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SYNOPSIS

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Tobacco and COVID-19 – What We Know So Far

Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

Key Findings

- Tobacco smoking may pose a theoretical increased risk of SARS-CoV-2 infection due to frequent hand-mouth contact during smoking; however, there is no conclusive evidence at this time.
- Studies on the association between tobacco use and SARS-CoV-2 infection have included only hospitalized patients and have not found significant association between current tobacco use and an increased risk of infection.
- There are reports that individuals with comorbidities have an increased risk of adverse COVID-19 related outcomes. Tobacco use is a known risk factor for many of these comorbidities.
- There is some evidence to suggest that smoking tobacco is associated with increased disease severity (e.g. admission to intensive care unit) and death among hospitalized COVID-19 patients. The risk of hospitalization due to COVID-19 infection among individuals who currently smoke cigarettes is unknown.
- No studies have assessed the impact of smoking cessation on COVID-19 infection, progression or outcomes.
- There is currently no evidence to confirm any link between tobacco or nicotine exposure in the prevention or treatment of COVID-19. The relationship between tobacco and COVID-19 is not well understood.
- Regardless of the relationship between smoking and COVID-19, there is evidence that quitting smoking at any age has health benefits and reduces risk from and impact of comorbidities associated with more severe COVID-19 disease.

Background

Tobacco use is the leading cause of preventable premature death globally and in Canada. In Ontario, 16,000 deaths are attributed to tobacco use each year and tobacco use contributes to significant direct health care costs every year (Public Health Ontario).

Determining the role of smoking tobacco in COVID-19 and related outcomes is important. If tobacco smoking is a confirmed risk factor for COVID-19 (infection or adverse outcomes), this may represent a modifiable risk factor, with opportunity to reduce risk in some individuals.

There has been much media attention around the role of tobacco smoking on COVID-19 infection, transmission, severity and mortality. The expectation is that smoking tobacco would predispose an individual to worse outcomes from COVID-19, as it has with other acute respiratory infections. However, the available evidence is conflicting at this time, with some studies finding a lower prevalence of current tobacco use among hospitalized COVID-19 patients. Caution should be exercised in attempting to draw conclusions.

This document examines the evidence on the effect of smoking tobacco on the susceptibility to and severity of COVID-19.

Methods

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

To identify tobacco-related evidence, systematic searches were completed on June 11, 2020. PHO Library Services conducted a search in MEDLINE, EMBASE, CINAHL, Global Health and Scopus. A grey literature search was conducted for the web sites of key organizations using a standard search strategy, to identify any grey literature reports. As this is a rapidly evolving area, to provide context, we included letters to the editor and commentaries within our searches. Additional published journal articles from tobacco control listservs that met inclusion criteria were also included in the body of evidence.

One reviewer screened titles and abstracts, and then full text versions for all papers for inclusion. A second reviewer screened 25% of the titles and abstracts, as well as 25% of full text versions of all papers for inclusion. Items for clarification were discussed among the two reviewers.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Smoking and Susceptibility to COVID-19 Infection

Smoking Behaviour

The act of smoking, which involves frequent hand-mouth contact, may increase the opportunity for the SARS-CoV-2 virus to enter the body for those who smoke (Berlin et al., Silva et al., World Health Organization). Smoking can also be a social activity among peers. Sharing cigarettes or other tobacco smoking devices, such as hookah/waterpipes, also presents a risk for transmission of COVID-19 (Public Health Ontario, Silva et al., World Health Organization, World Health Organization Eastern Mediterranean, Yasri et al.).

Cell Receptors

Studies on the relationship between smoking and the risk of SARS-CoV-2 infection, which requires cell entry via the angiotensin-converting enzyme 2 (ACE2) receptor, are conflicting. The focus of inquiry has been the role of ACE2 receptors and other enzymes in the susceptibility to COVID-19 infection. A few studies published before the COVID-19 pandemic reported that smoking and nicotine down-regulated ACE2 (reducing the number of ACE2 receptors available in the body) (Farsalinos et al.; Sachithanandan A.). Based on this, a hypothesis is that nicotine lowers ACE2 expression, thereby preventing viral particles from entering an individual's cells, with a possible role in reducing SARS-CoV-2 infection rates (Tindle et al.).

The results from studies since the start of the COVID-19 pandemic suggest the opposite, that nicotine from tobacco causes an up-regulation of ACE2, suggesting an increase in susceptibility or severity of SARS-CoV-2 (Brake et al., Cai et al., Charkladar et al., Choi et al., Guo FR., Leung et al., Li et al., Olds et al., Radzikowska et al., Russo et al., Saheb Sharif-Askrai et al., Smith et al., Zhang et al.). Zhang et al. also found that male smokers had the highest ACE2 expression level, higher than female smokers or non-smokers of either sex. This potentially explains elevated COVID-19 incidence in men, at least among those who smoke tobacco. Nonetheless, the clinical significance of these findings for SARS-CoV-2 infection risk remains unclear (Tindle et al.).

