Pertussis and Vaccine Prevention

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Introduction

Pertussis is an acute respiratory disease caused by a Gram-negative coccobacillus, called *Bordetella pertussis*, which is difficult to develop in culture media (fastidious) and proper identification requires non culture techniques such as PCR or serology. The disease can be serious in children less than six months. Recent outbreaks of pertussis cases are a challenge in many countries using cellular and acellular vaccines, even those countries with high vaccination coverage. Different strategies and improved vaccines are required to attain adequate global control of the disease.

Pathogenesis and Immunity

The infection is transmitted person to person via respiratory secretions of sick individuals. If exposure is extensive and within a close range, 80 to 100% of susceptible individuals may get infected. Seventeen susceptible individuals will be infected per every case (reproduction rate).[1] The infectious period may last three or more weeks absent an antimicrobial treatment.

The bacteria spreads through respiratory droplets to the ciliated epithelium in the upper respiratory tract and adheres via adhesins such as filamentous haemagglutinin, fimbriae, and pertactin. The pertussis toxin, on the other hand, penetrates the epithelium and significantly modifies the non-specific immune response such as chemotaxis, the complement system, phagocytosis, and specific immunity, by suppressing B and T cells. The pathogenesis of the encephalopathy is not completely clear and may be secondary to hypoxia, microhemorrhages or direct action of the pertussis toxin.[1]

The immune response to the natural infection or the use of vaccines is not completely characterized and seems to involve a humoral immune response and a cellular response. There is no defined serological correlate of protection. The natural infection produces an immune cellular response with interferon gamma secretion but no interleukin 5 (IL5), a classic response pattern of the T helper type 1 cells (Th1), which generates a more prolonged, but undefined, immunity than the vaccine-generated immunity.[1,2]

The Disease

The spectrum of the infection may involve from an asymptomatic manifestation up to the classic manifestation characterized by three periods: catarrhal, paroxysmal, and convalescent. The incubation period is 7 to 10 days.

The catarrhal period is the most infectious but the disease is rarely diagnosed in this phase. It lasts 1 to 2 weeks and it is indistinguishable from any upper respiratory tract infection.

The paroxysmal period is the defining one for the disease and it is characterized by nonproductive cough fits, followed by inspiratory stridor and posttussive emesis. It does not produce fever unless a superinfection occurs; the patient appears normal between coughing episodes. Cough may last up to three months and it may be evoked later on by other respiratory infections for years.

Pertussis affects individuals of any age but its manifestation is more severe in children under one year of age. In particular, infants younger than 3 months, who develop complications such as apnea, pneumonia, seizures or encephalopathy, have a fatality rate of 1.3% during the first month of life.

In adolescents and adults the infection may be asymptomatic; however, it may manifest as a prolonged, nonspecific cough but also as more classic episodes of paroxysmal cough with emesis and posttussive stridor. Studies in these populations show that 25% of adolescents and 40% of adults over 60 suffer from complications[3] such as sleep disorders, rib fractures, urinary incontinence and cough-induced syncope. The disease is also associated with work absenteeism, since between 1% and 4% of adult cases require hospitalization.[3,4]

The clinical manifestation of the disease is not only modified by age but also by vaccination: cases in vaccinated individuals are milder and less infectious than cases in non-vaccinated individuals.[5] The infectiousness of the disease is reduced with the use of antimicrobials as macrolides, but the symptoms are not modified unless the therapy is started early on in the catarrhal period.

The immunity conferred by the natural infection is more prolonged than the one conferred by the vaccines. A study of home contacts in Germany showed symptomatic reinfections only 15 to 20 years after suffering from pertussis.[6]

Diagnosis

The World Health Organization (WHO) has defined a confirmed clinical case as a person with a cough lasting at a minimum of 14 days with at least one of the classic symptoms (paroxysms of coughing, posttussive vomiting, inspiratory whooping) and, in newborns, as respiratory syndrome with apneas.[7] It is considered a laboratory-confirmed case if there is a culture, polymerase chain reaction (PCR), or positive-paired serology. Some countries have adapted the definition and added the epidemiologic link to a laboratory-confirmed case.[8,9]

