BACTERIAL MENINGITIS INCIDENCE IN THAI CHILDREN ESTIMATED BY A RAPID ASSESSMENT TOOL (RAT)

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Abstract. Acute bacterial meningitis is an important cause of morbidity and mortality in children. To estimate the incidence of meningitis caused by all types of bacteria in Thai children under five years of age, data were collected using a rapid assessment tool (RAT) and analyzed. Clinical and laboratory data from suspected meningitis cases for a one-year period were retrospectively collected from 5 selected catchment areas located in the 4 regions of the country. Adjusted incidences of confirmed bacterial meningitis were calculated based on laboratory quality and lumbar puncture rates. Seventy-five suspected meningitis cases were identified among 305,023 children under age five in the catchment areas, with an unadjusted incidence of 24.6 per 100,000. Of these, 66.2, 55.9, and 33.8% were unconfirmed bacterial, purulent, and confirmed bacterial meningitis cases, respectively. Among the confirmed bacterial meningitis cases, 39.1, 26.1, 21.7 and 13.0% were caused by *Haemophilus influenzae* type B, gram-positive cocci, gram-negative bacilli, and *Neisseria meningitidis*, respectively. After adjusting based on the RAT application, the incidence of confirmed bacterial meningitis was about double that of the unadjusted incidence. This study gives an interval of possible incidences of bacterial meningitis in children under age five, which is between the unadjusted (low estimate) and adjusted (high estimate) incidences.

INTRODUCTION

Acute bacterial meningitis is an important cause of morbidity and mortaility in children. The three most common etiologic agents are *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis*, which account for 90% of reported cases of acute bacterial meningitis in children >4 weeks of age (Peltola, 2000; Centers for Disease Control and Prevention, 2002). Determination of the etiology of bacterial meningitis and estimating the cost of the disease are important in guiding vaccination policies. Despite the fact that in many countries there is mandatory notification of meningitis cases, exact rates of meningitis are not known (Logan, 2008). One important obstacle is that bacterial meningitis is difficult to diagnose, those cases identified account for only a fraction of the true disease burden (WHO, 2001). The most important test in identifying or ruling out meningitis is analysis of the cerebrospinial fluid (CSF) through lumbar puncture (LP) which may not be available to physicians in the devel-

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oping world, such as parts of Thailand. (Straus *et al*, 2006).

The World Health Organization (WHO) has recently developed a rapid assessment tool (RAT) to be used in assessing Hib disease burden in developing countries (WHO, 2000, 2001). This tool provides a methodology for countries to rapidly assess the burden of Hib disease using as much local data as possible. The RAT was used in Thailand in 2002 to estimate the burden of Hib disease for use in policy making decisions regarding new vaccine introduction. This report analyzes part of the database to which we applied parts of the RAT methodology to estimate the incidence of meningitis caused by all types of bacteria, not just Hib. In this report we estimate the incidence of bacterial meningitis adjusted for inadequate laboratory facilities used to identify the causative agents and for suspected meningitis patients in whom a LP was not performed. This adjustment should make the estimate closer to the real incidence.

MATERIALS AND METHODS

Study site selection

Five of the 65 provinces of Thailand, representing all 4 geographic regions of the country, were selected as study sites. The provinces were Roi Et for the northeast, Ratchaburi from the central, Nakhon Si Thammarat from the south and Lampang and Phitsanulok from the north. The two northern provinces were the same provinces where the prospective study on Hib disease incidence was previously performed (in 2000). The other three provinces were selected using the following criteria: 1) a population not less than 250,000; 2) a substantial distance from provinces with advanced medical services, to ensure the catchment of the local health system; 3) a relatively high incidence of unspecified meningitis and encephalitis in the national surveillance system; 4) willingness to cooperate with local health authorities.

Catchment area definition

The catchment area for the province covered a total population of not less than 250,000. For small provinces, the catchment covered the whole province. For larger provinces, the catchment included all urbanized districts (municipalities) plus other additional districts to make up a total population of 250,000. Districts where the population crossed borders to seek medical care from facilities located in other provinces were not included in the catchment area for that district because the incidences in these districts were likely to be underestimated.

