Vaccination of Pregnant Women Against Pertussis

Background Information
Acknowledgements

This resource was prepared by HPS and NES. We would like to thank members of the National Pertussis Project Group for their constructive comments and Michelle White from the HPS graphics team for her technical skill in rapidly generating this document.

Health Protection Scotland is a division of NHS National Services Scotland.  
Health Protection Scotland website: http://www.hps.scot.nhs.uk

Published by Health Protection Scotland, NHS National Services Scotland, Meridian Court, 5 Cadogan Street, Glasgow G2 6QE.

First published October 2012

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Citation for this document:
Health Protection Scotland. Vaccination of Pregnant women against Pertussis. Background Information. Health Protection Scotland, 2012..

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Health Protection Scotland  
NHS National Services Scotland  
Meridian Court  
5 Cadogan Street  
Glasgow G2 6QE  
Tel: +44 (0) 141 300 1100  
Email: NSS.HPSEnquiries@nhs.net

Designed and typeset by:  
Graphics Team, Health Protection Scotland
Pertussis vaccination of pregnant women - background information

Pertussis infection

Pertussis also known as whooping cough, is a bacterial respiratory infection caused by *Bordetella pertussis*. Pertussis is a very infectious disease that is easily passed from one person to another. The bacteria are present in the back of the throat of an infected person and may be spread by coughing and sneezing.

Protection against pertussis infection is not life-long and even after natural disease, individuals can get re-infected and spread infection to others. The same is true after whooping cough vaccination, although infection in fully vaccinated individuals is normally milder.

Pertussis epidemiology

Pertussis typically has a cyclical nature with peaks every three to four years. The previous peak in Scotland was in 2008/2009 with 117 and 118 laboratory confirmed cases respectively. In 2012 there has been a dramatic increase in cases of pertussis with 983 laboratory confirmed cases reported between January and mid September 2012, this compares to 61 during the same period in 2011 and 84 during the same period in 2008 (the previous peak in cases).

Approximately 10% of laboratory confirmed cases in Scotland are in infants under one year and the majority of these in infants under 6 months of age – the group most susceptible to complications.

This dramatic increase in cases has also been reported in England and Wales (Kimietowicz 2012), the United States (Winter et al 2012, MMWR 2012) Australia, (Australian Government) New Zealand (New Zealand: Public Health Surveillance), Canada (Fisman et al 2011)

Implications of pertussis on young infants

Whilst pertussis infection occurs in all age groups, the highest incidence is among young infants.

Immunisation against pertussis is offered to infants at 2, 3 and 4 months of age, with all three doses required to achieve good protection. In the first weeks of life, before acquiring protection from immunisation, infants are most susceptible to pertussis and its complications.

Infants experience the highest rates of hospitalisation, complications including pneumonia, seizures and encephalopathy and death (Greenberg et al 2005).
Pertussis vaccination of pregnant women

The Joint Committee on Vaccination and Immunisation (JCVI) reviewed the available evidence on the strategies available to reduce the burden of infection among young infants and concluded the most effective way was to offer pertussis vaccination to pregnant women. The Scottish Government have introduced a temporary vaccination programme to vaccinate pregnant women to protect their infants. Immunisation is recommended from 28-38 weeks gestation, with the ideal time being weeks 28-32 (CMO letter: http://www.sehd.scot.nhs.uk/cmo/CMO(2012)09.pdf).

Immunisation within weeks 28 to 38 (and ideally weeks 28 to 32) of pregnancy may ensure greatest overlap between the period of maximal antibody levels in the pregnant women and the period of transplacental antibody transfer. Earlier immunisation within the period 28 to 38 (i.e. 28 to 32 weeks) weeks of pregnancy would also provide some protection to preterm infants who may be particularly vulnerable to complications from pertussis infection. Pregnant women who are now beyond week 38 of pregnancy should also be offered immunisation up to the onset of labour so that some direct protection may still be provided to the infant. Vaccination may also be offered to new mothers who have never previously been vaccinated against pertussis, up to when their child receives their first vaccination. A single dose of Repevax® is recommended in these circumstances and should be given as soon as possible after birth.

