Review Article

Benefits of maternal vaccination to prevent pertussis in infants

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ABSTRACT

Pertussis, also called whooping cough, is an infectious and preventable pathology that generates important child morbidity and mortality worldwide. There are different biological preparations for its use in infants, while for adolescents and adults is Tdap, (acellular vaccine of purified extracts of *Bordetella pertussis* (BP), combined with tetanus and diphtheria toxoid) that has been proposed as maternal vaccination (MV). The objective was to identify the benefits of MV in the prevention of childhood pertussis, a review was made in PubMed, Science Direct, EBSCOhosT, OvidSP and Embase databases (years 2008-2016) and an electronic alert system (January-April 2017). 1083 titles were identified and 44 articles were selected. After the MV (administered between 27 and 36 weeks of gestation) the passage of IgG-BP to the fetus is sufficient to generate adequate infant protection, generating two benefits: reducing infant morbidity (number of cases and hospital admissions) and decreasing mortality by pertussis. The MV offers 93% of effectiveness [95%CI: 81-97] and OR: 0.09 [95%CI: 0,03-0,25]. The MV is more favorable in each pregnancy than cocoon strategy, vaccination before pregnancy, before 26 weeks of gestation or in the postpartum. The use of MV is a safe and cost-effectiveness tool to prevent childhood pertussis.

Keywords: Infant mortality, Obligatory vaccination, Pertussis, Prenatal Care, Vaccination

INTRODUCTION

Pertussis, also called whooping cough, is an acute, infectious and usually severe respiratory disease with high mortality in infants younger than six years.[1-3] It is caused by *Bordetella pertussis* (BP) that is a cocobacillus exclusive in humans; it is transmitted by minute and contaminated particles that come from respiratory epithelium of the patient.[1,4-6] Germs of the same species, *B. parapertussis* and *B. holmesii,* are involved just like *B. bronchiseptica* (a pathogen that affects animals) but it also can infect immunocompromised patients.[7]

The pertussis disease causes respiratory compromise, rhinorrhea, sneezing, fever, cough and cyanosis by the accumulation of mucopurulent exudates in the respiratory tract.[5,8] Adults or children usually infect the newborns.[9,10]

Frequently, this illness appears in the childhood but it can affect at any age.[9-14]

Pertussis generates high rates of infant morbidity and mortality. It is a health public problem and its epidemic peaks have increased, for that reason, the notification is mandatory.[1,3,5,15-19] The World Health Organization pointed out that the number of notified cases around the world in 2012 was 249.556; 71.774 (28,7%) of them were in America.[20] The Center for Disease Control and Prevention from EEUU, showed that, in that country, the reported cases were 28.639 in 2013 and 32.971 in 2014 with a rise of 15%.[5] The highest rates were among adolescents and most of the deaths were in newborns less than three months of age. Pertussis is usually mild, moderate or even subclinical in adults and adolescents but it can be severe and produce pneumonia, convulsions and encephalopathy.[5,8-10,21,22]

In Colombia, during 2012, 11,404 pertussis cases were notified: 3,290 (28.8%) confirmed, 739 (6.4%) probable and 7,375 (64.6%) discarded; 69 patients died and 62 of them were under six months of age. The notifications grew to 13.626 and the confirmed cases were reduced to 2.754 in the next year. The incidence of confirmed cases was 8.5/100,000 inhabitants in 2012 and 5.5/100,000 inhabitants in 2013.[15,23] Pertussis is considered as a reemerging illness, in that sense, the Pan American Health Organization found that the number of cases had increased in Argentina, Brazil, Colombia, Chile, Guatemala, Mexico, Paraguay, Venezuela and United States of America.[18]

