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Review

Acellular pertussis vaccine use in risk groups (adolescents, pregnant women, newborns and health care workers): A review of evidences and recommendations

Angela Bechini, Emilia Tiscione, Sara Boccalini, Miriam Levi, Paolo Bonanni*

Department of Public Health, University of Florence, Italy

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ABSTRACT

Background: Pertussis is an acute infectious illness, caused by the bacteria *Bordetella pertussis* and commonly known as "whooping cough". Waning immunity after vaccination or after natural infection contributes significantly to the increasing incidence rates in adolescents and adults. Prevention of pertussis in industrialized countries is mainly based on immunization with acellular vaccines in combination with other antigens. A booster dose with an adult-formulation tetanus-diphtheria toxoid and acellular pertussis vaccine (Tdap) is now recommended for all adolescents by several countries, and replacement of the decennial Td dose with a single or more doses of Tdap is recommended for adults.
Objective: Our review aims at describing the current knowledge on the impact of acellular pertussis vaccination in adolescents and adults, with particular focus on specific risk groups: adolescents, pregnant women and their newborns, and health care workers (HCWs), and secondly at suggesting possible immunization strategies.
Methods: Data were retrieved by searches of Pubmed, references, from relevant articles and open-access websites.
Results: In countries where an adolescent booster dose was adopted, a certain decrease of incidence rates was observed. No serologic correlate of protection after immunization exists, but subjects with high antibody levels against pertussis antigens are less likely to develop the disease. Tdap vaccine was demonstrated to induce antibodies to pertussis antigens exceeding those associated with efficacy in infants, in both adolescents and adults. Tdap use in pregnant women seems to be safe and might represent a useful tool in order to prevent pertussis cases in the first months of life. Neonatal immunization with monovalent acellular pertussis vaccine can efficiently prime T and B cells and act as a basis for future immune responses. Cocooning strategies involving all those surrounding newborns have started to be implemented. Their impact on infant pertussis cases will be evaluated in the coming years. Coverage in HCWs should be increased, given their important role in pertussis transmission in health care settings.
Conclusions: Despite the more recent position paper of WHO gives priority to infant and childhood vaccination against pertussis and leaves adolescent, adult and risk group immunization as an option for the future, data are quickly accumulating to support the need to consider pertussis vaccination as a crucial preventative intervention even in adolescents and special risk groups.

Contents

* Corresponding author at: Department of Public Health, University of Florence, Viale Morgagni, 48 50134 Florence, Italy. Tel.: +39 055 4598511; fax: +39 055 4598935.
E-mail address: paolo.bonanni@unifi.it (P. Bonanni).

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1. Introduction

Pertussis is an acute infectious illness, caused by the bacteria *Bordetella pertussis* and commonly known as "whooping cough"[1]. Protection from infection is not lifelong, both when immunity is acquired due to natural infection or by active immunization. Immunity against pertussis decays 4–12 years after infant immunization, and 4–20 years after natural infection. Waning immunity after vaccination or after natural infection contributes significantly to the increasing incidence rates of cases in adolescents and adults [2].

Presently, prevention of pertussis in industrialized countries is mainly based on immunization with acellular vaccines in combination with other antigens. Acellular pertussis vaccines contain up to five specific purified or recombinant *B. pertussis* antigens, including pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and two fimbrial antigens (FIM 2 and FIM 3). Routine use of whole-cell pertussis vaccines was suspended in some countries in the 1970s/1980s because of concerns about potential adverse effects, but they are still in use in low-income countries, since they are considerably less costly and are demonstrated to be generally as efficacious as acellular vaccines. Besides, whole-cell pertussis vaccines are not licensed for routine use in older children, adolescents and adults [3–5].

The use of acellular vaccines started in 1981 in Japan, where the first acellular pertussis vaccine was developed during the Seventies, in the expectation that it would be as effective but less reactogenic than the whole-cell vaccine [6].

In USA, aP (acellular pertussis) vaccines were authorized since 1991 only for the last two doses (4th – 5th), and since 1997 for all five vaccine doses in children [5]. In European countries, different DTaP priming schedules with three doses under 24 months of age are used, and booster doses recommended up to 18 years of age, from one to four doses [7].

Pertussis has been largely controlled in children up to 10 years of age in industrialized countries, through the use of primary series of vaccine and booster doses in the second year of life, and before entering school [8]. Pertussis has been well controlled in Japan, the first country introducing acellular pertussis vaccine and a really dramatic decrease in pertussis incidence rates was registered in all age groups in more than 20 years (1982–2002) of acellular pertussis vaccine use for routine immunization [9].

Despite being a primary vaccination in all countries, pertussis remains a relatively common and underdiagnosed infection, with stable or increasing reported rates [10,11].

In the last twenty years, the epidemiology of pertussis has markedly changed. As a matter of fact, a shift of cases was observed from paediatric age subjects (children younger than 10 years) to adolescents, adults and children too young to be vaccinated or to have completed their infant immunization three-dose primary series [12–18].

In spite of the new recommended vaccination strategies for adolescents and special groups of adults (in particular pregnant women and health care workers – HCWs), mortality is still significant both in developing and developed countries [19,20]. While the effectiveness of acellular pertussis vaccine in the prevention of cases and hospitalization of children is well documented, as a direct effect of the implementation of national childhood immunization programs [21–25], the efficacy and the effectiveness of acellular pertussis vaccines in adolescents and particular groups of adults are a more recent area of study.

Our review aims at describing the current knowledge on the impact of acellular pertussis vaccination in adolescents and adults, with particular focus on specific risk groups: pregnant women and their newborns, and health care workers, and secondly at suggesting possible future immunization strategies.

