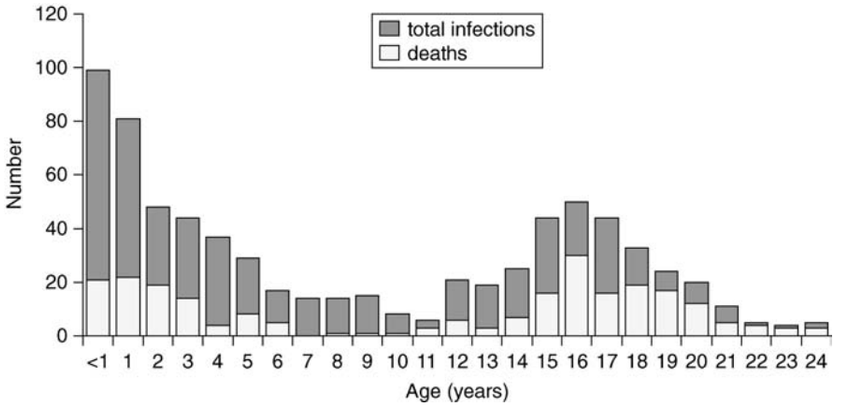

Figure 1 The distribution of meningococcal serogroup C cases and deaths by age, England only, 1998/1999. *Source*: Courtesy of Health Protection Agency.

Hib conjugate vaccine era, including ~12,000 cases of meningitis, and approximately 6% to 10% of cases were fatal. The cumulative risk was such that 1 in 200 U.S. children developed an invasive Hib infection prior to reaching age five years. Incidence rates among children <5 years of age were somewhat lower in some European countries, and in Scandinavia the peak incidence occurred among toddlers rather than infants.

In the pre-Hib conjugate vaccine era, certain subpopulations, such as Navajo and Apache native Americans (16,17) and Alaskan Inuits (18,19) in the United States and aboriginals in Australia (20–23), experienced incidence rates of invasive Hib disease, including meningitis, that were ~3- to 6-fold higher than children in the general population. The peak incidence in these subpopulations tended to occur somewhat earlier than in the general population (24). The introduction of routine Hib immunization in industrialized countries led to a striking decline in the incidence of invasive disease in these high-risk subpopulations (25–27), as well as in the general pediatric population (28–30).

EPIDEMIOLOGY OF DISEASE: SEROGROUP C MENINGOCOCCUS

In contrast to Hib, which causes a relatively stable burden of childhood meningitis in a given country, meningococci not only contribute a continuing burden of endemic disease but also cause epidemics with widely varying rates, occurring at unpredictable intervals. Worldwide, there are around 1.2 million cases of endemic and epidemic meningococcal disease each year, with an estimated 135,000 deaths (31). The disease can occur anywhere, but the largest and most frequent epidemics arise in the African meningitis belt, where epidemic waves of meningococcal disease occur every 5 to 12 years, usually because of serogroup A organisms, with serogroup C and W135 strains playing a smaller role.

Certain factors are thought to increase susceptibility to meningococcal infection including climate, crowded living conditions, upper respiratory tract infection, and waning population immunity. There is clear seasonal variation, with the highest incidence of endemic and outbreak disease in the winter months. Disease onset is often sudden, and even with correct treatment, individuals may be left with severe disabling sequelae, in particular brain damage and loss of limbs. The case fatality rate is high—10% to 20% of all cases of meningococcal disease die—but varies with serogroup, clinical presentation (meningitis, sepsis), and the availability of prompt antibiotic treatment.

In developed countries, serogroups B and C predominated as a cause of invasive disease prior to the availability of a vaccine against meningococcal C infection. From the mid-1980s and early 1990s, a disproportionate increase in cases of meningococcal disease caused by serogroup C was observed in a number of European countries including England and Wales, Greece (32), Spain (33), and the Republic of Ireland (34). In Canada (35) the proportion of serogroup C cases increased significantly from 24% in 1985 to 65% in 1992 against a background of increasing incidence of all meningococcal infection. The United States had a relatively low incidence of meningococcal disease, but outbreaks of serogroup C meningococcal disease also began to be observed more frequently from the early 1990s (36).

In the absence of MCC immunization, the peak incidence of meningococcal C disease throughout the developed world is in children aged under two years of age, with a secondary peak in individuals aged between 15 and 18 years (Fig. 1). The age distribution has changed during some epidemics with an increase in the proportion of cases observed in teenagers and young adults. This is important as, unlike disease due to meningococcal B or Hib infection, the death rates are highest in those aged between 15 and 18 years (Fig. 1). The case fatality rate for serogroup C disease is generally higher than that for serogroup B (37).

HIB VACCINE DEVELOPMENT

Immunology and Development

The key to Hib vaccine development was the recognition that serum IgG antibodies to polyribosylribitol phosphate (PRP), the capsular polysaccharide that covers Hib bacterial cells, is associated with complement-mediated bactericidal activity and with protection against invasive disease. The challenge to be met then was to discover how to actively elicit protective levels of IgG anti-PRP in young infants. An early-generation vaccine strategy, based on immunizing toddlers and preschool