5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study

*Elizabeth Molyneux, Shaikh Qamaruddin Nizami, Samir Saha, Khanh Truong Huu, Matloob Azam, Zulfiqar Ahmad Bhutta, Ramadan Zaki, Martin Willi Weber, Shamim Ahmad Qazi, for the CSF 5 Study Group**

Summary

Background **Bacterial meningitis is an important cause of morbidity and mortality in developing countries, but the duration of treatment is not well established. We aimed to compare the efficacy of 5 and 10 days of parenteral ceftriaxone for the treatment of bacterial meningitis in children.**

Methods **We did a multicountry, double-blind, placebo-controlled, randomised equivalence study of 5 versus 10 days of treatment with ceftriaxone in children aged 2 months to 12 years with purulent meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, or *Neisseria meningitidis*. Our study was done in ten paediatric referral hospitals in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam. We randomly assigned children who were stable after 5 days of treatment, through site-balanced computer-generated allocation lists, to receive a further 5 days of ceftriaxone or placebo. Patients, their guardians, and staff were masked to study-group allocation. Our primary outcomes were bacteriological failure or relapse. Our analysis was per protocol. This study is registered with the International Standard Randomised Controlled Trial Number Register, number ISRCTN38717320.**

Findings **We included 1004 of 1027 children randomly assigned to study groups in our analyses; 496 received treatment with ceftriaxone for 5 days, and 508 for 10 days. In the 5-day treatment group, two children (one infected with HIV) had a relapse; there were no relapses in the 10-day treatment group and there were no bacteriological failures in either study group. Side-effects of antibiotic treatment were minor and similar in both groups.**

Interpretation **In children beyond the neonatal age-group with purulent meningitis caused by *S pneumoniae*, *H influenzae* type b, or *N meningitidis* who are stable by day 5 of ceftriaxone treatment, the antibiotic can be safely discontinued.**

Funding **United States Agency for International Development.**

Lancet 2011; 377: 1837–45

Published Online May 26, 2011 DOI:10.1016/S0140-6736(11)60580-1

See Comment page 1809

*See webappendix for study contributors

University of Malawi Medical School Department of Paediatrics, Queen Elizabeth Central Hospital, Blantyre, Malawi (Prof E Molyneux FRCPCH); **Division of Maternal and Child Health, Aga Khan University, Karachi, Pakistan** (Prof S Q Nizami FCPS, Prof Z A Bhutta FRCPCH); **Department of Microbiogy, Dhaka Shishu Hospital, Dhaka, Bangladesh** (Prof S Saha PhD); **Children Hospital No 1, Ho Chi Minh City, Vietnam** (Prof K T Huu MD); **Department of Paediatrics, Wah Medical College, Islamabad, Pakistan** (Prof M Azam FRCPCH); **Department of Paediatrics, Abbasia Fever Hospital, Cairo, Egypt** (Prof R Zaki MD); **and Department of Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland** (M W Weber DrMedHabil, S A Qazi MD)

Correspondence to: Dr Shamim Ahmad Qazi, Department of Child and Adolescent Health and Development, World Health Organization, 20 Avenue Appia, Geneva 27, 1211, Switzerland **qazis@who.int**

Introduction

Bacterial meningitis is an important cause of morbidity and mortality in children in developing countries.[1,2] Prospective hospital-based and population-based studies in Latin America, Africa and, most recently, Asia have shown that *Haemophilus influenzae* and *Streptococcus pneumoniae* are the leading causes of bacterial meningitis in young children.[2–7] Worldwide, *H influenzae* type b causes about 173 000 cases of meningitis every year in children younger than 5 years (uncertainty range 85 300–226 000) and an additional 103 000 cases are caused by *S pneumoniae* (51 000–131 000).[8,9]

The mortality from meningitis is close to 100% in untreated individuals and is still up to 40% in children who receive appropriate antibiotic treatment in developing countries.[10,11] Most of these fatalities are within 72 h of admission to hospitals, and a high proportion of survivors have neurological sequelae.[2–6]

Early identification and prompt antibiotic treatment are essential for reducing mortality and morbidity. Standard treatment for meningitis has been chloramphenicol, often in combination with penicillin. However, pneumococcal resistance to penicillin is increasing worldwide, limiting the usefulness of this antibiotic for empirical treatment of meningitis, and in Africa resistance is increasing against both antibiotics.[12–15] In most regions, fewer than 1% of bacterial strains are highly resistant to both penicillin and third-generation cephalosporins.[16,17]

Third-generation cephalosporins given to children with bacterial meningitis result in rapid sterilisation of the cerebrospinal fluid in almost all patients.[18,19] Ceftriaxone is a highly effective antibiotic for treatment of meningitis, and it is the recommended treatment in many countries, but the optimum duration of treatment is uncertain and recommendations have varied.[20]

