ORIGINAL ARTICLE

Characteristics of an Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury—North Carolina, 2019

Lauren J. Tanz, Ariel Christensen, Kendall B. Knuth, Molly N. Hoffman, Dana Dandeneau, Kate Koehler, Zack Moore, Sally Herndon, Kevin Davidson, Aaron Fleischauer

BACKGROUND In August 2019, the North Carolina Division of Public Health (NCDPH) began investigating e-cigarette, or vaping, product use-associated lung injury (EVALI) cases as part of a national response. We describe clinical, epidemiologic, and laboratory findings of North Carolina EVALI patients.

METHODS NCDPH requested that physicians report cases of respiratory illness or bilateral pulmonary infiltrates or opacities in patients who reported using e-cigarette, or vaping, products and had no infection or alternative plausible diagnoses. We reviewed medical records, interviewed patients, and tested vaping products for substances.

RESULTS During August 13, 2019–February 18, 2020, 78 EVALI cases were reported in North Carolina. Median age of cases was 24 years (range: 13–72 years); 49 (63%) patients were male. Symptoms included cough (n = 70; 90%), shortness of breath (n = 66; 85%), and gastrointestinal symptoms (n = 63; 81%). Seventy-five patients (96%) were hospitalized, 32 (41%) required intensive care, and 12 (16%) required mechanical ventilation; none died. Among 20 patients interviewed, most reported using tetrahydrocannabinol (THC) (n = 16; 80%) or nicotine-containing products (n = 14; 70%). All obtained THC-containing products from informal sources, such as family, friends, or dealers, as THC is illegal in North Carolina. Among 82 products tested, 74 (90%) contained THC, cannabidiol, or cannabinol; 54 (66%) contained vitamin E acetate.

LIMITATIONS In North Carolina, EVALI is not reportable by law, and THC is illegal. Thus, cases and exposures are likely underreported.

CONCLUSIONS THC-containing products, particularly those containing vitamin E acetate, are associated with EVALI. Persons should not use these products, particularly from informal sources. Continued communication of health risks to persons who use e-cigarette, or vaping, products is essential.

E-cigarette, or vaping, products heat liquid to produce an aerosol for inhalation [1]. These devices often contain nicotine but can also be used to deliver tetrahydrocannabinol (THC, the primary psychoactive component of cannabis), cannabidiol (CBD), and other drugs [2, 3]. Additionally, e-cigarette, or vaping, product aerosol can include other harmful substances, including volatile organic compounds, heavy metals (e.g., lead), flavoring (e.g., diacetyl), and ultrafine particles that can be inhaled deeply into the lungs [2]. E-cigarette, or vaping, product use by adolescents and young adults has increased significantly in the past 5 years [1, 4–8].

During late July 2019, multiple cases of severe lung injury among persons who used e-cigarette, or vaping, products were reported to the Wisconsin Department of Health Services and Illinois Department of Public Health. Patients presented with respiratory, gastrointestinal, and constitutional symptoms that worsened over days to weeks before hospital admission. Chest radiographs showed pulmonary infiltrates, but no infectious etiologies were identified [9].

On August 13, 2019, a pulmonologist notified the North Carolina Division of Public Health (NCDPH) of 3 young adults with acute respiratory failure admitted to a single hospital. Two hypoxic patients required treatment in the intensive care unit, and all 3 had radiographic evidence of bilateral pulmonary opacities without infectious etiology. All 3 patients reported using THC-containing e-cigarette, or vaping, products. Between August 2019 and February 2020, the Centers for Disease Control and Prevention (CDC) coordinated a national investigation in collaboration with state and local health departments to characterize the increase in these lung injuries that were subsequently clinically defined as e-cigarette, or vaping, product use-associated lung injury (EVALI). By February 18, 2020, there were 2807 hospitalized patients reported from 50 states, the District of Columbia (DC), and two US territories; 68 deaths were confirmed in 29 states and DC [10]. National data suggest vitamin E acetate in THC-containing e-cigarette, or vaping, products is strongly linked to EVALI [10, 11]. We describe the clinical, epidemiologic, and laboratory findings of EVALI patients in North Carolina.

Electronically published August 16, 2021.

Address correspondence to Lauren J. Tanz, 4770 Buford Hwy, Chamblee, GA 30341 (ltanz@cdc.gov).

N C Med J. 2021;82(6):XXX-XXX.
0029-2559/2021/82602

Methods

Case Definitions

In collaboration with the CDC, the Council for State and Territorial Epidemiologists, and other affected jurisdictions, NCDPH developed an outbreak case definition. North Carolina's outbreak case definition differed slightly from the CDC's case definition, which required a negative respiratory viral panel to be considered a confirmed case [10, 12]. To be considered as having a case of EVALI in North Carolina, a patient must have used an e-cigarette, or dabbed (inhaled emissions produced by heating concentrated THC or other compounds) within 90 days before symptom onset, have signs (includes chest imaging abnormalities) or symptoms of respiratory illness, and have evidence of bilateral pulmonary infiltrates or opacities on chest radiograph or computed tomography (CT). Cases were classified as confirmed if results of all clinically indicated respiratory infectious disease testing were negative, including at least 1 laboratory or rapid diagnostic test for influenza. Cases were defined as probable if testing to rule out infection was not conducted, or if the patient's clinical team did not believe an identified infection was the sole cause of the lung injury. Additionally, confirmed and probable cases required the absence of an alternative plausible diagnosis.