No studies have directly assessed up-regulation of ACE2 and its association with increased susceptibility to SARS-CoV-2 infection (Farsalinos et al.). Questions remain around the role it plays in the susceptibility and severity of COVID-19 and the influence of current and former smoking on ACE2.

There are currently no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection among individuals who currently smoke tobacco cigarettes (World Health Organization). Gaining a better understanding about host factors, especially modifiable factors such as smoking, could be important in reducing susceptibility and severity of disease (Berlin et al., Cattaruzza et al.). In order to answer this research question, well-designed population-based studies that control for age and other relevant underlying risk factors are needed (World Health Organization).

Smoking and COVID-19 Disease Progression & Outcomes

There is a wide range of COVID-19 disease severity, from asymptomatic or mild, to moderate or severe disease, and death. Although most patients infected and diagnosed with COVID-19 have mild-to-moderate symptoms, approximately one in five individuals experience severe or critical illness (Government of Canada).

Smoking is an established risk factor for respiratory infections, has a significant impact on the immune system, activates inflammation, and has a strong relationship with pre-existing conditions (i.e., Chronic Obstructive Pulmonary Disease (COPD)) which have emerged as risk factors for COVID-19 severity and death (Cattaruzza et al., U.S. Department of Health and Human Services, World Health Organization). Evidence from other outbreaks caused by similar viruses such as Middle East Respiratory Syndrome (MERS), suggest that tobacco smoking could directly or indirectly contribute to an increased risk of infection, severity, disease progression and/or mortality from infectious respiratory diseases (World Health Organization Eastern Mediterranean).

Hospitalization

No peer-reviewed studies that directly estimate the risk of hospitalization with COVID-19 among individuals who currently smoke cigarettes were identified. The studies in this area focus on prevalence of smoking among hospitalized COVID-19 patients, and are summarized below.

Hamer et al. found a dose-dependent association between the risk of COVID-19 infection and worsening lifestyle scores (i.e., smoking history, physical activity, alcohol use, and obesity). Patients that were in the most unfavourable lifestyle category had a 4-fold higher risk of COVID-19 infection (RR=4.41; 95% CI, 2.52, 7.71), though for smoking alone the increased risk was modest (1.42, 1.12, 1.79), and associations between these and socioeconomic factors (including access to healthcare) were not addressed, which may confound the findings. The authors nonetheless conclude that preventative measures to mitigate these lifestyle factors could reduce the risk of severe infection and hospitalization.

Farsalinos et al. conducted a meta-analysis which pooled the prevalence of smokers among hospitalized patients across studies based in China. In this analysis, the authors analysed data for 5,960 hospitalized patients and found a pooled prevalence of 6.5% (1.4%–12.6%). When compared to the general population, which has prevalence of 26.6%, the prevalence of current smoking was much lower than expected. The authors concluded that current smoking does not appear to be a predisposing factor for hospitalization for COVID-19.

A meta-analysis by Emami et al. which also pooled the prevalence of smokers in 2,986 hospitalized patients across studies based in China, reported a prevalence of smoking of 7.6% (3.8%–12.4%).

Several observational studies that were not included in the above meta-analyses found that individuals who smoke tobacco made up approximately 1.8%–8% of hospitalized COVID-19 positive patients (Chow et al., Liu J. et al.). There have also been a number of small case studies that found no significant difference in severity among hospitalized COVID-19 patients based on smoking status (Toussie et al., Zheng Y. et al.).

An ecological study conducted by Tsigaris et al. found a negative association between smoking prevalence and COVID-19 occurrence at the population level in 38 European countries. The authors cautioned that this association may not imply a true or causal relationship.

Lippi & Henry conducted a meta-analysis of data from five studies totalling 1,399 patients. Their results suggested that active smoking is not significantly associated with severe COVID-19 disease. However, there were a number of errors identified by others in their methods, calculation, and conclusions (Guo FR.; Lo et al., Sánchez et al.). Guo FR. performed an updated meta-analysis based on Lippi and Henry's study, using corrected data, and did find a statistically significant association (OR = 2.2; 95% CI 1.3–3.7).

Zhao et al. conducted a systematic review and meta-analysis from seven studies (1,726 patients) and reported a statistically significant association between smoking and severity of COVID-19 outcomes among patients (OR = 2.0; 95% CI 1.3–3.1). Therefore, based on the pooled odds ratios, these results suggest that smoking increases the risk of COVID-19 severity by approximately twofold. However, the results of this analysis were heavily influenced by one study which, when removed, resulted in the association between active smoking and severe COVID-19 becoming no longer significant.

