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Infant hospitalisations and fatalities averted by the maternal pertussis vaccination programme in England, 2012-2017: Post-implementation economic evaluation

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## **Abstract**

In October 2012, a maternal pertussis vaccination programme was implemented in England following an increased incidence and mortality in infants. We evaluated the cost-effectiveness of the programme by comparing pertussis-related infant hospitalisations and deaths in 2012-2017 with non-vaccination scenarios. Despite considerable uncertainties, findings support the cost-effectiveness of the programme.

**Keywords.** maternal pertussis vaccination; Whooping Cough; Pertussis Vaccine; Economic Evaluation; Post-implementation

## **Introduction**

Following sharply increased pertussis-related incidence and mortality in infants, a pertussis vaccination programme for pregnant women was implemented in England in October 2012 as an outbreak control measure. The programme has been highly effective in England in protecting infants in the first two months of life [1]. Maternal vaccination has the advantage of conferring passive protection to the foetus via transplacental transfer of antibodies and of reducing maternal transmission to infants until they can be actively protected via primary immunisations [2].

In 2014, the Joint Committee on Vaccination and Immunisation (JCVI) agreed to continue the maternal programme for a further five years, with a decision to be made in 2019 about whether to maintain it as a routine programme [1]. This post-implementation evaluation hence reports on the 6-year impact and cost-effectiveness of the existing maternal vaccination programme (as compared to non-vaccination scenarios), using high-quality enhanced surveillance data to inform policy making.

## **Methods**

Our cost-effectiveness analysis focused on pertussis-related hospitalisations and deaths in infants aged 0-2 months (i.e., <3 months) in England between 2012 and 2017.

For the maternal vaccination programme, we used the Hospital Episode Statistics (HES) database to observe the number of hospitalisations (Finished Admission Episodes) of pertussis ("Whooping cough", ICD-10 code A37) in any diagnostic field for the period 10/2012-12/2017. For the non-vaccination scenarios, we considered

two approaches to estimate the number of infant hospitalisations potentially prevented through the maternal programme:

1. First, we applied the annual change in the number of hospitalisations (in age groups other than <3 months) after 2011 to infants aged <3 months (Supplementary Table 1). We considered the age groups of 3-11 months (i.e. up to 364 days; scenario S1), 6-11 months (S2), 1-2 years (S3), and 5-9 years (S4).
2. Second, we back-estimated the annual number of hospitalisations potentially seen without the maternal programme based on the observed number of hospitalisations in inpatients aged <3 months, the estimated vaccine effectiveness (VE) in infants (0.91) [1], and the annual(ised) vaccine coverage based on two data sources (ImmForm, S5; CPRD, S6):

$$\text{Estimated inpatients} = \text{Observed inpatients} / (1 - \text{VE} * \text{coverage})$$

ImmForm is a routinely collected extraction of records in >90% of general practitioner (GP) practices in England; CPRD (Clinical Practice Research Datalink) is a representative sentinel dataset of approximately 5% of GP practices in England. Following a change in how the data were extracted from ImmForm in April 2016, the reported coverage increased and aligned more closely to the estimates from CPRD, suggesting that ImmForm had previously underestimated coverage [1]. GP datasets were used as the maternal programme was delivered almost exclusively in primary care [3].

In terms of mortality, with the maternal vaccination programme in place, 17 deaths occurred due to pertussis in infants aged <3 months born between October 2012 and December 2017 [1]. Of these, two were to mothers who were vaccinated but too near to birth to confer passive protection (15 were to unvaccinated mothers). For all non-vaccination scenarios (i.e. S1-S6), the number of infant deaths was extrapolated based on the estimated number of hospitalisations and the case-fatality risk (CFR) for hospitalised infants aged <3 months in England from before the vaccination programme was introduced ( $16/513=0.0312$  between October 2011 and September 2012 [4]). We conservatively assumed the infant CFR without the maternal vaccination programme would not have returned to pre-resurgence levels given the continued and exclusive use of acellular pertussis vaccines in England since 2004, which are thought to have contributed to the resurgence of severe cases and deaths in infants and the elevated disease activity seen across all ages ever since 2012 due to diminished indirect protection from infection [1, 5]. In a scenario analysis, however, we explored the return of the CFR to pre-resurgence levels even without having adopted the maternal programme.

For both the vaccination programme and the non-vaccination scenarios, we assumed infants lost 0.10070 quality-adjusted life years (QALYs) per hospitalisation [4], and 25.6 vs 42.6 QALYs per fatality when discounting at 3.5% vs 1.5% (which were estimated from official statistics of life expectancy at birth in England in 2012-2017 and the estimated population norms of the quality of life in England by sex and age [6]).

We considered the costs of hospitalisations and the vaccination programme to the National Health Service (NHS) in England. The hospitalisation costs were based on NHS reference costs for 2012/2013 to 2017/2018 (Supplementary Table 2). The data

were obtained for 2006-2017 from HES and the Paediatric Intensive Care Audit Network (PICANet), and we used the data pre-dating the maternal vaccination programme for extrapolation of the non-vaccination scenarios in 2012-2017 (Supplementary Table 3).

For the costs of vaccination, we considered the published indicative list price of the vaccine and the annual service payment for administering the vaccine [7, 8]. The unit cost per patient was conservatively multiplied with the annual coverage rates of the higher estimates of CPRD [1], and the annual number of officially recorded maternities in England in 2012-2017 [9].

