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Review article

The consequential impact of JUUL on youth vaping and the landscape of tobacco products: The state of play in the COVID-19 era

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ABSTRACT

JUUL is a groundbreaking electronic cigarette (e-cig) and the preeminent vaping product on the market. We present an overview of the rapid and spectacular rise of JUUL and its remarkable fall within the timespan of 2015 – 2020. We highlight JUUL's entering the market in June 2015, becoming the industry leader in mid 2017, and experiencing a litany of setbacks by late 2019 through to early 2020. We address the role played by JUUL in the ongoing epidemic of youth vaping. We also feature competing views on the public health impact of JUUL use (in particular), and e-cig vaping (in general). We further highlight the latest trends in youth vaping and sales records for JUUL and tobacco cigarettes. In view of the ongoing pandemic of COVID-19, we briefly summarize the existing evidence on the relationship between vaping and smoking and the prevalence, disease course, and clinical outcomes of COVID-19.

1. An introduction to JUUL and youth vaping epidemic

JUUL (Juul Labs, Inc.) is a groundbreaking *'pod'*-based electronic cigarette (e-cig) (Hammond et al., 2020; Jackler and Ramamurthi, 2019; Goniewicz et al., 2019). Since its introduction to the US market in 2015, JUUL has dramatically changed the landscape of tobacco products (Huang et al., 2019; Jenssen and Wilson, 2019; Lee et al., 2020; Vallone et al., 2020). A combination of sleek and high-tech design, innovative nicotine delivery technology, appealing flavorings, and social media-based marketing (Vargas-Rivera et al., 2020; Hrywna et al., 2020; Kong et al., 2019; Nardone et al., 2019) has propelled JUUL to become the best-selling e-cig in the US (Huang et al., 2019; Lee et al., 2020). JUUL has accounted for nearly 75% of recent point-of-sale purchases of e-cigs, being the first brand to record $1.3 billion in annual sales in 2018 (Herzog and Kanada, 2021). The huge financial success of JUUL has spurred competitors, ranging from startups to "Big Tobacco" companies, to offer similar pod-based products (JUUL-alike or JUUL compatible), often at a fraction of the price of JUUL (Jackler and Ramamurthi, 2019; Williams, 2019). While purportedly intended for '*adult*' smokers, JUUL use is most prevalent among adolescents and young adults (Kong et al., 2019; Nardone et al., 2019; Willett et al., 2019; Case et al., 2020). Survey based research conducted during April – October 2018 showed that 30.2% and 21%, respectively, of high school- and college students self-reported past 30-day use of JUUL (Morean et al., 2019; Ickes et al., 2020). The alarming uptake of JUUL use by youth has drawn significant public health attention and concerns (Lee et al., 2020; Vallone et al., 2020; Case et al., 2020).

The addictive *'potential'* of JUUL, whose nicotine content is claimed to be equivalent to a pack of 20 cigarettes (Bowen and Xing, 2014; The Truth Initiative, 2021; JUUL Labs, Inc, 2021a), together with the immense popularity of JUUL among teens and young adults (Hammond et al., 2020; Goniewicz et al., 2019; Hrywna et al., 2020) has raised concern that a new generation of tobacco product users may be *en route* to nicotine dependence and addition (Lee et al., 2020; Creswell, 2019). There is also concern that JUUL use in youth may lead to gateway effects, such as initiation of smoking or cannabis use (Jenssen and Wilson, 2019; Case et al., 2020; Vena et al., 2020). Furthermore, JUUL vapor inhaled by users, is shown to contain many of the same toxicants and carcinogens as those found in tobacco smoke (Reilly et al., 2019; Talih et al., 2019, 2020; Mallock et al., 2020). These common constituents,