Complications, Medical Intervention and Mortality

Many studies suggest that smoking or history of smoking is associated with disease progression among hospitalized COVID-19 patients (Engin et al., Guo FR., Karanasos et al., Patanavanich et al., Vardavas et al., Wang et al., Zheng Z et al.). Karanasos et al. found that the impact of smoking on disease severity (critical illness, intensive care unit admission or mechanical ventilation, and adverse disease progression or refractory disease) of hospitalized COVID-19 patients appeared to be more prominent in younger patients without diabetes.

Current or past smoking was also found to be associated with severe complications from COVID-19 and requiring the need for medical intervention (e.g. intensive care unit admission and mechanical ventilation) (Alqahtani et al., Archie et al., Emami et al., Kabbani et al.). The current consensus from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) is that smoking is associated with increased severity of disease.

There is limited data on the impact of smoking on mortality from COVID-19. Alqahtani et al. conducted a rapid systematic review and meta-analysis. They found that there was a higher mortality rate (38.5%) among those hospitalized with COVID-19 who identified as a current or former tobacco user, than those that never smoked tobacco. Hu et al. and Karanasos et al. also found an increased risk of mortality among current and former tobacco users; however, Karanasos et al. results were inconclusive due to the low sample size. The WHO has concluded that based on the available evidence, smoking is associated with an increase in death in hospitalized COVID-19 patients. More evidence is needed to determine the impact of smoking on mortality from COVID-19 for individuals who have not be hospitalized.

Comorbidities

The WHO states that individuals with certain pre-existing non-communicable diseases (NCD) appear to be more vulnerable to developing severe illness with COVID-19. These NCD include cardiovascular disease (e.g., hypertension, coronary artery disease, stroke or related risk factors), chronic respiratory disease (e.g., COPD), diabetes, and cancer (World Health Organization).

To date, hypertension, cardiovascular disease, smoking and diabetes have been identified as the most prevalent co-existing disorders among patients with COVID-19 in hospital and among severe cases (Cattaruzza et al., Chow et al., Emami et al., Guan et al., Li et al., Luo et al.). Emami et al. conducted a meta-analysis and found that cardiovascular disease was the most prevalent comorbidity among hospitalized patients. Generally, based on some studies, having any comorbidity or a greater number of comorbidities is associated with worse clinical outcomes (Chow et al., Guan et al., Wang et al.). Others found a potential association with COVID-19 severity when active smoking was present along with a chronic condition, such as COPD (Choi et al., Leung et al., Zhao et al.).

Since many of these underlying health conditions can causally be associated with smoking, the independent effect of smoking on COVID-19 progression is difficult to assess (Berlin et al., Brake et al., Cattaruzza et al.). Many of the above-mentioned risk factors confirmed to increase COVID-19 severity are more frequent among people who use tobacco (Berlin et al., Cattaruzza et al.). For example, in high income countries, smoking is the primary cause for COPD (Brake et al., U.S. Department of Health and Human Services). Therefore, while smoking tobacco may not be an independent risk factor for COVID-19 it is a known risk factor for conditions that have been found to increase vulnerability for adverse COVID-19 outcomes.

Smoking Cessation and COVID-19

Although we did not identify studies addressing smoking and relapse from abstinence during an epidemic, previous studies have suggested that people who smoke and are exposed to natural disasters tend to smoke more than those unexposed and that people with past smoking are more likely to relapse (Silva et al., Yach D.). Activities such as smoking and other substance use could increase, not only as a form of distraction or behavioural avoidance strategy, but also as a result of the stress, anxiety or depressive symptoms that many are experiencing during the COVID-19 pandemic (Berlin et al., Garcia-Alvarez et al., Sun et al.). There is also concern that these changes could lead to relapse from abstinence (Berlin et al.).

There is preliminary data that shows the initial impact of the COVID-19 pandemic on substance use among Canadians 15 years and older. Statistics Canada conducted a survey to measure the percentage of Canadians who changed their weekly consumption of alcohol, tobacco products or cannabis. Overall consumption of tobacco use remained essentially unchanged. Canadians that reported "fair" or "poor" self-perceived mental health were more likely to report an increase in tobacco use compared to those that rated their mental health "excellent", "very good" or "good".

It has been hypothesized that smoking cessation could eventually reduce susceptibility to COVID-19 and the risk of severe illness with SARS-CoV-2 infections (Brake et al., Karanasos et al., Silva et al., Smith et al.). Some surgical literature suggests that four weeks of smoking cessation might lower the incidence of perioperative adverse events, which if applied to the context of COVID-19 infection, could be similar to a decrease in risk of adverse events among COVID-19 patients (Eisenberg et al.).

