR, was below 6.6^{10} RNA copies/mL (95% CI 6.2 – 6.9) [36]. However, an assessment of the public health and clinical value of this approach remains to be established and validated; and is therefore of limited public health value at this stage.

Sequence/phylogenetic analysis: Whole genome sequencing of the virus can support to assess whether the second episode is caused by a different virus variant compared with the first. Sequence/phylogenetic differences identified in viruses between the two apparently separate episodes of infection need to be assessed carefully, as the virus can also mutate within the host itself (i.e. while the host is infected), and since double infections are plausible (i.e. being infected simultaneously with two different strains of virus).

How common are COVID-19 reinfections?

Reinfections occur with other seasonal coronaviruses, and reinfections with another Betacoronavirus, hCoV-OC43, have been reported after 90 days [37,38]. A model of the protective immunity and reinfection dynamics of hCoV-OC43 and hCoV-HKU1 estimated that the average period of protective immunity was 45 weeks [39]. It has also been shown that the risk of reinfection with other coronaviruses is not necessarily tied to waning antibody titres, but can occur in the presence of relatively high and stable antibody titres [37].

A study by Abu-Raddad et al [40] of 133 266 laboratory confirmed cases identified 243 cases with positive swabs more than 45 days following their first SARS-CoV-2 episode and found that 54 cases had evidence of reinfection (second positive PCR with Ct values <30 or contextual information supporting the re-appearance of symptoms). In this study, no whole genome sequencing, viral culture or detection of sub-genomic RNA was performed, leaving uncertainty around whether the cases detected were true reinfections rather than long-term RNA positives or viral shedders. Still, the study estimated the risk of reinfection to be very low at 0.04% (95% CI: 0.03-0.05%), and the incidence rate of reinfections to be 1.09 (95% CI: 0.84-1.42) per 10 000 person-weeks.

Only six confirmed cases of SARS-CoV-2 reinfection have, to date, been published. More potential cases of reinfection are reported in the media and are under investigation, which will help to understand the likelihood and possible conditions that allow a second infection in a previous case. It is likely that the currently reported cases are an under-estimate due to lack of comprehensive testing, particularly early in the pandemic and, still today, among asymptomatic persons. So whilst we can foresee an increase in identified reinfection cases as testing capacity and testing rates increase (including of mild or asymptomatic individuals), at present, the evidence indicates that reinfection is an uncommon event. Challenges in adding to the current evidence-base in the near future include the possible lack of availability of results of investigations of an individual's first episode, and/or retaining stored laboratory samples from a first episode.

What is known about the role of reinfection in onward transmission?

In the six cases highlighted above there has been no evidence of onward transmission from the re-infected individuals to any close contacts.

There is furthermore very limited evidence from the scientific literature on the potential infectiousness of a re-infected individual (whether symptomatic or asymptomatic). Five studies of individuals with suspected reinfection were included in a recent review on the potential infectiousness of SARS-CoV-2 [4]. No transmission was reported from any of the supposed re-infected cases to their contacts, however contact tracing and follow-up was only explicitly described in one of the included studies. Care should be taken in interpreting the results of this particular review however, as all five included studies were each based on small sample sizes of individuals and furthermore, actual reinfection (i.e. infection by two separate viral strains) had not been established through viral sequencing, meaning that these observed cases might not have been actual events of reinfection.

Considering the limited evidence about onward transmission from re-infected cases to their contacts and applying the precautionary principle, asymptomatic and symptomatic re-infected individuals should be managed similarly to individuals with a first infection.

What do these observations mean for acquired immunity?

To date, SARS-CoV-2-specific IgG antibodies have been detected in nearly all individuals at the end of the follow-up period (up to 94 days) and over 90% of individuals who have been infected develop a neutralising antibody response [4]. In experimental animal models, infection with SARS-CoV-2 was been shown to protect rhesus macaques from subsequent challenge [41]. We do not know the duration of immunity following a SARS-CoV-2 infection and solid evidence on the role of antibodies in the clearance of the virus is lacking.

Reinfections are possible but the circumstances, associated symptoms and disease progression as well as the overall extent has yet to be extensively investigated and understood. The patient described by To et al did not have any detectable antibodies at the time of reinfection, but developed detectable neutralising antibodies after the episode of reinfection [10]. The antibody status in the cases reported by Tillett et al and Van Elslande et al was not measured after the patient's first infection, but antibody responses were observed following their second infection [11,12]. The case reported by Prado-Vivar et al detected no antibodies during the first episode of infection, although these were measured only four days post-symptoms onset; antibodies were present after the second episode of infection [13]. The role of antibodies and level of neutralising antibodies, as well as the time period between infection and decrease in antibody levels to a level conveying lower protective capability, have not yet been defined, and need to be investigated on larger population groups. The virus isolates in the described reinfection cases were confirmed to house different mutations, confirming infections with new virus variants in the patients. The number of mutations as well as the positions of the mutations in the genome might help to understand the possibility of reinfections and possible immune response escape. Investigations should also analyse the possibility of common mutations in the viral genomes from re-infected patients that could explain the virus's ability to re-infect. Furthermore, the level of divergence that a SARS-CoV-2 isolate needs in order to be able to re-infect a previously infected person needs to be understood.