The duration of treatment of bacterial infection in general, and of meningitis specifically, is not based on solid evidence.[11,21] For meningitis, the duration of antibiotic treatment is long and often continued in children with neurological sequelae, even though viable bacteria are no longer present, because the treating physician fears stopping prematurely. This prolonged treatment leads to unnecessary costs and potential side-effects related to admission to hospital, so it is not in the interest of the patient, the family, or the health system. The recommended duration of treatment is

7–10 days for meningitis due to *H influenzae* type b, 10–14 days for *S pneumoniae* meningitis, and 7 days for *Neisseria meningitidis* meningitis.[22,23]

Antibiotic treatment courses as short as 3–5 days are effective in children and adults with meningitis due to *N meningitidis*.[24–27] Some studies with small sample sizes have shown that shorter courses of antimicrobial treatment also cure bacterial meningitis due to *H influenzae* and *S pneumoniae* without increased rates of relapse or neurological sequelae.[28–36] An effective shorter antibiotic treatment regimen for serious childhood infections such as bacterial meningitis would make the use of more expensive antibiotics feasible and cost effective. We aimed to compare 5 with 10 days of treatment with parenteral ceftriaxone for bacterial meningitis in children.

Panel 1: **Study criteria for enrolment and diagnosis**

Exclusion criteria at enrolment

- Children aged 2 months or younger or bodyweight 3 kg or less
- Pre-existing neurosurgical conditions
- Seizure disorders, cerebral palsy, degenerative neurological disorders
- Cranial fractures
- Known immunodeficiency states, symptomatic AIDS
- Active viral infections
- Known hypersensitivity to cephalosporins
- Cyanotic congenital heart disease
- Previous random assignment in this study (child could not be randomly assigned on more than one occasion)
- Inaccessibility for follow-up
- Previous use of any parenteral antibiotics for 24 h before admission

Exclusion criteria for random assignment at day 5

Children were not randomly assigned to treatment groups if they met any criteria listed above or those listed below

- Meningitis due to any bacteria other than *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*
- Persistence of or growth of an organism from cerebrospinal fluid taken 48–72 h after admission
- Isolated organism resistant to ceftriaxone
- Serious adverse reaction to the drug given
- Presence of pyogenic brain abscess, subdural empyema, or intracranial suppurative thrombophlebitis
- Child developing another infection during admission to hospital that needed another injectable antibiotic

Diagnostic criteria for bacterial meningitis (any one of the four)

- Positive cerebrospinal-fluid culture or latex agglutination for *H influenzae*, *S pneumoniae*, and *N meningitidis*
- More than 10 white blood cells per mL of cerebrospinal fluid, with positive blood culture for the same organisms by day 3 of admission
- Cerebrospinal-fluid culture and latex agglutination both negative, but more than 100 white blood cells per mL with more than 50% granulocytes and cerebrospinal-fluid glucose less than 50% of blood glucose or less than 1·66 mmol/L
- More than 1000 white blood cells per mL of cerebrospinal fluid with 75% polymorphonuclear cells

Methods

Participants

Between September, 2001, and December, 2006, we did a multicountry, double-blind, placebo-controlled, randomised equivalence study of 5 versus 10 days of treatment with ceftriaxone in children aged 2 months to 12 years with purulent meningitis caused by *S pneumoniae*, *H influenzae* type b, or *N meningitidis*. Our study was done in ten paediatric referral hospitals in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam. These hospitals serve large populations and each admits more than 150 children with bacterial meningitis every year. Overall, *H influenzae*, *S pneumoniae*, and *N meningitidis* are the most common causes. Admitting clinicians at each hospital did lumbar punctures on children in whom bacterial meningitis was suspected clinically or in whom it needed to be excluded. On admission all these children had a complete history taken and were fully examined and weighed. The lumbar puncture was done and, if meningitis was suspected, intravenous access was established; blood samples were taken for full blood count, malaria parasites (thick film), plasma glucose, electrolytes (if possible), and blood culture; and treatment was started with ceftriaxone. All children underwent a second lumbar puncture 48 h after starting treatment (after two doses of intravenous ceftriaxone). If this second sample of cerebrospinal fluid still contained bacteria, the child was excluded from random assignment. Supportive management of fever, convulsions, fluid management, and feeding were in accordance with local treatment guidelines. Children alive on day 5 and those who were clinically stable or improving were considered for inclusion in our study. Panel 1 lists the exclusion criteria for the study and diagnostic criteria for bacterial meningitis.

We obtained written informed consent from parents or legal guardians. Separate consent was obtained for HIV testing with full counselling before and after. Our study was approved by the local institutional ethical review boards of the participating institutions in countries and WHO. Our study was monitored by an independent data and safety monitoring board (DSMB). All deaths and serious adverse events were reported to the DSMB. The DSMB met yearly to review the safety aspects of the study.

