

DEBATE

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# Do pneumococcal conjugate vaccines provide any cross-protection against serotype 19A?

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## Abstract

**Background:** Introduction of the 7-valent pneumococcal conjugate vaccine (7vCRM) in several countries has led to a rapid, significant drop in vaccine-type invasive pneumococcal disease (IPD) in immunized children. In the United States and some other countries with high antibiotic use, a subsequent rise in serotype 19A IPD has been taken to indicate that the 19F conjugate in the vaccine provides no cross-protection against the immunologically related 19A.

**Discussion:** We systematically assessed the clinical efficacy and effectiveness of 19F-containing vaccines against 19A disease or nasopharyngeal carriage by searching English-language articles in the electronic databases PubMed, Current contents, Scopus, and Embase from 1985 to 2008. The vaccine efficacy and effectiveness point estimates were consistently positive for modest protection against 19A IPD and acute otitis media (AOM). However, statistical significance was not reached in any individual study. No consistent impact of 7vCRM on 19A nasopharyngeal colonization could be detected. These findings are discussed in context of immunogenicity analyses indicating that 7vCRM induces functionally active anti-19A antibodies after the booster dose, and that other 19F-containing vaccine formulations may elicit higher levels of such antibodies after both primary and booster doses.

**Summary:** Taken together, these results suggest that 19F-conjugates can provide some protection against 19A disease. The magnitude of this protection in a given setting will likely depend on several factors. These include the anti-19A immunogenicity of the specific vaccine formulation, the number of doses of that formulation needed to elicit the response, and the burden of 19A disease that occurs after those doses. It is possible that a modest protective effect may be obscured by the presence of countervailing selection pressures (such as high antibiotic use) that favor an increase in colonization with antibiotic-non-susceptible strains of 19A.

## Background

Since the 7-valent pneumococcal conjugate vaccine (7vCRM; *Prevenar*<sup>™</sup>/*Prevnar*<sup>™</sup>; Wyeth Vaccines) was first introduced in the United States (US) in 2000, invasive pneumococcal disease (IPD) due to *Streptococcus pneumoniae* vaccine-serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) has dramatically decreased among children and adults [1-6].

Serotypes 6A and 19A were not included in 7vCRM and several other pneumococcal conjugate vaccines (PCVs) because it was anticipated that the immunological similarities of vaccine serotypes 6B and 19F, respectively, might elicit sufficient cross-protection [7]. There is now convincing evidence that the 6B conjugate contained in 7vCRM (in which the 6B polysaccharide is

conjugated to a non-toxic variant of diphtheria toxin) provides a high degree of cross-protection against 6A IPD [8,9], acute otitis media (AOM) [10], and even offers a significant level of herd protection [8]. An efficacy trial with the 11Pn-PD vaccine candidate (in which 6B was conjugated to the non-typeable *Haemophilus influenzae* protein D) also suggested cross-protection against 6A AOM [11].

For serotype 19A, some preclinical studies support the possibility of cross-protection. For instance, serum from infants immunized with a 19F tetanus toxoid conjugate provided protection against lung infection caused by both 19F and 19A in a murine model [12]. Nonetheless, clear clinical evidence of cross-protection against 19A disease by 19F-containing PCVs has been lacking. Indeed, the rise in 19A IPD in certain populations well immunized with 7vCRM would seem to argue against it

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[1-6]. In the US, for example, the incidence of 19A IPD rose in children >5 from approximately 2.5 cases/100,000 in 1998-9 (prior to 7vCRM) to 9 cases/100,000 in 2005 [5].

However, analysis of clinical and post-licensure studies with 7vCRM and other pneumococcal conjugate vaccines suggests a more complex situation. This review discusses the literature on cross-protection against 19A disease and colonization provided by 19F-containing vaccines, and relates these results to recently published immunogenicity data.

## Discussion

### Clinical efficacy and effectiveness data

Table 1 presents a review of prospective and retrospective clinical studies and post-licensure surveillance studies with 7vCRM and other 19F-containing vaccines. We wish to highlight two findings. First, in every analysis with 5 or more 19A cases (Figure 1), the anti-19A point estimate is positive, with values ranging from 13% to 67%. This suggests that the true efficacy or effectiveness is probably not null. Secondly, however, none of the anti-19A efficacy or effectiveness point estimates is, by itself, statistically significant.