Epidemiologic Investigation

NCDPH issued a press release and disseminated guidance in August requesting clinicians contact North Carolina Poison Control to report potential cases and discuss treatment and management [13, 14]. In addition to cases reported to NCDPH by North Carolina Poison Control, we also identified potential cases through active surveillance of emergency department (ED) visits reported in the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT), the state's syndromic surveillance system. ED visits with e-cigarette, or vaping, product use keywords and *International Classification of Diseases, Tenth Revision, Clinical Modification* codes for pneumonitis due to inhalation of oils and essences (J69.1); bronchitis or pneumonitis due to chemicals, gases, fumes, and vapors (J68.0); or cannabinosis (J66.2) were evaluated. During August 13, 2019–February 18, 2020, we conducted standardized medical record abstraction for all potential cases reported to NCDPH or identified in NC DETECT to determine if the patient's illness met the case definition and to collect information on demographic characteristics, inhalation exposures, and medical variables, including clinical assessment, diagnostic, and treatment variables. Additionally, abstractors assessed subspecialist consultation notes to evaluate clinicians' impressions of what they thought caused the illness.

We attempted to conduct standardized, in-depth interviews with all patients aged 18 years or older in whom confirmed or probable cases were classified before October 2, 2019 (n = 39). We collected demographic, symptom, and inhalation information within 90 days before symptom onset. This information included quantity and types of e-cigarette, or vaping, products used; substances used such as nicotine, THC, and CBD; frequency of use; purchase location; and hacking or modifying devices or e-liquids (i.e., any post-market modification not intended by the manufacturer). We attempted to contact each patient 4 times via phone before they were considered lost to follow-up for the interview. We did not interview patients classified after October 2, 2019, because of limited staff resources, and we determined there would be limited additional gain as information obtained from completed interviews was consistent between patients.

Product Collection and Laboratory Testing

We asked all interviewed patients to provide available e-cigarette, or vaping, products used in the 90 days before symptom onset for testing, including devices, liquids, and product packaging. Collected products were transported to the North Carolina State Laboratory of Public Health (NCSLPH) for laboratory testing. We used qualitative nontargeted gas chromatograph mass spectrometry (GC-MS) analysis to test product liquids for substances including nicotine, THC, CBD, cannabinol (another cannabis component), and vitamin E acetate. Although there are many potential toxicants in e-cigarette, or vaping, products, we specifically focused on vitamin E acetate because preliminary national data suggested it was likely involved in EVALI [15, 16]. We conducted inductively coupled plasma mass spectrometry (ICP-MS) analysis to test for a panel of metals, including arsenic, barium, beryllium, cadmium, lead, thallium, and uranium.

Statistical Analysis

We conducted descriptive analyses for confirmed and probable cases reported to NCDPH using data from medical records, interviews, and product collection. We reported results as proportions for categorical variables and medians and interquartile ranges (IQRs) for continuous variables.

Ethics

CDC reviewed this investigation for human subjects protection and determined it to be nonresearch. All records containing individually identifiable health information disclosed to NCDPH remain confidential as mandated by North Carolina General Statute 130A-12 and are not public record. Verbal consent was obtained before conducting patient interviews.

Results

Demographic Characteristics

Seventy-eight EVALI cases (59 confirmed; 19 probable) were reported to NCDPH during August 13, 2019–February 18, 2020. None of the patients died. Although cases were retrospectively identified and reported with symptom

onsets as early as May 2019, a sustained increase occurred during mid-July through late September (Figure 1). Patient median age was 24 years (range: 13–72 years); 14 (18%) were aged less than 18 years (Table 1). Forty-nine (63%) were male. Among 59 patients with known race/ethnicity, 50 (85%) were non-Hispanic White. Twelve patients (15%) had medical record evidence of preexisting respiratory disease, including 9 (12%) with asthma. Additionally, there was medical record documentation of a history of heart disease in 4 (5%) patients, anxiety in 19 (24%), and depression in 13 (17%).

Clinical Characteristics

Among 78 EVALI patients, 75 (96%) were hospitalized with a median hospitalization of 5 days (IQR: 4–8 days), and 32 (41%) required treatment in the intensive care unit. Noninvasive respiratory support (i.e., bilevel positive airway pressure, continuous positive airway pressure, high-flow nasal cannula, or supplemental oxygen) was required for 45 (58%) patients and mechanical ventilation was necessary for 12 (15%). Over half of hospitalized patients (n = 44; 59%) received care at another location (e.g., urgent care) for their lung injury before hospital admission. The median time from symptom onset to hospitalization was 6 days (IQR: 4–9 days).

