



## MEETING REPORT

# Expert consultation on pertussis

Barcelona, 20 November 2012

## 1 Background

Pertussis is a bacterial respiratory infection caused by *Bordetella pertussis*. Pertussis is a highly contagious disease with a reproductive number ( $R_0$ ) of 15–17. The most severe symptoms occur in infants and young children whereas the disease is usually milder in adolescents and young adults, who constitute a reservoir and are a source of spread to young children. Pertussis remains endemic worldwide and tends to be a cyclic disease, peaking every 3–5 years. The most effective preventive measure is immunisation and, in developed countries, acellular vaccines are given usually in combination with other antigens.

Over the last 20 years, the epidemiology of the disease has remarkably changed. There has been a shift observed from mainly paediatric cases (normally children <10 years of age) towards adolescents, adults and children too young to have been vaccinated or to have completed the primary series.

Mortality rates are still unacceptable, both in developing and developed countries. Despite the relatively high global vaccination coverage (82%) among infants receiving three doses of pertussis-containing vaccines, it is estimated<sup>1</sup> that in 2008 about 16 million cases of pertussis occurred worldwide, and 195 000 children died from the disease.

Since 2011, increases in the number of pertussis cases have been repeatedly reported in different regions of the world, even in those with sustained high vaccination coverage. In the countries of the European Union/European Economic Area (EU/EEA), the situation is evolving similarly, with many countries observing a growing number of cases, mostly in very young infants, adolescents and adults.

In summer 2012, the Netherlands, concerned about the growing number of cases and evolving epidemiology of the disease, requested the European Centre for Disease Prevention and Control (ECDC) to elaborate a common strategy to respond to the threat. Similar requests were made by other European countries. Therefore, ECDC organised a technical workshop in Barcelona, Spain, in November 2012 to seek a consensus on a common strategy to reduce the public health burden caused by pertussis in the EU/EEA countries. The agenda of the meeting can be found in the Annex.

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<sup>1</sup> Black RE1, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010 Jun 5;375(9730):1969-87.

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*The views expressed in this publication do not necessarily reflect the views of the European Centre for Disease Prevention and Control (ECDC).*

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## 2 Session I: Is pertussis an issue in the EU?

### 2.1 Pertussis in the EU

The reported incidence of pertussis disease in the EU/EEA countries has declined dramatically since the introduction of pertussis vaccines into national immunisation programmes over the past 50 years. However, reported pertussis incidence has increased markedly in almost all Member States and also in the USA and Canada, with a marked upsurge since 2011. This increase in reported incidence has occurred despite sustained high vaccination coverage levels and has been observed in all age groups including adolescents and adults, and notably among infants <1 year of age.

In order to assess the resurgence of pertussis in the EU/EEA, describe the changing epidemiology of pertussis in Member States, and identify strategies and interventions that may be successful in reversing this trend, ECDC launched a pertussis study. The study aims to analyse historical pertussis data reported from Member States through the EUVACNET and TESSy (case-based data) systems, and to describe the different pertussis vaccines, vaccination schedules and surveillance systems currently in use in Member States. Unfortunately, these data sets suffer from important limitations regarding the different types and completeness of surveillance data, microbiological diagnostic methods, and the lack of standardisation of case definitions used in Member States.

Case-based pertussis data from the Netherlands, Norway, Sweden and the United Kingdom reported through ECDC's TESSy system for the period 2006–10 were subjected to a time-series analysis for different age groups in order to predict the expected number of cases in 2011. Data from other Member States were too sparse for an analysis. Models were developed that included seasonal variation within years and epidemic cycles over multiple years. The reported number of pertussis cases exceeded the 95% upper confidence interval for the expected number of cases based on trends in 2006–10 in the Netherlands, Norway and the United Kingdom, but not in Sweden. For example, in 2011 the number of cases reported by the Netherlands exceeded the number of expected cases by 75%. In the Netherlands and Norway, the most affected age groups were children 5–9 years of age and adults  $\geq 30$  years of age. In the United Kingdom, the increase was seen primarily in infants <1 year of age, together with adults >30 years of age.

These data must be interpreted with care because of the different case definitions and microbiological diagnoses used for pertussis surveillance and the different vaccines and vaccination schedules employed to control the disease in these countries. It is also important to note that pertussis in adults is hugely underdiagnosed and underreported. Furthermore, it is not possible at this stage to ascertain if the case fatality rate due to pertussis is changing. Nevertheless, these analyses show clearly that pertussis epidemiology is changing and that an urgent and robust public health response is required.

