Reduced incidence of septic arthritis in children by *Haemophilus influenzae* type-b vaccination

**IMPLICATIONS FOR TREATMENT**

Heikki Peltola, Markku J. T. Kallio, Leila Unkila-Kallio

*From the University of Helsinki, Finland*

In many countries *Haemophilus influenzae* type b (Hib) is the second most common cause of septic arthritis in children. In Finland large-scale immunisation against Hib using conjugate vaccines began in 1986, four years after a multicentre prospective study of orthopaedic infections in children had started.

Since 1982, including six years before and ten after starting routine Hib vaccination, there has been a major change in the pattern of septic arthritis. From 1982 to 1988, 32 of 61 cases (53%) were caused by staphylococci, 22 (36%) by Hib and 7 (11%) by other bacteria. Since 1988, Hib infection has disappeared, and one-third of cases of childhood septic arthritis has been eliminated. This change has allowed us to reduce initial antimicrobial therapy for such children to cover only Gram-positive cocci. The more limited treatment is safer, reduces cost, and simplifies treatment.

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Septic arthritis of childhood is a serious complication of bacteraemia. Before antimicrobial agents were available the mortality could exceed 50% and severe late physical handicap was common. Deaths are now rare, but still occur, and complications develop in 10% to 50% of cases. *Staphylococcus aureus* is the commonest cause with *Haemophilus influenzae* type b (Hib) the next common after the neonatal period, particularly from three months to three years of age. In Finland, septic arthritis accounted for almost 25% of all Hib disease except meningitis and epiglottitis; in Argentina and Paraguay the proportion was 10% and 5%, respectively.

Before vaccination for Hib was introduced in Finland, the incidence of Hib arthritis from birth to 4 years was 4.9 per 100 000 per year and 7 per 100 000 in non-Aboriginal children in Australia; in Aboriginals it was 33 per 100 000. A worldwide incidence of 6 per 100 000 is probably a conservative estimate, since such infections are more common in developing countries; this implies that there are about 40 000 cases per year in the 631 million children in this age range.

Finland has the longest experience of the use of Hib conjugate vaccines in Europe, since large-scale vaccination started in 1986. It was considered that vaccination would probably change the epidemiology and hence the management of septic arthritis in children.

**Patients and Methods**

In 1982, we began a prospective study on acute joint inflammation in children in eight hospitals in Finland, using a protocol approved by their ethical committees. We included all children between three months and 15 years of age, in whom septic arthritis was suspected because of pain, limitation of joint movement, often visible joint swelling, and fever. We carefully recorded bacteriological documentation of the aetiology: local specimens and blood cultures were mandatory. A positive culture from a joint was taken as diagnostic, but a positive blood culture was accepted only if there were symptoms and signs of septic arthritis.

Routine investigations included measurement of the ESR (8 times) and serum C-reactive protein levels (12 times from finger-tip specimens) and radiography (4 times). Special follow-up forms were completed and all patients were followed up for at least 12 months.

The final analysis included only cases with full bacteriological documentation and was performed at the Helsinki University Central Hospital, Hospital for Children and Adolescents.

**Vaccination.** In Finland the first Hib conjugate, diphtheria toxoid conjugate (PRP-D), became available in 1986 and was tested in the field from 1986 to 1989. During the first two years, 50% of infants were offered PRP-D at the age of 3, 4 and 6 months, with a booster dose at 14 to 18 months. The other 50% received one dose of PRP-D and
the group-A plus C meningococcal polysaccharide vaccine at the age of 24 months.

Since 1988, mutant diphtheria toxoid conjugate \(^1\) (PRP-CRM, HbOC) and tetanus toxoid conjugate \(^2\) (PRP-T) have also been used. First, PRP-D was challenged by PRP-CRM in a randomised efficacy trial in 1988-9, \(^3\) then PRP-T alone was used in 1990-3 and changed back to PRP-CRM in 1994. From 1988, only two primary doses have been administered at the age of four and six months, with a booster dose at 14 to 18 months. These vaccinations are performed routinely by public-health nurses working in 1000 child-health centres under the supervision of local physicians. All vaccinations are free of charge, and voluntary vaccination coverage exceeds 95%. \(^4\)

### Results

Between 1982 and 1988, there were 61 cases of septic arthritis (Fig. 1); 32 (53%) were caused by staphylococci, 22 (36%) by Hib, 3 (5%) by Streptococcus pyogenes, 2 (3%) by pneumococci and 2 (3%) by meningococci.

In 1989 three years after the beginning of vaccination, there was a dramatic change in aetiology: Hib was no longer a causative agent (Fig. 1). There was no other change in incidence or distribution. Between 1989 and 1997, there were 46 cases of septic arthritis: 34 (74%) were caused by Staphylococcus aureus, 7 (15%) by Streptococcus pyogenes and 5 (11%) by pneumococci. Not one case of Hib arthritis has been reported from anywhere in Finland.

This change has allowed us to modify our antimicrobial therapy. Unless there are special reasons to consider another aetiology, suspected septic arthritis is treated with only clindamycin or a first-generation cephalosporin such as intravenous cephalothin, oral cefadroxil or oral cephalaxin. On rare occasions an effective penicillin such as flucloxacillin may be given. These antibiotics effectively cover Staph. aureus and streptococci, which are now virtually the only bacteria causing septic arthritis from birth to four years. This treatment policy has worked well, with no reports of failures of treatment or late sequelae.

### Discussion

The role of Hib in septic arthritis has been recognised only during a few decades, \(^5\) probably because the culture requirements of Hib delayed its recognition until chocolate agar became widely used.

Before Hib vaccination about 36% of cases of septic arthritis in Finland were due to this organism. After Hib vaccination, this cause has disappeared and the incidence of Hib meningitis, \(^6\) epiglottitis, \(^7\) and other Hib diseases has declined. This decrease occurred within three years of the introduction of PRP-D, although it is the conjugate with the least immunogenic potential, \(^8\) and for two years it was offered to only 50% of infants (Fig. 1). \(^9\)

Since 1988, vaccinations used three different conjugates, \(^10\) and have been given to practically all infants. This appears to have eliminated Hib from the aetiology of septic arthritis in this country, in part by reducing nasopharyngeal carriage. \(^11\) This effect of vaccination has not been associated with any increase in the absolute numbers of other types of infection. This is in contrast to the area around Kansas City in the USA, where the overall incidence of joint infection in children, mainly due to staphylococci and streptococci, seems to have increased in the past few years. \(^12\)

The change in the epidemiology has had clear implica-
ations for therapy. In Africa and some other areas *Salmo-
nella* species and other Gram-negative bacteria are common,27 but in Finland Gram-positive cocci are now the only relevant bacteria causing septic arthritis in children. For this reason, clindamycin and first-generation cephalosporins give adequate microbiological cover and also penetrate joints and bones very well. Narrowing of the antibacterial spectrum has simplified treatment, reduced cost, and exposed patients to fewer allergic and other adverse reactions.

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