Effectiveness of maternal pertussis vaccination in England: an observational study

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Summary

Background **In October, 2012, a pertussis vaccination programme for pregnant women was introduced in response to an outbreak across England. We aimed to assess the vaccine effectiveness and the overall effect of the vaccine programme in preventing pertussis in infants.**

Methods **We undertook an analysis of laboratory-confirmed cases and hospital admissions for pertussis in infants between Jan 1, 2008, and Sept 30, 2013, using data submitted to Public Health England as part of its enhanced surveillance of pertussis in England, to investigate the effect of the vaccination programme. We calculated vaccine effectiveness by comparing vaccination status for mothers in confirmed cases with estimates of vaccine coverage for the national population of pregnant women, based on data from the Clinical Practice Research Datalink.**

Findings **The monthly total of confirmed cases peaked in October, 2012 (1565 cases), and subsequently fell across all age groups. For the first 9 months of 2013 compared with the same period in 2012, the greatest proportionate fall in confirmed cases (328 cases in 2012 *vs* 72 cases in 2013, –78%, 95% CI –72 to –83) and in hospitalisation admissions (440 admissions in 2012 *vs* 140 admissions in 2013, –68%, –61 to –74) occurred in infants younger than 3 months, although the incidence remained highest in this age group. Infants younger than 3 months were also the only age group in which there were fewer cases in 2013 than in 2011 (118 cases in 2011 *vs* 72 cases in 2013), before the resurgence. 26 684 women included in the Clinical Practice Research Datalink had a livebirth between Oct 1, 2012 and Sept 3, 2013; the average vaccine coverage before delivery based on this cohort was 64%. Vaccine effectiveness based on 82 confirmed cases in infants born from Oct 1, 2012, and younger than 3 months at onset was 91% (95% CI 84 to 95). Vaccine effectiveness was 90% (95% CI 82 to 95) when the analysis was restricted to cases in children younger than 2 months.**

Interpretation **Our assessment of the programme of pertussis vaccination in pregnancy in England is consistent with high vaccine effectiveness. This effectiveness probably results from protection of infants by both passive antibodies and reduced maternal exposure, and will provide valuable information to international policy makers.**

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Introduction

In the UK, pertussis-containing vaccines have been used in infancy since 1957, at an accelerated schedule (at 2, 3, and 4 months of age) since 1990, and with acellular pertussis since 2004.[1] High coverage during the past two decades, combined with the 2001 introduction of a preschool booster for acellular pertussis from 3 years and 4 months of age, has achieved good disease control without additional boosters at older ages.[1] However, in late 2011, a national increase in confirmed pertussis cases was reported, initially restricted to adolescents and adults, but extending to young infants in 2012.[2] Resurgence of pertussis has recently been reported in several countries,[3–5] but the reasons are not yet fully understood. The improved availability of methods to confirm diagnosis (eg, serology and PCR), increased awareness among health professionals, and waning natural or vaccine immunity during periods of low pertussis activity have been suggested.[5] Changes in *Bordetella pertussis* organisms and decreased duration of protection or effectiveness against transmission with acellular pertussis vaccines (by comparison with whole-cell vaccines) have also been described.[5]

The high rates of disease in infants younger than 3 months and a concomitant increase in pertussis-related infant deaths led to an urgent review of potential control strategies by the UK's Joint Committee on Vaccination and Immunisation. In September, 2012, the UK Department of Health recommended a temporary programme to offer a five-component acellular-pertussis-containing vaccine, Repevax (Sanofi Pasteur MSD, Maidenhead, UK)—a diphtheria, tetanus, pertussis (acellular, component), and poliomyelitis (inactivated) vaccine, also known as dTaP/IPV—to all women between 28 and 38 weeks of pregnancy.[6] Repevax was available without delay in sufficient quantities required for the UK programme. Although the WHO Global Advisory Committee on Vaccine Safety has pronounced the safety of vaccination with inactivated vaccines in pregnancy, the effectiveness of a maternal immunisation programme for pertussis has not been shown.[7] We aimed to provide the first estimates of the effectiveness of a maternal pertussis vaccination programme in prevention of infant disease in England.

