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DEVELOPMENT OF STAPHVAX™, A POLYSACCHARIDE CONJUGATE VACCINE AGAINST *STAPHYLOCOCCUS AUREUS* INFECTION: FROM THE LAB BENCH TO PHASE III CLINICAL TRIALS*

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SUMMARY

Staphylococcus aureus is the most common nosocomial pathogen and is responsible for approximately one-third of hospital-acquired bacteraemias. The emergence of strains with multidrug resistance, including resistance to vancomycin, the antibiotic of last resort, presents the medical community with a major public health problem. Alternative therapies, including immunotherapy, have been in development for several decades. The discovery of *S. aureus* capsular polysaccharides from clinical isolates, and their importance to pathogenicity via anti-phagocytic activity, opened a new window of opportunity for development of vaccines and immunotherapy against this pathogen. A conjugate vaccine, StaphVAX™ that includes the two most prevalent capsular polysaccharides, types 5 and 8, coupled to a carrier protein efficient in promoting a Th2 response, was developed. In a recent Phase 3 clinical study in haemodialysis patients, StaphVAX™ was shown to prevent *S. aureus* bacteraemia for up to 10 months following a single immunisation. The history, epidemiology, serology, and development of StaphVAX™, including preclinical and clinical studies demonstrating efficacy are described in this review.

INTRODUCTION

S. aureus is the number one cause of infection in hospitalised patients, accounting for 20-25% of all nosocomial infections (*Pfaller* et al., 1998). Contrary to the general belief, bacteraemia is the most prevalent type of *S. aureus* infection in hospitalised patients, followed by lower respiratory tract infections and skin/soft tissue infections. In a recent and comprehensive survey that included clinical sites in the USA, Canada, Europe, it was found that *S. aureus* accounted for 22% of all blood infections (8,929 of 40,497 infections), 23.2% of all lower respiratory tract (3,371/14,552 infections) and 39.2% (2,928/7,474 infections) of all skin and soft tissue infections (*Diekema* et al., 2001, 2002).

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The ability of *S. aureus* to acquire antibiotic resistance and to adapt to new antibiotics is well established (*Lowy*, 2003). It is well recognised that the extensive use of antibiotics has resulted in increased resistance among. *S. aureus* clinical isolates. In some areas, more than 95% of *S. aureus* isolates are now resistant to penicillin or ampicillin and more than 50% have developed resistance to methicillin (*Brumfitt* and *Hamilton-Miller*, 1990; *Boyce*, 1990; *Begley*, 1994). Methicillin resistant *S. aureus* (MRSA) infections are observed primarily in hospital settings but there have been alarming reports recently of community acquired MRSA infections (*Naimi* et al., 2001). There are numerous examples demonstrating that vancomycin, presently the antibiotic of last resort against multidrug resistant *S. aureus* infections has been unable to clear *S. aureus* infections (*Moore* et al., 2003; *Grabs* and *Lord*, 2002; *Gopal* et al., 1976). The ability of *S. aureus* to become vancomycin resistant was long believed to be limited only to laboratory setting (*Noble* et al., 1992). However, the first clinical isolate of *S. aureus* with intermediate sensitivity to vancomycin (8-16 μg/ml) was identified in Japan (*Hiramatsu*, 1997,1998). Soon after this report, more isolates with intermediate resistance to vancomycin (VISA) were reported in the USA and elsewhere (*CDC*, 1996). VISA strains were found to adapt and develop intermediate resistance by thickening of their cell walls (*Lowy*, 2003). More recently the first truly vancomycin resistant *S. aureus* (VRSA) was isolated and reported (*CDC*, 2002). The newly isolated strain was found to have acquired vancomycin resistance by acquiring the van A gene identical to that found in vancomycin resistant enterococci (*Lowy*, 2003).

