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Mini-Symposium: Vaping – When e-commerce generates e-toxicity

An update on controversies in e-cigarettes

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Educational Aims

The reader will come to:

- Understand that e-cigarettes have been misleadingly marketed as "less harmful" alternatives to conventional cigarettes.
- Be aware that there is a rising incidence in e-cigarette use in young people worldwide.
- Recognise that e-cigarettes have a greater acute toxicity than tobacco (EVALI, e-cigarette or vaping associated lung injury) which leads to respiratory failure with an intense inflammatory response; and hence it is nonsense to assert that long term they are less toxic than tobacco
- Realise that second hand exposure to e-cigarettes is a health concern for bystanders.
- Be aware of the urgent need for stringent anti-vaping legislation.

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ABSTRACT

E-cigarettes are electronic nicotine delivery systems (ENDS) which mimic tobacco smoking without the combustion of tobacco. These devices have been misleadingly marketed as "less harmful" alternatives to conventional smoking tobacco products. The e-liquid in e-cigarettes include nicotine, a humectant and other additives including flavourings, colourants, or adulterants such as bacterial and fungal products.

In this review, we discuss the contrasting views of the tobacco lobby and most professional societies. We describe the epidemiology of the use of these devices, with a widespread and significant rise in youth e-cigarette use seen in both the USA and Europe. We also describe what is known about the toxicity and mechanisms of EVALI (e-cigarette or vaping associated lung injury). This characterised by respiratory failure with an intense inflammatory response. The presentations are diverse and clinicians should consider vaping as a possible cause of any unusual respiratory illness in patients who have a history of vaping or other use of e-cigarette-related products. Second hand exposure to e-cigarettes is also harmful through respiration and transdermal absorption. E-cigarettes have a worse acute toxicity than tobacco and their long-term toxicity is unknown, and we advocate for the immediate, most vigorous anti-vaping legislation possible.

BACKGROUND

E-cigarettes are electronic devices which belong to an enlarging number of electronic nicotine delivery systems (ENDS) that mimic tobacco smoking without combustion of tobacco [1]. These devices have been marketed as "safer" alternatives to conventional smoking tobacco products (CSTP) to:

a. help established smokers quit any form of tobacco usage, or
b. change to a 'safer' alternative form of "smoking experience" (in reality, nicotine addiction), or
c. prevent non-smokers from starting to smoke, while satisfying a craving for nicotine and providing other, less tangible benefits associated with the act of 'smoking' [2].

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The evolution of vaping devices from first generation of cig-a-like products to the sophisticated fourth generation devices underline the popularity and commercial success of this highly addictive and dangerous strategy. The global e-cigarettes (vaping) market was valued at about $14.05 billion in 2018 and is expected to more than double through 2022 [3].

The explosion of youth use and flurry of acute toxicities over the last few years swamps any potential harm reduction that may accompany adults switching from CSTPs to e-cigarettes.

The debate arises especially as in the UK they are seen as 'at least 95% less harmful than tobacco'. Public Health England (PHE) have endorsed and promoted e-cigarettes as a tobacco alternative, advocating a harm reduction approach. However, many non-smoking children and young people (CYP) are not using e-cigarettes to help them stop using CSTPs, so there is no mitigating harm-reduction. An increasing proportion are using e-cigarettes before CSTPs; a school-based study from UK that found that more than half of e-cigarette users had never used tobacco [4]. Among US e-cigarette users aged 18–24 years in 2015, 40% had never been regular cigarette smokers. E-cigarette use among US youths is associated with intention to smoke but not with intention to quit smoking [5].

By contrast, most paediatricians favour a much more cautious approach to e-cigarettes. This view places the protection of non-smokers, especially CYP as paramount and also focuses on the overall population impact, anticipating the ability of e-cigarettes to recruit a new generation of nicotine addicts, and almost certainly also, smokers. This is the stance adopted by the US National Academies of Science, Engineering, and Medicine (NASEM) [6], Australian Commonwealth Scientific and Industrial Research Organisation [7], Forum of International Respiratory Societies (FIRS, a collaboration of professional organisations and respiratory experts, made up of nine international societies) [8], The European Public Health Association (representing 40 national associations of public health), the European Commission, the World Health Organization (WHO).

FIRS has issued a position statement on e-cigarettes and ENDS use in youth which places protecting CYP at heart of the e-cigarettes debate [8] with stricter regulation and call for more research. The American Academy of Pediatrics also has castigated the use of e-cigarettes.

The WHO report on e-cigarettes suggested that regulations were needed to stop promotion of e-cigarettes to non-smokers and young people, minimise potential health risks to users and nonusers, stop unproven health claims about e-cigarettes, and protect existing tobacco control efforts

This review will discuss the contrasting views of the tobacco lobby and most professional societies. We describe the epidemiology of uptake and use of these devices, and cover what is known about the toxicity and mechanisms of lung injury.

Contrasting views of the tobacco lobby (and erroneous "relative health benefits logic") with those of professional societies:

PHE acknowledge that there are some risks and uncertainties and that e-cigarettes could not be called "safe," but continues to maintain risks outweigh benefits [9]. UK Royal College of Physicians (RCP) report acknowledges that "e-cigarettes are not currently made to medicines standards and are probably more hazardous than nicotine replacement therapy" [10]. It is also worth noting that the UK National Institute for Health and Care Excellence (NICE) excluded the use of e-cigarettes as an aid to smoking cessation in their guidelines.

The "at least 95% less harmful than conventional smoking" statement (above) is based on the outcome of a multi-criteria decision analysis (MCDA), in which a group of experts considered the harms to human health and well-being posed by using a wide range of tobacco products which was not based empirical data and did concede that the evidence was insufficient to reach a robust conclusion [11]. This did not stop robust conclusions being promulgated! Worryingly decreased use of smoking cessation services and medically tested pharmacotherapy has been observed in parallel with an increase in the use of e-cigarettes, indicating that alternative nicotine-containing products may be replacing evidence-based, effective smoking cessation tools [12].

