



## EDITORIAL

### Pertussis-like illness is not the same as pertussis<sup>☆</sup>

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Pertussis, caused by infection with the Gram-negative Bacterium *Bordetella pertussis*, is a nasty disease at any age, but most serious in young infants. They can suffer from apnea, bradycardia, paroxysmal spells, and life-threatening pulmonary failure associated with hyperleukocytosis caused by the effect of pertussis toxin (PT).<sup>1</sup> Treatment options are limited and focus on antibiotics to eliminate *B. pertussis* from the nasopharynx, thereby interrupting the chain of transmission, and symptomatic therapy to ameliorate the course of this disease. The success of treatment is quite variable and fatalities occur regularly. Protecting young infants from *B. pertussis* infection, therefore, is paramount. Immunizing close contact persons before or shortly after the birth of a child (so-called "cocooning") is a challenging strategy which has proven to be of suboptimal efficiency.<sup>2</sup> In contrast, providing newborns with a protective amount of anti-PT IgG antibodies via the placenta after immunization of pregnant women with pertussis component vaccines has demonstrated efficacy and safety.<sup>3</sup>

With this background, Nascimento and colleagues performed a case-control study in sentinel hospitals for pertussis in Recife, Brazil, to investigate the "protective effect of exclusive breastfeeding and effectiveness of maternal vaccination in reducing pertussis-like illness".<sup>4</sup> During the 2 year study period they identified 73 cases with a diagnosis of "pertussis-like illness" (clinically diagnosed in 71 of them) of which 29 were hospitalized, and 194 controls. Forty-seven (64%) of cases were born to mothers vaccinated against pertussis with Tdap combination vaccines during pregnancy as were 144 (74%) of the controls. They found

out that, in the univariate analysis, exclusive breastfeeding in children <6 months of age born to unvaccinated mothers demonstrated a protective effect against "pertussis-like illness" with an odds ratio of 0.27 (95% CI; 0.07, 1.00) and in children born to vaccinated mothers the protective effect had an OR of 0.21 (95% CI; 0.06, 0.69). In contrast, the protective effect of pertussis immunization in pregnancy had an insignificant OR of 0.70 (95% CI; 0.40, 1.34).

In Brazil, immunization during pregnancy (a term more precise than "maternal immunization"<sup>5</sup>) is recommended between the 20th and 36th gestational week according to the authors. Unfortunately, however, the authors do not tell us the exact timing of immunization during pregnancy in the mothers of cases and controls and whether there were differences between the 2 groups. This, however, is very important as the transfer of anti-PT antibodies from mother to child is suboptimal if immunization is too close to delivery.<sup>6</sup>

What do these findings tell us? First, and most importantly, the major shortcoming of this study is the imprecise case definition where infants with "pertussis-like illness" rather than confirmed *B. pertussis* infections were enrolled. Although most of them demonstrated clinical signs of pertussis such as paroxysmal cough (96%) and posttussive vomiting (53%), these characteristics are not exclusive and specific enough for pertussis caused by *B. pertussis* infection. It has been shown that a variety of viruses such as adenovirus, parainfluenza viruses 1, 2 and 3, and respiratory syncytial virus and bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* but also other representatives of the *Bordetella* species (e.g. *B. parapertussis* and *B. holmesii*) can cause this clinical entity and are not preventable by pertussis vaccines.<sup>7–10</sup>

This is problematic because there is a likelihood of undetermined magnitude that infants with "pertussis-like

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illness'' did, in fact, not have pertussis but had any other infection. This would explain the surprisingly poor effectiveness of Tdap immunization during pregnancy in this study which is in sharp contrast to the estimated 91% determined in England.<sup>11</sup> It would also explain the protective effect of breastfeeding which is not specific for one organism but by means of providing broad protection, especially against respiratory tract infections.<sup>12</sup>

Nascimento and colleagues are to be applauded that they studied an important question. Unfortunately, however, the case definition they used was not appropriate to come up with meaningful findings. Prevention of pertussis and death due to pertussis in neonates is a key priority of the Global Pertussis Initiative, which recommends that acellular pertussis immunization in pregnancy should be implemented as a priority in all countries if resources allow.<sup>13</sup> Hopefully, the findings of this study do not undermine this important health measure in Brazil.

