Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients

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ABSTRACT

Objectives: To characterize longitudinal symptoms of mild coronavirus disease 2019 (COVID-19) patients for a period of 6 months, to potentially aid in disease management.
Methods: Phone interviews were conducted with 103 patients with mild COVID-19 in Israel over a 6-month period (April 2020 to October 2020). Patients were recruited via social media and word to mouth and were interviewed up to 4 times, depending on reports of their unresolved symptoms. Inclusion criteria required participants to be residents of Israel aged 18 years or older, with positive COVID-19 real-time PCR results and nonsevere symptoms. The onset, duration, severity and resolution of symptoms were analysed.
Results: A total of 44% (45/103), 41% (42/103), 39% (40/103) and 38% (39/103) of patients experienced headache, fever, muscle ache and dry cough as the first symptom respectively. Smell and taste changes were experienced at 3.9 ± 5.4 and 4.6 ± 5.7 days (mean ± standard deviation (SD)) after disease onset respectively. Among prevalent symptoms, fever had the shortest duration (5.8 ± 8.6 days), and taste and smell changes were the longest-lasting symptoms (17.2 ± 17.6 and 18.9 ± 19.7 days; durations censored at 60 days). Longer recovery of the sense of smell correlated with the extent of smell change. At the 6-month follow-up, 46% (47/103) of the patients had at least one unresolved symptom, most commonly fatigue (22%, 23/103), smell and taste changes (15%, 15/103 and 8%, 8/103 respectively) and breathing difficulties (8%, 8/103).
Conclusions: Long-lasting effects of mild COVID-19 manifested in almost half of the participants reporting at least one unresolved symptom after 6 months. **Hadar Klein, Clin Microbiol Infect 2021;27:769**

Introduction

The coronavirus disease 2019 (COVID-19) has become a worldwide pandemic, with more than 80 million cases and over a million deaths (World Health Organization, 30 December 2020). COVID-19 symptoms as well as their severity and duration vary widely [1–4]. COVID-19 initially targets the human respiratory system, with the most common symptoms being fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of smell or taste, sore throat, congestion, nausea/vomiting and diarrhoea [5]. Other commonly

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reported symptoms include sputum production, haemoptysis and lack of appetite [6,7].

'Long COVID' is emerging as a phenomenon where patients have long-term unresolved symptoms [8,9]. These could be prolonged symptoms of COVID-19 or a post–COVID-19 syndrome for which dysfunction of the autonomic nervous system [10] has been proposed, although further research is needed to establish the cause or causes [11,12]. Moreover, the symptoms' order of appearance, severity, duration and lack of resolution have only been partly studied [13,14] and are the focus of the current study.

Methods

Design, setting and study period

This is a follow-up study of patients who participated in our previous study [15], which was performed in Israel, from 1 April 2020 to 12 October 2020. The study was conducted in accordance with the Declaration of Helsinki. The required ethics approval was granted (reference number HMO-0236–20). Informed consent was obtained from the patients over the phone.

Patients

Eligibility criteria included Israeli residents aged at least 18 years with positive COVID-19 real-time (RT) PCR results. Exclusion criteria were asymptomatic patients and patients with severe COVID-19 infection, defined as receiving respiratory support or intensive care unit admission. During recruitment (March 2020 to April 2020), the criteria for performing an RT-PCR test in Israel in patients with mild COVID-19 was the appearance of symptoms such as fever, cough or breathing difficulties along with an epidemiologic reason, such as having been exposed to a person with RT-PCR–positive disease or having been abroad in the last 14 days. Patients were recruited for phone interviews via social media (Twitter and Facebook) and word of mouth. Participants were not screened or targeted for experiencing smell and taste changes. The study announcement was included in the questionnaire (Supplementary Materials in the online version).