RATIONALE, IDENTIFICATION AND DEVELOPMENT OF VACCINE CANDIDATES

With the advent of antibiotics, development of immunological approaches to management of staphylococcal infections has languished. Despite the large body of work in support of such approaches, the prospect of an immune-based solution to staphylococcal infections has been clouded with uncertainty (*Foster*, 1991). *Wright* and *Douglas* (1989) noted that phagocytosis was already in 1903 considered a major line of defence against *S. aureus* infections. Another significant clinical finding was reported by *Quie* (1972), who discovered that immune compromised children with “chronic granulomatous disease” had frequent *S. aureus* infections and that these occurrences were directly related to the dysfunction of the phagocytic cells. In spite of these leads, attempts to identify and isolate *S. aureus* antigens that stimulate opsonic antibodies against clinically significant "conventional" isolates were unsuccessful. Eventually, most investigators abandoned the search for immunological strategies to protect against *S. aureus* infection. As Dr. David Rogers, a prominent investigator in the field stated at the New York Academy of Science "The Staphylococci: Ecologic Perspective" meeting in 1965, protective immunity and human antibody response to staphylococci "... have gone about as fur as they kin go" (*Rogers* and *Melly*, 1965; *Fattom* and *Naso*, 1996a).

In spite of its ability to produce a large variety of toxins and extracellular products (*Foster*, 1991), *S. aureus* cannot be generally equated with other organisms, such as *Clostridium tetani*, *Corynebacterium diphtheriae*, or *Bor-*

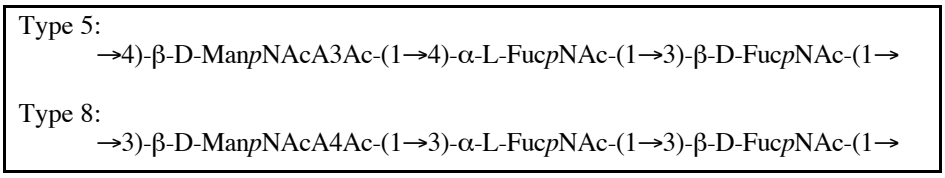

Figure 1: The structures of *S. aureus* types 5 and type 8 CP.

detella pertusis, which produce human illness primarily through elaboration of extracellular products and toxins. The hallmarks of *S. aureus* infection are dissemination of *S. aureus* through the blood and multiplication of the organism at the nidus of infection. *S. aureus* is part of the normal human flora and exists in the nasopharyngeal cavity of ~25% of healthy adults (*Essawi* et al., 1998a). Healthy people are not at risk for *S. aureus* infections and in fact can readily clear infections by this organism. Once hospitalised, however, *S. aureus* becomes the most common infectious agents in the hospital setting (*Diekema* et al., 2002). Systemic *S. aureus* infections such as endocarditis, osteomyelitis, meningitis, etc. often result from haematogenous seeding from bacteraemia due to the ability of *S. aureus* to evade immunological clearance mechanisms, especially opsonophagocytosis. Thus, staphylococcal pathobiology appears to be more like that of the pneumococci and meningococci rather than diphtheria, tetanus, or pertusis. For this reason, eliminating the organism from the host is of primary concern in preventing and treating staphylococcal infections.

In 1983 the field was advanced significantly when typing sera against *S. aureus* clinical isolates were developed (*Karakawa* and *Vann*, 1982). It was quickly shown that *S. aureus* clinical isolates possess capsular polysaccharides (CP) that contribute to the ability of the bacteria to evade opsono-phagocytosis. Subsequently, CP-specific antibodies were shown to mediate type-specific opsono-phagocytosis and bacterial killing by polymorphonuclear cells (PMNs) (*Karakawa* et al., 1988). Of the 13 known capsular types, two, types 5 and 8, were shown to comprise the majority of the clinical isolates (*Arbeit* et al., 1984; *Sompolinsky* et al., 1985). Recent studies using isolates from different countries showed that 93% *S. aureus* isolates were of either type 5 or type 8 (33% and 60%, respectively) (*Fattom* et al., 1995; *Essawi* et al., 1998b). These two capsular types also comprise >80% of *S. aureus* isolated from sheep, goats, cows with mastitis, and chickens with osteomyelitis (*Daum* et al., 1994; *Poutrel* et al., 1988). Ultimately, *S. aureus* types 5 and 8 CP were isolated, purified, and their chemical structures elucidated (*Fournier* et la., 1987; *Moreau* et al., 1990) (Figure 1).

