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Review

Live pertussis vaccines: will they protect against carriage and spread of pertussis?

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ABSTRACT

Pertussis is a severe respiratory disease that can be fatal in young infants. Its main aetiological agent is the Gram-negative micro-organism *Bordetella pertussis*. Vaccines against the disease have been in use since the 1950s, and global vaccination coverage has now reached more than 85%. Nevertheless, the disease has not been controlled in any country, and has even made a spectacular come-back in the industrialized world, where the first-generation whole-cell vaccines have been replaced by the more recent, less reactogenic, acellular vaccines. Several hypotheses have been proposed to explain these observations, including the fast waning of acellular vaccine-induced protection. However, recent mathematical modelling studies have indicated that asymptomatic transmission of *B. pertussis* may be the main reason for the current resurgence of pertussis. Recent studies in non-human primates have shown that neither whole-cell, nor acellular vaccines prevent infection and transmission of *B. pertussis*, in contrast to prior exposure. New vaccines that can be applied nasally to mimic natural infection without causing disease may therefore be useful for long-term control of pertussis. Several vaccine candidates have been proposed, the most advanced of which is the genetically attenuated *B. pertussis* strain BPZE1. This vaccine candidate has successfully completed a first-in-man phase I trial and was shown to be safe in young male volunteers, able to transiently colonize the nasopharynx and to induce antibody responses to *B. pertussis* antigens in all colonized individuals. Whether BPZE1 will indeed be useful to ultimately control pertussis obviously needs to be assessed by carefully conducted human efficacy trials. **C. Locht, CMI 2016;22:S96**

Introduction

Pertussis, also referred to as whooping cough, is a severe respiratory disease that can be life-threatening, especially in young children before the completion of the primary vaccination series. However, pertussis in older children, adolescents and adults also represents a significant disease burden, including in high-income countries [1]. In adults and adolescents the disease is usually not fatal, but it can lead to pneumothorax and rib fracture and other complications [2]. The major causative agent of whooping cough is *Bordetella pertussis* [3], although other *Bordetella* species, such as *Bordetella parapertussis* [4] and *Bordetella holmesii* [5], can also induce pertussis-like syndromes, albeit usually much less severe.

The first mention of a pertussis outbreak dates back to the sixteenth century, when Guillaume de Baillou described the 1578 epidemic in France [6], suggesting that the disease is relatively recent in human history. However, the description of Perinthus cough by Hippocrates around 400 BC may possibly refer to whooping cough as a disease already present in ancient times. *Bordetella pertussis* as the principal cause of whooping cough was identified in 1906 by Jules Bordet and Octave Gengou [7]. Initially named *Haemophilus pertussis*, the organism was later renamed *B. pertussis* in honour of one of its discoverers. *Bordetella pertussis* is a strictly human pathogen. No natural animal reservoir has been identified to date. It can colonize the human upper respiratory

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tract, but it does not usually disseminate outside the respiratory tract, except in rare cases of highly immunocompromised individuals [8]. The clinical manifestation of whooping cough varies substantially between individuals [9], depending on age and immune status through vaccination or previous infection (summarized in ref. [3]).

Pertussis vaccines and the resurgence of whooping cough

In 2008 the WHO reported close to 200 000 pertussis-related deaths [10], and globally more than 16 million pertussis cases are reported to occur every year [11]. Since the implementation of mass vaccination starting in the middle of the last century the numbers of pertussis cases and associated deaths have decreased tremendously, demonstrating the effectiveness of mass vaccination to combat the disease. Before the introduction of the first-generation, whole-cell vaccines against pertussis (wPV) the reported incidence of the disease in the USA was as high as 150 cases/100 000, which was certainly an underestimate, as probably only about 20% of cases were reported in the early twentieth century [12]. At that time, pertussis was the leading cause of death from communicable disease in young children. Since the 1950s, after the introduction of mass vaccination, the incidence of pertussis has declined dramatically to reach a nadir in the late 1970s in several countries [13]. However, concomitantly, whooping cough in adolescents and adults became increasingly common [14], suggesting that after childhood vaccination, adults become susceptible to the disease again and are able to transmit it. The efficacy of wPV has been extensively studied and was demonstrated as early as the 1940s [15]. As combination vaccines with diphtheria toxoid and tetanus toxoid, referred to as DTP vaccines, efficacy levels of >90% after three administrations given at 1- or 2-month intervals and starting at 2 or 3 months of age have been reported in recent studies [16–20]. However, the wPV substantially varied in efficacy, despite having passed the pre-clinical lot release qualifications, and for some of them it dropped to 30%–50% [21,22].

