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Revised recommendations for the prevention of secondary *Haemophilus influenzae* type b (Hib) disease

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This guidance has been endorsed by the Vaccine Preventable Invasive Bacterial Infections (VaPiBi) Forum of Public Health England and replaces the previous guidance published in 2009.[13a]

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1 Summary of changes to the revised recommendations

1.1. Definition of PROBABLE CASES for the purpose of chemoprophylaxis

Based on the most recent data (2010-12), Hib was not a significant pathogen in any age group, although it was responsible for two of the six CSF isolates in infants (<1 year). Only in individuals with clinically diagnosed epiglottitis was Hib responsible for 55% (11/20) of cases where *Hi* was isolated from a sterile site and serotyped. Therefore, our revised definition for 'Probable Hib' now only includes individuals with epiglottitis where *Hi* was isolated from a sterile site. Household contacts of index cases who fulfil the revised 'Probable Hib' definition should be managed in the same way as confirmed Hib cases for the purposes of chemoprophylaxis, which should be offered up to four weeks after onset of illness in the index case, if eligible (see **Figure 1**). All invasive *Hi* isolates should be submitted for serotyping, but infections in the neonatal period are nearly always due to non-typeable *Hi* (ntHi) and do not require public health action unless confirmed as Hib.

1.2. Definition of HOUSEHOLD CONTACT:

In order to maintain consistency of definitions with the UK meningococcal guidelines (www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947389261), we have re-phrased the definition of a household contact as '*any individual who has had prolonged close contact with the index case in a household type setting* ***during the seven days before*** *the onset of illness.'* The previous definition stated '…*within seven days of the index case developing invasive Hib disease.'*

1.3. Timing of CHEMOPROPHYLAXIS:

In the updated guidance, we clarify that chemoprophylaxis should be offered to all eligible contacts up to four weeks after onset of illness in the index case.

2 Introduction

Haemophilus influenzae serotype b (Hib) can cause severe life-threatening disease in healthy individuals and is a major global cause of childhood meningitis, pneumonia, epiglottitis, septicaemia, cellulitis, osteomyelitis and septic arthritis.[1-3] It is estimated that Hib causes three million cases of serious disease and 700,000 deaths annually worldwide, with case fatality rate of around 5% in developed countries and up to 25% in developing countries[3]. The organism can be carried asymptomatically in the naso- and oro-pharynx and acquisition most commonly results from asymptomatic carriers, rather than from cases. Individuals may transfer the organism to close contacts though airborne or droplet spread by coughing and sneezing. In the pre-vaccine era the vast majority (>80%) of cases occurred in children younger than five years of age, with the highest attack rates in those younger than two years. The introduction of Hib conjugate vaccine into routine childhood immunisation programmes has resulted in a greater than 90% reduction in the incidence of invasive Hib disease, through a combination of direct and indirect (herd immunity) protection.[4-11] Guidelines for the prevention of secondary cases of Hib in the United Kingdom were first published in 1991[12] and were updated in 1994 after the introduction of the Hib conjugate vaccine into the national infant immunisation schedule in 1992.[13]

In 2009, we published UK guidance for the prevention of secondary cases in the *Journal of Infection*.[13a] Compared to the general population, close contacts of individuals with invasive Hib disease (particularly in a household or pre-school setting) are at increased risk of developing invasive Hib disease compared with the general population. The greatest risk is the first week after the index case becomes ill, but secondary cases have been reported after this period. At the same time, index cases themselves also have a small but significant risk of a second episode of invasive Hib disease, mainly within six months of the initial episode.

In the 2009 guidance, we recommended that index cases aged <10 years should receive rifampicin chemoprophylaxis and the Hib vaccine after they recover from their infection.[13a] In addition, if there is a vulnerable individual (child younger than ten years or an immunosuppressed or asplenic individual of any age) among the household contacts of the index case, all members of that household, including the index case, should receive chemoprophylaxis as soon as possible.

Currently, most NHS hospital laboratories do not routinely serotype invasive *H. influenzae* (*Hi*) isolates. Instead, the isolates are usually sent to the Public Health of England (PHE) national reference laboratory, resulting in a delay of up to a week before serotyping results become available. In such cases, or if serotyping facilities are not available, we developed a definition for 'Probable Hib' for the purposes of chemoprophylaxis, which was based on the latest Hib epidemiology at the time (1993-2004). Since this guidance was published, however, the epidemiology of Hib disease has changed significantly. The introduction of control measures following the 2000-04 resurgence has led to further reductions in invasive Hib disease across all age groups, which had led to the revision of the 2009 guidance.

3 Epidemiology

3.1 Invasive Hib disease

In the pre-vaccine era, Hib was responsible for almost a thousand cases of invasive infections per year in England and Wales, mostly in children under five years of age.[14] Over half the cases (57%) presented with meningitis, 14% with epiglottitis, 8% with bacteraemia, 7% with cellulitis and 5% each with bone and joint infections or pneumonia.[14] The overall case fatality rate was 4% and was highest in adults over 65 years of age, who often had underlying medical conditions.[14] Clinical trials of Hib conjugate vaccines performed prior to licensure demonstrated excellent short-term protection against invasive Hib disease, with efficacy estimates of 83-100%.[15-17] The UK introduced the Hib conjugate vaccine into the infant immunisation programme at two, three and four months in October 1992, alongside a catch-up campaign providing one dose of vaccine to children under four years of age. This resulted in a dramatic reduction in the incidence of invasive Hib disease in the age group targeted for vaccination, from 21-44/100,000 in 1991 to 0.63/100,000 in 1998. A significant decline in the incidence of Hib was also noted in older children and in adults,[18] most likely due to a reduction in asymptomatic carriage among vaccinated children, which decreased the reservoir for infection, resulting in reduced transmission and herd protection.[19]

The rise in the number of cases between 2000 and 2003, particularly in children aged one to two years, is considered to have occurred because of a wearing-off of the initial catch-up programme, a greater than expected decline in vaccine effectiveness among children vaccinated in infancy and a temporary change in the diphtheria-tetanus-pertussis-Hib combination vaccine type offered to young infants.[4,20-22]