Procedures

Randomisation was done by site in permuted blocks of variable length of two, four, and six by a one-to-one ratio to the 5-day or 10-day treatment groups. The list was prepared and kept at WHO headquarters, Geneva, Switzerland. At each site, the treatment allocations were in sealed opaque envelopes, each with a unique study number held by a designated person. This person was not involved in the clinical care of the patients and prepared the study drugs daily for each patient. The syringe containing the drug was masked by an opaque sticker (because ceftriaxone has a faint yellow tinge and the placebo was colourless). The clinicians giving the

treatment, nurses, and patients were unaware of the contents of each syringe provided for each patient. Parenteral ceftriaxone (80–100 mg/kg bodyweight) was given once daily for 5 days before random assignment to the study groups. On day 5 after the start of treatment, enrolment criteria were reviewed, and eligible patients were randomly assigned to receive either ceftriaxone or placebo.

Our primary endpoint was the rate of bacteriological failure defined as positive cultures of cerebrospinal fluid or blood on days 6–40 for the originally identified organism or for *H influenzae*, *S pneumoniae*, or *N meningitidis* on days 6–40 in a patient from whom the first sample of cerebrospinal fluid had been culture negative. Our secondary endpoints were death and hearing, neurological, or visual sequelae at any time during the study.

All study staff were trained in study procedures and documentation. Patients were assessed daily and a study form was completed for each day, at discharge on day 10, and at each follow-up visit at which all children were assessed for hearing, visual, developmental, and neurological outcomes. After discharge, patients were reviewed on day 40 and day 190 after enrolment into our study, when full physical, neurological, and hearing assessments were done. Unscheduled visits were recorded and patients were managed in accordance with clinical need. Patients who did not keep their appointments were traced at home and encouraged to return for follow-up. If children were not found they were declared lost to follow-up.

Hearing was assessed by trained staff with otoacoustic emissions tests and at some centres by auditory brainstem response. All children were subsequently tested with age-appropriate hearing tests on the two scheduled follow-up visits (days 40 and 190). Hearing loss was classified in accordance with the International Classification of Impairments, Activities and Participation[37] as mild (26–40 dB), moderate (41–60 dB), severe (61–80 dB), and profound (>80 dB), and those identified with moderate to severe hearing loss were referred to local audiological services for management. Children were screened by age-appropriate tests for high-grade visual impairment, and those suspected of having any impairment were referred for an ophthalmological opinion. Neurological and developmental status was assessed and recorded by trained clinicians. The age and stages questionnaire[38] was used to assess development and the score was used to quantify delayed development in personal and social interactions, fine motor movements, gross motor movements, and competency in the use of language.

