costs (median $4567; Table 2) were much lower than those of HA-CRKP cases. The analysis highlights that HA-CRKP infections indeed led to substantially extra in-hospital medical costs and impose an excessive economic burden.

Note

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Caution Required in the Use of Administrative Data and General Laboratory Submissions for Influenza Vaccine Effectiveness Estimation

To the Editor—During the 1980s, observational study designs were used to estimate influenza vaccine effectiveness (IVE) against serious outcomes in older adults, through convenient, retrospective linkage of large, administrative data sets that were originally assembled for another clinical purpose [1, 2]. Unfortunately, these approaches led to biased IVE estimates, owing to unrecognized selection biases that were only later detected through the critical scrutiny of others [3, 4].

Since 2004, the test negative design (TND) has enabled IVE estimation against laboratory-confirmed influenza [5]. Despite improved outcome specificity, the TND remains an observational design that is susceptible to bias and beholden to core principles for valid vaccine effectiveness estimation: notably, accurate vaccine status ascertainment and consistent case finding [6, 7].

In estimating IVE against influenza-associated hospitalization in pregnant women, Thompson et al [8] retrospectively applied the TND to administrative data sets and general laboratory specimens, submitted at the clinician's discretion and pooled across multiple countries (Australia/Canada/Israel/United States) and seasons (2010–2016). Australia, however, contributed only 7 vaccinated participants in total, leaving us to wonder how it could have meaningfully contributed to multivariate analyses.

The authors reassure readers that "all sites reported high data-capture rates for influenza vaccination." However, the site contributing the most participants (Ontario, Canada) has reported substantial misclassification of influenza vaccine status in the physician billing claims used, with a sensitivity of just 32% among adults of childbearing ages [9]. A data set that misclassifies 6–7 of 10 vaccinated participants as unvaccinated raises serious validity concerns, generally leading to an underestimation of IVE. Since without an adjustment for this misclassification the authors considered their findings to be within expectation, with proper adjustments their findings would necessarily exceed expectation. Regardless, such intervention misclassification renders the quantification of intervention effects uncertain.

The authors started with 19 450 hospitalized, pregnant women who met an expansive list of administrative diagnostic codes that were labelled as acute respiratory *or* febrile illnesses, amongst whom just 6% were tested but 58% were influenza positive [8]. Such high test positivity within such a non-specific clinical entity and across seasons—spanning 5 months, on average—suggests a strong clinician bias in the selection of women to test. TND studies of IVE against hospitalization may be especially prone to selection biases since, in addition to patient health-care–seeking behaviors, physician inclinations and institution-specific algorithms influence who gets admitted, tested, and included. The impacts of these biases may vary in magnitude and direction, and their overall effects on IVE estimates are difficult to ascertain retrospectively.

To mitigate these concerns, it has become the standard of practice in prospective TND evaluations of IVE to require consistent clinical criteria for influenza testing [5, 10]. This is to help ensure that cases and controls emerge from the same source population, with comparable influenza exposure risks among vaccinated and unvaccinated participants. When investigators instead retrospectively apply the TND to general laboratory submissions, without standardization of the influenza testing indication, they inherit a greater burden of proof to show that their findings are valid. Such publications should document the criteria used by clinicians for influenza testing and display the proportion vaccinated among test-negative controls, with the data sufficiently stratified to demonstrate that controls represent the intended source population. Where privacy concerns preclude such a display, as cited by Thompson et al [8], then proper external scrutiny and validity assessment are also precluded.

The legacy of biased IVE estimation in older adults should serve as a caution whenever routine administrative or diagnostic data sets are used for secondary evaluation of intervention effects. Potential biases, though likely different between elderly adults and pregnant women, require the close scrutiny of all such convenience studies, regardless of the target group.

Note

from Pfizer for investigator-initiated studies unrelated to influenza vaccine and provided paid expert testimony for the Ontario Nurses Association, the Quebec Ministry of Justice, and GlaxoSmithKline. 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.

Danuta M. Skowronski,[1,2] Gaston De Serres,[3,4] and Walter A. Orenstein[5]

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Reply to Skowronski, De Serres, and Orenstein

To the Editor—We agree with Skowronski et al [1] that caution is required in conducting and interpreting studies of influenza vaccine effectiveness (IVE) using medical and public health data. Indeed, in our stratified results and discussion, we addressed many of the points the authors raised regarding IVE differences between sites, by illness severity (and thus thresholds for admission), and during peak and nonpeak weeks of influenza circulation [2].

We agree that clinician-ordered testing may bias IVE results if selection of who is tested is associated with both the risk of influenza positivity and the probability of influenza vaccination. Obviously, in the PREVENT cohort, clinicians often tested women with suspected influenza virus infection, and thus influenza positivity was high. Therefore, the risk of bias depends on the association between testing and the probability of vaccination. As we described in our article, published findings regarding this association are mixed. In a simulation study of the possible impact of selection bias on IVE estimates using the test-negative design (TND), Jackson et al found that bias from differential care seeking by patients was only meaningful (ie, reduced a true IVE of 50% by >5%) when vaccination doubled the likelihood of care seeking [3]. If we apply the same model but substitute clinician testing for patient care seeking as the action that selects patients into a study, Jackson et al's simulation suggests that clinician testing among vaccinated versus unvaccinated pregnant women would have to differ by >2-fold in order to meaningfully bias IVE estimates.

We acknowledge that the description of vaccination documentation in our article was limited, and greater detail on these methods is now published [4]. Most prospective IVE networks rely in part or entirely on self-reported vaccination status, which can increase false positive reports and thus reduce specificity of vaccine exposure measurement. In contrast, our study exclusively used vaccination documentation from medical records and registries, which can increase false negative records and thus reduce sensitivity. In a recent simulation study, Jackson et al concluded that low sensitivity presented a lesser risk of bias to IVE estimates using TND than did low specificity; records with only 40% sensitivity to true vaccination status could result in an IVE estimate of 40% when the true IVE is 50% [5]. This is consistent with our interpretation that we likely underestimated true IVE.

Finally, we are concerned that a reader might misinterpret Skowronski et al's observation that we focused on "general laboratory-submissions without standardization of the influenza testing-indication" to mean that we simply sampled all patients with clinical testing. Our study focused on real-time reverse transcription polymerase chain reaction testing among pregnant women hospitalized during weeks of local influenza circulation with a diagnosis associated with influenza in previous studies. Although prospective IVE networks play a vital role in IVE monitoring, further population-based research like PREVENT that builds on our methodological strengths and mitigates limitations is also needed to assess IVE in preventing less frequent and severe outcomes, such as influenza illness that is a primary or secondary cause of hospitalization during pregnancy.