Abbreviations: ACE2, angiotensin converting enzyme 2; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; e-cig, electronic cigarette; FDA, Food and Drug Administration; FTC, Federal Trade Commission; EVALI, e-cig, or vaping, product use-associated lung injury; ITC, International Trade Commission; nAChR, nicotinic acetylcholine receptor; NASEM, National Academy of Sciences, Engineering and Medicine NYTS, National Youth Tobacco Survey; NRT, nicotine replacement therapy; PHE, Public Health England; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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however, are detected at substantially lower levels in JUUL vapor than tobacco smoke (*i.e.*, generally at concentrations reduced by orders of magnitude) (Reilly et al., 2019; Talih et al., 2019, 2020; Mallock et al., 2020). Examples of the common constituents of JUUL vapor and cigarette smoke are carbonyl compounds, such as acetaldehyde (6.05 *vs*. 1,059.19 μg [in JUUL vapor *vs.* cigarette smoke]), formaldehyde (0.56 *vs*. 3.17 μg), acetone (24.9 *vs*. 775.6 μg), crotonaldehyde (0.85 *vs*. 40.42 μg), methacrolein (7.08 *vs*. 85.46 μg) (Talih et al., 2019), and free radicals (5.47–10.87 *vs*. 5.09 pmol/puff) (Reilly et al., 2019).

Limited data are available on the addictive potential of JUUL use, but only in adults (Nardone et al., 2019; Yingst et al., 2020). Contradictory results have been reported in small-size studies in which adult JUUL users have acknowledged dependence levels comparable to those of cigarette smokers (Nardone et al., 2019); although low-to-medium dependence on JUUL use, lesser than that of cigarette smoking, has also been reported (Yingst et al., 2020). The disparate results have been ascribed, at least partly, to differences in use frequency and patterns between JUUL users and cigarette smokers. Unlike tobacco cigarette, which is smoked typically in 5–15 puffs over 4–10 min, JUUL is vaped through intermittent puffing over a much longer period of time (Nardone et al., 2019). The latter may result in less pronounced fluctuations in blood nicotine levels in JUUL users, as opposed to smokers whose blood nicotine concentrations quickly reach high peaks and troughs. Thus, JUUL users may have distinct patterns of nicotine absorption and dependence as compared to smokers. Today, the nicotine-dependence and addictive potential of JUUL use, particularly in adolescents and young adults, remain to be fully investigated (Besaratinia and Tommasi, 2019, 2020).

2. Rapid and spectacular rise of JUUL

JUUL is a rechargeable, closed-system (non-refillable) e-cig that uses disposable cartridges (*i.e.*, pods) containing propylene glycol, glycerin, flavorings, and nicotine at high concentrations in the form of benzoate salt (3% or 5% nicotine by weight) (JUUL Labs, Inc, 2021a). As the most dominant e-cig on the market (Huang et al., 2019; Herzog and Kanada, 2021; Wells Fargo and Nielsen, 2019), JUUL represents a substantial evolution in design by efficient delivery of salt-based nicotine (protonated) rather than free-base nicotine (Bowen and Xing, 2014; Reilly et al., 2019; Talih et al., 2020). When inhaled, protonated nicotine is known to greatly reduce airway irritation as opposed to free-base nicotine (Bowen and Xing, 2014; Talih et al., 2019; Pankow, 2001; Ferris Wayne et al., 2006; Duell et al., 2018). This formulation of JUUL eases deeper inhalation, and ensures high delivery of nicotine to users, particularly new and tobacco-naïve youth who wish to avoid the harshness of combustible cigarettes and conventional e-cigs. The latter products deliver considerable amount of free-base nicotine (Nardone et al., 2019; Keamy-Minor et al., 2019). JUUL's compact size and stylish design, resembling a USB flash drive, low vapor output with minimally visible aerosol plume/cloud upon exhalation, variety of flavorings, and subtle scent, which can be passed off as perfume, are device features that make it immensely appealing to youth (Lee et al., 2020; Vallone et al., 2020; Hrywna et al., 2020; Kong et al., 2019). The small size, light weight, and easy to conceal JUUL can be used inconspicuously in places where smoking is prohibited; the practice is often referred to as "stealth vaping/JUULing" by teenagers in classrooms, school yards, or restrooms (Nardone et al., 2019; Ramamurthi et al., 2018; McKelvey and Halpern-Felsher, 2020). JUUL's innovative marketing strategy, relying heavily on social media, instead of traditional TV, radio, or print advertisements (Huang et al., 2019; Kavuluru et al., 2019; Ali et al., 2020; Russell et al., 2020), has made it hugely popular among adolescents and young adults. Of significance, these age groups are the savviest consumers of interactive computer-mediated technologies (Lee et al., 2020; Case et al., 2020).