2. Epidemiological background

The incidence of pertussis infections in adolescents is an emerging alarm especially for the risk of transmission to susceptible individuals (e.g., infants). A peak in the incidence of pertussis occurs in USA adolescents 11 through 18 years of age whose vaccine-induced immunity has waned after childhood immunization, also due to the fact that natural boosters are less frequent than in the past [26]. During 2004, the pertussis incidence rate in adolescents in USA was 30/100,000, representing 34–38% of all reported cases. Pertussis outbreaks involving adolescents were recognized in middle and high schools in USA [27,28].

A resurgence of pertussis has been observed in Canada, the United States and Australia since the 1980s, and in Europe some years later, with high but steady incidence in children younger than 1 year, whereas rates in adults doubled in 5 years [29]. Despite a high global immunization coverage of infants receiving three doses of pertussis containing vaccines (82%), it is estimated that in 2008 about 16 million cases of pertussis occurred worldwide and 195,000 children died from the disease [5,30].

In 2009, in European countries, a wide variation in reported rates of confirmed cases was registered, ranging from 0.02 to 115.5 per 100,000 with northern countries reporting higher confirmed case rates, the majority of which occurred in the 0–24 year age group. The observed differences may in part be related to vaccination policy and in part to differences in reporting procedures and surveillance systems, laboratory methods used and case definition applied [10,16,31–32].

Besides, the increased incidence of pertussis may be the result of currently better diagnosis, better reporting, and increased awareness of the disease compared to the past and, perhaps, suboptimal efficacy of some pertussis vaccines, including *B. pertussis* strain adaptation or more virulent strains appearance [33–37].

The improved use of PCR (polymerase chain reaction) and reduced use of culture throughout the U.S. has been suggested as a partial reason for the increased reporting of pertussis. PCR can provide timely results with improved sensitivity over culture. Since PCR inclusion in the CDC case definition in 1997, the proportion of confirmed cases has increased substantially, and many laboratories now use only PCR to confirm pertussis. The US CDC recommends that PCR be used together with culture, rather than as an alternative test [38,39].

In USA, since 2004, about 90% of pertussis-related deaths and severe complications occurred in infants aged <3 months.

Household members (most frequently the mother) were responsible for 76–83% of transmission of *B. pertussis* to this high-risk group [40–44].

Regarding health care workers, pertussis outbreaks in nosocomial settings are well described in many countries. The index case is often recognized in health care staff, and the transmission of *B. pertussis* occurred more frequently among colleagues than between HCWs and their patients [45–50]. HCWs or patients may serve as the source of pertussis in nosocomial outbreaks, which can result in substantial morbidity and expense of resources for control measures. Pertussis immunization of HCWs, testing and furlough of HCWs with prolonged cough could reduce the morbidity associated with pertussis outbreaks [51].

3. Materials and methods

3.1. Search strategy and selection criteria

Data for this review were retrieved by searches of Pubmed, references from relevant articles and open-access websites of WHO, US Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC). In order to verify the completeness of the PubMed database, we also performed the same key word searches with other databases (Web of Science, Embase, Pascal), but the results were virtually overlapping with regard to the subjects of interest, or supplied supplemental articles out of the scope of this review. The WHO website was consulted in order to identify countries that have added an adolescent booster dose to their schedules since the 2002 recommendation of the global pertussis initiative [52].

The search was limited to English-language publications involving humans. The search has been performed in order to identify articles preferably published between 2000 and 2012, using the terms/key words: “acellular pertussis vaccine” in combination with “efficacy”; “effectiveness”; “immunogenicity”; “epidemiology”; “incidence”; “impact”; “booster vaccine”; “adolescent/s”; “pregnant women”; “newborns” and “health care workers”; resulting in about 200 articles which were reduced to 44 on the basis of title and abstract. We excluded articles referring to childhood or infancy except in case they were related to neonates from women vaccinated during pregnancy. We also excluded papers which referred to whole-cell pertussis vaccine. Articles published before 2000 were also included to clarify specific issues; and further references were used for the Discussion section. Results of the search on evidences of acellular pertussis vaccine use are presented in the following order:

1. Adolescents
2. Pregnant women
3. Newborns
4. Health care workers

3.2. Mechanism of protection

The mechanism of protection against pertussis is not completely understood. Immune responses can be directed against a range of pertussis toxins and antigens including PT, PRN, and fimbrial antigens [53]. For pertussis, no serologic correlate of protection after immunization exists; in fact no antibody level against a single antigen or a combination of antigens is conclusively associated to clinical protection [54]. On the other hand, some clinical trials using acellular vaccines containing three and five antigens, have shown that subjects with high antibody levels against PT, PRN and FIM are less likely to develop the disease in a clinically evident form when exposed to the pathogen [55–59]. The presence of serum antibodies to PRN and PT is the most accepted method to assess the competence of the immune response to confer protection against pertussis and to estimate the persistence of immunity after vaccination. Multicomponent acellular vaccines, containing also other antigens of *B. pertussis* (FHA, FIM), may be even more effective [60–62].

In order to assess the potential impact of acellular vaccines against pertussis in adolescents and adults targeted by ‘new’ recommendations, we have directed our investigation also towards studies that showed a persistence of antibodies to the different pertussis vaccine antigens in the long term.

4. Results

4.1. Immunogenicity in adolescents and adults

Many trials completed in adolescents and adults demonstrated the immunogenicity and safety of acellular pertussis vaccines. The immunogenicity of the pertussis components of Tdap vaccines currently in use was evaluated by comparing the immune response rates of adolescents vaccinated with a single dose of Tdap with the immune responses of infants vaccinated with 3 doses of TDaP vaccine. The immune responses to vaccine pertussis antigens (anti-PT, anti-FHA, and anti-PRN) in adolescents 1 month after a single dose of Tdap were noninferior to those of infants after 3 doses of TDaP during clinical efficacy trial for both authorized vaccines. In detail, booster response rates to pertussis antigens were respectively for the 3-component vaccine: anti-PT, 84.5% (95% CI: 83.0–85.9%); anti-FHA, 95.1% (95% CI: 94.2–95.9%), and anti-PRN, 95.4% (95% CI: 94.5–96.1%) and for the 5 component vaccine anti-PT, 92.0% (95% CI: 89.3–94.2%); anti-FHA, 85.6% (95% CI: 82.3–88.4%); anti-PRN, 94.5% (95% CI: 92.2–96.3%); and anti-FIM 94.9% (95% CI: 92.6–96.6%) [63,64].

