

The U.K. Pediatric Pneumococcal Vaccine The Next Storm

The measles, mumps and rubella (MMR) vaccine was licensed in the United States in 1971 and used elsewhere in the world for years before the decision was made to introduce it in the United Kingdom, in 1988. The reasons for the seventeen years delay have never been made public and it is likely that they will never be.

At a meeting held on Friday June 4, 2004, the U.K. Joint Committee on Vaccination and Immunisation (JCVI) discussed several vaccines including the pneumococcal conjugate vaccine for children.

The Committee was reminded that *some uncertainty remained* about the long-term community protective effect from such vaccination and about the impact serotype replacement might have on the overall benefits.

In spite of that, “the Committee agreed *that further studies needed to be completed to find the most effective way to implement the vaccine into the UK schedule.*” [<http://www.advisorybodies.doh.gov.uk/jcvi/mins040604.htm>]

In February 8, 2006, just twenty months later, Medical News Today reported that the administration of the pediatric pneumococcal conjugate vaccine would start the United Kingdom by the end of the year and that the schedule would be two doses during the first year and a booster at age 13 months. The announcement mentioned that the vaccine “has been used throughout the USA for over 5 years and no undesirable side-effects have been reported.” [<http://www.medicalnewstoday.com/healthnews.php?newsid=37395>]

A Vaccine Adverse Events Reporting System (VAERS) search conducted on July 27, 2006 revealed that since March 28, 2000, there had been 11,611 reports including 362 deaths and 1,347 hospitalizations filed with VAERS following the administration of Prevnar® alone or with other vaccines. Obviously, a report to VAERS does not always mean that a certain vaccine actually caused a certain reaction.

Prevnar ® in the USA

On February 17, 2000, Prevnar®, a pediatric 7-valent pneumococcal conjugate vaccine was licensed in the United States for administration at 2, 4, 6, and 12-15 months to “prevent invasive pneumococcal disease”

“PREVNAR, *A Critical Review of a New Childhood Vaccine*”, by Michael Horwin, JD, MA published September 19, 2000, is a comprehensive review of that controversial vaccine and the many undeclared conflicts of interest that surrounded its development and trials. ⁽¹⁾

The Horwin report should be of particular interest to parents in the United Kingdom who will be contemplating having their children vaccinated when the program is started in the next few months.

The organism

The pneumococcus (*Streptococcus pneumoniae* or *Diplococcus pneumonia*) was isolated by Louis Pasteur in 1881. The organism is surrounded by a polysaccharide capsule. Differences in the composition of the capsule have helped identify over 90 capsular serological types. Both vaccine-induced and disease-induced immunity are type-specific.

Pneumovax 23 by Merck is an adult pneumococcal vaccine (PPV 23) that was licensed in the U.S. in 1983. It contains polysaccharides from types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F pneumococci (Danish classification). At the time the vaccine was licensed, those 23 bacterial types were responsible for 87% of reported bacteremic pneumococcal disease. The vaccine was not indicated for children under 2 because it failed to result in any measurable immunity. Pnu-Imune® 23 by Wyeth is also licensed in the U.S. but less used. One dose of vaccine is required except in certain conditions in which a second dose within 5 to 10 years is indicated.

After two decades of significant use, PPV 23 vaccination has not resulted in a change in the distribution of vaccine-type and non-vaccine-type organisms. *On the other hand, it has not been followed by clinically significant decreases in carrier rates among vaccine recipients.* ⁽²⁾

Until the late eighties, meningitis due to *Haemophilus influenzae* B (HIB) was the most prevalent bacterial meningitis in children under five. It also caused other very serious invasive diseases. The introduction of the polysaccharide and later the conjugate HIB vaccines was promptly followed by a significant reduction and practical elimination of HIB invasive disease.

With the success of conjugate HIB vaccines, *S. pneumoniae* (the pneumococcus) became the leading cause of bacterial meningitis in the United States. During the nineties, the incidence of pneumococcal meningitis among infants was around 10/100,000 - higher than any other group. ^(3, 4) This, together with the increased antibiotic resistance of the pneumococcus as a result of the inordinate use of antibiotics, prompted the development of Prevnar®.