There are several limitations in concluding that e-cigarettes are safe [13–15] but we would highlight that decisions made during this MCDA exercises were based on value judgements not evidence. The MCDA approach cannot be a substitute for a formal risk–benefit analysis, that should be undertaken for new products to which the public are exposed [2]. Transparency about the funding and organisation of this meeting have also been questioned [15].

PHE has argued that any evidence from RCTs do not capture the effects of e-cigarette use outside the specific conditions of a trial and so cannot be generalised to real life (thus at a stroke rubbishing all RCT evidence across the entire spectrum of medicine!). This does not stop them cherry picking evidence [16] to promote one of the very few trials that found that e-cigarettes, when administered in a highly controlled setting, in which subjects were also receiving an intensive behavioural intervention, achieved a higher quit rate than was seen with nicotine patches [17]. At one year, the rate of continuing e-cigarette use was fairly high as compared to nicotine replacement; effectively replacing one form of nicotine addiction with another. Switching to vaping is not solving the problem, merely substituting a new one. That trial itself had many limitations, including not comparing e-cigarettes with the most effective pharmaceutical interventions and, obviously, saying nothing about the use of e-cigarettes when used outside a structured behavioural programme [18].

The "harm reduction" strategy hypothetically might be a gain for smokers reluctant to quit (although the evidence for this statement is zero), but ex- and never-smokers probably have an increased risk of harm by using e-cigarettes. There is a substantial risk of undermining smoking cessation programmes and the renormalisation of smoking from widespread use of e-cigarettes. Their use should at most be allowed in that minority of high-risk smokers unwilling or unable to quit [19] and not promoted as a population-based strategy. As well as being an aid to quitting, e-cigarettes are seen as having a role for people who do not want to quit, offering a substitute for some of the cigarettes they would otherwise smoke [15]. However, this introduces the risk of dual use which can be especially harmful, as dual users would be exposed to two sets of substances, having the worst of both worlds. Although some dual use is inevitable during the quitting process, if this persists long-term health concerns remain. Dual use is popular [7]. A recent cohort study showed that dual use among daily "vapers" worryingly apparently remained above 80% after 12 months follow-up [20]. Of course, the best choice for these individuals is to quit tobacco and nicotine altogether. For those who have never smoked, especially youth, the best option is never to start using any tobacco or nicotine product.

Australia has banned nicotine-containing e-cigarettes and has had similar success to the UK in the area of smoking cessation by impressive tobacco control and not by the use of e-cigarettes [21].

This promotion of e-cigarettes by PHE has been described as "a reckless and irresponsible decision" [2]. England remains a global outlier on the question of e-cigarettes and this "English Exceptionalism" is from the perspective of using e-cigarettes as means to reduce the harm associated with smoking and bring potential benefits to existing smokers. This position has been hard to retreat from and has been referred to [14] as an example of what is termed

"escalation of commitment" or, by economists and behavioural scientists, "sunk cost fallacy". Once embarked on a course of action or line or argument, it is difficult to extract oneself. It leads to a situation in which evidence that supports the position being held is promoted, whereas that which challenges it is dismissed, probably due to underlying cognitive biases [14].

The human lungs are created to breathe clean air, not "reduced levels of toxins and carcinogens", and the human body is not meant to be dependent on addictive drugs [22,23]. We know the acute toxicity of e-cigarettes is greater than that of tobacco, there is no tobacco equivalent of EVALI (See Rubin et al *Paediatr Respir Rev* 2020; 36: 87–91); how therefore can any sane person confidently state that chronic toxicity is less? The question of whether vaping is safe or safer than smoking can only be answered if the total contents of each of the thousands of available vaping liquids are itemised and subjected to short-term and long-term toxicity testing; reassurances and extrapolations are no substitute for data.

Even the International CEO of Phillip Morris has written [24]:

"To be clear, smoke-free alternatives are not risk-free and should never be used by youth or non-smokers.

To be clear, the commercialisation of smoke-free alternatives cannot come at the expense of youth or people who don't smoke.

Responsible marketing also plays a vital role: Tobacco and e-cigarette manufacturers should market their products only to adults who smoke or use smoke-free products".

We join in this increasing call that the sale of e-cigarettes to the public should also be banned to avoid placing them readily in the hands of young people. They should be available only on prescription from smoking cessation clinics (although NICE would challenge their use even in this case) [25]. Clearly there is a disconnect between the putative use of e-cigarettes in a smoking cessation clinic, and the way they are being marketed. Traditional quitting methods, such as nicotine patches and gum, are usually offered by a pharmacy where a pharmacist can provide advice. The medical quitting methods are also regulated as health products with controlled levels of nicotine and the user may also be referred to psychological services for support fighting their addiction. E-cigarettes can be purchased in shops on the high street and users will not usually access any wider therapies to help them to quit. The regulations that apply to tobacco should be applied to e-cigarettes, including those relating to advertising, packaging, taxation and where they can be used [26]. The tide however may be turning with declining public perception that e-cigarettes are less harmful than cigarettes as the new evidence on the harms of e-cigarettes continues to accumulate [27].

Epidemiology of uptake

The extremely effective marketing strategy by the e-cigarette industry has been associated with a very significant surge in the uptake of vaping by CYP as many believe that e-cigarettes are safer and more socially acceptable. Nicotine-free vaping devices also appear to act as a gateway product in addition to being unsafe even despite nicotine being absent [28]. Not only are more CYP are taking up vaping, there is substantial evidence that e-cigarette use increases risk of ever using CSTPs among CYP i.e. a likely gateway to CSTPs. Widespread and significant rises in youth e-cigarette use are seen in both the USA and Europe [29]. However, it must be stressed that, as argued elsewhere [26], the dangers of nicotine addiction and other toxicity mean that whether they are a gateway to smoking is irrelevant. E-cigarettes are dangerous in their own right. Some of the factors related to e-cigarette use in CYP are listed in Table 1.

