Acute Bacterial Meningitis in Children Admitted to the Queen Elizabeth Central Hospital Blantyre, Malawi in 1996-97.

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Summary
In order to design appropriate interventions, we collected clinical and demographic data prospectively on all children aged one day to 14 years admitted with a diagnosis of bacterial meningitis (BM) from April lst 1996 to March 31st 1997 to the Queen Elizabeth Central Hospital (QECH), Blantyre Malawi. During the study period 267 children (2.7% of all paediatric admissions) were found to have BM; 83% were under 5 years of age, 61% under one year and 23% under one month. The most common causative organisms in the post neonatal period (n = 206) were *Streptococcus pneumoniae (27%), Haemophilus influenzae* type b (Hib) 21 %, and *Salmonella typhimurium* (6%). In the neonatal group (<l month, n = 61) the most common causes were *Streptococcus agalactiae (23%), S. typhimurium* (15%), *S. pneumoniae* (11. 5%) and other gram negative rods (11.5%). Nineteen of 21 salmonella infections were in children under one year of age and all *S. agalactiae* were in infants under three months. There was delay on presentation: the average length of fever was 4.6 days, 39.5% had convulsed prior to arrival and 57% had an altered level of consciousness. An initial diagnosis of malaria had probably contributed to the delay in 22.5% , (42 of 186 tested). Forty eight percent were < 80% weight for age, with 18% < 60 % weight for age. The overall mortality was 40%. The outcome was worst in salmonella infections, particularly neonatal salmonella BM with a case fatality rate (CFR) of 89% (8 of 9 cases). Coma on presentation worsened prognosis (mortality 64% if Blantyre Coma Score <3, 26% if > 3). Fifteen percent of survivors had sequelae on discharge. Twenty percent of Hib isolates were resistant to chloramphenicol, but all salmonellae were sensitive. Five percent of S. *pneumoniae* were resistant to penicillin and 8% to chloramphenicol. Earlier access to adequate health care and awareness of BM in a malaria endemic area would reduce mortality and morbidity. Vaccination against Hib infection would have reduced death by 18 (17%) and prevented sequelae in 7.

Introduction

There is much interest worldwide in the prevention and management of bacterial meningitis (BM). Booy *et al* reported that the incidence of meningitis due to *Haemophilus influenzae* type b (Hib), a major cause of paediatric BM, has been reduced by up to 98% in many parts of the world as a result of the use of Hib vaccine[1]. Vaccine coverage is not universal, however, and BM due to Hib and other organisms continues to be an important paediatric problem requiring good clinical management. There is renewed interest in such therapeutic interventions as the role of steroids as adjuvant therapy, and the ideal fluid regimen in the management of BM.

Descriptive studies of the existing causes and outcome of BM are important so that interventions can be planned and evaluated properly in the light of local data. Another function of such studies is to monitor the changing susceptibilities of bacteria to antibiotics so that current practice can be changed when necessary.

BM is a common cause of serious illness, disability and death in children in Malawi. Borgstein reviewed the BM admissions to the Queen Elizabeth Central Hospital (QECH) in 1982-3 in the only audit previously undertaken[2]. We therefore prospectively studied all the children admitted with BM to the paediatric unit at QECH over a one year period, and analysed the causes, clinical presentation, laboratory findings and outcome in these children.

During the 12 month study period 9,847 children were admitted to the paediatric wards of whom 267 (2.7%) were diagnosed as having BM.

Methods

Demographic and clinical data were collected prospectively on all children admitted from 1st April '96 to March 31st '97 who were suspected of having meningitis and in whom a lumbar puncture was done. A diagnosis of bacterial meningitis was made when a Gram stain of cerebrospinal fluid (CSF) revealed bacterial pathogens, or when culture of CSF yielded a pure bacterial growth. A diagnosis of probable or partially treated meningitis was made if the Gram stain and culture were negative but the CSF white cell count was greater than normal (> 10 WBC/cmm^3 in postneonatal children and >23 WBC/cmm^3 in neonates) and predominantly polymorphs, with an associated increase in protein and decrease in glucose levels. Protein and glucose concentrations were measured semi-quantitatively by dipsticks (Bayer, Multistix 8SG urine strip test).