Variables and definitions

An *ad hoc* questionnaire was developed [15] and fine-tuned within a consortium of chemosensory scientists, the Global Consortium for Chemosensory Research [16]. The questionnaire had five parts (Supplementary Materials in the online version), as follows: (1) general information (e.g. age, gender); (2) medical history (medical conditions, chronic medications); (3) current illness (23 physical signs and symptoms, RT-PCR swab test results and dates, subjective perception of recovery); (4) sense of smell; and (5) sense of taste. Participants were instructed to answer yes or no about their ability to taste separate taste modalities (sweet, salty, bitter and sour) and to rate their sense of smell/taste before, during and after their illness on a Likert scale from 1 to 10 (1 corresponding to 'no sense of smell/taste' and 10 to 'excellent sense of smell/taste'). The Likert scale is common in chemosensory research, providing a quantitative and easy-to-use intuitive scale, and was used to evaluate COVID-19–related smell and taste impairments [15,17,18].

The analysis included only the symptoms listed by the US Centers for Disease Control and Prevention (CDC) as of December 2020 (taste change, smell change, fever, dry cough, productive cough, muscle aches, headache, runny nose, sore throat, diarrhoea, breathing difficulty, vomit/nausea and fatigue) [5] or symptoms that were prevalent (>50%) in our sample.

Disease onset was defined as the first appearance of any of the COVID-19 symptoms listed above. Number of days after disease onset was calculated by subtracting the date of the first symptom to occur from the date of the symptom's appearance. Mean (±standard deviation (SD)) was calculated for each symptom. Unresolved symptoms refer to those that were unresolved at the 6-month follow-up interviews. Order of appearance was calculated from the onset dates reported by the participants for each symptom. Duration was calculated from the onset and resolution dates of each symptom. If patients reported unresolved symptoms (no resolution date) or could not report a precise resolution date during the period between the 6-week follow-up and the 6-month follow-up, the symptom's duration was censored at 60 days, as this was the longest calculated duration. This resulted in censoring of 8% (49/649) of the symptoms' durations at day 60. All patients ($n = 103$) were included in the analysis, regardless of their follow-up periods.

Maximal severity of smell and taste change was calculated as the difference between the rating of the respective sense level before the illness and its rating during the illness, rated on a scale of 1 to 10.

Procedures and follow-up

COVID-19–positive patients from our previous study [15] were further followed to monitor the progress of their illness and recovery. After receipt of agreement to participate, an explanation of the interview, including questions regarding levels of taste and smell, was read to the participant. Data were kept in Compusense Cloud online software (Compusense, Guelph, ON, Canada).

Patients who either had not recovered from their symptoms at the time of the first questionnaire or did not have two consecutive negative RT-PCR results at the time of answering the first questionnaire (as this was the Israeli Ministry of Health criteria for recovery at the time) were contacted 3 weeks after the initial interview for a second interview. If they had not fully recovered at their first follow-up, they were contacted again 3 weeks after their second interview for a third interview. All patients were contacted again approximately 6 months after their first interview. The number of patients who completed each interview and the dates of the interviews are presented in Fig. 1. Data from the four interviews were analysed for symptoms' characteristics, onset, duration, severity and resolution. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations were followed for reporting (Supplementary Materials in the online version).

Statistical analysis

Analyses were conducted using R 4.0.2 statistical software (https: //www.r-project.org/). Descriptive statistics are presented as mean and standard deviation.

Correlations were measured by Pearson correlation coefficients, and p values are based on a two-sided t test for nonzero correlation (n-2 degrees of freedom), as implemented by the 'cor.test' method. A level of $p < 0.05$ was used to determine statistical significance. For comparing symptom duration, regression lines were estimated by the ordinary least squares method. The p values for the pairwise comparisons between symptom durations were calculated by a two-sided Wilcoxon rank-sum test and adjusted for multiplicity using the Benjamini-Hochberg procedure [19].

