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Author Insights: Higher Pertussis Rates in Children Vaccinated With Newer Pertussis Vaccine

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The fewer adverse events associated with acellular pertussis vaccines compared with whole-cell pertussis vaccines may come at the cost of slightly less protection from pertussis infection, according an analysis by Stephen B. Lambert, MBBS, PhD, a scientist at Queensland Children's Medical Research Institute, and his colleagues. Image: Kris Kamusinski, Herston Multimedia Unit, Queensland Health

Acellular pertussis vaccines, which have become favored over whole-cell pertussis vaccines because they are associated with fewer adverse events, may offer children less protection from pertussis, according to a study published in *JAMA* today.

Ongoing pertussis outbreaks in the United States, Australia, and other parts of the world have prompted speculation about whether changes in pertussis bacteria, inadequate vaccination rates, or other factors might be driving these outbreaks. To probe the role of the shift from whole-cell pertussis vaccines to acellular pertussis vaccines in the 1990s, Australian scientists compared the reported rates of pertussis infection among 58 233 children born in 1998 who were vaccinated with the acellular vaccine, with the whole-cell vaccine, or with some combination of the 2 over the course of the 3-dose vaccination regimen. They found that the average annual rate of pertussis infection between 1999 and 2008 was more than 2.5 times higher among those who received 3 doses of the acellular vaccine than among those who received 3 doses of the whole-cell vaccine (13.2 vs 5.2 infections per 100 000 per year).

Stephen B. Lambert, MBBS, PhD, a scientist at Queensland Children's Medical Research Institute and one of the coauthors of the study, discussed the implications of these findings with *news@JAMA* via e-mail.

news@JAMA: Why was the switch made from whole-cell pertussis vaccines to acellular vaccines?

Dr Lambert: The switch was made to avoid the adverse events associated with whole-cell pertussis vaccines. Whole-cell vaccines were made up of entire killed *Bordetella pertussis* bacteria. They commonly cause local reactions—redness, swelling, pain at the injection site—and less frequently cause systemic adverse events such as fever; prolonged crying; and, on rare occasions, hypotonic hyporesponsive (floppy) episodes. All of these reactions are much less frequent with acellular vaccines, which are composed of a few subunits or parts of the pertussis bacteria.

news@JAMA: You found that children who received the acellular vaccine were more likely to later develop pertussis. What do you think is the most likely explanation?

Dr Lambert: The difference in the nature of immune response following whole-cell and acellular vaccination is the most likely explanation for our findings.

news@JAMA: Is there a mechanism that might explain why the acellular vaccines might be less protective?

Dr Lambert: At this stage, a definitive mechanism is unknown. Whole-cell vaccines contain many more antigenic targets than subunit acellular vaccines, and the combination of these targets and the greater preservation of their native conformation may induce more durable immune responses.

news@JAMA: For children in your study who received doses of both the acellular and whole-cell vaccines, there appeared to be some difference in their future risk of acquiring pertussis, depending on which vaccine they received first. Why do you think this was the case?

Dr Lambert: Children in our cohort who had received an initial dose of acellular vaccine but then received subsequent doses of whole-cell vaccines had higher rates of pertussis when compared to children who received the same number of whole-cell vaccines overall but whose first dose was a whole-cell vaccine. The nature of the initial dose appeared to be the key. Linked epitope suppression* may explain why initial exposure to acellular vaccine locks in future immune responses. Subsequent doses of whole-cell vaccine are not able to completely "reset" the immune response to match that provided by a first dose of whole-cell vaccine.

news@JAMA: Do you think your findings would likely apply in the United States or other developed countries?

Dr Lambert: Different whole-cell products, with variations in vaccine effectiveness, were used in the pre-acellular era, so findings may vary from country to country. However, a recent report summarizing the pertussis outbreak in Washington State, including a preliminary comparison with national US data, is consistent with findings from our study. These ecological data show lower counts and pertussis incidence in children who, based on their age, should have received the whole-cell vaccine, compared to immediately adjacent age groups where the acellular vaccine was used.

news@JAMA: What would you like clinicians to take away from these findings?

Dr Lambert: The key lesson is not to exclude whooping cough just because a child is fully up-to-date with their immunization schedule, particularly if they are of an age to have only received acellular vaccines.

news@JAMA: What about parents? Specifically, do you think parents should alter their vaccination plans based on your findings?

Dr Lambert: Absolutely not. Whilst there appears to be a difference in the level of long-term protection from whole-cell and acellular vaccines, the key lesson for patients, parents, and those delivering vaccines is that vaccination remains our best strategy for preventing pertussis. Clinicians and parents need to ensure children are up-to-date on their pertussis vaccination requirements. With the current high rates of pertussis in Australia and parts of the United States, timely protection of infants, who are at higher risk of serious complications and death, should be a priority.

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*Linked epitope suppression describes a phenomenon by which the immune response to an antigen is driven by the context in which it was first encountered. For pertussis vaccines, this means if the first dose was the acellular vaccine, future responses to other pertussis vaccines will be based on that initial response. That is, when exposed to a whole-cell vaccine after an initial dose of the acellular vaccine, the predominant response will be to the antigens in the acellular vaccine and not to the additional important antigens in the whole-cell vaccine. This response will only be reset when these additional antigens are presented decoupled from the antigens in the acellular vaccine.