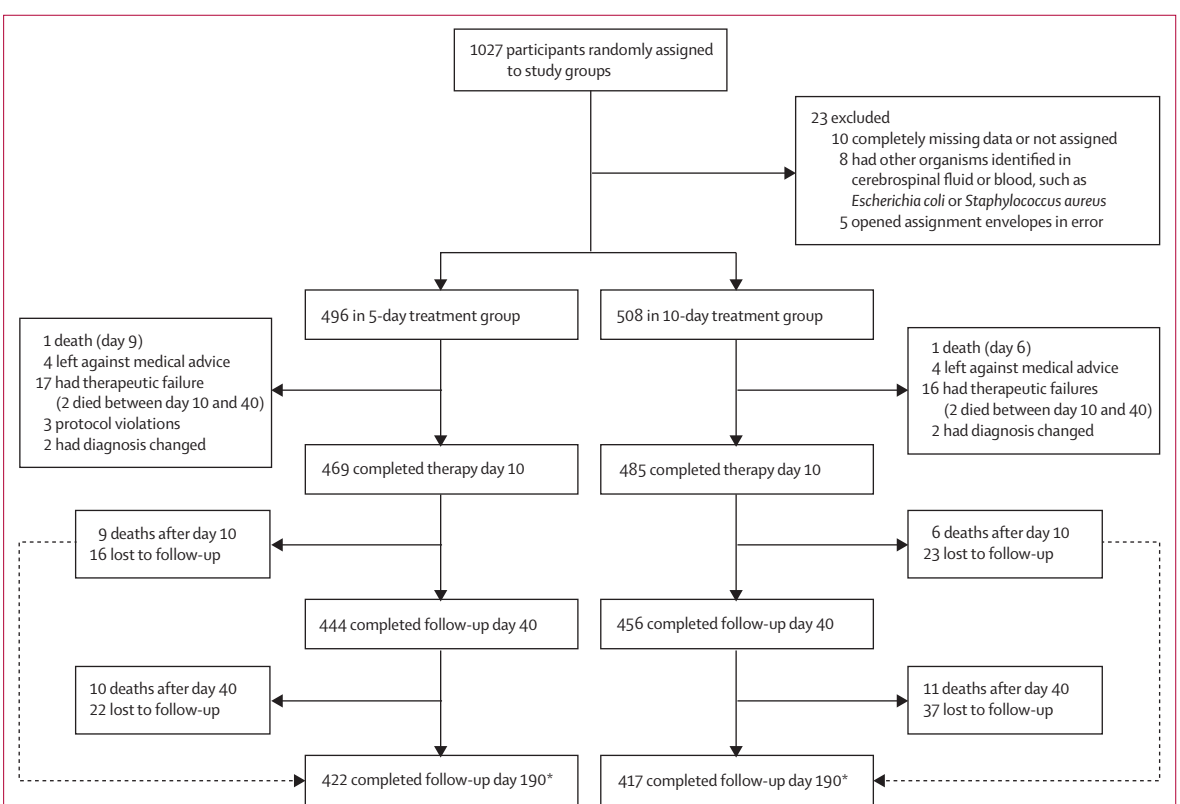

Figure: **Trial profile**
*Of the participants who were lost to follow-up at day 40, 19 patients (ten from the 5-day group and nine from 10-day group) were followed up at day 190; one patient from the 10-day group died after day 40.

***Panel 2:* Details of children not randomly assigned to study groups**

- 2000 children recruited on day 0*
- 180 did not have bacterial meningitis
  - 68 had blood in their cerebrospinal fluid
  - 42 had viral meningitis
  - 26 had encephalitis
  - 23 had tuberculous meningitis
  - 20 had epilepsy
  - One had candida meningitis
- 269 died before they were assigned to study groups
- 1551 children with bacterial meningitis were alive on day 5
  - 39 did not give consent
  - 18 left against medical advice
  - 42 lived outside the study area
  - 167 received antibiotics before admission
  - 47 were ill for more than 7 days before admission
  - 13 had previous cerebral palsy or were deaf
  - 16 had a neurosurgical disability
  - Three had a subdural abscess
  - 15 had other infections that needed other antibiotics or continued ceftriaxone (four with cellulitis, one with septic arthritis, one with empyema, nine with pneumonia)
  - Three had bacterial persistence
  - Two had cyanotic heart disease
  - 80 had other bacterial causes (70 had non-typhoidal *Salmonella* spp, five had α-haemolytic streptococci, one had *Escherichia coli*, two had *Salmonella typhi*, and two had *Acinetobacter* spp)
- 73 were judged by the treating physician as too sick to assign to a study group
  - 22 had persistent or difficult to control seizures and fever on day 5
  - 28 had persistence of fever on day 5
  - 19 had persistent seizures with no fever on day 5
  - Four had deteriorating level of consciousness (two with seizures)
- Six had no reason given for exclusion by treating physician
- 1027 were randomly assigned to treatment groups
- 23 were excluded after assignment
- 1004 were included in the per-protocol analysis

*Although persistence of convulsions or fever on day 5 were not study exclusion criteria, the treating physician (who could be different than the investigator) felt the child should not be randomly assigned to study groups.

	Number of children enrolled (%)	Dates of study accrual
Bangladesh (Dhaka Shishu Hospital, Dhaka)	175 (17%)	November, 2002, to December, 2006
Egypt (Abbasia Fever Hospital, Cairo)	50 (5%)	January, 2005, to December, 2006
Malawi (Queen Elizabeth Central Hospital, Blantyre)	366 (37%)	July, 2002, to December, 2006
Pakistan (Liaquat University Hospital, Hyderabad; Civil Hospital, Karachi; Department of Paediatrics, Aga Khan University, Karachi; National Institute of Child Health, Karachi)	153 (15%)	September, 2001, to December, 2006
Pakistan (Children Hospital, Pakistan Institute of Medical Sciences, Islamabad; Rawalpindi General Hospital, Rawalpindi)	96 (10%)	September, 2001, to December, 2006
Vietnam (Children's Hospital N°1, Ho Chi Minh City)	164 (16%)	September, 2001, to December, 2006

***Table 1:* Enrolment by study site for random assignment on day 5**

After random assignment, if the child developed a new fever (>38°C), or had persistent convulsions or a deteriorating coma score, we judged that the study treatment had failed and changed it or added to it in accordance with hospital guidelines. We made efforts to identify any intracranial complications, by cranial ultrasound where possible and CT scan when available. We classified children who returned with signs of meningitis within 2 weeks of discharge as having relapsed, and treated them in accordance with hospital guidelines. If a parent withdrew consent, or the protocol was violated, we withdrew the child from the study but continued to treat them with unmasked ceftriaxone to complete a 10-day course. Four monitoring visits, either by WHO internal monitors or independent external monitors, were made to each site to ensure protocol compliance, data management, and good clinical practice.