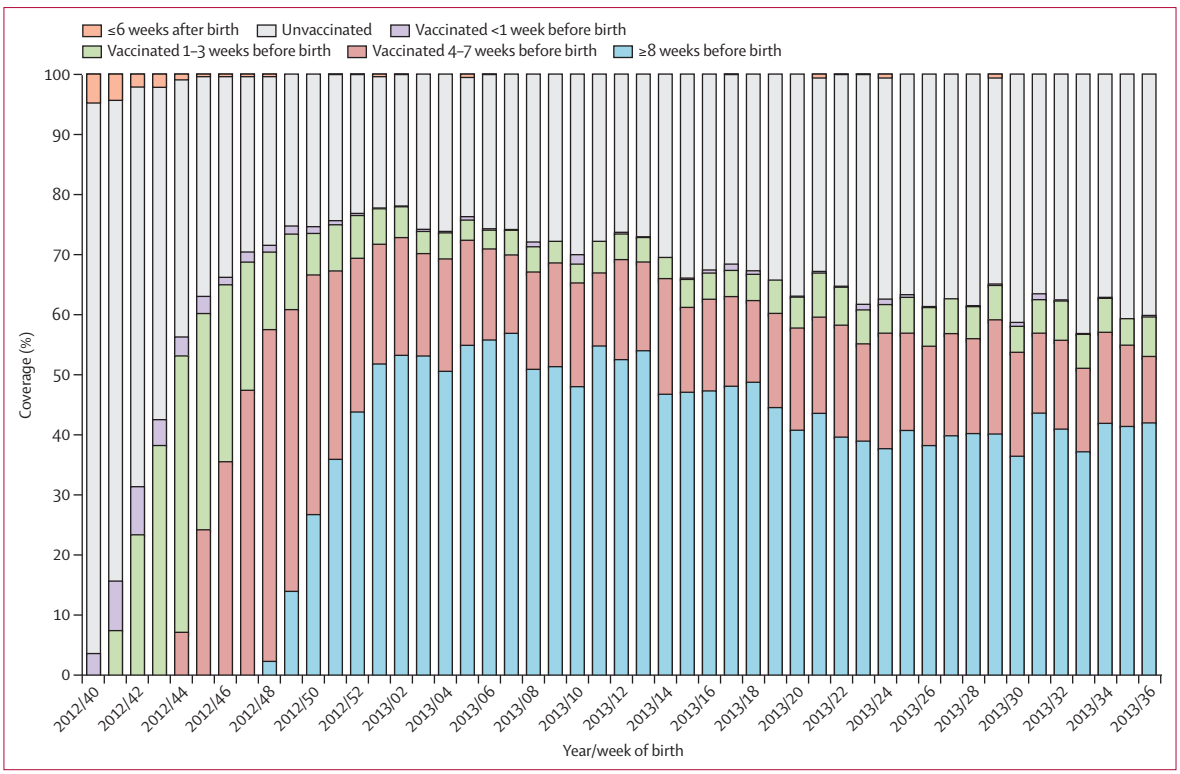

Figure 1: **Estimated maternal vaccine coverage by week of birth**
Figure shows coverage from week 40, 2012, to week 36, 2013. Figure based on data provided by the Clinical Practice Research Datalink.

For the **Clinical Practice Research Datalink** see http://www.cprd.com/intro.asp

Methods

Participants and data sources

For vaccine effectiveness calculations, we used data from the Clinical Practice Research Datalink (CPRD), a primary care dataset containing anonymised information for patients registered at 520 English general practices, which are representative of the population of England in terms of geographical distribution.[8] For each patient, basic demographic information, details of every consultation and diagnosis, and vaccination history are recorded. We estimated maternal vaccine coverage using CPRD data extracted in October, 2013, for the cohort defined as any woman recorded as having a livebirth from Oct 1, 2012, to Sept 3, 2013. Key variables within this cohort were birth year of the mother, date of the child's birth, and date of any pertussis-containing vaccine given during pregnancy.

For the **International Classification of Diseases 10** see http://apps.who.int/classifications/icd10/browse/2010/en

National coverage data for the pregnancy programme were collected each month for all women with an estimated delivery date that fell within the designated month.[9] These data are not available by maternal year of birth or week of vaccination, but were used to provide alternative estimates for sensitivity analysis.

