

***Haemophilus influenzae* type b Invasive Infection**

CDNA NATIONAL GUIDELINES FOR PUBLIC HEALTH UNITS

1. Summary

Public health priority

Urgent

Case management

Laboratory confirmation should be sought for patients suspected to have invasive *Haemophilus influenzae* type b (Hib) disease (see "Clinical presentation and outcome" below). The patient requires immediate hospitalisation and treatment. If treatment does not include an effective clearance antibiotic, the patient should also be given a course of rifampicin to eliminate nasopharyngeal carriage. Isolate the case using standard and droplet precautions for 48 hours after initiation of clearance antibiotic treatment.

Contact management

Defined contacts should receive rifampicin or other clearance antibiotics. Contacts receiving clearance antibiotics may continue to attend school/preschool/childcare. Parents of contacts should be advised to watch for signs and symptoms of Hib disease in contacts and to seek medical attention early should these occur. Increase public health surveillance for cases among defined contacts for a period of 60 days.

2. The disease

Infectious agent

H. influenzae is a Gram-negative coccobacillus that is a normal part of upper respiratory tract flora. Strains are either non-encapsulated or encapsulated with a polysaccharide capsule. Encapsulated *H. influenzae* isolates are classified into six serotypes (a to f) with the most common cause of invasive disease being *H. influenzae* type b (Hib).

Reservoir

Humans are the only known reservoir. *H. influenzae* can be carried asymptotically in the naso- and oro-pharynx. Carriage rates in the pre-vaccine era ranged from 0 to 9% (1) with one study reporting higher rates in children 2 to 3 years old (2).

Mode of transmission

Hib is predominantly transmitted from asymptomatic carriers by direct contact with respiratory droplets or discharges from the nose and throat. It can also rarely be transmitted from infected persons (3). Hib does not survive in the environment on inanimate surfaces (4).

Incubation period

The incubation period is uncertain, but probably from 2 to 4 days (3).

Infectious period

The infectious period lasts as long as organisms are present in the nasopharynx. Carriage is eliminated 48 to 72 hours after initiation of effective antibiotic treatment (3).

Clinical presentation and outcome

Hib causes meningitis, epiglottitis and a range of other infections such as septic arthritis, cellulitis and pneumonia. Hib is rarely isolated from the blood without a focal infection such as one of the above-mentioned being evident or developing subsequently. In older children meningitis more commonly presents with typical signs such as neck stiffness and photophobia. In infants, such typical signs are less common (3).

Epiglottitis (inflammation of the epiglottis) presents with respiratory obstruction, evidenced by soft stridor and often drooling, with the child remaining upright to maximise his or her airway, as well as systemic signs such as pallor and fever. Before the introduction of Hib vaccines, epiglottitis in children was almost always caused by Hib (5).

Before the introduction of routine Hib vaccination in Australia in 1993, the most common presentations of invasive Hib disease were meningitis and epiglottitis. The overall case fatality rate was approximately 5% (3) and one Australian study reported 17% of children surviving Hib meningitis had neurological sequelae on discharge (6).

Without appropriate treatment, Hib meningitis and epiglottitis are almost invariably fatal (7).

People at increased risk of disease

Prior to widespread vaccination, significant associations were found between Hib disease and household crowding and day-care attendance (8).

With current vaccination programs, unimmunised children younger than 5 years of age and unimmunised household contacts and day-care classmates of a person with Hib disease remain at increased risk of Hib disease. Aboriginal and Torres Strait Islander populations and people with chronic disease (eg sickle cell anaemia, antibody deficiency syndromes, and malignancies, particularly during chemotherapy) are also at increased risk.

Disease occurrence and public health significance

There has been a marked reduction in the number of notified Hib cases in Australia since the introduction of Hib vaccine. Invasive disease incidence declined dramatically from 1995 to 2005, and has since remained steady at a rate of 0.1 cases per 100,000 population or less, with the majority of cases in children aged less than 5 years (9). Australia now has one of the lowest rates of Hib in the world. However, the incidence remains disproportionately higher in Aboriginal and Torres Strait Islander people (2010 rate 1.4 compared to 0.07 respectively; rate ratio 20:1). (10).

Before the introduction of Hib vaccines to the routine immunisation schedule in 1993, Hib was the most common cause of bacterial meningitis in Australian children (11, 12), with an annual incidence rate in 1985-1987 in non-Aboriginal children of 25

per 100,000 and 150 per 100,000 Aboriginal children, under 5 years of age (13). Infection primarily affected children younger than 2 years, although epiglottitis caused by Hib most commonly occurred in older children, between 18 months and 5 years (5).

