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autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis.<sup>5</sup> Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state.<sup>6</sup>

Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins.<sup>7–11</sup> This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.

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Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, \*Frank Ruschitzka, Holger Moch  
frank.ruschitzka@usz.ch

Department of Pathology and Molecular Pathology (ZV, MH, HM), Department of Cardiology, University Heart Center (AJF, FR), Institute for Intensive Care Medicine (PS, RA, RAS), and Division of Infectious Diseases (ASZ), University Hospital Zurich, CH-8091 Zurich, Switzerland; and Department of Internal Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (MRM)

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## COVID-19: the case for health-care worker screening to prevent hospital transmission

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed unprecedented strain on health-care services worldwide, leading to more than 100 000 deaths worldwide, as of April 15, 2020.<sup>1</sup>

Most testing for SARS-CoV-2 aims to identify current infection by molecular detection of the SARS-CoV-2 antigen; this involves a RT-PCR of viral RNA in fluid, typically obtained from the nasopharynx or oropharynx.<sup>2</sup>

The global approach to SARS-CoV-2 testing has been non-uniform. In South Korea, testing has been extensive, with emphasis on identifying individuals with respiratory illness, and tracing and testing any contacts. Other countries (eg, Spain) initially limited testing to individuals with severe symptoms or those at high risk of developing them.

Here we outline the case for mass testing of both symptomatic and asymptomatic health-care workers (HCWs) to: (1) mitigate workforce depletion by unnecessary quarantine; (2) reduce spread in atypical, mild, or asymptomatic cases; and (3) protect the health-care workforce.

Staff shortages in health care are significant amidst the global effort against coronavirus disease 2019 (COVID-19). In the UK, guidance for staffing of intensive care units has changed drastically, permitting specialist critical care nurse-to-patient ratios of 1:6 when supported by non-specialists (normally 1:1) and one critical care consultant per 30 patients (formerly 1:8–1:15).<sup>3</sup> Fears of the impact of this shortage have led to other measures that would, in normal circumstances, be considered extreme: junior doctors' rotations have been temporarily halted during the outbreak; annual leave for staff has been delayed; and doctors undertaking research activities have been redeployed.

Workforce depletion will not only affect health care; the Independent Care Group, representing care homes in the UK, has suggested that social care is already “at full stretch”,<sup>4</sup> with providers calling for compulsory testing of social and health workers to maintain staffing.

In spite of this, a lack of effective testing has meant that a large number of HCWs are self-isolating (125 000 HCWs, according to one report<sup>5</sup>). In one small sample, only one in seven self-isolating HCWs were found to have the virus.<sup>6</sup> A letter to National Health Service (NHS) Trust executives on April 12, 2020, outlined that priority is being given to staff in critical care, emergency departments, and ambulance services to prevent the impact of absenteeism in those areas.<sup>7</sup> Increased testing capacity will enable all staff who are self-isolating unnecessarily to bolster a depleted workforce. Asymptomatic HCWs are an underappreciated potential source of infection and worthy of testing.

The number of asymptomatic cases of COVID-19 is significant. In a study of COVID-19 symptomatic and asymptomatic infection on the *Diamond Princess* cruise ship, 328 of the 634 positive cases (51.7%) were asymptomatic at the time of testing.<sup>8</sup> Estimated asymptomatic carriage was 17.9%.<sup>8</sup> Among 215 obstetric cases in New York City, 29 (87.9%) of 33 positive cases were asymptomatic,<sup>9</sup> whereas China’s National Health Commission<sup>10</sup> recorded on April 1, 2020, that 130 (78%) of 166 positive cases were asymptomatic. Moreover, transmission before the onset of symptoms has been reported<sup>11–14</sup> and might have contributed to spread among residents of a nursing facility in Washington, USA.<sup>15</sup> Furthermore, evidence from modelled COVID-19 infectiousness profiles suggests that 44% of secondary cases were infected during the presymptomatic phase of illnesses from index cases,<sup>16</sup> whereas a study of COVID-19 cases in a homeless shelter in Boston, MA, USA, implies that individual COVID-19 symptoms might

be uncommon and proposed universal testing irrespective of symptomatic burden.<sup>17</sup> Substantial asymptomatic transmission might also mean that current estimates of the basic reproduction number,  $R_0$ , for COVID-19 are inaccurate.<sup>18</sup>

HCW testing could reduce in-hospital transmission. In a retrospective, single-centre study in Wuhan, 41% of 138 patients were thought to have acquired infection in hospital.<sup>19</sup> At the Royal Gwent Hospital in Newport, Wales, approximately half of the emergency room workforce have tested positive.<sup>20</sup> Blanket testing near Venice, Italy, helped to identify asymptomatic cases and might have helped eliminate SARS-CoV-2 in a village.<sup>21</sup> Moreover, asymptomatic and presymptomatic HCWs continue to commute to places of work where personal protective equipment (PPE) might be suboptimal. This disease spread could, in turn, propagate out of hospitals: during a period of lockdown asymptomatic COVID-19 carriage among hospital staff could conceivably act as a potent source of ongoing transmission.