Nearly all patients (n = 75; 96%) presented with ≥1 respiratory symptom, including cough (n = 70; 90%), shortness of breath (n = 66; 85%), and chest pain (n = 27; 35%). Patients also commonly presented with gastrointestinal symptoms (n = 63; 81%), including nausea (n = 57; 73%), vomiting (n = 56; 72%), and diarrhea (29; 38%), and constitutional symptoms (n = 72; 92%), such as subjective fever (n = 68; 87%). Among 42 patients with known laboratory results, 27 (64%) had leukocytosis (white cell count greater than 11,000 per cubic millimeter) with neutrophil predominance (greater than 80% neutrophils). Median creatinine was 0.79 mg/dL (IQR: 0.60–0.90 mg/dL) suggesting normal renal function for most patients.

The case definition required an abnormal chest radiograph or CT with bilateral infiltrates or opacities. Among 70 patients who had a chest CT, additional findings included pleural effusion in 8 (11%) patients, pneumomediastinum in 3 (4%), and pneumothorax in 2 (3%); 1 patient had all 3 of these findings. Bronchoalveolar lavage (BAL) was performed on 20 (26%) patients; of these, 7 (35%) had oil red O staining of alveolar macrophages to detect lipids. Among these 7 patients, lipid-laden macrophages were detected in all BAL samples.

Exposure Information

We conducted interviews with 20 patients out of the 35 that we attempted to contact (response rate = 57%). All 20 patients reported use of e-cigarette, or vaping, products in the 90 days before symptom onset, and 18 (90%) reported at least daily use (Table 2). Among 18 patients who stated they used e-cigarette, or vaping, products daily, 9 (50%) used them more than 15 times per day. Daily use ranged from once per day to "all day" or "constantly." Among the 20 patients interviewed, most (n = 16; 80%) reported using THC-containing products; 14 (70%) reported using nico-

FIGURE 1.
Epidemic Curve of North Carolina Confirmed and Probable E-cigarette, or Vaping, Product Use Associated Lung Injury Cases (N = 78), by Week of Symptom Onset Reported to the North Carolina Division of Public Health during August 13, 2019–February 18, 2020

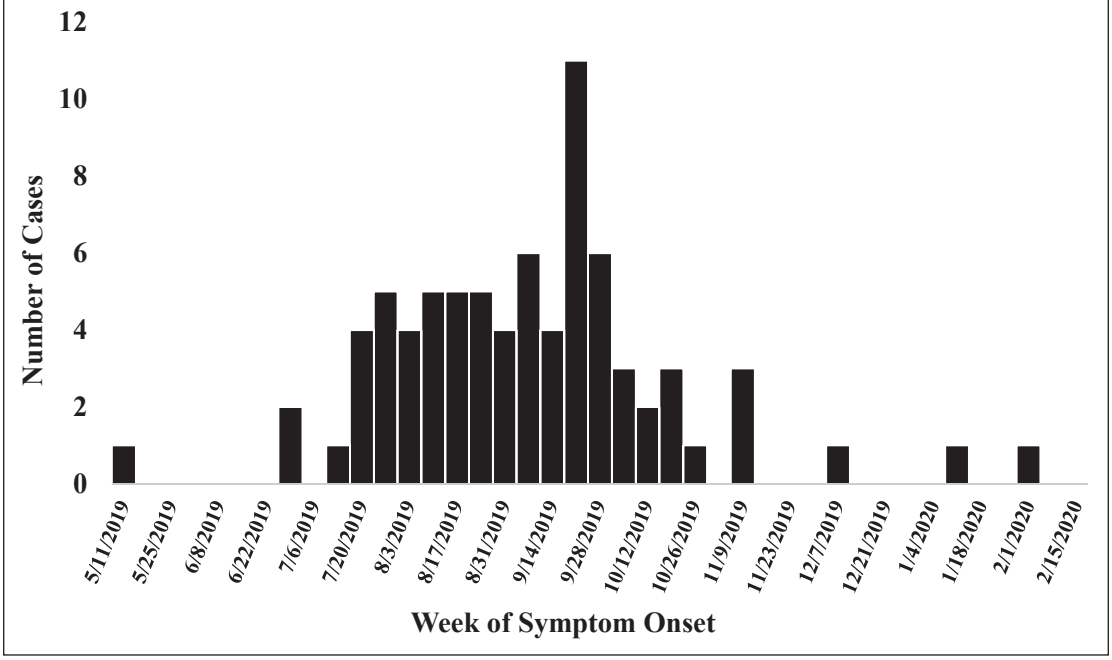

TABLE 1.
Demographic and Clinical Characteristics of North Carolina Patients with E-cigarette, or Vaping, Product Use Associated Lung Injury (N = 78)