Ordinary laboratory tests are not helpful except in unvaccinated children who exhibit leukocytosis with marked lymphocytosis. Confirmation of the infection requires detection of DNA, the agent itself, or the immune response. Therefore, PCR is considered the gold standard because it has high sensitivity and specificity. It is very useful in the catarrhal and paroxysmal phases but *Bordetella* DNA becomes undetectable after the third week of

the disease. It is very useful in adolescents and adults but serology (Ig A) performs better in this population since the diagnostic suspicion occurs later on. The culture is very specific but slightly sensitive and rarely available for clinical use. Immunofluorescence is not an advisable test given its variable sensitivity and specificity.[8]

Global Epidemiology

Pertussis continues to be a public health problem, including in countries with high coverages of vaccination. It follows an endemic pattern with outbreaks every 2 to 5 years. When analyzing incidence figures and the ethereal distribution of cases it is important to consider that despite being a notifiable disease, there is very significant underreporting amongst school-aged children, adolescents, and adults who are not suspected even with the classic manifestation. Studies with active case searches suggest between 10 and 1,000 undiagnosed cases per confirmed case.[9,10] In Latin America underreporting of pertussis is significant. In 2012, WHO reported 23,489 cases in the Americas, yet the CDC confirmed 49,000 cases only in the United States.[11]

Over the last thirty years there has been a progressive increase of reporting, in particular amongst school-aged children in developed countries. Starting in 2011-2012, a significant reemergence of infection has been observed in Canada, the United States, the United Kingdom, Switzerland, Germany, Australia, and Japan in spite of high vaccine coverages, with a high rate of cases in adolescents and adults.[11] This epidemiologic shift has been related to the fact that the protection conferred by the acellular vaccines used by developed countries is shorter (5 - 7 years), and there is greater suspicion and confirmation of cases through improved laboratory tests. The emergence of mutant *B. pertussis strains*, against which the vaccine confers no protection, is controversial since a recent study shows the presence of a high rate of strains lacking pertactin. This would not impact the effectiveness of the vaccine.[12]

In developing countries where cellular vaccines are used, the outbreaks have been less evident and the reported cases affect children under one year of age.[11] Argentina, Chile, and Colombia have described outbreaks in infants and do not report cases in other age groups probably due to a lack of clinical suspicion rather than a lack of cases.[8]

The source of infection in infants younger than one year of age is identifiable in 31 to 70% of the cases, including the parents, usually the mother, but also older siblings and grandparents.[13,14] The role of health-care providers in the transmission of *B. pertussis* to patients has also been properly documented, given community outbreaks.[15]

Vaccines

In the era prior to the introduction of pertussis vaccines, practically all children became infected with *B. pertussis* and presented the classic manifestation of pertussis. Countries with high vaccination coverages have managed to decrease the incidence and mortality[1] associated with pertussis by more than 90 percent. However, pertussis is still currently a public health problem since the inter-epidemic period that is maintained between 2 and 5 years has not been extended, similarly to what happened prevaccination. This is mainly due to the fact that the immunity conferred by the vaccines has a limited duration which does not exceed 4 to 12 years.[16] Also, circulation of this agent has not been significantly reduced in spite of the use of vaccines given the limited effect on colonization and infection as suggested by experimental evidence in primates.[17]

There are two types of vaccines available: whole-cell and acellular vaccines. Whole-cell vaccines (wP), available since 1940, are manufactured based on the whole cells of the inactivated (killed) bacteria and have about 3,000 antigens. They are only used in children younger than 7 years of age given the higher frequency of adverse reactions at a later age. They are used in combination with the tetanus (T) and diphtheria (D) toxoids, hepatitis B (Hep B) surface antigen and *H. influenzae* B (Hib) conjugate.

