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Will we have new pertussis vaccines?

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ABSTRACT

Despite wide vaccination coverage with efficacious vaccines, pertussis is still not under control in any country. Two types of vaccines are available for the primary vaccination series, diphtheria/tetanus/whole-cell pertussis and diphtheria/tetanus/acellular pertussis vaccines, in addition to reduced antigen content vaccines recommended for booster vaccination. Using these vaccines, several strategies are being explored to counter the current pertussis problems, including repeated vaccination, cocoon vaccination and maternal immunization. With the exception of the latter, none have proven their effectiveness, and even maternal vaccination is not expected to ultimately control pertussis. Therefore, new pertussis vaccines are needed, and several candidates are in early pre-clinical development. They include whole-cell vaccines with low endotoxin content, outer membrane vesicles, new formulations, acellular vaccines with new adjuvants or additional antigens and live attenuated vaccines. The most advanced is the live attenuated nasal vaccine BPZE1. It provides strong protection in mice and non-human primates, is safe, even in immune compromised animals, and genetically stable after *in vitro* and *in vivo* passages. It also has interesting immunoregulatory properties without being immunosuppressive. It has successfully completed a first-in-man clinical trial, where it was found to be safe, able to transiently colonize the human respiratory tract and to induce immune responses in the colonized subjects. It is now undergoing further clinical development. As it is designed to reduce carriage and transmission of *Bordetella pertussis*, it may hopefully contribute to the ultimate control of pertussis.

1. Introduction

In spite of a roughly 85% global vaccination coverage with up to 99% coverage in many countries, pertussis, also referred to as whooping cough, has not yet been controlled anywhere. In fact, the disease has made a spectacular resurgence in several industrialized countries with very high vaccination coverage. Pertussis is a severe, infectious and highly contagious respiratory disease. It affects all age groups and can be fatal, especially in very young infants.

2. Current pertussis vaccines

2.1. Whole-cell pertussis vaccines

Soon after the discovery of its main causative agent, *Bordetella pertussis*, first successful attempts to limit disease severity and to control an epidemic by vaccination with a whole-cell extract of *B. pertussis* have been reported [1]. Whole-cell vaccines, consisting of heat- or formalin-inactivated *B. pertussis* bacteria and combined with diphtheria- and tetanus-toxoid-based vaccines as DTP vaccines have been shown by pioneering clinical efficacy trials to be highly efficacious after three doses, especially against severe pertussis [2]. Since the massive implementation of DTP vaccines in the 1950s and 1960s, the disease burden has markedly lessened [3]. However, doubts about the safety of these vaccines, starting to be voiced already in the early 1960s, have led to the suspension or rejection of DTP vaccines in several countries, such as Sweden, Japan and the United Kingdom. These adverse reactions ranged from local swelling and pain, to systemic reactions, such as fiver, irritability, excessive crying and, in rare cases to encephalopathy [4]. The almost immediate recurrence of the disease after cessation of vaccination [5] strongly illustrates the effectiveness of the DTP vaccines to limit pertussis disease burden.

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2.2. Acellular pertussis vaccines

Nevertheless, distrust in the DTP vaccines has led to a general decrease in vaccination coverage in several countries, but also to efforts to develop safer and less reactogenic pertussis vaccines. These second-generation, acellular pertussis vaccines are composed of purified *B. pertussis* antigens, also combined with diphtheria and tetanus toxoids and are referred to as DTaP. They vary in antigenic composition from one to five *B. pertussis* antigens. Developed in Japan in the late 1970s, and then used in the early 1980s, the first acellular vaccine, consisting of purified pertussis toxin (PT) and filamentous haemagglutinin (FHA) [6], was subsequently evaluated for its reactogenicity and protective efficacy and compared to a vaccine containing only PT in a placebo-controlled phase III trial in Sweden [7]. The acellular vaccines were found to be less reactogenic than whole-cell vaccines [6] and highly effective in preventing pertussis disease [6,7]. Depending on the case definition, protection ranged from 50% to 80% and was better against severe disease than against the milder forms. These studies were followed by direct head-to-head comparative trials with different acellular vaccines, which included, in addition to PT and FHA, pertactin and two fimbrial serotypes, and with a whole-cell vaccine. A study enrolling close to 10,000 infants confirmed the improved safety profile of the acellular vaccines, compared to the whole cell vaccine [8]. It also showed that all the acellular vaccines were efficacious against typical pertussis disease, but that the five-component vaccine was more efficacious against mild disease than the mono-component or two-component vaccines. Curiously, in this study the whole-cell vaccine provided a protective efficacy of less than 50%, whereas efficacy reached 85% for the five-component acellular vaccine. A study simultaneously performed in Italy came to the same conclusion that the tested acellular vaccines, composed of PT, FHA and pertactin, were more efficacious that the whole-cell comparator [9]. However, in both studies, the protection conferred by the whole-cell vaccine, which was identical in both studies, was surprisingly low. In another trial, conducted in Senegal, in which a different whole-cell vaccine was compared to a two-component acellular vaccine, did not confirm superior efficacy of the acellular vaccine over the whole-cell vaccine, although it confirmed improved safety. In fact, DTaP recipients showed a significantly greater rate of pertussis than DTwP recipients [10]. In addition, this study revealed a shorter duration of protection procured by the acellular vaccine, compared to the whole-cell vaccine.

