

# Infant Hospitalizations and Fatalities Averted by the Maternal Pertussis Vaccination Program in England, 2012–2017: Post-implementation Economic Evaluation

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(See the Editorial Commentary by McIntyre on pages 1988–9.)

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

**Keywords.** maternal pertussis vaccination; whooping cough; pertussis vaccine; economic evaluation; postimplementation.

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

In 2014, the Joint Committee on Vaccination and Immunisation agreed to continue the maternal program for a further 5 years, with a decision to be made in 2019

about whether to maintain it as a routine program [1]. This postimplementation evaluation hence reports on the 6-year impact and cost-effectiveness of the existing maternal vaccination program (as compared with nonvaccination scenarios) using high-quality enhanced surveillance data to inform policy making.

## METHODS

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

For the maternal vaccination program, we used the Hospital Episode Statistics (HES) database to observe the number of hospitalizations (Finished Admission Episodes) of pertussis (“whooping cough”; International Classification of Diseases, 10th revision, code A37) in any diagnostic field for the period October 2012–December 2017. For the nonvaccination scenarios, we considered 2 approaches to estimate the number of infant hospitalizations potentially prevented through the maternal program:

1. First, we applied the annual change in the number of hospitalizations (in age groups other than <3 months) after 2011 to infants aged less than 3 months (Supplementary Table 1). We considered the age groups of 3–11 months (ie, 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 hospitalizations potentially seen without the maternal program based on the observed number of hospitalizations in inpatients aged less than 3 months, the estimated vaccine effectiveness (VE) in infants (0.91) [1], and the annual(ized) vaccine coverage based on 2 data sources (ImmForm, S5; Clinical Practice Research Datalink [CPRD], S6):

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

ImmForm is a routinely collected extraction of records in more than 90% of general practitioner (GP) practices in England; CPRD 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]. General practitioner datasets were used as the maternal program was delivered almost exclusively in primary care [3].

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In terms of mortality, with the maternal vaccination program in place, 17 deaths occurred due to pertussis in infants aged less than 3 months born between October 2012 and December 2017 [1]. Of these, 2 were to mothers who were vaccinated but too near to birth to confer passive protection (15 were to unvaccinated mothers). For all nonvaccination scenarios (ie, S1–S6), the number of infant deaths was extrapolated based on the estimated number of hospitalizations and the case-fatality risk (CFR) for hospitalized infants aged less than 3 months in England from before the vaccination program was introduced ( $16/513 = 0.0312$  between October 2011 and September 2012 [4]). We conservatively assumed that the infant CFR without the maternal vaccination program would not have returned to preresurgence 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 preresurgence levels even without having adopted the maternal program.

For both the vaccination program and the nonvaccination scenarios, we assumed infants lost 0.10070 quality-adjusted life-years (QALYs) per hospitalization [4] and 25.6 versus 42.6 QALYs per fatality when discounting at 3.5% versus 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 hospitalizations and the vaccination program to the National Health Service (NHS) in England. The hospitalization 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 Pediatric Intensive Care Audit Network (PICANet), and we used the data predating the maternal vaccination program for extrapolation of the nonvaccination 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 postimplementation economic evaluation, we discounted all QALYs and costs back to the base year of the immunization program introduction in 2012 [10].

## RESULTS

With the maternal vaccination program, the annually observed number of hospitalizations of pertussis inpatients aged less than 3 months was a mean of 207 in 2013–2017 (231 when annualizing over October 2012–2017) (Figure 1A), while the CFR

was a mean of 17 divided by 1211 = 0.014 between October 2012 and December 2017.

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

Depending on the nonvaccination scenario, the maternal vaccination program was estimated to have prevented 1400–4300 infant hospitalizations 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 hospitalizations and additional expenditures on vaccination (Figure 1B).