Samples (blood, cerebrospinal fluid, or both) were obtained aseptically before giving the antibiotic. Samples were labelled and immediately sent to the laboratory. Blood specimens were inoculated in trypticase soy broth with 0·25% sodium polyethanol sulphonate and incubated at 37°C for 7 days. Inoculated broths were subcultured on blood and chocolate agar plates on days 2, 3, and 7. Specimens of cerebrospinal fluid were cultured directly onto blood and chocolate agar plates and incubated at 37°C for 72 h. Specimens of cerebrospinal fluid that were negative by culture were tested for antigens of five common organisms (*H influenzae* type b, *S pneumoniae*, *N meningitidis*, group B streptococci, and *Escherichia coli*) with latex-agglutination reagents in accordance with manufacturer instructions. The latex-agglutination test was done only if the gram stain and culture of cerebrospinal fluid were negative by day 2. Isolates were identified with standard procedures.[39] Susceptibility testing was done with antimicrobial drugs with E-test after the standard procedure described by the Clinical Laboratory Standard Institute.[40] For HIV, serum samples were tested by at least two tests: Serodia-HIV particle agglutination (Fujirebio Inc, Tokyo, Japan), HIVSPOT (Genelabs Diagnostics, Singapore), Determine-HIV (Abbott Laboratories, Abbott Park, IL, USA), and Capillus-HIV (Cambridge Diagnostics, Galway, Ireland). Discordant tests were confirmed either by a third test or an in-house HIV PCR. Children younger than 15 months with a positive antibody test were confirmed with the HIV PCR.

Statistical analysis

We calculated the study sample size on the basis of an a-priori definition of equivalence of up to 1·5% difference of proven bacteriological failure up to day 40. The investigators' tolerance was for an increase from 0·5% to 2·0% of bacteriological proven treatment failures as a statement of equivalence. We estimated the sample size to be 1400 patients, 700 in each group (one-sided α of 0·05, power of 80%). We did two interim

safety and efficacy analyses, the first after one-third of patients had been enrolled and the second after two-thirds had been enrolled.

Our analysis was per protocol, which is suitable for equivalence trials. We stratified baseline characteristics by treatment groups to look for differences in the severity and characteristics of presenting illnesses. We summarised study variable with proportions, mean, median, and IQRs. We tested for equivalence between the two treatments by calculating the risk difference and two-sided 95% CI for the primary and secondary outcomes. We used SPSS (version 16) and Stata (version 11) for analysis. This study is registered with the International Standard Randomised Controlled Trial Number Register, number ISRCTN38717320.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SAQ and MWW, as employees of WHO, were involved in study design, collating analyses and interpretation of data, and writing of the report. The writing committee had full access to all the data in the study, and the principal investigators, SAQ and MWW, had final responsibility for the decision to submit for publication.

Results

The figure shows the trial profile. Panel 2 lists the details of children not randomly assigned to study groups. Table 1 shows the accrual of patients by site and table 2 lists the patients' baseline characteristics. 20 enrolled children had a positive second culture of cerebrospinal fluid. 17 were caused by *Salmonella* spp, two by *S pneumoniae* (who died before day 5), and one by *H influenzae* type b. Mean age at presentation was 38 months. On average children were ill for 4 days before enrolment.

Table 3 lists the outcomes of our study. There were no bacteriological failures with either 5-day or 10-day treatment. The proportion of children that completed treatment was similar between the two groups (figure). Treating physicians judged that treatment had failed in 33 children, equally divided in the two therapeutic groups. Four children were diagnosed with tuberculous meningitis. After discharge, 23 children had another episode of meningitis (table 3), of which two were classified as relapse (one child was infected with HIV) since the episodes were caused by the same organism within 2 weeks of discharge. Of 919 children seen on either day 40 or day 190, 140 had moderate or severe hearing loss, 14 had visual loss, and 51 other neurological sequelae (table 3). 16 children had both neurological and moderate to severe hearing loss. 41 children died within the 190 day study period (webappendix p 5), including two during admission to hospital, but only 15 deaths were related to the episode of meningitis for which they had been admitted. There was no statistical difference in study outcomes between the two groups whether as a whole or when analysed separately by bacterial cause (table 3). In children with pneumococcal meningitis, survival with sequelae was more common in the 10-day than the 5-day group (p=0·59; table 3). Of the 21 children with pneumococcal meningitis who died, 15 were infected with HIV: ten in the 5-day group and five in the 10-day group (p=0·6).

By day 40 after discharge, 39 children had been lost to follow-up, nine children had died in the 5-day group, and

