Autopsy Case Reports

Editorial

# Pertussis in young infants: a severe vaccine-preventable disease

Marco Aurélio Palazzi Sáfadi[a]

Sáfadi MAP. Pertussis in young infants: a severe vaccine-preventable disease [editorial]. Autopsy Case Rep [Internet]. 2015; 5(2):1-4. http://dx.doi.org/10.4322/acr.2015.010

Pertussis (also known as whooping cough) is a highly contagious disease mainly caused by the bacterium *Bordetella pertussis*. It is a strictly human disease and affects all ages.[1] However, the morbidity and mortality associated with pertussis are disproportionally high in young infants — the age group in which we observe virtually all hospitalizations, complications, and deaths related to pertussis.[2-4]

There is strong evidence in the literature showing that the severity of pertussis in these young infants is related to the production of toxins by *B. pertussis*, particularly pertussis toxin (PT). PT has a critical role in the pathogenesis of severe disease; it induces leukocytosis with lymphocytosis and elevated cAMP levels, which contribute to pulmonary vasoconstriction. Extreme leukocytosis is a marker of poor outcome in young infants with pertussis, and is frequently associated with severe hypoxemia, pulmonary hypertension, and death.[5,6]

The introduction of routine immunization programs against pertussis in children worldwide provided a substantial reduction in the incidence of the disease. However, control of the disease has never been achieved, and in the last decade a resurgence of pertussis was reported in several countries.[7,8] Although the reasons for this resurgence are not fully understood, the probable factors that explain the observed increased rates of disease worldwide are: (i) the availability of more sensitive techniques (polymerase chain reaction) for the diagnosis; (ii) increased awareness and more efficient reporting among healthcare workers; (iii) genetic changes in *B. pertussis* strains; and (iv) rapid waning immunity after acellular vaccines.[9]

The rapidly waning immunity, which occurs after either immunization or natural exposure to the causative agent, plays a critical role in disease transmission in the community. Several studies confirmed the importance of household contacts as the main source of pertussis transmission to unprotected young infants.[10-12] The absence of the classic pertussis symptoms in most of the infected adolescents and adults makes the recognition of the disease and the diagnosis difficult in this age group.

In order to anticipate protection against pertussis, the strategy of using pertussis vaccines during the newborn period has been attempted in several studies. Despite conflicting results, there was a trend toward lower responses to subsequent vaccine doses, either using whole-cell or acellular vaccines, which limited the utility of this approach.[13]

In an effort to provide indirect protection to vulnerable young infants, different vaccination strategies targeting adolescents and adults – in addition to children – were recommended in several countries, including vaccination programs with Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) for adolescents, adults, postpartum women, and household contacts of infants.[14,15]

[1] Department of Pediatrics – Division of Infectious Diseases – FCM da Santa Casa de São Paulo, São Paulo/SP – Brazil.

The implementation of adolescent programs with a single Tdap dose in the US resulted in a decrease in the incidence rates of disease among the age group targeted for the vaccination. However, the expected indirect effects of adolescent Tdap vaccination were not observed in other unvaccinated age groups, including infants.[16] The limited role that adolescents play in the transmission of disease to infants, the low coverage of vaccination programs among adolescents, and the limitations of the Tdap vaccine to protect against pertussis infection, were implicated in the lack of impact of this strategy on disease rates in young infants. Another intervention that was implemented with the aim of providing indirect protection to young infants was the "cocooning" strategy: the vaccination of postpartum women, plus adolescents and adults who have close contact with infants (including healthcare workers). Although parents and other caregivers of infants have been shown to be an important source of disease transmission to young infants, this strategy also proved to be of limited impact in the real world setting. The major challenge for the "cocoon" strategy is to achieve broad vaccination coverage among all potential close contacts of the newborn infant. Immunization of only postpartum mothers with the Tdap vaccine was demonstrated to be insufficient to reduce pertussis illness in infants ≤ 6 months of age.[17]

The persistent high rates of pertussis, which are associated with the unacceptably high morbidity and mortality observed in young infants (despite all the efforts to control the disease in this vulnerable age group) led the health authorities in several countries to recommend an alternative approach: the implementation of maternal vaccination programs for pertussis during pregnancy.[18,19] The rationale of this strategy is to provide protection for infants from birth through the trans-placental passive transfer of maternal antibodies. This strategy has the added benefit of protecting the mother against disease, potentially reducing household transmission, and preventing infant infection.