Public Health England (known as the Health Protection Agency before April, 2013) coordinates surveillance of all laboratory-confirmed pertussis cases in England. Laboratory confirmation of pertussis is available through culture at local microbiology laboratories, and PCR for infants admitted to hospital and serology by antipertussis toxin IgG, both at the national reference laboratory. We extracted laboratory-confirmed cases between January, 2008, and September, 2013, for analysis. Serology was not used to confirm cases in infants younger than 6 months because high concentrations of IgG can be due to maternal antibody. Patients aged 6 months or older, confirmed by serology only, who had been immunised against pertussis in the previous 12 months were excluded from the analysis because antibody to pertussis toxin from recent vaccination can confound serological diagnosis.[10] Data were extracted on Nov 18, 2013.

For all confirmed cases in infants born on or after Oct 1, 2012, details of the infant's vaccination history (when appropriate), mother's date of birth, and vaccination history were obtained by Public Health England from the general practitioner.

All hospital admissions in England with International Classification of Diseases 10 codes for whooping cough (A37·0, A37·1, A37·8, and A37·9) in primary or other diagnoses occurring between Jan 1, 2008, and Sept 30, 2013, were extracted from the hospital episode statistics dataset.

Statistical analysis

To investigate the programme effect on infant disease, age-specific proportionate changes in confirmed and hospital-admitted cases of pertussis before and after introduction of the maternal programme were calculated

with 95% CIs. From January, 2013, all babies younger than 3 months were born to women eligible for the pregnancy programme, and therefore cases in January–September, 2013, were compared with those in equivalent periods in 2012 and 2011. Similar comparisons were also made for older age groups.

We calculated vaccine effectiveness using the screening method (also known as case-coverage), in which vaccine effectiveness is one minus the odds of maternal vaccination in cases divided by the odds of vaccination in the population.[11] This design makes use of population-level coverage data to which each case can be matched on the basis of potential confounding variables. Each case was matched to coverage for mothers delivering in the same week (or the same fortnight from Dec 3, 2012) and with the same period of maternal birth year (grouped into ≥1990, 1985–89, and <1985). When maternal age was unknown, the case was matched to the average coverage in mothers with babies born in the same week.

Analysis was done with logistical regression, with vaccination status of the cases as the outcome and with an offset in the model of the log odds of the population coverage to allow for the individually matched coverage. Vaccine effectiveness was assessed according to the timing of vaccination, with the primary analysis based on vaccination at least 7 days before birth. We did additional sensitivity analyses, restricting analysis to children younger than 2 months and reducing coverage by a relative 20% (eg, from 70% to 56%), assuming that coverage was closer to the national routine estimate.[9]

Role of the funding source

The authors had sole responsibility for the study design, data collection, data analysis, data interpretation, and writing of the report. The authors are all employed by Public Health England, the study funder, which is a public body—an executive agency of the Department of Health. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

We estimated maternal vaccine coverage from English practices in the CPRD based on 26 684 women with a livebirth from Oct 1, 2012 (week 40, 2012) until Sept 3, 2013 (week 36, 2013). This figure represents about 4% of all livebirths in England in 2012 (694 241).[12] Maternal coverage by week of delivery peaked at 500 (78%) of 638 women in week 2, 2013, then fell gradually to 144 (60%) of 241 women giving birth in week 35, 2013 (end of August; figure 1). We compared these data with national data, in which coverage peaked at 59·6% in February, 2013, and then fell to a reported coverage of 56·4% in September, 2013.[9] The proportion of women in the CPRD database receiving vaccine less than a week before delivery decreased to less than 1% of those vaccinated by January, 2013 (1 of 506 women). Coverage was increased in women who delivered at an older age, with coverage in women born after 1990 (59% coverage) about 10% lower and in women born between 1985 and 1989 (66% coverage) about 4% lower than in women born before 1985 (70% coverage).

Cases of laboratory-confirmed pertussis increased during 2012, peaking at 1565 cases in October. There were 9353 laboratory-confirmed cases in 2012 and 1052 in 2011 (annual incidence 17·6 and 2·0 per 100 000, respectively). In infants younger than 3 months, pertussis incidence was consistently higher than any other age group, peaked every 3–4 years, and in 2012 (at 240 cases per 100 000 population) was more than double that in any recent peak year (figure 2). Hospital admissions in infants younger than 2 months were consistently higher than were laboratory-confirmed cases (tables 1, 2), although each followed a similar timecourse, seeming to peak before the introduction of the maternal programme.