	5-day treatment group	10-day treatment group
Number of boys	285 (58%)	280 (55%)
Age (months)	38·6 (42·5); 16 (6–61)	37·8 (41·6); 17 (6–61)
Presenting features		
Irritability	287 (58%)	288 (57%)
Duration of illness before admission (days)	3·8 (3·8); 3 (2–5)	3·5 (2·3); 3 (2–4)
Antibiotic use in previous 48 h	128 (26%)	138 (27%)
Drowsiness	229 (46%)	252 (50%)
Vomiting	291 (59%)	289 (57%)
Poor feeding	335 (68%)	340 (67%)
Seizures	262 (53%)	266 (52%)
Weight for age less than –3 Z score	37 (8%)	47 (9%)
Temperature (°C)	38·3 ± 1·0	38·4 ± 0·9
Systolic blood pressure (mm Hg; n=963)	97·1 (15·2); 100 (90–107)	97·7 (14·6); 100 (90–110)
Glasgow coma score (n=454)	12·6 (2·8); 13 (11–15)	12·9 (2·5); 14 (11–15)
Blantyre score (n=615)	4·1 (1·2); 5 (3–5)	4·1 (1·2); 5 (3–5)
Todd-Herson meningitis score (n=669)	3·7 (1·8); 3 (2·5–5)	3·6 (1·9); 3 (2–5)
Laboratory data		
Glucose in cerebrospinal fluid (mg/dL)*	32·6 (53·3); 15 (0–42·9)	36·1 (57·8); 18 (0–50)
Protein in cerebrospinal fluid (mg/dL)	214·0 (164·0); 200 (98–300)	207·5 (179·1); 200 (90–300)
Haemoglobin <6 g/dL	23 (5%)	41 (8%)
Haemoglobin 6–9 g/dL	201 (41%)	190 (37%)
Haemoglobin >9 g/dL	263 (53%)	265 (52%)
Total leucocyte count per µL (n=968)	17 861 (18 593); 13 700 (9475–20 000)	16 314 (11 279); 14 000 (9975–20 225)
Blood glucose <60 mg/dL	58 (12%)	52 (10%)
Blood glucose 60–79 mg/dL	73 (15%)	66 (13%)
Blood glucose ≥80 mg/dL	341 (69%)	361 (71%)
Cerebrospinal fluid culture positive†	227 (46%)	240 (47%)
Cerebrospinal fluid latex-agglutination test positive†	155 (31%)	143 (28%)
Cerebrospinal fluid gram stain (gram-negative bacillus, gram-positive cocci, gram-negative cocci)	188 (38%)	188 (37%)
Blood culture positive†	100 (20%)	100 (20%)
Bacteria identified by either means (significant clinically)†	334 (67%)	340 (67%)
Infected with HIV‡	51 (10%)	66 (13%)

Data are n (%) or mean (SD); median (IQR). *Glucose in cerebrospinal fluid in one centre was checked by urine dipstick method. †Positive for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitides*. ‡HIV-positive patients only reported from Malawi.

Table 2: **Baseline comparison between study groups**

See Online for webappendix

	5-day treatment group (n=496)	10-day treatment group (n=508)	Total	Risk difference (%; 95% CI)
Overall outcomes for all children				
Therapy successfully completed (10 days)	469 (95%)	485 (96%)	954	−0·92 (−3·6 to 1·8)
Antibiotic therapy modified after random assignment or therapy failure	17 (3%)	16 (3%)	33	0·3 (−1·9 to 2·5)
Changed diagnosis (to tuberculous meningitis)	2 (0%)	2 (0%)	4	0·009 (−0·7 to 0·7)
Adverse events to the study drug	0	0	0	..
Bacteriological failures	0	0	0	..
Another episode of meningitis	8 (2%)	13 (3%)	21	−0·95 (−2·7 to 8·2)
Relapse of meningitis	2 (0%)	0	2	−0·4 (−0·15 to 0·96)
Deaths related to meningitis only*	9 (2%)	6 (1%)	15	0·63 (−0·87 to 2·1)
Deaths due to any reason after cure (until follow-up at 6 months after enrolment)	22 (4%)	19 (4%)	41†	0·69 (−1·8 to 3·1)
Survival with sequelae	129 (26%)	138 (27%)	267	−1·2 (−6·6 to 4·3)
Hearing loss	105 (21%)	106 (21 %)	211	0·3 (−4·7 to 5·3)
Moderate or severe unilateral	22 (4%)	23 (5%)	45	0·09 (−2·7 to 2·5)
Moderate or severe bilateral	50 (10%)	45 (9%)	95	1·2 (−2·4 to 4·8)
Visual loss	4 (1%)	10 (2%)	14	−1·2 (−2·6 to 0·3)
Neurological sequelae including motor deficit, nerve palsies	21 (4%)	30 (6%)	51	−1·7 (−0·43 to 1·03)
Motor deficit	20 (4%)	29 (6%)	49	−1·6 (−4·3 to 0·98)
Cranial nerve palsy	4 (1%)	4 (1%)	8	0·02 (−1·1 to 1·1)
Afebrile seizures	3 (1%)	5 (1%)	8	−0·4 (−1·5 to 0·7)
Hydrocephalus	2 (0%)	6 (1%)	8	−0·8 (−1·9 to 0·3)
Developmental delay	25 (5%)	33 (7%)	58	−1·5 (−4·3 to 1·4)
Study outcomes by cause				
Streptococcus pneumoniae	n=154	n=181	n=335	
Death due to any reason after cure (all deaths)	12	9	21	2·8 (−2·5 to 8·1)
Survival with sequelae (all)	54	72	126	−4·7 (−15·1 to 5·7)
Antibiotic therapy modified after random assignment or therapy failure	2	3	5	−0·4 (−2·9 to 2·2)
Haemophilus influenzae	n=134	n=132	n=266	
Death due to any reason after cure (all deaths)	4	5	9	−0·8 (−5·1 to 3·5)
Survival with sequelae (all)	33	31	64	1·1 (−9·1 to 11·4)
Antibiotic therapy modified after random assignment or therapy failure	6	5	11	0·6 (−4·1 to 5·5)
Neisseria meningitidis	n=46	n=27	n=73	
Death due to any reason after cure (all deaths)	1	0	1	2·2 (−2·0 to 6·4)
Survival with sequelae (all)	6	3	9	1·9 (−13·4 to 17·3)
Antibiotic therapy modified after random assignment or therapy failure	1	0	1	2·1 (−2·0 to 6·3)
No cause identified	n=162	n=168	n=330	
Death due to any reason after cure (all)	5	5	10	0·1 (−3·6 to 3·8)
Survival with sequelae (all)	36	32	68	3·2 (−5·6 to 11·9)
Antibiotic therapy modified after random assignment or therapy failure	8	8	16	0·2 (−4·5 to 4·8)

