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.

Infection, Disease & Health (2020) 25, 210—215

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/infection-disease-and-health/

Discussion paper

SARS-CoV-2: The viral shedding vs infectivity dilemma

Arabella Widders [a,*], **Alex Broom** [b], **Jennifer Broom** [c,d]

[a] *Department of Medicine, Sunshine Coast Hospital and Health Service, Birtinya, 4575, Queensland, Australia*
[b] *School of Social and Political Sciences, The University of Sydney, Sydney, 2006, New South Wales, Australia*
[c] *Sunshine Coast Health Institute, Birtinya, 4575, Queensland, Australia*
[d] *School of Medicine, The University of Queensland, Brisbane, 4072, Queensland, Australia*

Received 29 April 2020; received in revised form 13 May 2020; accepted 13 May 2020
Available online 20 May 2020

KEYWORDS
SARS-CoV-2;
COVID-19;
Virus shedding;
Public health;
Transmission

Abstract Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over four million people worldwide. There are multiple reports of prolonged viral shedding in people infected with SARS-CoV-2 but the presence of viral RNA on a test does not necessarily correlate with infectivity. The duration of quarantine required after clinical recovery to definitively prevent transmission is therefore uncertain. In addition, asymptomatic and presymptomatic transmission may occur, and infectivity may be highest early after onset of symptoms, meaning that contact tracing, isolation of exposed individuals and social distancing are essential public health measures to prevent further spread. This review aimed to summarise the evidence around viral shedding vs infectivity of SARS-CoV-2.

Highlights

- Viral shedding has been demonstrated up to 63 days after symptom onset.
- The distinction between viral shedding and infectivity is important for the development of quarantine guidelines and policy.
- There is an earlier peak in viral load in SARS-CoV-2 than seen in SARS.
- Quantitative viral loads are higher in the nose than the throat.
- It is likely that asymptomatic and presymptomatic transmission is occurring.

* Corresponding author. Sunshine Coast University Hospital, 6 Doherty Street, Birtinya, Queensland, 4575, Australia.
E-mail address: arabella.widders@health.qld.gov.au (A. Widders).

https://doi.org/10.1016/j.idh.2020.05.002

Introduction

A novel coronavirus emerged in Wuhan, China in December 2019. Since then it has rapidly spread through China and around the world, infecting 4,262,799 people globally and resulting in 291,981 deaths as of May 13, 2020 [1]. This new virus was named SARS-CoV-2 due to its similarity with the virus that caused the SARS outbreak, including a similar receptor binding domain suggesting the ACE2 receptor as a possible target [2]. The disease resulting from infection with SARS-CoV-2 was declared a pandemic by the WHO on March 11, 2020 [3]. Transmission is thought to occur primarily through droplet and contact spread, however there is some concern for airborne transmission especially in the case of aerosolising procedures in health care settings. At time of writing there is no known antiviral treatment or vaccine for SARS-CoV-2 with treatment being only supportive. Vaccines are in development however they are likely many months away and therefore reducing community transmission is the most effective prevention.

The duration of viral shedding around a period of infection is often considered in determining an appropriate period of isolation as it is often used as a marker of infectivity. Guidelines for duration of quarantine are often developed to reflect this. However, interpretation of the infectivity of a person based on a positive PCR test can be inaccurate. As of March 21, 2020, Australian guidelines no longer require clearance swabs for people with mild illness not requiring hospital admission or those with severe illness who have been discharged home. These patients may now be released from home isolation if:

- At least 10 days have passed since symptom onset (mild cases only) OR at least 10 days since hospital discharge (severe cases); AND
- There has been resolution of symptoms for at least 72 h.

A number of other countries allow home isolation to cease 7 days after symptom onset rather than 10 days. Health and aged care workers in Australia still require 2 negative PCR swabs 24 h apart at least 7 days after symptom onset and 48 and 24 h after fever and symptom resolution respectively to receive clearance [4].

In the following review, the current evidence for viral shedding and infectivity of SARS-CoV-2 is explored.

Viral shedding of SARS-CoV-2

Respiratory shedding

Viral shedding (as detected by SARS-CoV-2 viral PCR testing) from respiratory tract specimens has been found to persist for up to 63 days after symptom onset and appears to outlast symptom resolution [5—10]. Median duration of shedding has been reported to be from 12 to 20 days [6,8,11], however a new paper published ahead of print studied 41 severe cases and found the median duration of viral shedding was 31 days [12].