In Finland, 510 healthy adolescents aged 10–13 years were enrolled to receive a 3-component acellular pertussis vaccine (Tdap3) vaccine and all vaccinees showed a significant rise (12- to 76-fold) in GMT of antibodies to tetanus and diphtheria toxoids and each of the pertussis antigens in the study vaccine. A 5-year follow-up study on the persistence of pertussis-specific antibody on the same subjects revealed that the PT IgG level achieved 1 month after booster vaccination with the combined Tdap vaccine was strongly predictive of persistence of immunity [65,66].

From August 2001 to August 2002 a trial was conducted at 39 US clinical centers in healthy adolescents and adults aged 11–64 years ($n = 4480$) in order to assess the immunogenicity and reactogenicity of a 5-component (PT, FHA, PRN, and fimbriae types 2 and 3) Tdap. Participants received a single 0.5 mL intramuscular dose of either Tdap or Td vaccine. Geometric mean antibody titers to PT, FHA, PRN, and FIM types 2 and 3 exceeded (by 2.1 to 5.4 times) levels in infants receiving a complete immunization course with DTaP. This Tdap vaccine produced strong immune responses to pertussis in both adolescents and adults [67].

In a multicentre study, the safety and immunogenicity of a Tdap vaccine was compared with a Td vaccine for booster immunization in adolescents. Enrolled participants were 4114 healthy adolescents aged 10–18 years who completed the childhood vaccination series against diphtheria, tetanus, and pertussis, and received the study vaccine. Results showed a comparable profile of tolerability and immune response between the Tdap and Td groups and concluded that in adolescents, the studied Tdap vaccine was immunogenic and induced antibodies to pertussis antigens (PT, FHA, and PRN) that exceeded those associated with efficacy in infants [68].

In a multicentre, prospective study, it was estimated that a single dose of Tdap vaccine in adolescents and adults ($n = 2781$), between the ages of 15 and 65 years, gave a protective efficacy of 92% (95%

CI: 32–99%) for pertussis, confirmed by culture, PCR or serologic assay [69,70].

4.2. Effectiveness in separate subgroup populations: adolescents, adults (pregnant women and HCWs) and newborns

Almost ten years after introduction of an adolescent or adult Tdap booster dose in several countries, data on disease reduction in the targeted age groups were lacking. Therefore, we focused our search on those countries in order to better understand the impact of acellular pertussis use in the targeted population groups.

4.2.1. Impact of Tdap booster vaccination in adolescents

The study of an epidemic in Germany in primary and secondary schools allowed to calculate the attack rate (%) and the relative risk (RR) of pertussis according to time since the last dose of vaccine after a complete primary vaccination course consisting of 4 doses. The overall attack rate was 15% (70/467), but it increased to 32% (16/50) among those who had received the last dose at least 9 years previously (RR = 1.39; 95% CI: 0.47–4.05). Results suggest that the decay of immunity started about 5 years after the last dose of pertussis vaccine and the RR increased with the time elapsed since the last vaccine dose [71].

In order to analyze the epidemiologic trends of laboratory-reported pertussis and to evaluate the current vaccination strategy in Austria, a 6-years prospective study (2000–2005) was undertaken. During the observation period the mean annual incidence increased from 6.4 per 100,000 population in 2000 to 11.1 cases per 100,000 population in 2005. Incidence rates (IR) were highest among children less than 1 year of age, decreasing IR were observed in children and adolescents up to 16 years old, but increasing rates were detected for persons 16 years of age and older. Besides, the mean age of reported pertussis cases in adults increased from 30 years in 2000 to approximately 44 years in 2005 [72].

During a large outbreak in North America, the incidence of pertussis and effectiveness of vaccination in a well-vaccinated, well-defined community was examined. Patients (n = 171) with a positive (PCR) test for *B. pertussis* from March 1 to October 31, 2010 were identified. Information on vaccination status were reviewed and 171 cases of clinical pertussis were identified, 132 of which in pediatric patients. There was an important rise of cases in patients aged 8–12 years. The rate of positive tests increased in preadolescents, peaking at age 12 years. Vaccination rates of PCR positive preadolescents were approximately equal to those of controls. Vaccine effectiveness was 41%, 24%, 79%, for age groups 2–7, 8–12, 13–18, respectively. These data suggest that the current schedule of acellular pertussis vaccine doses is insufficient to prevent outbreaks of pertussis. A marked increased rate of disease from age 8 through 12 years was noted, proportionate to the interval since the last scheduled vaccine dose. This first detailed analysis of a recent North American pertussis outbreak found widespread disease among fully vaccinated older children. Starting approximately three years after a former vaccine dose, attack rates markedly increased, suggesting inadequate protection [73].

