

Duration of SARS-CoV-2 Infectivity

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Abstract

After infection with SARS-CoV-2 prolonged SARS-CoV-2 RNA shedding was reported for several weeks. However, the duration of actual infectivity depends on the severity of disease and the immune status of the affected individual. Infectivity is highly unlikely nine days after symptom onset in immunocompetent individuals with a mild course of COVID-19. In patients with critical COVID-19 viable virus was detected in an upper respiratory sample 20 days after symptom onset, in patients with profound immunosuppression (e.g. ongoing chemotherapy) even up to 61 days. The three vaccines licensed in Europe and the US (BNT162b2 by Pfizer-BioNTech, mRNA-1273 by Moderna and the AZD1222 by Oxford-AstraZeneca) have been shown to be effective against risk of transmission and symptomatic infection with SARS-CoV-2 wildtype. First studies showed less efficiency against new virus variants, like P.1 or B.1.351. As a result, an individual approach is needed regarding hygiene measurements and isolation.

Manuscript

The ongoing SARS-CoV-2 pandemic led to a high number of deaths worldwide as well as an overload of healthcare systems and an economic collapse. One of the reasons can be attributed to the lack of knowledge about the duration of infectivity at the beginning of the pandemic, resulting in hospital isolation of patients and absence periods of employees. In particular, the absence of healthcare workers placed an unprecedented strain on healthcare systems. Thereupon, at least one negative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test from a respiratory specimen was required for ending isolation [1]. However, prolonged SARS-CoV-2 RNA shedding was reported for several weeks following infection [2-9]. The aim of this paper is to discuss the current state of knowledge about duration of SARS-CoV-2 infectivity and necessity of isolation.

The study performed by Sun et al. [2] investigated viral shedding on individuals with various forms of infection. The median duration of viral shedding in patients with mild infection was 15.6 days in oropharyngeal (OP) swab samples, 20 days in sputum samples, and 22.7 days in nasopharyngeal (NP) swab samples. In individuals with severe disease, the median duration of viral shedding was

33.9 days in throat swab samples, 30.9 days in sputum samples, and 32.5 days in NP swab [2]. A study performed in severely ill, hospitalized patients reported a median viral RNA shedding duration of 53.5 days, reaching a maximum of 83 days [3]. In addition to severe illness, higher age was demonstrated as a risk factor for prolonged viral shedding [4-9].

Concurrently, several studies were performed indicating that viral RNA shedding of SARS-CoV-2 does not relate with infectivity, defined as the detection of cultivable virus. However, the viral load, which is measured as RT-PCR cycle threshold (Ct) values, appears to correlate strongly with cultivable virus. In upper respiratory tract samples, the peak viral load was demonstrated to be approximately 1-2 days before to 3-5 days after symptom onset, followed by a rapid decrease [10-12].

Our previous study reported on the cultivation of viral RNA of NP or OP swabs in 15 healthcare workers, with prolonged detection of viral RNA in RT-PCR (up to 55 days after symptom onset) [13]. Ct values were over 30 in all samples, with all participants asymptomatic at the time of inclusion in the study following a mild or asymptomatic course of disease. Viable virions were not found in any of the taken swabs.

A French study obtained 183 samples from 155 SARS-CoV-2 positive individuals, with samples inoculated in cell cultures. There were no positive culture results from samples with a Ct value > 34 [14].

Wölfel et al. [10] performed longitudinal sampling of NP swabs in nine hospitalized COVID-19 patients with mild disease. Viable virus could not be isolated from samples collected eight days after symptom onset. Furthermore, the data indicated that isolation probability was low when the SARS-CoV-2 RNA load was < 5.4 log₁₀ copies/swab, which corresponds to a Ct value of approximately 29.5.

Bullard et al. [15] examined 90 upper respiratory tract samples from 19 COVID-19 patients with mild disease. Virus growth was not observed in samples with a Ct value > 24 and after more than eight days following symptom onset. The authors state that for every Ct unit increase the odds ratio for infectivity decreases by 32%. Interestingly, a meta-analysis of 79 studies (5340 individuals) concluded that no study detected viable virus beyond nine days of infection [4].