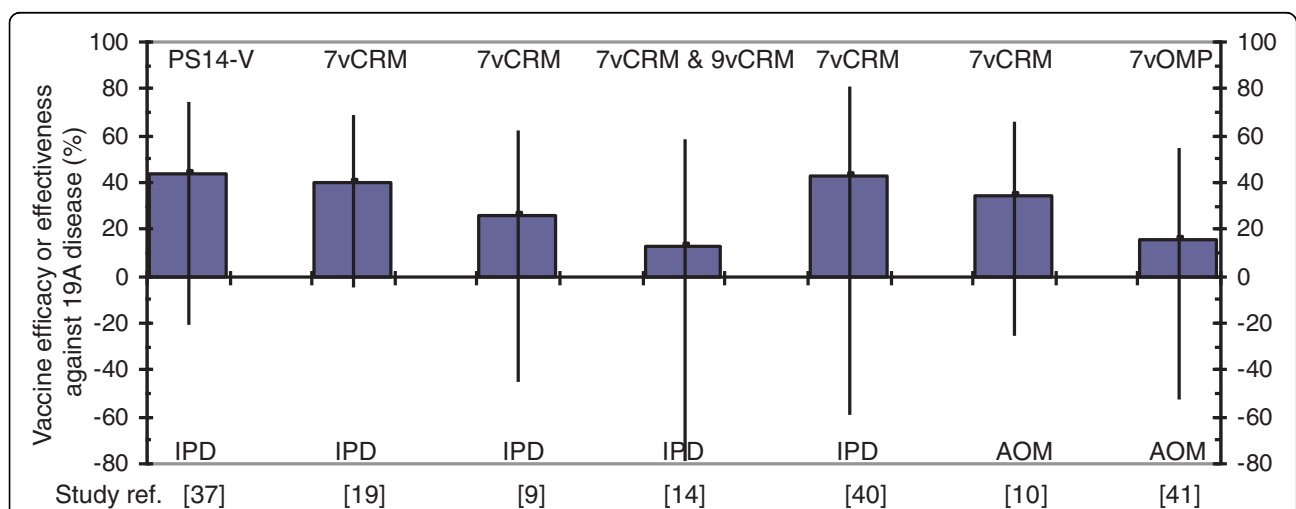
There is considerable variability in the point estimates in Table 1, which could conceivably be related to the different numbers of vaccine doses received by children in each study. There is support for this concept for 6B and 6A. Dagan et al., showed that whereas three primary doses (at 2,4, and 6 months of age) of 7vCRM significantly decreased both 6B and 6A nasopharyngeal colonization as measured in the 2<sup>nd</sup> year of life, two primary

doses alone (4 and 6 months) decreased 6B but not 6A colonization [13].

Two of the studies in Table 1 may provide some insight here. First, the analysis with the lowest point estimate for 19A cross-protection (13% [95% confidence intervals, -79% to 58%]) is a weighted meta-analysis [14] of four randomized, double-blind, placebo-controlled, efficacy studies using 7vCRM [15,16] or the related 9vCRM vaccine [17,18]. Twenty six of the 28 19A cases included in this analysis were contributed by the two 9vCRM studies conducted in Africa in which no booster dose was given.

Also potentially supporting the importance of a booster dose is the heterogeneous post-marketing experience with 19A in the US. The original report on the impact of 7vCRM introduction in the US pointed to a 40% ( $p = 0.09$ ) decrease in the incidence of serotype 19A IPD in children younger than 2 years of age between the pre-7vCRM years 1998-1999 and the first full post-7vCRM year 2001 [19]. This decrease contrasts with the rise in 19A disease detected starting in 2002 in the same active surveillance system [3] and which continued for several years [5]. The onset of the rise coincided with the severe shortage of 7vCRM in the US between 2001 and 2004 that resulted in many children receiving fewer than three primary doses and/or no booster dose [20].

