



EDITORIAL

Whooping cough – still a challenge^{☆,☆☆}

Coqueluche – ainda um desafio

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Globally, whooping cough (pertussis) is still an important cause of death in infancy and continues to be a public health concern even in countries with high vaccination coverage. In 2008, over 80% of all infants worldwide received three doses of pertussis vaccines.¹ Despite this, 15 million pertussis cases occurred worldwide, 95% of them in developing countries, and about 200,000 children died from the disease.¹

The causative agent of whooping cough, *Bordetella pertussis*, was isolated about one-hundred years ago. Before the development of the killed whole-cell vaccine and the implementation of mass immunizations in the 1950's, pertussis was the main cause of infant mortality.² Thereafter, the incidence of whooping cough in vaccinated infants and young children has dropped dramatically. Vaccinations were implemented in most countries and the programs were successful, but increasing publicity was focused on the adverse reactions.³

Due to increasing risk of adverse reactions by age and by vaccination times using the whole-cell vaccine, and less severity of whooping cough in older children, vaccinations were in most programs not given after the age of 24 months. Therefore, previously vaccinated children became again susceptible to pertussis at school age, and the incidence of pertussis increased particularly in school children. Of course, an increased awareness about pertussis risk and an increased use of diagnostic tests for pertussis influenced

the reported rates.⁴ The clinical picture in the earlier vaccinated children at school age was long-term cough, not cough with severe spells or whooping attacks as seen in non-vaccinated children. The coughing school children were not necessarily diagnosed as pertussis cases, and they further transmitted the *B. pertussis* bacterium to the infants within the families. During the two last decades of 1900's, many parents refused the pertussis vaccination, and the incidence of whooping cough again started to increase in infants.³

Thus, there was an urgent need for a new pertussis vaccine containing purified antigens instead of killed whole bacteria with less adverse reactions and with a possibility to vaccinate all-aged children. Acellular pertussis vaccine, injected jointly with toxin-based vaccines to diphtheria and tetanus, was introduced in 1981-1989 in Japan, and in 1991-1996 in most other countries.³ After the introduction of the new acellular pertussis vaccine, the booster vaccinations have been extended up to the age of 14-16 years in most countries. In future, pertussis may transfer to young adults, that is to the mothers and fathers of young infants, and the vaccinations of young adults may be required.⁵

The development of new techniques for viral and bacterial infections, firstly direct viral antigen detection by immune fluorescence or enzyme immune assays, and subsequently direct viral or bacterial genome detection by polymerase chain reaction (PCR), have opened a new time for research of respiratory infections. These new techniques have changed the one-agent-one infection concept on microbial etiology of respiratory infections. Not only multiple findings, but also multiple etiologies may be common in respiratory infections, including mixed viral-viral, mixed viral-bacterial and mixed bacterial-bacterial infections.⁶

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The observation that *B. pertussis* and certain viruses, especially respiratory syncytial virus can cause concomitant respiratory infections is 30 years old.⁷ Recent Finnish studies have confirmed that about 10% of non-vaccinated or partially vaccinated infants hospitalized for bronchiolitis at age less than 6 months with no suspicion of pertussis, have mixed RSV and *B. pertussis* infections.^{8,9} When the hospital records were analyzed retrospectively, the clinical pictures did not differ between *B. pertussis* positive and negative cases.

In this issue of the journal, Ferronato et al. publish their observations on viral infections in 67 Brazilian infants admitted for suspected pertussis at the average age of 2.0–2.5 months.¹⁰ PCR for *B. pertussis* was positive in 44% and immune fluorescence for respiratory viruses (mainly RSV) in 26%. Both *B. pertussis* and some virus were identified in 5% of the children. Cough followed by inspiratory stridor or cyanosis, as well as leukocytosis and lymphocytosis in blood predicted pertussis, whereas rhinitis and dyspnea predicted viral etiology.

In accordance, there is some evidence from earlier studies, that clinical features, such as age, presence of cough and absence of dyspnea, may be useful to separate *B. pertussis* from viruses in young children with respiratory infection. Among 141 North-American infants hospitalized for suspected pertussis, PCR was positive for *B. pertussis* in 15%, and in retrospective analyses, the positive infants were younger and presented with lower respiratory rate and higher blood lymphocyte counts.¹¹ Among 126 English children aged less than 5 months treated in the pediatric intensive care unit for respiratory infection, PCR or serology was positive for *B. pertussis* in 20%, and in retrospective analyses, the *B. pertussis*-positive infants presented with longer duration of cough, more apneas, more coughing spells, and higher blood lymphocyte counts.¹² Mixed RSV-pertussis infection was present in 36% of *B. pertussis*-positive cases. In all, 126 French children aged less than 4 months were recruited in a prospective study, and PCR was positive for *B. pertussis* in 16%, and the positive and negative infants differed significantly only for the presence of coughing spells.¹³ Mixed pertussis-RSV infection was identified in 12%.

Ferronato *et al.* concluded that the etiological diagnosis of viral infection by PCR may enable the reduction of the use of antibiotics, especially that of macrolides, for suspected but non-proved pertussis cases.¹⁰ Of course this is true, but the benefits are marginal. In addition, the identification of RSV or other respiratory viruses does not rule *B. pertussis* infection out, since mixed infections are common.^{8,9} Moreover, PCR is so sensitive that false-positive findings are possible, reflecting for example previous infection or clinically insignificant temporary carriage. When pertussis in young children is considered, under-treatment may be a more severe problem than over-treatment, since pertussis may be severe, even fatal in non-vaccinated or partially vaccinated infants.¹⁴ The bulk of the misuse of antibiotics comes from the treatment of common colds and other mild upper respiratory infections with antibiotics, including overtreatment of suspected acute otitis media with broad-spectrum antibiotics.

A recent Cochrane review, updated in 2011, included 13 clinical studies on the role of antibiotics in whooping cough, and the authors concluded that azithromycin and

clarithromycin are equally effective as erythromycin in the eradication of *B. pertussis* from the airways of children.¹⁵ Clinical experience suggests that macrolides relieve the symptoms of whooping cough in infants but not in older children. However, the research evidence for the effect of antibiotic therapy is mainly lacking or is negative even in infants.¹⁵ The differences in clinical responses between infants and older children comes from the duration of *B. pertussis* involvement, and thus, from the degree of airway damage. When damage has developed for weeks and the symptoms are non-specific, inflammatory disorders like asthma are merely suspected than acute infections. Treatment with macrolides prevents the spread of *B. pertussis* within the families, though research data on this is also scanty, old and based on trials with erythromycin only.^{16,17}

Whooping cough is – one-hundred years after the identification of the causative bacteria, seventy years after the start of the vaccination of infants using whole cell vaccine, and twenty-five years after the extension of vaccinations to all children using acellular vaccine – still a challenge. The acellular pertussis vaccine may be less effective than the whole-cell vaccine, and the universal use of pertussis vaccines has evidently led to genetic changes in the circulating *B. pertussis* strains.¹⁸ Therefore, the circulating strains and available vaccines need continuous evaluation and development. The cornerstones of the work against whooping cough are effective vaccines and extensive vaccination programs with high coverage rates. In the future, booster vaccinations through the whole life should be considered, not only to prevent disease in adults but also to prevent the disease transmission from adults to infants.¹⁹ Clinical and epidemiological studies, as well as clinical drug trials, are needed to optimize the diagnostics and treatment.

Conflicts of interest

The author declares no conflicts of interest.

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