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Case Report

The new health legacy: when pertussis becomes a heritage transmitted from mothers to infants

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Despite high vaccination coverage rates, there has been a gradual increase in reported pertussis cases. Although whooping cough affects all ages, young infants continue to suffer the greatest pertussis disease burden. Adolescents and adults are the primary source of infection for young babies. In this paper, we report two cases involving the likely transmission of pertussis from mothers to infants in Tunisia.

Introduction

Although pertussis vaccination has widely reduced the morbidity and mortality due to whooping cough, an 'apparent' re-emergence of this disease has been experienced worldwide in the last two decades (Munoz, 2006; Cherry, 2010; Zouari *et al.*, 2011). Several reasons for this resurgence have been proposed, including genetic changes in *Bordetella pertussis*, lessened potency of pertussis vaccines, waning of vaccine-induced immunity, greater awareness of pertussis, and the general availability of better laboratory tests (He & Mertsola, 2008). Of these possibilities, it is clear that what is most important is improved testing, which has contributed to the increase in reported pertussis (He & Mertsola, 2008; Cherry & Heininger, 2009). Another salient alternative is a greater awareness of pertussis brought out by the extensive number of publications, showing that there has been a huge under-recognition of the disease (Cherry, 2010).

The epidemiological situation of pertussis in Africa and particularly in Tunisia (North Africa) is poorly studied. In Tunisia, pertussis is a statutory notifiable disease and notification is exclusively based on clinical criteria. Vaccine coverage in Tunisian infants is very high: it accounted for 98 % in 2009 (Zouari *et al.*, 2011). The Tunisian vaccine schedule comprises a primary immunization with three doses of the whole-cell pertussis vaccine administered at the age of 2, 3 and 6 months. A booster dose is recommended at 18 months of age (http://www.santetunisie.rns.tn/msp/presentation/vaccination.html). Infants too young to be completely vaccinated account for the majority of pertussis-related complications, hospitalizations and deaths (de Greeff *et al.*, 2010; Zouari *et al.*, 2011). To protect infants against pertussis, the main sources of the infection must be identified. Several studies have investigated pertussis transmission to infants and young children. It appears that adolescents and adults – in whom the disease is asymptomatic – are the reservoirs and an important source of infection transmission to infants (de Greeff *et al.*, 2010; Baptista *et al.*, 2007, 2010; Cosnes-Lambe *et al.*, 2008; Bosdure *et al.*, 2008; Wendelboe *et al.*, 2007; Raymond *et al.*, 2007).

In this report, we describe two cases with the likely pertussis transmission from mothers to infants at the Children's Hospital of Tunis.

Abbreviations: C_q, quantification cycle; PT, pertussis toxin; qPCR, quantitative real-time PCR.

Case reports

Case 1

A 1-month-old female infant was admitted to the Department of Paediatrics B in our hospital because of progressive coughing, respiratory distress and cyanosis. She was delivered vaginally at term, to a 30-year-old mother. No pathology was reported for the baby's parents. The patient had a birth weight of 3200 g. She was breastfed during the first 2 weeks of life, then she was fed with pasteurized milk. Cyanogenic coughing started at the age of 28 days. One week later, the cough worsened with occasional choking and frequent post-tussive vomiting. A prolonged apnoea was also noted. The patient was intubated and then transferred to the Paediatric Intensive Care Unit (PICU).

At admission to the PICU, examination revealed mild fever (38.2 °C) and a weight of 2700 g. Respiratory rate was 45 breaths min^{-1} with persistent coughing and cyanosis. The oxygen saturation was 96 % on room air. Auscultation of the lungs was normal. There was a tachycardia (200

beats min^{-1}), with normal heart sounds and normal pulses. Blood pressure measured 80/56 mmHg. A chest X-ray showed right apical atelectasis. Laboratory examination showed a white blood cell count of 91 700 cells mm^{-3}. All routine bacterial cultures of throat, viral cultures and blood samples remained negative. Because of the hyperleukocytosis, pertussis was suspected. A nasopharyngeal aspirate was collected and sent to the Microbiology Laboratory at the same hospital for *Bordetella* testing. DNA was extracted using the High Pure PCR Template Preparation kit (Roche Diagnostics) according to the manufacturer's instructions. A quantitative real-time PCR (qPCR) based on the TaqMan technology, targeting the IS*481* and the IS*1001* sequences specific for *B. pertussis*, *Bordetella bronchiseptica*, or *Bordetella holmesii* and *Bordetella parapertussis*, respectively, was carried out. The primers and the probes chosen and the thermal cycling conditions used were those previously described by Kösters *et al.* (2001). The technique was used according to the consensus procedure (Riffelmann *et al.*, 2005). Regarding the possible cross-reactions with *B. holmesii* and *B. bronchiseptica*, another qPCR targeting the pertussis toxin (PT) promoter gene specific for *B. pertussis* was used as reported by André *et al.* (2008). Amplification was performed in an IQ5 real-time PCR detection system (Bio-Rad). Internal amplification control and external quality controls were also used as recommended for both qPCRs (Riffelmann *et al.*, 2005; André *et al.*, 2008).