Characteristic	n/N	%
Age (years)		
<18	14/78	18
18–24	26/78	33
25–34	22/78	28
35–44	9/78	12
≥45	7/78	9
Age, median (IQR)	24 (19, 34)	
Sex		
Male	49/78	63
Female	29/78	37
Race/Ethnicity		
White, non-Hispanic	50/59	85
Black, non-Hispanic	2/59	3
Other, non-Hispanic	1/59	2
Hispanic	6/59	10
Past Medical History		
Respiratory disease	12/78	15
Heart disease	4/78	5
Anxiety	19/78	24
Depression	13/78	17
Hospital Course		
Hospital admission	75/78	96
Intensive care unit admission	32/78	41
Respiratory support	57/78	73
Noninvasive respiratory support	45/78	58
Mechanical ventilation	12/78	15
Symptom onset to hospitalization, days, median (IQR)[a]	6 (4, 9)	
Hospital admission to discharge, days, median (IQR)[a]	5 (4, 8)	
Prior care before hospital admission[a,b]	44/75	59
Symptoms		
Respiratory	75/78	96
Shortness of breath	66/78	85
Any chest pain	27/78	35
Pleuritic chest pain[c]	10/77	13
Cough	70/78	90
Hemoptysis	6/78	8
Gastrointestinal	63/78	81
Nausea	57/78	73
Vomiting	56/78	72
Diarrhea[c]	29/77	38
Abdominal pain	17/78	22
Constitutional	72/78	92
Subjective fever	68/78	87
Chills	37/78	47
Weight loss	16/78	21
Fatigue or malaise	31/78	40
Headache	31/78	40
Vital Signs at Presentation		
Temperature ≥38°C	16/62	26
Heart rate >100 beats/minute	39/61	64
Respiratory rate >20 breaths/minute	28/61	46
Oxygen saturation <90%	13/62	21
Laboratory Results		
White cell count >11,000/mm[c] and neutrophils >80%	27/42	64
Creatinine, mg/dL, median (IQR)	0.79 (0.60, 0.90)	
Chest Imaging Findings[d]		
Abnormal chest computed tomography	70/70	100
Pleural effusion	8/70	11
Pneumomediastinum	3/70	4
Pneumothorax	2/70	3
Treatment		
Steroids	63/78	81
Antibiotics	75/78	96

Note. IQR = interquartile range
[a]Among patients admitted to hospital
[b]Received care at another location (e.g. urgent care or in outpatient setting) for lung injury before admission
[c]Data missing for one patient
[d]Among patients who had chest computed tomography

TABLE 2.
E-cigarette, or Vaping, Product Use Behaviors during the 90 Days before Illness Onset among Interviewed Patients (N = 20)

Behavior	n/N	%
E-cigarette, or vaping, product use		
Reported THC use	16/20	80
Reported only THC use	3/20	15
Reported nicotine use	14/20	70
Reported only nicotine use	2/20	10
Reported CBD use	6/20	30
Reported only CBD use	0/20	0
Reported both THC and nicotine use	10/20	50
Reported flavor-containing product use	15/20	75
At least daily use of e-cigarette, or vaping, products		
Any products	18/20	90
THC-containing products	12/16	75
Nicotine-containing products	12/14	86
Devices used with e-cigarette, or vaping, products		
Number of devices, median (range)	2 (1, 7)	
Disposable e-cigarette, or vaping, device	2/20	10
E-cigarette, or vaping, device with prefilled pods or cartridges	15/20	75
E-cigarette, or vaping, device with refillable tank	7/20	35
Mods	8/20	40
Vaporizer	3/20	15
Sub-ohm devices	1/20	5
Not sure	1/20	5
E-cigarette, or vaping, product brands		
Number of THC brands, median (range)	3 (1, 5)	
Number of nicotine brands, median (range)	1.5 (1, 8)	
THC-containing product purchase locations		
Vape shop	1/16	6
Gas station	0/16	0
Friend or dealer	15/16	94
Online	0/16	0
Preferred not to answer	1/16	6
Nicotine-containing product purchase locations		
Vape shop	9/14	64
Gas station	5/14	36
Friend or in-person dealer	1/14	7
Online	3/14	21
Other e-cigarette, or vaping, product use behaviors		
Add substances to prefilled cartridges	1/18	6
Hack or modify device or cartridge	2/19	11
Mix own e-liquid	0/18	0

Note. THC = tetrahydrocannabinol; CBD = cannabidiol

tine, and 6 (30%) reported using CBD. Three (15%) patients stated they only used THC-containing products and 2 (10%) reported exclusive use of nicotine-containing products; 10 (50%) reported both THC- and nicotine-containing products.

Patients reported using a median of 2 devices (range: 1–7 devices) during the 90 days before symptom onset. Use of e-cigarette, or vaping, products with pods or cartridges was most common (n = 15; 75%), although 7 (35%) reported using e-cigarette, or vaping, products with refillable tanks, and 8 (40%) reported using mods (i.e., devices in which users can vary voltage or watts). Most patients who reported brand information (11 out of 13; 85%) reported using more than 1 brand of THC-containing products (median: 3; range: 1–5) and 6 out of 12 (50%) reported more than 1 brand of nicotine-containing products (median: 1.5; range: 1–8). Among 16 patients who reported using THC-containing products, 15 (94%) purchased them from informal sources (e.g., friends or in-person dealers). In contrast, among 14 patients who reported purchase location for nicotine-containing products, all 14 (100%) reported purchasing them from vape shops, gas stations, or online; 1 patient also obtained nicotine-containing products from another person. Hacking or modifying devices (2 out of 19; 11%), adding substances to prefilled cartridges (1 out of 18; 6%), and self-mixing liquids (0 out of 18; 0%) were rare.

