children with purified unconjugated PRP, provided an intermediate step on the way. Infants and toddlers <18 months of age do not mount responses to unconjugated PRP, since, like other polysaccharides, it functions as a T-independent antigen. However, preschool children above 24 months of age do manifest responses to unconjugated PRP. In a large-scale controlled field trial (39) in Finland in which infants and children 3 months to 5 years of age were randomly allocated to receive unconjugated PRP or unconjugated meningococcal polysaccharide, the PRP vaccine did not protect infants and toddlers who were less than 18 months of age at the time of vaccination. By contrast, in the Finnish field trial, PRP conferred 90% efficacy in preventing bacteremic Hib disease among children who were 18 to 71 months of age at the time of vaccination. On the basis of the Finnish field trial data and on evidence of safety and immunogenicity in toddlers in the United States, the unconjugated vaccine was licensed by the FDA in 1985 and was recommended for routine immunization of children at 24 months of age. It was also recommended for administration to toddlers at 18 months of age if they were attending day care or were otherwise considered at increased risk of developing invasive Hib disease. However, post-licensure surveillance indicated that the impact of the unconjugated PRP vaccine was generally modest, and five different case control studies showed widely divergent results, with one study showing no efficacy and even suggesting an increased risk post vaccination (38–42).

Conjugate vaccines consisting of PRP covalently linked to a carrier protein fundamentally alter how the immune system interacts with the polysaccharide. When conjugated, PRP functions as a T-dependent antigen capable of eliciting serum anti-PRP antibodies in young infants and conferring immunological memory (that allows boosting) when reinforcing doses are administered (42–44). PRP conjugated to diphtheria toxoid (PRP-D) was the first conjugate vaccine to be licensed in the United States, in 1987 and was recommended for use in toddlers >15 months of age. In large-scale, randomized, controlled field trials, this Hib conjugate was efficacious in a study in Finland (45) but did not protect Inuit native Americans in a trial in Alaska (46). The first conjugates for use in young infants >2 months of age in the United States were licensed in 1988 and 1989, including Hib oligosaccharide conjugated to CRM_{197} (mutant diphtheria toxin) and PRP conjugated to the outer membrane protein of group B meningococcus (PRP-OMP), respectively. The efficacy of these two vaccines in preventing invasive Hib disease in U.S. infants was demonstrated in large-scale controlled field trials (47,48). A third vaccine for use in young infants, PRP conjugated to tetanus toxoid, was licensed in 1993 on the basis of the ability to generate equivalent serum anti-PRP responses in infants, compared with the other two conjugate vaccines licensed for infants (49,50).

In the United States, primary immunization of infants with PRP-T is recommended as a three-dose regimen, with doses given at two, four, and six months of age, while immunization with PRP-OMP is administered as a two-dose regimen at two and four months of age. A booster dose is given to toddlers at 12 to 15 months of age.

IMPACT OF HIB IMMUNIZATION REGIMENS

United States

Following the introduction of routine immunization with the Hib conjugate vaccines in the late 1980s, the incidence of invasive Hib disease plummeted by >90% within just three years (29). By 1999, the reduction was 99%, compared with the 1987 baseline incidence rates (23). Marked reductions in incidence of invasive Hib disease were noted in high-risk native American populations (25–27), as well as in the general population (28–30). However, as vaccination with Hib conjugate became widespread, some subgroups within the general population came to be identified that had low immunization rates (51). Moreover, the achievement and maintenance of control of Hib disease among Alaskan natives proved to be particularly challenging (25,52).

The Hib Experience in England and Wales

The United Kingdom introduced Hib conjugate vaccine into its routine childhood program in October 1992 to be given at two, three, and four months of age (53). A catch-up program was undertaken at the same time for other children under four years of age with Hib vaccine given as a single dose in those over one year. Unlike some other countries where Hib vaccine had been introduced, a booster dose was not recommended after the primary course.

Hib vaccine coverage quickly reached high levels and within a year had reached 92% for the primary schedule (54). Uptake for children aged one to four years was around 75% (55). The number of confirmed cases of invasive Hib disease in children under five years of age in England and Wales fell from 744 in 1991/1992, before Hib vaccine was introduced, to 37 by 1994/1995 (Table 1); a reduction of 95%. Follow-up studies at that time showed that anti-Hib antibodies remained above protective levels in most children for up to 12 months after vaccination (56) but were subsequently shown to fall significantly after this period (57). The high vaccine effectiveness calculated in the latter study was misleading as it was based on measures of both direct and indirect protection.

The catch-up campaign played a significant part in the success of the introduction of Hib vaccine (58). Targeting the one- to four-year age group resulted in high and prolonged

Table 1 Confirmed Cases of Invasive Hib Disease in England and Wales, 1991/1992 to 2007/2008

Age group	1991/1992	1992/1993	1993/1994	1994/1995	1995/1996	1996/1997	1997/1998	1998/1999	1999/2000	2000/2001	2001/2002	2002/2003	2003/2004	2004/2005	2005/2006	2006/2007	2007/2008
<1 yr	311	193	25	15	14	13	9	9	12	15	22	30	22	13	8	13	11
1–4 yr	433	408	33	22	17	19	13	17	34	52	88	131	40	21	30	33	18
5–9 yr	16	11	12	7	3	5	1	0	4	10	10	25	22	8	1	3	2
10–14 yr	15	7	1	1	1		2		2	2	3	4	4	5	5	4	1
15+ yr	66	80	43	30	31	21	18	20	35	34	61	109	108	82	64	54	52
Not known	5	16	4	2		3					2	2	2	2		1	
Total	846	715	118	77	66	61	43	46	87	113	186	301	198	131	108	108	84

Source: Courtesy of Health Protection Agency.