Aboriginal children acquired Hib infection at a much younger age than non-Aboriginal children and had a greater risk of death and disability (13).

3. Routine prevention activities

Vaccination

Vaccination is the most effective means of preventing invasive Hib disease. Hib vaccines are safe and effective (14, 15) and vaccination is recommended using a conjugated capsular polysaccharide antigen vaccine (PRP-T) as part of the Australian Standard Vaccination Schedule for all children at 6-8 weeks then at four, six and 12 months of age and for older persons with functional or anatomical asplenia. For further information on Hib vaccination refer to *The Australian Immunisation Handbook* at:

<http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home> .

Clearance antibiotics

Invasive Hib disease case management aims to protect those at greatest risk of disease by interrupting transmission via elimination of nasopharyngeal carriage in the case and also in contacts in defined settings.

4. Surveillance objectives

- To promptly identify cases and their close contacts so that public health action can be taken to prevent spread of disease
- To ensure careful observation of household and childcare contacts, especially those with incomplete vaccination, and immediately refer for medical evaluation if illness develops
- To identify outbreaks in order that further appropriate public health action can be taken
- To monitor the epidemiology of the disease, including the effectiveness of immunisation, and so inform better prevention strategies
- To monitor the effectiveness of current control measures and to provide an evidence base for further review of national guidelines

5. Data management

Confirmed cases of invasive Hib infection are notifiable and should be entered onto the notifiable diseases database ideally within one working day of notification.

6. Communications

Where applicable, public health unit to notify the state/territory communicable diseases agency of confirmed cases as soon as laboratory results are received. Provide the case's age, sex, date of onset, vaccination history, laboratory and clinical status, resident location, place of acquisition, indigenous status and follow-up action taken.

Upon completion of case follow up, the PHU should complete a National Centre for Immunisation Research and Surveillance (NCIRS) Hib *Enhanced Surveillance Notification* form¹ and return it to NCIRS.

7. Case definition

The current national surveillance case definition can be found at:

<http://www.health.gov.au/casedefinitions>.

Conjunctivitis is not considered to be an invasive infection for Hib (1).

8. Laboratory testing

Testing guidelines

All patients with suspected Hib infection should have blood collected for bacterial culture (and/or nucleic acid amplification testing (NAAT)) (also known as PCR) (see below) as soon as possible before, or as soon as possible after, antibiotics are administered. If cerebrospinal fluid (CSF) is obtained, microscopy can give earlier presumptive identification of *Haemophilus* species but definitive identification must still await confirmation by culture and/or NAAT.

Even though the incidence of Hib disease has declined, laboratories should continue routine serotyping of isolates obtained from normally sterile sites, which will usually require referral of isolates to a reference laboratory.

Microscopy

Visualising small, Gram-negative, pleomorphic coccobacilli with polymorphonuclear cells in CSF or specimens from other sterile sites is suggestive of *H. influenzae* but must be confirmed by culture/PCR and gives no indication of serotype. The sensitivity of a Gram stain performed on culture-positive CSF is reported to range from 50% to 86% but is decreased following antibiotic administration (16, 17).

Culture

The sensitivity of CSF and blood culture for detection of Hib infection is high unless antibiotic therapy has been started before sampling (16). Cultured isolates enable definitive typing.

Antigen Detection

Slide agglutination to detect Hib capsular antigen in CSF or blood is now seldom available in clinical settings and has limitations as a test for early diagnosis. However further characterisation of a *H. influenzae* isolate from a normally sterile site remains important (see below).

Nucleic acid testing

Isolates from sterile sites suspected to be *H. influenzae* should be always referred to reference laboratories for typing where NAAT, which is required for definitive typing, is available. Their contact details are provided in Appendix 4. Some reference laboratories may be able to perform NAAT on blood or CSF specimens directly.

¹ <http://www.health.qld.gov.au/cdcg/documents/ncirs-haem-flu-b.pdf>

9. Case management

Response times

Begin follow-up investigation within 24 hours of notification of a confirmed case. Earlier response may be appropriate if serotyping results are not likely to be timely.