Available details about Prevnar® from the Centers for Disease Control and Prevention (CDC) and the rationale for the Advisory Committee on Immunization Practices (ACIP) for its recommendation of the vaccine were published in the Morbidity and Mortality Weekly Report (MMWR) of October 6, 2000. ⁽⁴⁾

“The new 7-valent pneumococcal conjugate vaccine (PCV7; ** Prevnar,™ licensed in February 2000 and marketed by Wyeth Lederle Vaccines) should be a key addition to existing pneumococcal disease prevention measures... In 1998, estimated incidence in the United States of invasive pneumococcal infections among children aged <12 months and 12--23 months were 165 and 203 cases/100,000 population, respectively, with peak incidence occurring among children aged 6--11 months (235/100,000). In contrast, incidence among persons of all ages and among persons aged ≥65 years were 24 and 61/100,000, respectively...In the United States, the most common manifestation of invasive pneumococcal disease among young children is bacteremia without a known site of infection, which accounts for approximately 70% of invasive pneumococcal cases among children aged <2 years...With the success of conjugate vaccines in preventing invasive *Haemophilus influenzae* type b (Hib) disease, *S. pneumoniae* has become the leading cause of bacterial meningitis in the United States. Children aged <1 year have the highest incidence of pneumococcal meningitis, which is approximately 10/100,000 population...A substantial reduction in episodes of AOM (acute otitis media) was found. Vaccine impact was greatest for frequent otitis and tympanostomy tube placement...Among a subset of study children with spontaneously ruptured tympanic membranes, *S. pneumoniae* was cultured from the draining ears of 6 children vaccinated with PCV7 and 17 children who received the control vaccine (vaccine efficacy was 65% for AOM caused by vaccine-serotype pneumococci [P = 0.035]).”

Prevnar® includes seven purified capsular polysaccharides of *S. pneumoniae* [4, 6B, 9V, 14, 18C, 19F, 23F] each coupled with a nontoxic variant of diphtheria toxin, CRM197 (CRM, cross-reactive material).

The vaccine contains 0.125 mg of aluminum/0.5-ml dose as an aluminum phosphate adjuvant but no thimerosal. Five of the seven serotypes included in PCV7 (6A, 9A, 9L, 18B, and 18F) accounted for 86% of bacteremia cases, 83% of meningitis cases, and 65% of cases of acute otitis media (AOM) among U.S. children under 6 between during the years 1978 to 1994.

A review by **Lipsitch** in the CDC's Emerging Infectious Diseases *Perspectives* ⁽⁵⁾ detailed pneumococcal serotype replacement in several studies:

“...pneumococcal conjugate vaccine studies show considerable evidence of serotype replacement, as measured by nasopharyngeal carriage of nonvaccine type organisms. Increases in the carriage of nonvaccine serotypes have occurred in three major ongoing clinical trials of pneumococcal conjugate vaccines. In Gambia, carriage of nonvaccine serotypes was 79% in children receiving three doses of a pneumococcal conjugate vaccine (compared with 42.5% in controls). In trials of a 9-valent vaccine in South Africa, carriage of nonvaccine serotypes increased from 21% in controls to 39% in vaccine recipients. Serotype replacement was observed in the second of two large studies in Israel; the reason for the difference in outcome between the two studies remains unclear...”

Lipsitch concluded, “The occurrence of serotype replacement in three trials of pneumococcal conjugate vaccines confirms the validity of concerns expressed in anticipation of these trials...”

In the review, Lipsitch mentioned that “In the first phase-III trial for which data were presented, ⁽⁶⁾ no increase was observed in invasive disease from nonvaccine types (REF). While this result is encouraging, it may not be indicative of what will occur as conjugate vaccines enter widespread use in a variety of communities.”

It should be noted that Lipsitch was not referring to “carriage” but to actual invasive disease during the U.S. phase III trial and that, he cautiously suggested that things may be different after widespread use of the vaccine.

It is not known why the disturbing results of the foreign studies were not seriously considered by the CDC, the ACIP and the Food and Drug Administration (FDA).

Although most U.S. pediatricians were not aware of the problems encountered in the overseas trials, many wondered anyway what would or could happen with the planned wide use of Prevnar®.

- Would it result in an increase in cases of pneumococcal invasive disease due to non-vaccine serotypes?
- Could it lead to an increase in invasive disease caused by other bacteria like the HIB vaccine did?

Pediatricians were also puzzled as to how Prevnar® was going to “prevent” ear infections. It was well known that at least 60 percent of acute otitis media (AOM) were viral and that the pneumococcus was only one of several bacteria responsible. In addition, there were 90 + strains of pneumococcus and only seven in the vaccine.