#### 2.2.1 Pertussis in the Netherlands

In the Netherlands, a peak in pertussis cases was observed in 1999 and additional peaks occurred roughly every three years since then – in 2002, 2005, 2008 and 2012. In 1999, the vaccination schedule of 3, 4 and 5 months of age was changed to an accelerated schedule of 2, 3 and 4 months of age. A booster dose of diphtheria-tetanus-acellular pertussis (DTaP) vaccine at four years of age was introduced in 2003, and in 2005, domestically-produced diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine was replaced with DTaP for all doses administered. Since then, incidence rates among infants and children dropped significantly, but incidence among infants too young to be vaccinated, that is, <2 months of age, and among adults  $\geq 20$  years of age, has continued to rise.

Pertussis is underreported in the Netherlands. Most infections in adults are subclinical or mild, and there is evidence that <1% of cases among adults are notified. National seroprevalence data collected in 2006–07 suggested that 9% of the Dutch population  $\geq 10$  years of age are infected with pertussis annually. Compared with 1995–96, pertussis infections roughly doubled.

There is evidence that duration of immunity induced by the current DTaP vaccine may be shorter than that induced by the previous DTwP vaccine<sup>2</sup>, with only 50% of vaccinees protected after six years. There is also evidence that pathogen adaptation to vaccination has resulted in the emergence of pertussis strains with genetic characteristics that are able to infect individuals at higher levels of immunity. Together, these changes have caused a marked resurgence of pertussis in the Netherlands.

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<sup>2</sup> Information received after the meeting: This holds true for foreign wP vaccines; the Dutch wP vaccine was relatively weak, which explains that vaccine effectiveness of the infant series increased significantly after introduction of the aP vaccine. As to the preschool aP booster, protection decreases with time.

Pertussis P3 serotypes emerged globally after 1988 and are now dominant in many EU/EEA countries. They produce more pertussis toxin (Ptx) which appears to suppress immunity and reduce the duration of immunity among vaccinated or naturally infected individuals.

The main public health priority is to protect newborns. Efforts are being made to raise the awareness of healthcare providers and improve the timeliness of vaccination. In addition, other potential interventions were discussed, for example vaccinating pregnant women or 'cocooning' newborns by vaccinating one or both parents post-partum. In the long term, more effective vaccines must be developed, for example vaccines that neutralise proteins found in current pertussis strains and vaccines which induce Ptx-neutralising antibodies that last longer. In the future, chemically inactivated Ptx should be replaced with genetically inactivated Ptx. These improved antigens should be incorporated into combination products such as penta- and hexavalent pertussis-containing vaccines.

The remaining question is whether the emergence of pertussis strains adapted to current vaccines is associated with a country's (or region's) preference for DTwP or DTaP vaccines.

### 2.2.2 Pertussis in England and Wales

The United Kingdom introduced DTwP vaccine into the routine vaccination schedule in 1957 and in 1990 adopted an accelerated primary series at 2, 3 and 4 months of age. DTwP was replaced by DTaP in a pentavalent combination product from 2004. Pertussis notifications dropped to very low levels during 2002–10, but outbreaks were reported in schools and hospitals in the first months of 2011, with an initial marked increase in cases among teenagers and adults >35 years of age from the third quarter of the year. These increases continued in 2012 and spread to all age groups, including vulnerable infants <3 months of age. In October 2012, >1 500 laboratory-confirmed pertussis cases occurred in England and Wales.

A number of strategies have been considered to respond to this challenge. The Joint Committee on Vaccination and Immunisation supported the collation of further information in order to review the possible introduction of pertussis vaccination for healthcare professionals working with pregnant women and neonates. The impact of improvements in the timely administration of the primary series of pertussis-containing vaccine to young children was also considered. However, even if the first dose of pertussis-containing vaccine was given at exactly eight weeks of age, 50% of infant pertussis cases had already occurred, and vaccine efficacy was calculated at 74% (95% CI, 58–84%) after the first dose. By September 2012, 13 deaths had occurred among infants aged 4–9 weeks of age with confirmed pertussis. Nine of those deaths occurred in infants <9 weeks of age, that is, too young to have been vaccinated<sup>3</sup>. Therefore, starting in October 2012, adult diphtheria-tetanus-acellular pertussis-inactivated poliovirus (dTaP-IPV) vaccine was offered to all pregnant women in the United Kingdom as the only way to protect infants from birth.