There were 389,272 children under age 5 in the 5 studied provinces. Of these, 305,023 (78.4%) lived in the 5 studied catchments areas. The number of children of under age five per catchment was lowest in Lampang (11,184), and highest in Roi Et (92,082) (Fig 1). The differences in the number of children in each catchmant area were due to decisions made by data collection teams at each studied site according to the feasibility of complete data collection in a limited time.

In the catchment areas, all hospitals with the capability of diagnosing and treating pediatric meningitis were selected. A total of 27 hospitals, including 12 government, 10 private, and 5 military hospitals were selected. Cases visiting the hospitals without the capability of managing pediatric meningitis were transferred to hospitals with the capability. Therefore, the selected hospitals covered most suspected meningitis cases in the catchment areas.

Case inclusion criteria

The inclusion criteria for a case were: 1) a child between one month and five years of age and 2) living in the catchment area

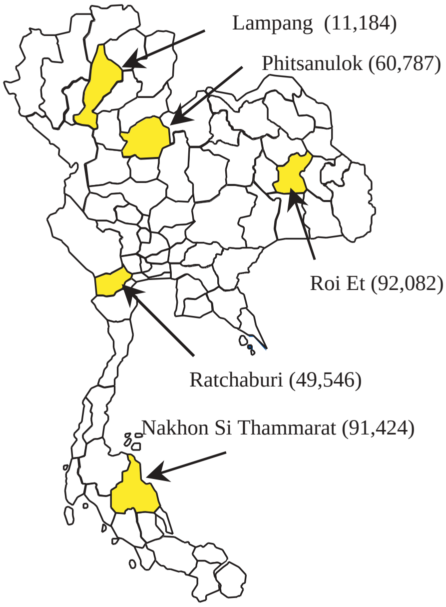

Fig 1–Study provinces and numbers of study subjects (N = 305,023).

and 3) having been diagnosed with meningitis, encephalitis, meningo-encephalitis, or having a central nervous system (CNS) infection, or having cerebro spinal fluid (CSF) with at least one of the following: turbidity or cloudiness, 100 or more white blood cells (wbc) per ml, 10-99 wbc/ml with a CSF glucose <40 mg% and a CSF protein >100 mg%, and an identified organism, and 4) having been admitted to the hospital during the study period of May 1, 2000 to April 30, 2001 for children living in Lampang or Phitsanulok and January 1, 2001 to December 31, 2001 for children living in Roi Et, Ratchaburi, and Nakhorn Si Thammarat.

Case definition

A case of suspected meningitis was defined as a child who met inclusion criteria. A case of purulent meningitis was defined as a child with suspected meningitis and CSF with at least one of the following: turbid or cloudy CSF, 100 or more white blood cells (wbc), and 10-99 wbc with a CSF glucose <40 mg% and a CSF protein >100 mg%. A case of confirmed bacterial meningitis was defined as a child with clinically suspected meningitis and bacteria identified in the CSF or on a blood culture, latex agglutination test, CIE, or Gram's stain.

Suspected meningitis cases with no lumbar punctures (7 cases) were classified as unconfirmed bacterial meningitis.

Data collection

Information regarding suspected meningitis cases was obtained from inpatient logbooks and data from laboratory logs. There were five data review teams. Each team was comprised of five to ten staff from the Department of Disease Control and Provincial Health Offices located in the studied province who reviewed the cases of the assigned catchment area. There were two international staff, one from the University of Melbourne and the other from Emory University School of Medicine, who joined the teams in Lampang and Nakhorn Si Thammarat, respectively. The reviews were supervised by the principle investigator.

Data analysis

At the core of RAT are two methods for estimating Hib disease burden: one method estimated Hib-related childhood meningitis (the meningitis incidence rate method) and a second estimated the proportion of children under five with pneumonia mortality attributable to Hib (the under-five mortality method). Both methods use local estimates of meningitis and pneumonia case fatalities in addition to other local data. In this study only the first method of the RAT was applied to adjust the number of bacterial meningitis cases that may have been misdiagnosed due to inadequate laboratory quality and/or a missed lumbar puncture and then to calculate the adjusted incidences of meningitis among children under five years of age.

Adjustments were made using the following equations:

(1) Adjustment for inadequate laboratory quality:

additional confirmed bacterial meningitis cases = (confirmed bacterial meningitis cases for a certain bacteria among purulent meningitis cases ÷ all confirmed bacterial meningitis cases among purulent meningitis cases) x (unconfirmed bacterial meningitis cases among purulent meningitis cases).