Confirmed cases in the first 9 months of 2013 were lower than in the equivalent period in 2012 for all age groups (table 1). Infants younger than 3 months had the highest incidence of laboratory-confirmed cases in both periods, but showed the greatest proportionate fall after introduction of the maternal vaccination programme (328 cases in 2012 *vs* 72 cases in 2013, –78%, 95% CI –72 to –83). This age group was also the only one in which the number of cases was lower in 2013 than in 2011 (118 cases in 2011 *vs* 72 cases in 2013, –39%, 95% CI –18 to –55). We noted a similar proportionate fall in hospital admissions for infants younger than 3 months in the first 9 months of 2013 (140 admissions) compared with the same period in 2012 (440 admissions, –68%, 95% CI –61 to –74) and 2011 (183 admissions, –23%, 95% CI –4 to –29; table 2). In the same period of 2013, the numbers of confirmed cases in infants aged 3–11 months, many of whom would have been born to women eligible for vaccination, decreased by 65% in 2013 compared with 2012 (84 cases in 2012 *vs* 29 cases in 2013), and were only marginally increased (4%) compared with 2011 (28 cases

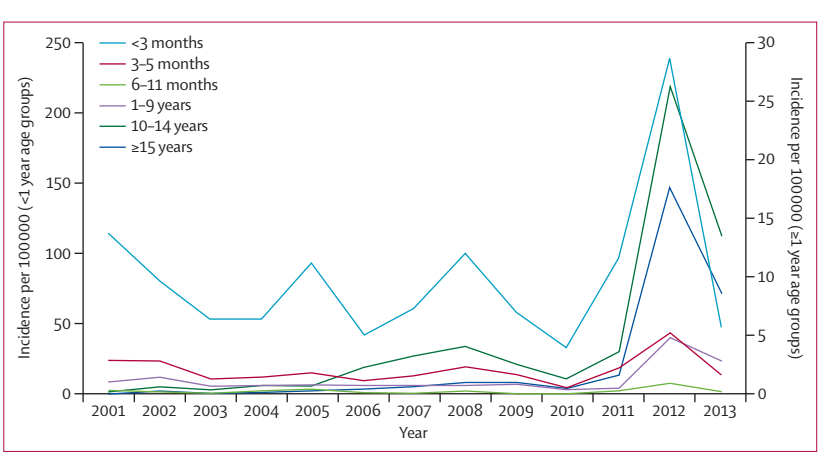

Figure 2: **Annual incidence of laboratory-confirmed cases of pertussis by age group**
Figure shows incidence from 2001 to 2013 in England only.

	2008	2009	2010	2011	2012	2013	% change 2013 *vs* 2012 (95% CI)	% change 2013 *vs* 2011 (95% CI)
<1 month	24 (3·4%)	16 (2·9%)	6 (2·0%)	16 (2·5%)	43 (0·7%)	10 (0·3%)	−77% (−90 to −53)	−38% (−75 to 46)
1 month	67 (9·5%)	43 (7·7%)	22 (7·2%)	57 (9·1%)	161 (2·7%)	37 (1·0%)	−77% (−84 to −67)	−35% (−58 to 0)
2 months	58 (8·3%)	29 (5·2%)	15 (4·9%)	45 (7·2%)	124 (2·1%)	25 (0·7%)	−80% (−87 to −69)	−44% (−67 to 7)
3–5 months	33 (4·7%)	20 (3·6%)	6 (2·0%)	21 (3·3%)	62 (1·0%)	22 (0·6%)	−65% (−79 to −41)	5% (−45 to 100)
6–11 months	8 (1·1%)	3 (0·5%)	3 (1·0%)	7 (1·1%)	22 (0·4%)	7 (0·2%)	−68% (−89 to −23)	0% (−70 to 234)
1–4 years	21 (3·0%)	19 (3·4%)	7 (2·3%)	10 (1·6%)	58 (1·0%)	41 (1·1%)	−29% (−54 to 7)	310% (102 to 818)
5–19 years	184 (26·2%)	121 (21·8%)	59 (19·4%)	124 (19·7%)	1128 (19·1%)	669 (17·6%)	−41% (−46 to −35)	440% (345 to 559)
≥20 years	307 (43·7%)	304 (54·8%)	186 (61·2%)	349 (55·5%)	4311 (73·0%)	2984 (78·6%)	−31% (−34 to −27)	755% (665 to 860)
Total number of cases	702	555	304	629	5909	3795	−36% (−38 to −33)	503% (454 to 557)
Reported deaths*	5 (CFR 3·4%)	1 (CFR 1·1%)	1 (CFR 2·3%)	3 (CFR 2·5%)	10 (CFR 3·0%)	2 (CFR 2·8%)	..	..