In contrast to the IPD and AOM data summarized in Table 1, there does not appear to be evidence of a consistent 7vCRM effect on 19A colonization itself (Table 2), even among different analyses within the same vaccine study population [21-23]. In fact, in some 7vCRM carriage studies at certain ages or time points, an



**Figure 1 Vaccine efficacy or effectiveness of 19F-containing vaccines against 19A disease.** Depicted are point estimates with 95% confidence intervals from individual studies or metaanalyses with at least five 19A cases. PS14-V, 14 valent polysaccharide vaccine; 7vCRM, 7-valent conjugate vaccine with crm197 carrier; 9vCRM, 9-valent conjugate vaccine candidate with crm197 carrier; 7vOMP, 7-valent conjugate vaccine candidate with outer membrane protein carrier; IPD, invasive pneumococcal disease; AOM, acute otitis media. See Table 1 for more study details.

**Table 1 Studies examining efficacy or effectiveness of 19F-containing vaccines against 19A IPD and AOM**

Study or Analysis	Vaccine	Vaccine regimen	Endpoint	Age group	Total Number of Subjects	Numbers of 19F Cases	% VE against 19F (95% CI)	Numbers of 19A Cases	% VE against 19A (95% CI)
Polysaccharide vaccine			IPD						
US indirect cohort analysis [37]	PS14-V*	1 dose as per US recomm.	IPD	> 5 y	2837 total cases	12 (vacc) 32(unvacc)	<b>11</b> (-86,56)	10 (vacc) 42(unvacc)	<b>44</b> (-21, 74)
Conjugate vaccines			IPD						
N. California Kaiser Permanente efficacy [15,38] <sup>a</sup>	7vCRM	2,4,6,12-15 mo	IPD after ≥ 3 doses	2 mo to ~3.5 y	18927 (vacc) 18941 (ctrl)	2 (vacc) 13 (ctrl)	<b>85</b> (32, 97)	0 (vacc) 1 (ctrl)	<b>67</b> (-719, 99)
Native Americans efficacy [16,38] <sup>a</sup>	7vCRM	2,4,6,12-15 mo	IPD after ≥ 3 doses	2 mo to 2 y	7532 (vacc) 7151 (ctrl)	0 (vacc) 1 (ctrl)	<b>68</b> (-677, 99)	1 (vacc) 0(ctrl)	<b>-185</b> (-900, 88)
South African HIV- efficacy [17,38] <sup>a</sup>	9vCRM	6, 10, 14 wks	IPD after 3 doses	6 wk to 6.2 y	18633 (vacc) 18626 (ctrl)	0 (vacc) 1 (ctrl)	<b>67</b> (-718, 99)	3 (vacc) 1 (ctrl)	<b>-200</b> (-900, 69)
South African HIV + efficacy [17,38] <sup>a</sup>	9vCRM	6, 10, 14 wks	IPD after 3 doses	6 wk to 6.2 y	1289 (vacc) 1288 (ctrl)	5 (vacc) 3 (ctrl)	<b>-67</b> (-595,60)	3 (vacc) 6 (ctrl)	<b>50</b> (-99, 88)
Gambia efficacy [14,39] <sup>a</sup>	9vCRM	6, 10, 14 wks	IPD after 3 doses	6 wk to 2.9 y	8718 (vacc) 8719 (ctrl)	0 (vacc) 2 (ctrl)	<b>80</b> (-317, 99)	6 (vacc) 7 (ctrl)	<b>14</b> (-155, 71)
<i>Meta-analysis of preceding efficacy studies<sup>(c)</sup></i>	<i>7vCRM &amp; 9vCRM</i>	<i>see individual studies</i>			<i>55099 (vacc) 54725 (ctrl)</i>	<i>7 (vacc) 20 (ctrl)</i>	<i><b>61</b> (13, 82)</i>	<i>13 (vacc) 15 (ctrl)</i>	<i><b>13</b> (-79, 58)</i>
US post-marketing surveillance [19]	7vCRM	2,4,6,12-15 mo; catch-up schedule for < 2 y	IPD (2 <sup>nd</sup> yr after launch)	> 2 y (not all vacc)	~433,000	79 (pre) 14 (post)	<b>83</b> (72, 90) (% decrease in estimated rate from pre-7vCRM)	20 (pre) 12 (post)	<b>40</b> (-5, 68) (% decrease in estimated rate from pre-7vCRM)
US CDC case-control [9]	7vCRM	2,4,6,12-15 mo	IPD ≥ 1 dose	3 to 59 mo	n.a.	34 discordant sets	<b>87</b> (65, 95)	46 discordant sets	<b>26</b> (-45, 62)
Canada (Québec) [40]: case-control	7vCRM	2,4,12 mo	IPD ≥ 1 dose	<5 y	n.a.	3 (vacc); 8 (unvacc)	<b>93</b> (61,99)	29 (vacc); 8 (unvacc)	<b>42</b> (-76, 79)
Conjugate Vaccines			AOM						
Finland [10]: efficacy (FinOM)	7vCRM	2,4,6,12 mo	AOM after ≥ 3 doses	6.5 to 24 mo	831 (vacc) 831 (ctrl)	43 (vacc) 58 (ctrl)	<b>25</b> (-14, 51)	17 (vacc) 26 (ctrl)	<b>34</b> (-26, 65)
Finland [41]: efficacy(FinOM)	7vOMP	2,4,6,12 mo	AOM after ≥ 3 doses	6.5 to 24 mo	831 (vacc) 831 (ctrl)	37 (vacc) 58 (ctrl)	<b>37</b> (1, 59)	22 (vacc) 26 (ctrl)	<b>16</b> (-53, 54)
Czech/Slovak [11]: efficacy (POET)	11Pn-PD	3,4,5,12-15 mo	AOM after ≥ 3 doses	5 to 27 mo	2489 (vacc) 2479 (ctrl)	24 (vacc) 43 (ctrl)	<b>44</b> (8, 66)	1 (vacc) 3 (ctrl)	<b>67</b> (-209, 97)