Taken together, evidence suggest that e-cigarette use in CYP does not decrease the likelihood of use of CSTPs and is a gateway to more CSTPs use and indeed dual use. CYP who believe e-cigarettes can help people quit smoking and perceive e-cigarettes to be less harmful than CSTPs are significantly more likely to report experimenting with e-cigarettes. Informing CYP about the lack of evidence that e-cigarettes aid smoking cessation, and the already known and the as yet unknown health risk of e-cigarettes may deter young adults from trying these products [30]. Indeed, for most smokers, using an e-cigarette is associated with lower odds of successfully quitting smoking [31]. Rather, they were more likely to switch from one tobacco product (cigarettes) to e-cigarettes rather than quit nicotine and tobacco altogether [17]. A recent study [32] has suggested that continued use of e-cigarettes by former smokers is associated with re-initiation of cigarette smoking.

Thus there is a strong, scientifically-based rationale that vaping is a risk factor for future smoking and for restricting youth access to e-cigarettes [33] despite suggestions by some that have downplayed the use of e-cigarettes and their link to CSTP use in adolescents [9,34]; continued surveillance is needed [Table 2] [35].

TOXICITY OF E-CIGARETTES

The basic components are:

- a reservoir (a tank of different sizes, cartridge or pod) that contains the "e-liquid". The lower electrical resistance but higher power in most recent generation devices increases the aerosol yield. The major portion of particle mass is well within the respirable size range to deposit in the alveoli and be rapidly absorbed into the blood stream [36,37]
- a wick typically made of cotton or silica that conducts the e-liquid to the metallic coil (the heating element)
- a battery (that generates electrical current to heat the metal coil). There are substantial differences in efficiency of nicotine delivery, device voltage, and other variables [38].

The e-liquid constituents are:

- Nicotine
- Trace chemicals from nicotine extraction from tobacco
- A liquid solvent/humectant to dissolve the flavours and nicotine and to promote moisture retention (e.g. propylene glycol (PG) or vegetable glycerine (VG)), and
- Other additives (e.g. flavourings, colourants)
- Adulterants including bacterial and fungal products in many liquids.

Not only are a range of tempting flavours available, there are options to "create your own ejuice" choosing the size of the bottle, levels of nicotine and different flavours [39]. 122 liquids studied contained substances having some level of hazard/risk of danger according to the globally harmonised classification system for respiratory irritants [25], in flagrant breech of European Union regulations. With some devices there is variability in the temperature that heats the liquid, which can reach 250 °C to create the aerosol [40]. It is unsurprising that burn and blast injuries have resulted from malfunctioning of these devices [41,42].

Even though levels of some potentially harmful ingredients from e-cigarettes are significantly lower than combustible cigarettes, it does not mean that e-cigarette aerosols are "harmless vapour" as industry has claimed in the past. Differences between inhalation and oral toxicology should be borne in mind while promoting the "safety" of vaping that is based on theoretical grounds, rather than observational science. Thus there are legitimate concerns over the health effects of inhaling various substances in e liquids [43–45].

Table 1
Some factors reportedly related to e-cigarette use:

Regulation: International variability [102]; increasing number of countries banning e-cigarettes [103]. Strong regulation can protect CYP from e-cigarettes	South Korea: since 2008, regulates e-cigarettes as tobacco products with prohibitions on indoor use, sales to minors, advertising bans, health warnings and taxes	Prevalence of the use in CYP remained stable at about 4% between 2011 and 2015
	USA: Until recently there has been little federal regulation and some restriction on the sale of e-cigarettes to CYP.	Rose dramatically from 1% to 11% during the same period [104]. High school student use has risen from 13% in 2014 to 27.5% in 2019 [105]. Approximately 2.1 million middle and high school students had used e-cigarettes in the past 30 days [106]
	UK: prior to 2015 e-cigarettes were only regulated as consumer products. Since October 2015 the sale of e-cigarettes containing nicotine to under 18 s was made illegal. On 20th May 2016, any advertising or promotion of electronic cigarettes and re-fill containers on any media platforms was prohibited. The only advertising still allowed is at point of sale and other location specific advertising such as billboards, and advertisements must meet regulations designed to prevent promotion to people under 18	The number of current e-cigarette users continues to grow as rise [35] (Table 2)
Experimentation: seems to be a major reason for the increased use of e-cigarettes by CYP	International Tobacco Control Four-Country Survey (USA, Canada, the UK and Australia), found that the prevalence of trying e-cigarettes was higher in young, nondaily smokers because of the perception that they were are not harmful or are less harmful compared with CSTPs. Health warning labels on nicotine vaping products (mandatory in England, not in USA, Canada, Australia) may not be noticed [107]	Cited reasons for use [35]: – 'Just to give it a try': • 52.4% of the users (current, ex-users and those who had tried at least once) • 70.6% amongst never smokers – 'I like the flavours': 14.4% – 'other people use them so I join in': 12.7% – 'I think they look cool': 1%
Acquisition: CYP can easily acquire vaping products	Minors are easily able to purchase e-cigarettes (and indeed CSTPs [108])) from the Internet because of an absence of age-verification measures [109]. Tobacco retailers are less likely to ask for identification, and more likely to sell to minors attempting to buy vaping products as compared to CSTPs [110]	61.9% buy them (most common means of purchase the internet: 24.5%) 35.2% are given them (most common source is friends: 24.5%) [35] In the recent EVALI outbreak (50% of those who reported using THC-containing products provided data on product source; 16% were only from commercial sources (recreational and/or medical dispensaries, vape or smoke shops, stores, and pop-up shops); 78% only from informal sources (family/friends, dealers, online, or other sources); 6% reported acquiring products from both sources [111]
CSTP initiation and use: E-cigarette use particularly among low-risk CYP is associated with increased risk for CSTP initiation and use [112]	Longitudinal studies [33,113–118] in the US and Canada [119] have shown a correlation between e-cigarette exposure and initiation and continued use of CSTP among CYP.	Two separate meta-analyses (91051 and 17389 CYP) [120,121] estimated that never-smoking adolescents and young adults who used e-cigarettes had between 2 and 4.3 times increased odds of intention to progression to cigarette smoking compared to never users. E-cigarettes appear to encourage CYP progression to established smoking [122]; and even if they do not nicotine-addiction must be prevented. E-cigarette devices may be a delivery system for illicit drugs [123]
Dual use: More than 60% of smokers wish to quit because they do not like being dependent [124], but switching to e-cigarettes does not break the nicotine addiction and indeed dual use is more risky than CSTP use	South Korea: e-cigarette use was strongly associated with current and heavier cigarette smoking [125] so those who had tried to quit CSTPs were more likely to use e-cigarettes but less likely to no longer use CSTPs UK:	In 2019, 39.8% of CYP were dual users [35]

