A Case-Control Study to Estimate the Effectiveness of Maternal Pertussis Vaccination in Protecting Newborn Infants in England and Wales, 2012–2013

Gavin Dabrera,[1,2,3] Gayatri Amirthalingam,[3] Nick Andrews,[4] Helen Campbell,[3] Sonia Ribeiro,[3] Edna Kara,[3] Norman K. Fry,[5] and Mary Ramsay[3]

[1]Field Epidemiology Training Programme, Public Health England, London, United Kingdom; [2]European Programme for Intervention Epidemiology Training, European Centre for Disease Prevention and Control, Stockholm, Sweden; [3]Immunisation, Hepatitis and Blood Safety Department, [4]Statistics, Modelling and Economics Department, Centre for Infectious Disease Surveillance and Control, and [5]Respiratory and Vaccine Preventable Bacteria Reference Unit, Public Health England, London, United Kingdom

(See the Editorial Commentary by Cherry on pages 338–40.)

Background. Infants with pertussis infection are at risk of severe clinical illness and death. Several countries, including the United Kingdom, have introduced maternal pertussis vaccination during pregnancy to protect infants from infection following national increases in pertussis notifications. The objective of this study was to estimate the effectiveness of maternal pertussis vaccination in protecting infants against laboratory-confirmed pertussis infection.

Methods. A case-control study was undertaken in England and Wales between October 2012 and July 2013. Cases were infants aged <8 weeks at onset with pertussis infection tested by real-time polymerase chain reaction or culture. Family doctors of each case were asked to identify healthy infants born consecutively after the case in each practice, to act as controls. Fifty-eight cases and 55 controls were included in this study. Odds ratios (ORs) were calculated for the association between maternal vaccination and infant pertussis infection. The vaccine effectiveness (VE) was calculated as 1 – OR. This was adjusted for sex, geographical region, and birth period.

Results. Mothers of 10 cases (17%) and 39 controls (71%) received pertussis vaccine in pregnancy. This gave an unadjusted VE of 91% (95% confidence interval [CI], 77%–97%). Adjusted VE was 93% (95% CI, 81%–97%).

Conclusions. Maternal pertussis vaccination is effective in preventing pertussis infection in infants aged <8 weeks and may be considered in other countries experiencing high levels of pertussis notifications.

Keywords. vaccination; pertussis; England; Wales; case-control study.

Several countries have observed recent increases in pertussis cases, including England and Wales [1], the United States [2], Portugal [3] and New Zealand [4]. These increases have occurred despite sustained periods of high reported vaccine coverage. In line with the expected cyclical pattern in England and Wales, where pertussis activity peaks every 3–4 years, cases increased in 2011, with an overall incidence comparable to that seen in the previous peak year (2008) but with unexpectedly high numbers of adult cases [1]. Pertussis activity continued to increase into 2012, however, and extended to all age groups including infants aged <3 months, who are at highest risk of severe complications, in whom there was an incidence of 240 cases per 100 000 [1, 5]. In 2012, there were 14 deaths among 429 infant cases infected with pertussis, compared with 7 deaths among 178 infant cases during 2008. [6].

In response to the national outbreak in the United Kingdom, from 1 October 2012, the Department of Health recommended that pregnant women be offered a single dose of acellular pertussis vaccine between 28

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Correspondence: Gavin Dabrera, MFPH, Centre for Infectious Disease Surveillance and Control, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK (gavindabrera@nhs.net).

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and 38 weeks' gestation, as a temporary measure to protect newborn infants [7]. This intervention had been recommended in the United States [8] but had not previously been used in Europe. The emergency measure rapidly achieved about 60% coverage [9], and similar recommendations for pregnant women have since been given in New Zealand [4], Belgium [10], and Israel [11].

