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New challenges in maternal and neonatal preventive strategies. Invest in vaccination recommended in pregnancy: pertussis

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ABSTRACT

This document related to the administration of pertussis vaccines on pregnant women has been created as Position Paper for SIGO, an Italian Society of Gynecology and Obstetrics, and includes the most recent information on prevention of pertussis disease and neonatal morbidity and mortality correlated to the infection.

Note: In this paper, with respect to the Italian version, the sections quoted from the "Piano Nazionale di Prevenzione Vaccinale (PNPV) 2017-2019" have not been reported as such, but their explanation is included in the text.

Keywords: Bordetella Pertussis vaccine; acellular vaccine; Vaccination in pregnancy; maternal immunization; neonatal immunization; neonatal protection; safety of vaccine; placental passage of igG; cocooning strategy; pertussis complications

SOMMARIO

Negli ultimi anni si è rilevato un aumento del numero di casi di Pertosse. La somministrazione del vaccino per difterite-tetano-pertosse (dTpa), durante il terzo trimestre di ogni gravidanza, deve essere considerata la migliore strategia protettiva contro le possibili complicanze che il batterio Bordetella Pertussis può causare al nascituro, soprattutto durante i primi mesi di vita.

La vaccinazione materna con dTpa dovrebbe esser considerata la principale strategia di immunizzazione per il neonato. In modo complementare, la "Cocooning strategy" dovrebbe essere adottata. Essa consiste nel vaccinare il padre e i parenti prossimi, che hanno un contatto diretto e quotidiano con il neonato, in modo tale da garantirne l'ottimale protezione.

INTRODUCTION

Although in the last decade neonatal mortality is decreased, a huge percentage of cases occur during the early neonatal period, and among the causes there are also infectious ones.

Pregnant women and neonates are more vulnerable to some infections, that turned out to be associated with increased morbidity and mortality.

The fact that vaccination during pregnancy, also known as immunization, is able to guarantee protection from some infections, either in pregnant women, fetuses and also neonates, is not a new scientific discovery. This is due to maternal antibodies, which are transferred through the placenta or breastfeeding.

Regarding the preconceptional period and all the preventive measures, it is possible to distinguish vaccines that have to be carried out in:

- Preconceptional period
- Pregnancy
- Breastfeeding

These recommendations have been in place for a long time, and are based on scientific evidence, expressed by National and International Autorities. These recommendations concern vaccinations advised in pregnant women and those that are contraindicated during the gestational period.

All fertile women, and in general women in the preconceptional period, should be protected for varicella, measles and rubella through vaccination.

There is an associated embryo-fetal risk in case of an infection acquired for the first time during gestation, especially during the early stages.

In case of varicella infection, maternal and neonatal risk is elevated also during the peripartum period.

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If a woman is not yet immune against these infections, it is fundamental to administer the vaccine soon after the delivery.

Vaccines available during pregnancy include:
- recommended vaccines: influenza, diphteria, tetanus, pertussis (dTpa)
- vaccines administered only in case of risk factors: hepatitis A and B, yellow fever, meningococcus

Regarding pertussis vaccination during pregnancy, recommendation to undergo this procedure was established by WHO, Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), American College of Obstetricians and Gynecologists (ACOG), ACIP or British Joint Committee on Vaccination, SAGE Committee. Similar recommendations have been introduced in 35 Countries worldwide, like Canada and Australia, and acquired by National Health Authorities in Europe, including Italy.

With respect to vaccination in fertile women, the italian policy 2017-2019 ("Piano Nazionale di Prevenzione Vaccinale (PNPV) 2017-2019") comprises an active proposal for measles-mumps-rubella and varicella in the preconceptional period, for rubella and varicella (or both) during the post-partum, and for influenza, diphtheria-tetanus-pertussis during pregnancy.

THE PROBLEM: PERTUSSIS

Pertussis is a respiratory disease caused by Bordetella pertussis, a Gram-negative coccobacillus that infects ciliated epithelial cells of the human respiratory tract. This disease is highly infectious and is transmitted via Flügges' droplets. It affects all age groups, in particular infants, representing one of the major causes of death within 1 year of age. Incubation period is 7.10 days (ranging between 1 and 3 weeks). The disease includes three stages: catarrhal stage, paroxysmal stage (with characteristic whooping cough) and convalescent stage.