Table shows total number of laboratory-confirmed cases of pertussis in January to September (inclusive) for 2008–13 in England. Data are number of cases in each age group and percentage of total cases in that year. CFR refers to deaths as a percentage of all cases in infants younger than 3 months. CFR=case fatality rate. *Deaths reconciled from hospital admissions data, follow-up of laboratory-confirmed cases, and death certification.

Table 1: **Laboratory-confirmed cases by age group**

	2008	2009	2010	2011	2012	2013	% change 2013 vs 2012 (95% CI)	% change 2013 vs 2011 (95% CI)
<1 month	31 (9·2%)	24 (10·3%)	10 (8·3%)	25 (10·1%)	73 (11·3%)	18 (6·5%)	−75% (−86 to −58)	−28% (−73 to 37)
1 month	112 (33·1%)	80 (34·5%)	38 (31·4%)	99 (40·1%)	209 (32·3%)	68 (24·7%)	−67% (−76 to −57)	−31% (−50 to −6)
2 months	85 (25·1%)	47 (20·3%)	26 (21·5%)	59 (23·9%)	158 (24·4%)	54 (19·6%)	−66% (−75 to −53)	−8% (−38 to 35)
3–5 months	55 (16·3%)	44 (19·0%)	21 (17·4%)	26 (10·5%)	108 (16·7%)	54 (19·6%)	−50% (−65 to −30)	108% (28 to 246)
6–11 months	22 (6·5%)	10 (4·3%)	7 (5·8%)	11 (4·5%)	30 (4·6%)	11 (4·0%)	−63% (−83 to −25)	0% (−61 to 154)
1–4 years	18 (5·3%)	16 (6·9%)	9 (7·4%)	9 (3·6%)	29 (4·5%)	21 (7·6%)	−28% (−61 to 31)	133% (2 to 479)
5–19 years	11 (3·3%)	7 (3·0%)	5 (4·1%)	7 (2·8%)	23 (3·5%)	12 (4·4%)	−48% (−76 to 9)	71% (−38 to 414)
20+ years	4 (1·2%)	4 (1·7%)	5 (4·1%)	11 (4·5%)	18 (2·8%)	37 (13·5%)	106% (14 to 284)	236% (68 to 631)
Total	338	232	121	247	648	275	−58% (−63 to −37)	11% (−7 to 33)

Table shows total number of hospital admissions for pertussis in January to September (inclusive) for 2008–13 in England. Data are number of admissions in each age group and percentage of total pertussis admissions in that year.

Table 2: **Hospital admissions by age group**

in 2011 *vs* 29 cases in 2013). In non-infant age groups in the same period, confirmed cases in 2013 fell proportionately less (between 29% and 41%) from 2012 (table 1), and increased relative to 2011. Similarly, hospital admissions in children and young people aged 1–19 years were lower in the first 9 months of 2013 than in 2012. Although numbers remained small, cases in adults aged 20 years or older were roughly double those in 2012 and more than triple those in 2011. No fall in hospital admissions was reported in any age groups aged 3 months or older in 2013 compared with 2011.

In 2012, there were 14 deaths in infants with confirmed pertussis, all of whom were born before the temporary vaccination programme was introduced. In 2013, there were three pertussis-related deaths in infants whose mothers were not vaccinated in pregnancy. These 17 fatalities in 2012 and 2013 were all in infants too young to be protected by vaccine (age 2–9 weeks at disease onset or sample date). There was a 79% fall in infant deaths from 2·02 per 100 000 livebirths in 2012 to 0·43 per 100 000 livebirths in 2013, consistent with the 79% fall in annual confirmed cases younger than 3 months of age between 2012 and 2013 (407 cases in all of 2012 *vs* 85 cases in all of 2013).