The question was why was another vaccine for ear infections added to the already substantial U.S. vaccination schedule when according to the American Academy of Pediatrics (AAP) “Approximately 80 percent of children with AOM get better without antibiotics and children whose ear infections are not treated immediately with antibiotics are not likely to develop a serious illness”? ⁽⁷⁾

More importantly, would Prevnar® reduce the incidence of recurrent otitis media with effusion (OME) and the need for insertion of ventilating tubes?

There were many rave reviews about Prevnar after its introduction, several by the same researchers who had done the original investigations. Sales of the vaccine were phenomenal and Wyeth-Ayerst's stockholders celebrated after each quarterly report.

As per its contract expiring on March 31, 2007, the ever generous CDC is still paying top dollar for the 6-year old vaccine: (US) \$57.59 per dose. Doctors and clinics buying direct, pay (US) \$ 69.25/dose. ⁽⁹⁾ According to the CDC's own figures for the last few years, *the four doses of Prevnar® amounted to about 40% of the total cost of recommended pediatric vaccines.*

The "financial performance" of the vaccine has been simply remarkable: "PREVNAR(R), Wyeth's vaccine to prevent invasive pneumococcal disease in both infants and young children, achieved net revenue of \$401 million for the 2005 fourth quarter, an increase of 18% over the 2004 fourth quarter. In 2005, Prevnar celebrated its fifth year on the U.S. market and more than 26 million doses were sold globally. Prevnar achieved worldwide net revenue of \$1.5 billion for the 2005 full year, an increase of 43% over the prior year. During 2005, Prevnar was launched in 13 international markets -- setting the stage for continued growth." ⁽⁸⁾

The "honeymoon" lasted until 2005 when researchers from the CDC disclosed results of one of their studies.

Journal of Infectious Diseases, December 2005

Post vaccine genetic structure of Streptococcus pneumoniae serotype 19A from children in the United States by [Pai R](#), [Moore MR](#), [Pilishvili T](#), [Gertz RE](#), [Whitney CG](#), [Beall B](#); [Active Bacterial Core Surveillance Team](#), CDC

"BACKGROUND: The introduction of the 7-valent conjugate pneumococcal vaccine (PCV7) in children may result in serotype replacement. We estimated the rate of increase of invasive pneumococcal disease (IPD) caused by serotype 19A in children <5 years old and determined the genetic composition of these isolates.

RESULTS: ...The rate of serotype 19A IPD in children <5 years old increased significantly from 2.6 cases/100,000 population in 1999-2000 to 6.5 cases/100,000 population in 2003-2004; this was accompanied by significant increases in penicillin nonsusceptibility (P=.008) and multidrug resistance (P=.002) among serotype 19A isolates. As was observed during the pre-PCV7 era, clonal complex (CC) 199 predominated within serotype 19A, representing approximately 70% of invasive serotype 19A isolates from children <5 years old during 2003-2004. New serotype 19A genotypes were observed during 2003-2004, including 6 CCs that were not found among pneumococcal serotype 19A isolates during surveillance in 1999.

CONCLUSION: Serotype 19A is, at present, the most important cause of IPD by replacement serotypes, and it is increasingly drug resistant. CC199 is the predominant CC among type 19A serotypes in children <5 years old. Our data suggest that some of the increase in rates of infection with serotype 19A may be due to serotype switching within certain vaccine type strains."

In the spring of 2006, there were several studies published that were all critical of Prevnar®.

PEDIATRICS, March 2006

Effect of combined pneumococcal conjugate and polysaccharide vaccination on recurrent otitis media with effusion by [van Heerbeek N](#), [Straetemans M](#), [Wiertsema SP](#), [Ingels KJ](#), [Rijkers GT](#), [Schilder AG](#), [Sanders EA](#), [Zielhuis GA](#)., Radboud University Nijmegen Medical Centre, The Netherlands

“BACKGROUND: Otitis media with effusion (OME) is very common during childhood. Because *Streptococcus pneumoniae* is one of the most common bacterial pathogens involved in OME, pneumococcal vaccines may have a role in the prevention of recurrent OME...

RESULTS: The overall recurrence rate of bilateral OME was 50%. Pneumococcal vaccinations induced significant 4.6- to 24.4-fold increases in the geometric means of all conjugate vaccine serotype antibody titers but did not affect recurrence of OME.