Clinical features are related to the age at which the patient is infected, to the immune system status, and to the timing of antibiotic therapy. Severity is inversely proportional to the age of the patient: in very young children, pertussis can initially have clinical manifestations other than cough, such as apnea and cyanosis, and it can determine severe respiratory, neurological and nutritional complications. Pulmonary complications are the most frequent (around 10% of cases) and can be fatal. Damage to the cerebral cortex can be so severe as to determine mental retardation, transient or permanent blindness, deafness, or nerve paralysis. Encephalitis is particularly concerning due to its association with death or permanent sequelae. In immunized patients, independently from the subject's age, pertussis can have an aspecific and less severe course, sometimes manifesting only as a persistent cough, without the characteristic whooping. These cases are not easily diagnosed and become an important source of transmission of infection, especially in infants within their first year of age, because of incomplete primary vaccination (Image 1). Etiologic diagnosis of pertussis requires laboratory investigations that differ depending on the time elapsed from the manifestation of cough. Within the first 2 weeks it is based on isolation of B. pertussis on nasopharyngeal samples; up to 4 weeks molecular analysis via PCR can be performed; at a later time, it is indicated to perform serologic analysis to look for antibodies against pertussis toxin. Antibiotic therapy with macrolides can prevent or mitigate clinical manifestations if administered during the incubation period or the initial catarrhal stage; it does not change the clinical course of disease if administered during the paroxysmal stage, even if it favors the elimination of the bacteria from the rhinopharynx, thus reducing transmission. The convalescent phase of disease can last several months. Over the last 20 years, susceptibility to pertussis increased, including adolescents and young adults. The WHO estimated that in 2008 there have been about 16 million cases of pertussis worldwide, of which 95% in developing countries and about 195.000 children died because of the disease. In recent years an increase in pertussis cases was recorded even in Countries with a high percentage of vaccination coverage, such as Australia, Canada, USA and UK, especially concerning neonates under 3 months of age, with consequent increase in mortality due to the disease. The source of infection has been identified in those closer to the neonates: the parents in more than half of the cases and siblings in 20%. Natural or acquired immunization to pertussis is not lifelong: it is believed to decrease after 4-12 years. For this reason, vaccination against pertussis has to be periodically repeated.

In Italy: accurate epidemiological data on pertussis are lacking due to a sub-optimal surveillance by health workers and frequent sub-diagnoses and/or sub-notification. The latter can be attributed to various factors: difficulty in reaching a diagnosis of pertussis due to an atypical clinical presentation, failure to confirm diagnosis

via laboratory analysis, scarce availability on the national territory of laboratories that offer diagnostic tests for this disease. All these factors contribute to the poor perception of diffusion of pertussis in Italy among health workers, pediatrician and general practitioners. Recent investigations conducted by the "Istituto Superiore di Sanità (ISS)" confirmed that B. pertussis is widely spread in the Italian population, even in adults. A seroprevalence study compared the percentage of recently infected adults recorded in 1996-97 with those of 2012-13. The major prevalence of "recent pertussis" was recorded in the age group 20-29, although what is of particular interest is the increase of subjects recently exposed to the disease in the age group >60, where the percentage grew from 18.6 to 38.8% ($p<0,0001$). As proof of these data, in the period 2001-2014 more than 7000 hospital admissions for pertussis have been recorded: 63.3% in patients <1 year of age (hospitalization rate = 59/100.000). As of August 2018, there have been 2 cases of pertussis related death within the first two months of life: there was no record of immunization during pregnancy. These 2 cases add to 6 more cases of neonatal deaths previously recorded: all neonates were less than 3 months old, 2 were born pre-term. In all cases, admission diagnosis was of bronchiolitis, leukocytosis and bilateral pneumonia. 5 of 6 neonates had severe pulmonary hypertension; 4 were not vaccinated; 1 had received only the first dose and in 1 of the 2 pre-term neonates vaccination was deferred.

Neither mother had received pertussis vaccination during pregnancy, nor over the 2 years preceding pregnancy. Because epidemiological data show that in children less than 1 year of age, the source of contagion is usually from an adult relative (32% from the mother, 19% from the father, 29% from siblings), diffusion of infection can be stopped only by reaching a high vaccination coverage among the general population. The major objective of pertussis vaccination is to reduce the risk of severe childhood diseases.