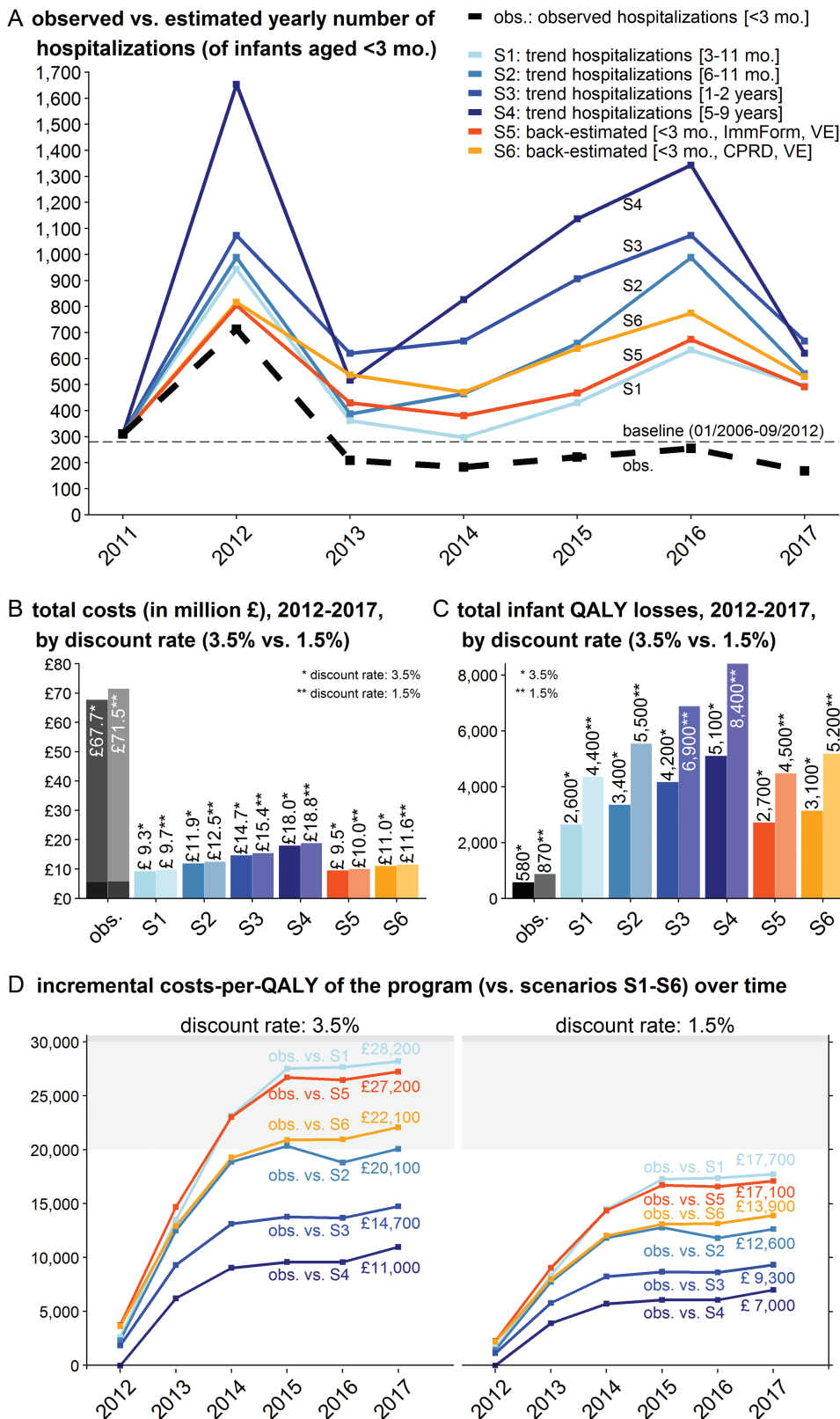
In terms of fatalities and QALYs, the maternal vaccination is estimated to have prevented 82–170 infant deaths and 2100–4500 or 3500–7500 infant QALY losses (discounted at 3.5% or 1.5%, respectively) (Figure 1C). Assuming the CFR to have returned to preresurgence levels even without maternal immunization, the program would have prevented an estimated 41–96 infant deaths and 1100–2700 or 1800–4400 infant QALY losses (discounted at 3.5% or 1.5%, respectively).

Overall, the incremental costs per QALY gained from the program versus the nonvaccination scenarios ranged between £11 000–£28 200/QALY and £7000–£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 preresurgence levels even without having adopted the maternal program (Supplementary Figure 1).

## DISCUSSION

In England, introducing the maternal pertussis vaccination program appears to have been cost-effective in reducing the annual number of infant hospitalizations 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 hospitalizations seems justified given the high proportion of pertussis-confirmed infants aged less than 3 months seen in the hospital in England (>90%) [11].



**Figure 1.** Findings of the postimplementation evaluation of the maternal pertussis vaccination program in England, 2012–2017, showing the observed versus estimated number of hospitalizations in infants aged less than 3 months annually (A); the total costs of the maternal program with the observed versus estimated number of hospitalizations without the program (B); the total infant QALY loss under the maternal program with the observed versus estimated total infant QALY loss without the program (C); and the cumulative incremental costs per QALY gained from the maternal program versus the nonvaccination program scenarios (D).

Abbreviations: CPRD, Clinical Practice Research Datalink; obs., observed hospitalizations; QALY, quality-adjusted life-year; S1–S6, scenarios 1–6; VE, vaccine effectiveness.

For the nonvaccination scenarios S1–S4, scenario S4 (ages 5–9 years) needs to be interpreted with caution given the low absolute numbers of hospitalizations and the resulting larger relative annual changes. Moreover, some of the younger infants within scenario S1 (ages 3–11 months) may still experience some residual protection from maternal immunization (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 and S6 may lack precision as they assumed no socioeconomic gradient for both disease risk and coverage [12]; an exploratory scenario analysis by region resulted in slightly higher incremental cost-effectiveness ratios (Supplementary Table 4).

Our analysis did not account for long-term disability in pediatric intensive care unit survivors [13] or explore additional parameter uncertainty, had a retrospective 6-year time frame only, and did not explicitly model transmission dynamics [5]. Contrasting 2 discount rates also helps illustrate their different impact on QALYs lost per infant death. Ongoing research explores the impact of implementing the program routinely.

In conclusion, despite the considerable uncertainties, our findings support the cost-effectiveness of the maternal pertussis vaccination program 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).

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

**Author contributions.** The authors had sole responsibility for the study design, data collection, data analysis, data interpretation, and writing of the report.

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**Potential conflicts of interest.** The Public Health England Immunisation Department has provided postmarketing 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. The other authors report no potential 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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