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Reply to Johnson

To the Editor—We thank Dr. Johnson for his questions raised regarding our definitions used for asymptomatic bacteriuria (ASB), cystitis and pyelonephritis, and potential implications on interpretation of our data. Namely, he states we may have categorized some patients as ASB that in reality clinicians may be reluctant not to treat, thereby negating the significance of our findings. Specifically, (1) those with only 1 localizing symptom of cystitis and no pyuria on urinalysis (UA), and (2) those lacking ≥ 2 typical urinary symptoms in the absence of a UA. Additionally, he suggests our requirement of fever in addition to localizing symptoms for pyelonephritis is overly sensitive. We have attempted to address these concerns below.

There are no established gold standard diagnostic criteria for cystitis or pyelonephritis in males. Of note, the Infectious Diseases Society of America (IDSA) treatment guidelines for cystitis and pyelonephritis from 1999 and 2011 explicitly state they do not contain recommendations on urinary tract infections (UTIs) in men [1, 2]. At the time of the Medication Use Evaluation project development, we modified existing diagnostic criteria to arrive at a clinically meaningful population of patients most likely to have symptomatic UTIs. After initial review of the manuscript, we further stratified patients with ASB into those with and without systemic inflammatory response syndrome (SIRS) criteria in order to provide clarity to the reader as to which patients represent a sicker group of patients whom clinicians may treat empirically. Our population was predominantly male (93%), 95% of which had a UA performed with the majority (89% [1882/2109]) showing evidence of pyuria. Additionally, we excluded neutropenic patients who in theory may not have pyuria in the presence of a UTI. Therefore, it is unlikely we had significant numbers of patients with UTIs with only one typical urinary symptom in the absence of pyuria.

To better define the distribution of symptoms among our ASB cohort and address the possibility we mislabeled patients with UTIs as ASB, we analyzed the cohort of patients with ASB not meeting SIRS criteria (n = 729) and found 364 (50%) had no signs or symptoms listed in Table 2, 12 (2%) had one symptom of cystitis alone in the absence of pyuria on UA, and 265 (36%) had only nonspecific symptoms including altered mental status, malaise, nausea, lethargy, pelvic discomfort, and/or vomiting. To address the concern regarding our definition of pyelonephritis, we analyzed the data and found 0.7% (7/961) of patients classified as ASB had flank pain and/or costovertebral tenderness alone, in the absence of fever. Additionally, 4% (36/961) of patients classified as ASB had fever alone. Therefore, a total 4.5% of patients with ASB met the 1999 IDSA guideline criteria for pyelonephritis and were potentially missed by our definition. The majority of patients classified as ASB either had no symptoms or nonspecific symptoms alone.

Based on these data, we stand by our conclusion that the majority of bacteriuria among inpatient Veterans likely represents ASB with significant opportunity for improved antibiotic use and overtreatment of ASB should be a major focus of antibiotic stewardship programs.

Note

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Ecological Fallacy, Nonspecific Outcomes, and the Attribution of Disproportionate Vaccine Benefits

To the Editor—In their recent publication, Luca et al [1] used an ecological design to compare all-cause pneumonia hospitalizations and associated costs in Ontario before (1992–2001) and after infant pneumococcal conjugate vaccine (PCV) availability—initially

as 7-valent PCV (PCV7) for private purchase (2001–2004), then as publicly funded programs of PCV7 (2005–2009), 10-valent PCV (2009–2010), and 13-valent PCV (2010–2014). The authors attribute large reductions in pneumonia hospitalizations to the direct and indirect effects of infant PCV—reaching a 45% reduction among infants and a comparable reduction of 40% in elderly adults.

However, virtually all of the reduction in pneumonia hospitalizations that Luca et al report among elderly adults accrued during the period when infant PCV7 was only available for private purchase [1, figure 1]. During that period, vaccine coverage was too low to attribute such reduction to the effects of herd immunity. A 40% indirect reduction in elderly adults is also improbable given that 14%–23% of pneumonias among hospitalized adults in Canada are still due to *Streptococcus pneumoniae* (two-thirds of which were 13-valent PCV serovars) [2]—requiring the unlikely precondition that >50% of all pneumonia cases before 2001 had that cause. Other disproportionate findings reported by the authors include an 80% reduction in pneumonia hospitalizations among children 5-17 years old—particularly puzzling given no reported benefit in children 2-4 years old who were curiously omitted from their Table 3. The latter should have benefitted most directly from a complete infant PCV series and would also be among the most likely to experience indirect benefits from vaccinated siblings or peers.

As shown by Luca et al [1], non-pneumonia hospitalizations gradually and substantially decreased in Ontario between 1992 and 2014 [1, figure 1]. The reasons for that decrease are unexplored, but the authors seem to assume the same endogenous factors equally explain temporal trends in pneumonia and nonpneumonia hospitalizations, and that these are therefore addressed by their difference-of-differences analysis. However,

pneumonia hospitalizations showed distinct seasonal variability and, before 2001, did not parallel the steady decline in nonpneumonia hospitalizations in elderly adults. Given interactions between influenza and secondary bacterial pneumonia [3–5], with further modification in influenza risk by age and subtype [6, 7], temporal trends in seasonal influenza epidemics should also have been examined.

Influenza A(H3N2) viruses are associated with more severe epidemics—particularly affecting elderly adults—and were more predominant during the 1990s, whereas A(H1N1) viruses have made greater contribution since 2000 [6–8]. The number of influenza-attributable hospitalizations estimated in Canada was about 80% higher during the 4 seasons 1997–1998 to 2000–2001, compared with the 4 seasons 2001–2002 to 2004–2005, which coincided with private-purchase availability of infant PCV7 [6]. The dramatic reduction in pneumonia hospitalizations that Luca et al attribute to infant PCV may be confounded by these endogenous differences in influenza activity before and after 2000. We note that the same design was previously applied, also in the province of Ontario, to estimate benefits before (1997–2000) and after (2000–2004) the Universal Influenza Immunization Program (UIIP) [9]. Similarly overlooking the natural variations in influenza activity, Kwong et al also reported disproportionate UIIP benefits, including 75% reduction in hospitalizations with just 20% increase in influenza vaccine coverage, and 32% relative reduction compared with provinces without UIIP, despite just a 10% difference in their vaccine coverage rates.

In summary, such ecological studies based on nonspecific outcomes suffer too many flaws to infer causality or to provide accurate quantification of vaccine-attributable benefits or their cost savings.

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unrelated to pneumococcal vaccine from GSK and Pfizer and provided paid expert testimony for the Ontario Nurses Association, the Quebec Ministry of Justice and GSK. D. M. S. has no conflict of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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