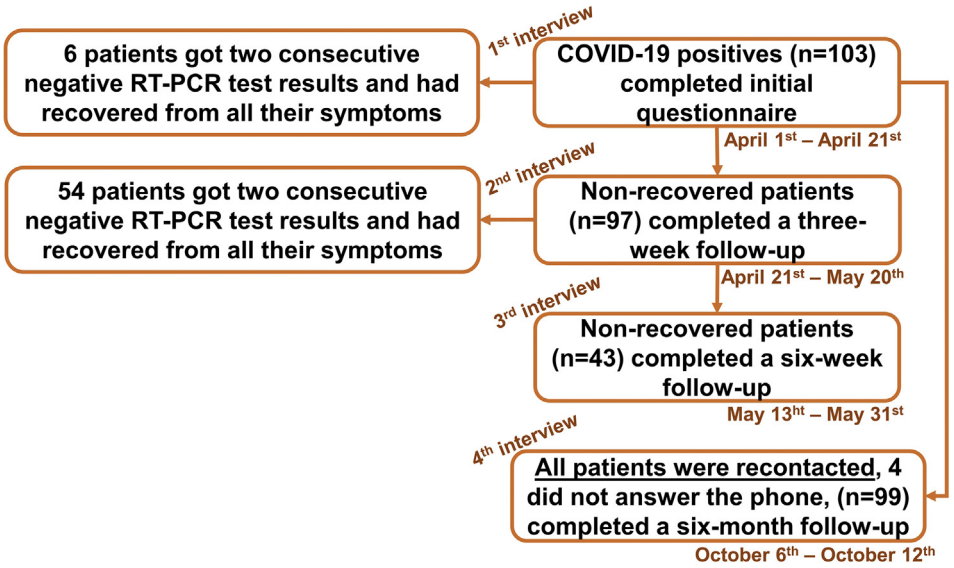

Fig. 1. Study design. Each of 4 interviews (initial interview, then 3-week, 6-week and 6-month follow-ups) is presented, with number of participants and start and end dates.

Results

Patient characteristics

One hundred forty-four RT-PCR–positive patients were recruited; 30 did not answer their phones. Two patients had missing information regarding rating of smell and taste symptoms, six patients were classified as having severe COVID-19 and three patients were asymptomatic, resulting in 103 patients who fulfilled the eligibility criteria for this study and had completed the first questionnaire. The mean ± SD age of the respondents was 35 ± 12 years and 64 were male. A total of 1.9% (2/103) reported blood pressure, 5.8% (6/103) respiratory disease, 1.9% (2/103) cardiac disease and 15.5% (16/103) obesity. The numbers of patients who completed each interview, as described in the Methods, are presented in Fig. 1.

Analysed symptoms

Of the 23 symptoms listed in section 3 of the questionnaire, 13 symptoms were included in the final analysis. Twelve were CDC symptoms as of December 2020 (taste change, smell change, fever, dry cough, productive cough, muscle aches, headache, runny nose, sore throat, diarrhoea, breathing difficulty and vomiting/nausea) [5], and an additional symptom was prevalent in more than 50% (53/103) of patients (lack of appetite). Fatigue is a current CDC symptom that did not explicitly appear in the original questionnaire but was self-reported by 18% (19/103) of the patients under 'any other symptoms' and was therefore included in the final analysis, resulting in a total of 14 symptoms analysed.

Order of symptoms' appearance

Symptoms usually appeared concomitantly. The first and second symptoms to appear were accompanied by additional symptoms in 69% (71/103) and 46% (47/103) of the patients respectively.

Headache, fever, dry cough and muscle aches were the first to appear in over a third of patients, appearing on average around the second day after disease onset. Fatigue, although not a typical first symptom among patients, appeared first in the majority of patients who reported it (Table 1). Each of the 14 symptoms analysed could occur first or co-first. Vomiting, breathing difficulty and diarrhoea were the most spread out in the order in which they appeared (Supplementary Fig. S1). Vomiting and diarrhoea appeared after the highest number of days from disease onset (Fig. 2).

Table 1
Symptoms in patients with mild coronavirus disease 2019 (COVID-19)

Symptom	First symptom, % of total	First symptom, % of those who experienced symptom	Second or higher symptom, % of total
Headache	44% (45/103)	69% (45/65)	19% (20/103)
Fever	41% (42/103)	61% (42/69)	26% (27/103)
Muscle aches	39% (40/103)	65% (40/62)	21% (22/103)
Dry cough	38% (39/103)	61% (39/64)	24% (25/103)
Lack of appetite	26% (27/103)	51% (27/53)	25% (26/103)
Runny nose	20% (21/103)	50% (21/42)	20% (21/103)
Sore throat	17% (18/103)	47% (18/38)	19% (20/103)
Taste change	17% (18/103)	23% (18/77)	57% (59/103)
Productive cough	15% (15/103)	34% (15/44)	28% (29/103)
Fatigue[a]	15% (15/103)	79% (15/19)	4% (4/103)
Smell change	15% (15/103)	21% (15/72)	55% (57/103)
Diarrhoea	9% (9/103)	38% (9/24)	15% (15/103)
Vomiting/nausea	7% (7/103)	33% (7/21)	14% (14/103)
Breathing difficulty	3% (3/103)	19% (3/16)	13% (13/103)

[a] Self-reported under "any other symptoms".