Vaccination of pregnant women in the United Kingdom was introduced as an outbreak response; as this is a temporary measure, it will be difficult to decide when to end this programme. Vaccine safety in relation to pregnancy outcomes is closely monitored by the Medicines and Healthcare Products Regulatory Agency and, to date, this initiative has been positively received by both the press and the public. Department of Health data show that at least 46% of eligible pregnant women (28–38 weeks' gestation) accepted vaccination during the first month it was offered. The World Health Organization (WHO) is expected to issue a statement in December 2012 to the effect that pregnancy is not considered a contraindication for receiving dTaP-IPV vaccine in the context of an outbreak response.

### 2.2.3 Pertussis in Sweden

Sweden used DTwP vaccine in the routine vaccination schedule from the 1950s until 1979, when it was suspended; vaccination was again recommended with DTaP vaccine from 1996 onwards. Laboratory-confirmed pertussis incidence ranged between 90 and 150 cases per 100 000 inhabitants during 1986–96, but then fell significantly to 2–16 cases per 100 000 in 2002–11. To counter waning immunity among children >5 years of age, identified among the first children to receive DTaP vaccine from 1996 onwards, a booster dose was introduced for 6–8-year-olds in 2007. A second booster dose for 14–16-year-olds was also introduced more recently. Reported routine coverage with three doses of pertussis-containing vaccine is >98% for all cohorts born in 1996 and subsequent years.

A long-term cohort study initiated in 1997 shows clearly that pertussis cases, incidence and hospitalisations among infants in Sweden have consistently declined to historically low levels today. The 10 pertussis deaths reported during the past 10 years all occurred among unvaccinated individuals. There were no deaths among vaccinated individuals.

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<sup>3</sup> Information received after the meeting: <http://webarchive.nationalarchives.gov.uk/20130107105354/> and <https://www.wp.dh.gov.uk/publications/files/2012/09/CMO-Pertussis-27-09-2012-FINAL.pdf>

Over 97% of laboratory-confirmed pertussis cases had cough for  $\geq 14$  days. Many of the remaining cases had received antibiotic treatment during the first two weeks post-onset. The administration of antibiotics in  $\leq 6$  days post-onset was associated with a shorter duration of cough. Case-contacts with cough were, in descending order of frequency, mothers, fathers, siblings, grandparents, other relatives, close friends, and paediatric clinic patients, which reflects normal patterns of contact with infants.

### 2.2.4 Pertussis in Germany

Pertussis vaccination recommendations and the quality of pertussis surveillance in East and West Germany differed markedly between the 1950s and 1991, when Germany reunified, and this difference persists today. In East Germany, pertussis vaccination coverage was  $>90\%$  in the 1980s. In West Germany, routine pertussis vaccination was suspended between 1974 and 1991. Vaccine uptake was slow until 1995 when DTaP was recommended. Today, there is still substantial variability in vaccination coverage by state and vaccine dose. Throughout Germany, coverage is lowest for the booster dose given to 14–17 year-old adolescents.

Pertussis will become a notifiable disease in Germany in 2013. Hospital discharge statistics indicate that pertussis surveillance was incomplete in the former West German states. Pertussis surveillance in the former East German states showed an increasing trend in 2002–12, with 3.2% of  $>37\ 000$  cases requiring hospitalisation, 38% of which were in infants, with a total of eight deaths. From 2002 to 2012, between 25% and 40% of reported pertussis cases among children 1–14 years of age were fully vaccinated.

Diagnostic methods vary between former East Germany states, with Saxony using polymerase chain reaction (PCR) more frequently than other former East German states, and mainly among cases in younger age groups. Data show the greatest increase in pertussis incidence in Saxony among children  $<5$  years of age, whereas the greatest increase in the other former East German states was among children 5–14 years of age.

### 2.2.5 Pertussis in France

DTaP vaccine was introduced in France in 1998, in a recommended routine schedule that includes doses at 2, 3 and 4 months of age and booster doses at 16–18 months and 11–13 years of age. Reported vaccination coverage for the primary series has been  $>95\%$  since 2007. The use of DTwP vaccine was suspended in 2005. Additional recommendations issued in 2004 included a mix of disease control strategies, for example requiring pertussis vaccination among healthcare workers, 'cocooning' newborns by vaccinating their parents, and increasing immunity among adults by providing boosters to individuals  $>25$  years of age.

