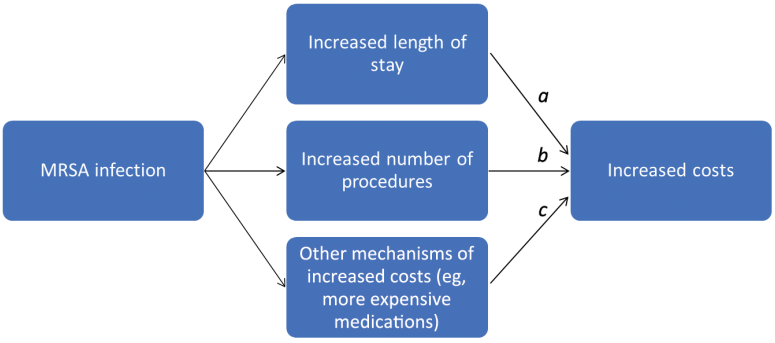

Figure 1. Causal diagram showing proposed relationships between MRSA infections, length of stay, increased number of procedures, other mechanisms of increased costs, and the costs of hospitalization. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

kidney injury. In a study of vancomycin compared with another antimicrobial for the treatment of MRSA infections in inpatients, suppose that a researcher used a propensity score analysis. The inclusion of length of hospital stay in the propensity score would adjust away the effect on the cost of vancomycin, resulting in increased length of hospital stay.

In the study by Klein et al, adjustment for potential mediators in the propensity score analysis leads to an analysis the outcome of which is the extent to which MRSA infection, compared with MSSA infection, leads to increased or decreased healthcare costs *not* associated with length of stay, need for procedures, or severity of illness. However, we do not believe that this was the authors' intent.

The presence of confounders of these intermediate variables (such as baseline comorbidities and their effect on both MRSA risk as well as length of stay) further complicates the analysis; a recent review discusses analytic methods for the problem of confounded intermediates [8].

We would be curious to see the results of an analysis that excludes from the propensity score derivation potential mediators of cost such as increased length of stay and increased number of procedures.

Notes

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Reply to Hemmige and David

To the Editor—Methicillin-resistant *Staphylococcus aureus* (MRSA) remains among the leading causes of mortality in the United States due to antibiotic-resistant infections [1]. However, as we recently reported, rates of methicillin-susceptible *S. aureus* (MSSA) increased between 2010 and 2014 [2], as did the costs for treating these infections [3]. In fact, our estimates for 2014 found that the average costs of MSSA pneumonia and other infections (which are primarily skin and soft tissue infections) were higher than comparable MRSA infections [3]. These results utilized propensity score matching (PSM) to reduce biases and dependence on model formulation in the results.

Hemmige and David [4] expressed concern that the inclusion of patient length of stay (LOS) and the number of procedures performed in the analysis may have biased the outcomes by being one of the causal factors driving the differences in costs between MRSA and MSSA infections. In developing the paper, we included LOS as a matching parameter because there is also a causal relationship between LOS and the acquisition of hospital-acquired infections (HAIs) [5–7], and *S. aureus* is a common HAI-causing pathogen [1]. Additionally, a multitude of factors, not just infections, can affect a patient's LOS, and we did not have information on infection timing. We were thus more concerned about the potential of matching patients with short and long LOSs that were due to other factors. We accounted for this in two ways. First, we matched on stratified LOS: ≤7, 8–14, 15–20, and 21+ days. Second, we conducted a subanalysis of patients with relatively short LOSs (≤10 days) and no mortality to reduce the bias from other factors driving LOS [3]. With regards to procedures, we included

them in the match, as *S. aureus* infections are more likely to be attributed to invasive procedures than they are to cause additional procedures [5–7].

