as Jackson pointed out, have any method of directly assessing underlying functional status. However, we did note that in addition to being older and more likely to have underlying conditions, statin users were more likely to have longer hospitalizations than non–statin users, which argues against statin users being healthier patients at baseline. We also found that similar proportions of statin users and non–statin users were admitted to the hospital from long-term care facilities. And, although Jackson cited several studies suggesting a healthy-user bias associated with statins, the literature does not uniformly support this hypothesis. One study from Spain that evaluated the impact of preadmission use of statins in preventing healthcare-acquired infections in the intensive care unit suggested that statin use may be a marker for poor underlying health status at baseline; in a cohort of patients requiring prolonged mechanical ventilation (duration, >96 hours), statin-treated patients were older and tended to have more severe comorbidities, as defined by Acute Physiology and Chronic Health Evaluation II scores [2].

We were unable to use negative controls, as recommended by Jackson, to assess specificity of the association between statin use and mortality from influenza. Our data came from the Center for Disease Control and Prevention’s (CDC) Emerging Infections Program (EIP) influenza hospitalization surveillance system. We did not collect detailed medication history other than statin use, precluding evaluation of negative exposures, such as other medications unlikely to be related to risk of influenza mortality. Similarly, the data collected did not allow for the assessment of negative outcomes (such as deaths occurring >30 days after the influenza test). We focused our efforts to ascertain deaths that occurred after hospitalization in a narrow time frame after hospitalization in order to limit our analysis to deaths most likely to be related to hospitalization for influenza.

Other researchers, however, have made efforts to control for potential healthy-user bias regarding statins and influenza, with some success. A similar surveillance system in the United Kingdom, the Influenza Clinical Information Network (FLU-CIN), collected clinical, epidemiological, and outcome data on patients admitted to participating hospitals with laboratory-confirmed pandemic influenza H1N1 infection [3]. Although their results were not statistically significant, likely because of a sample size that was smaller than that in our study (571 vs 3043 subjects), they documented a similar trend toward a protective effect between use of statins and severe outcome (defined as admission to a high-dependency unit, admission to an intensive care unit, or death; adjusted odds ratio, 0.81 [95% confidence interval, 0.46–1.38]). They attempted to adjust for healthy-user bias by including a term in their model that indicated the presence of a comorbidity not normally directly associated with statin use (presence of hypertension; asthma; chronic lung, liver, or renal disease; diabetes or other metabolic disease; or chronic neurological disease), without any impact on outcome.

Although perhaps these studies from the CDC’s EIP and the UK’s FLU-CIN networks could be considered lessons about the pitfalls of using surveillance data to draw conclusions about the association between statins and severe sequelae of influenza, we suggest that future investigation of statins as adjunctive therapy in the management of influenza is still warranted. Not only is there a growing body of evidence from observational studies that documents the impact of statins in sepsis, pneumonia, and influenza, the proposed mechanism is biologically plausible: not long after their introduction for treatment of hypercholesterolemia, the pleiotropic anti-inflammatory properties of statins were established [3–7]. Despite the constraints of observational studies and their inherent risk of bias, we maintain that statins

Reply to Jackson

To the Editor—We are grateful for the comments by Jackson about our article [1]. The issue of healthy-user bias is a certainly a legitimate concern, one that we raised ourselves and tried to explore as thoroughly as possible.

We attempted to control for underlying health status as best as we could by including age and various underlying conditions in our model, but we did not,...
are a promising area of exploration, as suggested by a recently published randomized, controlled trial (RCT) that demonstrated their efficacy in reducing the incidence of pneumonia among healthy participants (ie, men aged ≥50 years and women aged ≥60 years) who were randomized to receive either rosuvastatin or placebo [8]. As the first published RCT that evaluated an infectious disease outcome, it is unlikely to be biased by the healthy-user effect, and we suggest that RCTs are the most appropriate way to answer the question of whether statins can reduce severe sequelae of influenza virus infection.

Notes
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Ann Thomas
Oregon Public Health Division, Portland

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Received 4 April 2012; accepted 4 April 2012; electronically published 8 May 2012
Correspondence: Ann Thomas, MD, MPH, Oregon Public Health Division, 800 NE Oregon St, Portland, OR 97212 (ann.thomas@state.or.us).

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