Pertussis disease notification was suspended in 1986. France has established a paediatric hospital-based sentinel surveillance system for pertussis called RENACOQ, which covers about 30% of national paediatric admissions. Peaks in pertussis cases occurred in 1997, 2000, 2005, 2009 and 2012. From 1996 to 2012, nearly 4 000 confirmed pertussis cases were reported, more than 2 200 of which occurred in infants under 6 months of age. Among the cases in infants, 91% were laboratory confirmed (PCR or culture), 8% were clinically confirmed, and 1% were epidemiologically linked. Ninety-six per cent of the cases were hospitalised, 18% in intensive care, and 36 cases died (giving a case fatality rate of 1.6%).

Contact patterns were similar to those seen elsewhere, with 57% the cases infected by their parents, 22% by their siblings, 20% by others (mostly adults), and 1% unknown. The majority of the cases in infants were under three months of age, that is, too young to have received a full primary series of pertussis vaccine.

Starting in 2007, RENACOQ switched to a highly sensitive *Bordetella*-specific PCR, which is 50 to 100 times more sensitive than the former *pertussis*-specific PCR (see Chapter 3).

### 2.2.6 Pertussis in Italy

In Italy, DTwP vaccine was included in the recommended routine vaccination schedule in 1982. DTaP was introduced in 1995. Although initially vaccination coverage was relatively low, it recently increased. Reported coverage among infants  $<1$  year of age has been  $>95\%$  since 2006. However, reported coverage with a primary series among adolescents is  $<50\%$ , and significantly lower for a primary series plus booster doses.

A new vaccination strategy approved in 2012 includes a booster dose of Tdap vaccine in adolescence, one additional booster for adults and elderly individuals who already completed a full primary series, two doses of Td four weeks apart and one dose of Tdap 6–12 months later for unvaccinated individuals, and a booster dose of Tdap for parents, healthcare workers, nursery staff, and all other staff who handles newborns.

Pertussis surveillance in Italy is mandatory and relies mainly on clinical diagnosis, although laboratory confirmation through PCR or serology is available. Pertussis incidence declined consistently in all age groups during 1998–2011. Future plans include the switch to national laboratory diagnosis of pertussis through the establishment of a network of regional and local laboratories under the leadership of a national reference laboratory, and a revised communicable disease notification system as recommended by ECDC.

### 2.2.7 Pertussis in Norway

DTwP vaccine was administered to children born between 1952 and 1997. Starting in 1998, DTaP was given using a schedule of 3, 5 and 12 months of age. More recently, booster doses were added at seven years of age, and boosters are also recommended for adults every 10 years. Another booster for adolescents at 15 years of age will be introduced in 2013.

In 2011, serology for diagnostic confirmation of pertussis disease was standardised in accordance with ECDC recommendations. Today, over half of all diagnostic confirmations are done by PCR. Pertussis incidence has been relatively stable at around 100 cases per 100 000 inhabitants for the past decade, with mild peaks every 2–3 years. The highest incidence occurred in adolescents 10–19 years of age.

Incidence among infants and young children <2 years of age doubled during 2011–12. A large peak in pertussis cases was observed between October 2011 and February 2012, in the absence of a reported increase in hospitalisations or outbreaks, which coincided with a substantial increase in testing for *Mycoplasma pneumoniae*. Of 92 confirmed cases, 35 (38%) were unvaccinated and the rest had received 1–3 doses of DTaP in accordance with their ages. The average interval between completing the primary series and disease onset was 2.8 years (minimum 0.9 years, maximum 3.9 years), which demonstrates that immunity had waned relatively quickly. Pertussis P2 serotype emerged as the dominant strain.

### 2.2.8 Pertussis in Finland

In Finland, DTwP was replaced by DTaP in 2005. The routine vaccination schedule in Finland includes a primary series of DTaP, plus boosters at 7 and 15 years of age. The dose given at 15 years of age is TdaP. Vaccination coverage for the completed primary series has been ≥99% since 2000, whereas coverage with the booster at seven years of age is currently around 70%.