The unprecedented growth in JUUL's sales (Herzog and Kanada, 2021; Wells Fargo and Nielsen, 2019) concomitant with its tremendous popularity among young people (Vallone et al., 2020; Lin et al., 2020) prompted Altria, Philip Morris USA's parent company and one of the world's largest cigarette manufacturer, to acquire a 35% stake in JUUL in a deal worth $12.8 billion in December 2018 (Richtel and Juul, 2018). The deal valued Juul Labs at $38 billion (higher than the Ford Motor Company), with an annual revenue of nearly $2 billion (Wells Fargo and Nielsen, 2019). The Altria investment in JUUL was likely aimed at capturing the youth market; however, others have argued that it was also designed to sustain or improve cigarette sales by slowing down vaping market in which JUUL had played (and continues to play) a dominant role (Levy et al., 2020). Merging with or acquisition of competitor companies (especially small startups) by industry giants that are slow to innovate, is a common practice to stay on top of the market and maintain the *'status quo'*.

Contemporaneously, alarming trends of teens' use of JUUL within and outside the school premises were reported by concerned parents, educators, school superintendents, health care providers, and public health experts (Lee et al., 2020; Vallone et al., 2020; Leavens et al., 2019). As a result, the US Surgeon General declared 'youth vaping' an *'epidemic'* in the United States in December 2018 (US Department of Health and Human Services, 2018). Under pressure from the US Food and Drug Administration (FDA) who singled out JUUL as a particular cause for concern (Statement from FDA Commissioner Scott Gottlieb MD, 2018; US Food and Drug Administration, 2018), Juul Labs stopped the sale of flavored products (except menthol), suspended its social media accounts as well as broadcast, print, and digital advertising, announced plans to enhance age verification systems, and began advocating for increasing the minimum tobacco purchase age to 21 years (Creswell, 2019; JUUL Labs, Inc, 2021b).

However, the above moves have not led to satisfactory results in terms of reducing vaping prevalence in youth (*see*, section 6: "Youth vaping trends"). Recent data show that JUUL users quickly switched to menthol or tobacco flavored products that are still available from Juul Labs, or purchased their preferred flavorings and JUUL-alike products from competitors and imitators, often at a reduced price (Jackler and Ramamurthi, 2019; Vallone et al., 2020; Liber et al., 2020). Consequently, JUUL's sales bounced back from an initial dip within weeks after the above changes were made, and sales went on to rise even higher than they were before (Liber et al., 2020).

Currently, there are several dozens of JUUL-compatible products and knock off pod devices on the market, which similarly use the innovative salt-based e-liquid technology to offer equal or higher nicotine than JUUL (Lee et al., 2020; Vallone et al., 2020; Ramamurthi et al., 2018). Juul Labs has filed complaints with the U.S. International Trade Commission (ITC) as well as launched lawsuits against the manufactures of these copy-cat or counterfeit products, alleging infringement on its U.S. patented salt-based nicotine delivery technology and trademarks (JUUL vs Counterfeiters, 2018; JUUL Complaint to the US, 2018a, 2018b).

3. Remarkable fallout of JUUL: current and future challenges

As a consequence of mounting public pressure and numerous investigations, subpoenas, and lawsuits launched by federal, state, and local authorities as well as private entities, Juul Labs has faced many backlashes and undergone major changes in recent years. The Altria Group, Inc. wrote down its investment in the company by $4.5 billion in response to complaints from shareholders (Wells Fargo and Nielsen, 2019); the complaints are now turned into multiple class action lawsuits alleging, among other things, failure to conduct sufficient due diligence prior to investing in JUUL. In April 2020, the Federal Trade Commission (FTC) filed an administrative complaint, alleging that Altria's acquisition of JUUL shares and the associated agreements together eliminates competition and violates federal antitrust laws (Levy et al., 2020; Federal Trade Commission, 2020). The allegations will be tried in a formal hearing before an administrative law judge. The trial is scheduled to begin in 2021 (Federal Trade Commission, 2020).