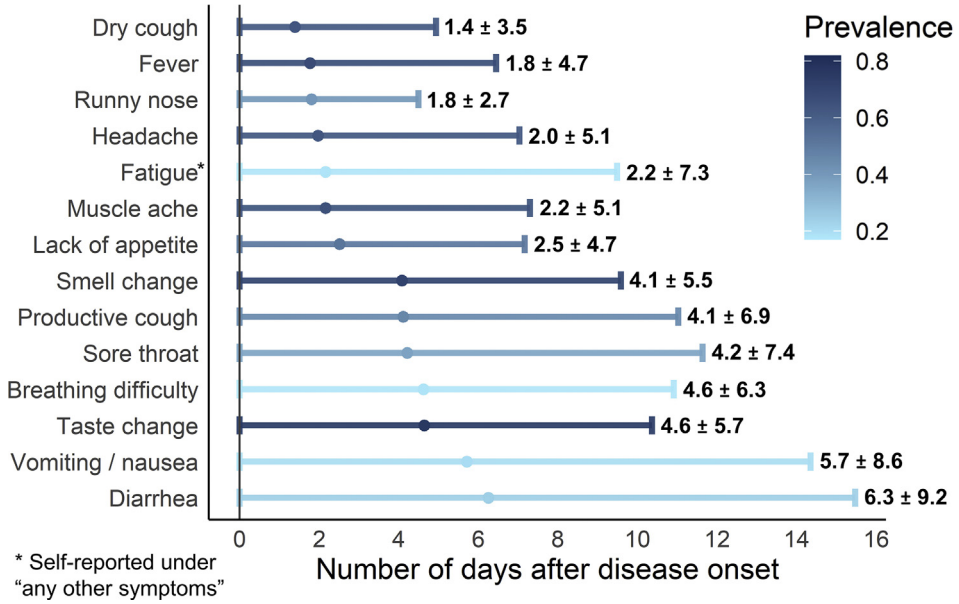

Fig. 2. Symptoms' order of appearance. List of symptoms is on *y*-axis; number of days after disease onset, *x*-axis. Mean ± standard deviation (SD) number of days after disease onset is presented for each symptom. Colour bar represents prevalence, with darkest colour indicating most prevalent symptoms.