Vaccine effectiveness was evaluated in Australia throughout the first extensive use of adolescent acellular pertussis vaccine by the screening method. The screening method estimates vaccine effectiveness (VE) using the formula VE = 1 − [PCV/(1 − PCV)][(1 − PPV)/PPV], where PCV is the proportion of cases in vaccinated subjects, and PPV is the proportion of immunized population (vaccination coverage). In Australia, a Tdap vaccine was licensed in 2000, but scarcely used before 2004, when a funded program became available for adolescents. The Australian National Immunisation Program started to use Tdap on 1 January 2004 in place of the reduced antigen diphtheria–tetanus (Td) booster dose formerly recommended at age 15–17 years [74]. A large cohort of adolescents (272,000 aged 12–19 years) was enrolled from May to December 2004 to receive Tdap during a mass vaccination program targeting all high school students in New South Wales (NSW), the biggest Australian state (population: 6.5 million). Estimated vaccine effectiveness was 78.0% (95% CI: 60.7–87.6%) for all study cases (n = 167), increasing to 85.4% (95% CI: 83.0–87.5%) for laboratory-confirmed cases (n = 155) [75].

Another interesting study was performed in Australia in order to evaluate the impact of adolescent pertussis immunization program between 2004 and 2009. The study compared the effect of three strategies (vaccinating a one-year age cohort versus the entire high school, with and without continued immunization of high school entrants) for providing a booster dose of adult-formulated Tdap vaccine to adolescents in Australia. The incidence rate ratio (IRR), as the primary outcome measure, was calculated by dividing pertussis incidence after the introduction of Tdap delivery programs by pertussis incidence during the most recent pre-program epidemic.

During the 2008–2009 epidemic period, the national-level IRR calculated among age cohorts targeted for Tdap was 0.6 (95% CI: 0.6–0.7), confirming the incidence reduction in vaccinated age groups, but among other age cohorts IRR was 1.1 (95% CI: 1.1–1.2). Only Western Australia, the jurisdiction in which Tdap was administered to the entire high school and to subsequent entrant cohorts, experienced sustained decreases in pertussis notifications in both adolescents and infants under 6 months of age (IRR: 0.4; 95% CI: 0.3-0.6) until 2009 [76].

At the end of 2007, a pertussis outbreak occurred at a nursery through twelfth grade school on St. Croix, US Virgin Islands. All students were screened for cough and clinical history was collected, including Tdap receipt. An attack rate of 10% among 499 students (51 confirmed or probable cases) was observed. Of 266 students aged 11 years, 31 (12%) had received Tdap. The calculated relative risk between unvaccinated and vaccinated subjects was 2.9 (no 95% CI reported). Forty-one unvaccinated students (18%) had confirmed or probable pertussis, compared with 2 (6%) of the vaccinated students; vaccine effectiveness was 65.6% (95% CI: −35.8–91.3%); when considering laboratory confirmed cases, VE increased to 70.6% (95% CI: −110.3–95.9) [77].

A retrospective analysis of nationally reported pertussis cases from January 1, 1990, through December 31, 2009 was performed in the United States in order to evaluate the impact of the adolescent Tdap vaccination program on pertussis trends. Data on pertussis incidence in the United States from 2005 to 2009 highlighted a difference between 11- and 18-year-olds and other age groups, suggesting that targeted use of Tdap among adolescents reduced disease particularly in that age group, while indirect effects of adolescent vaccination were not observed among infants younger than 1 year [78].

4.2.2. Impact of Tdap vaccination in pregnant women

A recent study established that the lack of maternal immunity is one reason for pertussis susceptibility in very young infants [79]. Nevertheless, it is difficult to determine the proportion of infants born with a protective concentration of maternal antibodies, since serologic correlates of protection are not established. Indirect proof suggests that maternal antibodies offer short lived protection against lethal pertussis [80].

The proportion of childbearing age women with serum antibodies to *B. pertussis* differs from community to community, but it is usually less than 50%. In a German study, measurable levels of antibodies against *B. pertussis* were found in 37% of the selected women, with a significantly higher prevalence of antibodies against pertussis in umbilical cord blood samples than in maternal blood samples. This is an evidence for an active placental antibody transfer, but the prevalence of detected antibodies suggests they are insufficient to protect the newborns efficiently against pertussis. In

general, the higher the antibodies concentrations in umbilical cord serum, the longer the newborn will be protected. On the other hand, antibody concentration in maternal serum depends on the timing of administration of the vaccine during pregnancy, the quality of the antigens and the time required to achieve maternal-fetal IgG transport. Besides, transfer of antibodies against pertussis to the offspring is influenced by various factors like the age of women at delivery, mothers' vaccination history and mothers' immune response and ability to generate IgG immunoglobulins [53,81].

In infants born to seropositive mothers, maternal antibodies (pertussis agglutinins) ranged from 2% [82] to [22–37%] [83], 54% [84] and to 63% [85]. Probably no more than 25% of infants are born with circulating antibodies [10].

Healy et al. found that maternal levels of IgG to PT, FHA, and FIM were very low and although these pertussis antibodies were transferred to the neonates, the low titres detected in infants (about half compared with their mothers) and their rapid decay, left the offspring with little protection against whooping cough [86].

Newborns from mothers who received Tdap during pregnancy had significantly higher concentrations of anti-DT (1.970 vs 0.571, $P < .001$), anti-TT (9.015 vs 4.237, $P = .004$), anti-PT (28.220 vs 11.010, $P < .0001$), anti-FHA (104.15 vs 26.830, $P = .002$), anti-PRN (333.01 vs 24.700, $P < .001$), and anti-FIM 2/3 (1198.99 vs 82.830, $P < .001$) when compared to newborns born from mothers who did not receive Tdap during pregnancy. There was a significant increase in the odds that newborns from mothers who received Tdap during pregnancy have antibodies that may provide protection against pertussis toxin (88.5% vs 40.4%; OR, 11.32; 95% CI: 4.10–31.24; $P < .0001$), and fimbriae 2/3 (98.1% vs 84.6%; OR, 9.27; 95% CI, 1.12–77.07; $P < .0146$) [87].

