chemotherapy; worse, there was a downward trend during study progress. A substantial amount of resources could be saved if a decision on treatment was made before a test was ordered: "intention to test is intention to treat." Unless healthcare provider and patient education about the benefits of preventive chemotherapy will be substantially improved, targeted testing for latent infection with *M. tuberculosis* has limited public health impact.

Although desirable, a substantially improved test to better define individuals at risk of future tuberculosis does not seem imminent. It is thus all the more important that only individuals are tested who are at a high risk of tuberculosis in the future and who are fully appraised of the treatment consequences.

Author Disclosure: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.201011-1881ED

What Does Multi-Pollutant Air Pollution Research Mean?

In the air we breathe, we encounter air pollutants in mixtures that result from different sources of pollution and the effects of atmospheric chemical transformation. A single-pollutant approach to air pollution management and research in the United States was partly motivated by the Clean Air Act, which identifies six criteria air pollutants that are the focus of air quality regulations based on monitored air concentrations. There has been a call for a move from a single-pollutant approach to air quality management to a "multi-pollutant" approach, motivated by generally acknowledged inadequacies in managing air quality one pollutant at a time (1). Moving away from the single-pollutant approach requires a shift in air pollution health research to provide a sound basis for multi-pollutant air quality management.

While there is yet no clear consensus as to what a multi-pollutant approach involves for air pollution epidemiology, new approaches must change the current way of specifying air pollutant concentrations (or exposures) in statistical models that estimate health effects. Reports of the health effects of air pollution have traditionally detailed effects of one pollutant at a time, despite obvious limitations of this approach. These effects are typically estimated from individual regression terms for concentrations of one or each of a few air pollutants that are intended to reflect a pollutant's effect on a health endpoint. However, it is generally understood by investigators that rather than being an effect of the single pollutant itself, as it nominally appears, this may in fact be a reflection of effects of emissions from a source, or of a common set of pollutants from a source, that are not explicitly specified in a regression model. The "single" pollutant term in these models in this case really serves as a surrogate term for a complex mixture of pollutants that are typically not measured in air pollution monitoring networks.

It has been common to use so-called multi-pollutant models that contain terms for estimated population exposure for several pollutants in the hope of identifying the pollutant, or subset of pollutants, responsible for the observed effects. There is growing awareness that these types of multi-pollutant models usually do not serve that purpose. In some settings, a pollutant term in a model may, paradoxically, be a better measure of

Both authors contributed to conception, writing, and critical review of this Editorial.

exposure to another pollutant than a measure of that other pollutant itself. For example, ambient ozone concentrations, in some settings at least, reflect personal exposure to ambient particulate matter better than personal exposure to ozone itself (2). Importantly, because different exposure estimates for some pollutants reflect population exposures with varying degrees of measurement error, the pollutant with the least measurement error will typically demonstrate stronger effects in a statistical model, regardless of the true strength of the effect of each pollutant (3, 4). These issues complicate interpretation of individual air pollutant effects.

A central aspect of a new multi-pollutant approach to air pollution epidemiology will be to attempt to model complex air pollution mixture effects more explicitly to gain better insight into the features of an air pollution mix that are most toxic. One approach has been to replace air pollutant concentration terms with regression terms intended to reflect exposure to pollution *sources* rather than a specific pollutant. A crude way is to use, for example, distance to large roadways or intensity of traffic within a prescribed radius to reflect exposure to motor vehicle emissions. An alternative has been to utilize data on a relatively large set of air pollutants to apportion the contribution of various sources, including traffic, to this pollutant mix and then include terms for these sources directly in regression models (5, 6). Yet another approach has been to use chemical components or pollutants as markers of a specific source; unfortunately, these markers are seldom specific for a single source, such as is the case for elemental carbon when used as a marker of diesel exhaust (7).