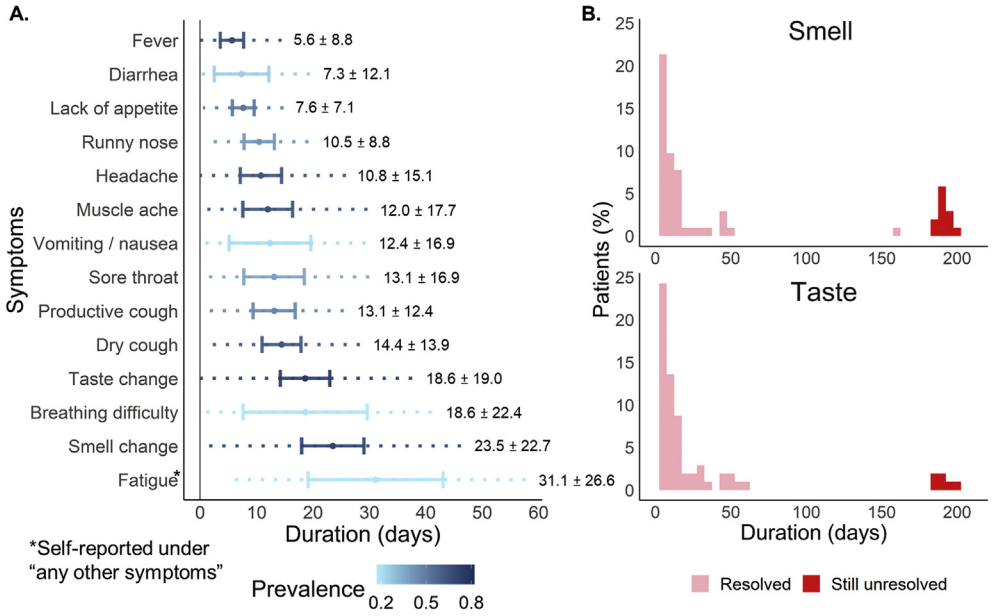

Fig. 3. Symptoms' durations. (A) List of symptoms is on *y*-axis; censored duration (days), *x*-axis. Standard deviation (SD) is presented as dashed line; 95% confidence interval, solid line. Censored mean ± SD duration is presented for each symptom. Censoring was done at 60 days for each duration. Colour bar represents prevalence, with darkest colour indicating most prevalent symptoms. (B) Duration of smell and taste changes are presented in bar charts and marked according to symptom's resolution, with pink representing resolved symptoms and red unresolved symptoms. Percentage of patients is shown on *y*-axis and duration of symptoms (days) on *x*-axis.

Symptom durations and resolution

Among symptoms prevalent in >50% of patients, fever had a shorter duration than most symptoms, with a censored mean ± SD duration of 5.6 ± 8.8 days, while changes in taste and smell had longer mean censored durations than most other symptoms (Fig. 3(A)). A comparison of all the symptoms is provided in Supplementary Table S1 in the online version.

Durations of taste and smell changes were widely distributed, and some remained unresolved (Fig. 3(B)). At the 6-month follow-up, 47 patients (46%) still reported experiencing unresolved symptoms, mainly fatigue (22%, 23/103), smell and taste changes (15%, 15/103 and 8%, 8/103 respectively) and breathing difficulties (8%, 8/103). The co-occurrences of the most prevalent symptoms at 6 months are shown in Fig. 4. Fatigue, breathing difficulties, memory disorders and hair loss were not typically reported during the initial 6-week follow-ups (thus 'new symptoms'), while other symptoms, such as muscle aches, headache and smell and taste changes, usually carried over from previous interviews (Supplementary Table S2).

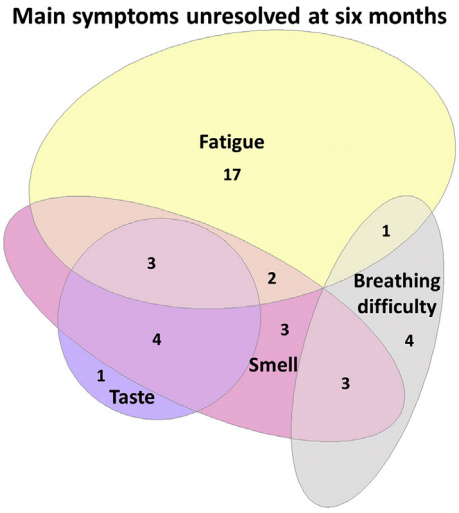

Fig. 4. Unresolved symptoms. Euler diagram of main unresolved symptoms collected at 6 months' follow-up. Number of patients experiencing unresolved symptom is indicated for each circle.

Smell and taste changes

Smell and taste changes appeared on average around the fourth day after disease onset (Fig. 2), were rarely the first symptoms to appear and were among the longest lasting. Smell (taste) durations had wide-ranging recovery times: ~30% (~40%) (30/103 (38/103)) were resolved within 10 days, an additional ~20% (~25%) (20/103 (27/103)) recovered within 60 days and 15% (7%) (15/103 (7/103)) were unresolved even after 208 days (Fig. 3(B)). Approximately 10% (12/103) could not recall onset or recovery dates and ~30% (~25%) (29/103 (24/103)) did not experience smell (taste) changes at all.

The durations of changes in smell and taste reported at the 6-week follow-up were highly correlated (0.71, $p < 0.001$) (Supplementary Fig. S2(A)). A weak yet significant correlation was found between change severity and its duration for smell (Fig. S2(B), correlation 0.37, p 0.0016) but not for taste (Supplementary Fig. S3). Moreover, some patients recovered from the smell change independently of how severe it was, while for others, recovery correlated with severity (Supplementary Fig. S2(B)). No characteristics of these subpopulations were identified.

