This minute will remain draft until ratified by JCVI at its next meeting

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of teleconference on Thursday Wednesday 30 August 2012 10.00am – 12.00am and post-teleconference discussion

Members

Professor Andrew Hall (Chair)
Dr Syed Ahmed
Professor Jonathan Friedland
Dr Maggie Wearmouth
Dr Jennifer Harries
Professor Matt Keeling
Mrs Pauline MacDonald
Mrs Anne McGowan
Dr Andrew Riordan
Professor Claire-Anne Siegrist
Dr Gabrielle Laing

Devolved administrations

Dr Nicola Steedman (Scottish Government)
Dr Elizabeth Reaney (DHSSPSNI)
Ms Melanie Davies (Welsh Assembly Government)

Invited observers and presenters

Dr Mary Ramsay (HPA)
Dr Richard Roberts (PHW)
Dr Gayatri Amirthalingam (HPA)
Dr Richard Smithson (PHANI)

DH

Professor David Salisbury CB
Ms Carolyn Heaney
Dr Tom Barlow (minute)
Mr Andrew Earnshaw (minute)
Mr Christopher Lucas (minute)
Dr Peter Grove
Mr Zeeshan Ali
Dr Karen Powell
Dr David Foster

MHRA

Dr Phil Bryan

1. The Chair explained that this *ad-hoc* meeting of JCVI via teleconference had been convened to consider whether a temporary programme should be introduced to offer pregnant women immunisation against pertussis to protect their newborn infants in light of the continuing outbreak of pertussis that is increasing in severity. As a routine immunisation programme is not being proposed at this stage, JCVI would be providing advice rather than recommendations under the NHS Constitution. Apologies for absence had been received from JCVI members: Professor Ray Borrow, Judy Breuer, Drs Anthony Harnden and Peter Baxter and Mr Chris Liffen.

2. The committee noted that following the discussions at the June 2012 meeting of JCVI an analysis had been produced by the Health Protection Agency (HPA) that showed that most infant cases of pertussis are below six weeks of age. Thus, greater adherence to the routine childhood immunisation schedule that offers the first immunisation against pertussis at two months of age or shifting the age at which the first immunisation is offered to six weeks of age (the earliest age at which the vaccine is authorised for use) would have little impact on the incidence of pertussis in

young infants who are the age group at highest risk of complications, hospitalisation and death from pertussis. Latest epidemiological data from England & Wales show that:

- laboratory confirmed cases of pertussis continue to increase with around 1700 cases in quarter two of 2012 with a higher number of cases expected in quarter three;
- most infant cases of pertussis continue to be below six weeks of age with a higher incidence in infants aged under three months than at any other point in over a decade;
- nine confirmed deaths in infants under one year of age have been reported up to week 39 in 2012, all of whom were unvaccinated, compared with between one and eight infant deaths annually over the period between 2001 and 2011.

3. The committee agreed that the current situation warranted consideration of a temporary programme to offer immunisation against pertussis to pregnant women to provide protection to newborn infants. Transplacental transfer of anti-pertussis antibodies from immunised pregnant women could provide protection to newborn infants over the first weeks following birth. This approach is likely to be the most effective immunisation strategy to provide protection for young infants.

4. The committee noted that Repevax® (containing diphtheria (low dose), tetanus, acelluar pertussis and inactivated polio antigens – dTaP/IPV), which is used in the routine childhood immunisation programme, was the vaccine available for immediate use for a temporary programme. There are sufficient stocks of this vaccine to support a temporary programme for at least six months without putting the routine childhood immunisation programme at risk from supply issues. Alternative vaccines would require procurement arrangements that would take some time to put in place. The diptheria, tetanus and acellular pertussis vaccines (Adacel® and Boostrix®) that are used in the United States (US), where routine immunisation of pregnant women was introduced in 2011, are not currently marketed in the UK.

5. The committee agreed that immunisation of health care workers in close contact with young infants as advised by the committee at its June 2012 meeting is of lesser priority.