Types 5 and 8 CP were found to be of small molecular size compared to CP of several other pathogenic bacteria. Furthermore, immunogenicity studies of the purified *S. aureus* CP showed them to be non-immunogenic in mice (*Fattom* et al., 1990). This property has been predictive for poor immunogenicity in infants and immunocompromised patients, two populations at high risk for *S. aureus* infections. Linking CP to carrier proteins to produce conjugate vaccines was shown to be effective in increasing the immunogenicity of bacterial polysaccharides and to confer T-cell dependent properties on their immune response (*Robbins* and *Schneerson*, 1990; *Chu* et al., 1983). Two conjugate vac-

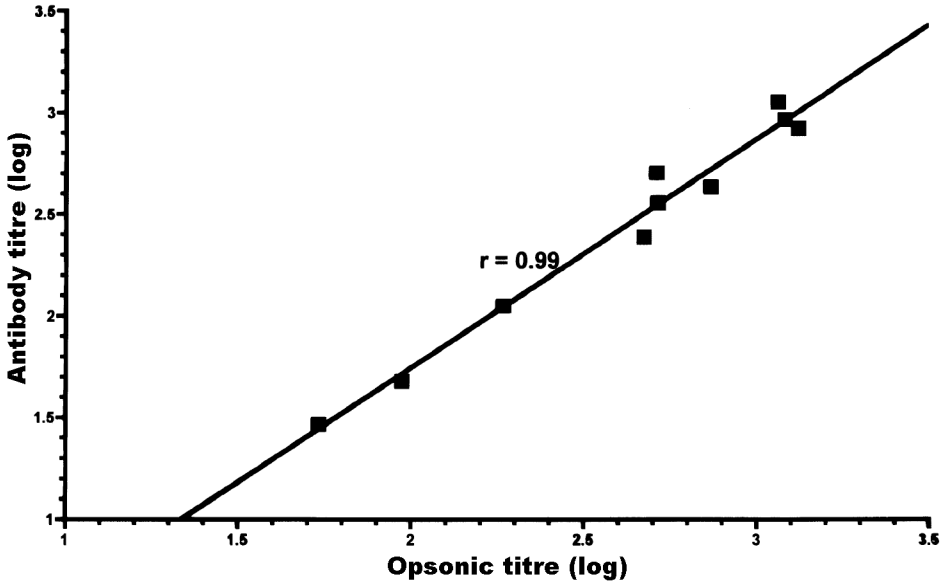

Figure 2: Opsono-phagocytosis of type 5 *S. aureus* by CP 5-rEPA conjugate induced antibodies in mice; correlation with ELISA antibodies
Opsono-phagocytosis assays were performed as described by *Karakawa* et. al (1988) except an HL60 cell line was used instead of freshly isolated human PMNs. The dilution that produced 50% kill was determined and the opsono-phagocytic titre was determined as $1/\text{dilution}_{50\%}$ after subtracting the background kill determined by the addition of non-immune sera.

cines, in which CP type 5 and type 8 were linked to carrier proteins, have been prepared using *Pseudomonas aeruginosa* exotoxin A as a carrier protein, and were evaluated in animals. Data showed that these conjugates elicited high antibody titres in mice and in rabbits. Moreover, the conjugation conferred T-cell dependent properties on the CP as evidenced by a booster response following a second injection or as shown upon carrier priming (*Fattom* et al., 1990).

Antibodies generated in vaccinated mice in response to monovalent conjugates (i.e. type 5 or type 8 CP conjugate alone) or a bivalent vaccine containing both type 5 and type 8 conjugates, exhibited both high affinity and type specificity. It was also found that antibodies generated by the vaccine(s) were functional in that there is a high degree of correlation between the amount of antibody by ELISA compared to opsonic activity. Figure 2 shows *in vitro* opsono-phagocytosis data generated by using murine sera from vaccinated mice.

