



EDITORIAL

The pertussis problem: classical epidemiology and strain characterization should go hand in hand^{☆,☆☆}



O problema da coqueluche: a caracterização da epidemiologia clássica e da cepa deve ser feita por todos

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In this issue of *Jornal de Pediatria*, Torres et al.¹ present a study on the incidence, clinical features, mortality, and vaccination status of patients with whooping cough in the state of Paraná, in the period of 2007 to 2013. They also provide genotypic data on the *B. pertussis* strains isolated. The study shows that pertussis in Paraná is on the increase, and that most severe symptoms and deaths occur in children younger than 2 months of age. The combination of classical epidemiology – which focuses on incidences, age distribution, and clinical features – with strain characterization is an important aspect of this paper, as only this combination allows us to fully understand the causes for the resurgence of pertussis.

Pertussis is on the increase across the world and, as the authors note, part of this increase is due to enhanced awareness among clinicians and improved detection through the introduction of polymerase chain reaction (PCR). These two factors have resulted in a more accurate assessment of the disease burden, which has tended to be underestimated. The increased accuracy of pertussis diagnosis has led some authors to suggest that the resurgence of per-

tussis is an artifact. However, current knowledge supports the assumption that there is a real increase in pertussis, mainly caused by two factors: waning of vaccine-induced immunity and adaptation of the pathogen by mutations in its DNA. The two factors are not independent, as pathogen adaptation reduces the period in which vaccines are effective and thereby increases the speed in which protective immunity wanes (see below). Hence, waning immunity and pathogen adaptation are two sides of the same coin.² Recent studies indicate that the switch from whole cell vaccines (WCVs) to acellular vaccines (ACVs) has also contributed to the resurgence of pertussis, because immunity induced by ACVs is of shorter duration compared to WCVs.^{3,4} It should be noted, however, that resurgence of pertussis is also observed in countries which have retained WCVs, underlining again, that multiple factors are involved (this study).^{5,6}

Pathogens do not only become resistant against antibiotics, but also against vaccines. However, the latter process is subtler, because vaccine resistance accrues in small steps and may therefore (initially) go unnoticed. Further, vaccine resistance is not absolute and does not imply that *B. pertussis* is able to cause disease in a highly immune host. The effect is less pronounced, in that adapted strains are able to infect hosts at a higher level of immunity (i.e. earlier after vaccination) compared to non-adapted strains. Obviously, this results in an increase in susceptible persons and thus in pathogen circulation.

Although studies in mice have shown that pathogen adaptation affects vaccine efficacy, such effects are difficult to establish in human populations, as they require long-term

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studies with large populations. Therefore, it is important to analyze the nature of the genetic adaptations in order to assess if they are expected to affect vaccine efficacy. In general this is the case with *B. pertussis*. The first adaptations in *B. pertussis* involved relatively small changes in surface proteins known to induce protective immunity: pertussis toxin (Ptx), pertactin (Prn), and fimbriae.² Later, changes in gene regulation were found, which resulted in an increased production of several virulence factors including Ptx and proteins involved in complement resistance.^{7,8} Such changes may result in increased immune suppression and immune evasion. The strains showing increased production of virulence factors belong to the so-called P3 (or *ptxP3*) lineage, which has recently spread worldwide and predominates in many vaccinated populations.^{9,10} Increases in the prevalence of P3 strains have been associated with increased notification in the Netherlands and Australia.^{7,11} A study, using pulsed-field gel electrophoresis (PFGE) to type Brazilian strains, identified two profiles which are found among P3 strains circulating in the US,^{12,13} suggesting that P3 strains are also present in Brazil. Indeed, the genome sequence of a Brazilian P3 strain has recently been published.¹⁴

The most recent adaptation of *B. pertussis* involves the loss of the production of Prn, a component of most ACVs. Prn-deficient strains predominate in a number of countries in which ACVs have been used for many years.^{15,16} Interestingly, Prn-deficient strains have not been observed in Poland, which uses a WCV.¹⁷ This suggests that the introduction of ACVs has selected for Prn-deficient strains, and that their emergence can be prevented by the use of vaccines which provide a broad immunity. It would be interesting to determine if Prn-deficient strains circulate in Brazil.

How could the study performed by Torres et al.¹ be improved? It must be realized that there will always be local constraints such as lack of funds, equipment, and expertise. Thus, this is not a criticism, but an attempt to paint the ideal picture. One suggestion is to use a typing method which allows for international comparisons. By sequencing polymorphic regions in the genes for the Ptx A subunit, the Ptx promoter (*ptxP*), Prn, and Fim3, important characteristics of current strains can be determined.¹⁸ Of course, the vaccine strain should be included to determine the extent of divergence with circulating strains. PFGE is also useful to type strains, but requires careful standardization and does not always reveal true genetic relationships.¹⁹ Single nucleotide polymorphism (SNP) typing has the discriminatory power of PFGE, is unequivocal, and reveals true genetic relationships. We have recently developed an economical, high-throughput SNP typing method.²⁰

To solve the pertussis problem, it is necessary to distinguish between short-term and long-term approaches. In the long term, we need to develop pertussis vaccines that induce longer-lasting immunity. In the short term, introduction of maternal vaccination can substantially decrease morbidity and mortality. Studies in the UK have shown that maternal vaccination is very effective (estimated vaccine efficacy 90%) and safe for mother and child.^{21,22} As many studies have shown, including the study by Torres et al., most severe pertussis and mortality occurs in infants younger than 2-3 months. If this category can be protected by maternal vaccination until the primary series have started, the most significant part of the pertussis problem may be solved.

The question that should then be addressed is whether the pertussis burden in adolescents, adults, and the elderly is severe enough to merit using limited resources in order to develop better pertussis vaccines.

Conflicts of interest

The authors declare no conflicts of interest.

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