While these alternative ways of specifying air pollutant effects have a more multi-pollutant flavor, they still fall short of the goal of being able to estimate effects of specific features of pollutant mixtures. For example, if a source is identified as being responsible for an adverse health effect, it may be important to know which features or components of the source emissions are most critical for producing toxicity. Another approach is to attempt to include all pollutant terms in a regression model that includes at least interaction terms for each pair of pollutants, in the hopes of capturing the total impact of air pollution as well as the synergistic or antagonistic effects of combinations of pollutants (8). While this may be possible with a few pollutants (which is often necessitated by the limited number of pollutants measured), the inclusion of only a small number of pollutants makes it likely that only a part of the total impact of the pollution mix is captured. On the other hand, use of a very rich (and therefore large) set of pollutants becomes intractable without applying some dimension reduction technique to reduce the number of variables and interactions. The resulting regression terms may not be interpretable, except possibly as sources, bringing us back to limitations in modeling source effects. Application and development of statistical methods that are appropriate for this complex setting are needed (8, 9).

The study by Hart and coworkers in this issue of the *Journal* (pp. 73–78) (10) is described as a multi-pollutant approach. The authors' approach is to estimate a limited number of individual pollutant (PM_{10}, NO_2, and SO_2) health effects, first individually and then in a model that included the several single-pollutant terms together. This is a "business-as-usual" approach, though the authors acknowledge in their discussion that individual pollutants are also markers of sources, with NO_2 a marker of traffic, PM_{10} a marker of traffic but also of other combustion and noncombustion sources, and SO_2 a marker of power plant emissions and other fossil fuel combustion sources. Clearly, this limited set of pollutants, necessitated by the available data, captures only part of the pollutant mix. Also, the modeling approach here does not attempt to address pollutant interactions that might begin to more fully describe a multi-pollutant picture. The authors' claim that modeling a small number of pollutants together is a unique feature of their study needs to be tempered by the fact that this is commonly done, although not often described as an approach to assessing "multi-pollutant exposures."

It is recognized that adoption of the multi-pollutant framework in air pollution epidemiology (8), as well as in experimental air pollution research, will not be easy or inexpensive (11, 12). Progress in air pollution sciences will require measurements of a rich array of air pollutants, and application and development of statistical methods that are suitable for a large and highly correlated number of variables and that can incorporate what is already known about their interrelationships. The payoff will be an air quality management program that protects public health through a better understanding of the features of a complex air pollution mixture that are most deleterious to health.

Author Disclosure: S.V. has received sponsored grants from the Environmental Protection Agency (EPA), the National Institutes of Health (NIH), and Health Effects Institute (each over $100,000). J.D.K.'s spouse has received consultancy fees from AiCuris ($10,001–$50,000), Astellas ($1,001–$5,000), and Infectious Design ($1,001–$5,000); industry-sponsored grants from Astellas and GlaxoSmithKline (each over $100,000); and royalties from UpToDate ($1,001–$5,000). He has received sponsored grants from the NIH and the EPA (each over $100,000), and his spouse has received sponsored grants from the NIH (over $100,000).

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DOI: 10.1164/rccm.201009-1520ED

Better Supportive Care, Less ARDS

Just Do It?

In this issue of the *Journal*, Li, Gajic and colleagues (pp. 59–66) suggest that the introduction of relatively simple hospital-wide and ICU-specific clinical measures may reduce the incidence of the acute respiratory distress syndrome (ARDS) (1). ICU outcomes are influenced by events before, during, and after ICU admission. The notion that, in part, ARDS is a preventable disease challenges us to understand these interesting data, and to reconsider our approach to the delivery of health care.

Perhaps the most notable recent example of improved delivery of health care, and prevention of disease, in the ICU is the reduction of catheter-related bloodstream infections following targeting of five simple clinical interventions: hand washing, full-barrier precautions, use of chlorhexidine, avoidance of the femoral approach, and removal of unnecessary catheters (2). Despite the quasi-experimental design, an accompanying Editorial (3) argued that these data were compelling and that the five components of the intervention should be widely adopted. Using this as a measuring stick, can we similarly draw strong conclusions about improved management, and perhaps prevention, of ARDS?