Antibiotic treatment was started immediately while awaiting the analysis of the CSF. Children over 3 months of age received parenteral chloramphenicol 25mg/kg/dose and benzylpenicillin 50,000 iu/kg/dose each 4 times a day; infants received benzylpenicillin 50,000 iu/kg/dose 8 hourly and gentamicin 2.5mglkg/dose 8 hourly. When bacterial susceptibities to antibiotics were known appropriate modifications were made to therapy if necessary.

Patients' fluid input was aimed to achieve no more than maintenance requirements, Capillary blood glucose was measured by strip test (BM - Test 1-44, Boehringer Mannheim) and repeated in the event of convulsions or deteriorating conscious level. When identified, hypoglycaemia was treated with 50% glucose (1 m/kg) diluted to a 20 or 10% solution and given by intravenous infusion. Data were entered and subsequently analysed using an Epi Info 6 software package.

Results.

Causative organisms

During the study period 1120 lumbar punctures were done and the CSF samples analysed. Of these, 267 children (54% boys) were diagnosed as having BM on the following basis:- organism identified

by culture and Gram stain	136 (50.9%)
by culture only	39 (14.6%)
by Gram stain only	15 (5.6%)
CSF polymorph leucocytosis (with increased protein and decreased glucose levels)	77 (28.8%)
Total diagnosed BM	267 (100%)

Fourteen hospital case notes were incomplete and outcomes were unknown for 7 children.

Table 1 Bacterial meningitis: culture results of 267 cases.

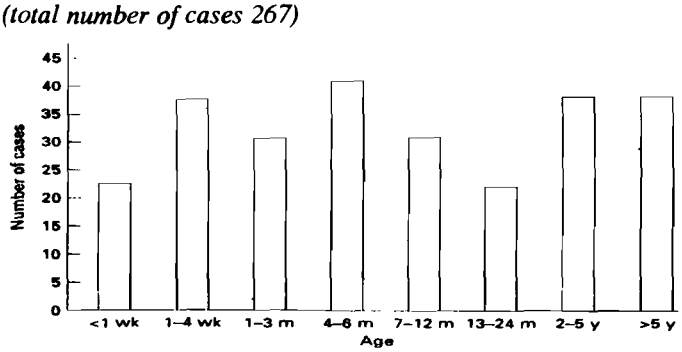
	Number	% of total cases	% of culture positive cases
Streptococcus pneumoniae	62	23.2	35.4
Haemophilus influenzae type b	44	16.5	25.1
*Salmonella species**	21	7.9	12
Streptococcus agalactiae	17	6.4	9.7
E. coli/Klebsiella species	10	3.7	5.7
*Neisseria meningitis***	7	2.6	4
Others†	14	5.2	8
No growth with positive microscopy	15	5.6	—
No growth with negative microscopy	77	28.8	—

†including Listeria monocytogenes, Streptococcus pyogenes, Staphylococcus aureus, Group D streptococci, Pseudomonas species, and Staphylococcus epidermidis. **N. meningitidis group B, 2 N. meningitidis other than groups A, B or C.

Patients with BM presented throughout the year, with a decreased rate of admissions in the hot dry season. The only cases with a distinct seasonal pattern were those caused by *S. typhimurium* of which 50% occurred in May, June and July, the cooler, drier months of the year.

The ages of children with BM ranged from one day to 14 years; 23% were under one month of age, 61 % under one year and 83% under 5 years.

