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Pertussis disease and transmission and host responses: insights from the baboon model of pertussis

Marta V. Pinto [a], Tod J. Merkel [b,*]

[a] *Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK*
[b] *Laboratory of Respiratory and Special Pathogens, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA*

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Summary Whooping cough is a highly contagious, acute respiratory disease, caused by the Gram-negative bacterium *Bordetella pertussis (Bp)*. Despite the introduction and widespread use of vaccines starting in the 1950s pertussis cases continue to be reported, with a significant global impact. The role of specific virulence factors in disease and the immune mechanisms associated with protection following natural infection or vaccination are still not completely understood.

The recently-developed baboon model of clinical pertussis provides a valuable tool for the study of pertussis. Baboons infected with *B. pertussis* exhibit all of the manifestations of human pertussis including paroxysmal coughing, mucus production, leukocytosis and transmission. The establishment of this model provides the opportunity to address unanswered questions about the natural progression of this disease and host responses to infection and vaccination in a very relevant model.

In this review, we present an overview of our knowledge of pertussis along with recent advances resulting from use of the baboon model. Remaining questions and future research directions are discussed. We hope that the knowledge gained through use of the baboon model of pertussis and clinical studies will allow the development of more efficacious vaccines, conferring long lasting protection against disease and transmission.

* Corresponding author. Laboratory of Respiratory and Special Pathogens, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA.
E-mail addresses: marta.valentepinto@paediatrics.ox.ac.uk (M.V. Pinto), tod.merkel@fda.hhs.gov (T.J. Merkel).

Introduction

Pertussis is an acute respiratory infection caused by the Gram-negative bacterium *Bordetella pertussis (Bp).* The severity of the disease manifestations depend on age and prior exposure to the bacterium, or to pertussis vaccine. Unimmunized infants present with the most severe disease.[1] Recognition of the disease can be challenging since manifestations range from asymptomatic to the classical presentation with spasmodic coughing associated with post-tussive vomiting, inspiratory whoop and cyanosis with milder but often persistent coryzal symptoms and cough in between.[1]

Whole cell pertussis (wP) vaccines were developed and introduced in the 1940–50s in several countries. Currently global pertussis vaccine coverage is approximately 86%, according to the World Health Organization (WHO).[2] Approximately 64% of countries worldwide use whole cell vaccine, including all the countries in the WHO South East Asia Region and 96% of the African Region.[3] In some high income countries, whole cell vaccines were replaced with acellular pertussis vaccines due to concerns over the reactogenicity of the whole-cell pertussis vaccine and availability of multivalent combination vaccines containing acellular pertussis antigens. Despite near universal vaccine coverage in infants, the rate of pertussis cases reported has steadily increased following the introduction of acellular vaccines in some of these countries[4–7] among individuals immunized both with acellular and with whole cell vaccines in early childhood.

Several hypotheses, which are not mutually exclusive, have been proposed to explain these resurgences of pertussis: a) higher awareness of the disease particularly in adults resulting in increased testing and reporting to public health authorities, b) improved diagnostic methods, c) evolution of circulating strains able to escape vaccine-induced immunity, d) shorter duration of protection of the acellular pertussis vaccines relative to the whole cell vaccines they replaced and e) differences in the nature of immune response after immunization with wP and acellular vaccines (discussed bellow).[4,8–11] There is evidence to support each of these hypotheses. Further studies utilizing, murine and baboon models of pertussis infection as well as clinical studies are required to develop a more complete understanding of the mechanisms of pertussis disease and the mechanisms underlying protective immunity following infection and vaccination.

Pertussis disease – epidemiology, transmission and clinical manifestations

Epidemiology

Although pertussis outbreaks in high income countries are very well-publicized, 95% of pertussis cases occur in low and middle income countries according to the WHO, with an estimated 16 million cases and 200,000 deaths worldwide attributed to pertussis each year.[12] Pertussis is therefore still considered one of the diseases most potentially preventable by vaccination, according to the WHO.[13]

The incidence of pertussis is cyclical, with epidemic peaks occurring every 3–5 years within a given region.[14,15] It is puzzling that this observed periodicity has generally been maintained from the pre-vaccine era through the introduction of two different types of vaccine in different periods and with varying vaccination coverage rates over time and place.[14,15] The length of inter-epidemic periods is probably driven by the prevalence of susceptible individuals in a population, primarily unvaccinated newborns and older individuals as well as vaccinated or previously infected individuals with waning immunity, relative to the number of individuals protected by vaccination, maternal immunization or immunity conferred by infection.[16]

A retrospective study by Broutin *et al.*, using a time series method, compared the impact of immunization on pertussis periodicity in 64 countries. The authors concluded that the vaccination had a positive impact in limiting disease transmission and herd immunity seemed to be established in countries where pertussis vaccines are part of the routine schedule.[16]

A rise in the incidence of pertussis in high income countries has been reported with epidemics in Europe, Australia and the US in the last decade.[17–19] In Europe, countries affected by resurgence include the UK and the Netherlands. In the UK the pertussis outbreak started on the second half of 2011. In 2012 a significant increase was also reported (2011: 1256 reported cases; 2012: 11,986).[20] The Netherlands also had a significant increase of the number the cases from 5447 in 2011 to 12,853 in 2012.[20] In both countries, infant and childhood vaccination coverage had remained very high during the preceding years excluding failure to vaccinate as a significant contributory cause.[21]

Several outbreaks have occurred across the USA in the last decade with peaks occurring in 2004–05, 2010, and 2012. The rates of disease were highest in children less than one year of age, with an incidence of 126.7 cases/100,000 individuals.[22] Vaccination coverage in the USA had also been consistently high throughout this period, varying between 94-95% for three and between 82.5–84.6% for four or more doses in 19–35 month-old children.[23]

Disease transmission

The reservoir of *Bp* is exclusively human[24] and the disease is transmitted via airborne droplets. The latter was first hypothesized in 1916 by Luttinger *et al.*,[25] although the first controlled study supporting the theory was performed only recently by Warfel *et al.*[26] The study was conducted in baboons and was designed to document whether airborne transmission occurred between animals while controlling for contact transmission. Infected and uninfected animals were housed together or separated by a space of up to seven feet (2 m) with transmission occurring in both scenarios[26] albeit more rapidly in the former (mean 10 days) than the latter (mean 19 days, $p = 0.0027$) demonstrating transmission efficiency as a function of the distance.

The determination of pertussis attack rates in humans is difficult. Prospective, household contact studies continue to be one of the best approaches. Previous such studies showed attack rates around 76% (64–86%),[26–32] although rates were variable between studies and may have been affected by differences between subjects' age and immune status due to prior vaccination or exposure. A longitudinal study conducted by Heininger *et al.* in a paediatric population