THE SOLUTION: PERTUSSIS VACCINATION DURING PREGNANCY

An adult who contracted pertussis can infect a not yet vaccinated neonate. The first few months of life represent a critical period; because of the absence of protection, there is a higher risk of developing an infection and severe respiratory and cerebral complications, which can be fatal. Vaccination at birth is not a valid option because the neonatal immune system is incapable of antibody production for the first 2 months. Preventive strategies to reduce the risk of pertussis in the first year of life are:

- Maternal immunization via vaccine administration either during pregnancy or during breastfeeding
- "Cocoon" strategy, as a complementary familial strategy

MATERNAL IMMUNIZATION VIA VACCINATION

The procedure is usually performed during the third trimester of gestation, and it stimulates maternal antibody production that are passed to the fetus through the placenta. This practice has proven safe and highly effective in protecting neonates from pertussis. Based on the fact that antibody-mediated response to pertussis decreases rapidly over time, Recommendations suggest that all pregnant women undergo pertussis vaccination in the third trimester, independently from their immune state and maternal antibody level. Every woman is advised to repeat the procedure at every pregnancy, even if consecutive. If the procedure is not performed during pregnancy, the vaccine can be administered during the breastfeeding period in order to obtain an antibody transfer through the maternal milk. The aim is still maternal vaccination during the third trimester because of higher efficacy in protecting the neonate. Recent studies showed that it is 85% more efficacious with respect to post-partum vaccination in preventing pertussis within the first 2 months of life.

IMMUNE BASIS OF PREGNANCY AND NEONATAL LIFE AND PRENATAL VACCINATION

The purpose of maternal immunization is to increase specific antibody concentration to increase their passive passage to the fetus and reduce its susceptibility to infections between birth and the time at which vaccination can be performed. The lack of exposure to antigens during prenatal life determines an immature adaptive immune system that cannot produce an adequate protective response to pathogens. After birth, maternal antibodies are transferred to the neonate transplacentally and through breastfeeding. Their level in the newborn decreases in about 6 months.

During pregnancy, the immune response results from the combination of signals and responses originating from both the maternal and feto-placental immune system. Physiologic and immune changes during pregnancy determine in the mother tolerance toward the fetus but also an increased susceptibility to infectious diseases.

In fact, during pregnancy the immune system seems to be "modulated" rather than "suppressed": the ability of the immune system to induce new responses and its memory are preserved, after either natural infection or vaccination, such as in a non-gravidic state. Changes in the Th1-Th2 system make it so that T-helper cells act through the Th2-mediated response (humoral immunity), rather than Th1 (cell-mediated immunity), stimulating B-lymphocytes and downregulating cytotoxic T-lymphocytes, and augmenting production of antibodies to be transferred to the fetus. The evaluation of maternal immunity to pertussis via antibody dosage and IgG values is not indicated because the results do not change the Recommendations to undergo vaccination during the third trimester of gestation. Studies demonstrated that immune responses in pregnant women are the same as any healthy adult: there is a peak after 1 month from pertussis vaccination and a decline of specific antibodies over 1 year. A recent Canadian study on 1752 plasma samples (from bio-bank) of women in their second trimester of gestation showed that in more than 95% of cases the IgG antibody titer was low (<35 IU/ml).

Indication to pertussis vaccination during each pregnancy is based on the evidence that antibodies undergo a rapid decline, so that their concentration is not adequate to guarantee neonatal protection.

Women vaccinated either before pregnancy or during a previous one, even if very close in time, cannot guarantee high and adequate antibody levels to passively protect the neonate.

TIMING AND MODALITY OF DIPHTHERIA-TETANUS-PERTUSSIS VACCINATION IN PREGNANT WOMEN

Recent evidence sustains the idea that the placenta has immune properties that modulate and interact with maternal immune responses. Maternal immunoglobulins, exclusively IgG, pass through the syncytiotrophoblast and reach the fetus. The major passage takes place during the third trimester, in particular over the last 4 weeks of gestation. At term of gestation, IgG concentration in fetal circulation is higher than that of the mother due to active passage. Many factors can influence this mechanism of transport, among which: placental integrity, non-infectious maternal pathologies, and regarding maternal immunization, the timing of vaccination and total concentration of IgG. Pertussis vaccination is performed via dTpa (diphtheria-tetanus-pertussis) vaccine.