A number of papers demonstrate prolonged viral shedding in severe illness. Liu et al. [13] investigated serial nasopharyngeal swabs from 21 confirmed cases and found 90% of mild cases had cleared the virus at 10 days after symptom onset whereas all severe cases had ongoing viral shedding. Severe cases were also associated with higher viral loads. Zheng et al. also found prolonged viral shedding in respiratory specimens in severe cases compared to mild cases in a 96 patient retrospective cohort study [11]. In contrast, To et al. found 7 of 21 patients had detectable viral load more than 20 days after symptom onset with no correlation between severity of illness and prolonged viral shedding [7].

The peak viral load in upper respiratory tract (URT) swabs appears to occur on day 4—6 after symptom onset whereas the quantitative viral load in lower respiratory tract samples may peak later [5,7,11,14]. It has been hypothesised that later peaks may correlate with more severe cases, and this is supported in the recent cohort study by Zheng et al. [11]. Higher viral loads have been demonstrated in swabs taken from the nose compared to the throat in most studies testing both sites [5,15,16].

Gastrointestinal shedding and detection in other clinical samples

Multiple studies have demonstrated the presence of SARS-CoV-2 RNA in the stool in a significant proportion of patients, however usually at lower levels than the respiratory tract. The peak viral load occurs later than in the respiratory tract and prolonged viral shedding has been found in the stool up to 33 days after negative respiratory PCRs even in the absence of gastrointestinal symptoms and with no correlation to disease severity [17]. Live virus has been isolated from faecal samples with a positive PCR result, however it is not consistently cultured and only small studies have been conducted [5,15]. ACE2 receptor is abundantly expressed in the gastrointestinal tract which may account for the presence of virus in the stool however it is also expressed in the kidney and there is minimal evidence of SARS-CoV-2 in urine to date [5,6,14,15,18,19]. Evidence of SARS-CoV-2 RNA in serum has been demonstrated in some studies however the proportion of positive samples is generally low [5,6,15,20].

Given the viability of virus cultured from stool samples, the possibility of faecal-oral transmission of SARS-CoV-2 cannot be excluded. It was hypothesised that during the SARS outbreak the virus may have been spread by aerosols or droplets originating in faecal matter in sewerage pipes so this could also be a potential risk with SARS-CoV-2 [21]. As well as suggesting a potential route of transmission, the presence of SARS-CoV-2 RNA in the stool may mean that wastewater can be used as a surveillance method for community spread. SARS-CoV-2 RNA has been found in sewage in Australia, the Netherlands and the USA [22].

Viral shedding in immunosuppressed patients

The experience in other respiratory viruses including SARS, MERS and influenza is that immunosuppression and other significant comorbidities such as diabetes mellitus result in prolonged viral shedding [23—25]. To date there has been only one study examining viral shedding in immunosuppressed patients infected with SARS-CoV-2. This paper studied 10 immunosuppressed renal transplant patients and found significantly prolonged viral shedding (mean 28.4) compared to controls (12.2 days) [9].

There is also some evidence that patients treated with a prolonged course of glucocorticoids during their illness have a longer duration of detectable virus however this may be related to the severity of the illness itself and requires further investigation [11,12].

Asymptomatic and presymptomatic transmission

The proportion of cases that are asymptomatic is unclear. Reported values range from 1% to 78% and, in general, asymptomatic cases are likely under-reported [26—29]. In addition, it is unclear what proportion of cases are truly asymptomatic (meaning they never developed symptoms) as opposed to those that are merely presymptomatic (meaning they had no symptoms at the time of the positive SARS-CoV-2 PCR but they did go on to develop symptoms at a later point). Arons et al. found that of 48 patients, 50% of patients from an aged care facility with positive PCR for SARS-CoV-2 were presymptomatic and 6% permanently asymptomatic [30]. Further evidence is needed in other age groups, especially younger groups, who are more likely to have mild disease.