Table 2
Current 11–18 year olds e-cigarette users in Great Britain [35].

	2015	2019
Tried	12.7 %	15.4 %
Current use	2.4 %	4.9 %
Regular use		
At least weekly	0.5 %	1.6 %
Less than weekly	1.9 %	3.3 %

These discussions about potentially harmful compounds in e-cigarettes should not shift the focus from the fact that these are primarily a very efficient nicotine delivery system.

Singly, or together, these factors may contribute to toxicity. Many different chemicals and particulate matter (PM) are inhaled at doses that vary with vaping techniques and user behaviour which impacts on the physics of aerosolisation and thus aerosol delivery to lungs. The potential for adverse health effects is huge [46].

Further, the mixing of primary active compounds with contaminants and / or pyrolysis of chemicals in the e-liquid (some of which are gases [e.g., ketene] and not easily measured in biologic samples) [47] is likely to produce a chemical milieu with its own unique toxicity [Table 3] [47]. The identification of a causative agent is also problematic given the extensive heterogeneity of compounds in vaping mixtures [48]. With regards to EVALI, no single product or substance has been linked to all cases; and given the

Table 3
Individual constituents of e-liquids are as follows.

Constituent	Amount	Purpose	Properties	Problem
Solvents:				
PG (Propylene Glycol) *and* VG (Vegetable Glycerin)	• 80% of the overall content of e-liquids [126] • Variable PG/VG ratio for e.g. 54%/46% vapour comprises of an average of 0.7 mg/puff of PG glycol and 0.6 mg/puff of VG [28]	• Primary solvents • Maximise the subjective sensation of the flavouring agents as well as the appearance of the aerosol [43] • PG creates the visible fume	• "generally recognised as safe" (GRAS) for use as food additives. The FDA GRAS approval does not apply to aerosolisation • There are no long-term studies of the effects of inhaling heated aerosolised VG or PG in humans	• Even one puff (without nicotine) gives inhaled concentrations high enough to cause airway irritation [28] • Substances that are GRAS when edible can cause respiratory disease when inhaled (for e.g. occupational asthma due to inhaled flour in bakers (who are mostly able to eat bread without problems) [44]; asthma caused by Thiamine when inhaled (in the production of breakfast cereals) [44]. • Long-term exposure to PG has been found to induce and exacerbate multiple allergic symptoms in children [127] • Acrolein (a suspected carcinogen) is generated from vaporising the humectant glycerine [2]
Ethylene glycol (EG), toluene, and 1,3-Propanediol, polyethylene glycol 400 (PEG 400), medium chain triglycerides (MCT) [40].	Traces	Commonly added to cannabis-based vaping products [40]	EG is an odourless, clear, and viscous liquid commonly used as an industrial solvent and as an antifreeze	The health consequences of long-term exposure to EG and other residual solvents from e-cigarettes have not been investigated. EG is a respiratory irritant and may be associated with greater toxicity compared with conventionally used VG and PG
Flavourings (The concept of GRAS when eaten but not inhaled also applies to flavourings). There are now tens of thousands of "legal" fluids on the market containing a myriad of ingredients and the numbers are growing rapidly: in the 17 months between May - August 2012 and December 2013-January 2014, there was a net increase of 10.5 brands and 242 new flavours per month [128]. The increase is accelerating; double flavour labels available on websites rose from 7764 in 2013–2014 to 15,586 in 2016–2017 [129]. Also many e-cigarette products contain more than one flavourant (average is approximately 6), and those with sweet flavours contain more chemicals compared with tobacco and menthol flavoured liquids [40]				
• Diacetyl ((2,3-butanedione) (DA) • Acetyl propionyl (AP) • 2,3-pentanedione • Cinnamaldehyde (cinnamon) • Benzaldhyde (cherry)	DA and AP are present in 74.2% of the samples out of 159 tested "sweet" e-liquids and aerosols from 36 manufacturers and retailers from 7 countries [130]	• DA occurs naturally in, for example, butter and beer • Classified by the FDA as GRAS as a food additive	Concentrations released into the air are highly dependent on temperature	• Overwhelming evidence of inhalational toxicity • DA was the major volatile compound present in the plant where bronchiolitis obliterans was first described in microwave popcorn workers [131]. • The respiratory epithelium is a target of DA toxicity [132] • Usage of DA substitutes cause dyspnoea and spirometric and diffusing capacity abnormalities with even 1 hour per day in production areas [133] • Dose-dependent pulmonary toxicity that may not manifest for many years
Metals [134]				
• Kanthal (an alloy of iron, chromium, and aluminium) • Nichrome (an alloy of nickel and chromium) • Tin and Lead • Essential metals (Manganese and Zinc)	Metal concentrations in aerosol and in the residual liquid in the tank are > 35 fold higher than in the original e-liquid	• Coils in vaping devices • Used in the joints and other parts of the device	Contact with the heating coil transfers several metals from the device to the e-liquid in the tank as well as to the inhaled aerosol	• Essential metals potentially toxic through inhalation