The vaccination of pregnant women against pertussis should induce high levels of pertussis antibodies with maximum antibody levels likely to be approximately two weeks after vaccination (Halperin et al 2011). The transfer of these protective antibodies across the placenta to the unborn infant should provide some protection against pertussis in the early weeks of life, when the incidence of pertussis infection and complications is greatest. There is evidence from the literature supporting efficient transplacental transfer of pertussis antibodies including, Gall et al (2011), Leuridan et al (2011), Van Savage et al (1990), MMWR (2011). Because no correlate of protection is known for pertussis, it is uncertain whether the increase in antibody levels acquired from transplacental transfer can be considered clinically protective, however high antibody concentrations are likely to protect better than low values.

The abbreviations of vaccines used in the Unites States and other countries are those in the source document/paper and may differ from the abbreviations used in the UK.
Vaccine safety

The vaccine available for use, Repevax®, contains a low dose diphtheria, tetanus, acellular pertussis and inactivated polio antigens (dTaP/IPV).

Tetanus and diphtheria toxoid vaccines have been extensively used in pregnant women worldwide for a number of years to prevent neonatal tetanus (Creizel & Rockenbauter 1999, Silveira et al 1995). Data on the safety of combined vaccines which have pertussis components are much more limited. The data which is available comes from small studies (Talbot et al 2010) and from post marketing adverse event reporting (Zheteyeva et al 2012).

In response to the increase of pertussis cases in the United States and the burden of disease among young infants the Advisory Committee on Immunisation Practices (ACIP) reviewed the available evidence and recommended a Tdap vaccination programme for pregnant women, with the vaccination preferably during the third or late second trimester (after 20 weeks gestation) (MMWR 2011).

ACIP review of the safety information:

The ACIP reviewed published and unpublished data from the Vaccine Adverse Event Reporting System (VAERS), Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries, and small studies (Gall et al 2011, Talbot et al 2010). ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria-toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic (Czeizel et al 1999, Silveria et al 1995). From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks’ gestation is preferred to minimise the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative (MMWR 2011).
### Selected references on pertussis vaccination of pregnant women

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<td><strong>Implications of pertussis in young infants</strong></td>
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Death registrations, laboratory confirmations and hospital episode statistics data indicated that 39 pertussis related deaths occurred during 2002-2009; 30 were in patients with laboratory confirmed pertussis. Of the 39 deaths, 36 (92%) were among infants, 29 (72%) of whom were <3 months. |
| **Greenberg et al (2005)** | A review article of the burden of pertussis in infants and children including clinical manifestations, morbidity, mortality, hospitalisation, complications and impact on child care for parents of children with pertussis. | Although pertussis was a common cause of death in infants in the prevaccine era and the mortality from pertussis has substantially declined in recent years, nearly all deaths from this disease still occur in infants younger than 6 months. Therefore pertussis in infants remains a major public health concern.  
Infants younger than 6 months of age are prone to complications associated with pertussis infection, such as pneumonia, seizures and encephalopathy and frequently require hospitalisation. The burden on parents of children with pertussis is significant and affects many aspects of the family life. |
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**Pertussis vaccination of pregnant women**

<p>| MMWR (2011) | The recommendations of the Advisory Committee on Immunisation Practices (ACIP) in USA. The ACIP Pertussis vaccine group reviewed unpublished Tdap safety data from pregnancy registries and the Vaccine Adverse Event Reporting System (VAERS) and published studies on use of Tdap in pregnant women. | ACIP reviewed published and unpublished data for two Tdap vaccines. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria toxoids (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus – and diphtheria – toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks’ gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative. |</p>
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<td>Gall et al (2011)</td>
<td>A study of 104 pregnant women at the University of Louisville (USA) to determine whether tetanus-diphtheria-pertussis vaccination (Tdap) in pregnancy provides newborns antibodies against pertussis compared to mothers who did not receive Tdap.</td>
<td>Newborns born from mothers who received Tdap during pregnancy had significantly higher concentrations of diphtheria antitoxin (P&lt;0.001), tetanus antitoxin (P=0.004), and antibodies to pertussis toxin (P&lt;0.001), filamentous hemagglutinin (P=0.002), pertactin (P&lt;0.001), and fimbriae 2/3 (P&lt;0.001) when compared to newborns from mothers who did not receive Tdap. There was a significant increase in the odds that newborns from mothers who received Tdap during pregnancy have antibodies that may provide protection against diphtheria (P=0.0141), pertussis toxin (P&lt;0.0001) and fimbriae 2/3 (P=0.0146). Administering Tdap during pregnancy increases antibody titres against diphtheria and pertussis antigens. Maternal Tdap may prevent neonatal pertussis infection.</td>
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| Healy (2012) | A review article of the vaccines recommended during pregnancy and the issues surrounding vaccination including maternal and infant disease burden, biological factors affecting immune response and placental transport of antibodies, optimal timing of immunisation, safety and acceptability. | The review reports that successful protection of mothers and infants through maternal immunisation depends on a number of biological factors. Placental transport of maternal pathogen specific IgG starts at week 17 gestation; however, the amount transported is minimal until approximately 34 weeks of gestation. Therefore, the optimal timing of maternal immunisation to protect infants is week 28 to 32 of gestation. This allows time for a robust maternal antibody response, ensuring that high levels of maternal IgG are present when placental transport is most efficient.