The main strategy to prevent pertussis is to vaccinate infants, adolescents and adults.[8,15] It is recommended applying the vaccine around two, four or six months of age with a new application at one years old and then at five years old. The vaccine is a compound of 15-20 millions of inactivated bacilli in formaldehyde; the triple bacterial vaccine is a pharmaceutical method combined with vaccines against diphtheria and tetanus. Other vaccine, called pentavalent, includes hepatitis B and *Haemophilus influenza*.[15] Additionally, the acellular vaccine is approved to be administrated since two months of age.[8] The absence of vaccination under that age makes the infant vulnerable to pertussis, it is for that reason that maternal vaccination (MV) is an interesting strategy to overcome this situation.[21,24-26] Tdap (acellular vaccine of purified extracts of adhesion molecules BP combined with tetanus toxoid and reduced diphtheria toxoid) can protect adolescents and adults, it is administrated with just one dose.[1,4,5,15,19,23] The objective of this revision was to identify the benefits of MV to prevent infant pertussis.

Literature review

Bibliographic investigation with a narrative revision. Clinical and epidemiologic studies, systematic revisions, consensus, expert meetings, meta–analysis, clinical guides and protocols were included. Type of participants: published articles about MV to prevent infant pertussis. Research strategy: it was carried out an electronic research in PubMed, ScienceDirect, EBSCOhost, OvidSP and Embase data bases between 2008 and 2016, as well as in Scielo, in the same period of time, but in Spanish. It was created an electronic alert system with the term maternal immunization in the period between January and April, 2017.

The tittles were identified and those repeated were eliminated. The summaries were revised to select those adjusted to the objective of this research. Two rounds of selection were carried out and the revision was done with the relevant articles (all the documents selected were in full text format). Another group of articles was added with the snowball sampling. The articles were checked separately taking into account the relevant contents in a data table in Microsoft Excel.

One thousand and eighty titles were identified, 402 of them (37.2%) was repeated, that´s why 678, in which the summaries had been revised, were preserved. Three hundred ninety-three articles did not adjust to the objective and were discarded. The remaining 285 (42.0%) were acquired in full text format. After that, at the first selection, 131 tittles were selected (46.6%); in the second selection, only 41 articles were considered appropriate. Additionally, with the alert system three publications were obtained from 2017 that, after being reviewed, were chosen.

Maternal vaccine and infant immunogenicity

The MV is a strategy, which aims to preserve healthy to the pregnant mother as well as taking advantage of the passage of antibodies through the placenta and generating immunity in the infant before he/she receives his routine vaccines.[3,6,9,12,13,24,27-29]

Regarding pertussis, immunogenic capacity that can be achieved with MV is observed in the clinical trial of Hoang, who administrated Tdap (in the group A) or a vaccine against tetanus (in the group B) in pregnant women from Vietnam.[30] There were no differences about IgG-BP among the groups before the vaccination: group A: 8,2 IU/ml [95%IC:6,4-10,6]; group B: 7,9 IU/ml [95%IC:4,9-10,4]. One month after vaccination, the IgG-BP raised to 33,1 IU/ml [95%IC:4,3-7,6] in the Tdap group; this was not evaluated in the other group. At the time of delivery, the levels were: group A: 17,3 IU/ml [95%IC:13,0-22,0; group B: 5,7 IU/ml [95%IC:4,3-7,6], P<0,001. It was detected the same difference in an umbilical cord sample: 21,0 IU/ml [95%IC:16,0-28,0] compared to 7,2 IU/ml [95%IC:5,6-9,4]. The difference remained significant before the vaccination of infants, 4,2 IU/ml [CI95%:2,9-5,9] and 0,8 IU/ml [95%CI:0,5-1,3],P<0,001. One month after completing the childhood vaccination there were no differences between groups of infants, 70,0 IU/ml [95%CI: 58,0-84,0] group A and 67.0 IU/ml [95%CI: 53,0-84,0] B-group, p=0.73. The findings were similar in antibodies against filamentous hemagglutinin and pertactin, two antigenic factors of virulence of BP.