These apparently conflicting observations illustrate the difficulties to manufacture consistently potent whole-cell vaccines. On the other hand, the efficacies of the acellular vaccines produced by different manufacturers tested in these trials were comparable when the same case definitions were used, suggesting a more robust consistency in the preparation of acellular vaccines. Together with an improved safety profile of the acellular vaccines, these considerations led many industrialized countries to gradually switch from whole-cell to acellular vaccines in the late 1990s, early 2000s. In most European countries, the US, Canada, Australia and Japan acellular vaccines are now exclusively used. The improved safety profile of acellular vaccines has increased the vaccine acceptance rate, which, as a consequence, has led to a second decline in pertussis incidences in countries where vaccination coverage had increased again [6,11]. Nevertheless, most countries in the world continue to use whole-cell vaccines, mainly due to cost issues and limited production capacities.

3. Current pertussis problems

Since the implementation of the acellular pertussis vaccines in most of the industrialized countries, a sudden and unexpected upswing in pertussis incidence and associated death rates has been observed, despite continuously high vaccination coverage [12–15]. However, a trend of this resurgence was already observed before the introduction of acellular vaccines, and some countries in which whole-cell vaccines are still in use also experience a rebound of pertussis [16]. Nevertheless, the introduction of acellular vaccines seems to have accelerated this resurgence. In Queensland, Australia, DTaP has replaced DTP in 1999 for the primary course of immunizations, implying that in the beginning the children received a primary course of only DTP, only DTaP or a mix of both. Ten to twelve years later, the pertussis incidence increase could be linked to the nature of the vaccines used for the primary vaccination. Higher rates of pertussis were found in children who had received 3 DTaP administrations compared to those who had received 3 DTP doses [17]. Intermediate pertussis rates were found in children who had received a mix, provided that the first dose was a DTP. Thus, priming with DTP was associated with a lower risk of developing pertussis than priming with DTaP, a difference that persisted for more than a decade. Subsequent studies have confirmed the unexpected rapid waning of effectiveness of acellular pertussis vaccines in other countries [18].

Rapid waning of acellular pertussis vaccine-induced immunity may thus be one of the reasons for the current resurgence in countries with high vaccination coverage. However, other reasons may also contribute [19]. They include increased awareness and better diagnostic tests, sub-optimal use of current vaccines, antigenic mismatch between the vaccines and circulating strains and lack of protection against *B. pertussis* transmission.

Numerous studies have shown allelic variations in *B. pertussis* that have evolved over the years since the introduction of mass vaccination [20]. However, whether this is a major driver in the current resurgence of pertussis, is still a matter of debate. Nevertheless, it is striking that since the introduction of acellular vaccines in many countries an increasing proportion of recent clinical isolates lack pertactin, one of the major antigens included in most acellular vaccines. This has not occurred in countries in which whole-cell vaccines are still in use [21]. In the US, 85% of the clinical isolates collected between May 2011 and February 2013 from 8 states did not produce pertactin [22]. Different molecular mechanisms were identified that account for pertactin deficiency. They ranged from point mutations in the pertactin coding region or its promoter to insertions and deletions, indicating that pertactin-deficient strains did not emerge by clonal expansion and argues for a selective advantage of strains lacking pertactin. In addition, the odds of infection by pertactin-deficient *B. pertussis* were higher in fully vaccinated compared to unvaccinated subjects, suggesting that this selective advantage was vaccine-driven. Importantly, the clinical manifestations of whooping cough caused by pertactin-negative or pertactin-positive *B. pertussis* are virtually indistinguishable [23], indicating that pertactin deficiency does not alter the disease severity. Studies in mice have suggested that pertactin-deficient strains have a competitive advantage over pertactin-producing strains to colonize the mouse respiratory tract in the context of vaccination with acellular pertussis vaccines, whereas in the absence of vaccination, this competitive advantage was not apparent [24].

Whereas the expansion of vaccine escape mutants and rapid waning of acellular vaccine-induced immunity have a likely contribution to the resurgence of pertussis, a third reason may be the inability of the current vaccines to prevent infection by and transmission of *B. pertussis*. For a long time, transmission of *B. pertussis* has been difficult to study in non-clinical models. The recent development of a baboon model offers now the possibility to study this in non-human primates. Acellular pertussis vaccines have been shown to protect against pertussis disease in baboons, but fail to prevent infection in this model [25]. Three human DTaP or DTP

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