\*PS14-V, 14 valent polysaccharide vaccine, contained 19F but not 19A; it was replaced in the early 1980s by the 23-valent vaccine containing both 19A and 19F serotypes. <sup>a</sup>Each of the 5 analyses (from 4 separate studies) is also included in the metanalysis in italics. Mo, month; n.a., not available; VE, vaccine efficacy/effectiveness; wk, week; y, year; vacc, active vaccine group; unvacc, unvaccinated; ctrl, control; 7vCRM, 7-valent conjugate vaccine with CRM197 carrier; 9vCRM, 9-valent conjugate vaccine candidate with CRM197 carrier; 7vOMP, 7-valent conjugate vaccine candidate with outer membrane protein carrier; IPD, invasive pneumococcal disease; AOM, acute otitis media

**Table 2 Studies examining efficacy or effectiveness of 19F-containing vaccines against 19A carriage**

Study & location	Vaccine	Vaccine regimen	Age group(s) sampled	Number of Subjects	Number of 19F isolates	Efficacy against 19F VE or OR (95% CI or p value)	Number of 19A isolates	Efficacy against 19A VE or OR (95% CI or p value)
South Africa [42]: double blind, randomized, efficacy	9vCRM	6,10,14 wk	9 mo	242 (vacc) 239 (ctrl)	19 (vacc) 32 (ctrl)	VE 42%* (p = 0.05)	7 (vacc) 11 (ctrl)	VE 37%* (NS)
Israel [43]: double blind, randomized efficacy	9vCRM	12-24 mo received 2 doses; ≥ 24 mo 1 dose	15-35 mo 36-≥ 48 mo	816 (vacc) 790 (ctrl) 1071 (vacc) 1073 (ctrl)	41 (vacc) 62 (ctrl) 57 (vacc) 52 (ctrl)	OR 0.58 (p = 0.08) OR 1.11 (p = 0.69)	n.a. = 113 total (all groups combined)	OR 0.60** (p = 0.38) OR 1.25** (p = 0.56)
US Navajo Apache [21]: double blind, randomized efficacy	7vCRM	2,4,6,12-15 mo (87%)	1-7 y (median 3.3y) All >12 mo since last dose	468 (vacc) 281 (ctrl)	24 (vacc) 16 (ctrl)	OR 0.89 (0.47-1.72)	12 (vacc) 10 (ctrl)	OR 0.71 (0.30-1.67)
US Navajo Apache [23]: double blind, randomized efficacy	7vCRM	2,4,6,12-15 mo	7 mo  12 mo 18 mo	227 (vacc) 226 (ctrl)  226 (vacc) 208 (ctrl) 239 (vacc) 219 (ctrl)	2 (vacc) 11 (ctrl)  7 (vacc) 8 (ctrl) 18 (vacc) 8 (ctrl)	OR not calculated because "small sample size resulted in non-convergence of model"	10 (vacc) 4 (ctrl)  3 (vacc) 7 (ctrl) 14 (vacc) 10 (ctrl)	OR 1.75 (0.41-7.58)  OR 0.38 (0.09-1.57) OR 1.68 (0.7-4.05)
US Navajo Apache [22]: double blind, randomized efficacy	7vCRM	Infants: 2,4,6, 12-15 mo; 12-23 mo: 2 doses	Unvaccinated children/adults in study households	2048 (vacc) 1376 (ctrl)	29 (vacc) 37 (ctrl)	OR 0.52 (0.31-0.87)	15 (vacc) 23 (ctrl)	OR 0.34 (0.16-0.75)
France [44]: effectiveness	7vCRM	≥ 1 dose	Children w/ AOM 6-24 mo (mean 14 mo)	575 (vacc) 1331 (ctrl)	59 (vacc) 178 (ctrl)	24%* (p = 0.06)	50 (vacc) 92 (ctrl)	-26%* (p = 0.2)
Greece [45]: effectiveness	7vCRM	12-23 mo: 2 doses (13%); ≥ 24 mo: 1 dose (85%)	13-76 mo (median 47 mo)	285 (vacc) 582 (ctrl)	24 (vacc) 64 (ctrl)	36%*	3 (vacc) 14 (ctrl)	58%*