The immunogenic impact is different according to the MV moment.[27] Healy found that pregnant preconceptionally vaccinated women, or in early pregnancy, did not present the necessary passage of the antibodies through the placenta to generate the prevention of pertussis in the infant.[29,31] Therefore, Tdap must be administered between 27-36 weeks of gestation.[5] The antibodies declined rapidly, so it is necessary to repeat the vaccination in each pregnancy.[9,12,32] It has been generally accepted that newborns with mothers vaccinated with Tdap during the third trimester of pregnancy have enough anti-BP antibodies to be protected before receiving the children´s scheme.[13,21,24,27,33]

Table 1: Infant morbidity and mortality reduction by pertussis.

Author	Country/Year	Study	Findings
Baxter, et al.	United States 2017	Retrospective cohort of 148.981 infants from a health care organization. Exposure: maternal Tdap application.	Effectiveness to reduce pertussis in the first two months of the infant's life. Effectiveness of the maternal vaccine: 91,4% [95%CI: 19,5-99,1]. Effectiveness of the vaccine applied before pregnancy: 68,6% [95%CI: -44,9 to 93,2]. Effectiveness of the vaccine applied to mothers after childbirth: 45,7% [IC95: -88,2 to 84,3].
Winter, et al.	United States 2017	Retrospective cohort of the California regional vaccination registry. The Tdap in pregnancy or in the first 14 days postpartum.	Effectiveness of the vaccine applied between 27-36 weeks gestation, compared to postpartum administration: 85,4% [95%CI: 33,0-96,7] for prevention in children younger than 4 weeks of age and 72,0% [95%CI: 30,0-89,0] for prevention in children under 12 weeks of age. Effectiveness of the vaccine applied at any time during pregnancy compared to the postpartum vaccine: 63,8% [95%CI: 10,6-85,4]. Vaccination between 27-36 weeks of gestation was more protective than before or after.
Vizzoti, et al.	Argentina 2016	Data analysis of the health surveillance system. Division of the country in regions of high and low coverage of maternal vaccination.	Reduction of pertussis, high comparison with low coverage: 51% [95%CI: 35-67],p<0,001. Reduction of pertussis, comparison of infants less than two months of age with six months of age: 44% [95% CI: 24-66],p<0,001.
Dabera, et al.	United Kingdom (England and Wales)2015	Cases-control study. Cases=children younger than 8 weeks of age with confirmed pertussis (PCR or culture). Controls = children without pertussis. Exposure: maternal application of Tdap.	Effectiveness not adjusted: 91% [95%CI: 77-97] Effectiveness adjusted: 93% [95%CI: 81-97] Maternal vaccination, OR: 0,09 [IC95%: 0,03-0,25]
Fernández, et al.	Spain 2015	Cost/benefit analysis. Estimate of the needed number to vaccinate (NNV). Two groups: maternal vaccination and cocoon strategy.	The number of parents, cocoon strategy, needed to vaccinate (NNV) to prevent hospitalization of children aged 0-2 months was 6.616. To prevent hospitalization in children under one year was 4.752 and to prevent one death was 936.715. The cost of vaccination to prevent a death was 15.783.648 EUR. With maternal vaccination the NNV was 1.451 to prevent hospitalization in infants from 0-2 months, of 1.331 to prevent hospitalization in children under one year and 205.420 to prevent one death. The cost of vaccination to prevent a death was 3.461.326 EUR.
Amirthalingam, et al.	England 2014	Data Analysis Public Health System. Comparison 2012 without vaccination and 2013 with maternal vaccination.	Confirmed cases: 36% reduction [95%CI: 33-38]. Hospital admission: reduction of 58% [95%CI: 37-63]. In younger children three months, confirmed cases reduced to 80% [95%CI: 69-87] and admission to hospital, reduction of 66% [95%CI: 57-75]. Effectiveness of maternal vaccination for pertussis prevention in children under three months: 91% [95%CI: 84-95].
Terranella, et al.	United States 2013	Cohort study. Compare Tdap in pregnancy, postpartum and cocoon strategy, (postpartum, father and grandfather).	Case reduction, maternal vaccination: 33%, maternal vaccination postpartum: 20%, cocoon strategy: 32%. Reduction hospitalization respiratory events, maternal vaccination: 30%, maternal vaccination postpartum: 19%, "cocoon strategy": 32%. Reduction of hospitalization in neurological events: maternal vaccination: 33%, maternal vaccination postpartum: 20%, cocoon strategy: 32%. Reduction of mortality, maternal vaccination: 49%, maternal vaccination postpartum: 16%, cocoon strategy: 29%.
Meregaglia, et al.	Italy 2013	Data from clinical cases reported in a surveillance system. Hospitalizations in children under 12 months of age. Cocoon strategy intervention and no vaccination.	In 2009-2010 non-vaccination, 46 hospitalizations. Attributable transmission risk of 32% = 33 hospitalizations, vaccine effectiveness: 28.3%. Assignable transmission risk of 40% = 30 hospitalizations, vaccine effectiveness: 34.8%. Attributable transmission risk of 55% = 23 hospitalizations, vaccine effectiveness: 50%. At low incidence of pertussis, the cocoon strategy may be poorly effective.