Ten deaths occurred in the first 9 months of 2012, and two in the first 9 months of 2013. Case fatality rates were similar in these periods for both years (table 1).

By Nov 18, 2013, 104 cases in infants younger than 3 months, born on or after Oct 1, 2012, and with a specimen or onset date up to the Sept 30, 2013, had been confirmed either by PCR or culture. Five cases with unknown maternal vaccination status and nine patients who received their first primary infant dose at least 7 days before onset of symptoms (none of whose mothers were vaccinated) were excluded from all analyses of vaccine effectiveness. The 90 remaining cases included 12 with maternal vaccination at least 7 days before birth, one with maternal vaccination within 7 days of birth, and one case in which the mother was vaccinated after birth (table 3). Gestational age was available for 66 infants, of whom ten (15%) were premature.

Table 4 shows estimates of vaccine effectiveness. The primary analysis for vaccination at least 7 days before birth in infants younger than 3 months gave a vaccine

effectiveness of 91% (95% CI 84 to 95). 82 cases were included in this analysis after exclusion of ineligible cases (one case in which the mother was vaccinated within 7 days of birth, and cases matched to zero coverage). Vaccine effectiveness was similar (90%) when we restricted analysis to infants younger than 2 months, but fell a little (from 91% to 84%) when coverage was reduced to a level that would more closely match routine coverage data.[9] For timing of maternal vaccination, vaccine effectiveness was the same (91%) for vaccination at least 28 days before birth and 7–27 days before birth, but was much lower at 38%, with a very wide 95% CI (–95 to 80), for mothers vaccinated between 6 days before and up to 13 days after birth.

Of the six confirmed cases in infants old enough to have completed their primary schedule (age ≥120 days) and born to mothers eligible for the programme, only two had completed their primary course before disease onset; neither of their mothers received a pertussis vaccine during pregnancy.

	Unvaccinated (n=76)	Vaccinated at least 7 days before birth (n=12)	Vaccinated between 6 days before and up to 13 days after birth (n=2)	Total (n=90)
Week of birth				
40–52 (2012)	31	3	2	36
1–12 (2013)	19	5	0	24
13–24 (2013)	16	3	0	19
25–37 (2013)	10	1	0	11
Maternal birth cohort				
Pre-1985	39	8	1	48
1985–89	18	3	0	21
Post-1990	13	1	0	14
Unknown	6	0	1	7
Sex of infant				
Girl	33	4	2	39
Boy	43	8	0	51
Gestational age at birth				
Preterm (<37 weeks)	9	1	0	10†
Fullterm (37–41 weeks)	44	8	2	54
Post-term (>41 weeks)	1	1	0	2
Unknown	22	2	0	24
Age at onset or specimen*				
<2 months	66	11	2	79
2–3 months	10	1	0	11
Age of infant at onset*				
Mean (days)	41·6	45·5	29·5	41·9
Parity (including infant case)				
1	20	1	0	21
2	13	5	0	18
3+	19	4	0	23
Unknown	24	2	2	28

Table shows cases included in vaccine effectiveness calculations at different intervals from delivery. *Age at onset was calculated using onset date when provided (n=62) and specimen date if an onset date was not available. †All at 32–36 weeks' gestation.

Table 3: **Description of the 90 confirmed pertussis cases in infants by maternal vaccination status**

Discussion

In the UK, pertussis vaccination for pregnant women was introduced at a time of heightened pertussis activity and a substantial rise in infant deaths.[6] The programme rapidly achieved coverage approaching 60%.[9] Although efficient placental transfer of pertussis antibodies has been shown after recent maternal immunisation with acellular vaccine,[13–15] we provide the first evidence of the effectiveness of pertussis vaccination in pregnancy to prevent infant disease (panel).

In England, pertussis incidence peaks every 3–4 years, with the highest number of cases each year in the third quarter running from July to September. In line with this seasonality, pertussis activity has fallen across all age groups since October, 2012. When compared with older age groups, surveillance suggests a disproportionately large fall in laboratory-confirmed cases and hospital admissions in infants targeted by the maternal vaccination programme, with no other interventions introduced after the outbreak was declared. These findings are consistent with a programme effect on infant disease.