Therefore, the authors should be encouraged to repeat the study and aim to make a firm microbiologically confirmed diagnosis of *B. pertussis* infection in infants with ''pertussis-like illness''. In infants, this means either by culture or specific PCR from nasopharyngeal specimens.<sup>14</sup>

## Conflicts of interest

UH is a member of the Global Pertussis Initiative and the «Collaboration of European Experts on Pertussis Awareness Generation» and has received honoraria for participation in associated live meetings from Sanofi Pasteur, the USA, and Sanofi, France, respectively.

## References

1. Nieves DJ, Heininger U. *Bordetella pertussis*. *Microbiol Spectr*. 2016;4.
2. Urwyler P, Heininger U. Protecting newborns from pertussis – the challenge of complete cocooning. *BMC Infect Dis*. 2014;14:397.
3. Heininger U, Riffelmann M, Bär G, Rudin C, von König CH. The protective role of maternally derived antibodies against *Bordetella pertussis* in young infants. *Pediatr Infect Dis J*. 2013;32:695–8.
4. Nascimento RM, Baptista PN, Lopes KA, Pimentel AM, Cruz FD, Ximenes RA. Protective effect of exclusive breastfeeding and effectiveness of maternal vaccination in reducing pertussis-like illness. *J Pediatr (Rio J)*. 2021;97:500–7.
5. Heininger U. Maternal immunization is not the same as immunization in pregnancy. *Hum Vaccin Immunother*. 2015;11:1074.
6. Eberhardt CS, Blanchard-Rohner G, Lemaître B, Boukrid M, Combescure C, Othenin-Girard V, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. *Clin Infect Dis*. 2016;62:829–36.
7. Mooi FR, Bruisten S, Linde I, Reuhsaet F, Heuvelman K, van der Lee S, et al. Characterization of *Bordetella holmesii* isolates from patients with pertussis-like illness in The Netherlands. *FEMS Immunol Med Microbiol*. 2012;64:289–91.
8. Hagiwara K, Ouchi K, Tashiro N, Azuma M, Kobayashi K. An epidemic of a pertussis-like illness caused by *Chlamydia pneumoniae*. *Pediatr Infect Dis J*. 1999;18:271–5.
9. Wirsing von König CH, Rott H, Bogaerts H, Schmitt HJ. A serologic study of organisms possibly associated with pertussis-like coughing. *Pediatr Infect Dis J*. 1998;17:645–9.
10. Heininger U, Stehr K, Schmitt-Grohé S, Lorenz C, Rost R, Christenson PD, et al. Clinical characteristics of illness caused by *Bordetella parapertussis* compared with illness caused by *Bordetella pertussis*. *Pediatr Infect Dis J*. 1994;13:306–9.
11. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet*. 2014;384:1521–8.
12. Christensen N, Bruun S, Søndergaard J, Christesen HT, Fisker N, Zachariassen G, et al. Breastfeeding and infections in early childhood: a cohort study. *Pediatrics*. 2020;146:e20191892.
13. Forsyth KD, Tan T, von König CW, Heininger U, Chitkara AJ, Plotkin S. Recommendations to control pertussis prioritized relative to economies: a Global Pertussis Initiative update. *Vaccine*. 2018;36:7270–5.
14. Guiso N, Berbers G, Fry NK, He Q, Riffelmann M, Wirsing von König CH, et al. What to do and what not to do in serological diagnosis of pertussis: recommendations from EU reference laboratories. *Eur J Clin Microbiol Infect Dis*. 2011;30:307–12.