<u>Vaccine safety</u>

6. The committee noted that there is long established use of diphtheria and tetanus vaccines in pregnant women with no safety concerns. Similarly, data on the use of polio vaccines during pregnancy raised no safety concerns. However, data on the use of acellular pertussis vaccines in pregnancy are more limited, although the available data do not give rise to safety concerns. It was also noted that Adacel® - one of the vaccines offered to pregnant women in the US – was similar in content to Repevax® with the exception of the additional inactivated polio components in

Repevax®. Adverse event reporting in Europe, while limited, indicated no serious adverse events associated with use of acellular pertussis containing vaccines during pregnancy. Whilst the Summary of Product Characteristics (SPC) for Repevax® stated that use during pregnancy was not recommended, this wording was due to the routine exclusion of pregnant women from clinical trials, and was not based on any specific safety concerns or evidence of harm and the use in pregnancy was not contraindicated. The committee concluded that use of Repevax® during pregnancy did not raise safety concerns. However, given that direct data are limited and that serious adverse events during pregnancy such as intrauterine deaths occur at a relatively high background frequency, there is potential for these events to be falsely attributed to vaccination. Therefore, it would be very important to monitor the safety of the vaccine in use. Given that the immunisation would be offered later in pregnancy (see below), vaccination could not be falsely associated with major foetal malformations.

7. It was explained that the Medicines and Healthcare products Regulatory Agency (MHRA) would monitor the frequency and type of adverse events using the Yellow Card Scheme and the Clinical Practice Research Datalink (CPRD) to follow pregnancy outcomes following vaccination. An assessment of the frequency of serious adverse events during pregnancy such as intrauterine deaths following vaccination compared with background levels could be made quickly. The committee supported this assessment and suggested that, in addition, a case control study that included vaccination history could provide additional reassurance about the safety of the vaccination.

8. The committee considered that women with repeat pregnancies should be offered immunisation during each pregnancy as this would ensure maximal transplacental transfer of antibody. Repeat vaccination might give rise to higher frequencies of temporary local (e.g. sore arm) or systemic (e.g. fever) reactions particularly for women who have already received their full course of tetanus, diphtheria and/or polio vaccinations and/or have received tetanus, diphtheria and/or polio vaccinations relatively recently. These reactions would not give rise to increased safety concerns in relation to the pregnancy. The benefit of immunisation during pregnancy to infants is likely to outweigh the potential increase in reactions in pregnant women.

9. The committee considered that there are no reasons why Repevax® could not be administered at the same time as influenza vaccine and/or anti-D treatment on safety or efficacy grounds should they need to be or wish to be administered at the same visit.

<u>Effectiveness</u>

10. The committee noted that, whilst there is good evidence for transplacental transfer of anti-pertussis antibodies, in the absence of a correlate of protection and any studies on the effectiveness of this approach against

infection or severity of disease, the effectiveness of prenatal immunisation against pertussis to protect young infants is uncertain. Antibody levels in the infant would be expected to wane rapidly following birth. Nevertheless, it is reasonable to assume that this approach would provide young infants with some important, although possibly not complete, protection against pertussis, and it is likely to be the most effective immunisation strategy to provide protection to young infants. Furthermore, immunisation of the pregnant women could prevent her becoming infected and passing on the infection to her infant. Given the uncertainties about the effectiveness of this approach, it would be important to evaluate the impact of the temporary programme on pertussis infection in infants.

11. The committee noted that, whilst some pregnant women may not have received primary pertussis immunisations, it was highly unlikely that they would have escaped natural pertussis infection at some point in their life. Thus, for almost all women a boosting immune response from immunisation during pregnancy should be expected with the induction of high antibody levels to facilitate transplancental transfer.