In a recent study, the influence of a pertussis booster vaccination on the transfer of maternal antibodies in nonpregnant women who received a Tdap booster vaccine between 2 consecutive pregnancies was examined. Efficient transplacental antibody transfer and significantly higher antibody titers against 3 pertussis antigens were observed in cord blood and in blood of 1-month-old infants born after a maternal booster vaccination, compared with results in their siblings born before the booster administration [88].

A concern that has been raised is the possible interference of pertussis-specific passive antibodies in infants who receive active immunization with DTaP. Some studies have suggested that the presence of maternal pertussis antibodies, as a consequence of vaccination with Tdap during pregnancy, can have a negative effect on vaccine response of their children after administration of DTaP vaccine. The inhibition of active pertussis-specific antibody production in those infants is referred to as "blunting". The clinical importance of blunting is not clear, but it is merely a temporary effect, because passive maternal antibodies decline rapidly, within the first six months of infants life (half-life of approximately six weeks in infant sera) [89–91].

At the present time, two clinical trials are being performed, one in Canada and another in USA, to assess the immune response of infants receiving DTaP immunization at ages 2, 4, and 6 months whose mothers received Tdap during the third trimester of pregnancy. These two trials will help to clarify the possible interference of maternal passive antibodies with infant immune response to primary DTaP vaccination [92,93].

Finally, a cross-sectional study was conducted in Houston (Texas) which evaluated the impact of maternal postpartum Tdap immunization on infant pertussis infection by comparing two time intervals: preintervention (July 2000 through December 2007) and postintervention (January 2008 through May 2009). During the intervention period pertussis education was incorporated into childcare and breastfeeding programs and Tdap vaccination was offered to postpartum women (67% of them received Tdap vaccine). The proportions of pertussis-infected infants born in the two periods were comparable. Immunization with Tdap vaccine only of postpartum mothers did not reduce pertussis illness in infants $\leq$6 months of age [94].

The cocooning strategy consists in the indirect protection of infants by immunity induced in family members. Restrictions of this strategy emerged during the last 5 years, because of the difficulties to implement cocooning widely. Moderate vaccination coverage of post-partum mothers was registered in countries where cocooning programmes were activated, but fathers and other family members were difficult to reach [95,96].

In order to overcome practical and logistical barriers, in an American feasibility study on Tdap use in a high-risk population (predominantly Hispanic, medically underserved, uninsured population at a Houston hospital), cocooning strategy was well accepted and successfully implemented by using standing orders for maternal postpartum Tdap vaccination and providing vaccinations on-site [96].

Another study demonstrated that administration of tetanus, diphtheria, and acellular pertussis vaccine in the neonatal intensive care units (NICU) is an effective means of increasing vaccination rates of parents, as showed in a feasibility study in which the overall parents vaccination rate was 86.9% of the screened population (598 eligible parents) [97].

4.2.3. Impact of acellular pertussis vaccination in newborns

Another possibility being investigated is the opportunity to increase the protection of young infants against pertussis using an additional dose of pertussis vaccine at birth. Although neonatal immunization does not generally lead to early and strong antibody responses, recent human studies have provided evidence that neonatal immunization with acellular pertussis vaccine can efficiently prime T and B cells and act as a basis for future immune response [98,99].

In a study, infants given pediatric-formulation of pertussis vaccine (DTaP) at birth, 2, 4 and 6 months showed a significantly lower response to diphtheria and 3 of 4 pertussis antigens, at 7 months of age, compared with controls (infants routinely immunized at 2, 4 and 6 months) [100]. However, other studies that used a dose of monovalent acellular pertussis vaccine (aP) at birth (rather than DTaP vaccine), followed by vaccination with DTaP-HBV-IPV/Hib at 2, 4 and 6 months, found increased antibody titres against pertussis antigens at 2 and 8 months of age, but an interference in the development of antibodies against *Haemophilus influenzae* type b and hepatitis B, while these infants developed a normal vaccine response to a booster dose in the second year of life. Additional studies are currently underway to further explore the potential of this approach to reduce death and morbidity from *B. pertussis* infection in the first 3 months of life and the importance of this interference [101,102].

Another Australian study evaluated antibody responses to 2 doses of monovalent acellular pertussis vaccine (aPV) before 2 months of age (at birth and at 1 month). Results suggested that this strategy induced significantly higher IgG antibody against pertussis antigens by 2 months of age without decreasing successive pertussis antibody responses. All seventy-six infants received hepatitis B vaccine (HBV) at birth followed by a combination vaccine including aPV, diphtheria, tetanus, *Haemophilus influenzae* type b (Hib), hepatitis B, polio antigens and 7 valent conjugate pneumococcal vaccine at 2, 4, and 6 months. There was a trend to lower antibody responses for hepatitis B and Hib with higher numbers of aPV doses [103].

4.2.4. Impact of Tdap booster vaccination in health care workers

Very few articles have been retrieved which evaluate the impact of acellular pertussis vaccination of health care workers apart from

those on vaccination policy recommendations. Just two studies on the persistence of antibodies in this population are reported below.

In Germany, antibody decay after a single dose of a monovalent acellular pertussis vaccine administered to health-care workers (HCWs) was monitored for 4 years after immunisation. Blood samples were collected 4 weeks (n = 246), 1 year (n = 187), 2 years (n = 53), 3 years (n = 134), and 4 years (n = 37) after vaccination. Peak median antibodies to PT, FHA, and PRN were 314, 785, and 84 EU/ml respectively. The titre of IgG anti-PT decreased slowly to a median of 29% (76 EU/ml), 18% (64 EU/ml), 19% (58 EU/ml), and 20% (63 EU/ml) of the peak value after 1, 2, 3, and 4 years respectively. IgG anti-FHA decreased more slowly, but showed similar decay patterns. After a rapid decline during the first year, antibodies remained rather stable for 4 or more years [104,105].