EFFICACY IN ANIMAL MODELS

Active immunisation with StaphVAX™ was evaluated in a lethal mouse challenge model and was shown to protect mice from *S. aureus* challenge. It was also observed that there was a correlation between antibody titres and protection in the surviving mice (*Fattom* et al., 1996a). To further evaluate the mechanism of protection demonstrated by active immunisation, immunoglobu-

Table 1: Longevity of S. *aureus* CP5 and CP8 immune response in healthy adult volunteers following administration of CP5 or CP8 conjugate vaccines

Vaccine (Lot #)	N[1]	Antibody concentration Geometric mean IgG levels and range (μg/ml)				%[Ab][2]
		Pre-immune	6 weeks	6months	47 months	
S. aureus T5-rEPA (Lot # 50179)	8/23	10 (7-13)	367 (246-479)	292 (255-289)	122 (68-128)	42
S. aureus T5-rEPA (Lot # 4907)	11/25	8 (6-13)	241 (177-350)	175 (51-115)	100 (73-141)	57
S. aureus T8-rEPA (Lot # 51008)	9/22	11 (9-25)	81 (60-116)	71 (51-115)	52[3] (41-68)	73

[1]Number of volunteers available for evaluation at 47 months/number of original participants.
[2]Antibody levels remaining at 47 months compared to 6 months (%).
[3]Type 8 levels were measured at 33 months post last immunisation.

lin G (IgG) was purified from plasma obtained from human volunteers who received a dose of the bivalent type 5 and type 8 conjugate vaccine, designated as StaphVAX™. The IgG, called Altastaph™, was used to passively immunise animals, which were subsequently challenge with *S. aureus* lethal challenge (*Fattom* et al., 1996b). The geometric mean CP-5 specific antibody level in animals administered Altastaph™ was 111 μg/ml on the day of challenge with a half-life of 6 days. All animals that received Altastaph™ were protected against the challenge. Moreover, compared to animals administered non-specific IgG, animals passively immunised with Altastaph™ and challenged with a sublethal dose of S. *aureus* showed a faster clearance of the bacteraemia. Examination of the passively immunised animals revealed that while kidneys and livers from immunised animals were free of infection, *S. aureus* abscesses developed in kidneys and livers of animals receiving control IgG (*Fattom* et al., 1996b). The efficacy of the StaphVAX™ specific antibodies was also shown in a rat endocarditis challenge model (*Lee* et al., 1997). These data confirmed that protection against *S. aureus* infection is an antibody-mediated mechanism and that the CP-specific antibodies could serve as a surrogate marker for *in vivo* protection. Moreover, these data may suggest also that *in vitro* opsono-phagocytosis is a reasonable predictor for *in vivo* protection.

IMMUNOGENICITY OF STAPHVAX™ IN HUMANS

The type 8 CP and type 5 CP conjugate vaccines were initially evaluated in healthy adult human volunteers (*Fattom* et al., 1993). A total of 76 vaccinees received two injections of either type 5 or type 8 conjugates in saline at 25 μg CP/dose. The vaccines were well tolerated. No significant systemic or serious local reactions were reported. Minor tenderness and erythema was observed in few volunteers, however, these reactions were transient and generally disappeared within 48 hrs.