*Decision about the association with meningitis was made after all deaths were reviewed by the data and safety monitoring board. Six in the 5-day group and one in the 10-day group were infected with HIV. †Of the 41 deaths, 25 were of children infected with HIV: 12 in the 5-day group and 13 in the 10-day group. All of children infected with HIV were in Malawi, eight of them with another episode of meningitis.

Table 3: **Outcomes by study group**

	5-day treatment group	10-day treatment group	Total
Positive culture of cerebrospinal fluid	227 (46%)	240 (47%)	467 (47%)
Haemophilus influenzae type b	85 (17%)	85 (17%)	170 (17%)
Streptococcus pneumoniae	115 (23%)	140 (28%)	255 (25%)
Neisseria meningitidis	27 (5%)	15 (3%)	42 (4%)
Latex agglutination test of cerebrospinal fluid	155 (31%)	143 (28%)	298 (30%)
H influenzae type b	79 (15%)	72 (14%)	151 (15%)
S pneumoniae	49 (10%)	56 (11%)	105 (11%)
N meningitidis	27 (5%)	15 (3%)	42 (4%)
Gram stain of cerebrospinal fluid			
Gram-negative bacilli	55 (11%)	51 (10%)	106 (11%)
Gram-positive cocci	110 (22%)	123 (24%)	233 (23%)
Gram-negative cocci	23 (5%)	14 (3%)	37 (4%)
Blood culture			
Positive for any study organism	100 (20%)	100 (20%)	200 (20%)
Negative for any study organism	363 (73%)	376 (74%)	739 (74%)
H influenzae type b	43 (9%)	37 (7%)	80 (8%)
S pneumoniae	49 (10%)	55 (11%)	104 (10%)
N meningitidis	8 (2%)	8 (2%)	16 (2%)
Organism identified by any test*	334 (67%)	340 (67%)	674 (67%)
H influenzae type b	134 (27%)	132 (26%)	266 (27%)
S pneumoniae	154 (31%)	181 (36%)	335 (33%)
N meningitidis	46 (9%)	27 (5%)	73 (7%)

*Positive by cerebrospinal fluid, blood culture, or latex agglutination test, or gram-negative diplococcic on gram stain.

Table 4: **Organisms identified at the time of enrolment by treatment**

six died in the 10-day group (figure). By day 190, a further 59 were lost to follow-up, ten children died in the 5-day group, and 11 died in the 10-day group. The causative bacteria were identified by culture of cerebrospinal fluid, latex-agglutination test, gram stain, or blood culture in 674 cases (table 4). *S pneumoniae* was the most common organism identified.

The DSMB recommended stopping the study after the second interim analysis, because a difference was unlikely to be found between the treatment groups within the projected sample size. At stoppage more than 1000 children had been enrolled. A preplanned sample size calculation had shown that this would provide equivalence limits of 4–7% for death and 0·5–2·4% for bacterial failures.

Dexamethasone was given at some sites: 437 of 1004 children received dexamethasone on the first day of antibiotic treatment; 428 received it for 2 days, 292 for 3 days, and 140 for 4 days. It was routine practice to give dexamethasone at all sites except Malawi; however, even where it was routine practice not all patients received it. 209 of 496 children in the 5-day group received dexamethasone compared with 228 of 508 in the 10-day group. Previous administration of dexamethasone did not affect the outcome in the patients overall or in either study group. Side-effects of antibiotic treatment were minor and similar in both groups.

Discussion

Our findings show that further antibiotic treatment is not needed in children beyond the neonatal age-group with purulent bacterial meningitis caused or presumably caused by one of the three major pathogens, and in whom the clinical condition is stable or improving by day 5 of treatment with ceftriaxone. Both death and long-term sequelae are the consequence of inflammatory and ischaemic neural damage,[41] which peak before or in the early stages of antibiotic treatment. Early diagnosis and prompt use of antibiotics are probably more important in reducing the mortality and morbidity than an extended antibiotic treatment regimen. Studies of short versus long duration of treatment with antibiotics have shown no difference in outcome (panel 3).

