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Brief report

Reduced risk of pertussis in whole-cell compared to acellular vaccine recipients is not confounded by age or receipt of booster-doses

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ABSTRACT

Several observational studies provide evidence that acellular pertussis vaccines (aP) are less protective against pertussis disease than highly effective whole-cell pertussis vaccines (wP), however, concerns have been raised that some of these findings may be confounded by age. By undertaking age-stratified and restricted analyses on a cohort of Australian children primed with either aP-only, wP-only or mixed pertussis vaccine schedules, we demonstrate that compared to aP the association of wP with increased protection from pertussis is not confounded by age, nor by aP booster-dose receipt.

1. Background

Since 2012, several observational studies from the United States (US) and Australia have reported the unexpected rapid waning effectiveness of acellular pertussis vaccines (aP) [1–6]. This occurred in a context of large pertussis epidemics, with a new pattern of highest disease rates among pre-adolescents despite high vaccination coverage [1–3].

Between 2008 and 2012, Australia experienced its largest and most sustained pertussis outbreak since national reporting in began in 1991 [7]. In Queensland, Australia (population 4.5 million, median age 37 years), [8] the epidemic peaked in 2011, with almost 9000 reported cases [9]. Pre-adolescent children had the highest pertussis rates, which peaked in 8 year olds (570/100,000/year), despite full pertussis vaccination coverage exceeding 80% in this group at 5 years of age.

Both the US and Australia replaced whole-cell pertussis vaccines (wP) with aP in the late 1990s, and the high pre-adolescent pertussis reporting rates coincided with the first birth cohorts to have received purely aP [1–3]. More rapidly waning protection from aP compared to wP has been proposed as a contributing factor to this epidemiology, with several studies providing evidence that aP vaccines are less protective against disease than wP [10–14].

In their population-based study in Northern California, Witt and colleagues found those vaccinated with wP had a lower risk of pertussis than those vaccinated with aP only [12]. However, as their study sample involved a wide birth cohort (born from 1990 to 2001) and was not age-stratified or age-adjusted [12], concerns were raised that age confounded the study findings [15,16]. These concerns have been lessened by studies with narrower birth cohorts. Also, in Northern California, a case-control study comparing the relative effectiveness of four pertussis vaccine doses administered to children <2-years of age at preventing pertussis among teenagers found those who received 4 wP doses were substantially more protected from pertussis than those who received 4 aP doses [13]. Among the strengths of this case-control study was the stratification of analysis by time of year and adjustment for gender, race, and medical clinic [13]. However, in their study which included children born from 1994 to 1999 (aged 10–17 years during the observational period), the authors were unable to adjust for age, as age was strongly associated with the type of pertussis vaccine received (aP or wP) [13]. Two population based cohort studies in Oregon and Queensland, Australia, which compared the

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risk of pertussis according to type of pertussis vaccine receipt in 3 and 1-year birth cohorts of children born from 1997 to 1999, and children born in 1998, respectively [10,11], reduced but did not remove the potential for confounding by age.

In our original study [10], we showed that for Queensland children born in 1998, pertussis reporting rates during a pre-epidemic period (1998–2008) and epidemic period (2009–2011) were higher in children who received a pure aP, compared to receipt of a pure wP, course. A 5-dose childhood vaccination schedule (at 2, 4, 6, 18 months and 4 years of age) was publicly funded for these children. To definitively confirm that increased pertussis risk seen in children with an aP vaccine history is not due to age confounding, in this report we present a re-analysis of that work using 3-month birth cohorts. We also present an additional analysis to investigate whether aP boosting following the primary-course could overcome the differential effectiveness of aP and wP priming.

2. Methods

The construction of the cohort under analysis has been described in full previously [10]. Briefly, reporting pertussis cases to the Queensland Health Department is mandatory. Using the Queensland vaccination register (QVR), we initially constructed a cohort of children born in 1998 who before 12-months of age had received ≥3 doses of any pertussis-containing vaccine from a Queensland vaccine service provider. Pertussis case reports within this cohort were linked to the QVR. As the QVR does not contain records of children who have not had a vaccination encounter, we were unable to construct a group of wholly unvaccinated children for comparison. Only first pertussis case reports were included.