\*Only case numbers provided in original paper; approximate % VE calculated for this table;

\*\*confidence intervals for odds ratios not provided in original publication.

Mo, month; NS, not significant; OR, odds ratio; VE, vaccine efficacy/effectiveness; wk, week; y, year. 7vCRM, 7-valent conjugate vaccine with CRM197 carrier. 9vCRM; 9-valent conjugate vaccine candidate with CRM197 carrier.

apparent *increase* in 19A carriage is observed (odds ratios greater than 1 or negative point estimates for efficacy) following vaccination, although these changes were generally not statistically significant [22]. This suggests that any effect of 7vCRM on 19A may be limited to prevention of disease once colonized, but not on preventing 19A colonization in the first place.

### Immunogenicity data

The ability of pneumococcal vaccines to induce functional anti-capsular polysaccharide antibodies is considered to be the major mechanism by which these vaccines prevent IPD [24,25]. Vaccine-induced antibody levels measured by ELISA [25] and especially by opsonophagocytic activity assays (OPA) against individual

pneumococcal serotypes have been shown to correlate well with clinical effectiveness [26]. Henckaerts et al. [24] showed that, following three primary doses of 7vCRM, virtually no child (3%) developed anti-19A OPA above the threshold suggested to correlate with clinical effectiveness against IPD (i.e., OPA titer ≥ 8) [25,26]. More recent studies from three different laboratories are consistent with these findings [27-29]. In contrast, a booster dose, of 7vCRM elicited some anti-19A OPA activity, with approximately 25%-30% of children having OPA titers ≥ 8 [29,30].

Other pneumococcal conjugate vaccines with distinct chemistries and carriers may have different immunological properties. For example, it has been observed that the periodate oxidation step used to link the 19F

polysaccharide to the CRM<sub>197</sub> carrier protein in 7vCRM prior to reductive amination alters the antigenicity of the polysaccharide [31]. In three separate studies [29,30,32], 20%-30% of children receiving a 3-dose primary series of PHiD-CV (a recently licensed 10-valent pneumococcal non-typeable *H. influenzae* protein D conjugate vaccine in which 19F is conjugated to diphtheria toxoid; *Synflorix*<sup>™</sup>, GlaxoSmithKline Biologicals) had 19A OPA titers  $\geq 8$ , compared with fewer than 5% of 7vCRM-immunized children in the same studies. Furthermore, a booster dose in the second year of life led to 19A OPA titers above this level in approximately 50% of PHiD-CV-immunized children and 30% of 7vCRM-immunized children [29,30].