An interesting observation from this study was that nearly all individuals, presumably due to repeated exposure to

Table 2: Evaluation of IgG subclasses at 6 weeks and 33-47 month post vaccination in adult volunteers receiving type 5 CP conjugate vaccine

CP	Lot #	Subclass	N	Antibody titres (GM-μg/ml)			reduction (%)
				Pre-immune	6 weeks	33-47 months	
T5	49704	IgG1	6	1.3	47.17[a]	17.64[b]	61
		IgG2	6	1.83	60.6[c]	26.51[d]	54
		IgG3	2	<0.1	1.47	0.69	53
		IgG4	0	<0.1	<0.1	<0.1	n.a.
T5	50179	IgG1	6	0.22	11.27[e]	4.57[f]	53
		IgG2	6	2.27	173.83[g]	43.2[h]	67
		IgG3	1	1.4	100	78	22
		IgG4	2	0.89	8.39	6.32	22

Unpaired t-test: *a vs. b*: p=0.008; *e vs. f*: p=0.041.
Mann-Whitney Rank Sum Test: *c vs. d*: p=0.004, *g vs. h*: p=0.047.

S. aureus not leading to clinical disease, have low levels of pre-existing antibody to *S. aureus* CP, and are therefore immunologically primed to the CP. In these early studies, background low levels of antibodies (approximately 10-15 μg/ml) to each of the CP were measured. Following a single dose of conjugate vaccines, there was a 10-20-fold increase in CP-specific antibody levels. Both IgG and IgM classes were induced after the first injection. A second injection of conjugate vaccine 6 weeks later did not stimulate a further increase in antibody levels, indicating that the first dose resulted in a near maximum booster response in these subjects. Sera were obtained from several subjects available for blood drawing at 47 months after type 5 vaccination and 33months after type 8 vaccination. The antibody levels were 42% to 57% of the levels measured 6 months after vaccination. Antibody levels to type 8 CP were approximately 73% of the values measured at 6 months after vaccination (Table 1). Evaluation of the different subclasses at the two time points revealed a similar decline in titre in all four IgG subclasses (Table 2). These data show that CP-conjugate vaccines elicit a long-term immune response with a slow decline over time and that there is no selective decline in titres among the different IgG subclasses.

The functionality of *S. aureus* antibodies in sera from healthy volunteers participating in subsequent StaphVAX™ clinical trials were tested in an *in vitro* opsono-phagocytic assay and compared to sera obtained prior to vaccination. Post-vaccination sera demonstrated significantly higher levels of type specific opsono-phagocytic activity. In addition, there was an excellent correlation between type specific antibody levels measured by ELISA and opsono-phagocytic (Figure 3).

TARGET POPULATIONS

Hospitalised patients in general and especially those undergoing invasive medical procedures including surgery are at risk for *S. aureus* infections.

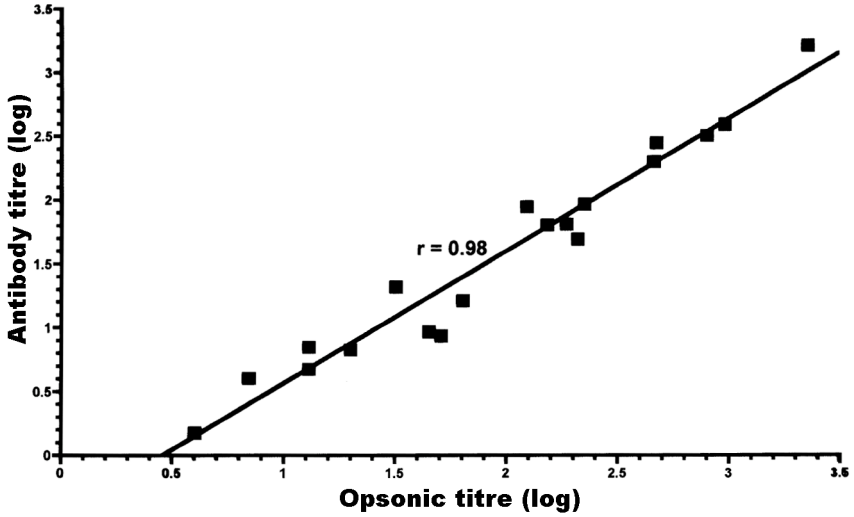

Figure 3: Opsono-phagocytosis of *S. aureus* type 5 by human sera from healthy volunteers immunised with StaphVAX™; correlation with ELISA antibodies
Opsono-phagocytosis assays were performed as described by *Karakawa* et. al (1988) except an HL60 cell line was used instead of freshly isolated human PMNs. Individual human sera were added to the reaction mixture and the 50% kill was determined. Opsono-phagocytic titres was determined as $1/\text{dilution}_{50\%}$