2.1. Age-stratified analysis

In the first analysis, we stratified children born in the cohort described above into four 3-month birth cohorts, and categorised the children by the nature of primary-course received: pure DTaP primary course (≥3 doses of DTaP <12-months of age) or pure DTwP primary course (≥3 doses of DTwP <12-months of age). We excluded mixed DTwP and DTaP recipients from this analysis. Receipt of aP boosters was not an inclusion or exclusion criterion. We compared pertussis reporting rates between children primed with purely DTaP and purely DTwP within each of the three-month age cohorts, during the Queensland epidemic period of 2009–2011.

2.2. Analysis restricted to pertussis booster receipt

In the second analysis, we restricted the cohort of children born in 1998 who before 12-months of age had received ≥3 doses of any pertussis-containing vaccine from a Queensland vaccine service provider, to include only children who received exactly two aP childhood booster doses from age 1 to 6 years. Children who received a childhood booster dose when ≥7 years of age, and/or an adolescent booster dose were excluded. We categorised children according to the nature of the pertussis primary-course received before 12-months of age. In addition to purely DTaP and purely DTwP primary-course recipients, children who received both DTaP and DTwP before 12-months of age, were described as mixed primary-course recipients. Mixed course recipients were further categorised by the nature of their first pertussis vaccine (DTaP or DTwP), and the number of DTwP vaccines received as part of their primary-course (1 or ≥2 doses). We compared 2009–2011 pertussis reporting rates between children by the nature of primary course received.

In both analyses we calculated average annual incidence rates and incidence rate ratios (IRR) of purely DTaP or mixed course priming compared to purely DTwP priming, with associated 95% confidence intervals (CI). Statistical significance was defined as $P < 0.05$. All analyses used Stata version 12 (StataCorp, College Station, TX). The Children's Health Services District Human Research Ethics Committee, Brisbane approved the study.

3. Results

3.1. Age-stratified analysis

Of 58,233 children born in 1998 with a record on the QVR, 32,783 (56.3%) received ≥3 doses of purely DTaP or ≥3 doses of purely DTwP before 12-months of age from a Queensland vaccine service provider. Approximately 86% of these children also received 2 aP booster doses between 1 and 6 years of age. There were 188 first pertussis reports among these children during 2009–2011.

Across each of the four 1998 3-month birth cohorts, children primed with DTaP had substantially higher rates of reported pertussis compared to those primed with DTwP (Table 1), with point IRRs between 2.5 and 4.5. The association was statistically significant across all 3-month birth cohorts.

3.2. Analysis restricted to pertussis booster receipt

Of children born in 1998 identified on the QVR, 34,555 (59.3%) had received two childhood aP booster-doses following their primary course. Overall, 212 first pertussis reports occurred among this booster-dose restricted cohort. Among these children, reported pertussis rates were highest in those primed only with DTaP and in those who received DTaP as the first dose in a mixed vaccine primary-course (Table 1). Compared to children who received a sole DTwP primary-course, those primed with DTaP only or who received DTaP as the first dose in a mixed primary-course, were at least three times more likely to be reported with pertussis. Analysis of the mixed primary course recipients showed that point incidence rates were higher among those who received DTaP as the first dose compared to those who received DTwP as the first dose (Table 1). However, the difference did not reach statistical significance when stratified for the number of DTwP doses received. Mixed primary course recipients who received only one compared to two doses of DTwP had higher point incidence rates.

4. Discussion

Our findings confirm that the increased protection associated with DTwP compared to DTaP priming is not confounded by age or receipt of aP childhood boosters. Results after stratification into three-month birth cohorts were significant within each cohort, despite the reduction in population size. These findings are similar to those from our original unstratified analysis, where children primed with DTaP had a pertussis IRR of 3.3 (95%CI: 2.4 to 4.5) compared to those primed with DTwP during the same epidemic period, 2009–2011 [10]. These findings are also consistent with findings from the US [11–13].

Our analysis confirmed the association between the type of pertussis vaccine and protection against pertussis disease among much narrower birth cohorts than previous studies [10–13]. The rapid and complete transition from primary course wP to aP use in Australia and the age-dependent nature of pertussis rates makes it difficult to remove potential confounding by age from population-based studies. Australia replaced DTwP with DTaP for the primary-course (given at 2, 4 and 6 months of age) for all infants in 1999. However, in Queensland the transition from DTwP to DTaP for priming occurred throughout 1998 and early 1999. This enabled us to minimise the potential for confounding by age by comparing

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