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## **COMMENTARY**

### **Efficacy of inactivated influenza vaccines in young children**

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Influenza virus infections cause infections in all age group, and disease severity is greatest in young children and older adults. In children <5 years of age, influenza is associated with an average of 100,000 respiratory deaths annually,<sup>1</sup> and as many as 1 million hospitalizations.<sup>2</sup> Notwithstanding those statistics, the majority of influenza virus infections in children are mild and self-limiting.

There is a wealth of evidence demonstrating the efficacy of inactivated influenza vaccines in children 3 to 16 years of age.<sup>3</sup> Far fewer trials have been done in young children below 2 years of age.<sup>3</sup> One controlled trial in 4081 children 6-23 months of age in Bangladesh estimated the efficacy of trivalent inactivated influenza vaccine to be 31% (95% confidence interval, CI: 18%, 42%) against PCR-confirmed influenza.<sup>4</sup> In the present study, Claeys et al. randomized more than 12,000 children to receive quadrivalent inactivated influenza vaccine or control vaccines, and included data from 11,404 in the primary “per-protocol” analyses of vaccine efficacy against PCR-confirmed influenza across 5 influenza seasons.<sup>5</sup> They reported vaccine efficacy estimates of 63.2% (95% CI: 51.8%, 72.3%) against moderate-to-severe influenza, and 49.8% (95% CI: 41.8%, 56.8%) against all influenza.<sup>5</sup> We agree with authors that protection against severe influenza requiring hospitalization is of greatest clinical and public health importance. However, as stated by the authors, there were very few hospitalizations, and protection against severe influenza was not documented in this study. Only 5 children met the criteria for severe influenza, and more than half of the children with moderate-to-severe influenza had fever >39°C as the condition meeting the criteria for moderate influenza.

One notable observation was the moderate vaccine efficacy against influenza A(H3N2) and the high efficacy against influenza B/Victoria despite the majority of isolates from participating children being antigenically mismatched with the vaccine strains.<sup>5</sup> As Claeys et al. noted, other studies have also demonstrated good vaccine efficacy and effectiveness in young children even against mismatched strains. We would encourage a follow-up analysis to examine VE against matched or mis-matched strains separately, and describe the degree of mismatch in more detail.

It should be noted that the mean follow-up period of each participant was only 4 months.<sup>5</sup> More than 70% of children in this study were recruited from countries with subtropical climates where influenza circulation is known to be prolonged or even year round.<sup>6</sup> It is important to confirm that annual vaccination can provide year-round protection in these locations.

The results presented by Claeys et al. include the important observation that vaccine efficacy against antibiotic use was 50% (95% CI: 40%, 58%).<sup>5</sup> Antimicrobial resistance is a major threat to global health. Increased use of influenza vaccines could contribute to reducing antibiotic resistance by preventing necessary and unnecessary antibiotic use that can be a consequence of influenza virus infections.<sup>7</sup>

In a subgroup analysis in children 6-17 months of age, the estimates of vaccine efficacy against moderate-to-severe influenza and all influenza were 48.8% (95% CI: 21.2%, 67.4%) and 43.3% (95% CI: 27.8%, 55.8%), respectively.<sup>5</sup> These confirm that influenza vaccination is efficacious in young children and, combined with the evidence that vaccination is safe,<sup>5</sup> support the recommendation in many locations that children

should receive influenza vaccination from 6 months of age onwards. However, there was a suggestion that vaccine efficacy might be lower in the youngest children below 2 years of age.<sup>5</sup> A recent study from Japan also reported lower vaccine effectiveness in children 6-11 months of age compared to older children.<sup>8</sup> There continues to be a need for improved influenza vaccines in younger children.

Early life exposure to particular influenza antigens has been associated with long-term protection against severe disease by influenza viruses from related phylogenetic groups.<sup>9</sup> In later life, immune responses to influenza virus infections and influenza vaccination appear to be influenced by early life exposures.<sup>10</sup> In existing studies, the earliest exposures to influenza antigens have occurred with natural infections. It is therefore unclear how long-term immunity will be affected when the first immune response to influenza is conferred by vaccination rather than infection. It would be extremely informative to conduct longer follow-up of children in this study or similar studies elsewhere, to determine how immunity develops following subsequent natural infections or vaccinations.<sup>11</sup>

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## **POTENTIAL CONFLICTS OF INTEREST**

BJC has received research funding from Sanofi for an observational study of influenza vaccine effectiveness in 2013-16, and has consulted for Roche. The authors report no other potential conflicts of interest.

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