To assess the implications of these decisions, we reanalyzed the data for 2014, excluding LOS and procedures from the matching process. In addition, we included data for 2015 and 2016 to assess trends since 2014. We found that the results from the original paper [3], that MSSA infections might be more costly in 2014, continued in 2015 and 2016 (Figure 1A). Removing LOS and procedures from the PSM algorithm resulted in an increase in the magnitude of this difference for pneumonia and other infections, though septicemia remained unchanged (Figure 1B). Restricting the analysis to patients who were discharged alive with an LOS ≤ 10 days found the results of including LOS and procedures in matching (Figure 1C) were similar to the results when excluding LOS and procedures (Figure 1D). The impact of MRSA infections on LOSs has been estimated to be between 2 to 8 excess days of hospitalization, depending on the type of infection [8, 9]; thus, there is

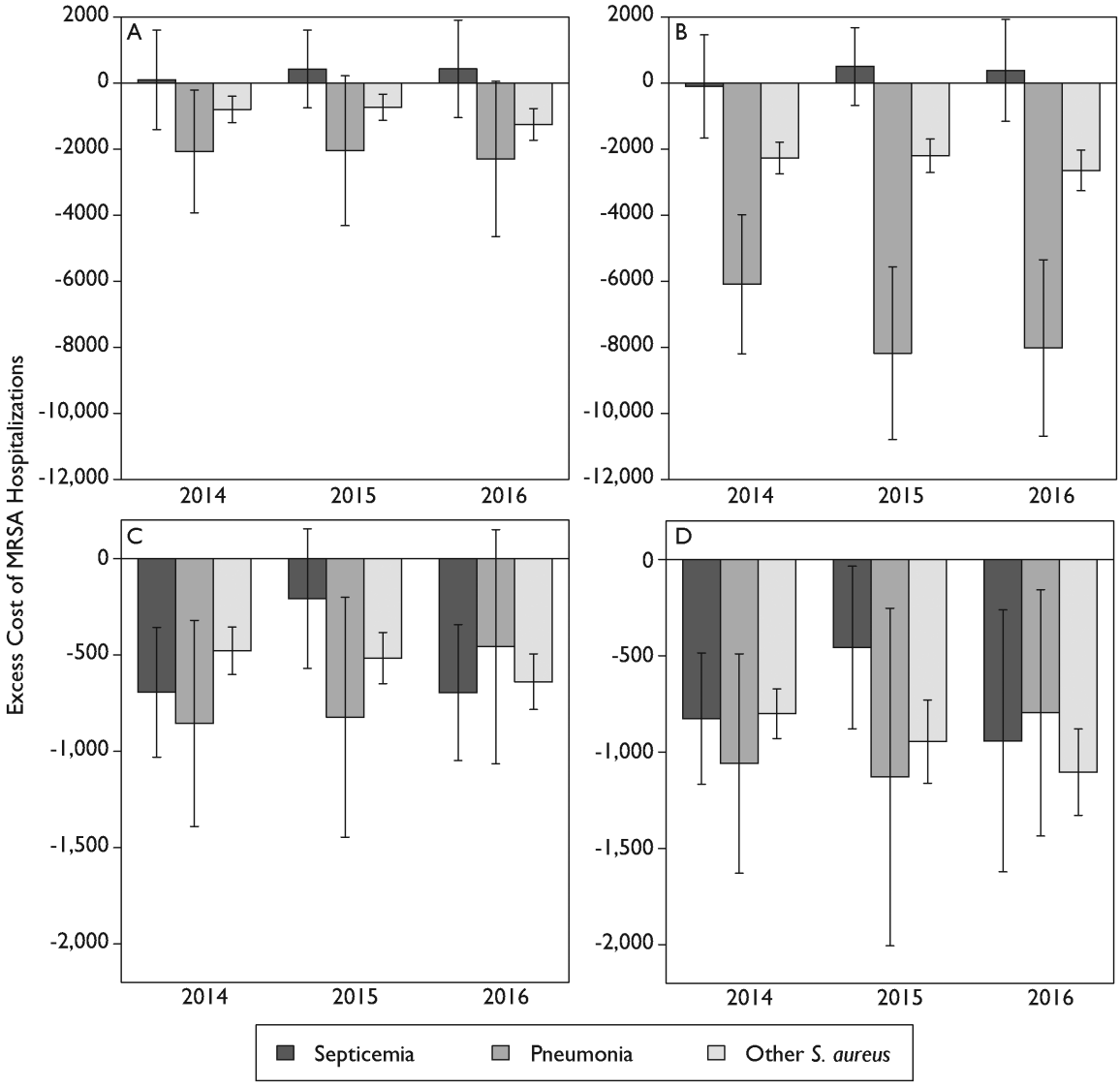

Figure 1. Comparison of different propensity score analyses of the excess cost of MRSA compared to MSSA hospitalizations by infection type, 2014–2016. The excess cost of MRSA-related hospitalizations, compared to MSSA-related hospitalizations, was measured as the mean cost of MRSA-related hospitalizations minus the mean cost of MSSA-related hospitalizations. The error bars are the 95% confidence intervals of the difference in the means, and negative values indicate that MRSA-related hospitalizations were, on average, less costly than similar MSSA-related hospitalizations. *A*, Estimated costs using a PSM algorithm accounting for LOS and numbers of procedures for 2014 (same as in the original paper) through 2016. *B*, Estimated cost without LOS and numbers of procedures in a PSM algorithm. *C*, Estimated costs for patients that were discharged alive with an LOS ≤ 10 days using a PSM algorithm including LOS and procedures for 2014 (same as in the original paper) through 2016. *D*, Estimated costs without LOS and number of procedures in a PSM algorithm for patients with an LOS ≤ 10. LOS was stratified as 0–7, 8–14, 15–20, and 21+ days to account for the endogeneity of infection risk in longer lengths of stay. Abbreviations: LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PSM, propensity score matching; *S. aureus*, *Staphylococcus aureus*.

likely a causal relationship, as suggested by Hemmige and David [4]. However, not accounting for the endogeneity of infection risks related to longer lengths of stay, as we did when we stratified LOS, likely biases the results. Our findings point out the importance of taking into account the potential causal pathways in defining covariates for matching, but also highlight the difficulties in defining causal pathways in complicated hospital stays. These results also highlight the trade-off in using big data sets in health care, which are more generalizable but may not be able to account for some granular aspects of patient care. Nevertheless, the larger implication of our study, specifically the relative costliness of MSSA infections, remains true at a national level, regardless of methodology.

