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Review

Experience with monocomponent acellular pertussis combination vaccines for infants, children, adolescents and adults—A review of safety, immunogenicity, efficacy and effectiveness studies and 15 years of field experience☆

Birgit Thierry-Carstensen[a,*], Tine Dalby[a], Michael A. Stevner[a], John B. Robbins[b], Rachel Schneerson[b], Birger Trollfors[c]

[a] Statens Serum Institut, 5 Artillerivej, 2300 Copenhagen S., Denmark
[b] National Institute of Child Health & Human Development, National Institutes of Health, Bethesda, MD 20892, USA
[c] Department of Pediatric Medicine, Sahlgrenska University Hospital-East, 416 85 Gothenburg, Sweden

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ABSTRACT

Combination vaccines containing a monocomponent acellular pertussis (aP) vaccine, manufactured at Statens Serum Institut (SSI), Denmark, have successfully controlled *Bordetella pertussis* infections in Denmark since 1997. The efficacy of this aP vaccine was 71% in a double-blind, randomised and controlled clinical trial. Its safety and immunogenicity have been demonstrated in infants, children, adolescents and adults. In approximately 500,000 children it was effective against pertussis requiring hospitalisation (VE: 93% after 3 doses) and against pertussis not requiring hospitalisation (VE: 78% after 3 doses). IgG antibodies against pertussis toxin (IgG anti-PT) response rates after booster vaccination of adults with tetanus, diphtheria and aP combination vaccine (TdaP) were considerably higher for this monocomponent aP vaccine containing 20 μg pertussis toxoid, inactivated by hydrogen peroxide (92.0%), than for two multicomponent aP vaccines inactivated by formaldehyde and/or glutaraldehyde: 3-component aP with 8 μg pertussis toxoid (77.2%) and 5-component aP with 2.5 μg pertussis toxoid (47.1%), without compromising the safety profile. In Denmark where this monocomponent aP vaccine has been the only pertussis vaccine in use for 15 years, there has been no pertussis epidemic since 2002 (population incidence 36 per 100,000), in contrast to neighbouring countries, where epidemics have occurred. This monocomponent aP vaccine can be used in combination vaccines for primary and booster vaccination against pertussis in all age groups and is an important tool for successful pertussis control.

Contents

* Corresponding author. Tel.: +45 3268 3598; fax: +45 3268 3872.
E-mail address: btc@ssi.dk (B. Thierry-Carstensen).

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1. Introduction

This review summarises experience from clinical trials and post-marketing data of a monocomponent aP vaccine which contains pertussis toxoid in a less denatured form and at a higher dosage than other aP vaccines in use [1,2]. In spite of the introduction of universal infant vaccination [3], pertussis remains one of the leading causes of vaccine preventable deaths with an estimated 50 million cases and 300,000 deaths occurring worldwide annually. Over the past two decades, there has been a modest but steady increase in reports of pertussis incidence in Europe, the USA and other parts of the World [4,5]. This increase in incidence is mainly seen in adolescents and adults [6]. Several possible reasons for the apparent increase in incidence have been suggested [6]: low vaccine coverage in infants, insufficient administration of booster doses, increased awareness of pertussis, availability of new diagnostic tools, decreased chance of natural boosting in the vaccination era, reduced longevity or quality of the immune responses induced by the acellular pertussis (aP) vaccines currently in use, and lastly new circulating genotypes of *Bordetella pertussis* (*B. pertussis*) [5,7,8]. aP vaccines contain from one to five pertussis antigens. It is generally agreed that antibodies against pertussis toxin (anti-PT) play a major role in protection [9–11] and all aP vaccines contain pertussis toxoid. In addition to pertussis toxoid, multicomponent aP vaccines contain varying amounts of filamentous hemagglutinin (FHA), pertactin (PRN) and/or fimbriae (FIM) types 2 and 3. The roles of the additional antigens in protection against pertussis, and the possible advantages obtained are subject of debate [9–11]. Interestingly, the monocomponent aP vaccine, which is the subject of this review, has successfully controlled *B. pertussis* infections in Denmark, at least as effectively as in neighbouring countries where multicomponent aP vaccines are used, supporting that pertussis toxoid is both essential and sufficient for a pertussis vaccine [10,12].