Virological findings in individuals with a mild course of disease predicting a lack of infectivity following eight to nine days are supported by epidemiological data. He and colleagues [16] compared clinical data from 94 COVID-19 patients as well as epidemiologic data of contact persons to evaluate transmission chains and serial intervals. These data indicated that the infectious period started at least two days before symptom onset, with the highest level of infectivity one day after onset, followed by a rapid decline within the following week. The mean serial interval was 5.8 days (4.8–6.8 days). Further contact studies demonstrated a serial interval of 4–5 days [17,18]. There was no transmission reported for 852 contact persons six days after symptom onset of the index person [17].

In summary, a short duration of infectivity can be assumed in immunocompetent individuals with a mild course of COVID-19. Infectivity nine days after symptom onset is highly unlikely. The Centers for Disease and Control Prevention recommend discontinuing quarantine in immunocompetent individuals with a mild disease course without hospitalisation ten days after symptom onset and at least 24 hours with no symptoms (except for anosmia or ageusia) [19]. In most countries (e.g., Germany, USA), health authorities do not request a negative SARS-CoV-2 RT-PCR test to discontinue quarantine.

Severely ill COVID-19 patients and immunosuppressive persons warrant a different view. In patients with pneumonia due to SARS-CoV-2, the viral load in upper respiratory samples can increase initially. The viral load has been documented to be highest during the second week following symptom onset [4]. The high risk of transmission

for healthcare workers in contact with breathing tubes or during intubation must be considered, even if symptom onset exceeds ten days.

In a study of 21 hospitalized COVID-19 patients with pneumonia, the median time from symptom onset to viral clearance in culture was seven days [20]. In one patient with severe disease, viable virus could be cultured in a lower respiratory tract sample up to 12 days after symptom onset. No viable virus was identified in samples with a CT-value ≥ 28.4.

Patients with critical COVID-19 that were admitted to the intensive care unit were demonstrated to potentially shed infectious virus for even longer periods [21]. In a patient with significant immunosuppression, viable virus was detected in an upper respiratory sample 20 days after symptom onset. The mean time of infectious virus shedding was eight days. The authors calculated a probability of less than 5% for isolating infectious SARS-CoV-2 15.2 days following symptom onset or if the viral load was below 6.63 log₁₀ RNA copies/mL. Furthermore, the authors demonstrated a decrease in the potential to grow viable virus with increasing numbers of neutralizing antibodies. Interestingly, viable virus was not detected in patients with neutralizing antibodies at a titre greater than 1:80.

In the study performed by Luo and co-workers [22], 391 SARS-CoV-2 infected index cases were examined in addition to 3410 close contacts. Disease severity correlated with the risk of transmission. The secondary attack rate was 0.3% for asymptomatic, 3.3–5.6% for mild to moderate, and 6.2% for severe or critical cases. Fever and coughing were associated with a higher risk of transmission.

However, the results should be interpreted with care, with a subset of patients being responsible for the majority of infectiousness. It can be assumed that approximately 80% of secondary transmissions are caused by 10–20% of infectious individuals [23–27]. This can be attributed to the yet ill-defined super-spreader status of infected individuals. For unknown reasons, some individuals are considerably more contagious than others and can infect up to several hundred individuals. Super-spreading is also described in other pandemic diseases, such as SARS, MERS, and influenza [28]. This phenomenon is described by the dispersion factor (k). The lower the k, the more likely individuals are infected from a small number of persons [28]. The k for the SARS-CoV-2 pandemic is considered higher for SARS or MERS but lower than that of the influenza pandemic in 1918 [26,29–31].

Super-spreader events are essential for spreading SARS-CoV-2, whereby a single event represents the starting point for many secondary infections [32]. Adam et al.

[25] analysed all infection clusters in 1038 cases in Hong Kong in early 2020. The study concluded that 19% of cases were responsible for causing 80% of all community cases, with large clusters originating from weddings, bars, and religious ceremonies.