Notes

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Oral Antibiotic Prescribing in Healthcare-associated Pneumonia Patients at Hospital Discharge

To the Editor—We read with interest the article by Vaughn et al [1] reporting increases in fluoroquinolone (FQ) prescribing at discharge in Michigan hospitals with antimicrobial stewardship programs targeting FQ use. We applaud the authors' efforts in quantifying the discordance in FQ use between the inpatient setting and at hospital discharge. This study highlights the critical need for stewardship interventions at discharge prescribing, a critical step in the hospital antimicrobial-use process [2].

Given the observed percentage of FQs prescribed at discharge in the study, we agree with the authors' discussion points that stewardship interventions should recommend alternative, narrow-spectrum antibiotics at discharge. However, in their analysis of non–intensive care patients, approximately 35% of pneumonia patients were classified as having healthcare-associated pneumonia (HCAP) and 86.6% of pneumonia patients who were prescribed a FQ received levofloxacin [1]. Since more than 40% of patients are unable to produce sputum or produce it in a timely manner [3, 4], many patients are treated empirically and have no microbiological diagnosis. Thus, we speculate that it may prove challenging for stewardship programs to recommend a narrow-spectrum nonpseudomonal oral regimen to a prescriber who has observed his or her HCAP patient clinically improve on empiric broad-spectrum intravenous antibiotics. This is an issue that has been observed at our institutions and has been documented by Madaras-Kelly et al [5], who found respiratory tract culture availability to be more associated with de-escalation in the inpatient setting but de-escalation still uncommon despite *Pseudomonas aeruginosa* (PsA) and methicillin-resistant *Staphylococcus aureus* not being identified in cultures.

The HCAP designation was not included in the 2016 Infectious Diseases Society of America and the American Thoracic Society hospital-acquired and ventilator-associated pneumonia guidelines. However, a separate entity or some modification of HCAP may be included in the next version of the community-acquired pneumonia guidelines [6]. It remains to be seen what criteria this upcoming guideline will acknowledge as a risk factor for multidrug-resistant pathogens such as PsA. This may well impact the number of