



## Clinical features of covid-19

The wide array of symptoms has implications for the testing strategy

Pauline Vetter *medical doctor*<sup>1 2 3</sup>, Diem Lan Vu *medical doctor*<sup>2 3 4</sup>, Arnaud G L'Huillier *medical doctor*<sup>3 5</sup>, Manuel Schibler *medical doctor*<sup>2 3 4</sup>, Laurent Kaiser *professor*<sup>1 2 3 4</sup>, Frederique Jacquieroz *medical doctor*<sup>3 6 7</sup>

<sup>1</sup>Geneva Centre for Emerging Viral Diseases, Geneva University Hospitals, 1211 Geneva 14, Switzerland; <sup>2</sup>Division of Infectious Diseases, Geneva University Hospitals, 1211 Geneva 14, Switzerland; <sup>3</sup>Laboratory of Virology, Geneva University Hospitals, 1211 Geneva 14, Geneva, Switzerland.; <sup>4</sup>University of Geneva, Faculty of Medicine, 1205 Geneva, Switzerland; <sup>5</sup>Pediatric Infectious Diseases Unit, Department of Child and Adolescent Medicine, Geneva University Hospitals and Medical School, Geneva, Switzerland; <sup>6</sup>Division of Tropical and Humanitarian Medicine, Geneva University Hospitals, 1211 Geneva 14, Geneva, Switzerland; <sup>7</sup>Primary Care Division, Geneva University Hospitals, 1211 Geneva 14, Geneva, Switzerland.

In January 2020, coronavirus SARS-CoV-2 was identified as the cause of an outbreak of severe pneumonia, now known to be a complication of the coronavirus disease 2019 (covid-19).<sup>1</sup> Since then, the spread of covid-19 has increased exponentially, with the World Health Organization declaring a pandemic on 11 March.<sup>2</sup> By 15 April, more than 1 900 000 cases and 123 000 deaths had been reported worldwide.<sup>3</sup>

Severe acute respiratory illness with fever and respiratory symptoms, such as cough and shortness of breath, comprise the working case definition used to select people for viral testing. This strategy captures typical symptomatic presentation, but imperfectly identifies unusual manifestations, such as patients without respiratory symptoms or only very mild symptoms. One widely cited modelling study concluded that up to 86% of cases might have been missed in China,<sup>4</sup> and reports of patients with unusual presenting symptoms are rising worldwide.

### Non-respiratory symptoms

Case series report gastrointestinal symptoms in 2-40% of patients,<sup>5 6</sup> and diarrhoea can be the initial manifestation of infection.<sup>7</sup> Whether SARS-CoV-2 leads to such symptoms directly by infecting the gastrointestinal tract, indirectly by neurological involvement,<sup>8</sup> or through production of cytokines remains unknown. Viral RNA has been detected in stool samples, sometimes at high levels.<sup>9</sup> This raises the possibility of faecal-oral transmission,<sup>10</sup> which would have clear implications for infection control.

Taste or olfactory disorders were noted in up to 53% of the cases in a small cohort from Italy,<sup>11</sup> and new anosmia is being proposed as a criterion for testing, especially in young people with few other symptoms.<sup>12</sup> In one woman with covid-19, magnetic resonance imaging showed bilateral inflammatory obstruction of the olfactory clefts<sup>13</sup> with no abnormalities of olfactory bulbs and tracts. Complete characterisation of patients

with covid-19 and anosmia needs further research, however, as this usually transient observation is described after many respiratory viral infections.<sup>12</sup> Animal models indicate that coronaviruses might track into the brain via the olfactory nerve or bulb or both, causing neuronal damage or death.<sup>14</sup>

Recent case series from China and the US describe other neurological symptoms among patients with covid-19, including ischaemic or haemorrhagic stroke, dizziness, headache, musculoskeletal disturbance, altered mental state, Guillain-Barré syndrome, or acute necrotising encephalopathy, without proof of direct viral invasion into the brain.<sup>15-17</sup> Systematic testing for SARS-CoV-2 should be considered in patients with acute neurological events during the pandemic.

Cardiovascular events that have been associated with covid-19 in preliminary observations include myocardial injury, especially in patients with severe infections,<sup>18</sup> myocarditis<sup>19</sup> and myopericarditis with reduced systolic function,<sup>20 21</sup> cardiac arrhythmias,<sup>22</sup> heart failure, and misdiagnosis as acute coronary syndrome. Covid-19 was associated with a hypercoagulable state in a retrospective cohort study from China, probably increasing the risk for venous thromboembolic events including pulmonary embolus.<sup>23</sup> Chest pain should therefore alert clinicians to the possibility of covid-19.

Finally, ocular manifestations such as conjunctival hyperaemia, chemosis, and increased secretions, were reported in up to 32% of infected patients in a Chinese case series, and SARS-CoV-2 RNA could be detected in tears.<sup>24</sup>

Diagnosis might be particularly complicated in specific populations: children frequently have milder disease than adults, with few or no symptoms.<sup>25</sup> It's not yet clear why SARS-CoV-2 may minimally infect children, lead to asymptomatic infection, or give rise to atypical symptoms that are missed by the conventional case definition.