Pertussis diagnostic confirmation is based mainly on serology, but testing is not standardised. Culture and PCR are used less frequently, except in infants and young children. A peak in pertussis incidence occurred in 2004, but otherwise incidence has remained relatively stable. The highest incidence of pertussis was observed among adolescents 10–19 years of age. One death attributed to pertussis was reported in 2012, in an individual whose pertussis vaccination had been postponed.

### 2.2.9 Pertussis in Austria

Austria switched from DTwP to DTaP vaccine in 1998. Since 2003, the vaccine has been delivered in the form of a DTaP-IPV-Hib-HepB hexavalent combination. Previously, the routine vaccination schedule consisted of a primary series at 3, 4 and 5 months of age plus a booster dose at two years of age. In 2010, the recommended schedule was changed to 3, 5 and 12 months, with boosters at 7–9 years of age, 18–20 years of age, and thereafter every 10 years. The primary series is provided free of charge, whereas the recommended booster doses are not publically funded.

Pertussis has been a notifiable disease in Austria for 50 years. Case-based surveillance data have been reported since 2009, when ECDC-recommended case definitions were adopted. A small peak in pertussis incidence was observed in 2001, but after 2009 annual incidence has consistently exceeded >5 cases per 100 000 population. During 2009–11, individuals <15 years were most affected, particularly in Styria province. However, many suspected and probable pertussis cases lack laboratory confirmation. Pertussis diagnostic confirmation is based mainly on serology, but testing is not standardised.

## 2.2 Recommendations

- ECDC should implement a comprehensive study across all Member States to examine the epidemiology of pertussis among infants <1 year of age in order to obtain more complete epidemiological, clinical and laboratory data with which to characterise the burden of disease, diagnosis and control of whooping cough. To optimise comparison between countries, hospital admission data might be useful in this respect.
- ECDC should encourage and support studies on the duration of pertussis immunity following natural pertussis disease and vaccination. Populations in countries where high vaccination coverage was only recently achieved should, in theory, exhibit less waning immunity than those where high vaccination coverage was achieved many years ago. This may help to explain why waning immunity is not observed uniformly across the EU/EEA countries.

## 3 Session II: Diagnostic challenges and pitfalls

### 3.1 Molecular epidemiology and surveillance

Whole-cell pertussis (wP) vaccines produced by different manufacturers differ in content and efficacy. This is in part due to limited reproducibility in the manufacturing process such that although wP vaccines contain the same pertussis strains, their immunological characteristics may vary slightly. Acellular pertussis (aP) are, in general, less reactogenic than wP vaccines. However, some aP products differ in composition and the immune response they induce may differ. Coverage in different age cohorts with these different vaccines influences disease transmission characteristics.

Successful disease surveillance requires effective training of, and close collaboration between, clinicians, epidemiologists and microbiologists. The tools required include a sensitive and specific clinical case definition, sensitive and specific diagnostic laboratory tests, and a national reference laboratory to validate test results. Pertussis diagnostic tests are generally expensive, with relatively high sensitivity but relatively low specificity, leading to an excess of false positive results.

Biological methods have evolved with the development of new technologies, but the pertussis pathogen has also been changing through adaptation to environmental stress created by vaccination and other factors. Changing patterns of human contact related to travel, social interaction, crowding and aging also contribute to the changing epidemiology of pertussis disease, making comparisons of disease incidence across the decades potentially misleading.

In 2008, ECDC recommended that Member States adopt standardised case definitions and a case classification scheme for clinically suspect, epidemiologically-linked and laboratory-confirmed pertussis. However, whooping cough can be caused by *Bordetella pertussis* and three other *Bordetella* species – *parapertussis*, *holmesii*, and *bronchiseptica*. Indeed, cases in adults are more often caused by the other species. Therefore, ECDC adapted the recommendations of the Global Pertussis Initiative and proposed a common whooping cough case definition and classification scheme (Table 1).

**Table 1: ECDC-recommended common whooping cough case definition and classification, 2012**

Clinical criteria:

- Any person with a cough lasting >2 weeks and >1 of the following three symptoms:
  - paroxysms of coughing;
  - inspiratory 'whooping';
  - post-tussive vomiting;
- or apnoeic episodes in infant's coughing;
- or in contact with confirmed case.

Epidemiological criteria:

- date of onset of symptoms;
- characteristics of the cough: duration, paroxysms, vomiting after cough, inspiratory whoop, worse during the night, no fever;
- contact with a patient with pertussis with a compatible duration of incubation (7–21 days);
- vaccine status: date of the preceding pertussis-containing vaccination.