qPCR turned out to be positive for IS*481* [quantification cycle (C_q)=24.18] as well as the PT gene (C_q=31.12), confirming *B. pertussis* infection in the young patient. Erythromycin therapy was started at a dose of 50 mg (kg body weight)$^{-1}$ per day in three divided doses for 14 days. Only after explicit asking did the baby's mother reveal that she had been coughing for several weeks (preceding her infant's onset of disease for >3 weeks). She gave a nasopharyngeal specimen for pertussis testing using the same qPCRs as for her infant. A positive assay result was reported for the former (C_q=33.76 and C_q=39.96, respectively). Antibiotic treatment with oral erythromycin was prescribed to her (500 mg for 14 days).

The outcome was favourable for the infant after 5 days of mechanical ventilation and antibiotherapy. She was extubated, no abnormalities were detected at examination and she was discharged from the hospital.

Case 2

Two weeks after the first case, a 2½-month-old female infant born at term with a weight of 2750 g was admitted to the Department of Paediatrics B. Her father was 42 years old with no pathologies. The mother, aged 35 years, had a history of pre-eclampsia. A first degree of consanguinity was reported. Symptoms started 7 days before admission with nocturnal coughing, whoops and cyanosis. Vomiting, apnoea or seizures were not reported. At admission, examination showed mild fever (38 °C) with more frequent coughing. The weight was 4800 g. Our patient had polypnoea (42 breaths min^{-1}) and the oxygen saturation was 95 % on room air. A tachycardia was also noted (120 beats min^{-1}). The auscultation of lungs and the cardiovascular exam were normal, and blood pressure measured 90/60 mmHg. The infant leukocyte count was 31 200 cells mm^{-3}. Blood culture and bacterial and viral cultures did not identify any pathogen. Pertussis was suspected. In the baby's health record, it was mentioned that she received a single dose of whole-cell pertussis vaccine at the age of 2 months. A specimen collected from the infant's nasopharynx was sent to the Microbiology Laboratory, as in the first case, for *Bordetella* investigation. The nasopharyngeal aspirate was reported to be positive for *B. pertussis* DNA (IS*481* C_q=14.50, PT C_q=21.30). The patient was placed under antibiotherapy with erythromycin at a dose of 50 mg kg^{-1} per day in three divided doses for 14 days. Afterwards, the investigation showed that the baby girl's mother had a 3-week history of prolonged paroxysmal cough and upper respiratory tract infection. qPCRs came back positive for *B. pertussis* for the mother (IS*481* C_q=31.17, PT C_q=38.03). Coughing became less frequent and the baby girl recovered. She remained hospitalized for another 5 months since she suffered from articular disorders, but had no further bouts of whooping cough.

Discussion

The epidemiology of pertussis remains enigmatic. A leading cause of infant mortality globally, its resurgence in several developed countries – despite the availability and use of vaccines for many decades – has caused alarm. Duration of immunity and epidemically significant routes of transmission across age groups remain unclear and deserve further investigation to better control pertussis burden (He & Mertsola, 2008). Furthermore, an upsurge in the reported incidence of whooping cough in adolescents and adults has been observed over recent years (Cherry, 2010). This is of particular concern, since these have been identified as sources of *B. pertussis* infection for infants who are too young to be fully vaccinated. Consequently, pertussis still remains a formidable foe in vulnerable neonates and infants in whom severe disease complications and death may occur (de Greeff *et al.*, 2010; Wendelboe *et al.*, 2007; Plotkin, 2005).

An essential step in reducing morbidity and mortality in neonates and infants is to identify the precise sources and reservoirs of *B. pertussis* infection and to assess which of these mostly contribute to the development of pertussis in the vulnerable group (de Greeff *et al.*, 2010; Baptista *et al.*, 2007, 2010; Cosnes-Lambe *et al.*, 2008; Bosdure *et al.*, 2008; Wendelboe *et al.*, 2007; Raymond *et al.*, 2007). This information will be key in determining which groups (defined by age) must be targeted in the expansion of existing immunization strategies, so that the residual burden of disease in infants is reduced.