(*continued on next page*)

Table 3 (*continued*)

Constituent	Amount	Purpose	Properties	Problem
Nicotine				
Free-based vs. newer salt-based (Rapid and higher absorption into the bloodstream that accelerates the delivery of nicotine to the brain as they allow high levels of nicotine to be inhaled with less irritation than free-base nicotine [105,135].	• Even when self-reported data suggest that 80% of adolescents choose products that do not contain nicotine, 99% of e-cigarettes sold in US actually do contain nicotine [77] • Typically varies between 3 and 36 mg/ml [43] • Greater than ±10% inconsistency between amount labelled and actual nicotine concentrations [136] in more than half of the top-selling products in the EU market (nine member states including pre Brexit UK) • One pod contains 40 mg of nicotine (at 59 mg/mL), more than the nicotine inhaled or absorbed when smoking an entire pack of cigarettes (22–36 mg). • Russia and the UK are the two of JUULs biggest markets Globally outside US [137] and even though the in the UK, regulations limit the amount of nicotine allowed within eliquids, JUULs are sold with < 20 mg of nicotine per pod in the UK (1)	The stated purpose of JUUL, a pod device, is to allow for efficient plasma nicotine absorption while minimising the harshness associated with inhalation of high concentrations of nicotine (38). Juul re-engineered their device to a 'Turbo' version for European sale in 2019, increasing nicotine delivery to US levels [138].		• Addictive • Can affect brain development, even in those who smoke infrequently • Harm childhood health generally (well summarised in a recent state of the art review [139] • Young people who become addicted to nicotine are at greater risk of becoming lifelong tobacco consumers • E-cigarettes with a higher nicotine level have been associated with an increased likelihood of starting tobacco smoking and the type of device used (mod versus penlike device) is strongly associated with frequency of tobacco smoking [140].
Bio-contamination				
Endotoxin or Beta D Glucan)	Bacterial (23%) and fungal (81%) contamination of single use and refillable e-cigarette products from 75 different manufacturers [141]			
• **"Illegal" substances"**				
Tetrahydrocannabinol (THC)	Played a role in 77% of the reported cases to date [142]		Because of a decrease in the typical marijuana odour, vape pens offer a "discreet" way to smoke in public, the leading reason why young adults choose to vape THC products [129]	
Vitamin E acetate [143,144]		Sticky with honey like consistency	Thickens or dilutes the vaping liquid	Unclear if this acts as a toxin or if lipids are simply a marker of exposure [81]. EVALI has been described with no vitamin E acetate in the e-cigarette liquids

very many different histopathologies, it would be surprising if this was the case.

Furthermore, there could be host factors/individual susceptibilities that contribute to toxicity that have yet to be described [49]. Not only are e-cigarettes users exposed to nicotine, ultrafine particles, and other toxicants, but some pulmonary toxicants are in e-cigarette aerosols at higher levels than tobacco cigarettes, including PG, and some flavourings and metals [8]. Hence e-cigarette aerosol is far from innocuous water, and, as we will show, although there is overlap with toxicity from tobacco smoking, vaping introduces toxins not found in tobacco [50].

In summary, e-cigarettes enable the ingestion of high concentrations of nicotine, mixed with potentially hundreds of other chemicals. The acute toxicity of most of these is little known, and even less is known about chronic, long-term toxicity. It should be noted that it took decades for the harm of tobacco to be appreciated, another cause to disallow premature acquittal of e-cigarettes. Furthermore, although there is overlap with the toxicity of tobacco, vaping introduces exposures and has effects which are not seen with tobacco [51,52]. Thus the idea that vaping is a safer, watered-down version of smoking, is scientific nonsense.

Marketing strategies

The vast and growing global market brings in to focus the very successful marketing strategies [including use of social media/influencers] with young people which will be discussed next.

The hypocrisy of the vaping industry, most of which is controlled by the tobacco industry, those pillars of rectitude and transparency, is shown in their marketing strategy. Compare it with

those of nicotine patches and gum; it is designed not to enable people to step down from smoking, but to attract a new generation of nicotine addicts.

Unlike eating or drinking, smoking is not a natural behaviour. The safety concerns of, flavourings have been addressed in Table 1; we will now discuss the role of flavourings in promoting nicotine dependency among youth. Flavourings are commonly added to the e-liquid to make the initial exposures more pleasurable. An online survey that asked 1005 New Zealanders aged 18–70 years the reasons for vaping showed that irrespective of smoking status, flavour was one of the main reasons respondents gave for vaping (smokers 83%; former smokers 77%; vaping-susceptible never smokers (VSNS) 80%). 64% of VSNS cited flavour as a reason for originally taking up vaping [53]. The vast majority (89%) of 18–25 years young adults from Australia preferred flavoured e-cigarettes (92% of smokers, 82% of non-smokers, 95% of never smokers), with fruit flavours the most popular [54].