Fig. 1 Age distribution of cases of bacterial meningitis (total number of cases 267)



Overall the four most common bacteria found were *Streptococcus pneumoniae, Haemophilus influenzae* type b (Hib), *Salmonella typhimurium* and Streptococcus agalactiae (Table 1), In the neonatal age group (<l month age, n = 61), the most common bacterial causes were *S. agalactiae 23%, S. typhimurium 15%, S. pneumoniae* 11.5% and 7 cases (11.5%) of other Gram negative rods. In the post-neonatal age group (n = 206) the most common bacterial causes were *S. pneumoniae (27%),* Hib (21 %) and *S. typhimurium (6%). Neisseria meningitidis* was isolated in only 7 cases. In 29% of all cases of BM no bacteria were isolated or seen on microscopy, and, of these, 18% were in children over 5 years of age.

Clinical signs and symptoms

Most children (71%) had a fever ≥ 38°C on presentation, but 25% (67 of 234) were afebrile on admission. (In 14 cases the admission temperature was not recorded). In the neonatal group 19% were afebrile at presentation. The length of history prior to admission was similar in all the post-neonatal groups (1-30 days with a mean of 4.6 days). In the neonatal cases no child was ill with fever for longer than 4 days prior to admission.

One hundred of 253 (39.5%) children in whom the records were complete had convulsed prior to admission. Fifty seven percent had an altered conscious level (Blantyre Coma Score* (BCS) < 5) and 37% of these were unresponsive to pain (BCS ≤ 2) . Irritability was a significant symptom in 63% with vomiting in 31 % and failure to breastfeed or drink in 50%.

Children who are admitted to the paediatric department are not routinely tested for HIV status. Though twenty three patients (9%) had either proven or clinically suspected HIV disease this is probably a considerable underestimate of the problem.

One hundred and sixteen (48.3%, n = 240) were <80% weight for age. Of these 18% (n=21) were <60% weight for age. Thirteen of 19 (68%) of the children with a salmonella infection and 100 of 248 (40%) with a non salmonella infection were <80% weight for age (p=0.03).

Some of the children were anaemic, 54 of 174 children (31 %) who were tested had a haemoglobin concentration (Hb) <8g/dl. In 85 (48.9%) the Hb was <10g/dl. Forty two of 186 children (23%) tested had a positive blood film for malaria parasites, with a variable parasitaemia unrelated to causative organism.

The admitting clinician only included the diagnosis of meningitis in the differential diagnosis in 48% of cases. Other commonly suggested diagnoses were cerebral malaria, pneumonia or sepsis.

* The Blantyre Coma Score (BCS), maximum score = 5, minimum score = 0.

Motor - maximum = 2 (able to localise), 1 = withdraws to pain, 0 = unresponsive.

Eye movement - maximum = 1 (follows), 0 = unresponsive

Voice - maximum = 2 (appropriate response), 1 = inappropriate or groaning, 0 = unresponsive. BCS of 2 is equivalent to Glasgow Coma Score of 8

The 17 *S. agalactiae* infections were all in children under 3 months of age. The 44 Hib infections were all in children under 5 years old with 54% under one year of age. S. *pneumoniae* affected all ages from 6 days to 14 years. With the exception of one 4 year old and one two year old, all salmonela infections (n=21) occurred in children less than one year of age, 43% were in babies aged one month or less. Five of the 7 cases of *N. meningitidis* meningitis were in children older than 1 year (Fig 2).

