COVID-19 reinfections

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ABSTRACT

Reports of SARS-CoV-2 reinfections are on the rise. This study focused on reinfections in patients with confirmed COVID-19 in the Czech Republic. Between 1 March 2020 and 9 November 2020, 362 084 cases with the onset of symptoms before 31 October 2020 were reported. Overall, 28 cases of symptomatic SARS-CoV-2 reinfections were identified, 11 in males and 17 in females, age range 25–80 years, median age 46 years. The interval between the first and second episodes of the disease ranged from 101 to 231 days, and the median interval was 201.5 days. During both symptomatic episodes, all patients have been tested by RT-PCR. Altogether 26 patients (92.9%) have been tested negative after recovery from the first episode of COVID-19. Symptomatic reinfections occurred in nearly 0.2% of all patients at risk. Most patients with reinfection had mild symptoms in both episodes, and only three episodes were moderate to severe. Thus, reinfections may have been underdiagnosed. In summary, COVID-19 reinfections are possible and not exceptional.

KEYWORDS
COVID-19 – coronavirus – SARS-CoV-2 – reinfection

SOUHRN

Fabiánová K., Kynčl J., Vlčková I., Jiřincová H., Košťálová J., Liptáková M., Orlíková H., Šebestová H., Limberková R., Macková B., Malý M.: Reinfekce covidem-19

Zprávy o výskytu opakovaných infekcí virem SARS-CoV-2 narůstají. Studie se proto zaměřila na výskyt reinfekcí u potvrzených případů onemocnění covid-19 v České republice. V období od 1. 3. 2020 do 9. 11. 2020 bylo nahlášeno celkem 362 084 případů s prvními příznaky do 31. 10. 2020. Bylo nalezeno celkem 28 případů opakovaných symptomatických onemocnění covid-19, z toho 11 u mužů a 17 u žen. Věkové rozpětí osob bylo 25–80 let, medián 46 let. Interval mezi první a druhou epizodou onemocnění byl v rozmezí 101–231, medián 201,5 dní. Všechny osoby byly v obou epizodách symptomatické infekce vyšetřeny metodou RT-PCR. Celkem 26 pacientů (92,9 %) bylo v období mezi epizodami onemocnění covid-19 testováno s negativním výsledkem. Symptomatické případy reinfekcí tvoří téměř 0,2 % ze všech osob v riziku z analyzovaného souboru. Většina osob s reinfekcí v souboru měla v obou epizodách mírný průběh, pouze 3 epizody byly střední či těžké. Řada dalších reinfekcí tudíž vůbec nemusela být diagnostikována. Stručně řečeno, reinfekce covid-19 jsou možné a nejsou výjimečné.

KLÍČOVÁ SLOVA
covid-19 – koronavirus – virus SARS-CoV-2 – reinfekce

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INTRODUCTION

Even though the new SARS-CoV-2 virus has been known for nearly one year, there are still many unclear points about the disease. As of early-November 2020, over 50 million people worldwide had been infected with the coronavirus. More than 12 million, or 25% of those, were people living in Europe. Among most patients, the antibody response to SARS-CoV-2 is detectable within 10 to 15 days after infection or after the onset of symptoms. In some patients with mild symptoms, antibodies can be detected after a longer time period, or cannot be found at all. In other types of human coronavirus diseases, the antibody levels decline over time, and reinfection with the same type of coronavirus is possible as early as 90 days after the first episode [1].

With COVID-19, it is still unclear how long the antibody response lasts after recovery and whether it provides protection against reinfection. The role of T-cell immunity in COVID-19 has not been fully elucidated either, but a recent study has shown that long-term memory T-cells persist at least in half of patients after recovery from COVID-19 [2].

Reports and scientific articles on SARS-CoV-2 reinfections are on the rise [3].

Therefore, we focused on reinfections among patients with confirmed COVID-19 as reported to the Infectious Diseases Information System (ISIN) in the Czech Republic. The goal was to find out whether reinfections with SARS-CoV-2 occur in this country, and if so, what the interval is between the first and second positivity episodes and, possibly, whether the time

