direct protection in this cohort; probably due to the high antibody levels achieved when children aged one year or older are vaccinated, even with a single dose (58). Toddlers have the highest rates of asymptomatic pharyngeal carriage of Hib (59,60), and Hib conjugate vaccine has been shown to dramatically reduce Hib carriage (61–63). Thus, the U.K. program, including the catch-up campaign, also provided high levels of indirect protection (herd immunity) by reducing Hib transmission across all age groups (66).

From 1999, the number of reported invasive Hib disease cases began to rise in children under five years (65). Increases in older age groups became apparent from 2001. A major factor was the greater than expected decline in vaccine effectiveness among children vaccinated in infancy (67) and most cases arose in fully immunized children (65). In children immunized in infancy between 1992 and 2002, vaccine effectiveness was estimated to decline from 61% in the first two years after vaccination to 27% after that ($p = 0.022$) (67). In 2000 and 2001, there were supply problems with diphtheria-tetanus-pertussis-Hib (DTP-Hib) combination vaccines containing whole-cell pertussis (wP). This led to the use of combined vaccines containing acellular pertussis (aP) vaccine (68), of which several have been shown to have reduced Hib immunogenicity (69,70), particularly at an accelerated immunization schedule such as that used in the United Kingdom. The reduced immunogenicity of these vaccines was not considered to be clinically relevant, as immune memory was still generated (71,72). A U.K. case control study, however, showed that children fully vaccinated with DTaP-Hib vaccine had a higher risk of vaccine failure than those fully vaccinated with a DTwP-Hib preparation, with increasing odds of disease for each dose of the DTaP-Hib vaccine (73). This was consistent with the reduced vaccine effectiveness in children immunized when the DTaP-Hib vaccine was in use (67). The decline in vaccine effectiveness after infant vaccination was still apparent, however, in infants who had only received DTwP-Hib vaccine (74).

The number of cases of invasive Hib disease in adults also rose from 20 in 1998/1999 to 109 in 2002/2003 (Table 1), higher than the average of 75 cases per year in the pre-vaccine era. This was attributed to a reduction in opportunities for natural boosting of immunity after routine infant immunization against Hib was introduced in 1992, resulting in a significant decline in serum antibody levels against Hib in adults (66). The resurgence of invasive Hib disease in younger children from 1999 then increased the risk of exposure to the organism and, therefore, the risk of infection among susceptible adults (66).

These observed increases in Hib disease culminated in a decision to conduct a Hib booster campaign from May 2003. All children between six months and four years of age were offered one additional dose of Hib vaccine. National vaccine coverage for the 6- to 12-month age group was 72% and 63% in those aged 13 to 48 months (68). The 2003 booster campaign had a major and rapid impact on disease in the targeted age group. This control was achieved by targeting the age group with the largest increase in cases, many of whom had received the less effective DTaP-Hib vaccine in their primary schedule. It was also suggested that this age group had become recolonized with Hib prior to the booster campaign (64), therefore becoming a source of transmission to others. This was supported by a carriage rate of 2.1% observed in one study of preschool children in 2003 (64), higher than that seen at other points during the post-vaccine era (63).

The decline in Hib cases in vaccinated age groups was soon followed by a reduction in older children and adults, suggesting that the booster campaign had again contributed significantly to indirect protection in the non-vaccinated. In 2003, the implicated DTaP vaccine was withdrawn and the use of DTwP vaccines was resumed. In September 2004, the recommended vaccine for infants was changed to a vaccine containing DTaP, inactivated polio, and Hib. This combination vaccine had a different aP component from the one implicated in the increase and had been shown to have a satisfactory immune response to the Hib component (75). In September 2006, a booster dose of the Hib conjugate vaccine was introduced at 12 months of age into the national schedule. Following the introduction of the routine booster dose, the incidence of invasive Hib disease has fallen again in toddlers and, presumably by reducing asymptomatic carriage, has led to a slow decline in older children and adults (68).

The Hib Situation in Other European Countries

The pre-vaccine incidence of Hib meningitis varied widely in Europe from 8 to 27 cases per 100,000 children under five years of age, with incidence of all invasive Hib diseases varying from 12 to 52 cases per 100,000 children under five years of age. Within the European Union countries, pre-vaccine rates were highest in Scandinavia and Iceland, with low rates in Mediterranean countries and differences within countries were also often observed (76). The first country to introduce national vaccination against Hib was Finland in 1986, followed by Iceland in 1989. Most other western European countries introduced vaccination between 1990 and 1996. The schedule used for Hib often followed the schedule used for DTP vaccination—with most countries having three doses in infancy followed by a booster in the second year of life. Exceptions to this included many Scandinavian countries and Italy, where two doses in infancy are followed with a booster at around 12 months of age, and the United Kingdom and the Republic of Ireland where only three doses in infancy were used initially (77).

Despite the use of different vaccines and the achievement of different levels of coverage, all countries have seen a major reduction in the annual attack rate of Hib within a few years of vaccine introduction (78–88). In most European countries, the incidence of Hib disease has remained stable and low in the post-vaccine era (77).

In addition to the United Kingdom, however, two other countries have experienced sustained increases in Hib incidence after a long period of good control. In Ireland, cases (incidence) of Hib disease fell from approximately 100 per year in the late 1980s (2.84/100,000 total population) to 10 cases or less per year by 2002 (0.26/100,000 total population). From 2003, however, the overall number of Hib cases and those in children under 15 years of age started to increase slightly. Cases in fully vaccinated children increased from a baseline of between 1 and 4 cases annually to 10 cases being reported between January and September 2005 (89). This increase in vaccine failures in Ireland was probably due to similar causes as that in the United Kingdom. Infants in Ireland were routinely immunized at two, four, and six months (with no booster), and DTaP-Hib combinations were introduced in 2001. In response to the increase, a Hib booster campaign commenced in Ireland in November 2005.

The other country that has experienced an increase is the Netherlands. Unlike the United Kingdom and Ireland, the