Other populations such as end stage renal disease patients (ESRD) on haemodialysis and other patients with chronic diseases such as residents of nursing homes are also at relatively high risk for *S. aureus* infections (*Fattom* and *Naso*, 1996b). While surgery patients are at high risk for *S. aureus* infections for a limited short period of time, patients with chronic disease, such as ESRD patients, are at continuous, long-term risk because of their underlying disease and routine medical procedures used to treat them (e.g. dialysis procedures). ESRD patients were chosen for the clinical development of StaphVAX™ (*Fattom* and *Naso*, 1996b) due to their relatively high incidence of *S. aureus* disease and their good response to StaphVAX™.

Other Early Clinical Trials

Initial clinical studies of type 5 and type 8 CP conjugates in healthy volunteers showed the vaccine components to be safe and immunogenic (*Fattom* et al., 1993). Subsequent trials evaluated a *S. aureus* monovalent type 5-rEPA conjugate in haemodialysis patients with ESRD (*Welch* et al., 1996). No serious local or systemic reactions or liver enzyme abnormalities were observed following the first or the second immunisation. Although a 18-fold increase in IgG antibodies to type 5 CP was observed, the geometric mean IgG level was 56% of that achieved in normal healthy volunteers immunised with same lot of vaccine. Furthermore, although all subjects responded with higher type 5 CP antibodies, only 13/16 responded with > 5- fold increase in titre, compared to 23/23 responders in normal healthy volunteers. Moreover, a faster decline in antibody level was observed in ESRD patients compared to normal healthy adults receiving the same vaccine six months after vaccination, 39% and 14%, respectively (*Welch* et al., 1996). These data indicated that while the *S. aureus* type 5 CP conjugate vaccine is immu-

Table 3: StaphVAX™ dose evaluation in haemodialysis patients[1]

Dose (μg) CP T5/T8	N	Type 5 IgG (μg/ml)			Type 8 (IgG μg/ml)		
		Day 0	Day 42	%[2]	Day 0	Day 42	%[2]
25/25	15	6	62	80	10	31	47
75/55	16	4	82	75	3	50	75
118/83	17	4	172	88	6	143	88

[1]Results are expressed as µg/ml IgG specific antibodies.
[2]Percent responders (>4fold increase and >25µg/ml IgG).

nogenic and can be used for active immunisation in some populations, other patient populations might require either higher doses of the vaccine or the use of the vaccine with an adjuvant.

The type 5 CP and type 8 CP conjugates were combined into one injection (StaphVAX™) and evaluated for immunogenicity in healthy volunteers and in ESRD patients. Results showed that the combining of the two conjugates did not affect the immunogenicity of each individual CP (Unpublished data). Furthermore, it was observed that CP-specific antibodies appear to peak in concentration within 10-14 days after immunisation confirming that the immune systems of most people are already primed to *S. aureus* CP. These results suggest that patients at short-term risk of *S. aureus* infection (e.g., elective surgery patients) might also benefit from vaccination.

StaphVAX™ was also evaluated in ESRD patients at higher doses than previously used in healthy volunteers. The antibody levels achieved were shown to be dose dependent however antibody levels were generally lower in ESRD patients than in healthy volunteers and they declined more rapidly (Table 3). Moreover, the percent of ESRD patients responding increased to nearly 90% at higher vaccine doses, a significant improvement over that achieved with lower doses in this population.