Furthermore, co-founder and former Chief Product Officer, James Monsees, has recently stepped down as advisor and Juul Labs' board member. The company parted ways with multiple top executives, and announced plans to lay off several hundred employees amid global cost-saving and reconstructing. With the pending FDA's pre-market reviewing of e-cig products, Juul Labs is currently mobilizing efforts to secure the necessary clearance to stay on the market. Joshua Raffel, a spokesman for the company, recently stated, "We fully understand the need to earn back the trust of regulators, policymakers, key stakeholders and society at large and reset our company and the vapor category". Regardless of how these renovations or reinvention efforts will shape the future of JUUL and determine its standing as a player in the industry, one thing is for sure: JUUL has ushered in a new era of innovative nicotine delivery systems.

Both the vaping- and tobacco industries have taken a note of JUUL's novel product design, efficient nicotine delivery technology, and targeted marketing, which have, and most likely, continue to inspire new products and innovative marketing strategies. With the same token, the public health community and regulatory agencies should remain cognizant of JUUL's strategies in targeting youth, a vulnerable and impressionable population. Such strategies are likely to be duplicated/emulated by current and future manufacturers of new and emerging tobacco products. For now, JUUL remains a record-setting and consequential innovation whose impact on youth vaping and the landscape of tobacco products will likely be felt for many years to come.

4. Public health impact of vaping

It is generally accepted that e-cig use/vaping exposes the users to substantially fewer and lower concentrations of toxicants and carcinogens as compared to smoking (Reilly et al., 2019; Talih et al., 2019, 2020; Mallock et al., 2020). However, the net public health effect of vaping (*i.e.*, harm *vs*. benefit) continues to be debated (Besaratinia and Tommasi, 2020). The scientific community, regulatory authorities, and the general public face two competing views on the health risks or benefits of vaping: on the one hand, vaping advocates refer to: (I) the "harm reduction" potential of e-cig use, especially for smokers who are unable/unwilling to quit; and (II) its utility for facilitating smoking cessation (Royal College of Physicians, 2016; Hartmann-Boyce et al., 2020). On the other hand, opponents argue against the adoption of an alternative tobacco product whose long-term health effects are largely unknown (Lee et al., 2020; Vallone et al., 2020; National Academies of Sciences, 2018). To reach a consensus, more conclusive scientific evidence will definitely be needed; the available data favor the view that vaping is likely to be less harmful than smoking, with the caveat that it may still pose a health risk on users that would otherwise be eliminated if neither product were used (Besaratinia and Tommasi, 2019).

Both the Public Health England (PHE) (Royal College of Physicians, 2016; McNeill et al., 2018) and the National Academy of Sciences, Engineering and Medicine (NASEM) reports (National Academies of Sciences, 2018) concur that children and adolescents should not use e-cigs, whereas adult vapers, particularly smokers who *'completely'* switch to e-cig use, can have reduced health risks as compared to cigarette smokers. The PHE estimates that vaping, while not totally risk-free, may be 95% less dangerous than conventional cigarette smoking, given the reduction in e-cig carcinogen load (Royal College of Physicians, 2016; McNeill et al., 2018). However, others do not agree with this stance, expressing concerns that: (I) many novice vapers, who were not interested in tobacco cigarettes, might have remained nicotine-naïve, if they had not experimented with e-cigs; and (II) a majority of smokers embraces dual use of both products (National Academies of Sciences, 2018). Whereas the former (I) might lead to nicotine-dependence among new vapers who would otherwise be never smokers, the latter (II) would promote continued smoking and vaping among dual users, which would not only undermine abstinence efforts but also re-normalize smoking in the society (Lee et al., 2020; Vallone et al., 2020; Besaratinia and Tommasi, 2020).

To fully reconcile the dichotomy of views on vaping is highly challenging, considering the existing gaps in knowledge (Besaratinia and Tommasi, 2019). For now, proponents' view focuses on two aspects: (I) the reduced harm potential of vaping as compared to smoking, with the greatest health gains among smokers who *'completely'* transition from tobacco cigarettes to e-cigs; and (II) the potential utility of vaping for helping smokers quit smoking (Hartmann-Boyce et al., 2020; McNeill et al., 2018). Conversely, opponents' perspective draws attention to two other aspects: (I) the accumulating evidence on the adverse biological consequences of exposure to toxicants and carcinogens present in e-cig vapor (despite their substantially reduced levels compared to cigarette smoke), (II) the *'potential'* for nicotine-dependence and addiction in novice vapers (National Academies of Sciences, 2018). The latter is most important during adolescence when the developing brains are more susceptible to influences on learning, memory, and attention (Lee et al., 2020; Vallone et al., 2020).