CONCLUSIONS: Combined pneumococcal conjugate and polysaccharide vaccination does not prevent recurrence of OME among children 2 to 8 years of age previously known to have persistent OME. Therefore, pneumococcal vaccines are not indicated for the treatment of children suffering from recurrent OME.”

The findings of this Dutch study paralleled those of a 2004 study from Kentucky looking at changes in the bacteriological isolates in cases of *acute otitis media*.

Pediatric Infectious Disease Journal September 2004

Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. [Block SL](#), [Hedrick J](#), [Harrison CJ](#), [Tyler R](#), [Smith A](#), [Findlay R](#), [Keegan E](#). Kentucky Pediatric Research, Inc., Bardstown, KY

BACKGROUND: Community-wide use of conjugated heptavalent pneumococcal vaccine (PCV7) in children <2 years of age could affect the microbiology of acute otitis media (AOM) in vaccinees, particularly for penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP).

RESULTS: Comparing each cohort (1992-1998 versus 2000-2003), the proportion of *S. pneumoniae* decreased from 48% to 31% ...and nontypable *Haemophilus influenzae* increased from 41% to 56%... The proportions of intermediate PNSP and resistant PNSP, respectively, were 16% and 9% versus 13% and 6% pre- and post-PCV7, respectively...

DISCUSSION: The overall proportion of *S. pneumoniae* isolates and vaccine serotypes in AOM were significantly reduced by community-wide use of PCV7 vaccine in our practice. The proportion of Gram-negative bacteria became 2-fold more frequent than *S. pneumoniae* in AOM in PCV7-vaccinated young children where PCV7 uptake was community-wide and supply was adequate.

There were actually three more disturbing studies published in April 2006.

Clinical Infectious Diseases, April 2006

Emergence of vaccine-related pneumococcal serotypes as a cause of bacteremia. [Steenhoff AP, Shah SS, Ratner AJ, Patil SM, McGowan KL](#). The Children's Hospital of Philadelphia

“BACKGROUND: The heptavalent pneumococcal conjugate vaccine (PCV7) has decreased the incidence of invasive pneumococcal disease among children in the United States. In the post licensure period, the impact of non-PCV7 serotypes against pediatric pneumococcal bacteremia is unknown.

CONCLUSIONS: During the post licensure period, there were significant decreases in the incidence of pneumococcal bacteremia caused by vaccine serotypes; however, rates of penicillin resistance and bacteremia due to vaccine-related serotypes increased.”

Pediatric Infectious Disease Journal, April 2006

Changing epidemiology of outpatient bacteremia in 3- to 36-month-old children after the introduction of the heptavalent-conjugated pneumococcal vaccine by [Herz AM, Greenhow TL, Alcantara J, Hansen J, Baxter RP, Black SB, Shinefield HR](#). Kaiser Permanente, Hayward, CA

“BACKGROUND: The introduction of routine vaccination with heptavalent conjugated pneumococcal vaccine has changed the overall incidence of bacteremia in children 3 months-3 years old.

RESULTS: Implementation of routine vaccination with the conjugated pneumococcal vaccine resulted in an 84% reduction of Streptococcus pneumoniae bacteremia ...By 2003, one-third of all pathogenic organisms isolated from blood cultures were Escherichia coli, one-third were non-vaccine serotype S. pneumoniae, the majority of the remaining one-third were Staphylococcus aureus, Salmonella spp., Neisseria meningitidis and Streptococcus pyogenes...

CONCLUSION: In the United States ...As the incidence of pneumococcal bacteremia has decreased, E. coli, Salmonella spp. and Staphylococcus aureus have increased in relative importance...”

Note: These results represent outcome of a longitudinal follow-up by the same team of the same population in whom the vaccine was originally tested.

New England Journal of Medicine, April 2006

Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. [Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, Thomas AR, Harrison LH, Bennett NM, Farley MM, Facklam RR, Jorgensen JH, Besser J, Zell ER, Schuchat A, Whitney CG](#); Active Bacterial Core Surveillance of the Emerging Infections Program Network., CDC

“BACKGROUND: Five of seven serotypes in the pneumococcal conjugate vaccine, introduced for infants in the United States in 2000, are responsible for most penicillin-resistant infections. We examined the effect of this vaccine on invasive disease caused by resistant strains.

METHODS: We used laboratory-based data from Active Bacterial Core surveillance to measure disease caused by antibiotic-nonsusceptible pneumococci from 1996 through 2004. Cases of invasive disease, defined as disease caused by pneumococci isolated from a normally sterile site, were identified in eight surveillance areas. Isolates underwent serotyping and susceptibility testing.