Recent literature indicates that immunocompromised patients can shed viable SARS-CoV-2 for at least two months. In a study by Aydillo and colleagues [32], 78 samples from respiratory specimens were collected from 20 patients with profound immunosuppression (e.g., chemotherapy, recent hematopoietic stem cell transplantation). Eleven patients had a severe course of disease compared to nine with only a mild course. Viral RNA was detected for up to 78 days after symptom onset. Virus growth in culture was observed until 61 days after symptom onset.

In individuals with severe immunosuppression, a SARS-CoV-2 RT-PCR test is necessary following an isolation period of 10 days in individuals with a CT-value >30. This is required to discontinue quarantine, even in individuals with a mild disease course. Neutralizing antibodies can be determined, with literature indicating high titres to be negatively associated with infectivity [13,21]. The peak response of neutralizing antibodies has been demonstrated to be 3–4 weeks after symptom onset [33]. However, weaker antibody responses have been reported in individuals with a mild course compared to patients with severe disease [34,35]. Further, immune-incompetent individuals may not be able to develop neutralizing antibodies. However, undetectable neutralizing antibodies must not be misunderstood as evidence of a lack of protection from SARS-CoV-2 infection and/or severe disease. Gallais et al. [36] stated that several contacts of patients with COVID-19 who failed to seroconvert, show evidence of a T cell response to SARS-CoV-2, suggesting the development of non-humoral immunity or prior T cell immunity due to a previous infection with other coronaviruses.

The role of children in the transmission of SARS-CoV-2 is not yet fully understood. It appears that children are less susceptible to SARS-CoV-2 infection, have a lower seroprevalence, and a less severe COVID-19 disease course than adults [37-43]. One population-based study indicates that children might not play a major factor in spreading COVID-19 [43]. Some experts warn against the collateral damage to children during the COVID-19 pandemic because of detachment to their normal social environment or reduced medical care visits despite the need, e.g., for vaccination [44]. However, sufficient data is missing to provide a recommendation for the duration of isolation of children.

Table 1 summarizes the recent patients' studies with different course of disease and the relationship between

viral load and cultivation.

In the last months, several new SARS-CoV-2 variants have been detected. The variants B.1.1.7 (first described in England) [45], B.1.351 (first described in South Africa) [46] and P.1 (first described in Brazil) [47] are especially worrisome because they are described as more transmissible [48-50]. It is too early to know the whole impact the rising of these variants will have on the COVID-19 pandemic. However, it can be assumed that a higher infectivity and rate of transmission will lead to a higher number of infection cases, more cases of hospitalisation and probably a higher mortality [51].

B.1.1.7, B.1.351 and P.1 have mutations in the spike protein of the virus, the target of the three vaccines licensed in Europe and the US – BNT162b2 by Pfizer-BioNTech, mRNA-1273 by Moderna and the AZD1222 by Oxford-AstraZeneca. The concern rises that the vaccine-induced neutralizing antibodies are less effective against these virus variants. However, data is scarce so far.

A small study including 16 participants vaccinated with Pfizer-BioNTech showed equivalent neutralizing titres to B.1.1.7 and non-B.1.1.7 lineages [52]. In a Phase II/III study of AstraZeneca, a vaccine efficacy against symptomatic SARS-CoV-2 infection was comparable for B.1.1.7 and non-B.1.1.7 lineages [53]. More of concern are the first results regarding the B.1.351 variant. First results showed that the Pfizer-BioNTech and Moderna vaccine are less potent against B.1.351 [54,55]. A trial performed in South Africa showed that AstraZeneca vaccine is significantly less efficient against mild to moderate COVID-19 caused by B.1.351 variants [56]. First investigations with Pfizer-BioNTech and AstraZeneca showed development of lower titres of neutralizing antibodies to P.1 lineage compared to virus wildtype but higher compared to B.1.351 [57]. Table 2 summarized the recent studies about the virus variants and vaccine efficiency.