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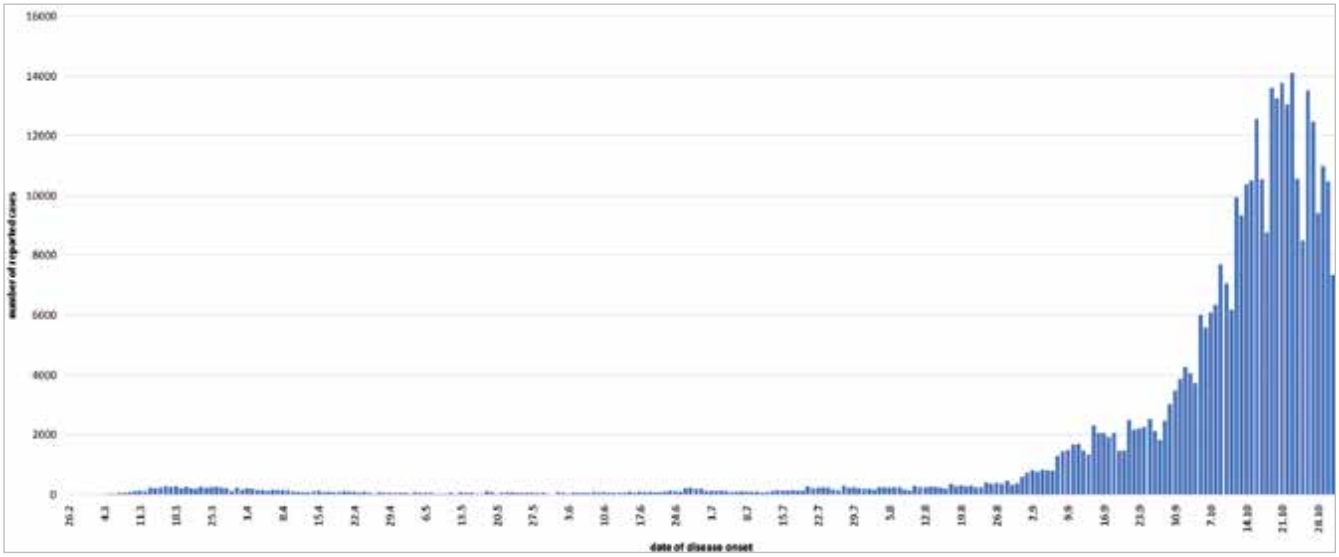


Figure 1. Cases of COVID-19 reported in the Czech Republic from the beginning of the epidemic to 31 October 2020 by date of symptoms onset*
*All cases with onset of symptoms before 31 October and reported to the Infectious Diseases Information System by 9 November 2020 have been included.

interval between the two episodes varies with the severity of the first episode.

During routine data reviews, the information system was searched for duplicates, among which cases of re-infection with SARS-CoV-2 in the same person were identified.

METHODS

The Infectious Diseases Information System, to which notifiable diseases have been reported at the national level, was searched for cases of SARS-CoV-2 reinfection with the onset before 31 October 2020 that had been entered in the database between 1 March 2020 and 9 November 2020. After detailed analysis of each case and data verification by the regional public health authorities, reinfection cases were identified and are presented below.

As the case definition for recurrent infections has not yet been established, our criteria are based on the findings of COVID-19 and other coronavirus infections. The following case definition of SARS-CoV-2 reinfection was used for inclusion: a patient with two episodes of RT-PCR confirmed infection with SARS-CoV-2 that occurred 90 or more days apart, both episodes were symptomatic, and the patient was symptom free in the meantime. Each case of symptomatic reinfection was verified by the regional public health authority. RT-PCR testing was performed by laboratories participating in the reporting system and meeting the ECDC and WHO criteria for SARS-CoV-2 testing. All symptomatic RT-PCR confirmed cases of reinfection were described in detail. The factors examined in both episodes were age, health condition, need for hospital admission, and, possibly, mortality. If the patient did not require hospital admission, the episode was classified as mild, if the patient was admitted to the hospital without needing to be placed in the ICU, the episode was classified as moderate, and if the patient needed the ICU care, the episode was classified as severe.

RESULTS

From 1 March 2020, when the first case of COVID-19 was reported in the Czech Republic, to 9 November 2020, 362 084 cases with the onset of symptoms before 31 October 2020 were reported to the Infectious Diseases Information System, with 78% of these cases being reported not earlier than in October 2020. The cases are presented by date of disease symptoms onset in Figure 1.

Cases of SARS-CoV-2 reinfections with both symptomatic episodes

The inclusion criteria were SARS-CoV-2 reinfection, the first episode ending no later than by 2 August 2020, and the second episode occurring at least 90 days apart. The group of persons at risk of reinfection (i.e., individuals that could become ill repeatedly in the study period) consisted of 16 582 patients. It was relatively small and only comprised 4.6% of all cases reported.