There are multiple case reports supporting transmission by asymptomatic and presymptomatic patients. Rothe et al. [31] reported on suspected asymptomatic transmission from a visiting Chinese national to a German patient who later tested positive for SARS-CoV-2. It was subsequently reported the Chinese patient may have been febrile and taken antipyretics around time of contact, however 2 further cases were traced back to contact with the German patient during the presymptomatic period. Bai et al. [32] reported on a presumed asymptomatic carrier transmission from a Wuhan resident to a family cluster in another Chinese city. The index patient remained asymptomatic and was isolated after symptom onset in her relatives however did not return a positive PCR result until Day 19 after leaving Wuhan, which is longer than the widely reported incubation period of less than 14 days. Another familial cluster of 4 patients were positive for COVID-19 in Shanghai, in which the first patient to show symptoms was essentially house-bound and exposed only to family members from Wuhan, all of whom developed symptoms at least a day after the onset of his illness [33]. A separate case report outlines two familial clusters with the only known exposure to confirmed SARS-CoV-2 a contact who went on to develop symptoms 24—48 h later [34].

Laboratory evidence also supports the possibility of asymptomatic and presymptomatic transmission. Pan et al. [14] demonstrated positive nasopharyngeal swabs for SARS-CoV-2 a day prior to symptom onset in 2 patients under active surveillance due to known exposure. Zou et al. [16] detected similar viral loads in nasal and throat swabs from a permanently asymptomatic patient compared to 17 symptomatic cases and in a study by Arons et al. [30], in which residents of an aged care facility in Washington, USA were screened for COVID-19, more than half of the SARS-CoV-2 positive patients (56%, n = 48) were asymptomatic at the time of their positive PCR test although, as highlighted above, only 6% remained truly asymptomatic. Notably He et al. [35] studied 77 infector-infectee transmission pairs and estimated that 44% of secondary cases were infected during the presymptomatic period of the primary cases.

The possibility of asymptomatic and presymptomatic transmission creates many challenges in regard to infection control. Further data are needed to more accurately estimate the proportion of truly asymptomatic cases and the risk of transmission, and therefore guide more effective policies. While social distancing and quarantining of confirmed contacts will likely reduce presymptomatic and asymptomatic transmission, accurately identifying and isolating these cases may be necessary to further reduce spread. Both contact tracing and extensive testing are strategies currently employed to identify possible cases however in Australia, as one example, widespread PCR testing of asymptomatic contacts or the community in general is not currently recommended. The performance and value of PCR testing in asymptomatic people is the subject of ongoing intensive discussion.

Diagnostic testing and infectivity

While there is evidence in SARS-CoV-2 infection for viral shedding both in asymptomatic patients and ongoing in patients after symptom resolution, the correlation between detectable viral RNA and transmissibility is still unclear. A positive RT-PCR result does not necessarily represent potential for viral transmission as this mode of testing cannot distinguish between infective virus and inactive virus and amount of viral RNA detected does not necessarily indicate greater infectivity.

Current evidence for SARS-CoV-2 suggests viral loads in URT swabs and sputum may peak earlier in the course of COVID-19 than is observed in SARS, where peak was around day 10 [16]. The early peak suggests transmission is likely to occur early in the disease course when the patient may be asymptomatic or only have mild symptoms. A pre-print study supports this hypothesis with the finding of a higher rate of infection in people exposed to index patients within 5 days of symptom onset than those exposed after this time [36]. In addition, a recently published study by He et al. [35] used clinical and epidemiological data to estimate that patients infected with SARS-CoV-2 may be infectious from 2.3 days prior to symptom onset, with a peak at 0.7 days prior. Together these findings suggest that containment methods successful in prevention of SARS transmission (i.e. isolating newly diagnosed cases) are unlikely to be effective in preventing spread of SARS-CoV-2. It highlights the importance of contact tracing, including at least the 48 h prior to symptom onset, and of social distancing in preventing further spread.

Wölfel et al. [5] demonstrated that live virus can be cultured from nasal/throat and sputum samples in patients with positive SARS-CoV-2 PCR, however, no live virus was successfully isolated after Day 8 from symptom onset despite ongoing high viral loads. Additionally, virus could not be isolated from samples with less than 10^6 copies/mL. A group from Taiwan were able to isolate SARS-CoV-2 from cultures of sputum samples in one patient up to 18 days post-symptom onset. Interestingly, the only symptom reported in this patient was fever, which resolved Day 9 after symptom onset [10].

Arons et al. [30] were able to isolate viable virus from nasopharyngeal and oropharyngeal swabs in 31 of 46 patients with positive SARS-CoV-2 PCR in total with positive

cultures up to 9 days after symptom onset. There was no significant difference in viral load between symptomatic, presymptomatic and asymptomatic cases and positive cultures were obtained from 13 of 20 symptomatic patients, 17 of 24 presymptomatic patients and in 1 of 3 patients who remained asymptomatic over the seven-day period after initial diagnosis.