(2) Adjustment for not having lumbar puncture results:

additional confirmed bacterial meningitis cases = [confirmed bacterial meningitis cases for a certain bacteria among purulent meningitis cases + confirmed bacterial meningitis cases of a certain bacteria among non-purulent meningitis cases + (1)] x (1 - percent lumbar punctures performed among suspected meningitis cases).

(3) Adjusted incidence:

adjusted incidence of confirmed bacterial meningitis cases = [(1) + (2)] ÷ (number of children under five in the catchment area) x 100,000.

(4) Unadjusted incidence:

un adjusted incidence of confirmed bacterial meningitis cases = confirmed bacterial meningitis cases ÷ (children under five in the catchment area) x 100,000.

RESULTS

Seventy-five suspected meningitis cases of all causes were identified, with an incidence of 24.6 per 100,000 for children under age five years (Table 1). The number of cases per catchment area varied from 33 in Nakhon Si Thammarat to 3 cases in Lampang. CSF was collected in 90.7% for all the catchment areas overall, but did not differ significantly among the catchment areas. The lowest percentage was found in Nakhon Si Thammarat (85%) and the highest found in Lampang and Phitsanulok (100%) (p = 0.552).

Of the cases in which CSF was collected (68), 45 (66.2%) were unconfirmed bacterial meningitis cases, 38 (55.9%) were purulent meningitis cases, and 23 (33.8%) were confirmed bacterial meningitis cases. The proportion of confirmed bacterial meningitis cases was 50.0% among purulent meningitis cases, compared to 13.3% among non-purulent meningitis cases (p = 0.002).

Of the confirmed bacterial meningitis cases, 9 (39.1%) were infected with Hib, 6 (26.1%) had gram-positive cocci in the CSF, including 3 cases with gram-positive diplococci in the CSF; 5 (21.7%) had gram-negative bacilli in the CSF; 3 (13.0%) had *N. meningitidis* in the CSF.

Of 75 cases, 4 died, giving a case fatality rate (CFR) of 5.3%, while the outcome of 5 cases (6.7%) was not known. One of the cases who died had Hib confirmed meningitis, with an Hib CFR of 11%. The other three cases were unconfirmed bacterial meningitis, with a CFR of 6%, p = 0.528. The Hib mortality case was a 5-month old. The other three cases with unconfirmed bacterial meningitis were ages one month, two months and three years. Among the survivors with suspected meningitis, there were no records of any sequelae after the acute episode.

Purulent, non-purulent, and confirmed bacterial meningitis had no seasonal patterns (Fig 2). In contrast, 71.2% of unconfirmed bacterial meningitis cases occurred from July to December.

The unadjusted incidences of suspected meningitis cases were unevenly distributed by region, with the highest in the central region, followed by the south, north, and northeast, with the incidences of 38.3, 36.1, 18.1 and 10.9/100,000, respectively (Table 2).

Table 1
Unadjusted numbers of suspected meningitis cases classified by catchment area, characteristics of CSF and causative organisms (*N*=75).

Type of meningitis	Catchment areas provinces						
	Lampang	Phitsanulok	Roi Et	Ratchaburi	Nakhon Si Thammarat	Total Number	%
1.Purulent CSF	(3)	(6)	(7)	(8)	(14)	(38)	(50.7)
H. influenzae type B (Hib)	1	2	0	2	3	8	21.1
Gram-positive cocci	0	0	1	0	3[a]	4	10.5
Gram-negative bacilli	0	0	0	1	3[d]	4	10.5
N. meningitidis	2	0	0	1	0	3	7.9
Purulent meningitis	0	4	6	4	5	19	50.0
2. Non-purulent CSF	(0)	(4)	(2)	(10)	(14)	(30)	(40.0)
H. influenzae type B (Hib)	0	0	0	0	1	1	3.3
Gram-positive cocci	0	1[b]	0	0	1[c]	2	6.7
Gram-negative bacilli	0	0	0	0	1[e]	1	3.3
N. meningitidis	0	0	0	0	0	0	0.0
Suspected meningitis	0	3	2	10	11	26	86.7
3. No CSF collected	(0)	(0)	(1)	(1)	(5)	(7)	(9.3)
Total (1+2+3)	(3)	(10)	(10)	(19)	(33)	(75)	(100.0)

[a] 3 cases of gram-positive diplococcus; of these, 1 case was *S. pneumoniae* identified from both CSF and blood cultures.
[b] *Streptococcus* group B identified from CSF latex agglutination test of a 10-day old newborn.
[c] *Streptococcus* group non-A, B, D from both CSF and blood cultures of a 4-month old child.
[d] *E. coli* from a CSF culture of a 6-month old with status post CSF shunt placement.
[e] *Klebsiella pneumoniae* identified from the CSF culture of a 1-year old child.

