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Pertussis vaccination in pregnancy — current data on safety and effectiveness

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ABSTRACT

Whooping cough/pertussis is a respiratory infection caused by the bacteria *Bordetella pertussis* and *Bordetella parapertussis*. The World Health Organization (WHO) has identified whooping cough as one of the least controlled diseases in all age groups. Clinically, the catarrhal phase manifests itself as flu-like, nonspecific symptoms: cough, runny nose, mild fever, which, regrettably, makes early diagnosis difficult. The severe course is more specific (an audible inspiratory whoop followed by paroxysmal cough and vomiting). Currently, in Poland the highest percentage of cases is observed in children aged 0–4 years, followed by children over 15 years of age, with peaks among teens and seniors. Notably, hospitalization, morbidity and mortality rates are considerable in children (especially infants). Vaccinating pregnant women against pertussis provides approximately 90% protection to infants in their first two months of life. It is an effective form of preventing pertussis in infants. Moreover, it is safe for pregnant women and their children. The Advisory Committee on Immunization Practices (ACIP) recommends Tdap vaccination to every pregnant woman between 27–36 weeks of pregnancy.

Key words: effectiveness; pertussis; pregnancy; safety; vaccine

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INTRODUCTION

Whooping cough/pertussis is a respiratory infection caused by the bacteria *Bordetella pertussis* and *Bordetella parapertussis* [1]. The infection is spread by droplets (*e.g.*, through coughing or sneezing). Although there is an effective vaccine, the World Health Organization (WHO) identified whooping cough as one of the least controlled diseases across all age groups. However, the most vulnerable groups are young children and adolescents. According to the WHO, whooping cough epidemics appear cyclically every 3–4 years. Pertussis is highly infectious, with one person infecting up to 17 susceptible people, and untreated people may be infectious for more than three weeks after the onset of cough. The incubation period of pertussis is between one and three weeks. Clinically, the milder catarrhal phase manifests itself as flu-like, nonspecific symptoms: cough, runny nose, mild fever, which, regrettably, makes early diagnosis difficult. Conversely, a severe course, called the paroxysmal phase is more specific (an audible inspiratory whoop followed by paroxysmal cough and vomiting) [1, 2]. Early antibiotic therapy may alleviate symptoms (when implemented before the onset of the paroxysmal stage). It should be noted that vaccination is the most cost-effective form of preventing whooping cough epidemics [2].

In Poland, mass vaccination against pertussis was launched in 1960. By that time, tens of thousands of cases had been reported, with whooping cough being one of the most common causes of death in children under the age of one. The number of reported cases decreased below 500 per year in the 80s. Regrettably, an increase in the incidence was recorded in the mid-90s. Therefore, in 2003, a booster dose of vaccines was introduced in Poland at six years of age. Currently, there is a high incidence of whooping cough with the cyclicality of the disease. Year 2012 was a critical for 40 years, with 4,684 cases being recorded, including 1,497 people who required hospitalization. Currently, the highest percentage of cases is observed in children aged 0–4 years, followed by individuals over 15 years of age, with peaks among teens and seniors [2–4].

In 2014, a total of 5.1 million cases of whooping cough and 85,900 deaths were estimated in children under 12 months old worldwide. Over 80% of cases and 95% of deaths occurred in low- and middle-income countries, where vaccination coverage was low [2]. The European Centre for

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Disease Prevention and Control (ECDC) report on Pertussis showed that 35,627 cases of the disease were registered in 30 European Union/European Economic Area (EU/EEA) countries in 2018. Young people aged 15 and above accounted for 62% of all cases. However, infants constituted the largest group at 44.4 per 100,000 population. As of August 2020, eight countries implemented a program of the vaccination of pregnant women and in five countries the vaccination program included a minimum of one booster dose of pertussis vaccination in persons over the age of 18 [5].

An increase in whooping cough incidence has been observed in recent years due to the rapid waning of post-vaccination immunity after vaccination with acellular vaccine in comparison with the previously used whole-cell vaccine [6].