The rationale for the program is based on evidence of transplacental transfer of maternal antibodies, which is maximal from 34 weeks' gestation [12]. Although an accepted serological correlate of protection is lacking, a dose of pertussis vaccine during pregnancy boosts antibody levels in the mother and should therefore provide passive protection to the newborn infant in the first months of life, prior to commencing the primary infant schedule at 8 weeks of age [13]. The strategy has the added benefit of protecting the mother against pertussis infection, which is important as mothers are a frequent source of infection for infant pertussis cases [14, 15]. Despite the theoretical basis, the effectiveness of this intervention in the prevention of infant disease had not been established prior to the introduction of the program.

The primary objective of this project was to estimate the maternal pertussis vaccine effectiveness (VE) in England and Wales in protecting newborn infants against laboratory-confirmed pertussis infection, using a case-control study design. The secondary objective was to determine if maternal pertussis vaccination was associated with shorter length of hospital stay among infant pertussis cases aged <8 weeks.

METHODS

We undertook a case-control study in England and Wales of infants born between 22 October 2012 and 11 July 2013. Cases were defined as infants aged <8 weeks at disease onset, who were positive by real-time polymerase chain reaction (qPCR) for *Bordetella pertussis* at the national reference laboratory (Public Health England Respiratory and Vaccine Preventable Bacteria Reference Unit, Colindale, London) or culture confirmed and the isolate referred to the national reference laboratory or reported to Public Health England [16]. The age limit of 8 weeks was chosen as this is the age at which primary immunizations are routinely offered, and we sought to exclude any potentially confounding protective effect from active immunization. Information on the mother's pertussis vaccination status was obtained by telephoning and sending a questionnaire to the patient's registered general practitioner (GP) to request the following information: whether the mother was vaccinated in pregnancy (and if so, date of maternal vaccination), and the gestational ages at vaccination and at delivery. To address the secondary objective, dates of hospital admission and discharge were collected for the pertussis cases only.

For each case, the GP was asked to identify 2 infants born consecutively after the pertussis case, from the same practice. As with the cases, information about the mother's pertussis vaccination status, date of vaccination, gestational age at delivery, and infant's date of birth and sex was collected for each control. GPs were asked to exclude controls with a known clinical or microbiological diagnosis of pertussis. As an additional measure to avoid misclassification of controls, national surveillance data from laboratory-confirmed cases were checked to ensure these controls did not match any confirmed cases.

As part of routine surveillance, telephone follow-up of infant pertussis cases with no response from GPs was also undertaken for cases to determine maternal vaccination during pregnancy.

General practice was chosen as the source for recruiting controls, as the maternal vaccination program was mainly delivered in this setting and it was therefore anticipated that the most reliable information on maternal vaccination status would be recorded on general practice information technology systems. As this was undertaken as part of a national outbreak response, ethical approval was not required and data collation was covered by existing information governance approvals [17].

Exposures

Vaccination in pregnancy was coded as a binary variable of either receiving vaccine or not receiving vaccine. The number of completed weeks' gestation at vaccination was also recorded. Cases or controls were excluded from analysis if maternal pertussis vaccination was not known, to avoid incorrect classification of the exposure. To adjust for variation in vaccine coverage over time, infants were categorized by date of birth into 2-month periods. Geographical area of the general practice (for the cases and controls) was coded as a binary variable, representing within London and outside London, as lower maternal pertussis vaccination rates have been observed in London compared with the rest of the country [18].

Sample Size Calculation

The sample size was dependent on the number of cases arising; however, to achieve reasonable precision for the VE estimate, we aimed to recruit 30 cases with 2 controls per case. This would give a 95% confidence interval (CI) of 25%–88% around a VE of 70%, assuming 70% vaccine uptake.

Statistical Methods

A matched case-control analysis was originally planned, matching cases and controls on the basis of their registered general practice. However, due to a lack of controls provided by GPs, an unmatched analysis was undertaken.

Unadjusted VE was calculated as VE = 1 – OR, where OR is the odds ratio for vaccination in pregnancy, between cases and controls. For the adjusted VE, the OR was calculated using

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logistic regression where the dependent variable was case or control status, and independent variables were receipt of vaccination in pregnancy, sex, geographical area, and 2-month birth period. These latter 2 variables were included to adjust for spatial and temporal variations in vaccine coverage. Sex was included as an a priori confounder.