E-cigarette, or Vaping, Product Testing

We collected 96 products from 10 patients, including e-cigarette, or vaping, devices, pods, and cartridges. Eighty-two products had sufficient liquid for GC-MS and were tested for substances. Seventy-four (90%) contained THC, CBD, or cannabinol, 7 (9%) contained nicotine, and 54 (66%) contained vitamin E acetate (Table 3). All 54 products that contained vitamin E acetate also contained THC; vitamin E acetate was not identified in any nicotine products tested. All 10 patients submitted at least 1 product that contained THC, CBD, or cannabinol, and 9 patients (90%) submitted at least 1 product that contained vitamin E acetate. All 96 products were tested for metals. Barium, cadmium, and lead were detected in all 96 (100%) products, thallium was detected in 3 (3%), uranium in 2 (2%), and arsenic in 1 (1%).

Discussion

Our findings describe an outbreak of EVALI among persons in North Carolina. This is part of a large and national outbreak. Although no deaths were reported among North Carolina residents, most patients required hospitalization. The occurrence of this outbreak, in addition to the recent rapid rise of e-cigarette use by young people, in North Carolina and nationally highlights the need to more fully understand health risks associated with use of these products and for public health agencies and health care providers to intervene more effectively.

National and North Carolina EVALI case data suggest that this outbreak primarily affected young adults who reported using THC-containing e-cigarette, or vaping, products [10]. Among the 20 North Carolina EVALI patients interviewed, most reported daily use of THC-containing e-cigarette, or vaping, products obtained from informal sources (e.g., friends or in-person dealers). These findings are similar to those reported from other states and nationally [9, 17–19]. Although we do not present data on brands of THC-containing products used, other states report that a high proportion of EVALI patients reported use of brands that are from informal, including illicit, sources [20, 21]. Additionally, national syndromic surveillance data suggest EVALI was a new phenomenon rather than increased detection of an underlying clinical syndrome that had previously been occurring [22]. This is separate from the simultaneously occurring youth e-cigarette, or vaping, product use epidemic driven mostly by nicotine-containing product use among adolescents aged less than 18 years [23].

Twenty-four percent of North Carolina EVALI patients had a history of anxiety and 17% had a history of depression, similar to estimates from other states [24–27], suggesting a potentially vulnerable population was affected. Additionally, over half of hospitalized patients received care for EVALI symptoms elsewhere prior to admission. Clinicians should consider EVALI as a potential diagnosis even for mild symptoms, as illness could worsen over time. These visits are also an opportunity for early interventions around e-cigarette, or vaping, product use.

NCSLPH was unable to test collected e-cigarette, or vaping, products for all possible substances, however we did identify THC, CBD, cannabinol, nicotine, glycerol, and metals. Importantly, 73% of THC, CBD, or cannabinol-containing products tested from North Carolina patients contained vitamin E acetate, a diluent and thickening agent used in some THC-containing products [28]. Additionally, 9 of 10 patients who provided products for testing had at least 1 product that contained vitamin E acetate. The Food and Drug Administration (FDA) also identified vitamin E acetate in 49% of THC-containing products submitted from US

TABLE 3.
Laboratory Test Results of Products Submitted by Patients with E-cigarette, or Vaping, Product Use Associated Lung Injury

	n/N	%	Lower reporting limit (ppb)[a]
Substances (N = 82)			
Tetrahydrocannabinol, Cannabidiol, Cannabinol	74/82	90	NA
Nicotine	7/82	9	NA
Vitamin E Acetate	54/82	66	NA
Terpenes	54/82	66	NA
Glycerol	17/82	21	NA
Menthol	5/82	6	NA
Metals (N = 96)			
Arsenic	1/96	1	6.0
Barium	96/96	100	0.6
Beryllium	0/96	0	0.3
Cadmium	96/96	100	0.24
Lead	96/96	100	0.3
Thallium	3/96	3	0.12
Uranium	2/96	2	0.015

Note. ppb = parts per billion
[a]Qualitative nontargeted gas chromatograph mass spectrometry analysis was used to test for substances and inductively coupled mass spectrometry analysis was used to test for metals.

patients [29]. Inhalation of vitamin E acetate might impact respiratory function [30–32]. Since October 2019, vitamin E acetate was detected in 48 of 51 BAL samples from patients in 16 US states (including 2 North Carolina EVALI patients) [11]. North Carolina and national data suggest that vitamin E acetate in THC-containing e-cigarette, or vaping, products is strongly linked with EVALI, although evidence is not sufficient to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products [19, 33]. Additionally, all 7 North Carolina patients with oil red O staining of BAL fluid had lipid-laden macrophages. It is unknown whether lipid-laden macrophages are markers of e-cigarette aerosol exposure or part of the illness process [34]. Similarly, while evaluating 5 North Carolina EVALI patients who presented to a single hospital in August and reported using THC-containing products, physicians hypothesized that inhalation of aerosolized oils might have resulted in lipoid pneumonia [35]. We also detected metals in most e-cigarette, or vaping, products provided by patients. Although it is unknown whether inhalation of metals contributed to the EVALI outbreak and whether the metals derived from the liquids or devices, some metals found in patients' products, such as cadmium and lead, can cause other detrimental health effects when inhaled [36, 37].