The claims by the e-cigarette industry sponsored research [55] that flavoured e-liquids are intended for adult smokers using e-cigarettes to quit smoking cigarettes and that flavours are not meant to appeal to youth is contradicted by their marketing strategies [56]. Young people (median age 18 years) believe advertisements for flavoured e-liquids target individuals about their age, not older adults [57]. Additionally advertisements for flavoured (vs. unflavoured) e-cigarettes elicit greater appeal and interest in buying and trying e-cigarettes [58]. Thus, flavours have an important role for online e-cigarette marketing. This is supported by fMRI evidence that shows that specific advertising content focussed on flavours, interferes with effective communication of health warnings. There is decreased attention to, and poorer memory of, health warnings, and increased attention to advertising content) which increases liking and intent to try these products [59]. This relative product preference for sweet/fruit versus tobacco flavour e-cigarette advertisements in college-age youth, especially non-smoking early experimenters (who otherwise have negative associations with tobacco) suggests a potential impact of advertising for flavours on youth initiation and decreased knowledge of health risks of e-cigarette use [59]. Encouragement via online videos and social media portrays e-cigarettes as attractive experimentation and are a potential for covert use may reinforce traditional cigarette smoking in teenagers [60].

The availability of multiple flavours (including fruit and sweet flavours that are the most popular in youths), the option to mix one's own flavourings, multimedia advertising that promotes 'natural' flavours and aromas, enhances the appeal to first-time users, encourages experimentation, maintains novelty, is associated with a higher likelihood, frequency and persistence of use [61–64]. Sweet taste increases the desirability of all e-cigarettes and potentiates the reinforcement of nicotine-containing e-cigarettes on an addictive mesocorticolimbic mechanism [65]. The public health problem that e-cigarettes purportedly help solve — by helping people who are users of CSTPs stop smoking by switching to vaping — is adequately addressed by liquids that are not flavoured to appeal to adolescents [66]. The fact that flavours are not needed for smoking cessation products is supported by the fact that evidence based [67] licensed forms of NRT (gum) can help people successfully stop smoking.

The marketing strategies are not restricted to flavours: online stores display implied and overt health claims and smoking cessation messages that are unsupported by scientific evidence, as well as celebrity endorsements, and collocate vaping products with Coronavirus medical supplies, creating an impression of safe space [39,68]. The newer sleek fourth generation Pod or Pod-Mods devices mimic commonly used electronics such as USB memory sticks or devices resembling lipstick or inhalers making them easy to conceal and appealing to young consumers [1]. Some have been referred to as the iPhone of e-cigarettes [69]. Ninety-five percent of the websites make explicit or implicit health-related claims, 64% have a smoking cessation–related claim, 22% feature doctors, and 76% claim that the product does not produce second-hand smoke. Comparisons to cigarettes include claims that e-cigarettes were cleaner (95%) and cheaper (93%) [68].

E-cigarettes are increasingly heavily promoted using social media [70–72]. This is concerning as teenagers often relate to social media influencers; posts featuring aesthetically pleasing images of male and female models that are known to alter young users' perceptions are frequent among the posts featuring vaping products. In the same study, pro-vaping Instagram hashtags like #vape were used up to 10,000 times more often than the FDA-sponsored hashtag #TheRealCost [50]. Worryingly, a considerable proportion of followers of vaping influencers on social media are underage (13–17 year-old) [50,73]. Even Tobacco companies like JUUL have used social media to promote vaping and to brand their products as safe, discrete alternatives to conventional cigarettes and have changed their approach only when "caught red handed" recently [74–76].

PROPOSED MECHANISMS OF LUNG DAMAGE:

EVALI (also called vaping associated pulmonary injury [VAPI] or "vaping-associated respiratory distress syndrome" (VARDS) for symptomatic vaping-exposed hypoxemic patients who also have abnormal chest imaging [46] is a syndrome characterised by respiratory failure with an intense inflammatory response. EVALI should be suspected in patients who have a history of vaping or other use of e-cigarette-related products. The presentations are diverse and clinicians seeing a respiratory "oddity", should think of vaping as a possible cause. A clinical algorithm for the workup of EVALI has been suggested [77].

Data mining from the internet and social media of 41,216 posts between 2008 and 2015 has shown that many of the symptoms of EVALI have been reported online for at least 7 years in in users of many different EC products [78]. Reports of pulmonary illnesses associated with e-cigarette use had been described in the literature before the first report of EVALI, going back as far as 2012 [79]. In 2019 there was on explosion of cases being reported and until 18 February 2020 (the last date of data collection), there were 2807 confirmed cases in the United States requiring hospital admission and 68 deaths [80]. Although cutting the e-liquid with cannabinoids has been implicated in ~80% of cases, there are still substantial numbers related to "pure" e-liquids. There is no uncertainty about acute toxicity of e-cigarettes.

Only a few patients with EVALI have undergone lung biopsy and in these cases there were findings consistent with acute lung injury and such as acute fibrinous pneumonitis, diffuse alveolar damage, foamy (lipid-laden) macrophages (seen in all cases).

The lung has a relatively limited repertoire of responses to acute injury regardless of cause, and the histopathologic findings of acute lung injury depend largely on the timing of the biopsy, (indeed if a biopsy is performed) relative to the time of injury and the underlying severity of the injury. The histopathology may be further modified by the need for ventilatory support and other therapy including steroids. When available, most biopsies in patients with EVALI show injury most noticeably around small airways with bronchiolitis, a common finding in inhalational lung injuries. These nonspecific findings, that are characteristic of toxic exposures, closely resemble what is seen with noxious chemical fume exposures, where increased surfactant turnover and impaired removal due to epithelial injury lead to intracytoplasmic accumulation of surfactant and foamy cytoplasmic change [81].

Histopathologic features described in EVALI include OP (organising pneumonia), DAD (diffuse alveolar damage), acute eosinophilic pneumonia, diffuse alveolar haemorrhage, acute fibrinous pneumonitis with organisation, foamy or vacuolated macrophages, foamy or vacuolated pneumocytes, intra-alveolar fibrin, bronchiolitis, bronchiolar mucosal ulceration, interstitial oedema, neutrophilic inflammation, chronic interstitial inflammation, pigmented macrophages. As EVALI appears to reflect a spectrum of responses to lung injury, it is possible that the various presentations of EVALI will respond differently to glucocorticoids [82]. Empirical treatment with glucocorticoids has been suggested as a treatment strategy [83] as experience from the EVALI epidemic has shown that patients who survived EVALI were more likely to have received glucocorticoids than those who died from the condition [84].