2. Development history and aP vaccine particulars

The pertussis toxoid in the Danish aP vaccine is inactivated by hydrogen peroxide, whereas other aP vaccines are inactivated using formaldehyde and/or glutaraldehyde. It has been shown that chemical inactivation of pertussis toxin by hydrogen peroxide results in a lower degree of epitope impairment [1,2] and thus in a better immunogen. The development of the Danish vaccine, presently manufactured at Statens Serum Institut (SSI), Denmark, was initiated in the 1980s at the National Institute of Child Health and Human Development (NICHD), National Institute of Health (NIH), Bethesda, MD, USA [13]. It was found to be safe and immunogenic in initial dosage finding trials in adults [14], 18–24-months-old children [15], and in infants [1,16]. After these early trials, the efficacy was demonstrated in Gothenburg, Sweden, during 1991–94 [17], Table 1 and Section 3. The selected dosage of 40 μg pertussis toxoid for the efficacy trial has subsequently remained unchanged in combination vaccine formulations for primary vaccination, whereas 20 μg has been established as sufficient for booster vaccination. All SSI combination vaccines are adsorbed to aluminium hydroxide and contain no preservative. During the last decade, the clinical development has continued with safety and immunogenicity trials in infants [18–20], children [21–23], adolescents [24] and adults [25,26] in various countries, Table 1 and Sections 4 and 5. The first regulatory approvals were obtained in 1996 in Denmark and Sweden, followed by other European countries in 1997 and the USA in 1998, and recently a booster formulation was approved for vaccination of children, adolescents and adults in 12 European countries. In Denmark combination vaccines containing monocomponent aP have been routinely used for primary vaccination of infants at 3, 5 and 12 months of age since 1997, and for booster vaccination of preschool children since 2003. The results of two large post-marketing effectiveness studies [27,28] are presented in Table 1 and Section 6, and a description of the epidemiological situation of pertussis in Denmark is given in Section 7. In the following, DTaP refers to combination vaccines intended for primary vaccination with full doses of diphtheria (D), Tetanus (T) and pertussis (aP) antigens, with or without inactivated poliovirus vaccine (IPV) and *Haemophilus influenzae* type b conjugate vaccine (PRP-T). TdaP refers to combination vaccine formulations for booster vaccination where the diphtheria (d) and pertussis (aP) dosages are reduced, except in the dosage finding trials [22,23] where TdaP was investigated in dosages of 20 and 40 μg pertussis toxoid.

3. Vaccine efficacy of monocomponent aP

3.1. Double-blind, randomised, controlled trial, DTaP (SSI)

The efficacy of the monocomponent aP vaccine was demonstrated in a double-blind, randomised and placebo controlled trial with DTaP (SSI), in Gothenburg during 1991–94, when pertussis was endemic in Sweden [17], Study A, Table 1. After active and double-blind follow-up for pertussis for a median of 17.5 months, the efficacy was 71%, (95% CI: 63–78%) defining a pertussis case according to the WHO definition recommended at that time. In fully DTaP vaccinated subjects with or without pertussis in the subsequent follow-up period, but with no pertussis ± 2 months from the time of sampling, the one month post-3rd vaccination geometric mean concentration (GMC) of IgG anti-PT was 145 IU/mL, Study A. At the end of the double-blind follow-up period, trial subjects who were still at risk of pertussis (i.e. pertussis cases were considered no longer at 'risk' of pertussis from the first day of cough) were followed during an open extension follow-up period of 6 months where the vaccine efficacy was 77%, (95% CI: 65–85%) [29], Study A.