Response procedure

Case investigation

The response to a notification will normally be carried out in collaboration with the case's health carers. Regardless of who does the follow-up, public health unit (PHU)/public health agency staff should ensure that action has been taken to:

- Confirm the onset date and symptoms of the illness
- Confirm results of relevant pathology tests
- Advise the reporting doctor of the role of the public health agency in investigating the possible sources of infection, and the identification and management of contacts. Advise them that public health staff will need to contact the case or relevant care-giver
- If possible, determine whether the case or relevant care-giver has been advised of the likely diagnosis before contacting them
- Ensure that contacts are identified and nasopharyngeal clearance antibiotics offered as detailed in Section 11. Contact management
- Collect clinical and epidemiological and laboratory data required to complete the NCIRS *Hib enhanced notification form*
- Obtain details and documentation of previous Hib immunisation, if any (date and batch number)

Case treatment

Public health personnel should ensure that clinical isolates (or specimens) are referred by the diagnosing laboratory to a reference laboratory for typing.

Patients suspected to have invasive Hib disease require immediate treatment. Refer to the current edition of *Therapeutic Guidelines: Antibiotic* for treatment guidelines.

One Australian study reported positive throat swabs from 34% of patients not given rifampicin (6). Rifampicin should be given to cases prior to discharge from hospital to ensure clearance of the organism if ceftriaxone or cefotaxime has not been used for in hospital treatment (25). Dosing regimens are the same as for contacts and provided below under "11. Contact Management".

If the treated patient is less than 5 years of age and has not been immunised, age-appropriate catch-up Hib vaccination should be given after discharge from hospital.

Education

The case or relevant caregiver should be informed about the nature of the infection and the mode of transmission. Discuss the risk of infection of contacts.

Isolation and restriction

When Hib is suspected, standard and droplet precautions should be practised for cases until ≥ 48 hours after initiation of clearance antibiotic therapy (3, 18, 19).

Exclude cases from school, preschool, childcare or other settings where there are susceptible individuals, especially young children and infants until completion of treatment, including clearance antibiotics (25).

Active case finding

Contacts (see definition below) should be advised to immediately seek medical advice should they develop symptoms. Contacts or caregivers should be asked to also inform the public health agency if they develop symptoms.

10. Control of environment

None routinely required

11. Contact management

Identification of contacts

Secondary cases in families and day care centres are now rare (3). Studies conducted before widespread vaccination showed that secondary spread was uncommon (18) but when it did occur, household and day care contacts of index cases were at a significantly higher risk of developing invasive Hib disease compared with the general population (1). These secondary cases among close contacts generally occurred within the first week after onset of disease in the index case (18).

Prior to widespread vaccination, Hib carriage rates in contacts of an index case were much higher than those in the general population. Carriage rates in day care contacts were also increased compared to non day care attendees of a similar age. (1). Comparable information about carriage is not available for the current era of widespread vaccination, but carriage would be expected to be much lower.

Interview the case or the case's carer as appropriate to identify household and childcare contacts.

Healthcare associated transmission of Hib infection between two children in an acute care hospital has been reported (20). Direct contact with the respiratory secretions of a case is generally considered significant. As appropriate, advise the case's healthcare provider about contact definitions and clearance antibiotic recommendations in the hospital setting.

Contact definition

Household contacts are those who had prolonged close contact with the index case in a household type setting in the seven days prior to the index case developing invasive Hib disease. Examples include living or sleeping in the same house, boyfriends/girlfriends, and sharing a dormitory or flat with the index case.

Childcare contacts are defined as any individual sharing with the index case any situation where children under 5 years of age are cared for with other children away from home in the seven days prior to the onset of disease in the case.

Contacts within the hospital setting are those people who have shared a hospital room with the case or healthcare workers who are directly exposed to the case's respiratory secretions prior to case completion of 48 hours of clearance antibiotics.

Prophylaxis

Clearance antibiotics

Rifampicin has been shown to eradicate pharyngeal carriage of Hib in 92 to 97% of contacts (1), and consequently may decrease the risk of secondary cases (18). Rifampicin is of no value more than 30 days after initial contact with a case. An Australian study showed that ceftriaxone and cefotaxime were effective alternatives for eliminating Hib nasopharyngeal carriage in cases (19). Others have extrapolated this finding to recommend ceftriaxone as an alternative clearance antibiotic for contacts unable to tolerate rifampicin (1).

Dosing regimens (1)

Rifampicin

Children and adults: 20 mg/kg as a single daily dose (maximum daily dose 600 mg) for 4 days.