Table 2
Regional unadjusted meningitis incidences.

Types of meningitis	Incidence (95%CI)				
	North	Northeast	Central	South	Total
Etiology (*N*=75)					
Confirmed bacterial	8.3(3.4-19.1)	1.1(0.1-7.1)	8.1(2.6-22.2)	13.1(7.1-23.6)	7.5(4.9-11.5)
Unconfirmed bacterial[a]	9.7(4.3-21.0)	9.8(4.8-19.3)	30.3(17.6-51.2)	23.0(14.6-5.8)	17.1(12.9-22.5)
CSF characteristic [a] (*N*=68)					
Purulent	12.5(6.1-24.7)	7.6(3.3-16.4)	16.1(7.5-33.2)	15.3(8.7-26.4)	12.5(8.9-17.3)
Nonpurulent	5.6(1.8-15.3)	2.2(0.4-8.8)	20.2(10.3-38.5)	15.3(8.7-26.4)	9.8(6.8-14.2)
Total (*N*=75)	18.1(10.0-31.8)	10.9(5.5-20.7)	38.3(23.8-61.1)	36.1(25.2-51.3)	24.6(19.5-31.0)

[a] Suspected meningitis cases with no lumbar punctures (7 cases) were also classified as unconfirmed bacterial meningitis cases but were excluded from classification.

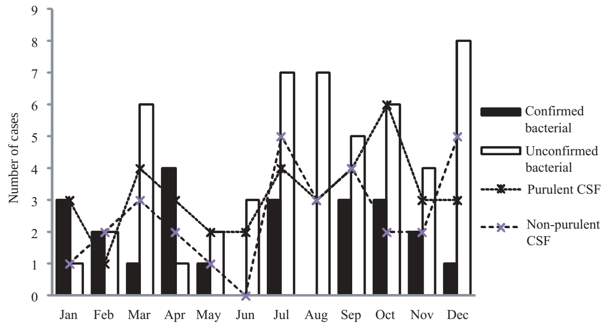

Fig 2–Distribution of the unadjusted number of meningitis cases by month[a] (N=75).

[a] Suspected meningitis cases with no lumbar punctures (7 cases) were also classified as unconfirmed bacterial meningitis cases, but excluded from the classification.

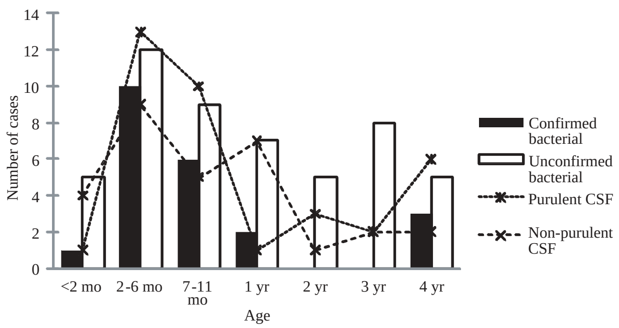

Fig 3–Age distribution of unadjusted number of meningitis cases [a] (N=73).

[a]Suspected meningitis cases with no lumbar punctures (7 cases) were also classified as unconfirmed bacterial meningitis, but were excluded from classification by CSF characteristics.

Compared to other regions, a much lower incidence of confirmed bacterial meningitis was observed in the northeast, with an incidence of 1.1/100,000, while incidences of 4.0-12.0/100,000 were observed in the other regions. The incidences of unconfirmed bacterial meningitis were unevenly distributed. They were higher in the central and south, at 30.3 and 23.3/100,000, compared to the incidences of 9.7 and 9.8/100,000 in the north and northeast, respectively. For the incidences classified by CSF characteristics, the incidences of purulent CSF meningitis were higher than those of nonpurulent CSF meningitis in the north and northeast, were lower in the central region and equal in the south, however, these differences were not statistically significant.

