regimen with known toxicities that are likely to result in pauses in or discontinuation of treatment is sent to the field without adequate tools for monitoring resistance.

The other major tragedy is that every year tuberculosis still affects approximately 10 million people and kills 1.5 million.[5] In light of these figures, we should not be dependent on one small, single-group, single-country study for evidence of the efficacy of the newest tuberculosis regimen. The study was rigorously conducted and laudably designed to report on definitive outcomes of durable cure and relapse; however, such approaches for the development of tuberculosis regimens do not correspond with the magnitude of the problem. Tuberculosis does not present insurmountable hurdles for the conduct of clinical trials. Even the creation of multidrug regimens with new agents from different developers is feasible, as evidenced by the recent history of treatment for human immunodeficiency virus infection and hepatitis C, both of which have new regimens developed and defined through multiple large trials. In contrast and tragically, the majority of evidence available to the World Health Organization in 2020 as it formulates treatment guidelines for drug-resistant tuberculosis comes from noncomparative or observational studies.[10,11] Such studies should serve as the adjunct to an evidence base of robust randomized, controlled clinical trials, rather than as its leading edge.

A rejuvenated program of innovative phase 2 and phase 3 clinical trials of new drugs and regimens, in conjunction with continued investment in tools for detecting and monitoring resistance, is required worldwide. It will take substantially greater investment and coordinated forms of collaboration among sponsors, industry, academic partners, and policy decision makers to develop and implement new evidence-based regimens that are fitting for a disease that has killed hundreds of millions of people. Until that happens, if the current inadequate investment path is held, history is bound to repeat itself — and for all the jubilation that comes with developing a new effective regimen, there will be more tragedy yet to come.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Vaping-Induced Acute Lung Injury

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A number of environmental agents are known to cause acute or subacute inhalation injury to the lung parenchyma. Indeed, emergency response guidelines for medical personnel describe toxic inhalation pneumonitis as a heterogeneous group of chemically induced injuries to the lung parenchyma as well as to the upper respiratory tract. The manifestations of such injury depend on the

characteristics (e.g., solubility, composition) and the amount of the toxic compound or compounds inhaled.[1] Much of what we know about toxic inhalation syndromes derives from high levels of exposure in either occupational settings (e.g., exposure to metals, solvents, acids, bases, ozone, phosgene, or chlorine dioxide) or community settings where fires or accidents may occur (e.g., factory explosions, derailments of chemical-bearing train cars, and overexposure to household cleaning agents). Depending on the type of chemical agent and the amount of material inhaled, patients may experience symptoms ranging from minor respiratory tract discomfort to acute airway injury and damage to the parenchyma with pneumonitis, alveolar edema, respiratory failure, and death. A common pathophysiological pathway includes inflammation, edema of airways with epithelial sloughing, alveolar inflammation, and edema with hypoxemia.[2]

In this issue of the *Journal*, Layden et al.[3] report updated findings regarding a cluster of cases from Illinois and Wisconsin in which patients presented with acute, severe respiratory distress after using e-cigarette (vaping) products. Two letters also published in the *Journal* add further support to vaping-induced respiratory distress: a six-case cluster from Utah[4] and a report of imaging changes seen in a range of cases.[5] The syndrome has been termed by the Centers for Disease Control and Prevention (CDC) as e-cigarette, or vaping, product use–associated lung injury (EVALI). The CDC reported that as of January 21, 2020, a total of 2711 patients had been hospitalized with EVALI; reports were made to the CDC from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and the U.S. Virgin Islands). A total of 60 deaths have been confirmed in 27 states and the District of Columbia.[6]

Initially, EVALI cases demonstrated a heterogeneous collection of pneumonitis patterns that included acute eosinophilic pneumonia, organizing pneumonia, lipoid pneumonia, diffuse alveolar damage and acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage, hypersensitivity pneumonitis, peribronchiolar granulomatous pneumonitis, and the rare giant-cell interstitial pneumonitis. Although the precise pathologic manifestations of the respiratory injury may be diverse, there is some consistent evidence that warrants attention. The majority (83%) of persons who vaped and became ill reported having used products with tetrahydrocannabinol (THC) or cannabidiol (CBD), which have been formulated with oils, such as vitamin E acetate; the remaining 17% reported using only nicotine vaping products, which are not routinely mixed with vitamin E acetate. As reported recently in the *Journal*, Blount et al.[7] found evidence of vitamin E acetate in bronchoalveolar-lavage samples obtained from 48 of 51 patients with EVALI in a convenience sampling. Coconut oil and limonene were also found in 1 patient each. Among the patients who had available laboratory data or who reported product use, 47 of 50 (94%) had detectable THC or its metabolites in the bronchoalveolar-lavage fluid or reported vaping THC products in the 90 days before the onset of illness. In bulk samples of THC-containing products that had been seized by law enforcement, vitamin E was found in 20 of 20 samples in 2019 and in none of 10 samples that had been seized in 2018.

A consistent pathologic feature that has been found in multiple reports is the appearance of lipid-laden pulmonary alveolar macrophages, many with vacuolization and often with vacuolated pneumocytes. These findings are typical of a chemical-induced pneumonitis. Although the presence of vitamin E acetate in most cases may represent a key, and common, exposure culprit, the toxicology may be more complicated. Specifically, the severe inflammatory response and edema may be a result of the pyrolysis products (some of which are gases [e.g., ketene] and not easily measured in biologic samples) of vitamin E oil rather than the parent compound itself. Nevertheless, the focus on vitamin E acetate and related compounds as chemical instigators of the EVALI outbreak is reasonable. Additional experimental studies in animals may provide information on whether exposure to vitamin E acetate alone can directly cause acute lung injury.

An audio interview with Dr. Christiani is available at NEJM.org

The focus of the outbreak has now turned to vaping products that contain THC, but it is important not to lose sight of the larger health issues around vaping. E-cigarette fluids have been shown to contain at least seven groups of potentially toxic compounds: nicotine, carbonyls, volatile organic compounds (such as benzene and toluene), particles, trace metal elements according to flavor,[8] bacterial endotoxins, and fungal glucans.[9] Two flavorants alone, diacetyl and

2,3-pentanediol, have been shown to perturb gene expression pathways related to cilia and cytoskeletal processes in normal human bronchial epithelial cells.[10]

As Layden et al. point out, the literature contains reports of acute lung disease — including acute eosinophilic pneumonia, respiratory bronchiolitis-associated interstitial lung disease, and hypersensitivity pneumonitis — that has also been associated with use of nicotine-containing liquids.[11-13] Since the industry has not been required by regulatory agencies to report all ingredients (nor their pyrolysis products), it would be imprudent to assume that patients with EVALI who report only nicotine vaping are underreporting THC use. Our default position as physicians is to believe our patients. The burden should be on the nicotine vaping companies to prove that their vaping fluids do not contain pulmonary toxicants capable of producing acute and chronic lung disorders. We need to heed the lesson from environmental public health regarding the precautionary principle that holds when a new product is developed that may have the potential for harm: it should be tested carefully for toxicity before being marketed widely.[14]

In light of this outbreak that is characterized clearly by a chemically induced acute lung injury, continued efforts should be made to increase public awareness of the harmful effect of vaping. Physicians should discourage their patients from vaping products that contain THC. If patients are using nicotine products to quit smoking, it would be prudent to switch to non–vaping-related nicotine substitutes until the toxicologic investigations of electronic-cigarette fluids are more complete.

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