Neonates (<1 month of age): 10 mg/kg daily for 4 days.

Ceftriaxone

Children 12 years or older and adults: 1g IM or IV daily for 2 days

Children younger than 12 years: 50mg/kg IM or IV daily for 2 days

Household

Clearance antibiotics are no longer routinely indicated unless the household contains a vulnerable contact. A vulnerable contact is:

- an infant <7 months of age (regardless of vaccination status), OR
- a child aged 7 months to 5 years who is inadequately vaccinated. To determine if child is inadequately vaccinated, use the Hib catch-up table in current edition of the *Australian Immunisation Handbook*) OR
- an immunocompromised or asplenic person of any age, regardless of vaccination status.

In these cases, all contacts in a household in which a case of invasive Hib infection occurs should receive rifampicin, with the exception of pregnant women or those with previous adverse reaction or other contraindication to rifampicin, for whom ceftriaxone may be used (19).

Childcare facilities

Based on pre-vaccination evidence, the risk of disease is lower for childcare contacts, compared to household contacts and approaches that of the general population when all contacts are older than 2 years (21-23). Pre-vaccine studies showed rifampicin reduced the risk of secondary cases in childcare groups, especially in those younger than 2 years (22, 24).

Where a group of childcare contacts:

- a) have levels of contact approaching that of a household², **and**
- b) at least one of these close contacts is either:
 - i. immunocompromised, OR
 - ii. a child less than 7 months of age (regardless of vaccination status) OR

² Examples of contact approaching that of a household: Family Day Care (where groups of children are cared for in a private home); Child care involving a group staying together in a single room for at least a four hour session.

iii. a child aged 7 to 24 months of age who is not adequately vaccinated,
offering clearance antibiotics to this close contact group should be considered. The intermingling of children of different age/room groups at the beginning and end of the day is usually of short duration and not sufficient to justify the use of clearance antibiotics.

Hospital / Health care facility

Clearance antibiotics are recommended for:

- vulnerable contacts (see definition under 'Household' above) who shared a hospital room with the case prior to completion of 48 hours of clearance antibiotics by the case and
- healthcare workers who have had direct contact with the case's nasopharyngeal secretions (eg undertaking intubation without a facemask; performing mouth to mouth resuscitation) prior to completion of 48 hours of clearance antibiotics.

Vaccination

Because of the length of time necessary to develop antibodies, vaccination does not play a major role in the immediate management of patients with Hib disease or their contacts. Nevertheless, Hib vaccine is routinely recommended, according to the catch-up schedule in the current edition of the *Immunisation Handbook*, for unvaccinated and inadequately vaccinated contacts less than 5 years old.

Education

PHU staff should manage the distribution of information to contacts or their carers (refer Appendices 2 and 3). Parents and carers of confirmed cases should be educated about the risks of secondary cases in siblings and other close contacts under 5 years of age, and of the need to seek early medical review if any close contacts develop symptoms consistent with Hib disease. Any suspect secondary cases should be urgently reported to public health units. Parents of confirmed cases and directors of childcare attended by a confirmed case should be informed of the need to observe children carefully and to refer any symptomatic possible cases for urgent medical assessment.

Isolation and restriction

Contacts receiving clearance antibiotics may continue to attend school, preschool or childcare.

12. Special situations

Multiple cases among children in childcare settings

If more than one case has occurred in a childcare facility within a 60 day period and vulnerable children (see above) attend, rifampicin should be offered to all children and staff who share the same indoor space as the cases. Children and staff in other rooms are usually not at elevated risk and do not require clearance antibiotics. (1, 22, 25).

The childcare centre director should strongly encourage all children entering childcare to be age-appropriately immunised.

Outbreaks/Multiple cases in another defined population

Even before Hib vaccination was widespread, epidemics were considered rare (18). However, should 2 or more cases occur within 60 days of each other in a discrete population (eg a boarding school or other institutional setting), the public health response should be based on the control principles outlined above in contact management and may require increased contact surveillance, clearance antibiotics and vaccination.

Cases in vaccinated children

Children with confirmed invasive Hib infection or recurrent invasive Hib disease after receiving 2 or more doses of PRP-OMP Hib vaccine (Pedvax Hib) or 3 or more doses of PRP-T-Hib vaccine (eg Infanrix Hexa), may be immunocompromised and should be referred for appropriate investigation and management (26).