We repeated this analysis, restricted to cases and controls with response from the GP postal questionnaire, to ensure the VE estimates remained consistent despite the different methods used to ascertain vaccine status of cases.

The number of weeks' gestation at the date of vaccination was calculated using information provided on returned forms. The rank-sum test was used to examine the effect of timing of vaccination on VE. This was restricted to cases and controls where the mother had been vaccinated to assess if there was a significant difference between these cases and controls in the number of weeks' gestation at time of maternal vaccination.

The length of stay for pertussis cases was calculated as the number of days between the admission and discharge dates provided by the GP. A length of stay of 0 days occurred when a case was assessed at hospital but was discharged the same day. The rank-sum test was used to assess if there was any significant difference in the length of stay for pertussis cases with a hospital admission, between those with a history of maternal pertussis vaccination and those without such a history.

RESULTS

Numbers of Participants

The number of eligible laboratory-confirmed cases (based on median time interval between onset date and specimen date for recruited cases) was 61. GPs returned forms with sufficient information for 30 cases and 55 controls. In addition, the routine telephone follow-up provided data for an additional 28 cases. Therefore, a total of 58 cases and 55 controls were included in the analysis. None of the controls matched known pertussis cases reported to national surveillance. The demographic characteristics of cases and controls are described in Table 1. Of the 58 cases, 34 (59%) were confirmed by qPCR, 22 (38%) by culture, and 2 (3%) by both methods.

Of the 58 cases included in the analysis, the mothers of 10 infants (17%) had been vaccinated during pregnancy (Table 2). In comparison, 39 mothers of 55 controls (71%) had been vaccinated during pregnancy. The unadjusted OR for vaccination in pregnancy was 0.09 (95% CI, .03–.23), giving an unadjusted VE of 91% (95% CI, 77%–97%). After adjustment for sex, geographical area, and birth period, the VE was similar at 93% (95% CI, 81%–97%).

Restricting this analysis to only the 30 cases and 55 controls with a response from the GP postal questionnaires provided similar estimates for the unadjusted VE (88% [95% CI, 62%–96%]) and the adjusted VE (90% [95% CI, 68%–97%]).

Table 1. Characteristics of Cases and Controls

Characteristic	Cases (n = 58)	Controls (n = 55)	*P* Value
Sex			
Male	35	28	.31*
Female	23	27	
2-month birth period			
October–November	13	17	.81**
December–January	13	9	
February–March	11	8	
April–May	13	13	
June–July	8	8	
Geographical region			
London	10	7	.60**
Outside London	48	48	

* χ^2 test.

** Fisher exact test.

Information on gestation at vaccination was available for 10 cases and 37 controls. The median gestations at vaccination were 31.5 weeks (range, 28–38 weeks) for cases and 33 weeks (range, 26–38 weeks) for controls. For vaccinated mothers, there was no statistically significant difference between cases and controls in the gestation at vaccination ($P = .85$).

Data on length of hospital stay were available for 47 cases. The median length of hospital stay was 4 days (range, 0–6 days) for 8 cases with a history of maternal pertussis vaccination and 3.5 days (range, 0–63 days) for 39 cases without a history of maternal pertussis vaccination. There was no statistically significant difference between these 2 groups in terms of length of hospital stay, according to the rank-sum test ($P = .58$).

DISCUSSION

We present findings of the first case-control study to estimate the VE of vaccinating pregnant women against pertussis to protect newborn infants. This case-control study has estimated a high VE of 93% for this intervention. This provides further evidence of the effectiveness of this temporary program in protecting newborn infants during the current outbreak. The observed VE is likely to be a combination of the direct effect of transplacental antibody transfer from mother to infant, and the indirect effect of protecting the mother from pertussis and potentially reducing household transmission and preventing infant infection.