During this period, invasive Hib disease in adults also increased to pre-vaccine rates. This increase was associated with a fall in the concentration of serum antibody to Hib in the adult population, indicating reduced immunity among unimmunised adults, possibly due to a reduction in opportunities for natural boosting of immunity to Hib in the vaccine era.[18] In 2003, a Hib booster campaign targeting all children aged six months to four years was introduced and the use of whole cell pertussis DTP-Hib combination vaccine for primary immunisation was resumed.[23] In September 2006, a routine booster dose of combined Hib-meningitis C vaccine was introduced into the national infant immunisation programme at the age of twelve months. This was accompanied by a catch-up booster campaign at school entry targeting children who would have been too young for the 2003 booster campaign and too old to receive the scheduled 12-month booster dose.[20] The introduction of control measures following the 2000-04 resurgence has led to further reductions in invasive Hib disease across all age groups such that, in 2012, there were only 14 laboratory-confirmed Hib cases (incidence 0.04/100,000 population) and only two were in children aged <5 years (0.06/100,000) **(Table 1).**

3.2 Hib carriage

Most studies on Hib carriage in the general population were performed in the pre-vaccine era, with reported carriage rates of 0-9% (Table 2). Carriage rates were much higher in children compared with adults, although infants were less likely to be carriers than older children.[24-28] Carriage rates increased with the number of children in the family,[29] and with the number of hours spent in day care centres.[28,30-33] Following a case of Hib disease, carriage rates were substantially higher among contacts of the index case. Paediatric day care contacts had carriage rates of 10-23%,[30,34] while household contacts had higher carriage rates of 26-32%,[29,34-37] particularly if the household contacts were children younger than five years (carriage rate, 33-66%).[29,32,34-36,38] Furthermore, family members of children who were colonised with Hib through contact with an index case in a day care centre were also likely to become colonised.[29,35,36]

Hib conjugate vaccination significantly reduced asymptomatic pharyngeal carriage in both vaccinated and unvaccinated populations.[39-43] In a serial survey of children aged one to four years attending playgroups, nurseries and child welfare clinics in England and Wales, prevalence of carriage fell from 4.0% (95% confidence interval (CI), 3.1-5.1%) prior to the introduction of vaccination in 1992 (*n*=1,531) to 0.70% (95% CI, 0.35-1.3%) in 1994 (*n*=1,563), and 0.0% in 1997 (*n*=458) and 2002 (*n*=384).[44] A UK study conducted after the increase in Hib disease reported a Hib carriage rate of 2.1% (95% CI, 0.7-6.0%) among 2-4 year-old children (*n*=176) in London.[45] In 2005, Hib was isolated from 4.2% of 855 children aged 6-16 years recruited from schools in Oxfordshire, while none of 385 healthy adults aged 20-40 years were carriers.[46] The introduction of the 12-month booster dose of the Hib conjugate vaccine is likely to have a further impact on population carriage of Hib.

3.3 Risk of a second episode in the index case

A second episode of invasive Hib disease in the index case is uncommon but recognised,[47-50] and usually occurs occur within six months of the initial episode.[48] It is often difficult to distinguish between re-infection and relapse, which can occur even if the index case receives appropriate prophylaxis to eliminate carriage.[49] Relapses are associated with poor serum antibody response to the primary infection and persistence of the organism in the pharynx despite treatment.[49] Re-infection tends to occur several weeks to months after the primary infection.[49,50] There are limited data on the risk of second episodes in the post-vaccine era. In the UK, only four cases with two distinct episodes of invasive Hib disease have been identified through enhanced national surveillance during 1992-2012. Two cases aged 12 and 77 years were unvaccinated, a six-year-old had received a catch-up dose of Hib vaccine when he developed his second infection and a seven-year-old had received three doses in infancy and a booster dose after his first episode of Hib at five years of age.

3.4 Risk of secondary cases

Almost all studies on secondary attack rates for invasive Hib disease were performed in the United States in the pre-vaccine era.[51-56] Although there were minor differences in the definition of close contact and duration of follow-up, it was possible to statistically combine studies on

secondary attack rates in households where contacts had been prospectively monitored for at least 30 days and had not received any chemoprophylaxis (Table 3). On the other hand, studies involving day care centres were found to be heterogeneous and, therefore, are presented separately for each age group (Table 4). These studies demonstrated that household and day care contacts of index cases were at significantly higher risk of developing invasive Hib disease compared with general population.[37,54] In addition, secondary attack rates generally appear to be lower for day care contacts than household contacts, although statistical analysis was not possible. This observation was most noticeable in two studies where there were no secondary cases among 935 [57] and 1321 [58] day care contacts observed. One retrospective cohort study proposed that the risk of secondary disease is almost negligible if the index case attended the day care facility for <18 hours/week or if the contacts attended <25 hours/week.[59] It should be noted that secondary cases among household and day care contacts can occur up to eleven months after the index case.[53-56] However, when published studies of secondary cases among household contacts were combined, 44% presented within the first four days and 68% within eight days.[52-55,57,58]

For both household and day care contacts, children younger than two years of age (particularly those under one year) were at greatest risk of developing secondary Hib disease, with a very low risk after the age of four years. While this observation may be true for the pre-vaccine era, there are no data on secondary attack rates in the post-vaccine era. Based on observations during the recent increase in Hib in the UK, in the absence of good population control, individuals of any age may be susceptible to Hib. It is likely therefore that, as a result of reduced opportunities for natural boosting following mass national immunisation campaigns for Hib,[18] and waning of protective antibody levels after infant immunisation (even in children receiving a booster dose of vaccine in the second year of life),[60,61] a proportion of older children and adults may not be adequately protected against invasive Hib disease.[5,62]

