Estimating Deaths Due to Influenza and Respiratory Syncytial Virus

To the Editor: Dr Thompson and colleagues[1] developed a statistical model to estimate deaths attributable to influenza and respiratory syncytial virus (RSV). We are concerned that their model was inappropriate. When designing a model to attribute causality to deaths, a reasonable initial approach would be to assume that the number of deaths due to a specific virus in any given week was proportional to the number of laboratory reports of that virus in that week. The total number of deaths would be the sum of the contributions from each virus, plus the seasonal background of deaths due to other causes. Similar models have been used successfully to estimate the proportion of gastrointestinal disease attributable to rotavirus[2] and the proportion of bronchiolitis and pneumonia attributable to RSV and other pathogens.[3] Additional terms and factors could be included to account, for example, for improving sensitivity of surveillance over time, but the core of the model would remain linear and additive.

An appropriate analysis could use linear regression, a generalized linear model (GLM) with a Poisson error distribution and an identity link, or maximum likelihood for a non-GLM. Instead, Thompson et al used a Poisson model in which the number of deaths increased exponentially with the number of laboratory reports and the effects of each virus (and the seasonal background) on the number of deaths were multiplicative rather than additive. We do not believe that there is plausible justification for fitting such a model to these data.

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To the Editor: Dr Thompson and colleagues[1] presented a model that uses influenza and RSV surveillance data to estimate virus-associated mortality. The authors propose that this model replace Serfling-type models, which have been used for 40 years to estimate deaths attributed to influenza by subtracting a model-generated baseline from observed winter deaths.[2,3]

The model of Thompson et al averages 34 470 (range, 7608-68 328) total seasonal influenza-related deaths for 1976-1999. This average, much higher than previous reports (approximately 20 000; range, 0-40 000 for 1972-1992),[3] suggests that the Serfling models underestimate the mortality burden and that the new model corrects this problem. In fact this is not the case. A Serfling-type model[4] estimated an average of 37 500 (range 0-74 500) all-cause excess deaths for 1976-1999. Both models report an increase in influenza-related deaths in the 1990s, which for Serfling models is fully explained by a rapidly increasing population of very elderly Americans (for whom influenza-related mortality risk increases exponentially),[5] together with increased circulation of the virulent subtype influenza A(H3N2).[4]

Although Thompson et al offer their model as superior, they do not provide graphical or statistical evidence of acceptable fit or model validation. Nor do they compare their influenza mortality estimates with those based on Serfling models. In fact, their individual season estimates of pneumonia and influenza deaths correlate poorly with Serfling estimates ($R^2<0.5$), and this comparison reveals an unexplained time dependency (FIGURE). The doubling in their surrogate measure of virus activity (from ≈8% to ≈16% influenza-positive specimens, Table 1[1]) over the study period leads to large underestimates (1970s) and overestimates (1990s) of influenza mortality relative to Serfling estimates. For perspective, the 1980-1981 season was considered very severe, yet the authors' model estimated only 4068 influenza-related pneumonia and influenza deaths compared with 9700 by a Serfling model.[1,4]

The Thompson model produces essentially constant estimates of RSV-related mortality for the 1990s, 80% of which are stated to be deaths in elderly individuals. If this is so, then the authors should be able to demonstrate a 40% increase in RSV deaths among those aged 85 years or older during the 1990s when this population increased by approximately 40%. Such straightforward validation would provide evidence that this model does indeed measure RSV deaths in the elderly population.

A model that requires the additional complexity of viral surveillance data for mortality estimates sharply limits historical comparison within the United States and eliminates comparison with most other countries. We propose that rigorous dem-

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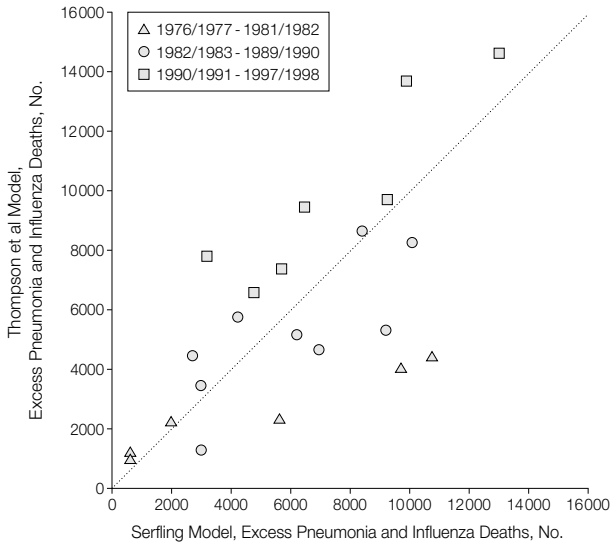
Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

Figure. Comparison of Seasonal Estimates of Pneumonia and Influenza Excess Deaths From a Serfling Model and the Thompson et al Model, Applied to Mortality Data From 1976-1998



onstrations of validity and benefit precede adoption of this new modeling approach.

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Funding/Support: Dr Blackwelder's work on this letter was supported by National Institutes of Health contract A1-15448.

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To the Editor: Total excess mortality has been used to measure the burden of influenza for many years. Dr Thompson and colleagues[1] stated that this death category includes diagnoses that "are not causally linked with respiratory viral infections." Seasonal total excess deaths, however, comprise a small proportion of total mortality; we believe that it is not possible with the limited clinical information on death certificates to accurately designate those complicated by influenza. Even cases listing burns or trauma as the underlying cause of death may be influenza-related if the virus infection occurred coincident with the trauma or was nosocomial. Because neither past nor the current proposed models are able to directly identify influenza-caused deaths, we see no reason to abandon total excess mortality and substitute attributable "respiratory and circulatory deaths." For the sake of continuity and comparability, we believe that the established category should be retained while assessing the value of alternative approaches.

Considering the current information, we believe that it is premature for Thompson et al to attribute 25% of wintertime excess mortality to RSV. Years of research have provided understanding of influenza epidemiology, pathogenesis, patterns of complications, and risk of death that underpin indirect attribution of causal relationships used to estimate influenza mortality. This quality of data is evolving for RSV but has not yet reached the same level of detail. Respiratory syncytial virus appears to be a cause of death among elderly persons in long-term care facilities but reports have been variable and inconsistent.[2] Respiratory syncytial virus has been noted as a cause of hospitalization of elderly persons but rates have been variable and the nature of complications such as bacterial superinfection and risk of death are not yet established. Additionally, the surveillance of RSV by the Centers for Disease Control and Prevention reflects primarily infections in infants and young children[3] during periods when many other viruses contribute to acute respiratory illness in adults.[4] The authors did not demonstrate how the yearly RSV prevalence in young children might be related to disease in older people.

Furthermore, the authors' estimate of influenza-related mortality does not appear to reflect a benefit of increasing influenza vaccine coverage of those aged 65 years or older. Despite immunization of 65% of elderly individuals in the United States by the end of the decade, the number of deaths increased. If influenza vaccination were effective, the proportion of deaths attributed to RSV by the authors' model should have increased; instead, it decreased during the last 3 years, 1996-1999. We conclude that improved protection for elderly individuals is needed.[5]

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In Reply: Mr Gay and colleagues suggest that we used an incorrect statistical model to analyze our data. We agree that it is important to confirm that analyses are appropriate for the data. We compared the effects of using a Poisson regression