Laboratory criteria:

- Direct on respiratory samples:
  - culture,
  - detection of bacterial *B. pertussis* DNA.
- Indirect:
  - detection of specific *B. pertussis* antibodies in the serum of suspected patients.

*Bordetella pertussis* can best be cultured during the first 2–3 weeks of cough when the test is 100% specific and around 70% sensitive among infants (less sensitive in adolescents and adults). It takes 5–8 days to culture *Bordetella pertussis*. Bacterial culture is cheap and simple to perform and is especially useful over the long-term in order to monitor the evolution of the bacterial population and identify antimicrobial resistance.

On the other hand, real-time PCR (RT-PCR) is highly sensitive and rapid, but it is expensive and technically more difficult to perform. The risk of false results due to contamination is high, so that RT-PCR requires dedicated

laboratory space, well-trained technicians, and standard operating procedures (SOPs) to be used effectively. Proficiency testing of laboratories performing RT-PCR is essential to ensure accuracy. In France prior to 2007, RT-PCR was used to test for the presence of *Bordetella pertussis*, but since then laboratories have switched to a highly sensitive test for all *Bordetella*. Therefore, results pre- and post-2007 cannot be compared directly. Furthermore, there is a risk that results may become uninterpretable if SOPs are not standardised as has been observed, for example, in California.

The basis of serological tests for pertussis should be the identification of pertussis anti-PtxIgG in serum. A single specimen with high titre of anti-PtxIgG is highly sensitive and specific for the diagnosis of recent pertussis infection.

The importance of analysing the evolution of the bacterial species such as *B. pertussis* and *B. parapertussis* under vaccine pressure was raised by France, which has been the first country to demonstrate the temporal increase of *B. pertussis* and *B. parapertussis* isolates not expressing pertactin (Bouchez et al, Vaccine 2009; Bouchez et al, CMI, 2011; Hegerle et al, CMI, 2012) and the collection of an isolate resistant to macrolides (Guillot et al, EID, 2012).

## 3.2 Recommendations

- To date, ECDC has issued guidance<sup>4</sup> but no recommendation on the standardisation of age-specific diagnostic methods including culture, RT-PCR and serology. The surveillance of pertussis should be treated similarly to that of measles and rubella, that is, standardised case definitions and reporting requirements should be mandated, laboratories should be proficiency-tested and implement SOPs, and countries should be encouraged to adopt standard disease control strategies.
- For RT-PCR, laboratories should go back to testing for *Bordetella pertussis* to ensure that results are interpretable and comparable between countries and across time periods.
- For serology, Western blot, immunofluorescence and similar diagnostic tests are not standardised and should not be used.
- To improve laboratory cost-effectiveness, the following testing regimen was recommended:
  - Cases with cough <14 days: perform culture and RT-PCR
  - Cases with cough 14–21 days: perform RT-PCR only
  - Cases with cough >21 days: perform RT-PCR on a secondary case or serology

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<sup>4</sup> Available from: <http://ecdc.europa.eu/en/publications/Publications/bordetella-pertussis-guidance-protocol-serological-diagnosis.pdf> and <http://ecdc.europa.eu/en/publications/Publications/Guidance-protocol-PCR-laboratory-diagnosis-bordetella-pertussis-parapertussis.pdf>

## 4 Session III: Vaccines and vaccination strategies

### 4.1 Round table discussion: pertussis immunisation in childhood

The chairperson led the participants through a discussion of alternative vaccination strategies, starting with a review of alternative vaccination schedules, highlighting their respective advantages and disadvantages. Participants noted that proposals to introduce a birth dose or a neonatal dose of pertussis vaccine were considered highly controversial.

Among the participants, a general consensus emerged on vaccination schedules that meet the following three conditions:

- The first dose of pertussis-containing vaccine should be administered at a very early age and in a timely fashion.
- The vaccination schedule should allow for adequate intervals between pertussis doses.
- The pertussis vaccination schedule should be relatively simple and not increase the number of contacts that an infant is required to make, i.e. the schedule should be compatible with schedules recommended for other vaccines so that pertussis vaccine can be administered simultaneously with other vaccines.

Participants noted the need for new pertussis vaccines. However, in the absence of adequate scientific evidence describing the biological basis for waning pertussis immunity, it remains unclear at this stage how to design an ideal vaccine.