4 The effectiveness of chemoprophylaxis

4.1 Eradication of carriage

Chemoprophylaxis aims to reduce the risk of secondary disease in the index case and among close contacts by eliminating carriage. In randomised controlled trials, rifampicin at a dose of 20mg/kg/day for four days eradicated pharyngeal carriage of Hib in 92-97% of contacts.[32,35-38,63-66] A lower dose of rifampicin at 10mg/kg/day for four days [37] or a shorter two-day course of 10mg/kg/day either daily[67] or twice daily[29] were less effective, possibly because of a lower peak antibiotic levels.[68] However, one prospective randomised controlled trial comparing a four-day course of rifampicin (20 mg/kg a day up to a maximum of 600 mg) with a two-day course at the same dose reported similar rates of clearance of Hib pharyngeal colonisation (94% vs. 92%) among family contacts, with identical 95% confidence intervals (73-99%), although this study was poorly powered, with only 18 and 24 participants in the two groups, respectively. Other antibiotics including cotrimoxazole, ampicillin, cefaclor and a single dose of ceftriaxone were less effective than rifampicin.[12,69,70] The efficacy of ciprofloxacin in eradication of Hib carriage has not been assessed, but has been shown to reach high concentrations in nasal secretions in healthy adults.[71]

Eradication of carriage was far more successful in families when all members were treated (97% vs. 64%; OR 21.5; 95% CI, 3.0-103).[32] However, the efficacy of eradication was significantly lower in children younger than five years, the age group at highest risk of secondary disease.[29,36] Furthermore, re-colonisation was very common in this age group, with 22-28% of treated carriers re-colonised within one to four weeks of rifampicin prophylaxis.[35,36] Rates of new acquisition of Hib among children with negative initial pharyngeal cultures were low and were significantly reduced among those receiving rifampicin prophylaxis compared with placebo for periods of up to one month after prophylaxis.[36-38]

Eradication of carriage in the index case is also important in order to prevent a second episode of infection and to reduce transmission of the organism to susceptible contacts. Hib carriage can be demonstrated in most index cases before initiating antibiotic therapy.[66] Antibiotics such as ampicillin and chloramphenicol that were previously used to treat Hib were not effective in eradicating pharyngeal carriage.[37,72] One prospective study of 38 children with invasive Hib disease reported that the organism was not recovered from throat cultures of any of the children beyond 14 hours after an intravenous antibiotic effective against the infecting Hib isolate (usually a combination of ampicillin with either chloramphenicol, a third generation cephalosporin or nafcillin) was initiated.[73] More recently, third-generation intravenous cephalosporins (cefotaxime or ceftriaxone) eradicated carriage in all 53 children with invasive Hib disease after three days.[74] However, only nine children were treated with ceftriaxone which is now often the empiric treatment of choice for serious infections in children. In adults, pooled analysis of four randomised clinical trials involving 292 patients with acute exacerbation of chronic bronchitis due to *H. influenzae* reported that treatment with moxifloxacin or macrolides (azithromycin or clarithromycin) reported higher bacterial carriage eradication rates at 7-37 days post-infection for moxifloxacin

compared with azithromycin (96.8% vs. 84.6%, *P*=0.019) and clarithromycin (90.1% vs. 64.2%, *P*=0.001).[75]

4.2 Prevention of second episodes

Eradication of carriage does not always lead to prevention of infection. No prospective trials on the use of rifampicin to prevent second episodes were identified. Cates and colleagues reported that seven of nine recurrent cases had received a full course of rifampicin prophylaxis.[49] The interval between first and second episodes varied from nine to 138 days, and the sites of infection were different in the first and second episodes. Six of the eight recurrent cases that were typed were caused by indistinguishable strains, although it is not possible to determine whether these were relapses or re-infections. All except one case were under twelve months of age.

4.3 Prevention of secondary cases

All clinical trials on the use of chemoprophylaxis to prevent secondary cases were performed in the pre-vaccine era.[12] Several prospective and retrospective observational studies performed between 1960 and 1986 compared the risk of secondary disease among those who received or did not receive rifampicin.[52,55-57,59,76] Because these studies reported only a small numbers of secondary cases, results were combined to give overall secondary attack rates in household (Table 5) and day care (Table 6) contacts. Table 6 shows that rifampicin reduces the risk of secondary disease by 94% among day care contacts in the 30-60 days following hospitalisation of the index case. Only one trial and none of the observational studies reported attack rates for household contacts (Table 5) and, although only a few children developed secondary Hib disease, none of the twenty secondary cases among household contacts [37,52,55,56] and only one of nineteen secondary cases among day care contacts had received rifampicin therapy.[37,57,59,76] There have been anecdotal reports of failures of rifampicin prophylaxis among household and day care contacts, usually due to a combination of failure by healthcare professionals to implement rifampicin prophylaxis and poor uptake and compliance by contacts.[77-79] [35-37,63,80] Rarely, resistance to rifampicin has been reported.[81] Re-colonisation after initial eradication can occur, and it has been suggested that rifampicin prophylaxis merely delays the onset of secondary disease.[59]

4.4 Control of outbreaks

In a recent UK day care centre outbreak, rifampicin chemoprophylaxis administered to all child (irrespective of vaccination status) and staff contacts of two index cases resulted in complete eradication of Hib pharyngeal carriage among contacts when re-tested a month later and no further cases of Hib disease.[82] In addition to household and day care settings, outbreaks of Hib disease have been reported in close communities [83] as well as paediatric [12] and geriatric [84] hospital settings. Rifampicin chemoprophylaxis has been used with the aim of interrupting transmission in these circumstances. However, the numbers involved in these outbreaks have been small and, in most instances, chemoprophylaxis constituted only one of a number of control measures undertaken.

