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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Editorial

Health policy implications of the links between cardiovascular risk and COVID-19

The COVID-19 pandemic is entering a new phase with a second wave of infections across the European and other major international regions [1]. There remain serious health policy challenges in dealing with the responsible SARS-CoV2 pathogen [2]. Schools and colleges are now re-opening, with associated risks of increased virus transmission to other children and students, teaching staff, families and their contacts. However, WHO advice on wearing of masks by pupils and students is being ignored and frequent, effective testing of teaching staff is not systematic.

Respiratory viral transmission is typically greater in colder weather therefore COVID-19 incidence is likely to increase in the Northern Hemisphere in the coming months. This will coincide with the influenza season. However well-established international influenza immunization programmes are likely to be less effective this winter. A higher incidence of influenza is to be expected due to reduced uptake of influenza immunizations – an unintended consequence of public health restrictions on mobility to control COVID-19. Many older people and others with medical disorders with most to benefit from protection from influenza by immunization now have reduced confidence in leaving home. They are therefore much less likely to be prepared to access community health services to receive an influenza immunization. An epidemic of simultaneous influenza and COVID-19 is therefore a serious concern. This would result in higher morbidity and mortality in vulnerable people and greater pressure on acute medical services.

The preferred approach to controlling and improving outcomes of COVID-19 is development of effective vaccines. In the meantime, public health measures are the mainstay for containing spread of infection with SARS-CoV-2, complemented by access to high quality supportive treatment and efforts to develop targeted approaches to reduce infection and disease severity in people at high risk of serious morbidity and death from COVID-19. However, eight months since this new respiratory syndrome was first reported to international authorities, effective test and trace systems have not yet been internationally implemented, even across all well-developed healthcare systems. For example, in the UK reporting of test results has fallen to below 50% within 24 hours and one in seven home testing kits are reported to fail to yield a result [3].

There are major global efforts underway to develop vaccines against COVID-19, with 19 candidates as of 31 July 2020 entered into clinical studies, including phase 2 and 3 trials [4]. However, their short and long-term effectiveness and safety remain to be established. The usual questions for a new vaccine remain to be answered. Will vaccines prevent COVID-19 or at least improve prognosis from the infection? Will groups at higher risk from COVID-19 respond as well as the often healthier volunteers in clinical trials? The timeline also remains uncertain for widespread public protection if and when safe and effective vaccines become available. International networks for pharmacovigilance against adverse effects of COVID-19 vaccines are needed, with for example Utrecht University in The Netherlands being commissioned by the European Medicines Agency as a hub for a Europe-wide network [5].

People with co-morbidities are more likely to be infected with SARS-CoV-2, especially those with hypertension, coronary heart disease, diabetes mellitus and obesity. They are also more likely to have worse outcomes from COVID-19, with similar associations in reports for example from China, the USA and Italy [6,7]. People with cardiovascular risk factors or established cardiovascular disease also experience a high case-fatality rate from COVID-19 [6,7]. For example, hypertension was reported in 40% of patients who died [odds ratio for death, 3.05 (95% CI: 1.57–5.92)] in a meta-analysis of over 40,000 confirmed COVID-19 patients in China [7]. In the same report, cardiovascular disease [CVD] was associated with a 5-fold increase in risk of death from COVID-19 [7]. Although the elderly are at greater risk of infection and death, younger adults are also at risk, especially those who are obese [8] and/or from Black and Asian ethnic minorities [9].

A recent meta-analysis of almost 400,000 subjects [8] reported that patients with a BMI over 30 kg/m^2 were ~50% more likely to develop COVID-19 – and for those with COVID-19, over twice as likely to be admitted to hospital for treatment, ~75% more likely to be admitted to an Intensive Care Unit and had a ~50% greater mortality than the less overweight. For patients from BAME groups, a lower BMI threshold of over 25 kg/m^2 appeared associated with worse severity from COVID-19.

In addition to being at increased risk of COVID-19, obese patients also appear less likely to respond effectively to the influenza immunization [10]. There are therefore concerns that obese people may also respond less well to immunization against SARS-CoV2. However, as examples of the global health challenge, obesity remains an international epidemic, despite international efforts, including Sustainable Development Goals for health adopted by the G7, G20 and BRICS countries [11], and despite its being recognized as a disease by many organisations [12] including by the American Medical Association since 2013, and the long-established role of obesity as a major contributor to serious disorders of the heart, brain and circulation, as well as many cancers, joint disease and poor mental health. The WHO estimates that obesity has tripled

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since 1975 and that by 2016 there were 650 million obese people globally (1.6 billion overweight) [13].

Reasons why Black and Ethnic minorities (BAME) are more at risk of infection with SARS-CoV2 and of worse outcomes from COVID-19 are unclear [9]. For example, in one study in the UK one third of patients admitted to ICU due to COVID-19 were from an ethnic minority [14], with similar reports from the USA. Possible reasons include a higher prevalence in BAME populations of cardiovascular risk factors e.g. hypertension, diabetes mellitus, insulin resistance and obesity, socioeconomic, cultural, or lifestyle factors and genetic predisposition. There may also be pathophysiological differences in susceptibility or response to infection due for example to increased prevalence of vitamin D deficiency. An increased inflammatory burden may also contribute to worse outcomes.

