



Commentary

Long-lived immunity to genetically detoxified pertussis vaccines

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Introduction

Despite a global vaccination coverage of more than 85%, pertussis is still circulating, even in highly immunized populations. It is today still one of the most prevalent vaccine-preventable childhood diseases, for which less than 5-year-olds pay the highest toll [1]. However, adolescents and adults are also susceptible to the disease and constitute an important reservoir for transmission to infants [2]. One of the major issues of current pertussis vaccines, especially of acellular vaccines, is fast waning of vaccine-induced immunity [3], a problem addressed by Pitisuttithum et al. [4] in this issue of EClinicalMedicine via the use of genetically detoxified acellular pertussis vaccines.

Two types of pertussis vaccine are currently in use. In most parts of the world, the first-generation, whole-cell vaccines are used, whereas most high-income countries have gradually switched to the second-generation, acellular vaccines. While acellular vaccines show an improved safety profile over whole-cell vaccines, it has now become apparent that immunity induced by the former wanes significantly faster than that induced by the latter [3]. Acellular vaccines are composed of up to five purified antigens, including filamentous haemagglutinin, pertactin, serotype 2 and serotype 3 fimbriae, as well as pertussis toxin, combined with alum [5]. All pertussis vaccines contain pertussis toxin, as antibodies neutralizing this toxin are essential and may be sufficient to protect against severe pertussis [6]. However, the toxin has to be inactivated, which usually occurs through chemical treatment with glutaraldehyde and/or formaldehyde.

Several decades ago, it was shown that pertussis toxin can also be detoxified through genetic modifications of its structural gene abolishing the enzymatic activity of the toxin, which is the molecular basis of its toxic action, while maintaining its immunogenicity [7]. In

contrast to chemical inactivation, site-specific genetic detoxification maintains the three-dimensional structure of the toxin, including important protective conformational epitopes [8].

Pitisuttithum et al. [4] show in this issue of EClinicalMedicine that acellular pertussis vaccines based on genetic inactivation of pertussis toxin provide longer-lived immune responses than acellular vaccines composed of chemically inactivated pertussis toxin. Adolescent participants of a randomized controlled trial who had received either one dose of a genetically inactivated stand-alone pertussis vaccine or combined with diphtheria and tetanus toxoids, compared with chemically detoxified acellular pertussis vaccine combined with tetanus and diphtheria toxoids were followed up for three years after vaccination. Previous studies by the same investigators had already demonstrated that genetically inactivated pertussis toxin is more immunogenic and induces higher levels of toxin-neutralizing antibodies than chemically inactivated pertussis toxin [9].

The study presented now indicates that antibodies to pertussis toxin, and in particular toxin-neutralizing antibodies persist substantially longer after vaccination of adolescents with genetically detoxified than with chemically detoxified pertussis vaccine. Toxin-neutralization titers upon vaccination with the chemically detoxified vaccine returned in most cases to base line within one year, after an initial transient rise at day 28 post-vaccination. In contrast, neutralization titers induced by the genetically inactivated vaccines remained high even three years post-vaccination. Only a modest decline in neutralization titers was observed between years 2 and 3 after vaccination, suggesting that they may persist beyond year 3.

These results may have important implications, as they suggest that protection offered by genetically inactivated acellular pertussis vaccines may wane substantially less rapidly than that induced by most current chemically inactivated vaccines. This may thus counter one of the main reasons for the resurgence of pertussis in fully vaccinated adolescents, despite adolescent booster vaccination [3]. Furthermore, in many countries, maternal vaccination with acellular pertussis vaccines is recommended at each pregnancy in order to protect the new-born child through placentally transmitted pertussis toxin-neutralizing antibodies. The longevity of these antibodies in the new-born is not yet well documented but is likely to depend on the amount of neutralizing antibodies transferred to the foetus during pregnancy. Long-lived neutralizing antibodies induced by maternal vaccination with genetically inactivated pertussis vaccines are thus likely to provide long-lasting immunity against severe and lethal pertussis in the offspring, which should last at least until the completion of the

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primary course of infant vaccination. The duration of these antibodies may perhaps be long enough to span several pregnancies.

While the study by Pitisuttithum et al. [4] provides compelling evidence allowing the medical community to hope that genetically detoxified pertussis vaccines may solve the problem of fast waning of acellular vaccine-induced immunity, it remains to be seen whether the persistence of pertussis toxin-neutralizing antibodies does in fact translate into persistence of protection against pertussis disease. Furthermore, it remains to be investigated whether such vaccines will have an impact on *Bordetella pertussis* infection and transmission, another major shortcoming of most current acellular pertussis vaccines [10]. Since the vaccine studied by Pitisuttithum et al. is already licenced and used in Thailand, answers to these questions may hopefully emerge soon.

Declaration of Competing Interest

The author declares no conflicts of interest.

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