Based on the defined criteria for symptomatic SARS-CoV-2 reinfections, 28 cases, 11 in males and 17 in females, were identified among the 16 582 patients at risk. The age range of patients with reinfection was 25 to 80 years, the median age was 46 years, and the interquartile range was 13.5 years (Table 1).

Table 1. Characteristics of patients with two symptomatic episodes of SARS-CoV-2 infection, sorted by age

ID	Sex	Age	Chronic condition	First epizode severity	Place of isolation	Number of days between epizodes	Second epizod severity	Place of isolation	Test sequential number + Date of test (dd.mm.) + Result of RT-PCR testing							
									Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 7	Test 8
1	M	80	diabetes	mild	LTCF	177	moderate	hospitalized	07.05. pozit.	08.05. neg.	10.05. neg.	16.10. neg.	29.10. pozit			
2	M	76	diabetes, cardiovascular disease	mild	LTCF	102	severe	hospitalized	22.07. pozit	31.10. pozit						
3	M	72	malignity	mild	home	205	mild	home	03.04. pozit.	17.04. neg.	20.04. neg.	22.10. pozit.	30.10. pozit.			
4	F	62	asthma	mild	home	137	mild	home	17.06. pozit.	30.06. neg	02.07. neg.	02.11. pozit.				
5	F	57	none	mild	home	203	mild	home	23.03. pozit	18.04. neg.	21.04. neg.	19.10. pozit				
6	F	56	none	mild	home	216	mild	home	05.04. pozit.	19.04. neg.	23.10. pozit.					
7	M	55	none	mild	home	212	mild	home	24.03. pozit.	01.04. pozit.	07.04. neg.	09.04. neg.	23.10. pozit.			
8	M	53	none	mild	home	214	mild	home	31.03. pozit.	09.04. neg.	14.04. neg.	18.10. pozit.				
9	F	50	malignity	mild	home	197	mild	home	27.04. pozit.	04.05. neg.,	11.05. neg.	13.05. neg.	18.05. neg.	02.10. neg.	31.10. pozit.	
10	F	49	none	mild	home	195	mild	home	17.04. pozit.	29.04. neg.	01.05. neg.	22.07. neg.	26.10. pozit.			
11	F	49	none	mild	home	200	mild	home	10.04. pozit.	24.04. neg.	27.04. neg.	21.10. neg.	01.11. pozit.			
12	M	47	none	mild	home	141	moderate	home	30.04. pozit.	15.05. neg.	18.05. neg.	11.09. neg.	16.09. pozit.	02.10. pozit.	12.10. neg.	
13	M	47	none	mild	home	206	mild	home	12.04. pozit.	26.04. neg.	12.09. neg.	14.10. neg.	17.10 neg.	19.10. neg.	21.10. neg.	26.10. pozit.
14	M	46	none	mild	home	164	mild	home	19.05. pozit.	20.05. pozit.	01.06. neg	03.06. neg	30.10. pozit.			
15	F	46	none	mild	home	231	mild	home	26.03. pozit.	22.04. neg.	23.04. neg	25.04. neg	12.06. neg.	24.10. pozit		
16	F	45	none	mild	home	101	mild	home	23.07. pozit.	31.10 pozit.						
17	F	45	diabetes, chronic pulmonary disease, allergy	mild	home	196	mild	home	09.04. pozit.	27.04. neg.	30.04. neg.	13.10. pozit.				
18	F	45	cardiovascular disease	mild	home	211	mild	home	27.03. pozit.	28.03. pozit	31.03. neg.	10.04. neg.	15.04. neg.	22.10. pozit.		
20	F	44	hypertension	mild	home	169	mild	home	05.04. pozit.	19.04. neg.	21.04. neg.	21.09. neg.	25.09. pozit.			
19	M	44	none	mild	home	224	mild	home	16.03. pozit.	08.04. neg.	23.10. pozit.	01.11. neg.				
21	F	42	none	mild	home	206	mild	home	30.03. pozit.	15.04. neg.	17.04. neg.	29.10. pozit.				
22	F	39	none	mild	home	229	mild	home	09.04. pozit.	22.04. neg.	23.04. neg.	21.10. pozit.				
23	M	34	none	mild	home	158	mild	home	07.04. pozit.	21.04. neg.	23.04. neg.	21.09. pozit.	24.09. neg			
24	F	30	none	mild	home	219	mild	home	20.03. pozit.	17.06. neg.	23.10. pozit.					
25	F	29	none	mild	home	139	mild	home	21.03. pozit.	03.04. neg.	05.04. neg.	14.08. pozit.	09.09. neg.			
26	F	27	none	mild	home	172	mild	home	31.03. pozit.	12.04. neg.	17.04. neg.	06.05. neg.	03.07. neg.	15.09. neg.	21.09. pozit.	01.10. neg
27	F	27	none	mild	home	215	mild	home	21.03. pozit.	07.04. neg.	09.04. neg.	20.10. pozit.				
28	M	25	none	mild	home	222	mild	home	24.03. pozit.	06.04. neg.	08.04. neg	29.10. pozit.	09.11. neg.			

