Safety and Reactogenicity of a low-dose Diphtheria-Tetanus-Acellular Pertussis Vaccine (Boostrix™) in Pre-school Indian Children

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***Objective**: To evaluate the safety and reactogenicity of a reduced-antigen-content combined Diphtheria-Tetanus-Acellular Pertussis (dTpa) vaccine in Indian pre-school children. **Methods**: GlaxoSmithKline Biologicals' combination dTpa vaccine was administered as a single booster dose to 347 children aged 4-6 years in seven centers across India. All children were subsequently followed up for two weeks for safety and reactogenicity assessment. **Results**: A total of 345 subjects completed the study and two subjects were lost to follow-up. One serious adverse event (head injury) unrelated to vaccination was reported. Otherwise, all subjects were in good health throughout the study period. Three subjects (0.9%) reported transient general symptoms (such as irritability and drowsiness), which prevented normal activity. Pain at injection site, swelling and redness was reported in 31.1%, 18.2% and 8.9% subjects respectively. Five subjects (1.4%) reported severe pain preventing normal movement. This resolved within 48 hours in all cases. There were no other severe local reactions including large injection site reactions. **Conclusion**: The reduced-antigen-content combined dTpa vaccine is safe and well tolerated in Indian pre-school children.*

Keywords: *Booster, Combination vaccine, dTpa, Safety.*

ALTHOUGH universal primary immunization against pertussis in infancy has been widely practiced for several years, there has nevertheless been an increase in the global incidence of the disease in older children, adolescents and adults(1,2). These affected individuals may in turn serve as reservoirs of infection to siblings too young to be vaccinated, placing them at risk of severe disease. Hence, it has been suggested that there is a need to provide booster immunization against pertussis, preferably together with diphtheria and tetanus at the age of school entry, when immunity against pertussis is known to wane(3).

Low-dose combination diphtheria-tetanus-acellular pertussis (dTpa) booster vaccines have been developed, which are efficacious and immunogenic in adults and adolescents and demonstrate a similar reactogenicity profile to that of standard booster diphtheria tetanus (dT) vaccines. Furthermore, when used as a booster in children, these vaccines induce similar immune responses to those seen with full-strength combination diphtheria-tetanus-whole cell per-tussis (DTPw) vaccines(4-6). The present study was undertaken to evaluate the reactogenicity and acceptability of this vaccine in Indian pre-school children.

Subjects and Methods

The study was conducted in seven centers across India between May to November 2004, according to the standards of Good Clinical Practices (GCP) of the International Council of Harmonization (ICH). Approval for the study was obtained from all institutional ethics committees and the Drugs Controller General of India. The study documentation was audited as a part of a sponsor

company Country Medical Department audit. Informed consent was obtained from the parents and guardians of all children prior to participation in the study. All the subjects recruited were required to have no contraindications to vaccination such as anaphylaxis or acute illness and to have received three priming doses of diphtheria-tetanus-whole cell pertussis vaccine in infancy and a booster at 18 months of age.

All subjects received a single dose of Boostrix™ vaccine [GlaxoSmithKline (GSK) Biologicals', Rixensart, Belgium], which is a combination diphtheria-tetanus-acellular pertussis vaccine containing not less than 2 IU of diphtheria toxoid, 20 IU of tetanus toxoid and three components of acellular pertussis antigens [pertussis toxin (PT: 8 μg), filamentous haemagglutinin (FHA: 8μg), pertactin (PRN: 2.5 μg). The vaccine was supplied in pre-filled syringes from a single batch. Subjects were followed up for safety and reactogenicity assessment. Solicited local and general symptoms were recorded by the parents on diary cards for the two weeks following vaccination. Local symptoms included pain, redness and swelling at the injection site. General symptoms included fever (the highest temperature recorded daily), irritability, drowsiness and loss of appetite which prevented normal activity. Unsolicited symptoms were recorded retrospectively by the investigator at the subsequent visit. All symptoms were graded according to severity.

Statistical analysis was performed to ascertain the percentage of subjects reporting adverse events within various parameters, with 95% confidence intervals (CI).

Results

Of the 347 children recruited, 345 completed the study and two subjects were lost to follow-up. There were no other withdrawals from the study. Male subjects comprised 53% of the population and the mean age was 4.4 years. All subjects were in good health with a mean body mass index of 13.9 kg/m^2. Compliance with the diary card requirements was 99.4%. *Table I* shows the incidence of solicited local adverse events during the two-week follow-up period. Pain at injection site was the most frequent complaint reported by almost one-third (31.1%) of subjects. However, the pain was severe to prevent normal daily activity in only five (1.4%) subjects. The pain resolved within 48 hours in all. Other local symptoms were swelling (18.2%) and redness (8.9%). These were not large in any of the cases.

Table II shows the incidence of solicited general adverse events during the two-week follow up period. Three subjects (0.9%) reported severe general symptoms, which prevented normal daily activity. Two of these subjects demonstrated increased irritability, while the other exhibited drowsiness. All subjects recovered within 24 hours. No high fever (>39.1ºC) related to vaccination was reported with any child participating in the study.

