

## Opening and Continuing the Discussion on Influenza Vaccination Timing

### TO THE EDITORS:

In the recent article “Economics of Influenza Vaccine Administration Timing for Children,” Lee et al<sup>1</sup> use a Monte Carlo decision analytic model to highlight the importance of vaccinating children against influenza earlier in the season. Models are extremely useful tools for shaping policy; however, models are mathematical representations requiring assumptions and are limited by the data available to populate them. We believe the authors underestimated the burden of influenza; therefore, model results should be interpreted with caution.

Lee et al use outpatient visit costs for influenza-related illness from a systematic review<sup>2</sup> and state that they inflated the value by 3% to approximate 2009 values. It should be noted that the outpatient visit cost (\$51) cited is a 1997 value taken from another article,<sup>3</sup> and that using a constant 3% rate to inflate historic prices to current dollars is inconsistent with good cost-effectiveness practice.<sup>4</sup> This approach could lead to significant underestimation of the cost of influenza vaccination.

In contrast, an analysis by Molinari et al, cited by Lee et al for other model inputs, uses a mean of \$95 and \$167 (2003 dollars) as the outpatient visit cost for non-high-risk children age 5 to 17 years and 0 to 4 years, respectively.<sup>5</sup> Furthermore, the published average reimbursement for a level 3 office visit for an established patient (*Current Procedural Terminology* code 99213) ranges between \$84 and \$113.<sup>6</sup> In addition to lower outpatient visit costs in the model, Lee et al use lower cost estimates than those used by Molinari et al for hospitalization (\$2421-\$2988 vs \$10,880-\$15,014) and medical cost of death (\$5000 vs \$28,818).<sup>7</sup>

We also believe the analysis by Lee et al underestimates the indirect costs of influenza. Although they included costs for lost productivity due to influenza vaccination office visits, the authors did not incorporate lost productivity costs for a parent’s missed work days due to a child’s influenza illness. In the analysis by White et al, the estimated indirect cost of parent’s missed work due to child’s influenza was \$61.33 (1997 dollars).<sup>3</sup>

Underestimation of the burden of influenza may impact the length of time influenza vaccination is considered cost-effective with the authors’ threshold of US \$50,000 per quality-adjusted life-year. Including a higher cost of the disease in the analysis may result in more favorable cost-effectiveness values for vaccination later in the season. Additionally, changes in the cost of disease may impact the difference in cost-effectiveness between live attenuated and inactivated influenza vaccines.

Finally, reducing secondary transmission of influenza to household members can have a significant impact in economic modeling.<sup>7</sup> The authors do not explore this important indirect benefit, which also can result in significant underestimation of differences in cost-effectiveness. Inclusion of the indirect protection would increase the

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benefits of influenza immunization and may extend the cost-effectiveness period of vaccination. Comprehensive sensitivity analyses can provide readers with a complete view of the cost-effectiveness of influenza vaccination.

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**Author Disclosures:** Ms Ryan and Dr Rousculp are employees of MedImmune, LLC, and report owning stock in the company.

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## IN REPLY:

One of the key purposes of computational models is to bring decision-making processes that normally reside within individuals' heads out into the open to catalyze discussion and raise important questions. A model also can serve as a virtual meeting table to assemble key decision makers such as public health officials, healthcare administrators, insurers, scientists, clinicians, and manufacturers. Therefore, we appreciate the thoughtful letter by Dr Matthew D. Rousculp and Ms Kellie J. Ryan from MedImmune in response to our study.<sup>1</sup>

By design, our model's baseline scenario was conservative about estimating the cost of influenza and hence the value of the intervention. However, additional scenarios and sensitivity analyses using all of Rousculp and Ryan's cost suggestions resulted in minimal changes in model outcomes. Because most infected children have a low risk of hospitalization and mortality, the overwhelming driving factors are influenza risk and vaccine cost. In fact, a large percentage of infected children are asymptomatic. After

December, influenza risk and consequently the vaccination's economic value drop precipitously. Therefore, only dramatic shifts in medical costs, much greater than those proposed by Rousculp and Ryan, would significantly change our results. Incorporating all of their cost suggestions collectively (including use of the Bureau of Labor Statistics consumer price index calculator to translate past costs to 2009 values, accounting for lost parent productivity, and using values from Rousculp and Ryan's suggested sources) had little impact.<sup>2-5</sup> The only change was that the incremental cost-effectiveness ratio of live-attenuated influenza vaccine (LAIV) remained below \$50,000 per quality-adjusted life-year (QALY), a frequently cited but debated threshold for cost-effectiveness, a little further into the influenza season: December rather than November.<sup>6,7</sup> When all the suggested changes were introduced together, the incremental cost-effectiveness ratios of both trivalent inactivated vaccine (TIV) and LAIV remained below \$50,000 per QALY through December from both the societal (\$12,049-\$39,167 per QALY for TIV, \$12,419-\$44,377 per QALY for LAIV) and third-party payer (\$18,883-\$44,543 per QALY for TIV, \$23,865-\$49,860 per QALY for LAIV) perspectives. These figures are close to our original reported values.

The only issue raised by Rousculp and Ryan that we could not incorporate into our model is vaccination's effects on secondary influenza transmission (ie, from the vaccinated individual to others), a limitation already stated in our article. Modeling secondary transmission is very complicated because it depends heavily on the individual's social network and the network's immunity status. For example, secondary transmission may be negligible for a 3-year-old who is in contact only with family members who have been vaccinated, but secondary transmission may be a factor for a 10-year-old early in the influenza season, when she will contact many susceptible (unvaccinated and unexposed to influenza) classmates. As the influenza season progresses, population herd immunity increases, thereby decreasing the probability of secondary transmission. The influenza risk data in our model suggest that by January a large percentage of the population has been either exposed to or vaccinated against influenza so that secondary transmission may be less important. But a future, more complex model may want to incorporate such possible transmission elements.

Ultimately, adding transmission will not change our study's most important take-away points: (1) timing of vaccination matters and future studies and planning should not treat vaccination as one en bloc intervention and (2) efforts to get the population vaccinated earlier may provide substantial value. Additionally, when resources are limited, getting children vaccinated earlier may be more important than of-

fering vaccination later in the influenza season. If anything, adding the effects on transmission may further enhance our findings. Our model is certainly not perfect; no study, whether a model or a clinical or epidemiologic study, is perfect. However, it may be among the first studies to address the issue of seasonal influenza vaccination timing in children and should not be the last.<sup>8</sup>

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