Lot variations, even between lots produced by the same manufacturer, and especially local and systemic adverse events that have been associated with wPV [23], have prompted the development of more defined, acellular pertussis vaccines (aPV). These vaccines contain one to five purified *B. pertussis* antigens (reviewed in ref. [24]). They all contain at least detoxified pertussis toxin (PT). Most of them also contain filamentous haemagglutinin (FHA) and pertactin, and some further contain fimbriae. In addition, aPV combined with diphtheria and tetanus toxoids, and collectively called DTaP, show a clearly improved safety profile over wPV [25], with initial efficacy levels, according to several phase III trials, approaching those of DTP after three administrations [24]. In a meta-analysis, overall efficacy of two-component vaccines (containing PT and FHA) was estimated to be 67%–70% [25], whereas three- and five-component vaccines reached 84% efficacy. The protective mechanism of aPV is still not fully established. However, household efficacy studies in children exposed to *B. pertussis* have shown a correlation between protection against pertussis disease and the presence of anti-PT and anti-pertactin antibodies, but not with anti-FHA antibodies [26]. The combination of an improved safety profile together with comparable efficacy to that of well-performing wPV has led to the progressive replacement of wPV by aPV in most of the western world. Except for Poland, all European countries have now switched to the use of aPV for the primary series [27]. However, wPV are still the most widely use pertussis vaccines globally, essentially because of the higher cost of aPV compared with wPV, which is not affordable in many resource-poor countries.

Thanks to the extended programme on immunization, the WHO estimates the global three-dose pertussis vaccination coverage at about 85% [28]. Nevertheless, pertussis is still not under control in any country [29] and represents today the most prevalent vaccine-preventable childhood disease. Its incidence has been rising for several decades in the industrialized world, especially in those countries that have switched from wPV to aPV. The USA has registered the highest number of cases since the 1950s [30]. The UK experienced nearly 10 000 cases in 2012 with 14 infant deaths [31]. Similarly, in Australia a large epidemic outbreak occurred between 2009 and 2011 [32]. Incidence increases have been observed in many other countries as well [33], although this does not necessarily imply that the overall incidence has increased planet-wide.

Several reasons for the apparent incidence increase in high-income countries have been discussed [34], including potential changes in surveillance systems, increased awareness, improved diagnostic tools, *B. pertussis* strain adaptation to escape vaccine-induced immunity and waning immunity.

Protection against pertussis disease and prevention of infection

Using wavelet analyses of pertussis incidence combined with investigations on genetic changes in *B. pertussis* clinical isolates, Althouse and Scarpino [35] have recently assessed the principal causes of the increase in whooping cough incidence. They based their study on two potential hypotheses: either vaccination coverage is too low or vaccinated patients can still be infected with *B. pertussis*, even if they are protected against the disease. However, as vaccination coverage with aPV in countries with increasing prevalence is generally very high, they favoured the hypothesis that the vaccines in use are insufficiently effective in preventing *B. pertussis* infection [36]. With this in mind, they examined whether vaccinated individuals can become infected by *B. pertussis* because (i) sterilizing immunity induced by the vaccines wanes fast, (ii) the pathogen has evolved by accumulating mutations to escape vaccine-induced sterilizing immunity, or (iii) the current vaccines fail to induce sterilizing immunity. By studying in detail the epidemiological profiles and the observed genetic variations of *B. pertussis* in countries like the USA and the UK, they concluded that the most parsimonious explanation for the pertussis resurgence in these countries is asymptomatic transmission by individuals fully vaccinated with aPV. Hence, aPV appears to block pertussis disease but does not prevent asymptomatic transmission of *B. pertussis*. This conclusion is consistent with the limited success of cocoon vaccination with aPV reported in several recent studies [37,38], although some level of effectiveness of cocoon vaccination has been reported in other studies [39]. Asymptomatic transmission of *B. pertussis* can occur through close contact with a susceptible host, breathing or coughing, although the distinction between asymptomatic infection and mildly symptomatic infections is difficult to define.

The conclusions by Althouse and Scarpino [35] are largely consistent with observations made on a recently developed non-human primate model. Non-clinical models to study pertussis pathogenesis and immune responses to vaccines have traditionally mostly made use of mice infected by aerosol, by nasal drops or by intracranial injection. Other models, including rabbits, rats, guinea pigs, puppies, marmosets and piglets, have also been developed to study pertussis [40]. All have been useful for the study of certain aspects of *B. pertussis* infection, but none of them entirely reflects the course of whooping cough as it is seen in human patients, and none of them have been shown to transmit *B. pertussis* to littermates. The exception is the recently developed baboon model. Weanling baboons can be readily infected via the nasal route with clinical isolates of *B. pertussis*. They exhibit high white blood cell counts and develop severe and persistent paroxysmal cough upon infection [41]. Furthermore, *B. pertussis* infection of baboons