4.5 Use of vaccination following a case of Hib

For index cases, current UK guidelines recommend that unimmunised children younger than ten years should be fully immunised after recovering from infection, while vaccinated children should have convalescent antibody levels measured and a booster dose of vaccine given if levels are below recommended protective levels.[1] In circumstances where antibody levels cannot be tested, the child should receive an additional Hib-containing vaccine.[1] The role of vaccinating household contacts to prevent secondary cases or control outbreaks is not known. Vaccination alone is probably ineffective in preventing outbreaks of Hib; the delay in antibody response to vaccination would not offer protection against most secondary cases, which occur within the first week after the index case. However, vaccination must be considered a valuable adjunct to chemoprophylaxis because it will boost immunity of previously vaccinated children with waning immunity and reduce Hib carriage, thereby preventing further transmission of the organism.[39]

5 Guidelines

The following guidelines on prevention of secondary disease have been developed following a review of the epidemiology of invasive Hib disease, the impact of immunisation and the impact of various interventions. The guidelines have been consulted on with paediatric infectious diseases specialists, microbiologists and public health consultants, and approved by the Health Protection Agency *Pneumococcus* and Hib Forum and the Health Protection Agency Vaccination Programme Board. The flowchart summarises the management of contacts following a case of invasive Hib disease in the index case (Figure). The Centers for Disease Control and Prevention (CDC) grading system [85,86] was used for all recommendations as follows:

- **Strongly recommended** on the basis of >2 consistent, well-conceived, well-executed studies with control groups or longitudinal measurements.
- **Recommended** on the basis of >1 well-conceived, well-executed, controlled, or time-series study; or >3 studies with more limited execution.
- **Indicated** on the basis of previous scientific observation and theoretic rationale, but case-controlled or prospective studies do not exist.
- **Not recommended** on the basis of published literature recommending against a practice.

5.1 Confirmed case of Hib

A confirmed case of Hib is defined as any individual who presents with clinical diagnosis of infection and Hib is isolated from a normally sterile site (RECOMMENDED). Unlike meningococcal disease, conjunctivitis is not considered to be an invasive disease for Hib.[87]

5.2 Probable case of Hib

Following the dramatic fall in invasive Hib disease after the introduction of the Hib vaccine, most hospitals do not routinely perform *H. influenzae* serotyping. Instead, the isolates are usually sent to reference laboratories, resulting in a delay of up to a week before serotyping results become available. Using data from the three most recent calendar years (2010-12), there were 1691 invasive *Hi* cases, including 270 in children aged <5 years **(Table 1**). Of these, 1243(73.5%) were serotyped and only 58 (4.7%) of those were Hib, whereas other encapsulated serotypes (a, c, d, e, f) and non-encapsulated *Hi* (ncHi) accounted for 181(14.6%) and 1004(80.8%) of the cases respectively. Hib was responsible for only 4.7% (54/1150) and 12.9% (4/31) blood and cerebrospinal fluid (CSF) culture isolates. Overall, Hib was not a significant pathogen in any age group, although it was responsible for two of the six CSF isolates in infants (<1 year) over the three-year period. The only group where Hib was responsible for more than 50% of cases was in individuals clinically diagnosed with epiglottitis and *Hi* was isolated from a sterile site (11/20, 55%). Based on these data, we have revised the definition for 'Probable Hib' to only include individuals with epiglottitis where *Hi* was isolated from a sterile site. Household contacts of index cases that fulfil the revised 'Probable Hib' definition should, therefore, be managed in the same

way as confirmed Hib cases for the purposes of chemoprophylaxis (**Figure**). All invasive *Hi* isolates should be submitted for serotyping, but infections in the neonatal period are nearly always due to non-typeable *Hi* (ntHi) and do not require public health action unless confirmed as Hib.

5.3 Vulnerable individual

A vulnerable individual is defined as (i) an immunosuppressed or asplenic person of any age (RECOMMENDED), or (ii) any child younger than ten years of age (RECOMMENDED).

5.4 Household contact

In the 2009 guidance, we defined the household contact as any individual who has had prolonged close contact with the index case in a household type setting within seven days of the index case developing invasive Hib disease.[13a] In order to maintain consistency of definitions with the UK meningococcal guidelines (www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947389261), we have re-phrased the definition of a household contact as '*any individual who has had prolonged close contact with the index case in a household type setting* ***during the seven days befor*** *the onset of illness'* (INDICATED). Examples of a household contact include living or sleeping in the same house, boyfriends/girlfriends, and sharing a dormitory, flat or hospital ward with the index case. Other types of contact (e.g. at work or school) would not be considered close contact, but each situation should be considered on its own merit, particularly if a vulnerable contact is involved and a close contact group can be clearly defined (INDICATED).

5.5 Pre-school or primary school contact

The term 'pre-school' is used synonymously with playgroup, nursery, day care or crèche. Pre-school and primary school contacts of an index case with invasive Hib disease should be defined separately for each case with the aim of identifying groups at higher risk of developing secondary Hib disease and, therefore, might benefit from prophylaxis (INDICATED). Examples of pre-school or primary school contacts, therefore, may include staff and children in the same playgroup/class/school/social activity group as the index case.

5.6 Pre-school or primary school outbreak

A pre-school or primary school outbreak is considered to have occurred if two or more cases of invasive Hib disease have occurred among pre-school contacts (staff and children) within 120 days of each other (INDICATED).

6 Chemoprophylaxis and vaccination

6.1 Timing of chemoprophylaxis

In order to maintain consistency of definitions with the UK meningococcal guidelines, we recommend that chemoprophylaxis should be offered to all eligible contacts *up to four weeks* after onset of illness in the index case (INDICATED).

6.2 Choice of antibiotic for chemoprophylaxis

Rifampicin at a dose of 20 mg/kg (maximum 600 mg) once a day for four days for adults and children older than three months is the prophylaxis of choice for eliminating carriage in the index case and among household contacts (STRONGLY RECOMMENDED) because it is highly effective (eradication rate of 92-97%) and Hib resistance to rifampicin is extremely rare (<0.1%) in the UK.[88] Infants younger than three months should receive 10 mg/kg once a day for four days (STRONGLY RECOMMENDED). It should be noted that the dose and duration for rifampicin prophylaxis against Hib are different from those recommended for prevention of meningococcal disease.[87] Pregnant and breastfeeding women should also receive rifampicin prophylaxis if there is a vulnerable individual among the household contacts (INDICATED) because the benefits of providing chemoprophylaxis to all household contacts, including pregnant and breastfeeding women, outweigh any potential risks. Patients should be made aware of interactions with other medications such as anticoagulants, anticonvulsants and particularly oral contraceptives, and possible staining of secretions, including urine. There is some evidence that third-generation intravenous cephalosporins may eliminate carriage in most cases, but published studies have been retrospective and uncontrolled, and involved a small number of cases only. Once daily intravenous or intramuscular ceftriaxone (50 mg/kg in children younger than twelve years, one gram for older children and adults) once a day for two days is, therefore, recommended as an alternative agent in an individual who is unable to tolerate or develops an adverse reaction to rifampicin (RECOMMENDED). Side-effects are uncommon but include diarrhoea, hepatic dysfunction and blood disorders. Treatment courses of oral ciprofloxacin (500 mg in adults and children older than 12 years, 250 mg for children aged 5-12 years, 125mg for children 2-4yrs) twice a day for five days or azithromycin (10 mg/kg, maximum dose 500 mg) once a day for three days may be used as alternatives, but their effectiveness in eradicating Hib colonisation among healthy individuals has not been determined (INDICATED). The use of ciprofloxacin in paediatrics has been limited because of concerns regarding irreversible quinolone-induced arthropathy documented in juvenile animal models, although such effects have not been observed in children despite extensive use.[89-91] Ciprofloxacin suspension is licensed for other indications in children over two years of age [92] and has been recommended for prophylaxis against meningococcal disease in adults and children.[87]