The other group of vaccines comprises acellular vaccines (aP and ap based on the antigen content level) developed in the 70s due to the fear of association of the whole-cell vaccines with neurological disorders in children, many of which were disproved later on. As of 1981, acellular vaccines are marketed in Japan and, as of 1991, in the United States. These vaccines have had the endotoxin removed and they only have between 3 and 5 highly-purified antigens such as pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae. They were associated with a lower frequency of local and general reactions. There are acellular vaccines for use in children and others for use in adolescents and adults with a lower antigen content that decrease adverse events.

Whole-cell vaccines and acellular vaccines have similar efficacy, inducing high levels of antibodies that inhibit adhesion to the respiratory epithelium and neutralize toxins; however, humoral immunity is insufficient since *B. pertussis* is not only an extracellular agent but it can also invade cells as pulmonary macrophages and stay there for months. Proper protection requires cell-mediated immunity. Whole-cell vaccines induce an immune response dependent on T helper type 1 cells (Th1) and, thus, memory immunity that generates longer protection. Therefore, the Pan American Health Organization (PAHO) recommends the use of this vaccine in infants. Acellular vaccines, in turn, induce Th2-type immunity with little memory.[18,19]

Children who only received acellular vaccines in their first year of life have a six-fold risk of suffering from pertussis during the school years or adolescence, as compared to those who received at least one dose of the whole-cell vaccine.[20] Recent information on the use of the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine among students 11 to 19 years shows that its effectiveness would not exceed 65 to 70 percent.[21]

In Latin America whole-cell vaccines are used in the primary schedule at 2, 4 and 6 months, with boosters during the second year of life and also between 4 and 6 years. Only some countries use an additional dose of the acellular vaccine in adolescence.[8]

The impact of the vaccine depends on high coverage and is particularly critical for this infection, whose reproductive number is very high and similar to the measles number. Therefore, coverage rates of 95% are needed for proper control. In Latin America, pertussis vaccine coverage was maintained at close to 90% in the 2005-2013 period, but it decreased to 88% in 2014. This decrease follows a declining trend over the last four years, but with great variability based on the countries and their districts. In 2014, only 20 of 40 countries in Latin America had coverages ranging between 80 and 95% and three of them only reached 50 to 84%.[22]

Other Control Strategies

The main control measure is to maintain high vaccine coverages, ideally over 95% for the third DTP (diphtheria-tetanus-pertussis) dose in the first year. This is not easy to achieve in other age groups so the agent continues to circulate and generate outbreaks. Consequently, other strategies have been used such as the method known as cocooning. This strategy intends to protect the newborn and young infant through immunization with acellular vaccines for the mother, and other family members in close contact with the child. This approach

has been used in countries such as Australia, France, Germany, and Costa Rica. The impact of these measures is limited, costly and quite burdensome. In Chile, it was used in some regions where 91% of the mothers were vaccinated in the postpartum period but only 60% of the other family members received the vaccine. Together with other measures, disease fatality was eliminated amongst children in these regions while using cocooning.[23] Considering that the immune response in vaccinated individuals takes about two weeks, this strategy would maintain the child unprotected during the first 2 to 3 weeks of life.

Ideally, the vaccine should be administered during pregnancy. The Tdap vaccine is not registered for use in pregnant women but the strategy is quite promising, since it allows earlier protection for the child by avoiding infection in the mother and attaining passive protection of the child through the transfer of prenatal antibodies.

Additionally, recent data shows that mothers vaccinated during pregnancy have significantly higher levels of anti-pertussis antibodies in their breast milk[24] and such impact should be assessed. In a recent study conducted in the United States with the Tdap vaccine during pregnancy,[25] levels of antibodies were compared in newly postpartum women with or without the vaccine and a significant increase of antibodies was observed against diphtheria, tetanus, pertussis toxin, FHA, pertactin and fimbriae in the vaccinated group. Additionally, observational studies and case-control studies in England — one country that uses this approach — show that the efficacy to prevent pertussis in children under 2 months would reach 90%.[26,27] The best age for vaccination would be between 27 and 30 weeks of gestation. In the United States, the recommendation is to revaccinate the mother with every new pregnancy. The vaccine is properly tolerated and it is not associated with complications for the mother or the fetus.[28] There is no interference with either pediatric vaccines of the infant or impact on the growth or development of the child.[28-30] This approach is used in the United States, New Zealand, Belgium, Israel, and the United Kingdom, and in several Latin American countries including Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Paraguay, Panamá and Uruguay. This strategy has proven to be the most cost-effective and it is currently recommended by the Global Pertussis Initiative.[31]