Unresolved smell change at the 6-month follow-up included both continuation from the 6-week follow-up and reappearance.

Discussion

Our study results indicated that headache, fever, dry cough and muscle aches were often the first symptoms to appear, while smell and taste changes were not. Fatigue was usually the first symptom among patients who reported it in the first interview. Notably, the low prevalence of fatigue in our study compared to other reports [20] is due to self-reporting under the 'any other symptom' question, rather than an explicit question in the questionnaire.

The mean duration of fever was the shortest, while the censored duration means of dry cough and smell and taste changes were the longest among symptoms prevalent in >50% of the patients. Smell (but not taste) change severity correlated with its recovery time, although for a group of patients the time to recover smell was unrelated to smell change severity. Almost half of the patients did not recover from all their symptoms 6 months after their first questionnaire, with most of them reporting fatigue, smell and taste changes and breathing difficulties. These unresolved symptoms occurred together or separately, and some were not reported during the previous follow-ups.

We found a slightly lower prevalence of taste and smell changes as first symptoms compared to Spinato et al. [21], possibly due to recall bias caused by retrospective data collection in our study. Our long (up to 6 months) follow-up and quantitative (rather than binary) monitoring of smell and taste changes probably account for the longer duration of smell and taste changes we found compared to other studies [22–24]. Subpopulations of patients for whom smell change severity was or was not related to resolution time was also reported by Gerkin et al. [25]. However, characteristics that might account for these groups require further exploration with larger number of patients.

Our findings are in line with other longitudinal studies of patients with mild COVID-19, which also found high variability in the clinical course of the disease and long durations (weeks after infection) of fatigue, shortness of breath [26] and smell and taste changes [27,28].

In light of the limited data available for patients with mild COVID-19, especially in the long term [9,11,26,27], our study provides important information that should be considered when considering the disease course over a 6-month period in ambulatory patients. Careful phone follow-up interviews further contributed to our findings' reliability.

Our study had several limitations. The findings are relevant for patients with mild disease only. Additionally, symptoms may manifest differently in patients of different races [29]. Testing policies at the time of patient recruitment may have also influenced this study's findings, as only patients with certain symptoms (fever, cough or breathing difficulty) along with having an epidemiologic reason were eligible for the RT-PCR test. No objective sensory testing was performed. Additionally, the retrospective data collection method used in this study may have resulted in recall bias. Furthermore, the recruitment of patients through social networks may also result in a biased sample (e.g. overrepresentation of younger patients, with higher education and income). Future studies should recruit patients through health services to avoid this limitation.

Patients were contacted for the second and third interviews only if they did not report recovery. In principle, it is possible that some of the recovered patients could experience recurrence of symptoms as well [30]. Therefore, for the 6-month follow-up, we contacted all the participants in the study for reports of unresolved symptoms. Long-term studies of larger groups of COVID-19 patients, with more data gathered during follow-ups, are required to further monitor and characterize the manifestations of long COVID [8,9].

In conclusion, we carefully mapped the start and end dates of various symptoms for 103 patients with mild COVID-19 in Israel. The results indicated that despite a wide variability in the symptoms' onset and duration, some symptoms (headache, fever, dry cough and muscle aches) are common as first or co-first symptoms. Fatigue, if it occurs, usually appears as a first symptom. Taste and smell changes do not typically occur first and are resolved either quickly (within patients' infectious time of 10 days) or longer and gradually, with the longest averaged duration among all prevalent symptoms. Interestingly, while dry cough appears relatively early, productive cough usually appears later. At the 6-month follow-up, 46% (47/103) of patients experienced unresolved symptoms, with symptoms either continuing throughout the illness (e.g. smell and taste changes) or appearing as new symptoms (e.g. memory disorders).

This information regarding the durations of the patients' symptoms might help us better understand COVID-19's long-term health complications, reduce the level of anxiety of patients and legitimize their concerns when needed. This study

paves the way for future long-term COVID-19 studies and advances us towards a better understanding and management of this disease.

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Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.02.008.

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