While the effects of smoking can last for years, smoking cessation causes an improvement in lung function and an overall decrease in chronic disease burden (U.S. Department of Health and Human Services). Health Canada outlines the immediate and long-term benefits of quitting smoking. Decreasing use of tobacco will help to prevent or slow conditions like cardiovascular disease, COPD and cancer, which exacerbate the severity of COVID-19 infection.

Based on the latest available evidence and the well-established harms associated with tobacco use, the recommendation is for people who use tobacco to take steps to quit by using proven methods such as toll-free quit lines, mobile text messaging programs, and nicotine replacement therapies (Government of Canada, Hartmann-Boyce J. et al., World Health Organization).

Smoking Tobacco as a Protective or Therapeutic Intervention for COVID-19

In early May 2020, the WHO released a statement that urged researchers, scientists and the media to be cautious about intensifying unproven claims that tobacco or nicotine could reduce the risk of infection with SARS-CoV-2 (World Health Organization). This statement was prompted by the release and media amplification of a controversial preprint article that hypothesized that nicotine could have a protective effect against SARS-CoV-2 infection.

It is important to distinguish between 'smoking' and 'nicotine' and the researchers did not propose a protective role for smoking, but rather nicotine having a role in counteracting infection (Dhillon et al.). They proposed that the SARS-CoV-2 virus is a nicotinic agent which competes with nicotine for the receptor and nicotine provokes an interaction between SARS-CoV-2 and the known receptor (ACE2) for

nicotine, thus blocking entry of the virus into the body's cells (Dhillon et al., Lutchman D.). Research is ongoing in this area.

Distinguishing medicinal nicotine treatment from cigarette smoking for prevention and treatment of COVID-19 is critical given the well-established harms smoking tobacco has on the body (Health Canada, Tindle et al., U.S. Department of Health and Human Services). In addition, given the wealth of evidence indicating that nicotine increases the effect of cardiopulmonary diseases and viral infections, as well as the well-documented negative impact of tobacco smoke on respiratory and overall health, it is unlikely that smoking will offer any therapeutic benefit in COVID-19 (Dhillon et al., Farsalinos et al., Tindle et al.). For these reasons, smoking would not be an appropriate and sustainable protective measure (Farsalinos et al.).

Before medicinal nicotine could be recommended for COVID-19, evidence of effectiveness is needed (Tindle et al.). To date there is currently insufficient information to confirm any link between tobacco or nicotine in the prevention or treatment of COVID-19 (Leung et al., Tsigaris et al., World Health Organization, Zheng Y. et al.).

Limitations of the evidence

Most of the studies on COVID-19 reviewed are limited by poor data quality and are also subject to significant sampling bias (Emami et al., Patanavanich et al., World Health Organization,).

Collecting smoking history and pre-existing conditions is challenging in an emergency context and it is possible that smoking status as well as other individual factors are underreported (Cattaruzza et. al., Chow N. et. al., Farsalinos et al., Jordan et al., Leung et al., Patanavanich et al., Polosa et al., Sachithanandan A., World Health Organization).

Characteristics of those who are hospitalized will differ by country and context depending on available resources, access to hospitals, clinical protocols and possibly other factors not considered in studies. (World Health Organization, Farsalinos et al.). These hospitalized patients have the highest risk and all are tested; therefore, the findings may not apply to the general population (Jordan et al.). Given that severe COVID-19 is associated with an older population (greater than 65 years) with comorbidities, in whom smoking rates are approximately 3-5 fold lower than that in the general population and the lack of community testing, it is likely that hospitalized patients may not reflect tobacco use patterns in the general population and the true impact of COVID-19 on those who currently smoke tobacco (Leung et al., Sachithanandan A.). In addition, since smoking is more prevalent among those of lower socioeconomic status, affordable access to hospital care might be an issue in many countries (Farsalinos et al., Sachithanandan A.).

Severity of disease is often not clearly defined and is inconsistent across studies (World Health Organization, Farsalinos et al.). This is also seen with categorization of smoking status; categorization is inconsistent across studies and combining categories that could impact the results, for example, people who never smoked included in the same category as unknown smoking status (Farsalinos et al.; Sánchez et al.).

One of the largest challenges for studies of COVID-19 is having large enough sample sizes to correct for confounders, such as co-morbidities (hypertension, diabetes, obesity, COPD), race, sex, and income, all of which might be associated with tobacco smoking and poor outcomes (Farsalinos et al.). Many studies did not make statistical adjustments to account for age and other confounding factors (World Health

Organization; Jordan et al.). Given the limitations in the data and evidence on the relationship between tobacco and COVID-19 caution must be made on making definitive statements around current findings.

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