The review acknowledges the important impact of advocacy on the part of healthcare providers for pregnant women. Evidence from seasonal flu suggests that healthcare providers attitudes and willingness to provide education about the value of vaccines is the greatest influence on a pregnant women's ultimate decision to receive a vaccine. |
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<td>Peters et al (2012)</td>
<td>Modelling work conducted in USA to estimate the potential impact of Tdap immunisation before delivery, at delivery and at the 2 week newborn visit on US infant hospitalisations.</td>
<td>Analysis reports that immunising parents before pregnancy or ≥2 weeks prior to delivery should reduce pertussis hospitalisations among infants 0-4 months by 2694-9314 if both parents are vaccinated, and by 1347-6909 if only mothers are vaccinated. Greater reductions in pertussis hospitalisations would be achieved if parents are immunised ≥2 weeks prior to delivery than after delivery or the 2 week newborn visit.</td>
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<td>Leuridan et al (2011)</td>
<td>A prospective multicentre study conducted in Antwerp, Belgium, to investigate the effect of a prepregnancy pertussis booster dose on maternal antibody titres in young infants. Paper presents interim analysis based on 24 women. Serum samples were taken from women at delivery of her first newborn, and from the offspring at 1 month of age. Women were offered a TdaP booster vaccine, and at the delivery of the second child blood taken from the mother, the cord and the newborn infant.</td>
<td>The study reports high immunologic response to acellular pertussis booster vaccination is found in pregnant women, as well as efficient transplacental transfer and significantly higher titres in 1 month-old infants, born after maternal booster vaccination compared with siblings born before the maternal booster.</td>
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### Pertussis vaccination postpartum period