The role of cellular immunity in the prevention of COVID-19 reinfection was not studied in the reported cases and needs to be investigated.

Options for public health response

Considerations for clinical management, contact tracing, isolation and infection prevention and control

The possibility of reinfection implies that individuals that have been infected once cannot be definitively considered to be immune. Although so far confirmed reinfections appear to be very uncommon events, more evidence and longer follow-up time is required to better understand duration of immunity, transmissibility and the likelihood and implications of reinfection. Given what is known currently, clinical management, infection prevention/control and contact tracing considerations are not likely to differ for a second infection as compared to individuals infected for the first time. Please refer to ECDC guidance on infection prevention and control [42], discharge and end of isolation criteria [43] and contact tracing [44].

Considerations for PCR/antibody testing and risk management for individuals re-exposed to SARS-CoV-2 following a previous infection

ECDC performed a survey of Member States to identify current approaches for the management of previously confirmed cases who have been re-exposed to SARS-CoV-2. Five countries replied. Three countries responded that they manage potential reinfections in the same way as the first infection or that they do not have a specific policy for management of re-exposures. Two countries only test potential cases of re-exposure if a time period of at least two or three months, respectively, has elapsed since the first episode. One country recommends testing for re-exposure in previously positive individuals in cases of severe illness requiring hospitalisation. The countries holding policies to test only after a specific time period passes do not require quarantine of the re-exposed individuals during that time. One country recommends that previously positive individuals who are re-exposed after three months should be quarantined until PCR results are available; they should be tested two days following the re-exposure and, if negative, be tested again after a further two days. If negative with two PCR tests, then the quarantine is lifted.

Due to the very limited number of reported cases of confirmed reinfection, it is not known what the risk of reinfection is among individuals who previously had COVID-19, however it cannot be ruled out [40]. Although there are no documented cases of onward transmission from a re-infected case, knowledge on this is also still evolving. Risk assessment, including relevant laboratory investigations, may be made for re-exposed cases, taking into account the overall immune status of a re-exposed individual, the results of antibody testing, and the level of contact that the individual has with vulnerable populations in order to assess the best method of managing and following them for potential disease development and risk of further transmission. While low level of exposure is by itself an indicator of a low risk of developing infection, a negative PCR test following repeat exposure, in the context of a positive IgG test, may also be considered indicators of lower risk of developing infection. Decisions on risk management need to take into account that the evidence on the protective immunity and the correlates of antibody levels with viral clearance is currently limited. Nonetheless, the testing of individuals that had a previous infection for SARS-CoV-2, if they are again exposed to a COVID-19 case after their first episode of the disease, would not only inform individual case assessments but also improve the current limited evidence-base on the risks of re-infection.

The suggestions above are based on limited evidence which is expected to evolve. ECDC will continue to reassess the evidence and update the options for response for re-infected cases as additional evidence becomes available.

Future considerations to support public health action

This is an emerging area which will impact on the way in which countries in the EU/EEA respond to and monitor COVID-19. The following suggestions are initial areas that ECDC believes may require consideration for public health response.

- There is a need for further studies to provide more robust data for decision-making on areas including duration of immunity, correlation of antibody levels with protective immunity and viral shedding, transmissibility, as well as the likelihood and implications of reinfection, including the infectiousness of re-infected symptomatic and asymptomatic patients.
- There is a need for a case definition to classify reinfections according to standardised laboratory investigations. Criteria for investigating possible reinfections also need to be defined. The US Centres for Disease Control and Prevention (CDC) have proposed such criteria.
- Data on reinfections need to be collected within surveillance systems. Variables to capture reinfections as well as the classification based on certainty would allow for a better understanding of the frequency of reinfection and allow for clinical and epidemiological description of cases.
- An investigation protocol, including clinical case definitions and laboratory procedures would support standardisation of clinical and laboratory investigations and make cross-setting comparisons or data pooling easier.
- Follow-up and analysis of well-defined patient cohorts will provide valuable insights on this topic. Routine testing in health care workers could provide an opportunity to collect systematic data to better understand the prevalence of reinfection in a defined population.
- Guidance and procedures on the management of close contacts will be needed so that they address the management of contacts that have previously had an infection.

Source and date of request

Internal ECDC decision, 4 September 2020

Consulted experts

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Disclaimer

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