Protecting the health of HCWs is paramount when staffing is limited. As well as by the provision of adequate PPE, the wellbeing of HCWs can be promoted by ensuring that infected colleagues are promptly tested and isolated. The scale of this problem is not yet fully understood, nor is the full potential for asymptomatic and presymptomatic HCWs to transmit infection to patients who do not have COVID-19, other HCWs, or the public. However, given that asymptomatic transmission has been documented, utmost caution is urged.<sup>11–14</sup>

Our own NHS Trust at University College London Hospitals, London, UK, will soon be testing asymptomatic HCWs. In partnership with the Francis Crick Institute in London, UK, where COVID-19 testing will be performed, this initiative is an attempt to further limit nosocomial transmission. It could also alleviate a

critical source of anxiety for HCWs.<sup>22</sup> A healthy, COVID-19-free workforce that is not burned out will be an asset to the prolonged response to the COVID-19 crisis. As testing facilities increase in number and throughput in the coming weeks, testing should aim to accommodate weekly or fortnightly screening of HCWs working in high-risk areas.

There is a powerful case in support of mass testing of both symptomatic and asymptomatic HCWs to reduce the risk of nosocomial transmission. At the time of writing, the UK is capable of performing 18 000 tests per day,<sup>23</sup> with the Health Secretary targeting a capacity of 100 000 tests per day by the end of April, 2020. Initially, the focus of testing was patients, with NHS England stating only 15% of available testing would be used to test NHS staff.<sup>24</sup> Although this cap has been lifted, symptomatic HCWs, rather than asymptomatic HCWs, are currently prioritised in testing. This approach could mean that presymptomatic HCWs who are capable of transmitting the virus are not being tested; if they were tested and found to be COVID-19 positive, they could be advised to isolate and await the onset of symptoms or, if no symptoms develop, undergo repeat testing.

As countries seek to flatten the growth phase of COVID-19, we see a significant opportunity in expanding testing among HCWs; this will be critical when pursuing an exit strategy from strict lockdown measures that curb spread of the virus.

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James R M Black, Chris Bailey,  
Joanna Przewrocka, Krijn K Dijkstra,  
\*Charles Swanton

charles.swanton@crick.ac.uk

Cancer Genome Evolution Research Group, University College London Cancer Institute, University College London, London, UK (JRM); Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London NW1 1AT, UK (CB, JP, KKD, CS); Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London, UK (CS); and University College London Hospitals NHS Trust, London, UK (CS)

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## Universal weekly testing as the UK COVID-19 lockdown exit strategy

The British public have been offered alternating periods of lockdown and relaxation of restrictions as part of the coronavirus disease 2019 (COVID-19) lockdown exit strategy.<sup>1</sup> Extended periods of lockdown will increase economic and social damage, and each

relaxation will almost certainly trigger a further epidemic wave of deaths. These cycles will kill tens of thousands, perhaps hundreds of thousands, of people before a vaccine becomes available, with the most disadvantaged groups experiencing the greatest suffering.

There is an alternative strategy: universal repeated testing.<sup>2</sup> We recommend evaluation of weekly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen testing of the whole population in an entire city as a demonstration site (preferably several towns and cities, if possible), with strict household quarantine after a positive test. Quarantine would end when all residents of the household test negative at the same time; everyone else in the city can resume normal life, if they choose to. This testing programme should be assessed for feasibility in one or more cities with 200 000–300 000 people. Such a feasibility study should begin as soon as possible and continue after the current lockdown ends, when the infection rate will be fairly low but rising. The rate at which the number of infections then rises or falls, compared with the rest of the UK, will be apparent within a few weeks. A decision to proceed with national roll-out can then be made, beginning in high-risk areas and limited only by reagent supplies. If the epidemic is controlled, hundreds of thousands of lives could be saved, intensive care units will no longer be overloaded, and the adverse effects of lockdown on mental ill health and unemployment will end.

A local population of 200 000 people, with 90% compliance, will require 26 000 tests per day, plus a small excess to offer daily antigen testing for National Health Service (NHS) staff and care workers. Such a study is likely to have the enthusiastic support of the population. Whatever the results, these data will enable policy to be based on real-time evidence, rather than modelling assumptions, of new infection rates in the expanding,



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