Reply to André et al

To the Editor—André et al make a valid point. Our most recent study may have been confounded by age. We admit and discuss this concern both in the study itself and in our response to Kiraly et al [1, 2] We cited a previously published subset of the current study, demonstrating a nearly 7-fold increased attack rate in the 8- to 12-year age group, and confirming that this was not caused by a selection or testing bias [3].

The possibility of confounding arises from a real-world event: Kaiser Permanente’s extraordinarily swift implementation of the acellular-only pertussis vaccine schedule in 1996. As a result, there is a distinct age break in the population—almost all of those born before 1996 have at least 1 whole-cell vaccine and those born afterward are almost exclusively naive to the whole-cell preparation. Because of this fact, we knew a priori that even a population-based methodology would have insufficient numbers in both vaccine groups to support meaningful age stratification.

The real world is messy, but population-based observational studies are part of this world. Our study contrasted those receiving any dose of whole-cell vaccine and those naive to the whole-cell vaccine. For an effect of the magnitude we report to be illusory, 1 of 2 conditions would need to be true—an extraordinary feat of randomness or a wholesale difference in the biology of immune response to the vaccine between school-aged children and adolescents. Neither seems plausible. To tease out whether age itself explains our findings, a different methodology that allowed greater power with smaller and more selective study population would be needed, for example, an age-matched case-control study.

Fortunately, our study does not need to stand alone. Klein et al published an excellent case-control study that includes age matching in Pediatrics a few months after our own appeared [4]. The study population is also drawn from Kaiser Permanente Northern California and acts as a validation of our findings in this concern. The odds ratio for those who received 4 whole-cell vaccines compared to those receiving 4 acellular vaccines was 5.64, almost identical to our population-based relative risk [4].

Combined with the growing literature on the waning immunity of acellular pertussis vaccine, these studies suggest that the shape of the age distributions of the 2010–2011 pertussis outbreaks in the United States was attributable to the transition from whole-cell to acellular vaccine [1, 3–5]. As the original studies for the approval of the acellular vaccine lasted only 22 months, and relied primarily on serological response for measurement of efficacy, they were not able to detect this waning immunity that presented itself when the vaccine was challenged by the high force of infection in the recent epidemic. It has been hypothesized that the serologic response may not reflect the T-cell–mediated immunity that is necessary for adequate durability for the pertussis vaccine [5, 6].

Because much of the United States implemented augmented pertussis vaccine campaigns in 2010 and 2011 during the epidemics, these findings also predict rising rates of attenuated pertussis cough illness in teenagers fully vaccinated by national guidelines in 2013, 2014, and onward as the age curve shifts to the right from those naive to the whole-cell pertussis vaccine. In California, where a law requiring the Tdap (tetanus, diphtheria, pertussis) vaccine to enter 7th grade went into effect at the end of the 2010 outbreak, we would expect a rise in cases now. Interestingly, the California Department of Health is reporting a spike of 815 cases of pertussis in 2013 (vastly above any recent past number, except 2010), almost all in fully vaccinated teenagers [7]. Further study seems warranted.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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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