In addition, the MV with Tdap offers two benefits: reducing morbidity and decreasing the infant mortality caused by pertussis (Table 1).

Reduction of infant morbidity by pertussis

Possibly this is due to the passage of maternal/fetal antibodies and the prevention related to the transmission of germs from the maternal respiratory tract.[3,12] Amirthalingam evaluated different population groups before and after the introduction of Tdap as MV.[34] There was a reduction in the 36% of confirmed pertussis cases, from 5,909 cases in 2012 to 3,795 in 2013, which represents a decrease of 58% in the admission to the hospital at all ages. The reduction percentages were higher in children under three years-old: 80% in confirmed cases and 66% in hospital admission. The MV efficacy was 91% in newborns under three months of age, if the vaccination had been carried out seven days before the delivery. No differences were found about the efficacy when it was compared to the MV carried out between 7 and 27 days before the delivery and at least 28 days before the birth.

In other situation, the efficacy decreased to 38% when the MV was carried out from 0 to 6 days before the delivery, or 1 or 3 days after the birth. Terranella found similar findings and observed that the MV reduce more the incidence of infant pertussis and its hospitalizations by respiratory complications than postpartum maternal vaccination (PMV): 33 and 38% versus 20 and 19%, respectively.[13] If it is carried out a PMV joined to a vaccination of the father and the grandfather, the figures will be similar to MV and the costs would be more elevated. Carcione did not identify differences in infant pertussis cases when the two parents were vaccinated in postpartum compared to those who did not get the vaccination: 1,9/1000 vs. 2,2/1000, HR: 0,91 [95%IC:0.55-1.53]. Besides, the PMV was not protective: HR: 1,19 [95%IC: 0,82-1,72].[35]

A case-control study pointed out about the good efficacy of Tdap applied as MV to prevent infant pertussis with a 93% adjusted by gender, geographic area and period at birth, it was similar to the observed reduction in the same population since the introduction of MV.[36] Equally, a cohort study analyzed 148,881 newborns, of which 17 presented pertussis at the first two months of age; it was estimated an efficacy of 91.4% in the administration of MV eight days before the delivery and 45.7% for PMV. Vizzotti estimated a reduction of pertussis of 51% in the high vaccination coverage compared to the low vaccination one.[37] When infants between 2 and 6 months of age were compared to infants older than six years-old it was detected a decrease of 44.0%. The aforementioned study seems the first to demonstrate the reduction of infant pertussis with MV in a developed country.