Impact on routine immunisations

12. The committee noted that there is conflicting evidence on the potential for the blunting of the immune responses to the first routine infant immunisation following immunisation during pregnancy. Thus, it was possible that immunisation in pregnancy could lead to immunity from the primary immunisations waning more quickly, possibly leaving children more susceptible to disease prior to the administration of the pre-school booster dose of dTaP/IPV or DTaP/IPV vaccines. Whilst the committee agreed that the potential for blunting was not a reason not to proceed with the immunisation of pregnant women, it would be very important to study the impact of the temporary programme on routine immunisations both in terms of immune responses and, if possible, on the clinical effectiveness of the primary immunisations in children up to three years of age.

Timing of immunisation

13. The committee noted that evidence suggested that transplacental antibody transfer was limited before week 17 of pregnancy and was minimal until week 34 of pregnancy. Studies suggest that antibody levels in adults peak about two weeks after a pertussis booster immunisation with significant decline over the following months. Therefore, levels of transplacentally transferred antibody may be sub-optimal for immunisation pre-pregnancy or early in pregnancy. Immunisation given earlier than week 20 in pregnancy might also be falsely associated with unrelated adverse events identified up to or at the routine 20 week anomaly antenatal scan. Thus, the committee considered that immunisation could be offered at one of the routine antenatal appointments following the routine week 20 anomaly scan. Immunisation within weeks 28 to 32 of pregnancy may be optimal. Immunisation within weeks 28 to 38 of pregnancy may ensure greater 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 weeks of pregnancy would also provide some protection to preterm infants who may be particularly vulnerable to complications from pertussis infection. Whilst immunisation after week 38 or shortly after birth would provide protection to the mother, and provide some indirect protection for the infant by lowering the risk of transmission of pertussis from mother to infant, it may provide little or no direct protection for the infant. Transplancental antibody transfer would be expected to be similar for each child for women carrying more than one child.

Communications

14. The committee considered that for the temporary programme to be effective a targeted communications campaign would be very important to explain clearly the risks from pertussis (and influenza), the benefits of immunisation during pregnancy to provide protection against pertussis (and influenza) and to address concerns about immunisation during pregnancy from women and their families and health practitioners. It would be important to present the current epidemiological information in any communications. It would also be important to correct misconceptions about the impact of breastfeeding. Whilst very important for infants' general health, it would provide little protection against pertussis (or influenza) infection.

    Action: Members were asked to provide the secretariat with any additional suggested areas that communications materials should cover.

Programme evaluation

15. The committee considered that it would be very important to evaluate carefully the impact of the programme on the protection provided to young infants and on the immunogenicity and effectiveness of routine infant immunisations. This would inform review of the temporary programme and provide important information for considerations about changes to the routine immunisation programme to improve pertussis control (see below). The committee supported proposals from the HPA for the evaluation of the programme but considered that it would be important to include, if possible, evaluation of the clinical effectiveness of routine infant immunisations against pertussis up to three years of age. The committee fully supported the safety monitoring proposed by MHRA and considered that a case control study of adverse events during pregnancy would be helpful.

Discontinuing the programme

16. The committee considered that is was difficult to determine at this stage under what circumstances the temporary programme should be stopped as this would depend on the future epidemiology of pertussis and the assessment of the impact of the temporary programme. As the temporary

programme would not control the outbreak, only lower its impact on the most vulnerable age group of the population, further considerations would be needed to assess the impact and cost effectiveness of a range of different immunisation strategies to control pertussis transmission better, including maternal, paternal and/or adolescent immunisations. The committee asked HPA to conduct these analyses and acknowledged that these complex analyses would take time to conduct. The committee agreed it should keep the temporary programme under review in light of the epidemiology of pertussis, evidence gathered by the HPA and MHRA and analyses of the impact and cost effectiveness of strategies to control pertussis better.