The acellular booster in adolescence is another strategy used in Argentina, Panama, Uruguay, and Chile.[11] Vaccination of health workers in contact with children is another option used in Argentina, Panama, and also in Chile during the last 2011–2012 outbreak. The duration of the protection of acellular vaccines is short but this strategy may be useful in outbreak situations. Finally, countries such as Canada, France, and the United States have opted for recommending universal vaccination of adults every 10 years with Tdap; however, such coverage would require special effort since observance of vaccination in adults is very low and the cost of this strategy is very high.

Conclusions

None of the strategies proposed will be able to adequately control pertussis, in particular with the progressive introduction of acellular vaccines that reduce the severity of the disease and mortality, but have minimal impact on colonization and transmission. Therefore, the development of improved vaccines should be a priority. Such vaccines must require less doses, must generate long-lasting and better quality immunity, and ideally be used from the newborn period onwards. Some of the vaccine candidates include products with a higher number of antigens,[32] as well as encapsulated vaccines with adjuvants that favor Th1 and Th17 response,[32-34] and also live attenuated vaccines administered nasally in the neonatal period. The latter vaccine candidates have successfully completed Phase I trials in humans.[32]

As we wait for improved vaccines to enter the market, the strategies recommended for Latin America are:

- To improve surveillance systems and use of PCR diagnostic confirmation of *B. pertussis* infection.
- To continue the use of cellular vaccines in countries currently following a whole-cell vaccination schedule while the duration of immunity provided by acellular vaccines is evaluated.
- To provide timely vaccination and maintain standardized DTP coverages above 95% throughout the region and the districts.
- To use the Tdap vaccine in pregnant women during the second and third trimesters.

References

1. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*, 6th ed. Philadelphia, Saunders, 2013:447–492.

2. Cherry J, Paddock C. Pathogenesis and histopathology of pertussis: implications for immunization. Expert review of Vaccines 2014:1115-112.

3. De Serres, G, Shadmani R, Duval B, Boulianne N , Dery P, Douville Fradet M et al. Morbidity of pertussis in adolescents and adults. *J Infect Dis* 2000; 182:174–179.

4. Rothstein E, Edwards K. Health burden of Pertussis in adolescents and adults. *Ped Infect Dis J* 2005; 24: S44-S47.

5. Preziosi MP, Halloran ME Effects of Pertussis Vaccination on Disease: Vaccine Efficacy in Reducing Clinical Severity CID 2003: 37: 772-779.

6. Wirsing Von Konig CH, Postels Multani D, Bock H,Schmidt HJ, Pertussis in adults frequency of transmission after household exposure. Lancet 1995: 346:1326-90.

7. WHO-recommended surveillance standard of pertussis. Available from: www.who.int/immunization_monitoring/diseases/pertussis_surveillance. Accessed May 24, 2016.

8. Falleiros Arlant LH, de Colsa A, Flores D, Brea J, Avila ML et al Pertussis in Latin America: epidemiology and control strategies. Expert Review of Anti-infective Therapy 2014;12: 1265-1275, DOI: 10.1586/14787210.2014.948846.

9. Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection. *Pediatrics* 2005; 115:1422–1427.

10. Celentano LP, Massari M, Paramatti D, et al; EUVAC-NET Group. Resurgence of pertussis in Europe. *Pediatr Infect Dis J*. 2005; 24:761–765.

11. Tan T, Dalby T, Forsyth K, Halperin S, Heininger U., Hozbor D., Plotkin S., Ulloa-Gutiérrez R, Wirsing von König HC. Pertussis across the Globe: Recent Epidemiologic Trends from 2000 to 2013. *Pediatr Infect Dis J* 2015; 34: e222–e232.