Due to the intrafamiliar contagion, where the parents are the transmitters in the 50% of the cases: grandparents with 8% and siblings with 20%, it has been proposed to apply the cocooning vaccination, also known as the cocoon strategy, to parents, relatives, caregivers and close friends.[8,13,17] This vaccination is characterized by its controversial cost–effectiveness and its difficult application but it is considered effective and safe.[3,12] Meregaglia estimated the necessary number of vaccinations, using the cocoon strategy, to prevent the hospital admission of infants with pertussis.[22] Moreover, the author concluded that 10,000 vaccinations must be applied to prevent the hospitalization in infants under 12 months, assuming that the parents had 32% risk of illness for the patients. Seventy-seven hospital admissions were found by pertussis in children under 3 months years old in the period between 2005-2010 for a rate of 34/10,000 inhabitants. If the risk of attributable transmission were 55%, 23 hospitalizations and 50% of effectiveness would be expected. The cocoon strategy is applied in several countries, especially in those where the morbidity is high; however, it has been said that this strategy is not suitable when the coverages of the vaccination are deficient.[38,39]

Infant mortality reduction by pertussis

The entity is endemic in many places and it can cause the death of newborns.[3,8,40,41] According to Chilean studies, 16 infants under six months of age died in 2011; 13 of 1,240 notifications with a fatality rate of 1.04% in 2012; three newborns died in 2013 and seven in 2014.[16] In United Kingdom were reported sixteen deaths by pertussis in infants under three months old that were born before the introduction of MV. 513 hospitalizations were registered in children of the same age and in the same period of time, which allowed to estimate a rate of fatal cases of 3,1% [95%IC: 1,7-4,7].[12] The death by confirmed pertussis in 17 infants between 2 and 9 weeks that born to unvaccinated mothers.[34] By means of a model that involves rates by year, Jan van Hoek considered the MV is effective to prevent the death of infants by pertussis, also is possible that the amount of deaths would be underestimated.[12] At the same time, Terranella concluded that the MV reduces the infant mortality by pertussis in a greater proportion than cocoon strategy, whose impact is less than PMV.[13] Fernández estimated that in Spain the MV was more favorable than cocoon strategy to reduce the mortality by pertussis in newborns under one year.[42]

Security and cost/effectiveness

As with MV, there has been a reduction in infant morbidity and mortality by pertussis, it is universally recommended using the vaccine in prenatal care.[3,18,21,25] However, it is important to note what has been defined in terms of security. Kharbanda, in a cohort study, noted that the MV was not associated with preterm birth RR; 1,03 [95% CI: 0,97-1,09], small for gestational age RR:1,00 [95%CI: 0,96-1,06]) or hypertensive disorders RR: 1,09 [95%CI: 0,99-1,20).[19] The same author found association with chorioamnionitis RR: 1,19 [95%CI:

1,13-1,26],, with small effect and possible confounding factor that needs to be extensively analyzed. Others authors have not observed adverse events in women, fetuses or neonates.[43-45] In a cohort study (46) were compared pregnant women with 32 or more weeks of pregnancy who accepted the MV with others who did not accept it, without observing differences in maternal adverse events, neonatal death, congenital malformations, APGAR, umbilical cord blood pH, chorioamnionitis, UCI need or artificial ventilation. Zheteyeva also did not identify fetal or neonatal fatal events; he suggested applying a MV with Tadp in all pregnant women, considering the intervention as safe.[47]

It is also important to establish the relation between cost and effectiveness.[8] Sartori concluded that the MV was better in Brazil in terms of cost-effectiveness and was a more useful intervention to prevent cases and deaths by pertussis in infants than not administering it.[48]

Five years earlier, Westra in the Netherlands, considered that the cocoon strategy and MV were cost-effectiveness interventions with increase in the cost of EUR 9.140.000 [95%CI: 9.082.000 to 9.333.000] and EUR 4.053.100 [95%CI: 3.982.400 to 4.456.300], respectively.[11] He estimated a profit of annual quality of life (QALY) due to lower disease and less death by the vaccination with 1.975 [95%CI: 438-3.805] for cocoon strategy and 1.166 [95%CI: 282-2.326] for the MV, calculating the rate of increase in cost-effectiveness (ICER)/QALY: EUR 4.600 [95% CI: 2.200 to 17.800] and EUR 3,500 [95%CI: 1,700-15,000], respectively. It was estimated the ICER/QALY 329.900 EUR [IC95: 256.900 to 1.071.400] for PMV. It is established that the ICER/QALY is calculated for each community and if it is less than EUR 20.000 it identifies intervention cost-effectiveness, so PMV is not cost-effectiveness as opposed to cocoon strategy and MV, being the first of these more expensive to implement but it generates a greater number of QALY. In the United States, the cost/QALY for MV was lower than for PMV: US $ 414.523 and US $ 1.172.825, respectively.[13]