Conclusion

17. The committee advised that, a temporary programme should be introduced to offer pregnant women immunisation against pertussis in response to the current outbreak of pertussis. Initially Repevax® should be used as this is the most suitable vaccine available for immediate use. The committee has no concerns about the safety of use of this vaccine at any stage in pregnancy. Therefore immunisation could be offered at one of the routine antenatal visits following the routine week 20 anomaly scan. However, in order to maximise the protection provided to newborn infants, immunisation should be offered at a routine antenatal visit within the period week 28 to week 38 of pregnancy with immunisation within the period week 28 to week 32 of pregnancy optimal.

18. Although the level of protection provided to newborn infants is uncertain, the committee concluded that this immunisation strategy could provide young infants with some important, although possibly not complete, protection against pertussis, and it is likely to be the most effective immunisation strategy to provide protection to newborn infants. It is important that the impact of the temporary programme on pertussis in infants be evaluated. The impact of the programme on routine infant immunisations should also be assessed, including the longevity of the antibody response in infants born to mothers that were, and were not, vaccinated during pregnancy.

19. The committee advised that, as there is potential for the immunisation during pregnancy to be falsely associated with adverse events, such as intrauterine death, that occur with a relatively high background frequency, careful monitoring and assessment of the frequency and type of adverse events is important to provide reassurance about the safety of the vaccine in pregnancy.

20. The committee notes that, whilst this measure should prevent cases of pertussis disease and deaths in infants, it will have no impact upon the transmission of pertussis across the population. Therefore, further work is needed to assess the impact and cost effectiveness of a range of strategies to improve pertussis control that will take some time to

complete. The committee will keep the temporary programme under review.

Annex A – declarations of interest

The following members declared interests in companies that manufacture and supply pertussis-containing vaccines (GSK, Sanofi-Pasteur MSD).

Member	Action	Interest
Ray Borrow	Non-personal, non-specific GSK, Baxter, Novartis, Pfizer and Sanofi-Pasteur MSD	The member is able to participate in the discussion and to vote
Judith Breuer	Non-personal, non-specific Sanofi-Pasteur MSD	The member is able to participate in the discussion and vote
Anne McGowan	Non-personal, non-specific GSK and Sanofi-Pasteur MSD	The member is able to participate in the discussion and to vote
Claire-Anne Siegrist	Non-personal, non-specific Sanofi-Pasteur MSD	The member is able to participate in the discussion and to vote
Andrew Riordan	Non-personal, non-specific GSK	The member is able to participate in the discussion and to vote

Annex B – evidence considered by the committee

Agenda item 1 of 1:

- Cover paper: Pertussis vaccination of pregnant women
- Minute of the 13 June 2012 meeting of the JCVI
- Papers:
    - Belloni et al (2003) Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics. 2003 May;111(5 Pt 1):1042-5.
    - Campbell H, et al (2012) Accelerating control of pertussis in England and Wales. Emerg Infect Dis. Jan;18(1):38-47.
    - Crowcroft NS and Pebody RG (2006) Recent developments in pertussis. Lancet 367(9526): 1926-36.
    - Cutts (1993) Congenital anomalies after oral poliovirus vaccination during pregnancy. Lancet 341, 1162.
    - Czeizel AE, Rockenbauer M. Tetanus toxoid and congenital abnormalities. Int J Gynecol Obstet 1999;64:253–8.
    - Englund et al (1995) The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. Pediatrics. 1995 Sep;96(3 Pt 2):580-4
    - Forsyth et al. (2005) Potential strategies to reduce the burden of pertussis. Pediatr Infect Dis J 24(5 Suppl): S69-74.
    - Fortner KB, Kuller JA, Rhee EJ, Edwards KM.(2012) Influenza and tetanus, diphtheria, and acellular pertussis vaccinations during pregnancy. Obstet Gynecol Surv. Apr;67(4):251-7.
    - Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011;204:334.e1–5.
    - Halasa et al (2008), Safety and immunogenicity of trivalent inactivated influenza vaccine in infants.J Infect Dis. 2008 May 15;197(10):1448-54.
    - Halperin BA et al (2011) Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis. 53(9):885-92.
    - Harjulehta-Mervaala T et al. (1993) Oral polio vaccination during pregnancy: no increase in the occurrence of congenital malformations. Am J Epidemiol. 138, 407
    - Harjulehta-Mervaala T et al. (1994) Oral polio vaccination during pregnancy: lacl of impact on fetal development and perinatal outcome. Clin Infect Dis. 18, 414-420.
    - Harjulehta-Mervaala T et al. (1995) Oral poliovirus vaccination and pregnancy complications. Acta Pbstete Gynecol Scand. 74, 262-265.
    - Healy CM, Rench MA, Castagnini LA, Baker CJ (2009) Pertussis immunization in a high-risk postpartum population. Vaccine 18;27(41):5599-602.