While a growing body of research shows the disease-causing potential of vaping (Dinakar and O'Connor, 2016; Benowitz and Fraiman, 2017; Schick et al., 2017; Shields et al., 2017; Caliri et al., 2020; Tommasi et al., 2019), new data are also emerging indicating that provision of free e-cigs in the context of randomized controlled trials is significantly associated with increased smoking cessation (Hartmann-Boyce et al., 2020; Wang et al., 2020a). Future research should gauge the health risks *vs*. benefits of vaping on the basis of three equally important factors: (1) how e-cig use affects youth initiation of cigarette smoking and/or nicotine-dependence, or other substance use; (2) the efficacy of e-cig use in adult cessation of cigarette smoking; and (3) the overall toxicity of e-cig use as compared to cigarette smoking in chronic users (Besaratinia and Tommasi, 2020; Dinakar and O'Connor, 2016; Benowitz and Fraiman, 2017; Schick et al., 2017; Shields et al., 2017). The net effect of vaping on the public's health can be determined when all the three factors are thoroughly investigated, both individually and in relation to one another, but not simply by examining each factor in a vacuum.

5. Assessing potential health risks of vaping in youth

Chemical analyses of JUUL/e-cig vapor have revealed the presence of some of the same toxicants and carcinogens as those found in cigarette smoke, including carbonyl compounds (*e.g.*, aldehydes: formaldehyde, acetaldehyde, acrolein), free radicals, volatile organic compounds, although generally at substantially lower concentrations (Kosmider et al., 2018; Son et al., 2020; Reilly et al., 2019; Talih et al., 2019, 2020; Mallock et al., 2020). The comparatively reduced levels of these chemicals in JUUL/e-cig vapor is consistent with the fact that unlike traditional cigarettes that 'burn' tobacco, JUUL or other e-cig devices 'heat' a liquid to produce an aerosol (vapor) that users inhale into their lungs (Jenssen and Wilson, 2019; Lee et al., 2020; Besaratinia and Tommasi, 2017; Farsalinos, 2018; Dinakar and O'Connor, 2016; Benowitz and Fraiman, 2017; Schick et al., 2017; Shields et al., 2017). *The reduced levels of toxicants and carcinogens in JUUL/e-cig vapor may imply lower health risk; however, they cannot equate to no risk* (Besaratinia and Tommasi, 2019). In fact, exposure to many of the same constituents of JUUL/e-cig vapor, at various concentrations, has been associated with a wide range of respiratory disease, cardiovascular disease, immune-related (inflammatory) disease, and cancer (Besaratinia and Tommasi, 2020; Dinakar and O'Connor, 2016; Benowitz and Fraiman, 2017; Schick et al., 2017; Shields et al., 2017). It should be stressed that the long-term health effects of JUUL/e-cig use are yet to be fully determined (Besaratinia and Tommasi, 2020). Therefore, it is imperative to investigate the health consequences of chronic JUUL/e-cig use, particularly among youth who are more likely to have little or no history of tobacco smoking (Besaratinia and Tommasi, 2017). Because adult JUUL users are more likely to be dual users (*i.e.*, alternate between vaping and smoking) or have a prior history of smoking (ex-smokers) (Jenssen and

Wilson, 2019; Case et al., 2020), it is advantageous to tease out the influence of (JUUL) vaping in youth users without the confounding effects of past smoking (Besaratinia and Tommasi, 2020).