In order to evaluate the persistence of immune response to one dose of aP vaccine in HCWs and child-care workers, a study was conducted in USA administering a vaccine containing 25 μg of PT and 3 μg of FHA to HCWs. One month after aP vaccination, the geometric mean levels of IgG anti-PT and IgG anti-FHA were 33.1 μg/mL and 34.7 μg/mL respectively. The GMC of IgG-anti-PT was comparable to the results of the previously cited study one month after vaccination, but it was higher 1 year after vaccination [106].

In France, a survey performed in 2007 investigated vaccination coverage among health care workers in the paediatric emergency and intensive care department. One third of participants declared they had received a booster dose of a pertussis containing vaccine in adulthood; adults younger than 30 years and medical health care workers had relatively higher coverage [107].

5. Discussion

Pertussis remains a major public health problem worldwide. Adolescents and adults are at the present time identified as the primary source of infection to susceptible and unprotected infants. Prevention of the disease has improved markedly due to several reasons, and especially to the availability of new vaccines and new combination vaccines [108–112].

In 2002, the Global Pertussis Initiative recommended that countries expand existing vaccination strategies to include a pertussis booster dose for adolescents and adults [113].

Several countries have recommended acellular booster doses with Tdap for adolescents (including Australia, Austria, France, Germany, the USA, Canada, Switzerland, New Zealand and several Italian Regions). Concerning adults, replacement of the decennial Td dose with a single or more doses of Tdap is recommended for adults by several countries adopted this new recommendation in their immunization campaigns (including the USA, Australia, Austria, few Italian Regions); some countries recommend selected immunization of child care workers and parents of newborns (e.g. Austria, Germany) [1,17,114–117].

Effectiveness of Tdap vaccine in adolescents and adults resulted to be high in adolescents ranging from 65.6% to 70.6% with a clinical case definition and increasing from 78.0% to 85.4% when considering laboratory confirmed cases but some problems have been observed in younger age groups [75–77].

According to Sin et al., the recommendation for the first booster vaccination between 9 and 17 years of age in place in Germany until 2006 was insufficient to protect school-aged children from pertussis. In this outbreak, the majority of cases could have been prevented by an early booster dose of a pertussis-containing vaccine [71].

The possibility of earlier or more numerous booster doses of acellular pertussis vaccine either as part of routine immunization or for outbreak control should be considered in order to avoid increasing incidence rate of pertussis in already fully vaccinated children, as reported by Witt et al. [73].

The experience in Australia shows that a broad school-based catch-up program followed by immunization of school entrants may be the most favourable strategy for the implementation of an adolescent Tdap programs. A pertussis vaccination catch-up program could have an impact on herd immunity and on the incidence of disease among infants [76].

In Austria, a country having introduced regular Tdap booster doses since 2002, pertussis incidence rates remain high among adults, implying that coverage rates with booster vaccinations for adolescents and adults are still too low. Reinforced application of the current booster strategy for adults is needed [76]. This is particularly relevant for health care personnel (HCP), who are at increased risk for acquiring pertussis which can be transmitted to susceptible contacts. In 2009, vaccination coverage for Tdap vaccine among adults in USA was 6.6%, while it was 17% among HCWs [44,118].

The National Immunization Survey-Teen (NIS-Teen) 2007 indicated substantial increases in uptake of new adolescent vaccinations, including Tdap which passed from 10.8% of vaccine coverage in 2006 to 30.4% in 2007 and to 68.7% in 2010. In Italy, according to the ICONA 2008 survey (a coverage survey based on the cluster sampling method), the Tdap immunization coverage in adolescents (subjects born in 1992) was 45.6% with three doses, 26.7% with four doses, and only 14.1%, with five doses, respectively [119].

To improve vaccination coverage among adolescents, health-care providers should take advantage of every health-care visit as an opportunity to evaluate vaccination status and administer vaccines when needed [120,121]. It is time to encourage providers to vaccinate adolescents on every possible occasion. Missed opportunities continue to be a major problem in meeting the targeted objectives [122].

According to American Academy of Pediatrics (AAP), intervals of less than 5 years for administering Tdap can be used, particularly in situations of high risk of acquiring pertussis, having complicated disease, or transmitting infection to vulnerable contacts. Available data (since 2005) support acceptable safety with an interval as short as approximately 2 years. The Society for Adolescent Medicine supports the use of Tdap among all adolescents and young adults ages 10–25 years. This vaccine should also be given simultaneously with other needed vaccinations to increase vaccination acceptance and reduce missed opportunities for immunization [123].

In order to protect newborns from pertussis, considering the risks-to-benefits ratio, it is reasonable to propose a Tdap dose to pregnant women, whose infants will be at important risk of exposure to pertussis. For instance, in areas that are experiencing extensive pertussis outbreaks, immunization with Tdap during the third trimester should be implemented [12,124].

Maternal vaccination would prevent infant infections from delivery until immunity is induced by active immunization. Besides, pregnancy is not a contraindication to Tdap (or Td) immunization [125]. The Td component of the vaccine has been successfully used during pregnancy for many years without warning of maternal or fetal damage [1]. Administration of Tdap during pregnancy has been less widely studied. However, in studies on adverse reactions to Tdap in pregnant and nonpregnant women, the frequency of pain, redness, and swelling were significantly less in pregnant women groups [53]. The latest ACIP recommendation is to use Tdap in unvaccinated pregnant women and all adolescents and adults who have close contact with an infant aged <12 months [19].

It has been suggested that Tdap immunization of mothers could inhibit an active pertussis-specific antibody production in their infants. Evidence for post-natal tolerance induction in human is currently limited to very few conditions [108] using

Table 1
Recommendations of the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention for use of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adolescents, adults and special risk groups (pregnant women and HCWs).