6.3 Hib vaccination

The current UK infant immunisation programme recommends a dose of Hib-containing vaccine at two, three and four months of age, followed by a booster dose at twelve months (STRONGLY RECOMMENDED). The choice of Hib-containing vaccine to be used at different ages will depend on what other immunisations the child has already received and on the availability of suitable preparations. Two Hib-containing vaccines are currently available in the UK: Pediacel® (diphtheria, tetanus, acellular pertussis, inactivated polio and Hib combination vaccine) which is recommended for infant immunisation), and Mentorix® (Hib and meningococcal C combination vaccine) which is recommended for booster doses at twelve months. Children younger than ten years who have never been immunised against Hib should receive the following course (RECOMMENDED):

- **0-2 months:** Await routine infant immunisation at two, three and four months, followed by the scheduled booster dose at twelve months.
- **3-9 months:** three doses of a Hib-containing vaccine at monthly intervals, followed by the scheduled booster dose at twelve months, which should be given at least a month after the last dose.
- **10 months:** two doses of a Hib-containing vaccine at monthly intervals, followed by the scheduled booster dose at twelve months, which should be given at least a month after the last dose.
- **11 months:** one dose of a Hib-containing vaccine followed by the scheduled booster dose at twelve months, which should be given at least a month after the last dose.
- **12 months and older:** one dose of a Hib-containing vaccine, which may be the scheduled booster dose at twelve months.

7 Recommendations

Action is only required if an individual fulfils the criteria for a *confirmed* or *probable* case **and** either (i) the index case is younger than ten years old, or (ii) there is a vulnerable individual in the household.

7.1 Index case

Young children who develop invasive Hib disease (i.e. index case) have a low but significant risk of a second episode of serious Hib infection (especially if younger than one year of age) and are also more likely to become asymptomatic carriers and transmit the organism to others. Thus, all index cases younger than ten years with *confirmed* or *probable* invasive Hib disease should receive rifampicin chemoprophylaxis prior to discharge from hospital (INDICATED) – chemoprophylaxis may be administered to the index case at any time during their inpatient stay. In addition, index cases of all ages with *confirmed* or *probable* invasive Hib disease should receive rifampicin chemoprophylaxis prior to hospital discharge if there is a vulnerable individual in the household (INDICATED).

Unimmunised and partially immunised index cases younger than ten years should complete their primary course of immunisation (see **Hib immunisation** above) (STRONGLY RECOMMENDED). Where possible, fully vaccinated index cases younger than ten years should have anti-Hib antibodies measured around four weeks after infection and an additional dose of a Hib-containing vaccine given if antibody levels are below the recommended 1 mg/ml (RECOMMENDED). If it is not possible to measure anti-Hib antibody levels or if there are concerns that the child might be lost to follow-up, then index cases older than twelve months and younger than ten years (irrespective of their Hib vaccination status) should receive an extra dose of a Hib-containing vaccine prior to hospital discharge in order to ensure high levels of anti-Hib antibodies and long-term protection against Hib.[5,93] Infants aged 5-10 months who have been appropriately vaccinated at two, three and four months, should also receive one dose of a Hib- containing vaccine prior to discharge from hospital to provide adequate protection until they receive their routine 12-month booster dose (RECOMMENDED). Index cases of any age with asplenia or splenic dysfunction who are previously unimmunised or partially immunised should complete immunisation according to national recommendations, while those who have previously completed vaccination against Hib with the final dose more than one year previously should receive an extra dose of the vaccine after recovering from their infection (INDICATED).[1]

Finally, children who develop invasive Hib disease after being fully vaccinated (particularly those who have received four doses of a Hib-containing vaccine) should have their anti-Hib antibody levels measured before and after re-vaccination with a Hib-containing vaccine once they have recovered from their infection. These children should also have total immunoglobulin levels and subclasses measured, and carefully assessed for evidence of an immune deficiency (RECOMMENDED).

7.2 Household contacts

Household contacts of index cases, especially young children and those with underlying medical problems such as immunosuppression and asplenia, are at significantly higher risk of developing invasive Hib disease than the general population. Therefore, all household contacts of the index case with *confirmed* or *probable* invasive Hib disease should receive chemoprophylaxis if there is a vulnerable individual in the household (RECOMMENDED). In such situations, the index case should also receive chemoprophylaxis irrespective of age. Chemoprophylaxis should be given as soon as the diagnosis of Hib is confirmed in the index case (RECOMMENDED). If there is likely to be a >48 hour delay in obtaining *H. influenzae* serotype results, then antibiotic prophylaxis should be given immediately to household contacts if the index case is considered to be a *probable* case of Hib (INDICATED). If there is a delay in obtaining *H. influenzae* serotype results and the index case is not considered to be a *probable* case of Hib, but a subsequent serotype result within four weeks of illness confirms Hib infection in the index case, then antibiotic prophylaxis should be given immediately to household contacts if there is a vulnerable individual in the household (INDICATED).