In summary, the duration of isolation adapted to the specific patient groups is crucial to prevent the further spread of SARS-CoV-2 and unnecessary long absence periods at work or isolation. However, it can be assumed that infectivity commences two days prior to symptom onset, with transmission, therefore, occurring in presymptomatic individuals. In addition, it is not possible to initially determine whether the super-spreader status persists. Therefore, prevention is an essential factor. These include the behaviour of individuals, such as physical distancing or wearing face masks, public health measures, e.g., travel restrictions, local lockdowns, rapid identification and isolation of infected persons, and large-scale vaccination programs. The spread of new SARS-CoV-2 variants may require even more strict measurements for prevention.

Reference	Study period	Sample size	Study population characteristics	Median age in years (IQR)	Obtained samples	Main findings
Laferl et al., 2021 [13]	April 2020 – June 2020	15	Out-patient, healthy HCW with prolonged viral shedding following a mild or asymptomatic course of disease	41 (22-59)	29 NP and 29 OP swabs	No cultivable virus with Ct values > 30
La Scola et al., 2020 [14]	February 2020 – March 2020	155	not reported	not reported	174 NP swabs and 9 sputum samples	No positive culture results from samples with Ct values > 34
Wölfel et al., 2020 [10]	First quarter of 2020	9	Hospitalized, otherwise healthy patients with mild disease	not reported	155 NP and OP swabs, 154 sputum samples	Viral isolation probability of <5% when RNA load was <5.4 log ₁₀ copies/mL (corresponding to a Ct value > 29.5)
Bullard et al., 2020 [15]	not reported	19	not reported	45 (30-59)	90 NP and endo-tracheal samples	No virus growth in samples with Ct values >24
Min-Chul et al., 2021 [20]	February 2020 – June 2020	21	Hospitalized patients with mainly moderate illness (71% pneumonia, 38% supplemental oxygen therapy)	62 (40-69)	165 NP and OP swabs	No viable virus in samples with a Ct value ≥ 28.4
van Kampen et al., 2021 [21]	March 2020 – April 2020	129	Hospitalized patients with mainly severe illness (69% ICU, 63% mechanical ventilation, 33% supplemental oxygen therapy); 23% immunocompromised	65 (57-72)	690 upper respiratory tract swabs and sputum samples	Isolation probability of <5% if viral load was below 6.63 log ₁₀ copies/mL (corresponding to a Ct value > 27); no viable virus detection when serum neutralizing antibody titre was > 1:80
Aydillo et al., 2020 [32]	March 2020 - April 2020	20	Patients with profound immunosuppression (e.g., chemotherapy, recent hematopoietic stem cell transplantation)	not reported	78 upper respiratory tract swabs	Viable virus detected up to 61 days after the onset of symptoms

Table 1: Summary of recent patients' studies with different course of disease and the relationship between viral load and cultivation. Abbreviations: IQR: Interquartile Range; HCW: Health Care Workers; NP: Nasopharyngeal; OP: Oropharyngeal; Ct: Threshold cycle; ICU: Intensive Care Unit.

Virus variant	First described	Vaccine efficiency
B.1.1.7	England [45]	<ul style="list-style-type: none"> • Pfizer-BioNTech: development of similar titres of neutralizing antibodies compared to virus wildtype [52] • AstraZeneca: effective against development of symptomatic infection [53] • Moderna: no data available
B.1.351	South Africa [46]	<ul style="list-style-type: none"> • Pfizer-BioNTech: development of lower titres of neutralizing antibodies compared to virus wildtype [54] • AstraZeneca: less effective against development of symptomatic infection [56] • Moderna: development of lower titres of neutralizing antibodies compared to virus wildtype [55]
P.1	Brazil [47]	<ul style="list-style-type: none"> • Pfizer-BioNTech: development of lower titres of neutralizing antibodies compared to virus wildtype but higher compared to B.1.351 [57] • AstraZeneca: development of lower titres of neutralizing antibodies compared to virus wildtype but higher compared to B.1.351 [57] • Moderna: no data available

Table 2: Summary of recent studies about virus variants and vaccine efficiency.

Further studies are needed to understand the clinical impact of the probably reduced efficacy of the Europe and USA licensed and used vaccines.

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