Children younger than two years old were at significantly higher risk of having confirmed bacterial meningitis (Fig 3). The majority (86.4%) of the confirmed bacterial meningitis cases were in this age group. This was also true for unconfirmed bacterial meningitis cases, but to a lesser extent. More than half (64.7%) of the suspected cases were unconfirmed bacterial meningitis cases younger than two years old. However, using CSF characteristics (purulent and nonpurulent), there was no association with age.

After adjusting for the quality of the laboratory and rate of lumbar puncture, the incidences of confirmed bacterial meningitis were about double compared to the unadjusted incidences (Table 3). By causative agents the unadjusted incidences for Hib, gram-positive cocci, gram-negative bacilli and *N. meningitidis* were 3.0, 2.0, 1.6 and 1.0/100,000, respectively, compared to the adjusted incidences of 6.1, 3.6, 3.3 and 2.2/100,000, respectively. Most (80-83%) of the adjustment was due to laboratory quality (Fig 4).

DISCUSSION

We believe this is the first report from Thailand of the incidences of bacterial meningitis estimated by adjusting for laboratory inadequacies and lumbar puncture rates, by application of the RAT technique. The cases of confirmed bacterial meningitis among children under age five ranged from 1.1 to

Table 3
Unadjusted and adjusted incidences of confirmed bacterial meningitis cases.

Meningitis	Unadjusted			Adjusted [a]		
	Cases	Incidence	95%CI	Cases	Incidence	95%CI
H. influenzae type B (Hib)	9	3.0	1.4-5.8	18.7	6.1	3.8-9.8
Gram-positive cocci[b]	6	2.0	0.8-4.5	11.0	3.6	1.9-6.7
Gram-negative bacilli	5	1.6	0.6-4.1	9.9	3.3	1.6-6.2
N. meningitidis	3	1.0	0.3-3.1	6.6	2.2	0.9-4.8
Total	23	7.5	4.9-11.5	46.2	15.1	11.2-20.4

[a] Adjusted for laboratory quality and lumbar puncture rate.
[b] Including 3 cases of gram-positive diplococci bacteria with unadjusted and adjusted incidences of 1.0 and 2.2/100,000, respectively.

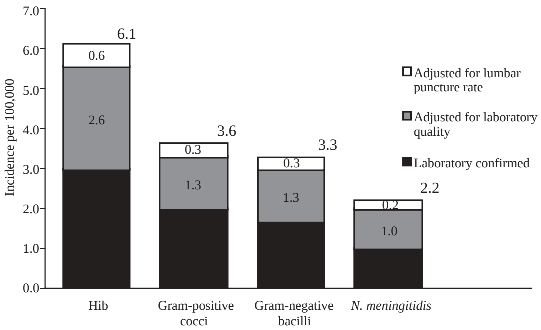

Fig 4–Confirmed bacterial meningitis cases incidences by causative agents, adjusted for laboratory quality and lumbar puncture rate.

26.8 per 100,000 in the five study provinces. CSF was collected in 90.7% of cases. Approximately half the cases had purulent meningitis; half had no organism identified. Hib was the most commonly identified bacteria, occurring in one-fifth of all cases, with an unadjusted incidence of 3.0 per 100,000. After adjustment for limitations in laboratory evaluations and lack of lumbar punctures, the estimated incidence was 6.1 per 100,000.

Cases enrolled in this study not only had meningitis, but some had encephalitis and others had signs, symptoms, and laboratory findings compatible with meningitis. Including non-meningitis cases, the proportion of bacterial meningitis cases out of the total meningitis cases in this study (33.8%) was higher than that found in the literature, which found bacterial meningitis in about 6% to 18% of all meningitis cases (Tatara *et al*, 2000; Nigrovic *et al*, 2002). The difference may not only reflect the etiological differences, but also other factors, such as age of the population, completeness of reporting, laboratory quality and lumbar puncture rates.