Concerning the gestational age at which it is advised to perform vaccination, current data supports the recommendation to undergo the procedure between weeks 28 and 32 of gestation (third trimester) because of higher antibody level in both maternal and fetal circulation.

The rationale behind this choice is based on the fact that specific antibodies concentration increases within the first 2 weeks after maternal immunization, so that specific IgG passing through the placenta would be at optimal level in neonates delivered at term. Adequate levels are not unquestionably reached by pre-term newborns. There would be advantages in performing vaccination during the second trimester, because there would be a higher antibody titer against pertussis in neonates born both at term and pre-term, in addition to providing more time for antibody passage during prenatal life and a higher amount of IgG in fetal circulation. Studies related to maternal vaccination in early pregnancy phases are few and do not support the choice of performing it during this period. Regarding the teratogenic risk related to pertussis/dTpa vaccination in the periconceptional period or during the first trimester, if there is no awareness of pregnancy, there is no reason to believe that it is increased. The risk can be considered unvaried with respect to that of the general population, both concerning congenital anomalies and miscarriage. Data derived from an English study, correlated to an emergency vaccination protocol, showed that there is significant protection also with delayed administration of the vaccine within 14 days from birth. According to the "Australian Technical Advisory group on Immunisation", if the vaccine is administered before the 28th week of gestation, it is not necessary to repeat it. In 2012 in the USA, the "American Committee of Immunization Practice" recommended dTpa vaccination for all pregnant women during every pregnancy. Efficacy of this vaccination against neonatal pertussis has proven to be 85% more effective than post-partum vaccination. Introduction of vaccination in the United Kingdom scored high

adhesion rates, 60% of pregnant women, leading to 91% of protected children under 3 months of age. In Argentina, dTpa vaccination administered to more than one million pregnant women lead to a drastic reduction of neonatal mortality (83.7%). Whenever pertussis immunization has not been reached during gestation, breastfeeding represents another valid modality of antibody production stimulation through vaccination. In this case the major immunoglobulin component to be passed to the baby via colostrum and milk is represented by IgA, but also some IgG and IgM: these will guarantee protection during the first six months of life. Maternal antibodies persist in the newborn for about 36-55 days.

"Immunologic BLUNTING". Some studies underlined a potential interference between maternal IgG and the neonate, hypothesizing responsibility of the former in inhibiting neonatal immune response to the same antigens after primary vaccination. It is demonstrated that this effect does not persist after booster dose. Clinical relevance of these findings is uncertain, but epidemiological data of countries that implemented maternal immunization don't show a negative impact on specific protection to pathologies such as pertussis.

"Cocooning" as a complementary strategy. The so-called "Cocoon" strategy implies the immunization of the neonate's close relatives, since they can be the source of infection. To this end, vaccination of health workers is also suggested. Recent evidence indicates how the "Cocoon" can have a positive impact on disease prevention, especially if high coverage is quickly achieved. Nevertheless, maternal immunization is still better in terms of cost/effectiveness and general impact with respect to "Cocooning", since the latter requires multiple doses for parents and relatives, making the strategy difficult to enforce in many countries.

Pertussis vaccines characteristics. Pertussis vaccine used in most of Western countries, including Italy, are "acellular" vaccines composed of purified antigens, not "whole cells" of B. Pertussis. Acellular pertussis vaccines can contain up to five different antigens that can induce circulating antibodies (IgG) production directed at both the pertussis toxin and other bacterial components (pertactin, filamentous hemagglutinin, fimbriae). Since their development in the early 90s, pertussis vaccines have been associated to those for diphtheria and tetanus. The rationale behind this association lies in the need for all three vaccinations to be periodically repeated, therefore adult booster doses are trivalent acellular vaccines with reduced antigenic quantity (dTpa) with respect to those for pediatric use (DTPa). Vaccines need to be refrigerated at 2-8°C to avoid freezing, which inactivates them. Administration in the adult consists of an intramuscular injection of 0.5ml in the deltoid muscle. Two different metanalysis showed higher efficacy of vaccines containing 3-5 components with respect to those with 1-2 components. The most relevant experiences, in terms of numbers, on dTpa during pregnancy are those conducted in the USA Argentina and United Kingdom, which used exclusively pertussis vaccines containing 3 to 5 components.