Since this was a post-implementation economic evaluation, we discounted all QALYs and costs back to the base year of the immunisation programme introduction in 2012 [10].

## **Results**

With the maternal vaccination programme, the annually observed number of hospitalisations of pertussis inpatients aged <3 months was a mean of 207 in 2013-2017 (231 when annualising over 10/2012-2017; Figure 1A), while the CFR was a mean of  $17/1,211=0.014$  between October 2012 and December 2017.

For the non-vaccination scenarios, the estimated absolute numbers of hospitalisations differed each year, but the trend over time in terms of peaks and troughs was similar across non-vaccination scenarios (S1-S6), and between the non-vaccination scenarios and the observed number of hospitalisations (Figure 1A). The similar trends suggest no sudden change had the programme not been adopted, providing some reassurance for the validity of the back-estimated scenarios S5-S6.

Depending on the non-vaccination scenario, the maternal vaccination programme was estimated to have prevented 1,400-4,300 infant hospitalisations in 2012-2017, at net economic costs of £50-£58 million (discounted at 3.5%) or £53-£62 million (discounted at 1.5%; Figure 1B). These costs reflect both decreased expenditures on infant hospitalisations and additional expenditures on vaccination (Figure 1B).

In terms of fatalities and QALYs, the maternal vaccination is estimated to have prevented 82-170 infant deaths and 2,100-4,500 or 3,500-7,500 infant QALY losses (discounted at 3.5% or 1.5%, respectively; Figure 1C). Assuming the CFR to have returned to pre-resurgence levels even without maternal immunisation, the programme would have prevented an estimated 41-96 infant deaths and 1,100-2,700 or 1,800-4,400 infant QALY losses (discounted at 3.5% or 1.5%, respectively).

Overall, the incremental costs-per-QALY gained from the programme vs. the non-vaccination scenarios ranged between £11,000-£28,200/QALY and £7,000-£17,700/QALY when discounting at 3.5% and 1.5%, respectively (Figure 1D). The changes seen in the incremental cost-effectiveness ratios over time reflect the cyclical nature of pertussis (Figure 1A), with peaks occurring every 3-4 years in England [1]. These values increased to £18,400-£52,000/QALY and £12,100-£33,500/QALY when assuming the CFR would have returned to pre-resurgence levels even without having adopted the maternal programme (Supplementary Figure 1).



## Discussion

In England, introducing the maternal pertussis vaccination programme appears to have been cost-effective in reducing the annual number of infant hospitalisations and deaths between 2012 and 2017 up to the published list prices of the vaccines, despite considerable uncertainties regarding the outcomes.

Our study focused on the most important cost factors from the NHS perspective, while ignoring the direct protection for vaccinated pregnant women and the resultant cocooning effect that may help reduce infection even after infant vaccination begins [1]. Our focus on infant hospitalisations seems justified given the high proportion of pertussis-confirmed infants aged <3 months seen in hospital in England (>90%) [11].

For the non-vaccination scenarios S1-S4, scenario S4 (ages 5-9 years) needs to be interpreted with caution given the low absolute numbers of hospitalisations and the resulting larger relative annual changes. Moreover, some of the younger infants within scenario S1 (ages 3-11 month) may still experience some residual protection from maternal immunisation (possibly a cocooning effect), while those aged 6-11 months (scenario S2) may experience diminished protection after primary vaccination due to blunting following maternal vaccination (despite no clinically significant blunting having been demonstrated in England [1]). Furthermore, the back-calculated scenarios S5-S6 may lack precision as they assumed no socio-economic gradient for both disease risk and coverage [12]; an exploratory scenario analysis by region resulted in slightly higher ICERs (Supplementary Table 4).

Our analysis did not account for long-term disability in PICU survivors [13], explore additional parameter uncertainty, had a retrospective 6-year timeframe only, and did not explicitly model transmission dynamics [5]. Contrasting two discount rates

also helps illustrating their different impact on QALYs lost per infant death. Ongoing research explores the impact of implementing the programme routinely.

In conclusion, despite the considerable uncertainties, our findings support the cost-effectiveness of the maternal pertussis vaccination programme in England in 2012-2017 up to the published list prices of the vaccines (which are higher than the confidential, and hence unknown, tender prices paid by the NHS).

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**Potential conflicts of interest.** The PHE Immunisation Department has provided post-marketing surveillance reports to Marketing Authorisation Holders which they are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports, which have not to date included pertussis-containing vaccines. HLB reports grants from the Healthcare Quality Improvement Partnership (HQIP) National Clinical Audit and Patient Outcomes Programme (NCAPOP) during the conduct of the study. This grant partially supports her role as the Paediatric Intensive Care Network (PICANet) Senior Statistician.

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## Figure

Figure 1. Findings of the post-implementation evaluation of the maternal pertussis vaccination programme in England, 2012-2017, showing the observed vs. estimated number of hospitalisations in infants aged <3 months annually (panel a); the total costs of the maternal programme with the observed vs. estimated number of hospitalisations without the programme (panel b); the total infant QALY loss under the maternal programme with the observed vs. estimated total infant QALY loss without the programme (panel c); and the cumulative incremental costs-per-QALY gained from the maternal programme vs. the non-vaccination programme scenarios (panel d).

Figure 1