It is increasingly recognized that the pathologic progression of ARDS develops more rapidly than previously appreciated, preceding clinically recognized changes. Early thoughts on an orderly timing of cellular infiltration, proliferation of type II cells, and then resolution and repair (4) have been challenged. Within 24 hours of intubation there is increased collagen turnover in the lung (5, 6), perhaps related to local expression of coagulation factor X and early induction of fibrosing alveolitis (7). Further, predictive biomarkers are elevated within a few hours of an insult (8, 9), well before any clinical suggestion of lung injury (10). The rapid timing of these pathophysiologic changes suggests that interventions need to occur as early as possible.

Using a retrospective population-based cohort study, assisted by the ability to capture all critically ill patients in their region, over the period 2001–2008, Li and colleagues (1) report a reduced incidence of ARDS from 82.4 to 38.9 per 100,000 person-years due to a fall in hospital-acquired ARDS. Concurrently there were a number of changes in healthcare delivery, specifically use of lower tidal volume in all ventilated patients, reduced transfusion of blood products and male-predominant plasma, improved treatment of sepsis and pneumonia, 24-hour onsite intensivist staffing, a hospital-wide rapid response team, and electronic medical records. While the severity of illness and number of comorbidities increased over this 8-year period, the all-cause ICU and hospital mortality, and length of stay, decreased; however, the case fatality rate of patients with ARDS did not change. Before accepting that improved delivery of health care prevented ARDS, we need to examine these data more closely; indeed, the authors rightly caution against a cause-effect relationship based on their observational study design.

Li and colleagues (1) defined hospital-acquired ARDS as the 1994 American-European Consensus Conference (AECC) criteria (11) more than 48 hours after hospital admission, and admission ARDS as AECC criteria within 6 hours of hospital admission. However, as the greatest reduction in ARDS incidence occurred 6 to 48 hours after admission, calculated as the total number of patients with ARDS minus admission and hospital-acquired ARDS (Table 3), well within the time period that ARDS is thought to occur following a predisposing factor (12), these patients should not be classified as having hospital-acquired ARDS. This does not preclude the notion that ARDS is preventable; there is no reason that changes in healthcare delivery may not reduce the risk of ARDS earlier than 48 hours after hospitalization. In addition, there may have been changes in Emergency Department and prehospital care that influenced the risk of developing ARDS.

The AECC criteria for the diagnosis of ARDS include the identification of a predisposing (at-risk) factor—for example, pneumonia, sepsis, aspiration of gastric contents, polytrauma, and multiple transfusion. While the study design employed by Li and colleagues study did not allow them to prospectively identify these factors, diagnostic related group (DRG)-based estimates of these predisposing conditions were unchanged or increased throughout the period of the study. This makes it less likely that the reduction in incidence of ARDS they observed was attributable to a decrease in the population of patients at risk for ARDS, addresses the spirit of the AECC criteria, and is an example of their novel methodology.

As Olmsted County is geographically isolated, with one ICU provider, the estimated incidence of ARDS is reliable. We (13) used a similar advantage to estimate the incidence (28 cases per 100,000 person-years) and 28-day mortality (34%) of ARDS in three Australian States. Rubenfeld and coworkers (14) estimated the incidence of ARDS in King County as 58.7 cases per 100,000 person-years, still not as high as the initial estimate by Li and colleagues (1) of 82.4 per 100,000 person-years. It may be that a relatively high baseline in this study might have made the observed reductions more dramatic; however, these differences might also reflect variability both in healthcare, including transplantation and aggressive chemotherapy, and in ICU access. The AECC criteria do not specify a requirement for mechanical ventilation, and nonventilated patients with ARDS who are cared for outside the ICU (15) are not included in Li and colleagues' data, perhaps introducing another area for bias. However, ICU access does not appear to have been a limiting issue; the ICU utilization per capita (1,000 patients per year from a population base of 123,000 residents) is around twice that found in Australia. Irrespective, this is unlikely to have influenced the result, as access was similar across the study period.

Despite some uncertainties, Li and colleagues report a convincing reduction in the incidence of ARDS in their county