In order to optimize antibody transfer and protection at birth, taking into account the results from antibody kinetics studies performed in healthy adults,[20] the recommendation is to vaccinate women between 28 and 38 weeks of gestation.[19] The short persistence of anti-pertussis antibodies in women previously vaccinated emphasizes the need to recommend a Tdap dose in each pregnancy.[21]

A few years after being implemented, the recent publication of data on the uptake, safety, and effectiveness of the pertussis vaccination program for pregnant women in the UK, as well as the impact on disease rates in infants, is encouraging and provides robust evidence in favor of this intervention.[22-27]

The results of the first two studies evaluating the effectiveness of the program, using different methods, have each shown for the very first time that maternal immunization with an acellular pertussis vaccine provided around 90% protection against disease in young infants.[25,26]

By December 2014 in the UK, more than 60% of pregnant women received a dose of the pertussis vaccine—the highest rate since the start of the program in October 2012. The reduction in disease rates has been observed in infants under 6 months of age who are targeted by the maternal pertussis vaccination program, without an impact on other age groups. After the introduction of the pregnancy program in the UK, 10 deaths had been reported in young infants with confirmed pertussis, of which 9 were born to mothers who had not been vaccinated against pertussis.[27]

Furthermore, no evidence of an increased risk of adverse events among these women or their infants was reported in clinical trials, in observational cohort studies, or in post-marketing surveillance reports evaluating the safety of pertussis vaccines during the third trimester of pregnancy.[22-24]

In Brazil, the same phenomenon reported in other countries was also observed with increasing rates of cases, hospitalizations, and deaths related to pertussis in recent years. In 2013, 109 pertussis-related deaths were reported – a number 7-fold higher than the average number of deaths reported annually in the period from 2001 to 2010. More than 80% of the deaths occurred in infants younger than 3 months of age. To address this serious situation, in late 2014, the Ministry of Health announced the introduction of the Tdap vaccine for all pregnant women in Brazil.[28] Argentina, Uruguay, Costa Rica, Mexico, Panama, Israel, New Zealand, and Belgium – among other countries – also implemented maternal vaccination programs for pertussis during pregnancy, following the examples from the US and the UK.[29]

Although continued surveillance is still needed to provide more robust evidence of the long-term safety and effectiveness of Tdap immunization programs during pregnancy, the early results of these programs are encouraging, which highlights the importance of educating healthcare providers and the public on the benefits of maternal immunization in order to achieve control of pertussis in young infants. The great challenge of this intervention appears to be the goal of a high coverage among the pregnant women cohort to optimize the impact of the vaccination program. All countries that can afford the costs of a Tdap vaccination program in pregnant women should not postpone the decision to implement these recommendations. It is time to vaccinate pregnant women!

Finally, maternal immunization during pregnancy also seems to be a very attractive strategy to control other diseases that are potentially preventable by vaccines. In the next coming years, the experience accumulated with tetanus, influenza, and pertussis will pave the way for the development of maternal vaccination programs against other severe diseases for the young infant, such as those caused by group B streptococcus and respiratory syncytial virus.

## REFERENCES


1. Cherry JD, Heininger U. Pertussis and other Bordetella infections. In: Feigin RD, Cherry J, Demmler-Harrison GJ, Kaplan SL, Steinbach WJ, editors. Feigin and Cherry's textbook of pediatric infectious diseases. 6th ed. Philadelphia: WB Saunders Co.; 2009. p. 1683-1706.

2. Amirthalingam G, Gupta S, Campbell H. Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. Euro Surveill. 2013;18(38):20587. http://dx.doi.org/10.2807/1560-7917.ES2013.18.38.20587. PMid:24084340.

3. Cortese MM, Baughman AL, Zhang R, Srivastava PU, Wallace GS. Pertussis hospitalizations among infants in the United States, 1993 to 2004. Pediatrics. 2008;121(3):484-92. http://dx.doi.org/10.1542/peds.2007-1393. PMid:18310196.

4. Haberling DL, Holman RC, Paddock CD, Murphy TV. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. Pediatr Infect Dis J. 2009;28(3):194-8. http://dx.doi.org/10.1097/INF.0b013e31818c9032. PMid:19209089.

5. Paddock CD, Sanden GN, Cherry JD, et al. Pathology and pathogenesis of fatal Bordetella pertussis infection in infants. Clin Infect Dis. 2008;47(3):328-38. http://dx.doi.org/10.1086/589753. PMid:18558873.

6. Pierce C, Klein N, Peters M. Is leukocytosis a predictor of mortality in severe pertussis infection? Intensive Care Med. 2000;26(10):1512-4. http://dx.doi.org/10.1007/s001340000587. PMid:11126265.

