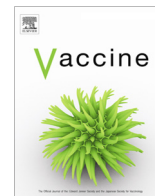




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Pertussis: Biology, epidemiology and prevention

Mitra Saadatian-Elahi^{a,*}, Stanley Plotkin^b, Kingston H.G. Mills^c, Scott A. Halperin^d, Peter B. McIntyre^e,
Valentina Picot^f, Jacques Louis^f, David R. Johnson^g^a Pôle Santé, Recherche, Risques et Vigilances Groupement Hospitalier Edouard Herriot, Unité d'Hygiène, Epidémiologie et Prévention, 5 Place d'Arsonval, 69437 Lyon cedex 03, France^b University of Pennsylvania and Vaxconsult, LLC, USA^c School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland^d Canadian Centre for Vaccinology, Dalhousie University, The IWK Health Centre and Nova Scotia Health Authority, Halifax, Nova Scotia, Canada^e National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney, NSW, Australia^f Fondation Mérieux, 17 rue Bourgelat, 69002 Lyon, France^g Global Medical Affairs, Sanofi Pasteur, Swiftwater, PA, USA

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ABSTRACT

Despite long-standing vaccination programs, substantial increases in reported cases of pertussis have been described in several countries during the last 5 years. Cases among very young infants who are at greatest risk of pertussis-related hospitalizations and mortality are the most alarming. Multiple hypotheses including but not limited to the availability of more sensitive diagnostic tests, greater awareness, and waning vaccine-induced immunity over time have been posited for the current challenges with pertussis. The conference "Pertussis: biology, epidemiology and prevention" held in Annecy-France (November 11–13, 2015) brought together experts and interested individuals to examine these issues and to formulate recommendations for optimal use of current vaccines, with a particular focus on strategies to minimize severe morbidity and mortality among infants during the first months of life. The expert panel concluded that improving vaccination strategies with current vaccines and development of new highly immunogenic and efficacious pertussis vaccines that have acceptable adverse event profiles are currently the two main areas of investigation for the control of pertussis. Some possible pathways forward to address these main challenges are discussed in this report.

1. Introduction

Pertussis, commonly called whooping cough, is a highly infectious disease that was previously a universal rite of passage for older infants and young children. The discovery in 1906 of its causative organism, *Bordetella pertussis*, led to the development of whole-cell pertussis (wP) vaccines, which by the late 1940s were combined with diphtheria (D) and tetanus (T) toxoids. Countries that instituted broad DTWP vaccination programs beginning in the mid-20th century saw pertussis dramatically decrease over subsequent decades. However, concerns over reactogenicity prompted some parents to refuse wP-containing vaccines for their children and some countries to discontinue their programs [1]. Less reactogenic acellular pertussis (aP) vaccines were developed to address these concerns. They were deployed in Japan

approximately 35 years ago; in North America, Australia and some European countries about 15–20 years ago; and more recently in other middle- and high-income countries.

During the last 5 years, multiple countries (e.g., Australia, the United Kingdom, and the United States of America) have experienced substantial increases in reported cases of pertussis [2,3]. Cases among very young infants who are at greatest risk of pertussis-related hospitalizations and mortality are the most alarming. Multiple hypotheses have been posited for the current challenges with pertussis, including:

- More sensitive diagnostic tests combined with greater pertussis disease awareness;
- Inadequate vaccination schedules and poor compliance with vaccination recommendations;
- Evolution of circulating pertussis strains to evade vaccine-induced immunity;
- Suboptimal priming by and decreased duration of protection from aP compared to wP vaccines.

* Corresponding author at: Groupement Hospitalier Edouard Herriot, Service d'Hygiène, Epidémiologie et Prévention, Bâtiment 1, 5, place d'Arsonval, 69437 Lyon cedex 03, France.

E-mail address: mitra.elahi@chu-lyon.fr (M. Saadatian-Elahi).

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The Fondation Mérieux organized a conference (11–13 November 2015) entitled: “Pertussis: biology, epidemiology and prevention” in Annecy, France (“Les Pensières” Conference Centre). The purpose of this symposium was to bring together experts and interested individuals to:

- Explore the latest trends in pertussis epidemiology;
- Better understand the reasons for these trends;
- Discuss potential ways in which pertussis vaccines might be improved and the practicalities of their introduction into routine use;
- Formulate recommendations for optimal use of current vaccines, with a particular focus on strategies to minimize severe morbidity and mortality among infants during the first months of life.

This report provides a summary of the issues discussed, key findings and areas for future research and development.

2. Pertussis epidemiology and vaccine impact: some examples

While the long-standing use of pertussis vaccines has greatly reduced the disease burden, pertussis continues to be a public health concern, even in some countries with well-established childhood vaccination programs. The following sections give an overview of the observed changes in the epidemiology of pertussis in a number of countries.