Differences in OPA levels may reflect variability not only in the quantity, but also in the quality of the antibodies elicited by different conjugates. Nurkka et al. studied the functionality of cross-reactive antibodies induced by 7vCRM, 7vOMPC (polysaccharides conjugated to outer membrane proteins from *Neisseria meningitidis*, Merck Sharpe & Dohme), and 11Pn-PD, each with 19F conjugated to different carrier proteins [33]. In serum samples selected to have similar antibody concentrations as measured by ELISA, the 19A OPA titers were higher in the 11Pn-PD group than in the two other groups [33].

## Conclusion

The clinical efficacy, effectiveness, and immunogenicity studies summarized here suggest that immunization with 19F-containing pneumococcal conjugate vaccines can provide some direct protection against 19A disease. Nonetheless, the limited anti-19A activity of 7vCRM in particular, which appears insufficient to prevent 19A colonization, was evidently also insufficient to prevent or reverse [5] a net rise in 19A disease in young children in countries where high antimicrobial use has led to greatly increased colonization by antibiotic non-susceptible strains, including certain clones of 19A [5,34-36]. This does not exclude the possibility, however, that the modest effect of 7vCRM on disease may have attenuated or slowed down the rise. In any case, a protective effect of 7vCRM against 19A is likely to be most readily detectable in fully immunized children following a booster dose, and unfortunately, much of the IPD burden occurs prior to that time [19]. On the other hand, certain vaccines with different conjugation methods and carrier proteins have shown immunological cross-reactivity against 19A, even following a primary dose series, and could conceivably show greater protection against disease. Whether they offer any protection against 19A colonization remains to be determined. Accordingly, the potential for clinically significant cross-protection against 19A (and 6A) disease needs to be independently considered for each new vaccine.

## Methods

To systematically assess the clinical efficacy or effectiveness of 19F-containing vaccines against 19A disease or nasopharyngeal carriage, we searched for English-language articles in the electronic databases PubMed, Current contents, Scopus, and Embase from 1985 to 2008, with the latest search conducted 15 May 2009. The keywords used were "*S pneumoniae*" "19A", "19 A", "pneumococcal vaccine [MeSH Terms]", "carriage", "colonization", "invasive pneumococcal disease", and "acute otitis media." In addition, we also consulted recent reviews describing clinical trial results on nasopharyngeal carriage with 7vCRM for further references and, where possible, searched abstracts from major infectious diseases meetings in 2008 and the first half of 2009. For studies on disease, we only included reports in which the authors themselves provided vaccine efficacy or effectiveness calculations for 19A. The results are summarized in tabular format in lieu of a formal meta-analysis, as the latter was considered inappropriate due to the large variability in study design (efficacy or effectiveness), vaccine dosing schedule, vaccines used, and disease endpoints (IPD, AOM). Because there were relatively few reports of vaccine effect on 19A nasopharyngeal carriage that included vaccine efficacy or effectiveness calculations, we also included studies where we could make those calculations based on case numbers.

## • Summary

- Since the introduction of the 7-valent pneumococcal conjugate vaccine (7vCRM), a rise in serotype 19A disease has been observed in the US and some other countries with high antibiotic use, and this has been taken to indicate that the 19F conjugate included in the vaccine does not provide any cross-protection against serotype 19A.
- However, clinical and post-licensure studies with several 19F-containing vaccines, including 7vCRM, consistently report modest clinical cross-protection against 19A disease in fully immunized individuals.
- Consistent with this finding, 7vCRM elicits anti-19A functional antibody responses that are detectable after the booster dose.
- New pneumococcal conjugate vaccines using different conjugation methods or carrier proteins which elicit earlier and/or higher functional anti-19A antibody responses could be more cross-protective against 19A disease than 7vCRM.

## Footnote

Prevenar/Prevnar is a trademark of Wyeth Vaccines.

Synflorix is a trademark of GlaxoSmithKline group of companies.

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#### Authors' contributions

WPH reviewed the literature and, together with BH and LS, analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

#### Competing interests

**Financial support:** GlaxoSmithKline Biologicals paid for all costs associated with the development and the publishing of the present manuscript. The corresponding author had full access to the data and final responsibility for submission of the publication.

**Competing interests:** Drs. Hausdorff, Hoet and Schuerman declare they are employed and own stock in GlaxoSmithKline Biologicals, which has a licensed pneumococcal conjugate vaccine.

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