From our study findings, it appears the unadjusted incidences of confirmed bacterial meningitis underestimate the overall real incidence of bacterial meningitis. This may be explained by the limited capacity of some laboratories to carry out adequate investigation in suspected meningitis cases. Therefore, to adjust the incidence by adjusting for the limited capacity of the laboratory is justified, especially among purulent CSF cases. The purulent CSF cases were more likely to be confirmed bacterial meningitis cases. The proportion of confirmed bacterial meningitis cases, among those with purulent CSF findings, (50.0%) was significantly higher than that of non-purulent CSF findings

(13.3%) (p=0.002). These proportions can be applied for the whole year and in different age groups, since there was neither seasonality nor age relationship to CSF findings. However, there were some differences by region (Table 2). These differences may reflect variability in laboratory quality and/or disease etiologies.

The validity of the adjustment depends on the capability of the laboratories which varied from facility to facility, but the adjusted factors using the RAT applied equally to all laboratories. Some laboratories in the studied areas not only performed CSF cultures and Gram's stains, but also carried out other investigations, such as hemoculture, latex agglutination test (LA), and CIE. These investigations were performed in provincial hospitals in 4 provinces but not in the northeast. These hospitals covered 70.7% of all the suspected meningitis cases enrolled in this study. These investigations increase the sensitivity for detecting the causative bacteria among suspected meningitis cases (Gray and Fedorko, 1992). Therefore, the unconfirmed bacterial meningitis cases in these provincial hospitals would have a lower chance of being bacterial meningitis with the adjusting factor applied. Therefore, the adjustment would give an over estimation of the number of cases.

Due to the above reasons the estimated incidence of meningitis should be somewhere between the unadjusted incidence, as a low estimate, and the adjusted incidence, as a high estimate. Therefore, the Hib incidence should fall between 3.0 and 6.1/ 100,000, which are unadjusted and adjusted incidences, respectively. This is in line with the estimate from a prospective population based study done in Thailand in 2000 (3.8/ 100,000) (Rerks-Ngarm *et al*, 2004). The Hib incidence is also in line with low rates of Hib meningitis found in retrospective and prospective studies from other parts of Asia (Lau *et al*, 1995; Sung *et al*, 1997; Kamiya *et al*, 1998; Yang *et al*, 1998; Lee *et al*, 2000; Kilgore *et al*, 2002).

Regarding the etiologies and age distributions for meningitis cases, the findings from this study are compatible with a study from Children's Hospital, Bangkok, where Hib was the main causative agent for bacterial meningitis among young children, especially those under one year of age (Chotpitayasunondh, 1998). *S. pneumoniae* is the second most common bacterial cause of meningitis in Thai children, while it is the most common etiology of community acquired bacterial meningitis in Thai adults comprising 11.7-28% of all causes (Chotmongkol *et al*, 2000; Khwannimit *et al*, 2004). Of the 6 cases of gram-positive cocci miningitis in our study, 3 had gram-positive diplococci, which were most likely *S. pneumoniae* miningitis cases. Therefore, the incidence of pneumococcal meningitis cases in Thai children should be about 1.0-2.2/ 100,000. The estimated incidence of pneumococcal meningitis in this study is also in line with that found in a prospective study (Rerks-Ngarm *et al*, 2004).

The overall case-fatality rate in this study was much lower than that found in the Children's Hospital, at 5.3% *vs* 12.9-25.6%, respectively (Chotpitayasunondh, 1998). This difference probably reflects improvement in treatment . There was no seasonality in confirmed bacterial meningitis cases similar to a report from the national surveillance system (Division of Epidemiology, 1998). However, unconfirmed bacterial meningitis cases tended to occur more often (12 cases) during the second six months of the year. On further analysis no significant relationships or clusters of cases happened.

In conclusion, Hib, gram-positive cocci, gram-negative bacilli and *N. meningitidis* were the most common causes of bacterial meningitis among Thai children in this study. RAT is an inexpensive and useful tool for rapid assessing suspected bacterial meningitis cases. RAT can be used to adjust the incidences estimated by conventional methods to decrease the bias of underestimation caused by inadequate laboratory evaluation and lumbar puncture rates. However, in areas where better laboratories are available, overestimates of the incidences using RAT may occur. RAT does not deal with some issues, such as the completeness of case enrollment and the impact of antibiotic use prior to admission. The results of this study give a range of possible incidences for bacterial meningitis in children under five years old, which is between the unadjusted (low estimate) and the adjusted (high estimate) incidences.

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