We have no long-term health data on health hazards of e-cigarettes. However in addition to the catastrophic acute presentations of EVALI, there is also now emerging data that shows current use of e-cigarettes appears to be an independent risk factor for respiratory disease in addition to all CSTP smoking [31] over a three year follow up period.

There is a growing body of literature that e-cigarette (with or without nicotine), use may lead to effects that are not dissimilar to CSTP at a cellular, clinical, and population level. As well as some toxicities that are similar to CSTP, others seem to be unique to e-cigarettes. For example, human pulmonary epithelial cells from lung biopsy samples showed that about 300 proteins are differentially expressed in smoker and e-cigarette user airways, with only 78 proteins common to both groups. Acute pulmonary toxicity of e-cigarettes has been studied in cell culture, animal models, and human volunteers and are well described in detail in an excellent reviews [43,85].

Table 4
Pulmonary effects of e-cigarettes [43,86–89].

Pulmonary inflammation
Oxidative stress
Protease-mediated lung tissue damage
Increased airway hyper-reactivity
Increased airway resistance
Decreased antimicrobial activity
Down regulation of host defence genes
Increased resistance of bacteria to antimicrobial factors
High levels of particle deposition
Increased epithelial necrosis and cytotoxicity
Direct mucociliary dysfunction
Acquired cystic fibrosis transmembrane conductance regulator dysfunction, increased mucus viscosity and reduced Airway Surface Liquid height leading to impaired mucociliary clearance

Second hand exposure

Many users of e-cigarettes believe second hand aerosol (SHA) is simply steam (although the vapour may look like steam, it does not contain any water), have limited understanding of SHA, its constituents or its possible effects on others [Table 4]. They rely on the absence of information about harm, and their sensory experiences and perceptions of others' views of vaping, to support the conclusion that SHA pose few, if any, risks to bystanders [90]. However, effects of SHA vaping exposure are largely unknown. E-cigarettes are not emission-free and their pollutants lower indoor air quality with hazardous chemicals contained in the exhaled air

Table 5b
Mechanisms of lung injury and radiology findings for non-USA cases.

Proposed mechanisms of lung injury	CXR findings	CT findings
Hypersensitivity pneumonitis	Not mentioned	Bilateral ground glass changes in the upper and mid-zones with perihilar bronchial wall thickening and retained secretions in the dependant airways
Bronchiolitis obliterans	Diffuse micronodular opacities in both lungs	Diffuse bronchiolitis manifested by innumerable tree-in-bud opacities throughout both lungs with subpleural sparing
Unspecified EVALI	Not mentioned	Bilateral poorly defined centrilobular nodular infiltrates with bronchial wall thickening
Unspecified EVALI	Not mentioned	Diffuse ground-glass opacities consistent with diffuse alveolar haemorrhage
Unspecified EVALI	Left lower alveolar infiltrates	Bilateral lower lobe consolidation with air bronchograms, pleural effusion and peri-bronchial ground glass opacities in the upper and medium right lung
Lipoid pneumonia	Bilateral diffuse infiltrates throughout both lung fields	Diffuse ground-glass opacity and subpleural cysts bilaterally
Toxic pneumonitis and areas with organising pneumonia	Not mentioned	Hilar lymphadenopathy, fibrotic areas, diffuse ground-glass opacities

Table 5a
Patient characteristics and vaping constituents for non-USA cases.

Age (years)	Gender	Country	Use of CSTPs	CSTPs duration	e-cigarettes/vaping duration	Contents 1: Nicotine	Contents 2: THC	Contents 3: Humeactants	Contents 4: Flavourings
16	Male	England	Yes	1 year at least	Recently	Yes	No; Cannabis used 1 year ago	VG and PG	Yes
17	Male	Canada	No	Not available	5 months	No	Yes	Not available	Yes- presumed diacetyl
18	Male	Belgium	Yes	6 months	3 weeks	Yes	Yes	Not available	Unknown
22	Male	Germany	No	Not available	2 years	Yes	No	Not available	Not available
31	Female	Spain	Not mentioned	Not available	3 months	Yes	No	Not available	Unknown
34	Female	England	Yes	10-pack-year history, stopped 5 years ago	3 years	Yes	No	VG	Yes
34	Male	Germany	Yes	17-pack years, stopped 1 year ago	1 year	Yes	No	Not available	Not available

from an e-cigarette smoker [91]. There is a potential health concern of SHA exposure via both respiration and dermal absorption. In particular, ultrafine particles formed from supersaturated 1,2-propanediol vapour can be deposited in the lung, and aerosolised nicotine seems capable of increasing the release of the inflammatory signalling molecule NO upon inhalation [92]. Non-smokers (exposed ≥2 h/day) have been found to absorb nicotine from SHA e-cigarette aerosol similar to second hand tobacco smoke exposure as measured by salivary cotinine concentrations [93]. Parents may perceive e-cigarette aerosol as safe for children [94]; parents who were dual users of cigarettes and e-cigarettes were more likely to have strictly enforced smoke-free policies than vape-free policies for the home, were less likely to have strictly enforced smoke-free policies for the car and vape-free policies in the home and car than parents who only use traditional cigarettes. SHA exposure to vaping was described as the most likely cause of hypersensitivity pneumonitis in a 37 year old adult [95].

EVALI outside the US

Currently, the volume and pattern of adverse respiratory events reported in association with e-cigarette use or vaping in the UK do not seem to reflect the trends emerging from the USA. This difference of magnitude may be due to differences in regulations, nicotine strengths available, chemical substances and devices used, and proportional use by younger populations. However, it may also be due to a lower index of suspicion among healthcare professionals in the UK. A proposed UK case definition for EVALI is similar to the CDC definition but requires use in the 30 days prior to symptom onset (as opposed to 90 days) [96].