### 4.2 Round table discussion: adolescent/adult vaccination (including cocooning)

Participants criticised that many EU/EEA countries do not require a proof of pertussis vaccination (and several other vaccine-preventable diseases, such as measles) for healthcare professionals. As a result, nosocomial spread of pertussis between patients and healthcare workers, and vice-versa, is common. Concrete proposals for mandatory vaccination were unsuccessful because of legal obstacles in many Member States.

In many countries, a substantial proportion of adolescents and young adults lack immunity to pertussis. Reasons are the absence of prior exposure to wild *Bordetella*, the failure to receive vaccination, or waning of vaccine-induced immunity. Although participants placed heavy emphasis on identifying and vaccinating adolescents and young adults, it was noted that this may have limited impact on reducing exposure among very young infants who remain the main focus for prevention.

### 4.3 Round table discussion: vaccination of pregnant women

Participants felt that the vaccination strategies with the best prospects for success were those that provide pertussis vaccination to pregnant or post-partum women and are able to protect the newborn from birth or very soon thereafter.

However, there is a major perceptual barrier in the public health community and the general public regarding the vaccination of pregnant women due to a perceived safety risk. The USA was the first country to recommend pertussis vaccination to pregnant women in certain situations starting in 2008. Universal vaccination of pregnant women in each pregnancy was implemented in October 2011, although uptake remains at extremely low levels. Participants felt that more information is needed on the impact of this strategy in other countries in order to develop effective advocacy for EU/EEA countries.

The United Kingdom guidelines recommend administering one dose of pertussis-containing vaccine from 28–38 weeks gestation, and ideally between 28–32 weeks gestation. In the USA, to maximise the maternal antibody response and passive antibody transfer to the infant, the recommended ideal timing for Tdap administration is 27–36 weeks gestation<sup>5</sup>. There is no requirement to screen patients for recent receipt of Td boosters, despite recommendations that Td should not be repeated too often. The issue of prematurity and maximal transplacental

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<sup>5</sup> Information received after the meeting: Morbidity and Mortality Weekly Record 2013;62:131-136



antibody transfer should be taken into account when setting the gestational age for pertussis vaccination of pregnant women.

Participants highlighted the need to pay close attention to the quality of advocacy, information and social mobilisation when introducing pertussis vaccination for pregnant women. Different antenatal strategies may be needed for pregnant women who go to midwives prior to delivery rather than those who see gynaecologists. Participants also identified a need for a monovalent acellular pertussis vaccine for use in such programmes.

## 4.4 Conclusions

The incidence of pertussis disease has recently increased in many but not all EU/EEA countries. The increased incidence is most notable among infants <1 year of age and adolescents and young adults. There was agreement that improvements in the prevention of pertussis in very young infants, in which the disease is most severe, is a priority.

The epidemiological surveillance of pertussis requires standardisation across the EU/EEA, particularly the standardisation of laboratory diagnostic methods. ECDC has issued guidance but no specific recommendations on the standardisation of diagnostic methods, for example regarding the use of PCR, preferred serologic analyses, or recommendations on which pertussis antibodies to measure. Guidelines for the use of PCR technology should revert to pertussis-specific analyses and unify standard operating procedures (SOPs) throughout the Member States.

There is a high degree of variation among Member States on pertussis vaccination schedules, guidelines for healthcare workers and vaccination strategies for pregnant and post-partum women. Consensus was expressed that ECDC should publish a report of this meeting and use this opportunity to advocate the harmonisation of strategies and SOPs.

The Innovative Medicines Initiative (IMI), a large European public-private initiative for improved public health solutions, has proposed that countries report and analyse registry data in order to contribute to a better understanding of pertussis epidemiology throughout the EU/EEA.

The meeting reached consensus that while confidence in currently available pertussis vaccines remains strong, in the long-term the development of more immunogenic new vaccines, preferably achieving a full schedule with fewer doses, is urgently required.

The United Kingdom decision to vaccinate pregnant women was welcomed. Participants agreed that all Member States should monitor events carefully to see how much impact the implementation of this strategy will have on pertussis incidence among infants <1 year of age, and also if any issues emerge regarding vaccine safety or blunting of the immune response to primary infant vaccination.