In addition, unimmunised and partially immunised children younger than ten years should complete their primary immunisation (see **Hib immunisation** above) (STRONGLY RECOMMENDED), while those who only received three doses of Hib vaccine in infancy should receive an extra dose of the vaccine as soon as possible (RECOMMENDED). If this extra dose is delivered under twelve months of age, then the routine booster dose of Hib-containing vaccine should be given at twelve months of age, with an interval of at least one month between the two doses (INDICATED). Individuals of any age with asplenia or splenic dysfunction who are previously unimmunised or partially immunised should complete immunisation according to national recommendations.[1] Individuals in this group who have previously completed vaccination against Hib with the final dose more than one year previously, should receive an extra dose of the vaccine as soon as possible (INDICATED). The opportunity should also be taken to ensure that all household contacts younger than ten years are uptodate with their other routine immunisations (STRONGLY RECOMMENDED).

7.3 Contacts in the pre-school or primary school setting

For all index cases younger than ten years of age, the families of children attending the same pre-school group or primary school as the index case should be informed that they should seek medical advice if their child develops a fever and/or becomes unwell (INDICATED). For settings where a group of children who have levels of contact approaching those in the household can be defined – for example, a small number of children attending the same child-minder for several hours each day – offering prophylaxis to the close contact group should be considered. Families should also be encouraged to ensure that their children are up-to-date with all their immunisations (STRONGLY RECOMMENDED). In case of an outbreak (two or more cases of Hib disease within 120 days), as well as the above, chemoprophylaxis should be offered to all room contacts, including staff (RECOMMENDED). In addition, unimmunised and partially immunised children younger than ten years should complete their primary immunisation (see **Hib immunisation**

above) (RECOMMENDED) and those who received only the accelerated Hib immunisation schedule at two, three and four months should receive an extra dose of the vaccine as soon as possible (RECOMMENDED).

8 Conclusions

The introduction of the Hib conjugate vaccine into national infant immunisation programmes has dramatically reduced the incidence of invasive Hib disease across all age groups. However, breakthrough cases do occur and can potentially transmit the organism to susceptible individuals. A short course of rifampicin remains highly effective in eliminating asymptomatic carriage, thereby reducing the risk of invasive Hib disease. The new prevention guidelines take into account the changes in the epidemiology of Hib disease following the introduction of the Hib conjugate vaccine, the shifts in the age-specific susceptibility of Hib disease, antibiotic susceptibility of the organism and current empiric antibiotic treatment of serious bacterial infections in adults and children.

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10 Tables and figures

Table 1. Laboratory reports of invasive *Haemophilus influenzae* disease by age-group and serotype in England and Wales during 2010-2012.

Table 2. Hib carriage among unvaccinated children before the introduction of routine Hib vaccination.

Table 3. Secondary attack rate among US household contacts within 30 days of hospitalisation of the index case. It was possible to combine studies on secondary attack rates in households because the chi-squared test for heterogeneity showed that the attack rates were not significantly different (p=0.4 for any Hib disease, p=1.0 for both the <2 year-old and <4/<5 year-old age groups; for Hib meningitis, p=0.6 for < 2 year-old, p=0.9 for the <4/<5 year-old and p=0.10 for the >4 year-old age group).

Table 4. Secondary attack rate among US day care contacts within 60 days of hospitalisation of the index case of any invasive Hib disease. Studies on secondary attack rates in day care centres were found to be heterogeneous for each age group (p=0.011 for the <2 year-old age group and p=0.003 for the <4/<5 year-old age group) and, therefore, are presented separately.

Table 5. The effectiveness of rifampicin in preventing secondary Hib disease in household contacts 30 days after hospitalisation of the index case.[38] . The protective efficacy of rifampicin was calculated using the formula: 1- (risk with rifampicin / risk with no rifampicin).

Table 6. The effectiveness of rifampicin in preventing secondary Hib disease in day care contacts 30-60 days after hospitalisation of the index case. The protective efficacy of rifampicin was calculated using the formula: 1- (risk with rifampicin / risk with no rifampicin).

Figure 1. Guidelines for the management of close contacts of Hib – updated June 2013

Table 1. Laboratory reports of invasive *Haemophilus influenzae* disease by age-group and serotype in England and Wales during 2010-2012.

	<1m	1-11m	1-4y	5-14y	15-24y	25-44y	45-64y	65-84y	85+	unknown	Total
Total *H. influenzae*	**76**	**80**	**77**	**37**	**67**	**187**	**338**	**571**	**247**	**11**	**1691**
not serotyped (% total)	14 (18.4)	16 (20.0)	18 (23.4)	6 (16.2)	19 (28.4)	57 (30.5)	100 (29.6)	145 (25.4)	62 (25.1)	11 (100.0)	**448 (26.5)**
All serotyped (% total)	62 (81.6)	64 (80.0)	59 (76.6)	31 (83.8)	48 (71.6)	130 (69.5)	238 (70.4)	426 (74.6)	185 (74.9)	0 (0.0)	**1243 (73.5)**
Hib (% known serotype)	0 (0.0)	8 (12.5)	2 (3.4)	2 (6.5)	4 (8.3)	6 (4.6)	18 (7.6)	14 (3.3)	4 (2.2)	0 (0.0)	**58 (4.7)**
H. influenzae a,c,d,e,f (% known)	1 (1.6)	11 (17.2)	10 (16.9)	5 (16.1)	2 (4.2)	18 (13.8)	43 (18.1)	73 (17.1)	18 (9.7)	0 (0.0)	**181 (14.6)**
ncHi (% known)	61 (98.4)	45 (70.3)	47 (79.7)	24 (77.4)	42 (87.5)	106 (81.5)	177 (74.4)	339 (79.6)	163 (88.1)	0 (0.0)	**1004 (80.8)**
***H. influenzae* from blood**	**72**	**55**	**56**	**31**	**51**	**144**	**266**	**501**	**240**	**11**	**1427**
not serotyped (% total)	12 (16.7)	5 (9.1)	8 (14.3)	4 (12.9)	10 (19.6)	26 (18.1)	49 (18.4)	94 (18.8)	58 (24.2)	11 (100.0)	**277 (19.4)**
All serotyped (% total)	60 (83.3)	50 (90.9)	48 (85.7)	27 (87.1)	41 (80.4)	118 (81.9)	217 (81.6)	407 (81.2)	182 (75.8)	0 (0.0)	**1150 (80.6)**
Hib (% known serotype)	0 (0.0)	6 (12.0)	2 (4.2)	2 (7.4)	3 (7.3)	5 (4.2)	18 (8.3)	14 (3.4)	4 (2.2)	-	**54 (4.7)**
H. influenzae a,c,d,e,f (% known)	1 (1.7)	7 (14.0)	9 (18.8)	5 (18.5)	2 (4.9)	16 (13.6)	42 (19.4)	72 (17.7)	18 (9.9)	-	**172 (15.0)**
ncHi (% known)	59 (98.3)	37 (74.0)	37 (77.1)	20 (74.1)	36 (87.8)	97 (82.2)	157 (72.4)	321 (78.9)	160 (87.9)	-	**924 (80.3)**
***H. influenzae* from CSF**	**0**	**6**	**4**	**0**	**3**	**4**	**10**	**6**	**0**	**0**	**33**
not serotyped (% total)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (25.0)	1 (10.0)	0 (0.0)	-	-	**2 (6.1)**
All serotyped (% total)	-	6 (100.0)	4 (100.0)	-	3 (100.0)	3 (75.0)	9 (90.0)	6 (100.0)	-	-	**31 (93.9)**
Hib (% known serotype)	-	2 (33.3)	0 (0.0)	-	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	-	-	**4 (12.9)**
H. influenzae a,c,d,e,f (% known)	-	3 (50.0)	1 (25.0)	-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	**4 (12.9)**
ncHi (% known)	-	1 (16.7)	3 (75.0)	-	2 (66.7)	2 (66.7)	9 (100.0)	6 (100.0)	-	-	**23 (74.2)**