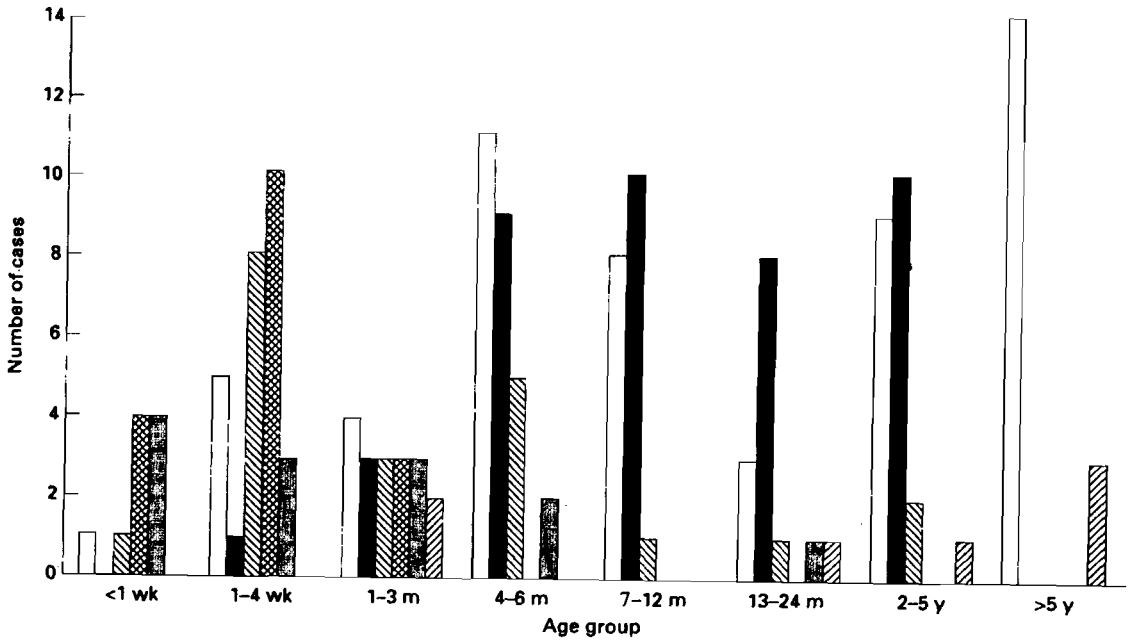


Figure 2: Major meningitis pathogens by age group. □ *S. Pneumoniae;* ▩ *S. agalactiae;* ■ *H. Influenzae;* ▧ *Salmonella;* ▨ *N. meningitidis;* ▩ *Other GNB.*

Fifty nine children (23%) had received antibiotics (usually one or two doses of oral or parenteral penicillin) prior to admission. In the group in whom no causative bacterium was isolated this figure was 50%.

Irritability and failing to suck were prominent symptoms in the younger children. Neck stiffness and irritability were important signs in the older group (Table 2).

Table 2: Symptoms of bacterial mengitis by age group.

	Percentage positivity by age			
Symptom	< 1 month	1-12 months	1-5 years	> 5 years
History of fever	87	89	91	95
Irritable	67	66	56	61
Bulging fontanelle	67	49	16	NA*
Neck stiffness	12	44	63	86
Headache	NA	6	25	78
History of fever <3d	56	53	54	46
BCS <3	30	31	36	47
BCS <4	58	55	51	71
Convulsions	25	42	47	46
Not sucking	72	46	42	37
Vomiting	15	34	44	33

*NA, not applicable.

Over half the patients presented with altered consciousness (BCS ≤ 4 in 57%) and over a third (39%) with convulsions. In the infants with *S. agalactiae* meningitis one third had a reduced coma score and a quarter had a history of seizures. Irritability, failure to suck and fever occurred in 88% of these children.

Outcome

The overall mortality was 40%. There was no significant difference in mortality between the neonatal and postneonatal groups (34% v 41 %). Eighteen children were removed from hospital before they had recovered. In every case this occurred early in the illness when the child was very ill. As these children were unlikely to have survived we have included them in the mortality figures.

The culture negative group (assumed to be partially treated BM, n=75) fared as badly (mortality 37%) as those in whom bacteria were seen or isolated. This group was comparable in age, sex, presentation and length of history with the rest of the children studied. The outcome was worst in the group of patients with salmonella infections (Table 3). Neonates with salmonella meningitis were at particular risk, with a case fatality of 8 out of 9 (89%) cases. Malnourished children with weight for age < 60% (n=21) had a 62% mortality compared with 37% in those >60% weight for age (n = 205), p = 0.02. The best outcome was in the *S.agalactiae and N.meningitidis* groups.