Age groups (years)	11–12	11–18	19–64	Over 65	Health care workers	Pregnant women
Recommendation	A single dose of Tdap: during a preventive healthcare visit	A single dose of Tdap vaccine only if recommended childhood vaccination series for diphtheria, tetanus, and acellular pertussis was completed	A single dose of Tdap vaccine	Subjects who are in, or anticipate being in, close contact with an infant younger than 12 months should receive a single dose of Tdap	All HCWs, regardless of age or of time since the last Td dose, should receive a single dose of Tdap as soon as feasible, if they have not previously received Tdap	A single dose of Tdap vaccine preferably in the third or late second (after 20 weeks gestation) trimester

whole-cell pertussis vaccines [83,126], or Neisseria meningitidis group C polysaccharides (MenC PS) [127,128]. Importantly, conjugation to a carrier protein is sufficient to prevent the reduction of subsequent responses to Hib [129,130] or MenC PS [131].

A study strongly suggests that cocooning strategy should be directed at immunizing all household and key contacts of newborns with Tdap vaccine, not just mothers because targeting only mothers creates an incomplete cocoon of protection around the infant, who is vulnerable to pertussis infection from other unimmunized and susceptible contacts for several months [94].

On the other hand, it was estimated that 66% of source cases of pertussis disease to young infants were close contacts, while transmission from casual contact with community members was 34% (95% CI: 24–44%), increasing to 47% using different definition of source case and a more sensitive analysis. Casual contact appears to be responsible for a considerable amount of pertussis transmission to young infants [132].

The GPI (Global Pertussis Initiative) recommended implementation of the cocoon strategy in countries where it is economically feasible [113]. The cocooning strategy has been recommended in some developed countries – including Australia, France and Germany – since the early 2000s [5]. Feasibility studies demonstrated high acceptance rates of pertussis immunization in parents of newborns especially in countries where infant's mortality from pertussis has increased markedly in recent years [94]. Finally, a possible obstacle to the implementation of such strategy might be sticking to the previously recommended minimum interval between booster doses (Tdap can now be administered regardless of interval since the last tetanus- or diphtheria- toxoid containing dose) [108].

Direct protection of infants may be conferred also by neonatal vaccination. Neonatal immunization with acellular pertussis vaccine can provide a basis for future immune responses.

On the other hand, DTaP vaccination at birth showed a significantly lower response to diphtheria and 3 of 4 pertussis antigens at two months. Monovalent aP vaccines seemed to overcome such problem. A single dose of monovalent aP vaccine at birth or two doses (at birth and at 1 month) could increase antibody titres against pertussis antigens by 2 months of age without decreasing successive pertussis antibody responses, but could interfere the antibodies response against *Haemophilus influenzae* type b and hepatitis B [101,102]. More exhaustive studies on monovalent aPV vaccination at birth are desirable to assess antibody responses and the possibility to decrease morbidity and mortality from *B. pertussis* infection in the first 3 months of life [101].

Vaccination against pertussis is recommended for health care workers (HCWs) because they are at increased risk for acquiring and transmitting such disease to susceptible contacts, especially in neonatal care units [133,134].

Recommendations for immunization practices applicable to disease prevention among HCWs in USA were updated in 2011. The aim of this revised recommendations was to reduce pertussis morbidity among adults, maintain the standard of care for tetanus and diphtheria prevention and to reduce the transmission of pertussis to infants and in health-care settings.

A brief summary of the main changes from the 1997 version [134] is described below:

Use of Tdap in healthcare personnel [135]

- All HCWs, regardless of age, should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap.
- The minimal interval between Td and Tdap doses was removed, and Tdap can now be administered regardless of interval since the last tetanus or diphtheria-containing vaccine.
- Tdap is not currently licensed in the United States for multiple administrations. After receipt of Tdap, HCP should receive routine booster immunization against tetanus and diphtheria according to previously published guidelines.
- Hospitals and ambulatory-care facilities should provide Tdap to HCP and use approaches that maximize vaccination rates (e.g., education about the benefits of vaccination, convenient access, and the provision of Tdap at no charge).

In Table 1, current recommendations of the Advisory Committee on Immunization Practices for Tdap vaccine administration are summarized [124,134].

In conclusion, in order to reduce the circulation of *B. pertussis* and to protect infants against severe disease, a single approach may not be sufficient, and multiple immunization strategies applied in a concerted mode may be necessary. Universal paediatric immunization programs with DTaP should be continued, and a universal decennial Tdap booster program implemented, starting in preadolescents and continuing throughout adulthood, including persons aged $\geq$65 years. A special focus should be directed to groups at high risk of transmission (HCWs, pregnant women). This is a difficult task considering the low immunization coverage of adults in all countries worldwide [8]. Universal adult vaccination is a logical goal for the ultimate elimination of pertussis disease, but feasibility issues remain an obstacle to its implementation [40].

Although the last available WHO Position Paper on pertussis vaccination does not presently recognize the opportunity to recommend pertussis booster doses for adolescents, adults, health care workers or the cocoon strategy, our review demonstrates that many data have accumulated during the last years, making it evident that immunization policies in those age groups and at risk groups are crucial for the control of pertussis and its mortality. WHO recommends what is generally clear in a definitive manner, with a special care to developing countries. On the other hand, the WHO Position Paper leaves a door open to consider changes to the recommendations in the presence of new evidence [5].