Table 2. Hib carriage among unvaccinated children before the introduction of routine Hib vacination.

Country	Year	Age (years)	Population surveyed	Number of children	Hib carriage rates %	Reference
Alaskan Eskimos	1981	≤5	Population-based	121	5.0	94
China	2000	<5	Children with diarrhoea or dermatitis	214	1.9	95
Denmark	1990	≤8	Day care centres	265	0.0	96
Dominican Republic	1998	<4	Population-based	983	7.7	25
England	1995	3-4	Population-based	79	6.3	41
England and Wales	1992	1-4	Local playgroups, nurseries and child welfare clinics	1531	4.0	44
Finland	1991	3	Child health centre	398	3.5	40
Gambia	1992	1-2	Population-based	1992	11.8	43
Hong-Kong Chinese	1995	≤5	Population-based	621	0.0	97
Hong-Kong Vietnamese	1995	≤5	Population-based	300	1.3	97
Indonesia	1998	≤2	Population-based	484	4.6	24
Japan	1997	<4 9 13	Population-based	474 154 167	0.8 3.2 3.0	26
Papua New Guinea	1993	<3	Population-based	100	9.0	98
Swedish	1990	≤6	Random day care centre	49	8	30
Thailand	2005	<5	Hospital outpatients	492	7.0	27
Turkey	2000	<10	Child health clinics, day care centres & elementary schools	1382	7	99
Turkey	2002	7-12	School students	300	3	100
United States	1985	≤8	Day care centre	66	10	31
United States	1979	25mo*	4 day care centres	98	1.0	65
United States	1979	18mo*	Child health centres, not attending day care	58	6.9	65
Wales	1986	≤6	Routine health checks or primary schools	996	1.1	28

* median age

Table 3. Secondary attack rate among US household contacts within 30 days of hospitalisation of the index case. It was possible to combine studies on secondary attack rates in households because the chi-squared test for heterogeneity showed that the attack rates were not significantly different (p=0.4 for any Hib disease, p=1.0 for both the <2 year-old and <4/<5 year-old age groups; for Hib meningitis, p=0.6 for < 2 year-old, p=0.9 for the <4/<5 year-old and p=0.10 for the >4 year-old age group).

Age of secondary case	**Attack rate % (95% CI)* [numbers]**			
	Any invasive Hib	**Reference**	**Hib meningitis**	**Reference**
<2 years	1.8 (0.04-9.4) [1/57]	[51,54]	3.8 (1.4-8.0) [6/159]	[53,55]
<4 or ≤5 years	2.0 (0.5-5.0) [4/202]	[51,54]	2.1 (1.1-3.5) [14/676]	[52,53,55]
≥4 years	0 (0-0.8) [0/479]	[51]	0.02 (0.001-0.13) [1/4256]	[52,53]

* Binomial exact confidence intervals (CI)

Table 4. Secondary attack rate among US day care contacts within 60 days of hospitalisation of the index case of any invasive Hib disease. Studies on secondary attack rates in day care centres were found to be heterogeneous for each age group (p=0.011 for the <2 year-old age group and p=0.003 for the <4/<5 year-old age group) and, therefore, are presented separately.

Age of secondary case	**Attack rate % [numbers]**				
Reference	[51] *	[57]	[58]	[59]	[76]
<2 years	3.2 [1/31]	0 [0/361]	0 [0/361]	2.7 [10/376]	1.7 [5/292]
<4 or ≤5 years	1.1 [1/91]	0.2 [1/487]	0 [0/960]	1.2 [6/486]	0.4 [8/2024]
≥4 years	0 [0/70]	0 [0/87]	-	-	0 [0/237]

* 30 days follow up

Table 5. The effectiveness of rifampicin in preventing secondary Hib disease in household contacts 30 days after hospitalisation of the index case.[38] The protective efficacy of rifampicin was calculated using the formula: 1- (risk with rifampicin / risk with no rifampicin).