We conducted a literature search on PubMed, MEDLINE and EMBASE from inception to 7 May 2020 (last search). Eligible case reports and case series relating to e-cigarette, or vaping, associated lung injury (EVALI) were included. The keywords for the search strategy were ("e-cigarette" or "vaping") and ("lung injury" or "EVALI" or "pneumonitis" or "bronchiolitis " or "pneumonia" or "severe"). The search was restricted to articles in the English language. The reference lists of relevant papers were hand-searched to identify any further relevant studies.

Our inclusion criteria included the following: (a) age ≤ 35 year and (b) patient presenting to a hospital outside of the United States of America (USA). Our rationale for excluding cases presenting in USA is because these have been described at length in the existing literature.

Six papers [97,79,98–101]) met our inclusion criteria and were considered in the analysis (Tables 5a–5d; the papers were

Table 5c
Further investigative work up for non-USA cases.

Histopathology	BAL	Microbiology	First recorded lung function
Alveolar spaces contain macrophages and evidence of haemorrhage. A few alveolar spaces lined by fibrin suggesting early hyaline membrane formation. No granulomas were identified	Moderate numbers of macrophages, neutrophils and eosinophils (20%) consistent with active inflammation	Rhinovirus only	FEV1 3.52 L, z score – 1.91, FVC 3.68 L, z score – 2.73, TLC- 5.91 L, z score – 0.82. TLCO-9.02, z score – 0.92.
Mild interstitial septal thickening secondary to acute inflammatory cells in the septi and type 2 pneumocyte hyperplasia. The airspaces are distended by a mixture of fibrin balls, neutrophils, macrophages and myofibroblast proliferation, with incorporation of myofibroblasts into the septi	83% neutrophils	Negative for infection	FEV1 of 1.28 L (31% predicted), forced vital capacity (FVC) of 2.56 L (52% predicted), FEV1/FVC of 50%, residual volume of 3.55 L (227% predicted), normal total lung capacity (6.02 L, 91% predicted) and low-normal diffusion capacity corrected for alveolar volume (99% predicted)
Acute diffuse alveolar damage with fibrosis	45% of macrophages, 42% of neutrophils, 7% of lymphocytes and 6% of eosinophils	Negative for infection	Not mentioned
Mildly fibrosed bronchial wall	Bloody, 40% macrophages, 50% neutrophils	Negative for infection	Not mentioned
Not done	lipid laden macrophages (55%), lymphocytes(28%) and neutrophils (17%)	Negative for infection	Not mentioned
Extensive accumulation of lipid-filled macrophages and deposition of cholesterol clefts and some inflammation representing lipoid pneumonia	18% lymphocytes, 2% neutrophils, 68% macrophages and 2% eosinophils	Negative for infection	FEV1 = 1.23 L (50% predicted), FVC = 1.37 L (48% predicted) and FEV1/FVC = 89%, TLCO 1.9 (24% predicted), KCO = 1.15 (59% predicted) and TLC = 1.62 L (40% predicted)
Multifocal granulomatous inflammation, pneumonitis, organising pneumonia	39% macrophages, 3% neutrophils, 7% lymphocytes	Negative for infection	TLC 83% of the desired value, FEV1/FVC 86%), diffusion capacity 56% of the desired value

Table 5d
Management and outcome for non-USA cases.

Highest level of respiratory support	Length of hospital stay (days)	Steroids	Route of steroid	Duration of steroids	Short term outcome < 3 months	Medium term outcome 3–36 months
ECMO	35	Yes	IV	≥4 weeks	discharged	Fully recovered
ECMO	47	Yes	IV	≥4 weeks	discharged	Partial recovery (lung function)
ECMO	28	Yes	IV	<4 weeks	Death	
Oxygen	12	Yes	Oral	<4 weeks	discharged	Fully recovered
Oxygen	12	Yes	IV	<4 weeks	discharged	Fully recovered
Oxygen	Not mentioned	Yes	Oral	≥4 weeks	discharged	Partial recovery (lung function)
Nil	2	Yes	Oral	<4 weeks	discharged	Fully recovered

published between 2018 and 2020. The age range of the seven patients was between 16 and 34 years, presenting to hospital in 5 different countries including England, Canada, Belgium, Spain and Germany.

We looked at the contents of the e-cigarettes, including nicotine, cannabidiol, humeactant and flavourings, which are summarised in the Tables 5a–5d. We also reported on the clinical course of young people presenting to hospital with EVALI; the suspected mechanism of injury is varied and include hypersensitivity pneumonitis, bronchiolitis obliterans and lipoid pneumonia.

Three out of the seven patients required respiratory support with Extracorporeal Membrane Oxygenation (ECMO). Steroids were used in all of the reported cases. One patient died from EVALI and two had ongoing consequences of the EVALI in the medium term, as shown by clinical parameters and spirometry.

EVALI is being increasingly reported outside of USA. Our review of the literature supports that e-cigarettes have potential harmful effects, including death, for young people.

CONCLUSIONS

In summary, e-cigarettes, largely promulgated by the tobacco industry, have worse acute toxicity than tobacco; their long-term toxicity is unknown. They have no documented benefits, but instead are acting as a 'nicotine trap' to ensnare a new generation of addicts. The most vigorous anti-vaping legislation is mandatory.

DIRECTIONS FOR FUTURE RESEARCH

- There is a need for continued vigilance to determine acute and long term toxicity
- Monitor trends in the of use of e-cigarettes in children and young people, and how best to prevent experimentation and the slippery slope to addiction
- Understand also the health effects of second hand exposure

AUTHOR AGREEMENT

We certify that all authors have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

DECLARATIONS OF INTEREST

None.

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