Our results provide good evidence for pregnant women and health professionals to make informed decisions about the effectiveness of maternal vaccination in protecting babies from birth. Health professionals' advice has been shown to be

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Table 2. Results of Vaccine Effectiveness Analysis

Cases		Controls			
Total No.	History of Maternal Pertussis Vaccination, No. (%)	Total No.	History of Maternal Pertussis Vaccination, No. (%)	Unadjusted VE, % (95% CI)	Adjusted VE[a], % (95% CI)
58	10 (17)	55	39 (71)	91 (77–97)	93 (81–97)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Adjusted for sex, geographical area, and birth period.

important in a woman's intention for influenza vaccination during pregnancy [19] and against pertussis postpartum [20].

The findings of this study support those obtained using the screening method, where VE in England was 90% (95% CI, 82%–95%) for laboratory-confirmed cases in infants aged <2 months [5]. The agreement between both the screening method and the case-control method presented here provides robust evidence that this program is highly effective. The case-control method used was not dependent on the accuracy of estimates of population vaccine coverage, as we obtained individual-level data for cases and controls. Our findings in this study are also consistent with results from a clinical trial which have shown that maternal vaccination during pregnancy is associated with significantly higher levels of pertussis antibodies at birth, both in mothers and infants [21]. In addition, this study is consistent with the reduction in infant pertussis cases, hospitalizations, and infant pertussis-related deaths in England demonstrated following the introduction of the maternal vaccination program [5].

We were unable to confirm previous research that demonstrated shorter hospital admissions for pertussis among infants who had received a single dose of pertussis vaccine (as part of primary immunizations), compared with those who had not [22]. This is probably due to a small number of cases in vaccinated children and the overall short median duration of hospitalization (even in unvaccinated babies).

As there were insufficient matched pairs with complete information, we undertook an unmatched analysis. This would most likely have led to a lower estimate of VE [23], but the high value obtained and the concordance with estimates from the screening method suggests that this effect was limited [5]. It is possible that infants with a maternal history of pertussis vaccination were less likely to be recognized than those without such a history; however, pertussis infection tends to be clinically severe and so any bias in identification during a well-publicized national outbreak is likely to be minimal.

Although data on case vaccination status were obtained by both postal and telephone follow-up, whereas data on controls were obtained by questionnaire only, our second analyses using only cases with a postal questionnaire suggest that the effect of any potential bias was limited as this did not substantially affect the VE estimate.

We did not collect information on breastfeeding status of mothers of cases and so we were unable to determine if there was any additional protective effect through transfer of antibodies in breast milk. Other potential confounders may include number of children in households, childcare attendance, smoking, and maternal education; unfortunately, we were not able to collect these data and so we were unable to adjust for these in our analysis.

The findings of this study should be generalizable to other high-income countries, where there have been increases in notified pertussis cases despite established vaccination programs. A recently published pharmacovigilance study in the United Kingdom failed to identify any increase in adverse maternal or neonatal outcomes in relation to maternal pertussis vaccination [24]. Some countries have not yet recommended maternal pertussis vaccination, despite limited evidence for alternative strategies [25]. For example, some countries have recommended a cocooning strategy, where close contacts of infants are vaccinated to reduce exposure [26]. However, this strategy has reportedly been challenging to implement [27] and requires significant resources in terms of vaccinating multiple family contacts.

We recommend that public health services in countries experiencing high levels of pertussis notifications in infants consider this measure to protect the newborn. In addition, for countries recommending this strategy, these findings should be communicated to both pregnant women and health professionals to promote higher uptake.

Notes

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Author contributions. G. D. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. G. D., G. A., N. A., H. C., and M. R. were all involved in the study design. N. K. F. was responsible for providing laboratory confirmation

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data from potential cases of pertussis that formed the study population. G. D., G. A., H. C., S. R., and E. K. contributed to the implementation of data collection. G. D. and N. A. undertook data analysis. G. D. drafted the manuscript, and all other authors contributed to the revision of this prior to submission.

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Potential conflicts of interest. The Immunisation Department has provided vaccine manufactures with postmarketing surveillance reports, which the Marketing Authorisation Holders 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. All authors: No potential conflicts of interest.

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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