Reply to Townsend

From the Authors:

Townsend raises important points regarding the implementation of the 2019 update of the American Thoracic Society/European Respiratory Society Technical Statement spirometry standards (1). These standards were developed to apply to spirometry in any facility in which spirometry is conducted by an operator. As noted in the standards, there may be additional requirements for spirometry in occupational surveillance. Specialized pulmonary function laboratories that have operators with higher levels of training and/or higher-grade equipment may well have internal policies for accuracy and precision exceeding the requirements of these standards.

The need for operator training, such as that provided by recognized spirometry training programs in several countries, was added to these standards to emphasize its importance in quality assurance. Although some changes in maneuver acceptability criteria place more of an onus on the operator, the standards also introduce improvements in the spirometry software to aid the operator in conducting acceptable maneuvers, particularly regarding achieving an acceptable end of forced expiration.

The final inspiration, which is listed in the 2005 standards (2) as an alternative protocol, is widely used and can aid in the interpretation of spirometry. The spirometry examples in Figures 5–10 of the 2005 standards (2) show a full flow–volume loop that includes inspiration, but using this inspiratory component for quality control was not addressed. The task force felt that the addition of a maximal inspiration after maximal expiration provides another quality control indicator that the maneuver began at TLC. However, the standards state that if the final maximal inspiration is not performed, or is submaximal, it does not affect the acceptability of the maneuver.

The standards provide two procedures for spirometry maneuvers: one for expiration and inspiration and the other for expiration only. We agree with Townsend that it would have been preferable to label the latter as an "expiration-only protocol," rather than "expiration-only devices." Although the expiration–inspiration protocol is the preferred option, it was not our intent to suggest that devices capable of measuring both inspiration and expiration could not be used for the expiration-only protocol.

Although the Global Lung Function Initiative reference values (3) are recommended as the default set for spirometry systems, facilities conducting spirometry may choose to use different reference value sets that are deemed more appropriate for their population or for longitudinal studies. Therefore, for occupational spirometry testing in the United States, choosing to use the National Health and Nutrition Examination Survey III spirometry reference values (4) is in full compliance with the 2019 Update of the American Thoracic Society/European Respiratory Society Spirometry Standards. A study has shown that although Global Lung Function Initiative and National Health and Nutrition Examination Survey III have similar predicted values for FEV_1 and FVC, the lower limit of normal for FVC is lower when using the Global Lung Function Initiative (5). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Brian L. Graham, Ph.D.*
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Irene Steenbruggen, R.P.F.T.
Isala Hospital
Zwolle, the Netherlands

ORCID ID: 0000-0003-1794-7682 (I.S.).

*Corresponding author (e-mail: brian.graham@usask.ca).

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The authors are the co-chairs of the task force that developed the official American Thoracic Society Document, "Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement."

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Are Electronic Cigarette Users at Risk for Lipid-mediated Lung Injury?

To the Editor:

Recent case series and related commentary published in the *Journal* highlight the recent epidemic of acute lung injury associated with e-cigarette use and its remaining obscure nature (1, 2). Although this

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cluster is novel, pulmonary illness associated with e-cigarette use is not new: there are at least seven published case reports from 2012 to 2018 describing similar conditions in e-cigarette users, with no identifiable infectious etiology (i.e., acute lung injury, atypical pneumonitis, eosinophilic pneumonia, hypersensitivity pneumonia, or lipoid pneumonia). Interestingly, of these seven reported cases, lung cell samples obtained via lavage or biopsy were available for five (3–7), and all five exhibited abnormally lipid-laden macrophages. Lipid-laden macrophages were also a prominent feature (>50%) in BAL of more recent case series from Utah (8). Such macrophages can trigger an inflammatory immune response (9) leading to lipoid pneumonia and other pneumonitis-like reactions. One report suggested that residual lipids in vegetable glycerin derived from incompletely processed vegetable oil might be the exogenous source of lipid in an e-cigarette user diagnosed with lipoid pneumonia (5). However, most of the publications related to this new entity focused on tetrahydrocannabinol, and a recent case series from the Mayo Clinic suggests chemical pneumonitis as a more probable etiopathology (10). The fact that not all e-cigarette–related lung injury cases were associated with tetrahydrocannabinol use, and that tetrahydrocannabinol vaping usually involves an oil vehicle (e.g., butane hash oils), does not rule out an important role for lipid-mediated lung injury in this clinical entity. This is particularly important to keep in mind given that most e-cigarette liquids contain vegetable glycerin as an essential component (helps make the e-cigarette aerosol visible). The implication is that many e-cigarette users who are currently asymptomatic (or experiencing milder symptoms for which they do not seek medical attention) may be undergoing lipid deposition in their airway, with concomitant inflammatory changes induced by lipid-laden macrophages and other immune cells. Therefore, we urge clinicians treating patients with acute and unexplained pulmonary complaints to identify whether the patient is an e-cigarette user and, if so, to obtain detailed history about their use and, when possible, to collect cell samples to determine whether evidence of lipid exposure is present. Similarly, we urge researchers to investigate lipid exposure and inhaled toxic substances in e-cigarette users systematically. Most important, we call for regulators to implement immediately strict regulation that prevents lipid and inhaled toxicants emissions from all e-cigarettes sold in the United States. ■

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Thomas Eissenberg, Ph.D.
Virginia Commonwealth University
Richmond, Virginia

Wasim Maziak, M.D., Ph.D.*
Florida International University
Miami, Florida

*Corresponding author (e-mail: wmaziak@fiu.edu).

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Reply to Eissenberg and Maziak

From the Author:

The letter from Eissenberg and Maziak is a welcome reminder that although most of the cases of e-cigarette or vaping product use–associated lung injury (EVALI) have been associated with tetrahydrocannabinol (THC)-containing liquids, cases have also been reported in which only nicotine-containing liquids were used. As of December 17, 2019, a total of 2,506 hospitalized EVALI cases have been reported to the CDC from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and the U.S. Virgin Islands), with 54 deaths in 27 states and the District of Columbia (1). Of 1,782 hospitalized patients for whom complete information was available on substances used in e-cigarette or vaping products in the 3 months before symptom onset, 13% reported exclusive use of nicotine-containing products (1). These data provide the basis for the CDC recommendation that "the best way for people to ensure that they are not at risk while the investigation continues is to consider refraining from the use of all e-cigarette, or vaping, products" (2). Since the publication of the Triantafyllou and colleagues case series and the accompanying editorial, more information has become available about the EVALI cases associated with vaping of a class of largely counterfeit THC-containing products of unknown origin, with "Dank Vapes" being

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