RESULTS: ... An increase was seen in disease caused by serotype 19A, a serotype not included in the vaccine.”

CONCLUSIONS: The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older persons after the introduction of the conjugate vaccine. There was an increase in infections caused by serotypes not included in the vaccine.”

The study findings were featured in a Reuters Health Report on April 5, 2006: “The Active Bacterial Core Surveillance of the Emerging Infections Program Network, headed in this phase of study by Dr. Cynthia G. Whitney, tracked rates of antibiotic-resistant pneumococcal disease in the United States between 1996 and 2004.

Rates of penicillin-resistant strains peaked in 1999 at 6.3 cases per 100,000 and fell to 2.7 cases per 100,000 cases in 2004, for a decline of 57 percent. Rates of multiple drug-resistant pneumococcal infections peaked at 4.1 cases per 100,000 in 1999 to 1.7 cases per 100,000 in 2004, for a drop of 59 percent.

Between 1999-2004, penicillin-resistant *S. pneumonia* strains fell 81 percent among children less than two years of age, and fell 49 percent among individuals aged 65 and older. Rates of all resistant diseases caused by vaccine serotypes fell 87 percent.

However, there was an increase in resistance to serotype 19A-related disease, from 2.0 to 8.3 cases per 100,000 in children less than two years of age. This strain was not included in the conjugate vaccine.

"Physicians should be seeing fewer treatment failures due to resistant pneumococci in their patients," Whitney told Reuters Health. "However, pneumococci have shown a remarkable ability to adapt and we need to continue to use antibiotics carefully if we want to preserve the benefits that the pneumococcal conjugate vaccine is having on resistance.”⁽⁹⁾

The above under the title “**Pneumonia vax has lowered drug-resistant pneumonia**” is not likely to ring alarm bells. Yet the findings by CDC investigators clearly indicate that:

- While rates of all resistant diseases caused by the vaccine serotypes fell 87 percent, rates of serotype 19A-related disease, a deadly type in the very young, rose by 315 percent between 1999 and 2004
- And while rates of multiple drug-resistant pneumococcal infections peaked at 4.1 cases per 100,000 in 1999, rates of serotype 19A-related disease in children less than two years of age – the most vulnerable age group- peaked at a remarkable 8.3 cases per 100,000 in 2004.

- Lastly, that in addition to serotype 19A, there are some 80 (EIGHTY) serotypes of pneumococcus that were not included in the vaccine, each with its own cadre of troubles.

A study published more recently was even more disturbing.

PEDIATRICS, May 2006

Effect of pneumococcal conjugate vaccine on nasopharyngeal bacterial colonization during acute otitis media. [Revai K](#), [McCormick DP](#), [Patel J](#), [Grady JJ](#), [Saeed K](#), [Chonmaitree T](#). Department of Pediatrics, University of Texas Medical Branch, Galveston, TX 77555-0371, USA.

The heptavalent pneumococcal conjugate vaccine (PCV7) has been shown to reduce the incidence of acute otitis media (AOM) caused by *Streptococcus pneumoniae* by 34% and reduces the overall incidence of AOM by 6% to 8%. More recent studies have shown increases in the proportion of *Haemophilus influenzae* and *Moraxella catarrhalis* in the middle-ear fluid of PCV7-immunized children. There has been no report on the effect of PCV7 on all 3 bacterial pathogens combined, either in the middle-ear fluid or nasopharynx of individual children with AOM. We investigated the impact of PCV7 on nasopharyngeal colonization with bacterial pathogens during AOM in the pre-PCV7 and post-PCV7 vaccination eras. Four hundred seventeen children (6 months to 4 years of age) were enrolled onto AOM studies between September 1995 and December 2004. Of these, 200 were enrolled before the vaccine use (historical controls), and 217 were enrolled after the initiation of PCV7 vaccination (101 were under immunized, and 116 were immunized). Although the nasopharyngeal colonization rate for *S pneumoniae* was not different between the 3 groups, a significantly higher proportion of PCV7-immunized children with AOM were colonized with *M catarrhalis*. Overall, the mean number of pathogenic bacteria types isolated from immunized children (1.7) was significantly higher than in controls (1.4). The increase in bacterial colonization of the nasopharynx during AOM could be associated with an increase in AOM pathogens and theoretically can predispose PCV7-immunized children with AOM to a higher rate of antibiotic treatment failure or recurrent AOM.