TABLE I– *Incidence of Local Symptoms within 2 Weeks of Vaccination (n = 345)*

Symptom	Intensity	N	(%)	95% CI of percentages
Pain	Any	108	(31.1)	26.3 – 36.3
	Prevents normal movement	5	(1.4)	0.5 – 3.3
Redness	Any	31	(8.9)	6.2 – 12.4
	> 20 mm	0	(0.0)	0.0 – 1.1
Swelling	Any	63	(18.2)	14.2 – 22.6
	> 20 mm	0	(0.0)	0.0 – 1.1

TABLE II–*Incidence of General Symptoms Within 2 Weeks of Vaccination (n=345)*

Symptom	Relationship and intensity	N	(%)	95% CI of percentages
Drowsiness	Any	15	(4.3)	2.4 – 7.0
	Related	6	(1.7)	0.6 – 3.7
	Related - Severe	1	(0.3)	0.0 – 1.6
Irritability	Any	28	(8.1)	5.4 – 11.5
	Related	15	(4.3)	2.4 – 7.0
	Related - Severe	2	(0.6)	0.1 – 2.1
Loss of	Any	33	(9.5)	6.6 – 13.1
Appetite	Related	12	(3.5)	1.8 – 6.0
	Related-Severe	0	(0.0)	0.0 – 1.1
Fever	Any	60	(17.3)	13.5 – 21.7
	Related	29	(8.4)	5.7 – 11.8
	> 39.1ºC Related	0	(0.0)	0.0 – 1.1

What this Study Adds

- Booster formulation of dTpa vaccine (Boostrix™) is safe and well-tolerated in Indian children aged 4 to 6 years, who have previously completed primary vaccination and a booster dose at 16-20 months of age with DTPw vaccine.

Two subjects reported unsolicited symptoms which the investigator considered to be related to vaccination. One subject suffered from disturbance in attention, another had a rash, both resolved within a few days. Neither was described as severe by the investigator. There was one serious adverse event (an accidental head injury) that was considered unrelated to vaccination by the investigator.

Discussion

Data from the West suggests that pertussis continues to be a problem among older children and adults, who may in turn infect neonates awaiting vaccination(7). However, compliance with pertussis boosting has been found to be low after primary dosing in the first year of life(8). The main cause for this poor compliance seems to be increased reactogenicity observed with whole-cell pertussis vaccines in older age groups. A reduced-antigen-content acellular pertussis vaccine is claimed to be advantageous in reducing the incidence of these reactions thus making it more acceptable for the recipients and their parents, and consequently improving compliance and coverage(6).

In a study of Thai pre-school children, the dTpa vaccine was found to be significantly less reactogenic than the DTPw vaccine(8). In turn, our study found a similar reactogenicity for the same dTpa vaccine in Indian children as observed in Thai children(8). Though no direct comparison has been made with dTPw vaccine in the current study, the observed adverse effect profile appears to be better than that reported with DTPw vaccine in this age group. This advantage over whole-cell vaccines can be expected to allay parental concerns of vaccine reactions and thus encourage and increase the uptake of booster doses in pre-school children.

Immunological evidence from the Thai study indicated that the booster response of the dTpa vaccine was as seroprotective as the DTPw vaccine for diphtheria and tetanus and had similar rates of vaccine response (over 95%) for all pertussis antigens(8). Studies in Taiwanese children aged 6 to 8 years and adolescents aged 15 to 20 years, and in Singaporean adults aged 18 to 60 years have also shown high immunogenicity after the same dTpa vaccine(9,10). In a study from United Kingdom also, dTpa vaccine demonstrated high immunogenicity in pre-school children(11).

When a full dose diphtheria-tetanus-acellular pertussis vaccine (DTPa) was compared with a reduced-antigen-content dTpa vaccine in Israeli pre-school children, no significant differences with respect to immunogenicity were observed(12). Hence, various studies in disparate parts of the world show that the use of dTpa vaccine does not compromise the protection of children from the three diseases and is less reactogenic when compared to more traditional vaccines. Immunity following primary acellular pertussis vaccines is considered to be effective longer and wane more slowly than whole-cell pertussis vaccines(13). A dTpa vaccine therefore offers protection with a lower booster dose along with lower reactogenicity and potentially longer protection.

The observed high disease burden due to pertussis in adolescents and adults worldwide, together with the increasing availability of dTpa vaccines with high immunogenicity and low reactogenicity profiles, have prompted global experts in the field to recommend universal adolescent pertussis boosting in all countries where it is economically feasible(14). This vaccine has proven to be safe and afficacious in adults and adolescents(5). This study demonstrates that it also appears to be well tolerated by Indian pre-school children.

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Competing interests: Dr. S.K. Datta and Dr. H.L. Bock are employees of GlaxoSmithKline Biologicals.

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