The existing literature on the potential health risks of vaping is often criticized by the fact that the study subjects in many reports mostly consist of adult e-cig users with a past or current history of smoking, *i.e.*, vapers ex-smokers or dual users, respectively (Royal College of Physicians, 2016; Hartmann-Boyce et al., 2020; National Academies of Sciences, 2018; McNeill et al., 2018). This has complicated the interpretation of the results as it is unclear whether the observed effects in the e-cig users are: (I) due to persistent effects of past smoking (in former smokers) or current smoking (in dual users); (II) solely caused by current vaping; or (III) a combination of the two factors (Besaratinia and Tommasi, 2020; Royal College of Physicians, 2016; Hartmann-Boyce et al., 2020; National Academies of Sciences, 2018; McNeill et al., 2018). Investigating the health consequences of JUUL use in youth will provide a unique opportunity to disentangle the biological effects of 'exclusive' vaping while ruling out smoking as a confounder (Besaratinia and Tommasi, 2017).

6. Youth vaping trends

Recent analysis of the 2020 National Youth Tobacco Survey (NYTS) showed declines in current e-cig use among U.S. high school- and middle school students as 19.6% of high schoolers (3.02 million) and 4.7% of middle schoolers (550,000) reported current e-cig use in 2020; these nationally representative data are driven from self-administered survey of students during January 16 to March 16, 2020 (*i.e.*, likely before the actual impact of COVID-19 pandemic in the U.S.; *see*, next section) (Wang et al., 2020b). By comparison, in 2019, 27.5% of high school students (4.11 million) and 10.5% of middle school students (1.24 million) reported current e-cig use (Wang et al., 2020b).

Most recently, the results of Monitoring the Future (MTF) survey, which is an annual nationally representative, cross-sectional sample of U.S. 10th and 12th graders surveyed between February and June from 2017 to 2020, revealed slightly different but consistent trends (Miech et al., 2021). Of significance, MTF prematurely stopped data collection on March 14, 2020 due to COVID-19 concerns. The MTF survey in 2020 showed that vaping prevalence for 10th and 12th grade high school students was 22% for past 30-day use, 32% for past 12-month use, and 41% for lifetime use; these levels are not significantly different from those found by the same survey in 2019 (Miech et al., 2021). The differences in use rates between the 2020 MTF and NYTS surveys may have arisen due to several reasons. For example, the MTF only surveyed 10th and 12th graders, compared to the NYTS surveying all middle- and high school grade levels; the MTF data collection in 2020 was shortened due to the COVID-19 pandemic; and students might differ in their willingness to respond truthfully to an academic *vs.* government-sponsored survey (Wang et al., 2020b; Miech et al., 2021).

Altogether, despite the NYTS' reported declines in current e-cig use among U.S. middle- and high school students in 2020, it is important to underscore that approximately 3.6 million American teens have still used e-cigs ('current' users), of whom 80% reported using flavored products, such as fruit, mint, menthol, and candy, desserts, or other sweets flavored e-liquid (Wang et al., 2020b). Together, these data show that until early March 2020, nearly one in five high school students and one in ten middle school students in the U.S. have actively used e-cigs, which is indicative of a continued youth vaping epidemic.

7. The global pandemic of COVID-19: State of vaping and smoking

Since the outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan, China, in December 2019, the disease has spread to 192 countries, and become a global pandemic (Huang et al., 2020; Zhu et al., 2020; Wu et al., 2020; JHU CSSE COVID-19 Data, 2021). As of April 1, 2021, the disease has infected over 129 million and killed more than 2.8 million people, worldwide (JHU CSSE COVID-19 Data, 2021). The U.S. holds the unenviable record of having approximately one-quarter of the global cases and one-fifth of all deaths related to this disease (JHU CSSE COVID-19 Data, 2021).

The global pandemic of COVID-19 has wreaked havoc on virtually all aspects of daily life, including lifestyle habits, such as substance use, specifically, smoking and vaping. Concerns about smoking and vaping predisposing to COVID-19 have caused changes in tobacco cigarette and e-cig use frequency and patterns in diverse populations (Li et al., 2020; Gaiha et al., 2020; Klemperer et al., 2020; Tattan-Birch et al., 2020; Sharma et al., 2020). Also, stay-at-home mandates and pandemic-related restrictions, especially on social gatherings, where tobacco product use and sharing of e-cig devices are most common (particularly among youth), have impacted the accessibility, point of purchase, and use environment for e-cigs and cigarettes (Gaiha et al., 2020; Tattan-Birch et al., 2020). Furthermore, investigators have started to decipher how the underlying biological mechanisms and behavioral factors involved in smoking and vaping may modulate COVID-19 infection, transmission, and clinical outcomes (Klemperer et al., 2020; Sharma et al., 2020; Gaiha et al., 2020).