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<td>Halperin et al (2011)</td>
<td>Two sequential studies conducted in Halifax, Nova Scotia. The first was a nonrandomised, open study of a 5-pertussis component Tdap vaccine (tetanus toxoid, diphtheria toxoid, pertussis toxoid (PT), filamentous hemagglutinin (FHA), fimbriae types 2 &amp;3 (FIM) and pertactin (prn)) given to women of childbearing age; the second was a randomized, open study of Tdap or no vaccine in postpartum women. Serum levels of immunoglobulin (Ig) G and IgA against pertussis antigens, serum levels of IgG against diphtheria and tetanus, and breast milk levels of IgA against pertussis antigens were measured at various times after vaccination.</td>
<td>In both studies, the antibody response was relatively rapid, with serum IgG and IgA levels beginning to increase noticeably by days 5-7 and approaching peak levels by day 14. Greater than 68% and 84.4% of IgG and IgA responders, respectively, achieved ≥ 90% of their maximum titre by day 14. The diphtheria and tetanus antibody kinetics followed a similar time course. Breast milk levels of IgA against PT, FHA, and FIM were first detectable at day 7, peaked by day 10, and then slowly decreased through day 28. Antibodies against PRN showed a similar response, although the peak occurred at day 14. There were no significant antibody responses in the control group. Although the antibody response to a dose of Tdap in healthy nonpregnant women of childbearing age and postpartum women occurs by day 14 and is suggestive of an anamnestic immune response, it may not be sufficiently rapid to protect infants in the first weeks of life.</td>
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<td><strong>Safety studies</strong></td>
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<td>Creizel &amp; Rockenbauter (1999)</td>
<td>An Hungarian study, to investigate the teratogenic potential of tetanus vaccination during pregnancy, using population based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (1980-1994).</td>
<td>Of 35,727 pregnant women who had babies without any defects in the study period (control group) 33 (0.09%) were vaccinated with tetanus. Of 21,563 pregnant women who had offspring with congenital abnormalities, 25 (0.12%) had tetanus vaccination. This difference was not significant (p=0.39). The case-control pair analysis confirmed the safety of tetanus vaccination during pregnancy.</td>
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<td>Silveira et al (1995)</td>
<td>Results of the Latin America Collaborative Study of Congenital Malformations (ECLAMC) on the safety of tetanus toxoid in pregnant women. Data collection began in 1967, from nine countries throughout South America.</td>
<td>Hospital based case-control study of 34,293 infants with congenital anomalies and 34,477 matched controls. No statistical differences were found between the group with congenital anomalies and control groups, exposed or not exposed to tetanus toxoid.</td>
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<td>Talbot <em>et al</em> (2010)</td>
<td>An observational postlicensure safety study among healthcare personnel who were vaccinated with Tdap during a suspected pertussis outbreak at a New England medical centre. The primary objectives were to assess the safety of administering Tdap to healthcare personnel at an interval shorter than 2 years since previous Td/TT and to assess the risk of clinically important adverse events after Tdap in the healthcare personnel population. A secondary objective was to describe reactogenicity of Tdap among a small group of pregnant women and persons aged 65 years and older.</td>
<td>Of the 4524 vaccinated healthcare personnel, 2221 (49.1%) completed a safety survey which met criteria for analysis. Non-inferiority analysis found that rates of moderate and/or severe injection sites adverse events were not significantly greater in those vaccinated &lt;2 years than in those vaccinated ≥2 years after previous Td/TT. Three serious adverse events were reported during the 2 months after vaccination, none in persons who were ≥65 years, pregnant or received Td/TT &lt;2 years before. Findings add to the body of evidence that a short interval between Td/TT and a single dose of Tdap is safe. 16 women were pregnant at the time of vaccination. Four, 8 and 4 women were in first, second and third trimesters, respectively. All 16 reported giving birth to full-term infants who had normal newborn evaluations.</td>
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<td>Zheteyeva et al (2012)</td>
<td>Study to characterise reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women who received tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap). VAERS is a spontaneous reporting system coadministered by CDC and FDA in America. Monitors vaccine safety and accepts adverse event reports following receipt of any US licensed vaccine. VAERS is not designed to assess causal associations between vaccines and adverse events; its primary purpose is to detect potential vaccine safety concerns that may be further investigated in defined populations.</td>
<td>Authors searched VAERS for reports of pregnant women who received Tdap from Jan 2005 to June 2010 and conducted a clinical review of reports and available medical records. (a time period prior to the ACIP recommendation for Tdap vaccination of pregnant women). Authors conclude during a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning patterns in maternal, infant or fetal outcomes.</td>
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<td>D'Acremont et al (2008)</td>
<td>A small longitudinal study from Switzerland of 53 women who received travel vaccines while pregnant and 53 women attending the clinic who had at least one child about the same age as the vaccinated case and who had no vaccination during pregnancy. Children were followed for a range of 1 to 10 years.</td>
<td>The most frequently administered vaccine was hepatitis A (55% of cases), followed by di-Te (34%), IM poliomyelitis (23%), yellow fever (12%), A-C meningitis (8%), IM typhoid (4%), and oral poliomyelitis (4%). Rates of premature births were 5.7% in both groups; congenital abnormalities were 1.9% in the vaccinated cohort versus 5.7% in the nonvaccinated one. This small study found no indication that travel vaccination had deleterious effects on child outcome and development.</td>
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MMWR (2011) Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged < 12 months – Advisory Committee on Immunisation Practices (ACIP), 2011. Morbidity and Mortality Weekly Report 60 (41) 1424-1426 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm


Theilen U., Johnston ED. & Robinson PA (2008) Rapidly fatal invasive pertussis in young infants – how can we change the outcome? BMJ 337: 39575.715787.80 http://www.bmj.com/content/337/bmj.39575.715787.80


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