- Healy CM, Rench MA, Baker CJ (2011) Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis. Jan 15;52(2):157-62.
- Healy CM (2012) Vaccines in pregnant women and research initiatives.Clin Obstet Gynecol. 2012 Jun;55(2):474-86.
- Heinonen et al. (1973) Immunizationduring pregnancy agaiunts poliomyelitis and influenza in relation to childhood malignancy. Int J Epidemiol. 2, 229-235.
- Heinonen, Sloane and Shapiro. Birth defects and drugs in pregnancy. Birth defects and drugs in pregnancy. Littleton, Mass: John Wright Publishing Sciences Group Inc.1977. p. 314–19, 473–4, 486–7.
- Le T, et al (2004) Immune responses and antibody decay after immunization of adolescents and adults with an acellular pertussis vaccine: the APERT Study.J Infect Dis 1;190(3):535-44.
- Morbidity Mortality Weekly Report (MMWR) Vol. 60 / No. 41 October 21, 2011
- Ornoy et al (1990) Spontaneous abortions following oral poliovirus vaccination in first trimester. Lancet. 800-801.
- Ornoy and Tenenbaum (2006) Pregnancy outcome following infections by coxsackie, echo, measles, mumops, hepatitis, polio and encephalitis viruses. Reprod Toxicol.
- Peters TR, et al. (2012) Potential impact of parental Tdap immunization on infant pertussis hospitalizations. Vaccine. 10;30(37):5527-32.
- Sheridan et al (2012) Number and order of whole cell pertussis vaccines in infancy and disease protection.JAMA. Aug 1;308(5):454-6.
- Silveria CM, Caceres VM, Dutra MG, Lopes-Camelo J, Castilla EE. Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. Bull World Health Organ 1995; 73:605–8.
- Slone et al. (1973) Maternal drug exposure and fetal abnormalities. Clin. Pharmacol. Ther. 14, 648-653.
- Talbot EA, Brown KH, Kirkland, KB, Baughman AL, Halperin SA, Broder KP. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine 2010;28:8001–7
- Van Rie A, Wendelboe AM, Englund JA. Role of maternal pertussis antibodies in infants. Pediatr Infect Dis J 2005;24(5 Suppl):S62–5.
- Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92.
- Ward JI, et al (2006) Bordetella Pertussis infections in vaccinated and unvaccinated adolescents and adults, as assessed in a national prospective randomized Acellular Pertussis Vaccine Trial (APERT).Clin Infect Dis. 15;43(2):151-7.

  - Weston WM et al(2012) Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix(®)): results of two randomized trials. Vaccine. 30(9):1721-8.
  - Wood et al (2010) Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age.Pediatr Infect Dis J. 2010 Mar;29(3):209-15.
  - Zheteyeva et al (2012) Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. American Journal of Obstetrics & Gynecology 59.e2
- Analysis of the number of pregnant women in the UK
- Summary of Product Characteristics – Repevax®
- NICE clinical guideline 62 Antenatal care - Routine care for the healthy pregnant woman, guidance on antenatal appointments.
- Presentation on the epidemiology of pertussis
- Proposals for the evaluation of a programme
- Analysis of infant deaths from pertussis.