Pertussis, commonly known as whooping cough, is a highly contagious disease of the upper respiratory tract caused by the gram-negative bacterium *Bordetella pertussis*. Pertussis infection tends to be mild in adults and adolescents, but infants too young to be protected by vaccination are much more susceptible to severe disease and fatality. Prevalence of pertussis is cyclical, with outbreaks occurring every 3–4 y. However, in recent years, excessive cases of pertussis have been seen in several developed countries, despite high vaccine coverage rates. This resurgence of pertussis disease, particularly in the very vulnerable group of infants less than 3 months, is a current major public health concern. In response, several countries including the UK, United States, Australia and Belgium, have introduced maternal vaccination programs aimed to protect the infant through boosting maternal antibody levels and hence increase trans-placental antibody transfer. These programs have been extremely successful in reducing pertussis disease in young infants, and infants born to vaccinated mothers have elevated PT and FHA antibodies compared with maternal sera. However, there are concerns that the presence of elevated maternal antibodies could blunt the infant’s primary response to pertussis vaccination, as has been previously shown for other vaccines including measles, hepatitis A and influenza.

Caboré et al. describe in this issue of *Virulence*, how maternal Tdap vaccination impacts on the infant’s antibody avidity following booster vaccination. Avidity is the strength of antibody-antigen binding, and as avidity maturation requires B cell somatic hypermutation and clonal selection, it is a reflection of B cell memory to specific antigens. The samples utilised are from a previously published prospective controlled cohort study, which measured the transfer of vaccine-specific antibodies to infants following maternal Tdap vaccination (Tetanus, Diphtheria, acellular Pertussis; Boostrix®), and the infant’s antibody responses following their first 3 doses of pertussis-containing vaccine. A subsequent study from this group has also reported infants’ antibody levels before and after their booster dose at 15 months, the routine schedule in Belgium. The current study adds additional information regarding the avidity of antibodies from these same subjects, pre- and post- booster. The impact of maternal vaccination on antibody avidity in infants was measured by performing ELISAs for antibody against diphtheria toxin (DT), tetanus toxin (TT) and pertussis antigens (pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn)) in the presence and absence of 1.5M ammonium thiocyanate (NH₄SCN). NH₄SCN is a dissociating agent that separates high and low avidity antibodies, and thus the principle of the assay is that by comparing the antibody levels between treated and untreated serum, a Relative Avidity Index (RAI) is generated. The protocol followed in this study is that of Almanzar et al. and a similar method has been used in several pertussis studies, though sometimes with varying concentration of NH₄SCN. Avidity was measured on samples taken before and one month after the infants’ fourth vaccine dose at 15 months of age. This is the first comparison, to our knowledge, of antibody avidity to a booster dose in infants born to pertussis-vaccinated and unvaccinated pregnancies.

In this current study, samples tested before the booster dose (15 months of age), demonstrated no difference in antibody avidity to any antigens between babies born to vaccinated and unvaccinated mothers. As
expected based on previous studies demonstrating that repeated vaccine doses increases antibody avidity, the booster dose increased avidity in all groups and to all antigens. However, the increase in avidity to DT was not significant in the maternally-vaccinated group. In addition, post-booster avidity to PT was lower (mean 68.1% RAI) than in the non-maternally-vaccinated group (mean 78.7% RAI). Whether this difference is clinically significant is currently unknown, and individual RAI levels against PT in both groups all reach above the 40% “moderate” cut-off. However, this does mirror previous data from this group that show reduced PT titres in these infants post-booster.

It would be interesting for the avidity investigations presented in this current study to be extended to measure avidity following the initial vaccination course to generate more data on avidity dynamics between birth and 15 months. Studies from before maternal Tdap vaccination was introduced found that higher anti-pertussis maternal antibodies had no impact on infant’s responses to acellular pertussis vaccines. However, evidence is accumulating that responses to the pediatric acellular vaccine are modulated by the elevated maternal antibody provided by maternal Tdap vaccination. A study in the UK showed that infants whose mothers had been vaccinated during pregnancy have lower post-vaccine anti-PT, FHA and FIM antibody titres than a historical cohort of infants from non-vaccinated pregnancies. A controlled cohort study, from which the samples for this current study are derived, also demonstrated that infants’ born to Tdap-vaccinated mothers have a blunted antibody response against PT and DT following their first 3 doses of pertussis-containing vaccine. Whether there is a difference in antibody avidities at these time-points is not known, and could provide useful data regarding the early functionality of antibody in infants born to maternally-vaccinated mothers.

One limitation of the study is that the method followed was optimised for assessing avidity of anti-FHA and –PT antibodies, and the authors only retested the conditions for anti-PT before using the same conditions for all other antigens. As the original methods paper stated that the “success of each dissociating agent in interrupting the antibody–antigen binding seems to be highly dependent on the kind of investigated antigen and its specific antibodies,” it would have been prudent to test that the protocol was suitable for the additional antigens tested in this study. For example, the RAI of DT was generally lower than other antigens, but this could be because the conditions utilised were not optimal for this antigen. Almanzar et al report that the assay is not suitable when antibody levels are < 1 IU/mL for IgG-anti-PT and < 5 IU/mL for IgG-anti-FHA. IU/ml levels against TT and DT in this cohort were both <1 IU/mL pre-booster and <5 IU/mL post-booster, and the cut off for testing TT and DT avidity was not determined. Hendrikx et al. have reported using the same conditions for anti-Prn antibody avidity, so it may be that the same concentration of NH4SCN is also suitable for this antigen, although Hendrikx et al. standardized antibody concentration before testing, which was not done in this current study. Given the simplicity and convenience of this assay, and the potential importance of measuring antibody avidity in vaccination studies, future efforts should be directed toward optimising this protocol for all antigens of interest in future antibody avidity studies. In addition, as pointed out by the current authors, this assay is likely to be most useful when assessing avidity “within a defined setting”, and care must be taken when comparing RAI scores across different sites.

The novel avidity data in this current study is encouraging, as it suggests that maternal Tdap vaccination has minor impact on the priming of immunological memory in infants both before and after their booster dose, although we should continue to monitor anti-PT avidity. No correlates of immunity have been defined for pertussis, but high antibody titres are associated with protection against disease. The clinical significance of any blunting in antibody titres or avidity in infants born to vaccinated mothers remains unknown. Given the country-specific variability in timing of booster vaccination, it would be advantageous for these investigations to be repeated in other settings. It is clear that any additional information regarding antibody functionality, including data on antibody avidity, as presented in this current study, will be invaluable when assessing the impact of current and future maternal vaccination strategies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

TR is supported by the NIHR Imperial Biomedical Research Centre and BH and BK are supported by the MRC.

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