12. Breakwell L, Kelso P, Finley C, Schoenfeld S, Goode B, Misegades, LK et al. Pertussis Vaccine Effectiveness in the Setting of Pertactin-Deficient Pertussis. *Pediatrics* 2016; 137.1-10. DOI: 10.1542/peds. 2015-3973.

13. Perret C, Viviani T, Peña AM, Abarca K , Ferres M. Fuente de infección de *Bordetella pertussis* en lactantes hospitalizados por tos ferina. *Rev Med Chile* 2011; 139: 448-454.

14. Schellekens J, Wirsing von Konig C-H, MD, Gardner P. Pertussis Sources of Infection and Routes of Transmission in the Vaccination Era. *Pediatr Infect Dis J* 2005; 24: S19–S24.

15. Sandra TJ, Gidengil CA, Lee GM. Pertussis vaccination of healthcare workers. *Clinical Microbiology Reviews* 2008; 21: 426-434.

16. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of Immunity Against Pertussis After Natural Infection or Vaccination. *Pediatr Infect Dis J* 2005;24: S58–S61.

17. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci* USA 2014; 111:787-92.

18. Ryan M, Murphy G, Ryan E, Nilsson L, Schackley F, Gotherforss L et al. Distinct T cell subtype induced with whole cell and acellular pertussis in children. *Immunology* 1998; 93: 1-10.

19. Rowe J, Macaubas C, Monger TM, Holt BJ, Harvey J, Poolman JT, et al. Antigen- specific responses to diphtheria-tetanus-acellular pertussis vaccine in human infants are initially Th2 polarized. *Infect Immune* 2000; 68: 3873–7.

20. Klein NP, Bartlett j, Fireman B., Rowhani-Rahbar A, Baxter R. Comparative effectiveness of Acellular versus whole cell pertussis vaccine in teenagers. *Pediatrics* 2013;131 :1716-1722.

21. Terranella A., Rea V., Griffith M, Manning, Sears, S, Farmer A, Martin S, Patel M. Vaccine effectiveness of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine during a pertussis outbreak in Maine. *Vaccine* 2016; 34: 2496–2500.

22. Technical Advisory Group on Vaccine-preventable Diseases (TAG). XXIII Meeting Varadero, Cuba 1-3 July, 2015.

23. Informe situación epidemiológica de tos ferina Chile, Semana Epidemiológica 1 a 24 (al 16/06/2012). Unidad de Vigilancia, Dpto. Epidemiología DIPLAS/MINSAL.

24. Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Peri R et al. The induction of breast milk pertussis specific antibodies following gestational tetanus–diphtheria–acellular pertussis vaccination. *Vaccin*e 2014; 32: 5632–5637.

25. Gall SA, Meyer JA , Pichichero M. Maternal immunization with Tetanus, Diphtheria and Pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol* 2011 204 : 334–335.

26. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 2014; 384:1521–8.

27. Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Fry NK, and Ramsay M. 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: 333-337.

28. Muñoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, 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 May 7; 311(17):1760–1769.

29. Hardy-Fairbanks AJ, Pan SJ, Decker MD, Johnson DR, Greenberg DP, Kirkland KB, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatr Infect Dis J* 2013 Nov; 32(11):1257–1260.

30. Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics* 1995; 96 (3 pt 2): 580–584.

31. Forsyth K, Plotkin S, Tan T, Wirsing von König CH Strategies to Decrease Pertussis Transmission to Infants. DOI: 10.1542/peds.2014-3925.

32. Poland GA: Pertussis outbreaks and pertussis vaccines: New insights, new concerns, new recommendations? *Vaccine* 2012, 30:6957–6959.

33. Locht C, Mielcarek N. New pertussis vaccination approaches: en route to protect newborns? *FEMS Immunol Med Microbiol* 2012, 66:121–133.

34. Garlapati S., Eng NF, Kiros TG, Kindrachuk J, Mutwiri GK, Hancock RE, et al. Immunization with PCEP microparticles containing pertussis toxoid, CpG ODN and a synthetic innate defense regulator peptide induces protective immunity against pertussis. *Vaccine* 2011 29(38):6540-8. doi: 10.1016/j.