Surveillance of pertussis is known to underestimate the true burden of disease, particularly in adolescents and adults. In England, surveillance in infants (particularly on the basis of hospital admissions data) is thought to be the most complete and reliable indicator of pertussis circulation in the population. Therefore, the fall in both confirmed cases and infants admitted to hospital at a time of heightened public and professional awareness is likely to be genuine. Since 2002, widespread use of serology testing, which is rarely used to confirm pertussis in infants, along with concerted efforts to raise awareness among health professionals in 2012 has probably improved case ascertainment in older age groups (ie, adolescents, teenagers, and adults in particular).

Our assessment of the maternal vaccination programme in England shows a high point estimate for vaccine effectiveness of 91% with good precision (95% CI 84 to 95). This high estimate results from both the protection conferred to the infant through passive antibody and any additional benefit from the infant's mother no longer being a potential source of infection. Differences in estimates of vaccine effectiveness based on timing of maternal vaccination suggest that the protection was mainly due to placental transfer of antibodies.

The effectiveness of vaccination given too late to provide passive protection through intrauterine antibody transfer, was lower at 38%, although there was insufficient power to precisely determine the size of this contribution. The main effect in these cases would be through reduced maternal exposure (or less likely as a result of antibodies in breast milk[18]). The size of this effect is consistent, however, with estimated proportions of infant cases attributable to maternal contact.[19–22]

	Percentage of cases vaccinated	Average matched coverage*†	Vaccine effectiveness‡
Infants <3 months of age			
Vaccination at least 7 days before birth	15% (12/82)§	62%	91% (84 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (12/82)§	49%	84% (71 to 93)
Infants <3 months of age by timing of maternal immunisation			
Vaccination at least 28 days before birth	14% (10/69)¶	63%	91% (83 to 95)
Vaccination 7–27 days before birth	3% (2/72)||	19%	91% (70 to 96)
Vaccination 0–6 days before or 1–13 days after birth	3% (2/68)**	5%	38% (−95 to 80)
Infants <2 months of age			
Vaccination at least 7 days before birth	15% (11/71)	61%	90% (82 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (11/71)	49%	82% (67 to 90)

Data are % (n/N), %, or % (95% CI). *Average matched coverage is the average of the matched population coverage estimates for all cases included in the analysis. †For cases in which the mother matched to zero coverage, that case was dropped from the analysis because it did not contribute information. ‡Vaccine effectiveness calculated on the basis of matched coverage on each individual, not with average matched coverage. §90 cases minus one case vaccinated within a week of birth and seven cases matched to zero coverage. ¶90 cases minus three cases vaccinated at other times before birth and 18 cases matched to zero coverage. ||90 cases minus 11 cases vaccinated at other times before birth and seven cases matched to zero coverage. **90 cases minus 12 cases vaccinated at other times before birth and ten cases matched to zero coverage.

Table 4: **Effectiveness of maternal pertussis vaccine by infant age at onset and timing of vaccination**

Panel: Research in context

Systematic review

We searched PubMed and Scopus for articles published in English from Jan 1, 1940, and Jan 1, 1960, respectively, to March 31, 2014, with the terms "pertussis", "pregnancy", and "vaccine" or "pertussis", "pregnancy", and "immunisation". Human studies with any experimental or observational designs with the administration of pertussis-containing vaccines at any stage of pregnancy were reviewed and any identified systematic reviews were used to obtain further primary studies of relevance.

Interpretation

Several studies have shown transfer of maternal pertussis antibodies to the infant, but we were unable to find any studies measuring protection against clinical disease in the infant. Anecdotal reports have suggested that high concentrations of maternal antibodies induced by whole-cell vaccine might protect the infant in the first few months of life,[16] and findings from a 2012 study in baboons showed that neonatal animals can be protected against *Bordetella pertussis* disease by passively transferred maternal antibody.[17] We believe that our finding that maternal immunisation with an acellular-pertussis-containing vaccine can provide about 90% protection against infant disease is the first time that this protection has been shown.