WHO IS EXPOSED TO SEVERE AND COMPLICATED WHOOPING COUGH?

Whooping cough may occur at any age, but the disease is especially virulent and life-threatening in infants [6]. The manifestations of the disease may be mild in adults and adolescents and is often undiagnosed, increasing the chances of disease spread in the environment. This, in turn, contributes to the possibility of transmitting the infection to infants who may not be vaccinated [5]. Children (especially infants) are a group in which hospitalization, morbidity and mortality rates are particularly high. Non-specific symptoms in children make the diagnosis difficult. In young children whooping cough may lead to complications such as apnea, seizures, encephalopathy, pneumonia and even death [2].

PERTUSSIS PREVENTION IN PREGNANT WOMEN

Vaccinating pregnant women against pertussis provides 90% protection to infants in their first two months of life, that is, until they may be vaccinated [2, 7]. Vaccinating pregnant women against whooping cough was initiated in response to outbreaks after 2010, when an alarming, worrying number of deaths of young children was recorded in the US and the UK. In 2015, the WHO recommended that pregnant women and infants over six weeks old should be vaccinated against whooping cough. It is impossible to vaccinate children earlier, as the presence of maternal antibodies may suppress post-vaccination immunogenicity. Numerous studies showed that the cocoon strategy (vaccination of people in direct contact with exposed children) and vaccination after delivery were ineffective in protecting children [2].

A retrospective cohort study involving 148,981 children born in Northern California, the USA, conducted between 2010 and 2015, revealed that the immunization coverage of pregnant women against tetanus, diphtheria and pertussis (Tdap) increased from 11.9% in 2010 to 87.4% in 2015, and the confirmed vaccine efficacy was 91.4% in infants under two months of age [6, 7].

In early infancy, when the child may not yet be vaccinated against pertussis (Tdap) the only protection is provided by antibodies passed from the mother during pregnancy [6]. If the pregnant woman was not vaccinated against whooping cough, the level of antibodies drops significantly at six weeks of age and is undetectable around four months of age [8]. In contrast, pregnant women vaccinated against Tdap transmit antibodies to the fetus, so that high levels of antibodies to pertussis are maintained in infants up to one dose of Tdap vaccine [9]. Numerous researchers emphasized that vaccinating pregnant women against whooping cough provided a more effective protection for the infant than the cocoon strategy in which the closest contacts are vaccinated [6, 10–13].

Currently, the only safe vaccines administered to pregnant women are acellular vaccines, which contain highly purified individual B pertussis components [2]. Infants are protected by immunoglobulins that passively pass through the placenta or into human milk. The half-life of maternal immunoglobulin is 42 days. Numerous studies confirmed significantly higher levels of anti-whooping cough immunoglobulins in the children of mothers vaccinated during pregnancy [14–16].

PERTUSSIS VACCINE SAFETY AND EFFECTIVENESS IN PREGNANCY

The latest systematic review of the literature assessing the efficacy and safety of pertussis vaccination with Tdap during pregnancy, including Medline, Embase and clinicaltrials.gov in 2010–2019, conducted by the Immunization Unit of the Koch Institute in Berlin, finally qualified 22 studies (randomized, cohort, and clinical control). This included 14 studies on the safety of Tdap in pregnancy and the fetus (1,400,000 pregnant women in total) and eight efficacy studies on the prevention of whooping cough in infants during the first three months of life (855,546 mother-infant pairs in total) [17]. Those studies showed that vaccination with Tdap during pregnancy did not increase the risk of stillbirth [18–22], neonatal death [20, 21], preterm birth under 37 weeks gestation (interestingly, according to some researchers, the frequency of deliveries before 37 weeks was lower among women vaccinated against whooping cough during pregnancy) [18, 19, 21–26], low birth weight (both under 2500 g and under 1500 g) [19, 20, 25] or birth defects [18, 19, 21, 22, 24, 27] in a child. Safety was also proved as regards the risk of pre-eclampsia and eclampsia. Two studies even showed a reduction in the risk of pre-eclampsia [20, 23, 25, 27].