2.1. The United States of America

DTwP vaccine was introduced in the USA in the late 1940s, leading to a substantial drop in the annual number of case reports of pertussis, reaching a nadir in 1976 [1]. It has been experiencing regular (every 3–4 years) epidemic peaks in reports of pertussis since the late 1970s, with these peaks substantially increasing in magnitude beginning in 2004–05. The USA transitioned from DTwP- to DTaP-containing vaccines from 1991 to 2001, first with the school-entry and toddler doses, later with the infant doses. The Tdap booster for adolescents and adults was introduced in 2005, and coverage rates with this vaccine among adolescents surpassed 80% by 2012 [4]. However, Tdap vaccine uptake among adults has been much lower [5]. Overall and adolescent-specific case reports decreased for several years following the introduction of Tdap vaccine, but rose again in 2010. Reported cases exceeded 48,000 in 2012, the highest number since 1955 [6]. In addition to a considerable number of deaths in young infants, high incidence rates were observed in children 7–10 years of age and in adolescents 13–14 year olds. Age-group specific trends observed in 2014 were similar to those in 2012, but there was also a peak in 16 year olds [6]. The increased pertussis cases among 13–14 year olds in 2012 and among 16 year olds in 2014 raise concerns about the duration of Tdap’s effectiveness when given to adolescents whose previous pertussis vaccinations were exclusively acellular [7,8]. In the past, mothers have been the most commonly cited source of infection in the United States [9] while siblings are now identified as the major source of transmission to young infants [10]. This epidemiology shift supports the change in recommendations in the US to include Tdap vaccination during every pregnancy.

2.2. Australia

The vaccination schedule in Australia has been the subject of several changes over time in an attempt to improve the control of pertussis [11,12]. However, pertussis continues to be a public

health concern in the country. During the last 10 years, the average annual notification rate was more than 3 times that of the previous decade [13]. In contrast, early infant hospitalization and mortality rates have remained unchanged, largely attributable to increased diagnosis of milder disease due to the availability of PCR testing [14]. The pattern of age-specific notifications has changed substantially, with cases aged <15 years representing an increasing proportion of all cases during the 2008–2011 epidemics [11]. Although the infant pertussis mortality rate has not changed much over time, there has been a progressive increase in deaths during early infancy, with all 10 infant deaths occurring among those <2 months of age in the period 2006–2012 [13]. Starting in March 2009, parents and general practitioners in successive Australian jurisdictions were asked to bring the first infant vaccine dose forward to 6 weeks of age, as advancing that first dose by 2 weeks was estimated to reduce the number of notified cases and hospitalizations by 8–9% [15]. Although ‘cocoon’ doses for parents were recommended nationally in 2003 to provide indirect protection to newborns, cocoon doses were not free of charge until 2009, by when most states and territories provided Tdap vaccine to parents in response to epidemics. However, subsequent evaluations found only modest benefit in reducing pertussis risk in early infancy [16–18]. Lack of impact of cocooning was in part related to recently vaccinated siblings (3–4 years of age) emerging as the most common source of transmission following discontinuation of the 18-month booster dose in 2003 [19,20]. Following the availability from England of robust effectiveness data on maternal antepartum vaccination [21], this was formally endorsed as the preferred strategy in April 2015. From mid-2015, maternal vaccination during pregnancy has been fully funded by all jurisdictions separately, with strong consumer and professional support. A decision about cost-effectiveness of this intervention for the National Immunisation Program is expected soon.

2.3. England

Routine pertussis immunisation has been introduced into the national immunisation schedule in 1957 and has undergone a number of changes to optimise the control of infant disease. These included the introduction of an accelerated infant schedule (3 doses of wP vaccine at 2, 3 and 4 months of age) in 1990, the inclusion of aP vaccine in the early preschool booster dose in 2001 and the switch from wP to aP vaccine in the primary infant schedule in 2004. Despite sustained high vaccine coverage, England experienced a sizeable increase in infant disease and deaths during 2012 [22]. In response to this dramatic increase, the department of health recommended that pregnant women receive a dose of Tdap-IPV vaccine, ideally at 28–32 week’s gestation [21]. Vaccine coverage was over 55% in the first year of the programme and reached a steady rate of above 60% in 2015. Vaccine effectiveness measured by screening and case-control methods was high, exceeding 90% [21,23]. The impact of the programme, as measured by annual age-specific laboratory-confirmed pertussis incidence rate showed that cases in infants <3 months have been held at low levels, suggesting that this strategy could be considered in other countries with large number of early infant pertussis notifications. Evaluations are on-going and, if continued through the next UK epidemic, should further increase understanding of the programme impact.

2.4. Africa

There is a paucity of data regarding the burden of *B. pertussis* in South Africa, and in Africa in general. Since July 2009, immunisation against pertussis in South Africa involves DTaP-IPV/Hib at 6, 10, and 14 weeks and again at + 18 months. The high prevalence

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