The above information reveals that previously, only 34% of cases of acute otitis media due to pneumococcus improved following vaccination with Prevnar. Because the pneumococcus only caused a certain percentage of all cases of otitis media (~25%), in the best case scenario, *only 6-8 % of the total number of cases of AOM, actually improved following the administration of Prevnar.*

This study revealed that vaccinated and unvaccinated children had similar pneumococcal colonization rates and that a “*significantly*” *higher percentage of Prevnar-vaccinated children with AOM were colonized with Moraxella catarrhalis. The authors conclude that because the mean number of pathogenic bacteria types isolated from children who received Prevnar was significantly higher than in children who had not received the vaccine, vaccinated children were less likely to respond to antibiotic treatment and more susceptible to recurrent episodes of ear infections.*

In spite of all of the above and in preparation for the United Kingdom launch of Prevnar®, S.C. Clarke of the University of Southampton Medical School will be publishing “Control of

pneumococcal disease in the United Kingdom - the start of a new era” in the August 2006 issue of the Journal of Medical Microbiology. ⁽¹⁰⁾

The Clarke Medline abstract states:

“In 2000, a multi-valent pneumococcal conjugate vaccine, known as Prevnar, was licensed for use in infants and young children in the USA. The subsequent introduction of the vaccine into the childhood immunization schedule in that country led to a significant decrease in pneumococcal disease. The vaccine is effective against invasive and non-invasive pneumococcal infection, can be used in young children as well as adults and, like all conjugate vaccines, provides long-lasting immunity. Moreover, it reduces the incidence of antibiotic resistance because a number of resistant serotypes are targeted by the vaccine. Prevnar, also known as Prevenar, has since been licensed in numerous countries, including the UK. On 8 February 2006, the Departments of Health in England, Scotland, and Wales announced the inclusion of Prevenar in the childhood immunization schedule. This announcement has important implications for pneumococcal infection, disease surveillance and immunization policy in the UK.”

When Prevnar® was launched in the United States in 2000 pentavalent vaccines had not arrived on the scene yet. Pediarix®, a vaccine containing DTaP, Hepatitis B and Inactivated Polio Virus (IPV) vaccines was licensed on December 13, 2002. Since then, many if not most U.S. infants have received a dose of hepatitis B vaccine in the nursery, then a dose of Pediarix®, HIB and Prevnar® at 2, 4 and 6 months of age.

A recent VAERS search revealed that during a period of 11 months, from January 1, 2005 to November 30 2005 inclusive, VAERS registered 28 death reports following the administration of Prevnar®, Pediarix® and HIB vaccines.

VAERS Report	Received	State	Age Year	Sex	Vaccine Date	Symptoms Date	Days SPT	Death Date	Days Death
231965	1/4/2005	VA	0.2	M	8/26/2004	8/26/2004	0	8/27/2004	1
232015	1/6/2005	CA	0.1	M	12/27/2004	12/27/2004	0	12/27/2004	0
232507	1/19/2005	CA	0.4	M	1/5/2005	1/9/2005	4	1/9/2005	4
233066	1/28/2005	IA	0.4	M	1/10/2005	1/14/2005	4	1/14/2005	4
233419	2/4/2005	IA	0.4	M	1/28/2005	2/1/2005	4	2/2/2005	5
233427	2/7/2005	CA	0.5	M	8/10/2004	8/11/2004	1	8/11/2004	1
235154	3/18/2005	NY	0.2	M	3/14/2005	3/15/2005	1	3/15/2005	1
235456	3/28/2005	SC		F	1/20/2005	1/20/2005	0	1/20/2005	0
235675	4/1/2005	GA	0.3	M	1/26/2005	1/27/2005	1	1/27/2005	1
235687	4/1/2005	CA	0.2	F	3/30/2005	3/31/2005	1	3/31/2005	1
236715	4/28/2005	OH	0.2	F	3/8/2005	3/10/2005	2	3/11/2005	3
239722	6/13/2005	TN	0.4	M	5/12/2005	5/16/2005	4	5/16/2005	4
239724	6/13/2005	KY	0.2	M	12/28/2004	1/3/2005	6	1/3/2005	6
240408	6/24/2005	TN	0.2	M	6/17/2005	6/18/2005	1	6/18/2005	1
240945	7/5/2005	WV	0.2	M	6/21/2005	6/27/2005	6	6/27/2005	6
241542	7/20/2005	NJ	0.3	F	6/13/2005	6/14/2005	1	6/14/2005	1
241557	7/20/2005	MN	0.2	M	7/11/2005			7/13/2005	2
242400	8/8/2005	AR	0.4	F	7/20/2005	7/22/2005	2	7/22/2005	2
243253	8/22/2005	AL	0.2	M	8/18/2005	8/19/2005	1	8/19/2005	1
243594	8/30/2005	MO	0.2	M	8/19/2005	8/21/2005	2	8/21/2005	2
244138	9/14/2005	GA	0.3	F	9/12/2005	9/13/2005	1	9/13/2005	1

