



Tobacco smoking and COVID-19 infection



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Taxes on the sale of tobacco products provide enormous revenue for governments and the tobacco industry provides millions of jobs globally; but tobacco also causes death in 50% of consumers and places a heavy, preventable toll on health-care systems. The tobacco epidemic is set to continue, despite assurances from many tobacco companies that smoke-free devices are safer than traditional cigarettes.

During the coronavirus disease (COVID-19) pandemic, the issue of tobacco smoking and risk for acute respiratory infection is again topical. Much of the global focus on tobacco prevention and cessation focuses around non-infective respiratory, cardiovascular, and cancer related deaths, and much of the e-cigarette promotional rhetoric revolves around potentially saving billions of lives that might otherwise be lost due to these non-infective outcomes. The risk of infectious complications is, however, the predominant focus and concern in low-income and middle-income countries, particularly during pandemics. Some countries, for example South Africa and India, have banned the sale of tobacco products during lockdown periods. Whether this ban is justified and supported by evidence of harm from the combined effect of tobacco use and COVID-19 is uncertain, as is whether current smokers can be expected to simply stop during a pandemic.

Robust evidence suggests that several mechanisms might increase the risk of respiratory tract infections in smokers. Smoking impairs the immune system and almost doubles the risk of tuberculosis infection (latent and active) due to impairment of immune function; specifically, smoking affects the macrophage and cytokine response and hence the ability to contain infection. Similarly the risk for pneumococcal, legionella, and mycoplasma pneumonia infection is about 3–5-times higher in smokers. Users of tobacco and e-cigarettes have increased adherence of pneumococci and colonisation, as a result of the upregulation of the pneumococcal receptor molecule (platelet activating receptor factor); smokers are also 5-times more likely to contract influenza than non-smokers.

Data from the previous Middle Eastern respiratory syndrome coronavirus (MERS) and severe respiratory syndrome coronavirus (SARS) is scarce. A single study from Korea reported a 2.55 (95% CI 1.1–5.9) increased risk of mortality in smokers with MERS, but this study included only eight smokers. For COVID-19, data are also scarce; one review did not report on smoking as a risk factor for infection, but did report an increased risk of severe disease (relative risk [RR] 1.4 [95% CI 0.98–2.00]) and need for mechanical ventilation or death (RR 2.4 [1.43–4.04]) for current smokers. Another meta-analysis did not find an association between current smoking and disease

severity. The largest study to date (pre-print), from the UK, reports an increased risk for death in current smokers compared with never-smokers of 1.25 (95% CI 1.12–1.40) when adjusted for age and sex, which decreased to 0.88 (0.79–0.99) when fully adjusted.

Mechanistic studies postulate that the increased susceptibility to infection might be due to upregulation of the angiotensin converting enzyme 2 (ACE2) receptor, the main receptor used by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to gain entry to host mucosa and cause active infection—an apparently unique mechanism to this virus. Current smokers have increased gene expression of ACE2, than previous smokers and non-smokers. In addition, there is an association between FEV₁ and ACE2 gene expression. Despite this association, it is unclear whether modification of ACE2 receptor frequency or availability has an effect on mortality. Certainly, patients on ACE inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs) do not appear to be at increased risk of infection or death. Non-peer-reviewed data released from France suggests that smoking might have a potential protective effect against SARS-CoV-2 infection, via interaction with the acetylcholine receptor, but these data have not been confirmed and should not in any way be an indicator to start or continue smoking.

The challenge for studies of COVID-19 is to have large enough sample sizes to allow correction for confounders, such as hypertension, diabetes, obesity, race, sex, and chronic obstructive pulmonary disease (COPD), all of which might be associated with tobacco smoking and poor outcomes. Currently, no evidence suggests that e-cigarette use increases the risk of being infected by SARS-CoV-2.

It is possible that the period of self-isolation and lockdown restrictions during this pandemic could be used by some as an opportunity to quit smoking, but realistically only a minority of people will achieve cessation. For the majority, the increased stress of a potentially fatal disease, possibility of loss of employment, feelings of insecurity, confinement, and boredom, could increase the desire to smoke. During the financial collapse of 2008, tobacco shares were one of the only shares to increase.