Our investigation has limitations. First, EVALI is not required to be reported by clinicians in North Carolina; identification relies on passive clinician reporting. Additionally, the case definition captured primarily severe illness, and we might have missed less critical manifestations. Thus, total number of EVALI cases reported in North Carolina might be an underestimate. Second, our confirmed case definition differed from the CDC's in that we did not require a negative respiratory viral panel. However, all North Carolina cases would have met at least the CDC's probable case definition. Third, medical records contained missing data, particularly with respect to vital signs and laboratory results, potentially because of differences in clinical care and reporting by hospitals. However, our results on clinical presentation of EVALI patients in North Carolina are similar to those reported elsewhere [11, 17, 18, 38]. Fourth, we only interviewed 26% of EVALI patients and excluded patients aged less than 18 years (18%) from interviews. Therefore, information obtained from interviews might not be generalizable to all North Carolina EVALI patients. Additionally, these interviews rely on self-report of e-cigarette, or vaping, product use behaviors and may be subject to reporting and social desirability biases. Furthermore, recreational THC use is illegal in North Carolina which may have resulted in underreporting. However, the proportions of patients who reported THC- and nicotine-containing product use in North Carolina are similar to those reported nationally [10]. Fifth, we were only able to collect e-cigarette, or vaping, products from 13% of all EVALI cases. However, as only interviewed cases could submit products, we did collect e-cigarette, or vaping, products from 50% of interviewed cases. Cases that submitted products might not be representative of all EVALI cases, and they might have been less likely to submit disposable products, as these are typically discarded. Sixth, we were unable to test any aerosols and could not quantify the amount of metals in products. Because exposure occurs through the inhalation of aerosol, we cannot determine whether and in what quantity patients directly inhaled constituents in e-cigarette, or vaping, products. However, we did identify vitamin E acetate in e-cigarette, or vaping, products from North Carolina patients, which was found in 48 BAL samples from US EVALI patients [34]. Lastly, part of the data query used keywords related to e-cigarette, or vaping, products, and clinicians might have started using these keywords after seeing EVALI in news or health alerts; this could have led to increased detection of an existing event rather than identification of a new outbreak. However, temporal trends of ED visits suggest this outbreak represents a new event [22].

In conclusion, our findings support the CDC's recommendations that persons should not use THC-containing e-cigarette, or vaping, products, particularly from informal sources such as friends, family, or in-person dealers [10]. However, informal sources are likely in North Carolina given that THC-containing products are illegal in the state. Vitamin E acetate should not be added to e-cigarette, or vaping, products. In addition to EVALI, use of THC-containing products has been associated with a wide range of health effects, particularly with prolonged frequent use. The best way to avoid potentially harmful effects is to not use THC-containing e-cigarette, or vaping, products [10]. Persons who engage in ongoing THC use that leads to significant impairment or distress should seek evidence-based treatment from a health care professional [10]. NCDPH is working to integrate evidence-based substance use treatment into health and behavioral health systems. Although we identified anxiety and depression in a subset of North Carolina EVALI patients, it is unknown whether these are related to THC use in this population and how behavioral health treatment would impact EVALI. Regardless, evidence-based policy and systems and environmental change might be important for behavioral change in this population. E-cigarette, or vaping, products should never be used by youth, young adults, or women who are pregnant. Additionally, adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products. FDA-approved nicotine replacement therapies, as well as behavioral health counseling from a health care provider, should be the first-line interventions to help people quit smoking [10, 39]. NCDPH has also developed tobacco and e-cigarette prevention and cessation resources as well as e-cigarette health advisories to educate health care providers, school leaders, parents, other caregivers, and the public on the harms of e-cigarette, or vaping, product use. Additionally, NCDPH publicly promotes the use of QuitlineNC (1-800-QUIT-NOW or https://www.quitlinenc.com), which provides free cessation services to any North Carolinian. Guidance for health care providers who evaluate

and care for patients with suspected EVALI is available from the CDC [40–42]. NCMJ

Lauren J. Tanz, ScD epidemic intelligence service officer, Epidemic Intelligence Service, Division of Scientific Education and Professional Development, Centers for Disease Control and Prevention, Atlanta, Georgia; epidemic intelligence service officer, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Ariel Christensen, MPH environmental epidemiologist, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Kendall B. Knuth, MPH CSTE applied epidemiology fellow, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina; CSTE applied epidemiology fellow, Council of State and Territorial Epidemiologists, Atlanta, Georgia.

Molly N. Hoffman, MPH CSTE applied epidemiology fellow, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina; CSTE applied epidemiology fellow, Council of State and Territorial Epidemiologists, Atlanta, Georgia.

Dana Dandeneau, MPH CSTE applied epidemiology fellow, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina; CSTE applied epidemiology fellow, Council of State and Territorial Epidemiologists, Atlanta, Georgia.