PHASE III EFFICACY TRIAL

StaphVAX™ was formulated to contain 100 μg each CP conjugated to rEPA for evaluation of its efficacy against *S. aureus* bacteraemia in a Phase III, double blinded, randomised, stratified, and placebo controlled clinical trial. Eighteen hundred ESRD patients on haemodialysis were enrolled to receive either one injection of StaphVAX™ or phosphate buffered saline (PBS). Patients were stratified by their nasopharingeal carriage of *S. aureus* and dialysis access. The primary endpoint of the trial was prospectively defined as significant reduction in *S. aureus* bacteraemia for one year. The safety and the immunogenicity of StaphVAX™ were secondary endpoints in this study. The vaccine was shown to be safe and elicited high levels of antibodies to both type 5 and type 8 CP components with 88% responding to type 5 and 84% responding to type 8. At peak CP-specific geometric mean antibody titres were approximately 230 μg/ml and 206 μg/ml for type 5 and type 8, respectively. At 54

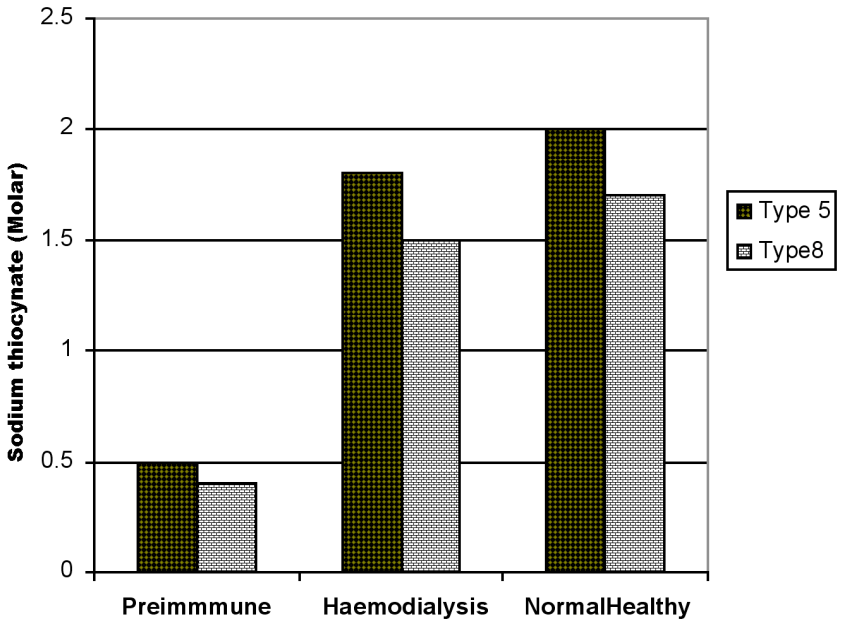

Figure 4: Comparison of the affinity of StaphVAX™ induced antibodies from healthy volunteers and haemodialysis patients.
Human sera were diluted to yield an OD of 2.0 in ELISA plates coated with the appropriate polysaccharide. The amount of thiocyanate added to result in 50% reduction in OD was determined. Results are expressed as geometric mean sodium thiocyanate concentrations.

weeks post vaccination, the antibody levels declined to approximately 74 μg/ml for type 5 and 65.5 μg/ml for type 8. The efficacy of StaphVAX™ at one year, the primary end point for this study, was 26% (reduction in bacteraemia) compared to placebo and was not statistically significant (p=0.228). In a *post-hoc* analysis evaluating the performance of the vaccine through various earlier time points, however, StaphVAX™ was shown to reduce *S. aureus* bacteraemia by 64% through 32 weeks follow-up (p=0.02) and by 57% through 40 weeks (p=0.02). When the antibody levels were matched with the efficacy, it appeared that protection fell off when geometric mean antibody levels in the population fell below approximately 80 μg/ml (*Shinefield* et al., 2002).