Here, we suggest a few steps to help reduce tobacco use during this pandemic and hopefully long after. First, every smoker should be encouraged to stop, be provided with advice, support, and pharmacotherapy, if available; times of crisis can often provide the impetus to stop smoking. Banning tobacco sales might not be wholly effective if people are still able to access cigarettes and so other measures need to be implemented to discourage tobacco use. In South Africa, before the pandemic, the

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For more on **global smoking and respiratory infection epidemics** see

Infect Dis Clin North Am 2010; **24**: 693–703

For more on **smoking and tuberculosis** see

Am J Respir Crit Care Med 2014; **190**: 1430–06

For more on **smoking and impaired immune response** see

Thorax 2014; **69**: 363–70

For more on **e-cigarette vapour and pneumococcal adherence** see

Eur Respir J 2018; **51**: 1701592

For more on **smoking and influenza** see *J Infect* 2019; **79**: 401–06

For the **Korean study** see

Int J Infect Dis 2017; **58**: 37–42

For the **review on COVID-19 and smoking** see *Tob Induc Dis* 2020; **18**: 20

For the **meta-analysis on smoking and severity of COVID-19** see *Eur J Intern Med* 2020; **75**: 107–08

For the **pre-print OpenSAFELY study** see *medRxiv* 2020; 2020.05.06.20092999

For more on **ACE2 expression in smokers** see *JAMA Cardiol* 2020; published online April 23. DOI:10.1001/jamacardio.2020.1624.

For more on **ACE2 expression** see *Eur Respir J* 2020; **55**: 2000688

illegal cigarette trade was thriving and according to news reports, virtually all smokers have ready access to cigarettes, provided they can afford the inflated prices.

Second, we need more data; many of the H1N1 influenza cohorts did not report on smoking status, which is also the case for many other infectious diseases. To determine the effect smoking might have on infection, it is essential that every person tested for COVID-19, and for other respiratory infectious diseases, should be asked about their smoking history. All outcomes related to screening, testing, admission, ventilation, recovery, and death need to be evaluated relative to smoking status and adjusted for comorbid conditions, such as ischaemic heart disease and COPD.

Finally, the world should aim to be tobacco free, but given the intricate web of finance, taxes, jobs, lobbying,

and payments made to officials, this is unlikely to happen in the near future. However, the battle against tobacco use should continue, by assisting smokers to successfully and permanently quit. Avoiding COVID-19 now, but having lung cancer or COPD later on, is not a desired outcome; therefore, any short-term interventions need to have long-term sustainability.

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For more on ACEIs and ARBs and COVID-19 see *JAMA Cardiol* 2020; published online April 23. DOI:10.1001/jamacardio.2020.1624

For more on the illegal cigarette trade in South Africa see *Trends in Organized Crime* 2019; published online Nov 22. DOI:10.1007/s12117-019-09372-9

Film

Pandemic: examining readiness for infectious disease outbreaks

Pandemic was released a few days before WHO declared the novel coronavirus disease 2019 (COVID-19) a public health emergency of international concern. Fortuitous timing, but if there is one lesson from Netflix's thorough new documentary series, it is that the world is always on the brink of an epidemic of catastrophic potential. *Pandemic* largely focuses on influenza, though a visit to a live animal and seafood market in Vietnam offers a reminder of the range of zoonotic diseases that can emerge from all those creatures kept in close quarters. As befits its subject matter, the series takes a global perspective, examining the readiness, or lack thereof, for the outbreak that we know is coming.

The lengthy running time, almost 5 h over six episodes, allows for a leisurely look at the different elements of epidemic preparedness. We track attempts by a small biotechnology firm to develop a universal influenza vaccine, efforts by researchers on different continents to monitor the pathogens that circulate in bats and migrating birds, and the exhausting work that goes into maintaining a cash-strapped rural hospital in the USA. A foray to the Ebola-stricken states of the Democratic Republic of the Congo highlights the hazards of epidemic response in regions where insecurity and mistrust are rife; while a trip to Rajasthan, India, shows how poverty and overcrowded living conditions permit infectious diseases to proliferate.

The programme makers even find room for the vaccine-hesitant. The charming Caylan Wager, a mother and self-proclaimed independent wellness advocate, outlines a reasonable argument against mandatory vaccination. But it is only reasonable if you do not think about the

consequences. In the most depressing storyline to unfold in *Pandemic*, a bill that would restrict the grounds on which parents in Oregon, USA, can refuse to have their children vaccinated fails to become law.

It is an expansive and honest documentary; a clear-sighted exploration of just how difficult it is to pre-empt a pandemic. "With the proper risk mitigation measures, there is no excuse for any outbreak to become more than an outbreak", points out Dennis Carroll, former director of USAID's emerging threat unit, partway through the series. The participants in *Pandemic* fight tirelessly for public health, at no small cost to their personal lives. But all that energy and purpose is not typically matched by adequate resources and political engagement. As the outcome of the Oregon bill amply demonstrates, progress is never guaranteed.

Talha Khan Burki



Courtesy of Netflix



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Pandemic: how to prevent an outbreak
Netflix, 2020
Season 1, 6 episodes