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Early View

Correspondence

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COVID-19 and vaping: risk for increased susceptibility to SARS-CoV-2 infection?

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With great interest we read and commend the study done by Russo and colleagues, highlighting their findings that nicotine induces an increase in angiotensin-converting enzyme-2 (ACE2) expression in human bronchial epithelial cells (HBEpC) and is mediated

by α7-subtype nicotinic receptors (α7-nAChR) (1). It raises the concern that all electronic nicotine-delivery systems may put users at greater risk of succumbing to COVID-19.

We along with Leung et al. have shown that ACE2 expression is upregulated in the small airway epithelia of smokers and patients with COPD (2, 3). In particular we observed increased ACE2 expression in type-2 pneumocytes and alveolar macrophages along with the small airway epithelium of smokers compared to healthy never-smokers (2). Similar studies are yet to be done in the context of electronic cigarettes (e-cigarette), heat-not-burn device (IQOS) or waterpipe exposure to human airways. ACE2 is the binding site for SARS-CoV-2, mediating entry of the virus into cells (4). Binding affinity between the spike (S) proteins of the virus and ACE2 on respiratory cells has been identified to be much higher than any previously identified human coronavirus. The significance of such overexpression of ACE2 in smokers should not be ignored. COVID-19 and progression of severe pneumonia may be more likely to occur in smokers, particularly in those that have smoking-related comorbidities (5). We are beginning to elucidate the role of traditional cigarette smoking and nicotine-driven changes to the lungs in the context of coronavirus transmission and susceptibility. Cigarette smoke has been identified and linked to increasing expression of the binding site for the cause of the 2020 pandemic (SARS-CoV-2) via mediating nicotine receptors. With this, an avoidable and potentially gigantic risk-factor has emerged for COVID-19, as the pandemic continues to claim ultimate grasp over the year of 2020.

Here, we bring to the discussion whether the increased susceptibility and virulence of SARS-CoV-2 via α7-nAChR and the upregulation of small airway ACE2 expression may also be relevant for those who vape using nicotine-based e-cigarettes. E-cigarette vapour studies, although in their infancy, have already shown that they can enhance the virulence and inflammatory profile of pathogens such as *Streptococcus pneumoniae* among other

deleterious biological effects (6). Vaping intensifies pneumococcal adherence through an increase in platelet-activating factor receptor expression, ultimately rendering those who vape with an increased risk of pneumonia (7, 8). We, among others have previously shown that e-cigarettes and IQOS are not “safer”, as having a vast pro-inflammatory response (9). We compared cigarette smoke versus e-cigarette and IOQS on airway epithelial and smooth muscle cells (9). All tested pathological biomarkers were elevated in cells exposed to e-cigarette aerosols and IQOS, which included chemokine CXCL8, extracellular matrix proteins and markers of mitochondrial dysfunction. We found these products toxic to the cells, evident from decreased cellular viability and integrity. More devastatingly, vaping also interfered with cellular energetics. Our results further substantiate current research that e-cigarettes and IOQS are indeed detrimental with increases in oxidative stress, inflammation, infections and airway remodelling in the lungs of these device users. As the scientific evidence mounts, confirming the fears of e-cigarettes and IQOS, strongly associated with the development and progression of debilitating lung diseases (10), now may be the prime time to include all electronic nicotine delivery systems in the vocalisation of concerns concerning tobacco-related death and disease.

We recirculate the simple notion that the lungs are not designed for the chronic inhalation of anything but air and that the indication for a smoking and nicotine induced increase in ACE2 is more evidence to the stacking weight of toxicity that tobacco is for humanity. Given the role of the nicotine receptor, vaping may also lead to the upregulation of ACE2. Research in this area will be invaluable in the development of e-cigarette research and providing trusted, peer-reviewed and real evidence for the youth of the 20s. We strongly recommend that the World Health Organisation and countries act to advance their efforts to reduce smoking, vaping and waterpipe use. During a pandemic it is difficult to focus on anything other than the immediate threat. The "primacy of rescue" has overwhelmed preventive action.

Additional research into the relationship of smoking, all electronic nicotine delivery systems to infection, transmission and progression of COVID-19 is required. Progress towards easily identifying those susceptible to severe disease or capable of asymptomatic transmission are important goals for managing the disease at a community level. COVID-19 is a dress rehearsal for the next pandemic, and the next, and the one after that - the new norm.

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