Table 3: Outcomes in acute bacterial meningitis.

Cause	Total Number	Died*	Sequelae
Bacterial meningitis overall	260	104 (40)	24 (9.0)
Strep pneumoniae	59	27 (45.8)	8 (13.6)
Haemophilus influenzae	42	18 (42.9)	8 (19)
Salmonella sp.	21	12 (57.2)	1 (5)
Group B strep	17	2 (11.8)	0
E. coli/Klebsiella sp.	10	3 (30)	2 (20)
No growth and negative microscopy	75	28 (37.3)	3 (4)

*Fatal outcome includes absconders.

Two thirds of the deaths occurred within 72 hours of admission, 29% on the first, 28% on the second and 7% on the third day. Only ten percent of deaths occurred later than one week after admission.

A concomitant malaria parasitaemia did not worsen the prognosis. There was no correlation between the mortality and WBC count in the CSF on admission.

The mortality rate was 64% in those presenting with a coma score of 3 or less; compared with 26% with a better score (p<0.0000004). A history of convulsions did not significantly affect outcome.

Fifteen percent of survivors had sequelae on discharge. In children with Hib infections (n = 42) the proportion of survivors with sequelae was 33% and in S. *pneumoniae* infections (n=59) sequelae occurred in 25% of survivors. Two children with salmonella infections, none with *S.agalactiae* or other Gram negative rod infections, and 4 in the 'no growth' group had sequelae.

Antibiotic susceptibilities

In the *S. pneumoniae* infections 5% were resistant to penicillin and 8% to chioramphenicol. One child who had *S. pneumoniae* meningitis relapsed with an infection which was resistant to both antibiotics. In the Hib infections 20% were resistant to chloramphenicol and 50% to ampicillin. The *S. agalactiae* isolates were all penicillin sensitive though 12% were resistant to chloramphenicol. All the salmonella species were sensitive to chloramphenicol.

Relapses

Six children relapsed with BM.

One salmonella infection recurred two weeks after completion of 14 days antibiotic treament and the child developed hydrocephalus.

A child with a partially treated BM (no growth on presentation) reappeared two months later with similar CSF findings but a positive blood culture for S. *typhimurium.*

An infant whose CSF grew an unidentified unusual gram negative rod responded well to 14 days' therapy, but presented one month later with purulent CSF.

The child with a *S. pneumoniae* infection resistant to chloramphenicol was treated for 10 days with benzylpenicillin and chloramphenicol. After the initial infection she was discharged apparently well, only to return 3 weeks later with a *S. pneumoniae* infection with reduced susceptibility to both benzylpenicillin and chloramphenicol infection. She died 4 days later.

An infant with hydrocephalus, and CSF from which no bacterium was isolated, relapsed with purulent CSF 8 days after completion of antibiotic therapy for the first infection.

A 12 year old girl, who recovered from pneumococcal meningitis, was readmitted a year later (outside the study period), unconscious with periorbital oedema, papilloedema, seizures, fever and a rash. She died within 12 hours of admission. No lumbar puncture was done but blood cultures grew S. *pneumoniae.* A postmortem brain smear showed brain tissue heavily infiltrated by gram positive diploccocci.

Discussion.

Meningitis in children

Bacterial meningitis (BM) remains a large and serious problem in this paediatric population. The number of admissions with this diagnosis over one year has more than doubled since 1982[1], in parallel with a similar increase in overall numbers of hospital admissions. *S pneumoniae* and (HiB) were the predominant agents in BM in both studies.

Salmonella infections

There has been a relative increase in the incidence of BM due to *S typhimurium, with* 2/100 cases in 1982 and 21 of 267 (8%) in 1997. BM due to salmonella was more likely to be fatal than BM due to other organisms (Table 1). The case fatality rate was 57% in cases with salmonella infections and 37% in non salmonella infections.