8. Does smoking or vaping predispose to COVID-19?

It is biologically plausible that smokers and vapers may be at increased risk of COVID-19 because chronic use of tobacco cigarettes and e-cigs may weaken respiratory system and compromise immune response (National Academies of Sciences, 2018; The US Surgeon General, 2014). Inhalation of many chemicals present in both cigarette smoke and e-cig vapor (Dinakar and O'Connor, 2016; Benowitz and Fraiman, 2017; Shields et al., 2017) is known to elicit inflammatory response (Caliri et al., 2021), which may exacerbate the inflammation caused by COVID-19 (Samet, 2020). This may, in turn, trigger/promote 'cytokine storms' and hyperinflammatory immune response that are features of severe cases of COVID-19 (Kaur et al., 2020; Mehta et al., 2020). Also, COVID-19 mainly affects the lungs because SARS-CoV-2 enters the host cells via the angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of the lungs (Letko et al., 2020). The virus uses a special surface glycoprotein, named "spike" protein, to attach to ACE2 (interchangeably called 'ACE2 receptor'), and enter the host cell (Letko et al., 2020; Ou et al., 2020). Thus, the ACE2 receptor provides the entry point for the coronavirus to enter the cells, exert its effects, and cause COVID-19 (Turner et al., 2004). Of significance, ACE2 is up-regulated (more abundant) in smokers as compared to nonsmokers (Smith et al., 2020; Lee et al., 2020).

Behaviorally, there are also grounds to suggest that COVID-19 can disproportionately affect smokers and/or vapers. Behavioral factors involved in both smoking and vaping, such as hand-to-mouth movements and touching face, may elevate risk of COVID-19 infection and transmission, especially when practiced in the absence of protective behaviors, such as proper hand washing (Berlin et al., 2020). In addition, sharing e-cig devices, which is common among vapers, especially youth (McKelvey and Halpern-Felsher, 2020) (likely reduced due to 'stay-at-home' mandates and restrictions on social gatherings), may help spread the disease, by facilitating transmission from asymptomatic cases.

Also put forward is a competing hypothesis that nicotine protects against COVID-19 (Changeux et al., 2020) based on the premise that (I) nicotine exerts anti-inflammatory effects against COVID-19 by activating the nicotinic acetylcholine receptor (nAChR); and (II) nicotine down-regulates ACE2 expression through modulation of the renin–angiotensin–aldosterone system (Farsalinos et al., 2020; Tindle et al., 2020). Clinical trials and observational studies in health care workers and patients are currently underway to investigate whether nicotine patches could be used for COVID-19 prevention and/or treatment (Changeux et al., 2020; Castelnau, 2020). However, it should be

stressed that there is a clear distinction between *"potential"* utility of nicotine for COVID-19 prevention or treatment, when administered through transdermal patches, as opposed to nicotine being inhaled via smoking or vaping. At a minimum, the former of the two (*i.e.*, smoking) is a susceptibility factor for, if not a cause of, many comorbidities predisposing to COVID-19 infection and poor outcomes. These comorbidities include chronic obstructive pulmonary disease (COPD), cancer, cardiovascular disease (CVD) [*e.g.*, cardiomyopathy, coronary artery disease, and heart failure], chronic kidney disease, type 2 diabetes mellitus, diabetes, and obesity (Centers for Disease Control and Prevention, 2021). Therefore, regardless of the hypothetical utility of nicotine for prevention or treatment of COVID-19, it is simply not an option to encourage people to 'smoke' as a way of protecting against this disease.