Vaccine safety. Regarding vaccine safety during pregnancy, we can refer mainly to two recent Reviews published in 2017. Data related to maternal, fetal and neonatal safety support the use of pertussis vaccination during pregnancy. dTpa vaccination is performed at the gestational age in which there is a reduced risk of both inflammatory response and teratogenic effects.

The safety of maternal vaccination is evaluated based on the possible adverse outcomes:

- Maternal complications
- Obstetric complications
- Feta-neonatal complications

Maternal complications. Maternal adverse manifestations related to the vaccine consist of local and systemic events. Evidence did not show an association between pertussis/dTpa vaccine administration and the increase in maternal adverse effects severity. Few local reaction and pain at the anatomic site of injection are reported.

Obstetric complications. In those patients who underwent vaccination with respect to those who did not receive it, available evidence demonstrates that there is not an increase in severe obstetric antenatal complications, such as hypertensive diseases (preeclampsia and eclampsia) or preterm delivery. Regarding the risk of developing chorioamnionitis, an observational study showed a higher risk in those women who received vaccination with respect to the ones who did not received it (6.1% in vaccinated women, 5.5% in not-vaccinated women). Authors consider the data to be correlated to a "residual confounding" (Adjusted Relative Risk 1.9, 95% CI 1.13-1.26), due to fact that the study did not demonstrate an association between pertussis vaccine administered in the prenatal period and the increased premature delivery risk. This is an important clinical consequence related to chorioamnionitis. The previously mentioned

complication was not supported in 2 other observational studies conducted on a small sample.

Fetal and neonatal complications. There is no available evidence showing the possible association with an increased risk of relevant fetal and neonatal complications (such as fetal or neonatal loss, preterm delivery, restricted intrauterine growth -LBW (Low Birth Weight) e SGA (Small for Gestational Age) - and congenital anomalies) in those patients who received vaccination at the end of the second trimester or during the third trimester.

There are not data on the correlation between dTpa vaccine during pregnancy and the increased risk for autism disease.

Co-administration. It is possible to administer dTpa and influenza vaccine together in the same pregnant patient. Despite the lack of specific evidence, the Guide to Vaccination Contraindications 2018, approved by NITAG (National Immunization Technical Advisory Group) and by "Consiglio Superiore di Sanità", stated that anti-D specific immunoglobulins in non-immunized pregnant women with negative Rh factor and a Rh-positive partner can be administered together with any inactivated vaccine, including dTpa, in different sites or at any interval between the doses.

COUNSELING THE PREGNANT WOMAN

Maternal pertussis immunization, as well as seasonal influenza vaccine, represents a preventive measure that impacts both the mother and the neonate.Although maternal pertussis and influenza immunization is advantageous, it is still not routinely done, and it is often extremely limited due to cultural and organizational barriers. There are many factors that influence maternal acceptance of pertussis vaccination, such as level of education, working conditions and knowledge of the safety of immunization during pregnancy. From the patients' point of view, vaccinations are perceived as limited both in terms of safety and efficacy, not necessary or even risky for them and the fetus or neonate. Lack of knowledge concerning the risks of disease and safety and efficacy of vaccines, has been often quoted as a barrier during pregnancy, highlighting the need for a clear education in this field. Pregnant women are given numerous behavioral indication and prescriptions, but in this scenery, vaccinations are not perceived as a priority, especially if not clearly recommended by the doctor or the obstetrician. Studies carried out in countries such as Belgium and England, with high gestational pertussis vaccine coverage, showed that the most effective recommendation was the one given by the gynecologist or GP. Among English obstetricians the majority recognized the importance of the above-mentioned vaccinations during pregnancy but desired a more extensive access to efficacy data; only 1 out of 4 felt adequately trained to discuss this issue. Communication strategies designed for pregnant women, should be oriented on the risk/benefit of immunization with respect to the disease, and on how the former protect the neonate. This information is fundamental for the pregnant woman to decide to undergo vaccination. Vaccinations must become a pillar of prenatal cure and misunderstandings between health personnel and patients on what to do must be eliminated. Recommendations by health workers are the most significant factor in deciding whether to undergo vaccination or not; in fact, compliance to vaccination is between 5 and 50 times higher if the recommendation comes from the doctor or another health worker, who must also ensure that the woman is protected for varicella, rubella and measles in the prenatal period; if not, recommends this vaccination in the post-partum period. It is important to know current recommendations and a correct communication strategy has to be adopted to communicate with confidence this knowledge to the patient. The use of illustrated pamphlets is helpful when talking to the future mother; these can be found on scientific societies websites such as that of the Center for Disease Control and Prevention (https://www.cdc.gov/pertussis/pregnant), the Public Health England and the Italian Ministry of Health. Technical sheets on vaccines should be considered as reference during the conversation with the pregnant woman, pointing out that the data contained in them have been approved at the European level by the European Medicine Agency (EMA). The American College of Obstetricians and Gynecologists (ACOG) made a table containing all the information on vaccinations that can be administered during pregnancy, such as influenza, diphteria-tetanus-pertussis, and also on those that are contraindicated (such as live attenuated vaccines) or those that should be administered post-partum.