Infectious diseases might be harder to identify in older people, whose symptoms could be masked. A mild pneumonia might cause only fever, a fall, or confusion, leading to misdiagnosis. Diagnostic delay has serious consequences for older adults, including increased mortality and nosocomial transmission.<sup>26</sup> The threshold for testing should be lowered in this vulnerable group.

## Few or no symptoms

Risk of transmission by people with few or no symptoms remains to be quantified. Case reports indicate that runny nose or sore throat can be isolated symptoms.<sup>30</sup> Testing strategies that exclude patients with few symptoms are likely to miss a substantial proportion of cases.

Similar viral loads have been documented in the upper respiratory tract of both symptomatic and asymptomatic cases<sup>27</sup> and in the presymptomatic phase.<sup>28</sup> In one quarantined cruise ship, up to 50% of positive cases were asymptomatic or presymptomatic at the time of testing.<sup>29</sup>

Available evidence from observational and modelling reports indicates that up to 12% of transmission occurs before an index case develops symptoms.<sup>31,32</sup> This has important implications for the effectiveness of any testing strategy and for contact tracing and containment measures. To curtail active transmission of SARS-CoV-2, testing should be extended far beyond people who fit a narrow case definition and other populations currently considered at risk. The current strategy will not capture the full picture, missing a substantial number of patients with atypical presentations or few symptoms. Worse, restrictive testing criteria could lead to unrecognised cases transmitting the virus in healthcare settings or the community and to delays in appropriate patient triage and management.

Broad population screening for SARS-CoV-2 infections, isolation of confirmed cases through contact tracing and quarantine combined with social distancing, and large serological studies will be critical to slowing the spread of covid-19.

We thank Olivia Heller for editorial assistance.

Provenance and peer review: Commissioned; not externally peer reviewed.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

- Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-3. 10.1038/s41586-020-2012-7 32015507
- World Health Organization. WHO director-general's opening remarks at the media briefing on covid-19. 11 March 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>
- World Health Organization. Coronavirus disease 2019 (covid-19). Situation report 85. [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200415-sitrep-86-covid-19.pdf?sfvrsn=c615ea20\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200415-sitrep-86-covid-19.pdf?sfvrsn=c615ea20_2)
- Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). *Science* 2020;eabb3221. 10.1126/science.abb3221 32179701
- Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. 10.1056/NEJMoa2002032 32109013

- Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. *Allergy* 2020; 10.1111/all.14238.
- Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut* 2020;gutjnl-2020-320891. 10.1136/gutjnl-2020-320891 32139552
- Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020. 10.1002/jmv.25824 32104915
- Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020. 10.1038/s41586-020-2196-x 32235945
- Hui DSC, Zumla A. Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. *Infect Dis Clin North Am* 2019;33:869-89. 10.1016/j.idc.2019.07.001 31668196
- Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis* 2020;ciaa330. 10.1093/cid/ciaa330 32215618
- Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg* 2002;128:635-41. 10.1001/archotol.128.6.635 12049556
- Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of covid-19. *JAMA Otolaryngol Head Neck Surg* 2020. 10.1001/jamaoto.2020.0832 32267483
- Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008;82:7264-75. 10.1128/JVI.00737-08 18495771
- Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with covid-19 in Wuhan, China: a retrospective case series study. SSRN 3544840 [Preprint]. 2020.
- Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. Covid-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020; 201187. 10.1148/radiol.2020201187 32228363
- Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following covid-19: a single center, retrospective, observational study. SSRN (Preprint). 10.2139/ssrn.3550025.
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;S2213-2600(20)30079-5. 10.1016/S2213-2600(20)30079-5 32105632
- Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (covid-19) with myocardial injury and mortality. *JAMA Cardiol* 2020. 10.1001/jamacardio.2020.1105 32219362
- Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (covid-19). *JAMA Cardiol* 2020. 10.1001/jamacardio.2020.1096 32219357
- Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (covid-19) pandemic. *J Am Coll Cardiol* 2020;S0735-1097(20)34637-4. 10.1016/j.jacc.2020.03.031 32201335
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan. *JAMA* 2020; 10.1001/jama.2020.1585.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62. 10.1016/S0140-6736(20)30566-3 32171076
- Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (covid-19) in Hubei Province, China. *JAMA Ophthalmol* 2020; 10.1001/jamaophthalmol.2020.1291 32232433
- Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020;e20200702. 10.1542/peds.2020-0702 32179660
- McMichael TM, Currie DW, Clark S, et al. Epidemiology of covid-19 in a long-term care facility in King County, Washington. *N Engl J Med* 2020. 10.1056/NEJMoa2005412 32220208
- Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. *N Engl J Med* 2020;382:1278-80. 10.1056/NEJMc2001899 32069388
- Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382:1177-9. 10.1056/NEJMc2001737 32074444
- Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (covid-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020;25:25. 10.2807/1560-7917.ES.2020.25.10.2000180 32183930
- Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970-1. 10.1056/NEJMc2001468 32003551
- Qian G, Yang N, Ma AHY, et al. A COVID-19 transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis* 2020;ciaa316. 10.1093/cid/ciaa316 32201889
- Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:411-5. 10.15585/mmwr.mm6914e1 32271722

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>