Parent-to-infant transmission may now play a greater role than child-to-child transmission in maintaining circulation of *B. pertussis* (de Greeff *et al.*, 2010; Baptista *et al.*, 2010; Cosnes-Lambe *et al.*, 2008; Bosdure *et al.*, 2008; Wendelboe *et al.*, 2007; Raymond *et al.*, 2007). In this paper, pertussis was confirmed by quantitative PCR in the young patients as well as in their mothers. It was likely that mothers were the source of the infection for their daughters. In the two cases, no other contacts had a cough illness prior to illness in these patients. The C_q values observed in the qPCR were higher in the samples from the mothers than in those from the babies, which indicates a lower amount of *B. pertussis* DNA being present in the specimens from the mothers. This is consistent with the hypothesis that the infections in the mothers preceded those in the babies.

Our finding that mothers play an important role in the transmission of pertussis is in agreement with previous studies (de Greeff *et al.*, 2010; Baptista *et al.*, 2010; Cosnes-Lambe *et al.*, 2008; Bosdure *et al.*, 2008; Wendelboe *et al.*, 2007). Many years ago, reports of mother-to-newborn transmission were infrequent, although strong underestimation of such events was reported due to the unrecognized symptoms in the mother (Plotkin, 2005). More recently, in a prospective study conducted by de Greeff *et al.* (2010), mothers were identified as the likely source of infection in 38 % of the cases. An American study also indicated that among adults, mothers are the most important single source of infection for their infants (Bisgard *et al.*, 2004). Another study reported that 50 % of the mothers were the source of infection against 34 % of the fathers (Bosdure *et al.*, 2008). Cosnes-Lambe *et al.* (2008) have proved that PCR testing for *B. pertussis* in household contacts allows the diagnosis of atypical whooping cough in unvaccinated young infants and found that 47 % of mothers were the source of infection. Fathers were reported to be less important in pertussis transmission, especially in the first 3 months of life (de Greeff *et al.*, 2010). Adolescents, grandparents and health-care workers have also been suggested as sources (de Greeff *et al.*, 2010; Baptista *et al.*, 2007, 2010; Cosnes-Lambe *et al.*, 2008; Bosdure *et al.*, 2008; Wendelboe *et al.*, 2007; Raymond *et al.*, 2007). Raymond *et al.* (2007) concluded in their study that testing household contacts may allow the detection of intra-familial infection, leading to an earlier diagnosis of pertussis in young infants.

Ensuring pertussis vaccination of adults and adolescents in close contact with an infant is warranted to prevent transmission of pertussis to vulnerable infants, particularly those who are too young to be immunized (de Greeff *et al.*, 2010; Baptista *et al.*, 2010). One strategy adopted by many countries, including Canada, Austria, Australia, France and Germany, was the introduction of adolescent immunization (Plotkin, 2005). Although this universal vaccination is thought to reduce the risk of the disease later in life as well as the transmission to infants, there are insufficient data to support the addition of a booster dose in this age group (WHO Publication, 2011).

A further strategy to protect newborns and infants under the age of 1 year is to increase 'herd immunity' by vaccinating close contacts including post-partum women before hospital discharge, and household and care-giver contacts (Healy *et al.*, 2011; de Greeff *et al.*, 2010; Wendelboe *et al.*, 2007). This targeted vaccination strategy, called 'cocooning', is considered to be the only protection against pertussis available to young infants except vaccination during pregnancy (Mooi & de Greeff, 2007). However, this selective immunization has not been widely implemented, largely because of a lack of necessary infrastructure, a need for education, reimbursement issues and logistical barriers (Healy *et al.*, 2011; Plotkin, 2005). The unproven effectiveness of this strategy has led the World Health Organization to conclude that there is inadequate evidence to recommend it (WHO Publication, 2011).

Currently, it seems unlikely that the persistence of pertussis can be controlled with the available immunization schedules. Promising vaccination strategies to decrease the rebounding pertussis incidence have been discussed. The Strategic Advisory Group of Experts on immunization (WHO, 2010) highlighted the importance of monitoring not only the coverage of vaccination among infants but also the on-time coverage, as the risk of death from pertussis is greatest during the first few months. We personally believe that an active surveillance system for whooping cough in Tunisia has to be implemented and that improving cocooning vaccination with introducing maternal immunization as previously shown could be key in decreasing the pertussis burden in infants.

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