Over the same 12 month period as the study reported here, salmonella species were the most frequent finding (46% of 297) in positive blood cultures taken from paediatric patients of all ages and with a variety of diagnoses in the same paediatric unit. This increase in salmonella infections may be associated with the rise in the prevalence of HIV which was first recognised in Malawi in 1985.

In a recent audit of BM in 201 children in Cape Town, Hussey *et al (1997)* showed N. *meningitidis* (50%), *H. influenzae* (37%) and *S. pneumoniae* (13%) to be the most common causes of BM in the post neonatal group[3]. Other developing countries in Africa and Asia found similar common causative organisms though in slightly different proportions[4-13]

In Kigali, Rwanda, in 1983-1989[9], salmonella species caused 13% of infections in 681 children < 5 years of age and Chotpitayasunondh reported a significant number of salmonella infections in Bangkok in 1990 to 1994.[13] These figures are similar to those found in our study (Table 4).

***Table 4:** Bacterial causes of paediatric meningitis in various parts of the world*

		Bacteria (%)						
Place	Years	HI	Spn	NM	Salm	GNR	NG	Comments
Dhaka	87-94	47	32	8.1		8.3	31	<5 years, total 852
Kigali	83-90	31	36.5	11.5	13		21	75% <5 years, total 681
Greece	90-94	41	8	51				<5 years not neonates, total
Bangkok	80-94	42	22.2		12.4			0-15 years total 618
Recife	91-92	33	10	27			25	1 mth-16 years, total 179
Islamabad	90-92	22.4	6.7	8.9			44.9	2 mth-12 years, total 89
Blantyre	96-97	16.5	23.2	2.6	7.9	3.7	28.8	0-14 years, total 267
Maputo	91-92	37	8	22.3			26.8	1 mth-16, years total 70
Cape Town	91-92	36.8	12.9	50.2				2 mth-14 years, total 201
P. Moresby	89-90	24	18.5				50.9	Total 108
Dakar	70-79	19.6	28.7	10.7			26.5	> 1 mth, total 3422
USA	86	45	18	14				Multistate, excludes neonates, 82% reduction in HI 85-91

Malnutrition

Nearly half (48%) of the children in our study were <80% weight for age. Those with BM due to salmonella were more commonly malnourished ($^{14}/_{21}$= 67%) than those in other groups (96/239 = 40%). The case-fatality was 51% (58 of 113) in the cases who were < 80% weight for age and 28% (34 of 122) in children whose weight for age was > 80%. A study in Lusaka showed similarly poor outcomes in malnourished children.[14]

Case-fatality

The overall case-fatality and outcome of BM in this hospital remains similar to those reported in 1982 - 40% of patients died in the present series, a further 9% being left with serious neurological sequelae; the figures for 1982 were 36% and 12%. The case-fatality rates (CFR) in children with BM in our study are similar to those reported from other developing countries (Table5).

Table 5: Case fatality rate (and sequelae) for acute bacterial meningitis

	Bacteria						
Place	HI	Spn	NM	Salm	GNR	NG	Overall
Kigali	52		39	38			
Bangkok							45.5 (17.3)[a]
							26.3 (11.4)[b]
Recife							24 (44)
Islamabad							12 (26)
Maputo							36 (29.1)
Blantyre	38.9 (18)	43.5 (13)		57.2 (5)	30 (20)	38 (4.1)	40 (9)
Cape Town	5.3 (20.7)	19.2 (37.5)		1 (8.6)			5
PNG							167 (10)
Dakar	33.5	59.5	13.9			40	44.2
Developed countries	3.8	15.3	7.5				4.8 (17.5)
Resource poor countries							8.1 (27)

Meta analysis by Baraff *et al.* (1993) of 45 reports on 4920, aged 2mth-19years world wide. [a]1980-87, [b]1987-90, all deaths from *S pneumoniae.* HI, *Haemophilus influenzae;* Spn, Streptococcus pneumoniae; NM, *Neisseria meningitidis;* Salm, *Salmonellae* species; GNR, Gram negative rods other than Salm/HI; NG, No Growth.