Kate Koehler, BS, BA chemical terrorism and threat coordinator and hemachemistry manager, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Zack Moore, MD state epidemiologist, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Sally Herndon, MPH branch head of Tobacco Prevention and Control Branch, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Kevin Davidson, MD pulmonologist, Pulmonology & Critical Care, WakeMed Hospital, Raleigh, North Carolina.

Aaron Fleischauer, PhD career epidemiology field officer, Center for Preparedness and Response, Centers for Disease Control and Prevention, Atlanta, Georgia; career epidemiology field officer, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina.

Acknowledgments

Disclosure of interests. No interests were disclosed.

References

1. Surgeon General's Advisory on E-cigarette Use Among Youth. 2018. https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf
2. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016. http://www.ncbi.nlm.nih.gov/books/NBK538680/. Accessed April 23, 2019.
3. US Department of Health and Human Services. Centers for Disease Control and Prevention. Office on Smoking and Health. E-cigarette, or Vaping, Products Visual Dictionary. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf. Published February 4, 2020.
4. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. JAMA. November 2019. doi:10.1001/jama.2019.18387
5. Tobacco Prevention and Control Branch, North Carolina Department of Health and Human Services. North Carolina Youth Tobacco Survey Middle & High School Fact Sheet. https://www.tobaccopreventionandcontrol.ncdhhs.gov/data/yts/docs/2017-YTS-Fact-Sheet-FINAL.pdf. Accessed November 27, 2019.
6. Kowitt SD, Osman A, Meernik C, et al. Vaping cannabis among adolescents: prevalence and associations with tobacco use from a cross-sectional study in the USA. BMJ Open. 2019;9(6):e028535. doi:10.1136/bmjopen-2018-028535
7. North Carolina State Center for Health Statistics. 2016 BRFSS Survey Results: North Carolina. E-Cigarettes. https://schs.dph.ncdhhs.gov/data/brfss/2016/nc/all/ECIGNOW.html. Published August 9, 2017. Accessed November 27, 2019.
8. North Carolina State Center for Health Statistics. 2018 BRFSS Survey Results: North Carolina. E-Cigarettes. https://schs.dph.ncdhhs.gov/data/brfss/2018/nc/all/ECIGNOW.html. Published August 16, 2019. Accessed November 27, 2019.
9. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report. N Engl J Med. September 2019:NEJMoa1911614. doi:10.1056/NEJMoa1911614
10. CDC. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. https://www.cdc.gov/lunginjury. Published 2019. Updated February 28, 2020.
11. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. N Engl J Med. December 2019:NEJMoa1916433. doi:10.1056/NEJMoa1916433
12. CDC. 2019 Lung Injury Surveillance Primary Case Definitions. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/assets/2019-Lung-Injury-Surveillance-Case-Definition-508.pdf. Updated September 18, 2019.
13. North Carolina Department of Health and Human Services. Three Hospitalizations Among Patients Who Reported Vaping. https://www.ncdhhs.gov/news/press-releases/three-hospitalizations-among-patients-who-reported-vaping. Published August 16, 2019.
14. North Carolina Department of Health and Human Services. Severe Acute Pulmonary Disease among People who Reported Vaping. https://www.tobaccopreventionandcontrol.ncdhhs.gov/ecigs/VapingPulmonaryInjury-NC-ClinicianGuidance-083019.pdf. Published August 30, 2019.
15. U.S. Food & Drug Administration. Lung Injuries Associated with Use of Vaping Products. https://www.fda.gov/news-events/public-health-focus/lung-injuries-associated-use-vaping-products#Analysis
16. New York State Department of Health. New York State Department of Health Announces Update on Investigation into Vaping-Associated Pulmonary Illness. https://www.health.ny.gov/press/releases/2019/2019-09-05_vaping.htm
17. Moritz ED, Zapata LB, Lekiachvili A, et al. Update: Characteristics of Patients in a National Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injuries — United States, October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(43):985-989. doi:10.15585/mmwr.mm6843e1
18. Lewis N, McCaffrey K, Sage K, et al. E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury — Utah, April–October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(42):953-956. doi:10.15585/mmwr.mm6842e1
19. Ellington S, Salvatore PP, Ko J, et al. Update: Product, Substance-Use, and Demographic Characteristics of Hospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, August 2019–January 2020. MMWR Morb Mortal Wkly Rep. 2020;69(2):44-49. doi:10.15585/mmwr.mm6902e2
20. Gaub KL, Hallyburton S, Samanic C, et al. Patient Characteristics and Product Use Behaviors Among Persons with E-cigarette, or Vaping, Product Use–Associated Lung Injury — Indiana, June–October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(49):1139-1141. doi:10.15585/mmwr.mm6849a3
21. Navon L, Jones CM, Ghinai I, et al. Risk Factors for E-Cigarette, or Vaping, Product Use–Associated Lung Injury (EVALI) Among Adults Who Use E-Cigarette, or Vaping, Products — Illinois, July–October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(45):1034-1039. doi:10.15585/mmwr.mm6845e1
22. Hartnett KP, Kite-Powell A, Patel MT, et al. Syndromic Surveillance for E-Cigarette, or Vaping, Product Use–Associated Lung Injury. N Engl J Med. December 2019:NEJMsr1915313. doi:10.1056/NEJMsr1915313
23. King BA, Jones CM, Baldwin GT, Briss PA. The EVALI and Youth Vaping Epidemics - Implications for Public Health. N Engl J Med. 2020;382(8):689-691. doi:10.1056/NEJMp1916171
24. Lewis N, McCaffrey K, Sage K, et al. E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury — Utah, April–October 2019. MMWR Morb Mortal Wkly Rep. 2019;68:953-956. doi: 10.15585/mmwr.mm6842e1

25. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. Lancet. 2019 Dec 7;394(10214):2073-2083. doi: 10.1016/S0140-6736(19)32679-0
26. Gaub KL, Hallyburton S, Samanic C, et al. Patient Characteristics and Product Use Behaviors Among Persons with E-cigarette, or Vaping, Product Use–Associated Lung Injury — Indiana, June–October 2019. MMWR Morb Mortal Wkly Rep. 2019 Dec 13;68(49):1139-1141. doi: 10.15585/mmwr.mm6849a3
27. Heinzerling A, Armatas C, Karmarkar E, et al. Severe Lung Injury Associated With Use of e-Cigarette, or Vaping, Products–California, 2019. JAMA Intern Med. 2020;180(6):861–869. doi:10.1001/jamainternmed.2020.0664
28. Downs D. Amid vape pen lung disease deaths: what exactly is vitamin E oil? Leafly. https://www.leafly.com/news/health/vape-pen-lung-disease-vitamin-e-oil-explained. Published 2019.
29. The Food and Drug Administration. Lung Illnesses Associated with Use of Vaping Products. https://www.fda.gov/news-events/public-health-focus/lung-illnesses-associated-use-vaping-products. Published November 29, 2019.
30. Kamal MdA, Raghunathan VA. Modulated phases of phospholipid bilayers induced by tocopherols. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2012;1818(11):2486-2493. doi:10.1016/j.bbamem.2012.06.016
31. Massey JB, She HS, Pownall HJ. Interaction of vitamin E with saturated phospholipid bilayers. Biochem. Biophys. Res. Commun. 1982;106(3):842-847. doi:10.1016/0006-291X(82)91787-9
32. Casals C, Cañadas O. Role of lipid ordered/disordered phase coexistence in pulmonary surfactant function. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2012;1818(11):2550-2562. doi:10.1016/j.bbamem.2012.05.024
33. Krishnasamy VP, Hallowell BD, Ko JY, et al. Update: Characteristics of a Nationwide Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, August 2019–January 2020. MMWR Morb Mortal Wkly Rep. 2020;69(3):90-94. doi:10.15585/mmwr.mm6903e2
34. Schier JG, Meiman JG, Layden J, et al. Severe Pulmonary Disease Associated with Electronic-Cigarette–Product Use — Interim Guidance. MMWR Morb Mortal Wkly Rep. 2019;68(36):787-790. doi:10.15585/mmwr.mm6836e2
35. Davidson K, Brancato A, Heetderks P, et al. Outbreak of Electronic-Cigarette–Associated Acute Lipoid Pneumonia — North Carolina, July–August 2019. MMWR Morb Mortal Wkly Rep. 2019;68(36):784-786. doi:10.15585/mmwr.mm6836e1
36. Abadin H, Ashizawa A, Stevens Y-W, et al. Toxicological Profile for Lead. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 2007. Available online: http://www.ncbi.nlm.nih.gov/books/NBK158766/.
37. Faroon O, Ashizawa A, Wright S, et al. Toxicological Profile for Cadmium. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 2012. Available online: http://www.ncbi.nlm.nih.gov/books/NBK158838/. Accessed December 6, 2019.
38. Ghinai I, Pray IW, Navon L, et al. E-cigarette Product Use, or Vaping, Among Persons with Associated Lung Injury — Illinois and Wisconsin, April–September 2019. MMWR Morb Mortal Wkly Rep. 2019;68(39):865-869. doi:10.15585/mmwr.mm6839e2
39. National Cancer Institute. Using Nicotine Replacement Therapy. https://smokefree.gov/tools-tips/how-to-quit/using-nicotine-replacement-therapy. Published 2019.
40. Siegel DA, Jatlaoui TC, Koumans EH, et al. Update: Interim Guidance for Health Care Providers Evaluating and Caring for Patients with Suspected E-cigarette, or Vaping, Product Use Associated Lung Injury — United States, October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(41):919-927. doi:10.15585/mmwr.mm6841e3
41. Jatlaoui TC, Wiltz JL, Kabbani S, et al. Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use–Associated Lung Injury — United States, November 2019. MMWR Morb Mortal Wkly Rep. 2019;68(46):1081-1086. doi:10.15585/mmwr.mm6846e2
42. Evans ME, Twentyman E, Click ES, et al. Update: Interim Guidance for Health Care Professionals Evaluating and Caring for Patients with Suspected E-cigarette, or Vaping, Product Use–Associated Lung Injury and for Reducing the Risk for Rehospitalization and Death Following Hospital Discharge — United States, December 2019. MMWR Morb Mortal Wkly Rep. 2020;68(5152):1189-1194. doi:10.15585/mmwr.mm685152e2