Appendix A. Summary of the main results of the review

References	At risk group	Study population (number)	Type of vaccine and schedule	Type of study or settings	Results
Tran Minh NN, 1999 [65]; Edelman K, 2007 [66]	Adolescents	16-year-old subjects boosted 5 years before	3-component (PT, FHA, PRN) Tdap vaccine: a booster dose at 11–13 years	Persistence of pertussis-specific antibody and cell mediated immunity (CMI) after booster immunization of adolescents	Significant rise (12- to 76-fold) in GMT of antibodies to each pertussis antigens in the study vaccine; PT IgG level 1 month after booster vaccination was strongly predictive of persistence of immunity
Pichichero ME, 2005 [67]	Adolescents and adults	11–64 years (n = 4480)	5-component (PT, FHA, PRN, and fimbriae types 2 and 3) Tdap vaccine	Immunogenicity and reactogenicity of Tdap5 vaccine	GMT of antibodies to all pertussis antigens exceeded (by 2.1–5.4 times) levels in infants receiving a complete immunization course with DTaP
Pichichero ME, 2006 [68]	Adolescents	10–18 years (n = 4114)	3-component (PT, FHA, PRN) Tdap vaccine compared to Td vaccine(control)	Prospective, randomized, observer-blinded, multicenter, comparative study on the safety and immunogenicity of Tdap compared to Td vaccine	The studied Tdap was safe and immunogenic and induced pertussis antibodies that were higher than those associated with efficacy in infants
Ward JI, 2006 and 2005 [69,70]	Adolescents and adults	15–65-year-old subjects (n = 2781)	A single dose of Tdap vaccine 3-component (PT, FHA, PRN) Tdap vaccine (n = 1391) compared to hepatitis A vaccine (control) (n = 1390)	Multicenter, randomized, double-blind vaccine trial on incidence of pertussis, vaccine safety, immunogenicity, and protective efficacy	Protective efficacy of 92% (95% CI: 32–99%) for pertussis
Rank C, 2009 [75]	Adolescents	A cohort of 272,000 subjects aged 12–19 years vaccinated during the mass vaccination program in New South Wales, the biggest Australian state. VE analysis was based on 167 cases	3-component (PT, FHA, PRN) Tdap vaccine	Vaccine effectiveness (VE) evaluated by the screening method: VE = 1 − [PCV/(1 − PCV)][(1 − PPV)/PPV], where PCV is the proportion of cases in vaccinated subjects, and PPV is the proportion of immunized population (vaccination coverage)	Vaccine effectiveness (VE) was 78.0% (95% CI: 60.7–87.6%) for all study cases (n = 167), increasing to 85.4% (95% CI: 83.0–87.5%) for laboratory-confirmed cases (n = 155)
Wei SC, 2010 [77]	Adolescents	499 students aged ≥11 years at a nursery twelfth grade school. VE analysis was based on 51 confirmed or probable cases	Tdap vaccine Estimate of 12% vaccination coverage in the school	Outbreak settings at a nursery twelfth grade school	Vaccine effectiveness (VE) was 65.6% (95% CI, −35.8–91.3%); VE increased to 70.6% (95% CI, −110.3–95.9) considering laboratory confirmed cases
Skoff TH, 2012 [78]	USA population	200,401 pertussis cases were reported in the United States from 1990 to 2009	Tdap vaccine	Retrospective analysis of nationally reported pertussis cases, January 1, 1990, through December 31, 2009 in the United States	Targeted use of Tdap among adolescents reduced disease preferentially in this age group (11–18 years)

Appendix A (*Continued*)

References	At risk group	Study population (number)	Type of vaccine and schedule	Type of study or settings	Results
Gall SA, 2011 [87]	Pregnant women and their newborns	104 pregnant women and 104 newborns	5-component (PT, FHA, PRN, and fimbriae types 2 and 3) Tdap vaccine during pregnancy	Study on the immunogenicity of Tdap administered during pregnancy and evaluation of antibodies levels to pertussis antigens in maternal and umbilical cord blood samples	Administering Tdap during pregnancy increases antibody titers against pertussis antigens in the offspring
Leuridan E, 2011 [88]	Women	24 nonpregnant women	3-component Tdap vaccine administered to women between 2 consecutive pregnancies	A prospective multicenter study to examine the influence of a pertussis booster vaccination on the transfer of maternal antibodies	Significantly higher antibody titers against 3 pertussis antigens were observed in cord blood and in blood of 1-month-old infants born after a maternal booster vaccination compared with results in their siblings born before the booster administration
Halasa NB, 2008 [100]	Newborns	50 infants between 2 and 14 days of age	5-component DTaP (PT, FHA, PRN, and fimbriae types 2 and 3) vaccine administered at birth and hepatitis B vaccine or hepatitis B vaccine alone (control)	A prospective, randomized, controlled pilot study to evaluate the immunogenicity of an additional birth dose of DTaP	An additional birth DaP dose was safe but associated with a significantly lower response to 3 of 4 pertussis antigens, at 7 months of age, compared with controls
Knuf M, 2008 and 2010 [101,102]	Newborns	121 newborns between 2 and 5 days of age	A dose of monovalent acellular pertussis vaccine (aPV) at 3 component (PT, FHA, PRN) or hepatitis B vaccine (control) at birth followed by vaccination with DTaP-HBV-IPV/Hib at 2, 4 and 6 months	Phase II, double-blinded, controlled study on the immunogenicity of monovalent acellular pertussis (aPV) vaccination at birth.	Increase of antibody titres against pertussis antigens at 2 and 8 months of age. Interference in the development of antibodies against *Haemophilus influenzae* type b and hepatitis B. Normal vaccine response to a booster dose in the second year of life
Wood N, 2010 [103]	Newborns	76 newborns enrolled within 120 hours of birth	Two doses of monovalent acellular pertussis vaccine (aPV) at 3 component (PT, FHA, PRN) before 2 months of age (at birth and at one month of age)	A randomized, nonblinded trial of administration of monovalent acellular pertussis vaccine (aPV) to newborn infants	Significantly higher IgG antibody against pertussis antigens by 2 months of age without decreasing successive pertussis antibody responses. Interference in the development of hepatitis B and Hib antibodies with higher numbers of aPV doses

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