Sequelae are likely to be underdiagnosed, as only gross abnormalities are recorded on discharge, follow-up is erratic and no detailed tests of hearing or learning ability are done.

Countries with poor outcomes all have several similar circumstances that may contribute to this. There is delay in presentation, leading to longer histories of fever on presentation. Children are referral of children with BM to hospital.

Conclusions

Meningitis remains a devastating illness in which there has been little improvement in outcome over the last thirteen years in children admitted to our hospital. There is a clear need to teach moth-

Table 6: Selected features influencing management and outcome for children with ABM in developing countries

	Delay in presentation				
Location	Fever (days)	Coma (% at presentation)	Seizures	Nutrition	Anaemia
Dakha	5.7	Drowsy 43%	47%		
		Coma	12%		
Blantyre	4.6	BCS < 556.8%	39.5%	48.3%<80% W/A	48.9%<10g/dl
		BCS < 219%		38.3%<60% W/A	14.2%<8g/dl
Cape Town	2.29	Stupour/coma 13.9%	20.4%	23%<80% W/A	53%<10g/dl
Maputo	2.47	Coma 12.9%	64%		
Egypt	3-5	Coma 60%			
Recife	>3 (51%)	Coma moderate 50%	30.1%	15% Mild	
		severe 6.7%		7%	
PNG	>3 days (44%)	Coma 16.6%		25.9% < 80% W/A	45%<10g/dl
				3.7% < 60% W/A	21% < 8g/dl
Blantyre	9% proven or suspected of HIV (no routine done)				
	22.6% parasitaemic on presentation				
Lusaka	14 of 75 tested were sickle test positive 10 AS and 4 SS				

more severely ill, with a significant number having had seizures prior to admission, or being found to have altered consciousness on arrival (Table 6) the presence of coma being associated with a poor outcome in this as in other studies.

Pre-treatment

Many children are given injections or pills prior to admission. Injections are usually from a health worker but pills may have been acquired in the market. Pre-treatment may be the reason why no bacteria were isolated in 29% of cases. We assumed that these children were partially treated prior to admission. The mortality in this group is nevertheless high (38%).

Neisseria meningitidis

Few cases of *N. meningitidis* were seen in our study. It may be that this agent is currently uncommon in southern Malawi; alternatively *N. meningitidis infections* may respond rapidly to self-administered antibiotics - several of the organism-negative cases of pyogenic meningitis may have been due to this agent. Some meningococcal infections may progress too rapidly for patients to reach hospital.

Malaria

Concomitant infections of malaria and meningitis occurred in 42 of 186 tested children. The presence of malaria parasitaemia in association with meningitis did not influence the mortality but may have contributed to the difficulties in diagnosis that the junior admitting doctors experienced. Malaria is so common that even medical attendants are liable to miss meningitis and assume the cause of acute neurological manifestations is malaria. The mortality rate was similar in the children in whom meningitis was suspected at admission to hospital and those in whom the diagnosis was initially unrecognised. Nevertheless a mistaken diagnosis of malaria is likely to contribute to delays both by parents and health workers in the initiation of correct treatment for BM and ers and carers to seek medical help quickly when a child is ill; and also for clinicians to be wary of missing cases of meningitis where malaria is endemic.

One fifth of Hib infections were resistant to chloramphenicol, and all are resistant to penicillin. The first line antibiotic therapy for meningitis is under review.

The introduction of the Hib vaccine into the routine immunisation schedule would have reduced the number of meningitis cases by 42 (16%), deaths by 18 (17%), and prevented sequelae in 8 children. A totally effective pneumococcal vaccine would have reduced the number of cases by 59 (22%) and of sequelae by 8 (33%).

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