Abbreviations:
LTCF-long term care facility

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The interval between the first and second episodes ranged from 101 days to 231 days, the median was 201.5 days. The interquartile range was 48 days.

All 28 patients with reinfection were RT-PCR tested in both episodes. Twenty-six patients (92.9%) were found negative when retested between the two episodes.

Twenty-five patients had a mild course in both episodes and did not need hospital admission. Two patients were admitted to the hospital during second episode, an 80-year-old man with diabetes and a 76-year-old man with diabetes and a cardiovascular disease who was admitted to the hospital with a severe course of COVID-19 during second episode that subsequently led to death. A 47-year-old man was an exception, without any known chronic condition; the first mild episode was followed by a moderate episode, but the patient subsequently declined hospitalization as reported by the regional public health authority.

Twenty patients with reinfection did not have any known chronic condition, and eight other patients had underlying diseases: asthma 1x, diabetes 1x, hypertension 1x, cardiovascular disease 1x, malignity 2x, and comorbidity 2x (diabetes, chronic pulmonary disease, and allergy 1x; diabetes and cardiovascular disease 1x).

Other cases of SARS-CoV-2 reinfection

In the database of COVID-19 cases, 54 other cases of reinfection were identified, but they did not meet the criterion of two symptomatic episodes.

Of these 54 cases of reinfection, 18 patients had the first episode asymptomatic while the second episode was symptomatic; the interval between the first episode and the onset of the second episode ranged from 121 to 216 days. Twelve other patients had an asymptomatic first episode, but the data on symptoms in the second episode were missing. The interval between the two episodes ranged from 100 to 208 days. Altogether 10 patients had both episodes symptom free, and the two episodes occurred 98–175 days apart. Eleven other patients had a symptomatic first episode and remained symptom free in the second episode. The interval from the onset of symptoms in the first episode to the diagnosis of the second episode was 105–218 days.

Three cases failed to meet basic criteria, i.e., two symptomatic episodes occurring at an interval of 90 days or longer. For the first case there was asymptomatic episode followed by symptomatic episode after 86 days. For the second case there was symptomatic episode followed by the second asymptomatic episode after 87 days. For the third case there was the first asymptomatic episode followed by symptomatic episode after 87 days. This means that possible shortening of the interval for two episodes of covid-19 infection from 90 to 85 days would increase the cohort by only 3 additional cases.

DISCUSSION

In autumn 2020, some countries and regions are facing a second wave of COVID-19 epidemic, and the risk of SARS-CoV-2 infection to the population is rising. As the testing for the new coronavirus becomes faster and more accessible, and the number of tests performed is increasing, reports on possible reinfections start to appear [4, 5, 6, 7].

This study includes all COVID-19 cases in the Czech Republic with the onset before 31 October 2020 that they were reported to the Infectious Diseases Information System by 9 November 2020. Nevertheless, due to delayed reports, the actual number of cases by the end of the study period may be somewhat higher than that shown in Figure 1.

To meet the predefined criterion of a 90-day interval between the two episodes, the first episode of SARS-CoV-2 infection would have to happen by 2 August 2020. To this day, the cumulative number of cases in the Czech Republic was only 16 582, so only 4.6% of all cases reported in the study period. While the first case of COVID-19 was identified on 1 March 2020, most cases (78%) were diagnosed in October 2020, during the second wave of the COVID-19 epidemic. In this light, 28 SARS-CoV-2 reinfections with two symptomatic episodes no less than 90 days apart occurred in 0.17% of all patients at risk of reinfection (28 out of 16 582). If 54 asymptomatic patients are taken into account, the overall rate of reinfections is even higher, reaching 0.49% (82 out of 16 582).

