Reply to Decker et al.

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We thank Decker et al. [1] for further describing the limitations of using an immunization information system (IIS) and pertussis surveillance data to evaluate Tdap vaccine effectiveness (VE). We concur that our observational study has inherent limitations, but believe the results still provide useful information regarding Tdap effectiveness and provide support for using an IIS to investigate VE.

As described in our article [2], our VE estimates and incidence rate ratio (IRR) estimates comparing Tdap brands may be confounded by factors for which we were not able to control. Geographic location was associated with the brand received and the risk of pertussis. In the cohort of adolescents who received Tdap during 2008-2011 (‘Tdap Cohort’), we adjusted for geographic region, but agree that residual confounding may exist, possibly affecting the IRR estimates. In additional analyses, when stratified by region and adjusted for county of residence and 6-month period of Tdap receipt, the risk of pertussis was lower among Boostrix recipients than among Adacel recipients in every region. To further investigate the effects of potential uncontrolled confounding factors on our results, we conducted a propensity score analysis [3]. Propensity scores (PSs) for receiving Adacel were calculated using county of residence, 6-month period of Tdap receipt, birth year, and age at Tdap receipt as predictors of receiving Adacel. PSs were ranked and stratified into quintiles. Quintile-specific IRR point estimates comparing the incidence of pertussis among Boostrix recipients vs. Adacel recipients ranged from 0.60 to 0.79. The combined, adjusted IRR across all strata was 0.72 (95% CI: 0.59-0.87). In these additional analyses, the results were similar to the original results: pertussis incidence was lower among Boostrix recipients than among Adacel recipients. This difference was observed in every level of
likelihood of Adacel receipt and in every region. However, we acknowledge that our results may still be confounded by factors for which we were not able to measure and control.

We also thank Decker et al. for providing an opportunity to further discuss how information bias (e.g., misclassification of Tdap brand) may have impacted our results. To evaluate Wisconsin Immunization Registry (WIR) data quality, the Wisconsin Division of Public Health recently compared immunization histories documented in WIR to immunization histories documented in patient medical records (MRs). Although the patients included in the WIR evaluation were born during 2009 and, therefore, had not received Tdap, the immunization administration dates evaluated (during years 2009-2011) overlapped with the Tdap administration dates among the Tdap Cohort. Results indicated that 97% of immunizations documented in the MRs were documented in the WIR, and 96% of trade names and 95% of lot numbers were accurate when compared to the MRs. These results suggest widespread misclassification in WIR of Tdap receipt or brand is unlikely.

If the extent of misclassification of Tdap receipt or brand differed between cases and non-cases, or was dependent on misclassification of disease, then our observed difference in effect by brand could be the result of bias [4]. However, to have resulted in consistently lower incidence rates for Boostrix recipients in every region and every likelihood of Adacel receipt, this type of misclassification would need to have occurred among providers in every region and at every level of likelihood of Adacel receipt. We believe this is unlikely. As previously described [2], we minimized differential ascertainment of Tdap receipt between cases and non-cases by using WIR as the only source of Tdap history. To investigate the impact of brand misclassification on our
IRR estimate comparing brands, and we conducted sensitivity analyses using a 5% brand misclassification rate, based on the frequency of misclassification observed during the WIR evaluation. When both cases and non-cases had brand randomly reclassified at this rate, the IRR estimate [0.67 (95%CI: 0.56-0.78)] was similar to, but closer to 1.0 (no difference between brands), than our original estimate [0.62 (95%CI: 0.52-0.74)] [2]. When 5% of cases among Adacel recipients were reclassified to be Boostrix recipients, the IRR estimate [0.72 (95%CI: 0.60-0.85)] was closer 1.0, but also consistent with our original results.

As we described [2], it is possible that our observed difference in pertussis incidence by Tdap brand could be biased due to misclassification or uncontrolled confounding, inherent features of observational studies. However, we believe the magnitude of bias is negligible for the aforementioned reasons. It is biologically plausible that Boostrix and Adacel varied in effectiveness because they have different formulations [5] and elicit different levels of pertussis antibody responses [6]. Further investigation is needed to evaluate differences in Tdap effectiveness by brand and DTaP formulations received during childhood.
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