9. Relationship between tobacco product use and COVID-19 disease course and outcomes

A living rapid review of research studies from around the world has been conducted to assess the relationship between smoking status and rates of infection, hospitalization, disease severity, and mortality from COVID-19 (Simons et al., 2020). *We note that, as of today, the review has not been expanded to vaping.* The living review is updated regularly as new data from published studies become available. The latest version (v.7; based on search of MEDLINE and medRxiv for published articles and pre-prints up to August 25, 2020) identified a total of 347 new records, with 233 studies included in a narrative synthesis and 32 studies included in meta-analyses. The review found uncertainties in the majority of 233 studies arisen from the recording of smoking status. Notwithstanding these uncertainties, compared with overall adult national prevalence estimates, recorded current smoking rates in most countries were *'lower'* than expected. In a subset of higher quality studies ($n = 17$), current smokers had a slightly reduced risk of testing positive for SARS-CoV-2, but appeared more likely to present for testing and/or receive a test as compared to never smokers. Data for current smokers on the risk of hospitalization, disease severity, and mortality were non-conclusive, but trended towards a small, yet important, increase in risk for severe disease, while showing no association with hospitalization or mortality from the disease. Former smokers were at elevated risk of hospitalization, disease severity, and mortality from COVID-19 as compared to never smokers (Simons et al., 2020). The findings of this living review underscore the need for rigorous studies to obtain high-quality and reliable data as the research community around the world faces unprecedented challenges to navigate work in the COVID-19 era.

10. The impact of COVID-19 pandemic on sales of tobacco products

Whereas Juul Labs, Inc. reported $1.9 billion in sales in the first nine months of 2019, the company's revenue dropped to $1.1 billion during the same period in 2020 (Maloney, 2021). The estimated revenue for Juul Labs, Inc. in the last quarter of 2020 was $340 million (Maloney, 2021). While the underlying reasons for the observed changes in JUUL's sales remain to be investigated, concerns about vaping safety, especially in the aftermath of "e-cig, or vaping, product use-associated lung injury (EVALI)" outbreak (Besaratinia and Tommasi, 2020; Centers for Disease Control and Prevention, 2020), bans on flavored vaping products (Nguyen, 2019; Yang et al., 2020; Gravely et al., 2020), together with stay-at-home mandates and pandemic-related restrictions, affecting accessibility, purchase, and use environment may deserve special attention (Gaiha et al., 2020; Tattan-Birch et al., 2020).

Of significance, the drop in JUUL's sales during the pandemic has coincided with a rise in tobacco cigarette sales (Maloney, 2021; Alltucker, 2021). Recent reports show that the decades-long decline in U.S. cigarette sales has halted during the pandemic (Maloney, 2021; Alltucker, 2021). Data from U.S. Treasury Department show that cigarette sales increased 1% in 2020 after dropping 4 to 5% each year since 2015 (Alltucker, 2021). Recently, Altria reported 4.9% increase in sales to $6.3 billion in the quarter ended December 31, 2020, compared to $6.0 billion in 2019. Altria's revenue from cigarette and cigar sales was $5.6 billion in 2020 (Maloney, 2021).

Altogether, the highly complex relationship between vaping and smoking, which existed pre-COVID-19 era (Besaratinia and Tommasi, 2020), seems to have further evolved during the pandemic, with multiple factors driving the prevalence of vaping and smoking, in similar or different directions, as reported for various populations (Simons et al., 2020). The prevalence of vaping and smoking as well as sale trends for JUUL and other vaping products and tobacco cigarettes in the U.S. and around the world in the coming year(s) will depend on a wide range of determinants of which COVID-19-related issues will likely top the list.

11. Concluding remarks

As the pandemic of COVID-19 continues, we are poised to accumulate more data on the prevalence and long-term outcomes of this disease in large populations with better-defined characteristics, including underlying health conditions and lifestyle habits, such as smoking and vaping. At the same time, we should underscore the importance of conducting well-designed studies with rigorous methodologies and adequate statistical power, which can produce reliable data and ensure reproducible results. Ideally, these studies should use laboratory assays for biochemical validation of smoking/vaping status, diagnostic tests with high sensitivity and specificity for COVID-19, and other molecular methods to delineate the pathophysiology of this disease. Completion of these studies should help definitively demonstrate the impact of smoking and vaping on COVID-19 infection, transmission, and clinical outcomes. As we adapt to a post-COVID-19 world, and learn how to navigate work under many newfound regulations and restrictions, the challenges ahead may seem overwhelming, but definitely worth tackling.

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Author contributions

AB: Conceived the study, Performed literature search, Wrote the manuscript; ST: Performed literature search, Co-wrote the manuscript.

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