Both episodes of COVID-19 in all re-infected patients were diagnosed by RT-PCR, i.e., by direct detection of nucleic acid of SARS-CoV-2, which is the gold standard for the diagnosis of coronavirus infection. However, no test has 100% specificity and/or 100% sensitivity. Accuracy of viral RNA swabs in clinical practice varies depending on the site and quality of sampling. Other factors influencing accuracy are the stage of the disease, virus replication rate, and viral clearance. In practice, test performance may differ from the sensitivity and specificity declared by the manufacturer, and the rate of false-negative and/or false-positive results should also be taken into account [8, 9].

Recent studies almost certainly ruled out the possibility that a second infection would be merely a continuation of a first infection. The Hong Kong and Nevada teams sequenced the viral genomes from the first and second episodes of COVID-19 in humans and found enough evidence to conclude that each of the two episodes was caused by a different variant of SARS-CoV-2. Data on antibody response in reinfections have not been available yet [10].

Unfortunately, neither sequencing nor serology data have been available for our study patients with reinfections. However, records of negative results in one to six RT-PCR tests between two episodes of SARS-CoV-2 infection have been available for 26 patients (92.9%).

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The protective role of antibodies or T-cell-induced immunity against SARS-CoV-2 still remains unclear. The detection of antibodies, specific antibody titers, is considered as the evidence of antiviral immunity and virus neutralisation in the plasma.

Most patients develop antibodies to SARS-CoV-2 between days 10 and 21 after infection, although mild cases may need longer time to produce antibody response. In few patients, IgM and IgG antibodies are not detectable at all [11, 12]. So far, we can only speculate that patients with severe COVID-19 disease are developing more antibodies. This could provide possible explanation for the fact that we see reinfections in our cohort exclusively in those who had a mild first COVID-19 episode.

Most patients (> 91%) after primary infection with SARS-CoV-2 have IgG antibodies and neutralizing antibodies in the serum (> 90%). The levels of antibodies to other types of coronaviruses decline within 12–52 weeks after the onset of symptoms, and reinfections with these coronaviruses have also been reported [13].

Antibodies to SARS-CoV-2 are detectable within up to 94 days after infection, and recent studies mostly have shown that antibodies peak between weeks 3 and 4 after infection and remain relatively stable for up to four months after the diagnosis [14].

However, the activity of neutralizing antibodies declines considerably over time [15].

Health condition in general and immunosuppression can play an important role in reinfection, as shown by a case report from Belgium [16].

Given the high number of asymptomatic SARS-CoV-2 infections and limits to the testing platforms, it is not possible to determine with certainty how often reinfections occur in the population. Some cases are picked up accidentally within the contact tracing process. Abu Raddad et al. [17], similarly to our study, did not perform whole genome sequencing for their patients. They have concluded that false positivity cannot be ruled out in asymptomatic persons and that it is not possible to prove reliably whether the cases under study actually are reinfections or persisting primary infections. However, the fact that all of 28 study patients had two symptomatic episodes practically rules out the possibility of false positivity.

CONCLUSION

Documented COVID-19 reinfections are rare despite the high number of cases reported to date. Among the records analysed, symptomatic reinfections were identified in nearly 0.2% of patients, and if asymptomatic cases are taken into account, reinfections occurred in nearly 0.5% of all patients at risk of reinfection. However, the fact that most of our study patients with reinfection had mild symptoms in both episodes suggests that reinfections may be underdiagnosed. Severe reinfections were also observed, mostly in patients with comorbidities as a risk factor for severe illness. The detection of reinfection in several patients along with the ambiguities regarding the generation, persistence, and protectiveness of the immune response support the recommendation for use of COVID-19 vaccine even in those who already recovered from SARS-CoV-2 infection in the past.

In this context, emphasis needs to be put on the importance of influenza vaccine during the COVID-19 pandemic as it may be beneficial by facilitating differential diagnosis and preventing the overload of health services due to influenza. Apart from this, influenza vaccine plays a crucial role in the protection of the elderly population that is particularly vulnerable to COVID-19. From the public health perspective, it is important to continue the influenza vaccination programmes in the winter seasons to come [18].

The COVID-19 disease has probably become part of our lives, like other common respiratory diseases. We will have to get used to the fact that SARS-CoV-2 will be permanently present in the human population and we will have to learn to live with it.

There are still several of unclear points regarding SARS-CoV-2 reinfections, more exactly how long after the disease antibody response will persist, under what circumstances reinfections occur, and how the immune system responds to reinfection. In summary, COVID-19 reinfections are possible and not exceptional.

Further studies, experience, and data are needed to properly assess the situation and to make a qualified estimate of the needs.

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