# Annex. Expert consultation meeting on pertussis, Hospital Sant Joan de Deu, Barcelona, Spain

## Agenda

Tuesday, 20 November 2012

08:30–09:00 Welcome and registration

Session I. Is pertussis an issue in the EU? Chair: Roel Coutinho, Netherlands, RIVM

09:00–09:10 Introduction, Pier Luigi Lopalco, ECDC

09:10–09:40 Insights from the USA. Perspectives, Thomas Clark, CDC (20' presentation + 10' discussion)

09:40–10:05 Insights from the EU. Perspectives, Lucia Pastore Celentano (15' presentation + 10' discussion)

10:05–10:25 The situation in the Netherlands, Frits R. Mooi, RIVM (10' presentation + 10' discussion)

10:25–10:45 The situation in the United Kingdom, Hellen Campbell, HPA (10' presentation + 10' discussion)

10:45–11:15 Coffee break

11:15–13:00 Epidemiological update from other European countries

Chair: Pier Luigi Lopalco, ECDC

Pertussis epidemiology in Sweden: Rosemarie Carlson

Pertussis epidemiology in Germany: Wiebke Hellenbrand

Pertussis epidemiology in France: Emmanuel Belchior

Pertussis epidemiology in Italy: Stefania Iannazzo

Pertussis epidemiology in Norway: Didrik Frimann Vestrheim

Pertussis epidemiology in Finland: Terhi Kilpi

Pertussis epidemiology in Austria: Daniela Schmid

Discussion 30'

13:00–14:00 Buffet lunch

Session II. Diagnostic challenges and pitfalls, chair: Adoración Navarro, ECDC

14:00–14:30 Molecular epidemiology and surveillance Nicole Guiso, Institut Pasteur (20' presentation + 10' discussion)

Session III. Vaccines and vaccination strategies, chair: Pier Luigi Lopalco, ECDC

14:30–15:15 1. Round table discussion: Pertussis immunisation in childhood. Chair: Donato Greco, Italy

15:15–16:00 2. Round table discussion: Adolescent/adult vaccination (including cocooning). Chair: José Antonio Navarro, Spain

16:00–16:30 Coffee break

16:30–17:00 3. Round table discussion: Pregnant women's vaccination. Chair: Alberto Tozzi, Italy

Session IV

17:00–17:45 Road map: The way forward, chair: Roel Coutinho, RIVM

17:45–18:00 Conclusions and action plan, Pier Luigi Lopalco, ECDC

## Questions to be discussed during the three round table sessions

First session. Pertussis immunisation in childhood.

- More appropriate schedule: 2–4–6 months, 2–4–12 months, 2–3–4 or 3–5–12 months (specific question to Spain, United Kingdom and Sweden/Italy representatives)
- Need for preschool booster (Early or late, one or two?)
- Neonatal vaccination: clinical significance of blunting
- Can we expect benefits from early immunisation (six weeks)?
- Need to vaccinate 'on time' (timeliness of the first two doses of vaccine)
- Different priming according to the first/s pertussis vaccine received
- Need for new and better vaccines: longer duration of protection and higher effectiveness, Th1 priming, fewer number of doses
- Are the newly emerging *Bordetella pertussis* strains an issue?

Second session. Adolescent/adult vaccination (including cocooning)

- Do vaccines prevent subclinical infection and transmission?
- Current data regarding efficacy/effectiveness of vaccination (direct protection and impact in infant morbidity)
- Current data regarding duration of antibodies
- Absence of a serologic surrogate of protection
- Need for adolescent dose?
- Logistic aspects regarding adult vaccination and cocooning: price, periodic boosters, reactogenicity, vaccine uptake, role of cocooning in areas of low pertussis incidence, etc.
- Vaccination of healthcare workers (all healthcare workers or only healthcare workers working in paediatric-neonatology or maternity wards, hospitals and primary care centres)
- Postpartum immunisation: waning of immunity and logistic issues. Absence of protection on the more vulnerable period (first 2–3 weeks of age)

Third session. Pregnant vaccination

- Current data about safety (mother and infant)
- Placental transfer of antibodies (34 weeks of pregnancy)
- Rapid antibody decay in newborns
- Blunting with pertussis, Hib and HBV routine vaccines
- Vaccine uptake (countries' experiences with flu vaccine)
- Best moment to vaccinate women: third trimester?
- How to protect the very premature infant
- Periodic boosters, logistic and economic issues
- Are data available from the USA (November 2011), the United Kingdom (October 2012) and Ireland regarding impact in newborns?