A further consideration in the understanding of infectivity of SARS-CoV-2 is the issue of seroconversion. At time of writing it is still unclear how seroconversion relates to infectiousness in patients with SARS-CoV-2. Viral shedding has been shown to persist despite seroconversion, and virus has also been successfully cultured after the detection of antibodies to SARS-CoV-2 [5,10]. Up to half of patients with SARS-CoV-2 have been found to develop an antibody response by Day 7 after symptom onset, with the vast majority seroconverting by Day 15 [5,37]. Serological testing may also identify patients with past infection without PCR positivity and has been used in surveillance to identify previous SARS-CoV-2 infection and provide the infectious link between known cases [38]. Serological testing may provide greater utility in estimating the prevalence of past SARS-CoV-2 infection within the community and its use is becoming more widespread worldwide as the pandemic progresses. While there is not definitive evidence for long-term immunity with seroconversion, positive serological testing has been proposed as a possible strategy to identify those with immunity, which would be especially useful in healthcare workers.

In general, these findings suggest positive RT-PCR later in the course of SARS-CoV-2 infection does not necessarily correlate with viable virus and therefore with infectivity. In presymptomatic and asymptomatic patients there is some data to suggest that the virus is likely to be viable early in the course of infection. Many questions remain regarding infectivity of patients with SARS-CoV-2, especially in regard to symptom status and positivity in PCR and serology assays, and appropriate infection control policy. Further research with larger sample sizes studying PCR and antibody positivity, virus viability and infection rates directly is required to confidently describe the correlations and the bearing these tests have on infectivity.

The social importance of SARS-CoV-2 test interpretation

Gaining a better understanding of the significance of clinical diagnostics regarding viral shedding and infectiousness over time is important for both clinical and social reasons. As identified above, there are currently considerable gaps in our knowledge regarding viral shedding over time and across contexts, and the concrete risks to patients themselves, healthcare workers and the community at large. Diagnostics, in this case, has the considerable potential for providing data but also, and somewhat paradoxically, raising levels of uncertainty (i.e. positive results versus clarity around actual significance). Practices of testing, and their interpretations, thus have considerable implications for healthcare services burden, potential over-treatment (or under-treatment), as well as producing further uncertainty in the community of the 'silent threat' posed by those who have come into contact with SARS-CoV-2. Among many other implications, the identification of viral RNA on PCR without sufficient evidence of risk, or significance, offers the potential for inducing further social stigma within and beyond the clinical environment. Whilst sensitivity of testing is a vital aspect of the challenge of SARS-CoV-2, so too is moderating the need for testing, versus utilising best-evidence of likely risks/costs. What remains critical is incorporating best evidence of viral shedding and infective risk into routine care practices, which seek to reduce excess intervention and fear amongst healthcare workers and the community. This must include educational communication, based on nuanced understandings of viral shedding, which would usefully allay community/political fears around transmissibility, as well as reduce burden on healthcare services. In sum, further detailed exploration of viral shedding and its clinical/social significance would serve a range of purposes including: reducing potentially unnecessary isolation practices and length of care; increasing containment/intervention in cases of genuine risk where shedding was previously underrecognised; reduce in social stigma around those who are no longer ill but perceived as a potential threat; and, reduce in clinical and community uncertainty and fear around the ambiguities of the 'tail end' of SARS-CoV-2.

Summary of findings

There is evidence of ongoing viral shedding after symptom resolution in SARS-CoV-2 infection which may be prolonged in the faeces compared to respiratory secretions. Immunosuppression and disease severity also appear to extend the duration of viral shedding. However, there is not convincing evidence that duration of shedding correlates with duration of infectivity.

There is not a clear association between viral load and infectivity, but the earlier peak in viral load in SARS-CoV-2 infection suggests infectivity may be higher earlier in the course than would be expected based on a SARS model.

Current data indicate live virus isolation is less likely from Day 8-9 after symptom onset but may be possible from respiratory samples taken up until Day 18 after symptom onset supporting the potential for transmission until that time. Most patients seroconvert by Day 15 after symptom onset. While the risk of transmission after symptom resolution may be lower, it cannot be ruled out with the available evidence.