7. World Health Organisation (WHO). WHO Surveillance and burden: pertussis. Geneva: WHO; 2014 [cited 2015 Feb 26]. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/

8. Centers for Disease Control and Prevention (CDC). 2014 Provisional pertussis surveillance report. Atlanta: CDC; 2014 [cited 2015 Feb 25]. Available from: http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2014.pdf

9. Cherry JD. Epidemic pertussis in 2012--the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367(9):785-7. http://dx.doi.org/10.1056/NEJMp1209051. PMid:22894554.

10. Bisgard KM, Pascual FB, Ehresmann KR, et al. Infant pertussis: who was the source? Pediatr Infect Dis J. 2004;23(11):985-9. http://dx.doi.org/10.1097/01.inf.0000145263.37198.2b. PMid:15545851.

11. Wendelboe AM, Njamkepo E, Bourillon A, et al, Transmission of Bordetella pertussis to young infants. Pediatr Infect Dis J. 2007;26(4):293-9. http://dx.doi.org/10.1097/01.inf.0000258699.64164.6d. PMid:17414390.

12. Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010;50(10):1339-45. http://dx.doi.org/10.1086/652281. PMid:20370464.

13. Edwards KM, Berbers GA. Immune responses to pertussis vaccines and disease. J Infect Dis. 2014;209(Suppl 1):S10-5. http://dx.doi.org/10.1093/infdis/jit560. PMid:24158958.

14. Broder KR, Cortese MM, Iskander JK, et al, Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-3):1-34. PMid:16557217.

15. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011;60(41):1424-6. PMid:22012116.

16. Skoff TH, Cohn AC, Clark TA, Messonnier NE, Martin SW. Early Impact of the US Tdap vaccination

program on pertussis trends. Arch Pediatr Adolesc Med. 2012;166(4):344-9. http://dx.doi.org/10.1001/archpediatrics.2011.1093. PMid:22213608.

17. Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. Clin Infect Dis. 2012;54(1):78-84. http://dx.doi.org/10.1093/cid/cir765. PMid:22075790.

18. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep. 2013;62(7):131-5. PMid:23425962.

19. Davies SC. Temporary programme of pertussis (whooping cough) vaccination of pregnant women. London: Public Health England; 2012 [cited 2015 Mar 02]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338567/PHE_pertussis_in_pregnancy_information_for_HP_2014_doc_V3.pdf

20. Halperin BA, Morris A, Mackinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis. 2011;53(9):885-92. http://dx.doi.org/10.1093/cid/cir538. PMid:21946190.

21. Healy CM, Rench MA, Baker CJ. Importance of Timing of Maternal Combined Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Immunization and Protection of Young Infants. Clin Infect Dis. 2013;56(4):539-44. http://dx.doi.org/10.1093/cid/cis923. PMid:23097585.

22. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311(17):1760-9. http://dx.doi.org/10.1001/jama.2014.3633. PMid:24794369.

23. Zheteyeva YA, Moro PL, Tepper NK, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012;207(1):59.e1-7. http://dx.doi.org/10.1016/j.ajog.2012.05.006. PMid:22727350.

24. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ. 2014;349:g4219. http://dx.doi.org/10.1136/bmj.g4219. PMid:25015137.

25. Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015;60(3):333-7. http://dx.doi.org/10.1093/cid/ciu821. PMid:25332078.

26. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014;384(9953):1521-8. http://dx.doi.org/10.1016/S0140-6736(14)60686-3. PMid:25037990.

27. Public Health England. Pertussis vaccination programme for pregnant women: vaccine coverage estimates in England, September to December 2014 . London; 2015. Health Protection Report, 6 [cited 2015 Feb 27]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/408500/hpr0715_prtsss-vc.pdf

28. Brasil. Ministério da Saúde. Epidemiology of pertussis. Brasília: Ministério da Saúde; 2014 [cited 2015 May 29]. Available from: http://portalsaude.saude.gov.br/images/pdf/2014/julho/15/Tabela-de---bitos-por-Coqueluche.%20Brasil,%20Grandes%20Regi%C3%B5es%20e%20Unidades%20Federadas.%201998%20a%202013.pdf

29. Safadi MA. Control of pertussis in infants: time has finally come? Expert Rev Vaccines. 2015;14(6):781-3. http://dx.doi.org/10.1586/14760584.2015.1043274. PMid:25968349.

## FINANCIAL AND COMPETING INTERESTING DISCLOSURE

**No writing assistance was utilized in the production of this manuscript.**

**Correspondence**
Marco Aurelio P. Sáfadi
Department of Pediatrics
Division of Infectious Diseases
FCM da Santa Casa de São Paulo
Rua Afonso Braz, 579, Cj 45, São Paulo/SP – Brazil
CEP: 04511-011
Phone: +55(11) 3053-3005
**E-mail**: masafadi@uol.com.br