Opsono-phagocytosis is the principal mechanism for clearance of infections caused by Gram-positive bacteria including *S. aureus*. Circulating antibodies to CP recognise invading *S. aureus* cells and opsonise them. Complement is deposited on opsonised cells and binds to polymorphonuclear cells (PMNs) through complement receptors that induces the phagocytosis of the opsonised cells by PMNs. Examining the calculated protective antibody levels for S. aureus from our study reveals that they are far higher than those observed with other bacterial infections such as pneumococcal and meningococcal infections. The requirement for high antibody levels to protect against *S. aureus* bacteraemia may be related to health condition of ESRD patients. These patients often suffer from uncontrolled diabetes, hyper-uraemia, impaired complement, and low complement receptor density on their neutrophils, in addition to other defects or impairments in the perform-

ance of their lymphocytes. These conditions may cause an inefficiency and impairment of the opsono-phagocytosis mechanism (*Pirofski* and *Casadevall*, 1998; *Haag-Weber* et al., 1989; *Nolan* et al., 1978). Further, an optimum performance of these immune functions for protection against invading bacteria would require a high quality and functionality of the elicited antibodies. The affinity of antibodies generated by StaphVAX™ in haemodialysis patients was evaluated and compared to that exhibited by antibodies generated in immunocompetent healthy volunteers (Figure 4). The amount of thiocyanate needed to prevent CP-specific antibodies from binding to immobilised antigen is proportional to the affinity of the antibodies. Data presented above show that the affinity of anti-CP antibodies produced by StaphVAX™ in haemodialysis was equivalent to that of antibodies induced in healthy volunteers. Moreover, when tested in an *in vitro* opsono-phagocytosis assays, the antibodies to type 5 and type 8 CP generated in the ESRD patients performed equally well to the antibodies formed in healthy volunteers. (*Fattom* et al., 2004).

EXTENDING THE EFFICACY

Haemodialysis patients are at continuous and long-term risk patients for *S. aureus* infection and could benefit from the presence of protective levels of antibodies at all times. A periodic booster immunisation may be needed to rebuild trough concentrations of antibodies and restore or prolong the efficacy of the vaccine beyond the 10 months of significant protection seen in the phase 3 trial. Previous experiences with conjugate vaccines in adults showed that a booster immunisation at six weeks after the first immunisation did not result in boosting the antibody levels (*Fattom* et al., 1993; *Chu* et al., 1983; *Schneerson* et al., 1986). To see the effects of booster immunisation on specific antibody levels and vaccine safety when the booster is given longer periods of time after the initial vaccination, seventy-nine ESRD patients, previously immunised with StaphVAX™ in the phase 3 trial, were recruited for a booster study. These subjects had received their initial vaccination with StaphVAX™ 2-3 years previous to the booster. Results from the booster study showed that the CP-specific antibodies levels increased to about 60% of the peak levels achieved with the first immunisation resulting in >80% of the participants achieving or exceeding the calculated protective levels i.e. ~80µg/ml. In addition, the decline of specific antibody levels after the booster was slower than that observed after the initial immunisation.

PLANNED CONFIRMATORY EFFICACY STUDY

In a currently planned confirmatory Phase III clinical trial of StaphVAX™ in ESRD patients on haemodialysis, a booster immunisation will be administered at 8 months and its impact on the levels of CP-antibodies and on extension of efficacy will be evaluated.

CONCLUSION

StaphVAX™, an experimental *S. aureus* polysaccharide conjugate vaccine, was shown to be safe, immunogenic, and efficacious, as determined by reduction in *S. aureus* bacteraemia through up to 10 months post-immunisation, in ESRD patients. Preliminary booster studies strongly suggest that ESRD patients can respond to booster immunisations with StaphVAX™ with increased levels of vaccine-specific antibodies. Studies are planned to further evaluate the value of booster doses to prolong efficacy in patients who may be at long-term risk for infection. Since StaphVAX™ induces high levels of CP-specific antibodies within 10-14 days post-immunisation, the vaccine may also have potential in preventing *S. aureus* infections in individuals at short-term risk for infection. For patients such as surgery patients, one immunisation with may be sufficient to achieve protective levels of antibody throughout the risk (e.g., hospitalisation) period. Additional safety and immunogenicity clinical trials of StaphVAX™ in several patient populations at short-term risk of *S. aureus* infections are being planned.

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