ACE-2 (angiotensin converting enzyme II) is the key docking protein by which the COVID-19 virus binds to cells [15]. This is also the key cell entry receptor used by the initial SARS-CoV [15]. ACE-2 is mainly found on vascular endothelial cells, the renal tubular epithelium and the Leydig cells of the testis. Copies of the ACE-2 protein are present in increased numbers in patients with risk factors for heart disease. ACE-2 could thus be a therapeutic target in the treatment of COVID-19. However enzymatic activity of ACE-2 controls activation of the renin-angiotensin-aldosterone system (RAAS), a current therapeutic target in cardiovascular and renal disease. There were concerns that common medicines such as ACE inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs) used to treat hypertension or heart failure by inhibiting the renin-angiotensin system could adversely affect ACE-2 expression. However, studies to date in SARS-CoV-2-infected patients do not suggest that these RAAS modulators influence susceptibility to the infection or cause more severe COVID-19.

Indeed, in a meta-analysis of almost 29,000 patients with COVID-19, use of RAAS inhibitors for any condition showed a trend to lower risk of death or critical events (odds ratio 0.67, 95% CI 0.43 to 1.03, $p = 0.07$). Within the hypertensive cohort, treatment with ACEi or ARBs was associated with one third less mortality from COVID-19 (odds ratio 0.66, CI 0.46 to 0.96, $p = 0.03$) and a one third reduction in the combined end-point of death and critically severe outcomes (odds ratio 0.67, CI 0.50 to 0.91, $p = 0.01$) [16]. This was however an observational study and there is as yet no evidence as to whether adding an ACEi or ARB to treatment would influence the outcome of COVD-19.

SARS-CoV2 can cause acute or delayed myocardial injury, with features that mimic ST-elevation myocardial infarction (STEMI); the virus may also cause arrhythmias and acute coronary syndromes. Myocardial injury is found in over 25% of critical cases of COVID-19 and presents in 2 patterns: acute myocardial injury and dysfunction on presentation and delayed myocardial injury that develops as illness severity intensifies [6]. There are also potentially serious drug–cardiac disease interactions affecting patients with COVID-19 and associated cardiovascular disease, for example from empirical anti-inflammatory treatments [6].

SARS-CoV2 may also cause hypercoagulability, resulting in unexpectedly severe lung damage from widespread thromboses and disseminated intravascular coagulation, adding to lung injury from COVID-19 pneumonia [17]. These features suggest complement-mediated thrombotic microangiopathy as a contributory factor and may give clues to treatment beyond anti-coagulation to prevent life-threatening microangiopathy [17,18].

An indirect factor in COVID-19-related increased severity of cardiovascular disease is malnutrition in patients self-isolating at home. This may directly increase risk of falls, heart attack and stroke, especially when patients continue diuretics and other blood pressure-lowering medicines despite reduced oral intake of food and drink – a recognized cause of hypotension and falls. Other indirect reasons for concern about increased prevalence and severity of cardiovascular disease because of the COVID-19 pandemic include poorer recognition and control of cardiovascular risk factors and established serious disorders of the heart, brain and circulation due to reduced access to medical services. Particularly in less developed countries, public transport is vital for access to health care facilities. Both public transport services and activities of medical facilities have been seriously limited during COVID-19 restrictions and availability of funds to pay for medical services has been severely reduced. For example, in India over 75% of the country's substantial workforce of 100 million migrant workers lost their jobs overnight, public transport services were critically reduced, and many healthcare facilities closed [19].

Increasing recognition of these links between cardiovascular risk and disease and severity of COVID-19, including mortality, offer opportunities to improve outcomes of COVID-19 in the large number of patients with these common disorders. Understanding the pathophysiology and exploring potential solutions and treatments to reverse worse outcomes in patients at increased cardiovascular risk is a priority for health researchers and clinical health services around the world. This is all the more pressing as there is an international epidemic of the preventable cardiovascular risk factors which have been linked to increased severity of COVID-19.

Health policy makers also need to take steps to extend influenza immunization to all groups now recognized to be at risk of more serious COVID-19, including the obese, others with increased cardiovascular risk and people from black and other at risk ethnic minorities. Policy makers will need to make extra efforts to make sure that these vulnerable people take part in influenza immunization programmes. This requires measures to make sure that accessing points of care will not put people at risk of acquiring COVID-19. Policy makers also need to build public awareness of the current extra importance of influenza immunization and confidence in the safety of accessing medical services.

The involvement of policy makers to ensure sustained financial and social solutions for COVID-19 is urgently needed to complement the efforts against COVID-19 of health professionals, regulators and the pharmaceutical and biotechnology industries. These efforts will not be successful without also addressing the cardiovascular and other factors that contribute to higher risk from COVID-19. Links to the severity of COVID-19 make it all the more pressing for policy makers and public health agencies to address underlying causes and to reduce the incidence and severity of preventable cardiovascular risk.

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