ITALIAN VACCINATION POLICY 2017-19

The italian vaccination policy 2017-19, introduced some innovations such as dTpa vaccine during pregnancy. This decision originated because of an increase in pertussis cases among the Italian population. Similar epidemiological data are observed regarding the levels of seroprotection against diphteria and tetanus. These pathologies are toxin mediated and need individual protection since herd protection cannot be established. Every year in Italy around 50 cases of tetanus are notified, 80 % of which in subject > 64 years of age, mainly women, and with a mean of 21 deaths/year. Vaccine coverage and seroprotection decrease with increasing age: it is estimated that more than 74% of subjects over 65 years of age are not protected against tetanus. As far as diphteria is concerned, a recent European study showed how in Italy the percentage of non-protected individuals is about 45% in the adult population, rising to 73% between 65-74 years of age. The PNPV 2017-2019 includes, free of charge, the dTpa and influenza vaccines among those recommended during pregnancy.From an organizational point of view, it is impossible to draft a unique operative modality that guarantees reaching all pregnant women in the adequate gestational period to offer vaccinations. A regional format should be identified in order to adequately inform women and have them consciously adhere to the proposed vaccinations. The gynecologist must have an active role, together with the Public Health system, and other figures such as pediatricians, GPs and obstetricians, to define a course of action concerning gestational vaccination programs.

CONCLUSIONS

Gestational vaccination plan must be considered an efficient and necessary strategy to protect the mother, the fetus and the neonate. In particular, during pregnancy the following vaccinations should be recommended:

- Pertussis (dTpa) vaccine
- Seasonal influenza vaccine

Given the increased number of pertussis cases, maternal administration of dTpa vaccine has to be considered the best protective strategy for neonates against B. pertussis infection during the first few months of life. It can also protect from possible related complications, sometimes severe and/or lethal, that can damage the non-vaccinated newborn that cannot undergo immunization yet. There is no evidence related to maternal immunization regarding maternal risks, increase of obstetrical complications and/or perinatal complications. There are no side effects for the fetus or the newborn, who in turn will be protected thanks to the transplacental passage of maternal immunoglobulins during the prenatal period. Better awareness and training on recommendations to give pregnant women are necessary among health workers. Easier access to vaccinations is also needed. Pregnant women need clear information and reassurance in order to understand how to protect their child and themselves through gestational immunization. Common objective for both health workers and future mothers is to protect so that preventable infections don't become causes of "near miss" or of increased morbidity and mortality.This paper was written with the aim of increasing immunization rates during pregnancy in relation to pertussis through dTpa vaccination during gestation.

KEY POINTS

- Vaccination during pregnancy is defined as maternal immunization, and its final aim is neonate protection.
- The vaccine used in Italy for maternal immunization, is not monovalent, it is a combined vaccine that includes Diphteria toxoid - tetanus toxoid and acellular pertussis (dTpa).
- Vaccine has to be administered to all pregnant women during the third trimester, between the 28 and 32 weeks of gestation or in any case 4 weeks before the delivery.
- Maternal immunization has to be performed during each pregnancy; in the same woman it must be repeated in consecutive pregnancies, even if separated by short time interval.
- The control of maternal immunologic status for pertussis (neither for tetanus nor diphteria) through antibodies levels dosage is not strictly indicated, because this data cannot change current recommendations.
- Influenza vaccine can be administered concomitantly with the dTpa vaccine.

CONFLICT OF INTEREST

There is no conflict of interest.

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