Several studies showed a trend towards a slightly higher incidence of chorioamnionitis in Tdap-vaccinated pregnancies than in unvaccinated women [the relative risk

(RR) ranged from 1.04 (95% CI: 0.98–1.11) to 1.53 (95% CI: 0.80–2.90)], but only in three studies were the estimates statistically significant [19, 21, 24, 25]. Four studies assessed the incidence of fever after Tdap vaccination in pregnant women. In general, fever occurred in 0.03–3% of pregnant women and was more common in those vaccinated against whooping cough than in unvaccinated ones. The authors pointed out, however, that the accepted definition of fever varied in different studies [18, 26, 27].

A retrospective cohort study assessed the association between the vaccination of pregnant women with Tdap vaccine and the subsequent development of autism spectrum disorders (ASD) in children. It included 81,993 children born in single pregnancies in 2011–2014 in Kaiser Permanente Southern California hospitals. On average, vaccination was performed at 28 weeks of gestation. ASD was diagnosed in 1.6% (1,341) children, and the follow-up period was between 1.2 and 6.5 years. The study showed that the vaccination of pregnant women with Tdap did not increase the risk of ASD in the offspring [HR: 0.85 (95% CI: 0.77–0.95)] [28]. A recent study by the same researchers, including over 85,000 children born in 2011–2014 showed that the vaccination of pregnant women with Tdap vaccine at any time during pregnancy did not increase the risk of attention deficit hyperactivity disorder (ADHD) in their offspring. ADHD was diagnosed in 1% (882) of children and there was no correlation between vaccination with Tdap during pregnancy and an increased risk of ADHD in the children of vaccinated women [HR: 1.0 (95% CI: 0.88–1.14)] [29].

The authors of the study concluded that although fever and chorioamnionitis were diagnosed slightly more frequently in women vaccinated with Tdap during pregnancy, vaccination was not found to increase the risk of clinically significant consequences for the pregnant women and their children. Due to the generally low quality of data, the authors recommended to continue the monitoring of the safety of Tdap in pregnant women, including the occurrence of chorioamnionitis and its sequelae [19, 21, 24–27].

Regarding the effectiveness of Tdap vaccination during pregnancy, the vaccination was found to reduce the risk of developing laboratory-confirmed pertussis by 78–93% [6, 30–32] in the first two months of life and by 69–91% [30, 31, 33] in the first three months. Additionally, having received Tdap vaccine up to two years before the current pregnancy was also associated with some degree of protection [6].

WHEN TO GET VACCINATED?

Regrettably, no international consensus has been reached on the most appropriate time to vaccinate pregnant women. Recommendations as to when to vaccinate pregnant women vary by organization and range between 16 and 38 weeks of pregnancy. The Joint Committee on Vaccination and Immunization (JVCI, UK) recommended vaccinations between 16–32 weeks of gestation (ideally after 20 weeks). In contrast, in 2013, the Advisory Committee on Immunization Practices (ACIP) issued recommendations that recommended the Tdap vaccination of every pregnant woman, regardless of the time of the previous vaccination, between weeks 27–36 of pregnancy to ensure the maximum possible transplacental transfer of antibodies [2, 34]. In Poland, the Minister of Health identified groups for which vaccination against diphtheria, tetanus and pertussis is recommended. They include, among others, pregnant women between 27 and 36 weeks of pregnancy and people from the environment of newborns and infants up to 12 months of age [35]. A vaccination after 38 weeks of pregnancy may not ensure the transfer of antibodies across the placenta, so it may be unable to provide the infant with immunity. However, it may prevent a pregnant woman from becoming ill, which might later protect the child [2].

CONCLUSIONS

According to the ECDC and the WHO pertussis remains a challenge for public health in Europe. Therefore, high vaccination coverage is necessary to provide indirect and direct protection to infants and young children, i.e., groups that manifest the most severe symptoms. Booster doses in adolescents and adults, healthcare professionals and pregnant women should be considered. The vaccination of pregnant women is effective in preventing pertussis in infants and is safe for pregnant women and their children.

Conflict of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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