Fernández estimated that the MV was more favorable than cocoon strategy in number needed to vaccinate (NNV) and in cost/benefit in Spanish population.[42] However, Lugnér studied the sensitivity in the Netherlands and compared the cost-effectiveness of three infant protection strategies against pertussis: infant vaccination in the first two months, MV and PMV, the last one had a more attractive ICER, 890.00 EUR/QALY with annual cost of 1.8 million.[9] The MV had 126.000 EUR/QALY and annual cost of three million Euros. The PMV had 318.000/QALY and cost 3.7 million euros/year. So that, none of the three strategies was cost-effectiveness according to thresholds established in said country (EUR 20.000-50.000).

It has been pointed out that cocoon strategy is not efficient to reduce hospitalizations and deaths in communities with a low incidence of infection.[22] About this, Skowronski showed that in the period between 2005 and 2009 in Canada, the NNV was over 10.000 to prevent one hospitalization and one million to prevent death of infants younger than one year.[41]

As the incidence becomes lower, the needed resources to achieve a further reduction are greater. In the study conducted in Italy, where it was also determined that the NNV to prevent hospitalization in younger children of one year was 10.000, the cost per case avoided was high: greater than EUR 100.000.[22] It should be kept in mind that cost/effectiveness is dependent on the incidence, which for future years may be uncertain.[12] In the Spanish population, the cost of vaccination to prevent death is much greater with the cocoon strategy than with the MV: EUR 15.783.648 compared with EUR 3.461.326, respectively.[42]

In 2011 the Center for Disease Control [CDC] and Prevention's Advisory Committee on Immunization Practices [ACIP] recommended Tdap to pregnant women who previously had not received it; in 2013 it was extended to each pregnancy, independent of the previous vaccination and between 27-36 weeks of gestation (1,43).[49] Similarly, the entities indicated to avoid previous recommendations about the use of PMV.[50]

The Global Pertussis Initiative, an international expert group on pertussis, recommended the MV as a first-line intervention, and cocoon strategy as a second line to decrease pertussis in infants in 2015.[51] The WHO demonstrated that the MV is an important cost-effectiveness strategy for preventing pertussis in infants who do not yet receive the regular vaccination schedule.[8] This coincides with the findings of Vilajeliu, who found a strong correlation between levels of IgG-BP antibodies in mothers and in their infants.[14] The immunogenic efficacy to reduce infant morbidity and mortality has a favorable impact on health care, family and social conditions.[52]

Although, the MV is more favorable than the cocoon strategy to apply Tdap in parents, siblings, grandparents or health personnel who have contact with infants less than 12 months old; it is a complementary strategy to administrate the vaccine at least two weeks before the contact.[3,8,29,35]

The coverage of the MV should be increased universally; a study in the French population showed a change from 22% in 2009 to 61% in 2014.[17,10,35,50] Entities that develop public health care policies must offer and stimulate the MV to prevent childhood pertussis in the third trimester.[2,16,27,35,50,53] Health professionals must timely enforce vaccination, which is an activity that is part of the prenatal control.[10,50] Beside, at pregnancy, Tdap can be given concurrently with the influenza vaccine and it remains safe in pregnant women who previously received a vaccine against tetanus.[2,45]

CONCLUSION

The MV with Tdap generated two benefits in terms of the prevention of childhood pertussis. First, there was a reduction in the number of cases reported and in the hospital admission. Second, the decrease in mortality at the first months of age. The MV is a safe strategy for pregnant women, fetus and neonates; also, it is more cost-effectiveness than cocoon strategy and PMV.

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