Transmission by asymptomatic or minimally symptomatic individuals also appears likely and highlights the importance of contact tracing and isolation of exposed individuals, especially as transmission potential may be maximal early in the course of infection.

Further research is needed to determine the viability of the virus outside the respiratory and gastrointestinal tract at different stages of infection in both asymptomatic and symptomatic individuals. This will improve understanding of transmission risk and allow greater certainty around guidelines for appropriate contact tracing and quarantine periods.

Conclusion

Establishing when a person with SARS-CoV-2 is infectious, and hence what policy should be developed around

quarantine, repeat testing and social isolation, is a critical issue globally at present. Interpretation of the evidence requires a sophisticated level of scientific understanding of modes of testing which is challenging for healthcare professionals and policy makers and complicates community communication around policy. In addition, there are significant limits to the current evidence which continue to be explored as the pandemic progresses.

Authorship statement

JB conceived of the study, reviewed and revised drafts and approved the final version. AW performed the review, wrote the initial draft, revised drafts and approved the final version. AB reviewed and revised drafts and approved the final version.

Declaration of Competing Interest

None.

Funding

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

Ethical considerations

Ethics approval is not required as this is a discussion paper.

Acknowledgements

None.

References

[1] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time [Internet] Lancet Infect Dis 2020 Apr 24. https://doi.org/10.1016/S1473-3099(20)30120-1.

[2] Wan Y, Shang J, Graham R, Baric RS, Li F [Internet]. In: Gallagher T, editor. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus, vol. 94. J Virol; 2020 Mar 17. e00127. https://doi.org/10.1128/JVI.00127-20 (7)20.

[3] World Health Organisation. Coronavirus Disease 2019 (COVID-19): Situation Report-51 [Internet]. [cited 2020 Mar 18]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf.

[4] The Department of Health. Coronavirus disease 2019 (COVID-19) [Internet][cited 2020 Mar 26]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm; 2020.

[5] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019 [Internet] Nature 2020. https://doi.org/10.1038/s41586-020-2196-x.

[6] Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore [Internet] J Am Med Assoc 2020 Apr 21;323(15):1488–94. https://doi.org/10.1001/jama.2020.3204.

[7] To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study [Internet] Lancet Infect Dis 2020 Apr 24. https://doi.org/10.1016/S1473-3099(20)30196-1.

[8] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [Internet] Lancet 2020 Mar 28;395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

[9] Zhu L, Gong N, Liu B, Lu X, Chen D, Chen S, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China. Eur Urol 2020 Apr 18;77(6):748–54. https://doi.org/10.1016/j.eururo.2020.03.039.

[10] Liu W-D, Chang S-Y, Wang J-T, Tsai M-J, Hung C-C, Hsu C-L, et al. Prolonged virus shedding even after seroconversion in a patient with COVID-19 [Internet] J Infect 2020 Apr 24. https://doi.org/10.1016/j.jinf.2020.03.063.

[11] Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study [Internet] BMJ 2020 Apr 21;369: m1443. https://doi.org/10.1136/bmj.m1443.

[12] Zhou B, She J, Wang Y, Ma X. The duration of viral shedding of discharged patients with severe COVID-19 [Internet] Clin Infect Dis 2020 Apr 17. https://doi.org/10.1093/cid/ciaa451.

[13] Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19 [Internet] Lancet Infect Dis 2020 Apr 24. https://doi.org/10.1016/S1473-3099(20)30232-2.

[14] Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples [Internet] Lancet Infect Dis 2020 Apr 1;20(4):411–2. https://doi.org/10.1016/S1473-3099(20)30113-4.

[15] Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens [Internet] J Am Med Assoc 2020 Mar 11. https://doi.org/10.1001/jama.2020.3786.

[16] Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients [Internet] N Engl J Med 2020 Feb 19;382(12):1177–9. https://doi.org/10.1056/NEJMc2001737.

[17] Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples [Internet] Lancet Gastroenterol Hepatol 2020 May 1;5(5):434–5. https://doi.org/10.1016/S2468-1253(20)30083-2.

[18] Han Y, Yang H. The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): a Chinese perspective [Internet] J Med Virol 2020 Jun 1;92(6):639–44. https://doi.org/10.1002/jmv.25749.

[19] Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis [Internet] J Pathol 2004 Jun 1;203(2): 631–7. https://doi.org/10.1002/path.1570.