Age of secondary case	Attack rate % [numbers]		Protective efficacy of rifampicin (95% CI)*
	No rifampicin	Rifampicin	
<2 years	0 [0/33]	0 [0/26]	-
2-3 years	3.3 [3/92]	0 [0/69]	100 (-199-100)%
<4 years	2.4 [3/125]	0 [0/95]	100 (-194-100)% (p=0.26)
≥6 years	0 [0/406]	0 [0/242]	-

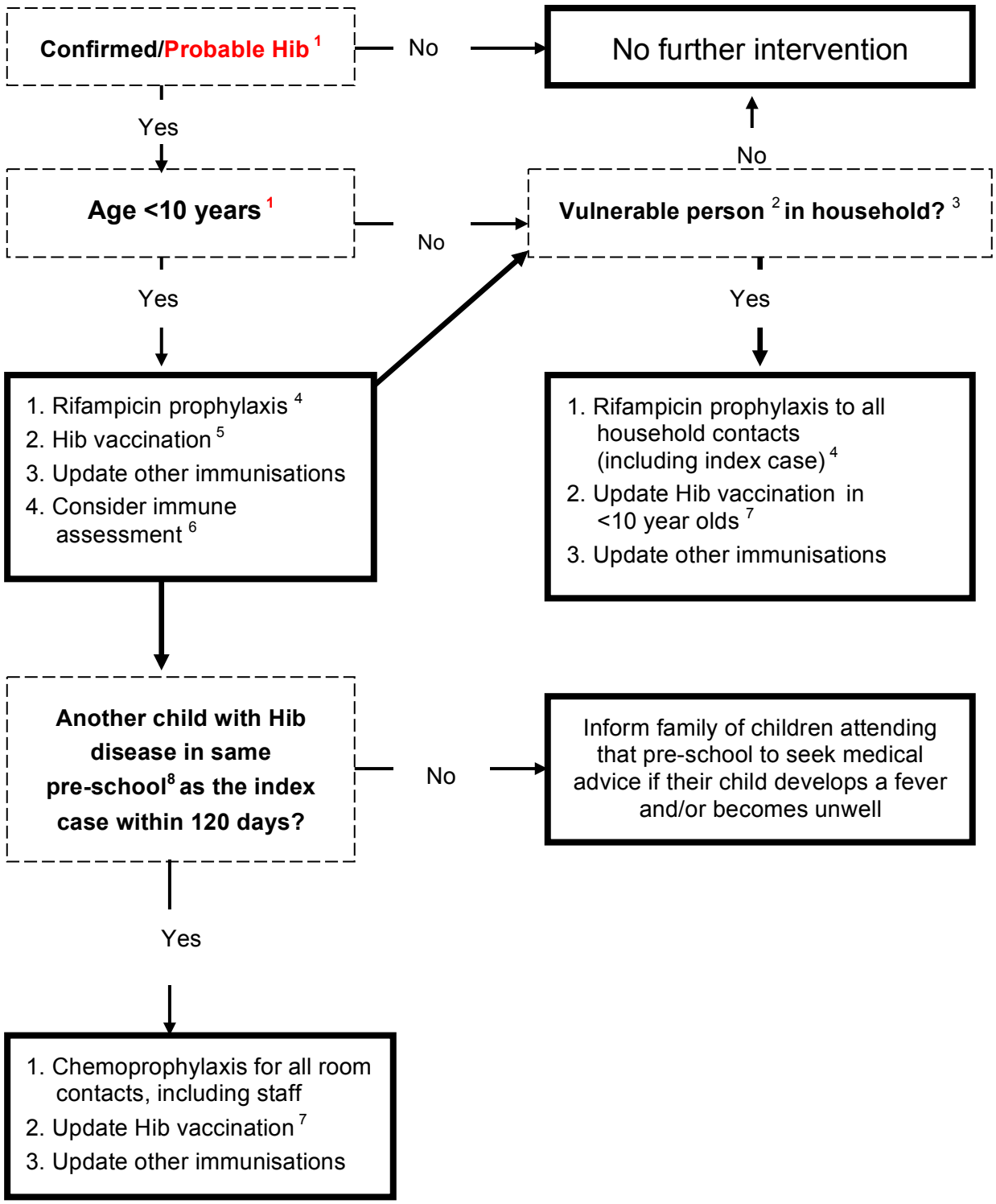
* Binomial exact confidence intervals (CI)

Table 6. The effectiveness of rifampicin in preventing secondary Hib disease in day care contacts 30-60 days after hospitalisation of the index case. The protective efficacy of rifampicin was calculated using the formula: 1- (risk with rifampicin / risk with no rifampicin).

Age of secondary case	Attack rate % [numbers]		Protective efficacy of rifampicin (95% CI)*	Reference
	No rifampicin	Rifampicin		
<2 years	1.51 [16/1060]	0.13 [1/799]	92 (37-99)% (p=0.002)	[51,57,59,76]
2-3 years	0.42 [2/480]	0 [0/460]	100 (-320-100)% (p=0.5)	[51,57,76]
≥4 years	0 [0/324]	0 [0/500]	-	[57,76]
≥6 years	0 [0/40]	0 [0/93]	-	[51]
Total	1.14 [18/1580]	0.07 [1/1352]	94 (52-99)% (p=0.003)	

* Binomial exact confidence intervals (CI)

Figure 1. Guidelines for the management of close contacts of Hib – updated June 2013



1. **Confirmed case**: Clinical diagnosis of infection AND either (i) isolation of Hib from a normally sterile site, OR (ii) detection of Hib antigen in blood or cerebrospinal fluid; **Probable case** (if serotyping not readily available or unavailable) = individual of any age with a clinical diagnosis of epiglottitis and Hi isolated from a sterile site). Invasive *Hi* isolates in neonates are nearly always ntHi but need to be confirmed by serotyping.
2. **Vulnerable person** = any child <10 years of age; or, an immunosuppressed or asplenic person of any age
3. **Household contact** = any individual who had prolonged close contact with the index case in a household type setting during the seven days before the onset of illness.
4. Children aged >3 months and adults should have **Rifampicin** 20 mg/kg (max 600 mg) once a day for 4 days. **Infants <3 months** should receive 10 mg/kg once a day for 4 days. Pregnant women should also be treated.
5. **Hib vaccination of index case** = if unable to measure anti-Hib antibodies at 4 weeks after infection, then vaccinate prior to discharge from hospital irrespective of Hib vaccination status
6. Children with Hib vaccine failure should also have total immunoglobulin levels and subclasses measured, and carefully assessed for evidence of an immune deficiency.
7. Ensure all children <10 years are fully immunised against Hib; those who only received 3 doses in infancy should receive another dose of Hib vaccine. Asplenics should be immunised according to national guidelines
8. **Pre-school** is used synonymously with playgroup, nursery, day care, crèche and primary school.