The vaccination programme in England seems to have been well accepted, with routine coverage peaking at 60%—higher than the reported uptake for the seasonal influenza programme in pregnant women.[9,23] The heightened media coverage of pertussis (including infant deaths), together with positive reporting of the UK pregnancy programme, could have been important in encouragement of high levels of acceptance in pregnant women and health professionals. Peak population coverage estimates, based on data from the CPRD (a sentinel primary-care-based data source), were about 20% higher than the published national coverage figures.[9] Because the programme in England was mostly delivered in general practice, we used a primary care data source as the most reliable source of coverage data for our analysis. By contrast, the data for routine monthly coverage are limited by incomplete returns and are probably an underestimate. However, sensitivity analysis reducing the estimated coverage by a relative 20% did not have much effect on the overall vaccine effectiveness, which remained high at 84%. The coverage estimates were matched on the most important confounders (period of delivery and maternal age). Coverage varied by maternal age, which was a potential confounder because it will also be correlated to parity and other factors that could be associated with her likelihood of developing or acquiring pertussis. Information on such additional factors (eg, parity, ethnic group, and socioeconomic factors), which might also be related to both the likelihood of vaccination and the risk of pertussis in infants, was not sufficiently complete to be controlled for in our analysis.

Vaccine safety is another important component of the assessment, together with an investigation of whether maternal antibodies might interfere with infants' primary immune responses. The Medicines and Healthcare Products Regulatory Agency has undertaken a safety study using the CPRD data, and trials relating to infants' primary response are underway in North America.[24–27] Public Health England is also evaluating antibody responses to primary immunisation in infants of vaccinated mothers to assess whether there is any attenuation. These studies will provide important data about response to pertussis and other routinely administered vaccine antigens in the presence of increased concentrations of passively transferred maternal antibody. National surveillance data do not, as yet, suggest a relative increase in cases in infants aged 6–11 months; despite small numbers, reassuringly in fully vaccinated infants, whose mothers received pertussis vaccine during pregnancy, no breakthrough infections have been reported. A separate case-control study is being done to confirm these estimates by an independent method. Furthermore, the UK Joint Committee on Vaccination and Immunisation will need to make a decision about whether continuation of the maternal programme would be cost effective beyond the outbreak scenario.

The main aim of pertussis vaccination programmes is to reduce the burden of severe disease and death in susceptible young infants.[28] Despite good coverage with

effective vaccines, the burden of disease in young infants remains high compared with other vaccine-preventable infections. The options to further reduce infant mortality from pertussis have therefore focused on additional strategies such as cocooning or neonatal vaccination.[28] Data about the effectiveness of these strategies are lacking; cocooning relies on vaccination of everyone likely to have contact with the newborn and is difficult to implement, whereas neonatal vaccination inevitably leaves the infant at risk until they have responded to the first or subsequent doses. More recently, attention has turned to vaccination in pregnancy, which is now routinely recommended for women in every pregnancy in the USA,[29] New Zealand,[30] and Belgium.[31] No published data about national coverage, programme, or vaccine effectiveness are yet available from these countries. Our finding that maternal immunisation with an acellular-pertussis-containing vaccine can provide about 90% protection against infant disease could change the preferred approaches, at least in countries that have access to an acellular-pertussis-containing vaccine suitable for administration in pregnancy. However, extrapolation of our findings to the use of whole-cell-containing vaccines in pregnancy will need additional data about immunogenicity and safety.

Contributors

GA, NA, HC, EK, SR, EM, and MR were all involved in the concept and design of the evaluation of the pertussis vaccination programme for pregnant women, and contributed to the analysis of the data. NF was responsible for the laboratory testing of clinically suspected pertussis cases at the national reference laboratory that are included in the analysis. KD extracted the CPRD data for analysis. GA drafted the paper, and all authors were involved in revision and approval of the final content before submission.

Declaration of interests

We declare no competing interests. The Immunisation, Hepatitis and Blood Safety Department has provided vaccine manufactures with post-marketing surveillance reports (not pertussis-containing vaccines to date), which the companies 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. Respiratory and Vaccine Preventable Bacterial Reference Unit National Reference Laboratory has received unrestricted educational grants for conference attendance and travel grants for meeting attendance from vaccine manufacturers.

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