244255	9/19/2005	IA	0.4	F	9/6/2005		9/7/2005		
244917	10/5/2005	CA	0.3	M	9/19/2005	9/19/2005	0	9/19/2005	0
244965	10/5/2005	IL	0.2	M	9/29/2005	10/1/2005	2	10/1/2005	2
245770	10/20/2005	MO	0.4	M	10/11/2005	10/17/2005	6	10/17/2005	6
246641	11/2/2005	MO	0.4	M	6/15/2005	6/21/2005	6	6/21/2005	6
247332	11/14/2005	CT	0.3	F	9/22/2005	9/25/2005	3	9/25/2005	3
247838	11/18/2005	MS	0.3	F	10/18/2005	10/19/2005	1	11/19/2005	1

The United Kingdom has its own 5 in 1 vaccine, Pediacel® that contains DTaP, IPV and HIB. Four reports of seizures following Pediacel were already received by JABS (Justice, Awareness, and Basic Support).

In addition, concerns remain about the efficacy of the HIB component of the combination vaccine. A previous DTaPH vaccine released in the UK was not as effective as promised and several children developed HIB disease. To correct the situation, a HIB vaccination catch-up campaign was launched in February 2003. [<http://www.dh.gov.uk/assetRoot/04/01/35/16/04013516.pdf>]

It will be interesting to see what will happen when Prevnar is actually added to the UK pediatric schedule.

* * *

To review

- Increases in the carriage of *non-vaccine serotypes* in major pre-licensure clinical trials of 7 and 9-valent pneumococcal vaccines in Gambia, Israel and South Africa were not publicized before Prevnar a 7-valent vaccine, was licensed in the United States in 2000.
- A highly Prevnar-vaccinated population of children with acute ear infections had a marked increase in Gram-negative bacteria isolates that are almost always more difficult to treat than pneumococcus.
- Although pediatric pneumococcal vaccination produced significant antibody titers, it did not seem to affect the course of pediatric recurrent otitis media with effusion, the second target of the Prevnar® vaccination program.
- New serotype 19A genotypes have appeared in the last three years making serotype 19A, an increasingly drug resistant strain, the leading cause of invasive pneumococcal disease.
- As the incidence of pneumococcal bacteremia decreased with the use of Prevnar, blood stream infections with the more serious E. coli, Salmonella, and Staphylococcus aureus have increased.
- Similarly, significant decreases in the incidence of pneumococcal bacteremia caused by vaccine serotypes were accompanied by increased incidence of bacteremia due to penicillin resistant *vaccine-related* serotypes.
- An increase in infections caused by pneumococcal serotypes not included in the vaccine is now becoming obvious.
- Prevnar® may be less effective (or not effective at all) in preventing acute ear infections as previously claimed. Vaccination may therefore lead to significant colonization by other pathogens that are potentially more resistant to antibiotics and likely to cause prolongation or recurrence of ear infections.
- An inordinate number of reports of adverse events have been filed with VAERS, the Vaccine Adverse Event Reporting System, after Prevnar® vaccination administered alone or with other vaccines. Though such reports do not signify causality, they nevertheless deserve attention.
- Prevnar at least in the United States is unacceptably expensive.

Conclusions

- Prevnar®, a 7-valent conjugate vaccine had shortcomings even before it was licensed in the United States in 2000
- Several serious problems related to the wide use of Prevnar® have recently been reported in the United States and can only be expected to increase with time
- In the United States, an honest re-appraisal of Prevnar® including its unacceptably high cost is long overdue
- The Prevnar® experience in the United Kingdom will be interesting to watch
- Only time will tell whether the benefits of the proposed three doses of Prevnar® will outweigh their risks.

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