[20] Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes [Internet]

Emerg Microb Infect 2020 Feb 17;9(1):386—9. https://doi.org/10.1080/22221751.2020.1729071.

[21] Hung LS. The SARS epidemic in Hong Kong: what lessons have we learned? [Internet] J R Soc Med 2003 Aug;96(8):374—8. https://doi.org/10.1258/jrsm.96.8.374.

[22] Ahmed W, Angel N, Edson J, Bibby K, Bivins A, O'Brien JW, et al. First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: a proof of concept for the wastewater surveillance of COVID-19 in the community [Internet] Sci Total Environ 2020:138764. https://doi.org/10.1016/j.scitotenv.2020.138764.

[23] Liu W, Tang F, Fontanet A, Zhan L, Zhao Q-M, Zhang P-H, et al. Long-term SARS coronavirus excretion from patient cohort, China [Internet] Emerg Infect Dis 2004 Oct;10(10):1841—3. https://doi.org/10.3201/eid1010.040297.

[24] Memish ZA, Assiri AM, Al-Tawfiq JA. Middle East respiratory syndrome coronavirus (MERS-CoV) viral shedding in the respiratory tract: an observational analysis with infection control implications [Internet]. 2014/10/24 Int J Infect Dis 2014 Dec; 29:307—8. https://doi.org/10.1016/j.ijid.2014.10.002.

[25] van der Vries E, Stittelaar KJ, van Amerongen G, Veldhuis Kroeze EJB, de Waal L, Fraaij PLA, et al. Prolonged influenza virus shedding and emergence of antiviral resistance in immunocompromised patients and ferrets [Internet]. 2013/05/23 PLoS Pathog 2013;9(5). https://doi.org/10.1371/journal.ppat.1003343. e1003343—e1003343.

[26] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention [Internet] J Am Med Assoc 2020 Apr 7;323(13):1239—42. https://doi.org/10.1001/jama.2020.2648.

[27] Nishiura H, Kobayashi T, Miyama T, Suzuki A, Jung S, Hayashi K, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19) [Internet] Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.020.

[28] [Internet] The COVID-19 task force of the department of infectious diseases and the IT service istituto superiore di Sanita. Integrated surveillance of COVID-19 in Italy. 2020. Available from: https://www.epicentro.iss.it/en/coronavirus/bollettino/Infografica_24aprile ENG.pdf.

[29] Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate [Internet] BMJ 2020 Apr 2;369:m1375. https://doi.org/10.1136/bmj.m1375.

[30] Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility [Internet] N Engl J Med 2020 Apr 24. https://doi.org/10.1056/NEJMoa2008457.

[31] Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany [Internet] N Engl J Med 2020 Jan 30;382(10):970—1. https://doi.org/10.1056/NEJMc2001468.

[32] Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19 [Internet] J Am Med Assoc 2020 Apr 14;323(14):1406—7. https://doi.org/10.1001/jama.2020.2565.

[33] Yu P, Zhu J, Zhang Z, Han Y. A familial cluster of infection associated with the 2019 novel coronavirus indicating possible person-to-person transmission during the incubation period [Internet] J Infect Dis 2020 Feb 18. https://doi.org/10.1093/infdis/jiaa077.

[34] Tong Z-D, Tang A, Li K-F, Li P, Wang H-L, Yi J-P, et al. Potential presymptomatic transmission of SARS-CoV-2, zhejiang province, China, 2020 [Internet] Emerg Infect Dis J 2020;26(5):1052. https://doi.org/10.3201/eid2605.200198.

[35] He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19 [Internet] Nat Med 2020. https://doi.org/10.1038/s41591-020-0869-5.

[36] Cheng H-Y, Jian S-W, Liu D-P, Ng T-C, Huang W-T, Lin H-H. High transmissibility of COVID-19 near symptom onset [Internet] medRxiv 2020 Jan 1. https://doi.org/10.1101/2020.03.18.20034561. 2020.03.18.20034561.

[37] Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019 [Internet] medRxiv 2020 Jan 1. https://doi.org/10.1101/2020.03.02.20030189. 2020.03.02.20030189.

[38] Yong SEF, Anderson DE, Wei WE, Pang J, Chia WN, Tan CW, et al. Connecting clusters of COVID-19: an epidemiological and serological investigation [Internet] Lancet Infect Dis 2020 May 12. https://doi.org/10.1016/S1473-3099(20)30273-5.