Most clinicians are particularly concerned about adequate treatment of meningitis caused by *S pneumoniae*, a notoriously difficult pathogen to eliminate. It is notable that the outcome of the subgroup of cases with proven pneumococcal meningitis is similar in the two treatment groups in our study.

Hearing deficit is one of the most common complications of bacterial meningitis and can vary from 5% to 36% in survivors.[43–47] Deficit was similar between our study groups during and by the end of our study. We expected this finding because we believe that the hearing deficit is due to cochlear damage caused by the infection and the host's inflammatory response, and by the time of random assignment on day 5, this damage had already been done. Similarly, neurological deficits including developmental delay, quadriplegia, and isolated cranial-nerve palsy, or any of these in combination, happened in a similar proportion of children in the two groups: 21 in the 5-day group and 30 in the 10-day group (p=0·29).

At the design stage of our study, we decided to restrict our trial to ceftriaxone, even though combination treatment with chloramphenicol and penicillin were still the first-line treatment recommended by WHO.[1] The emergence of pneumococci and *H influenzae* increasingly resistant to conventional first-line treatment is making the combination of chloramphenicol and penicillin less useful in meningitis treatment. Ceftriaxone has several advantages that make it the first-line treatment of meningitis in most developed countries. In developing countries, the cost was the principal disadvantage but this has reduced in recent years since the expiration of the drug's patent. There are substantial advantages to a shorter course of in-hospital treatment. Indirect costs of admission to hospital are important constraints for poor families. The maintenance of intravenous access over a 10-day period is difficult and is a burden on the scarce hospital resources available in many developing countries. Risk of nosocomial infections and spread of hepatitis B and other infections during admission to hospital are major risks. Short hospital stays reduce in-patient numbers, bed occupancy, and total management cost. Early discharge to home means less loss of family income because of loss of working hours.

Panel 3: Research in context

Systematic review

Before this study, we searched Medline and Embase for studies comparing short-course with long-course antimicrobial treatment for childhood bacterial meningitis. Our search terms were "bacterial", "paediatric", "pediatric", "children", "childhood", "short course", "therapy", and "antibiotic". We limited the search to publications in English, but not by date. We also searched reference lists of articles identified by this strategy and this was updated during the write-up of our study. Previous studies were small and did not give a conclusive answer. Several were limited to one cause, different antibiotics were used, and outcome measures varied. A recent systematic review[42] summarised five trials with a total of less than 400 patients and found no difference between short and long treatment duration, but suffered from the variability of treatment approaches.

Findings

Our study was powered to answer the question of short-course versus long-course treatment with ceftriaxone in childhood bacterial meningitis. It was done where bacterial meningitis is common, included the most important causes, and also children infected with HIV. Our results are conclusive and confirm previous small study findings.

The overall outcome of meningitis in our study is far from good, even with optimum antimicrobial treatment and much better care than is routinely available in the participating countries. Many children died in the first few days before random assignment, or left hospital with sequelae. To prevent this burden of disease, preventive vaccines are vital and their development and deployment are of crucial importance. The *H influenzae* type b vaccine, as part of the pentavalent vaccine, was introduced into the Malawian expanded programme for immunisation in February, 2002. The number of cases of meningitis caused by *H influenzae* type b fell substantially and, by 2005, the incidence rates fell from 20–40 per 100 000 to almost zero.[48] Nevertheless, prompt access to good quality care is important for every infected child. This means improving health systems—a difficult and daunting task.

We did our trial in children presenting with purulent meningitis presumably caused by *S pneumoniae*, *H influenzae* type b, and *N meningitidis*, and could find evidence for these organisms in 67% of our cases. We excluded organisms other than the three main bacterial causes of meningitis from our trial, in particular non-typhoid salmonellae, which might become more prominent as other causes decline. Invasive infections caused by non-typhoid salmonellae are common in malarial parts of Africa. In such settings a gram stain of cerebrospinal fluid is helpful in identifying the presence of bacteria. Non-typhoid salmonellae are adapted to

survival in the intracellular environment, which makes them difficult to eradicate and means that they need longer treatment courses than usual. A third-generation cephalosporin with a quinolone (eg, ceftriaxone and ciprofloxacin) are recommended to be given for 4–6 weeks.[49] Clinicians advise that cerebrospinal fluid should be re-examined at the end of treatment to ensure bacterial clearance.[49,50] For this reason we do not suggest that a 5-day short course would be adequate for meningitis caused by these organisms.

Our study had several limitations. First, hearing assessment was done with different methods at the various sites. For this reason we included only moderate to severe hearing loss in our final analysis, to avoid inclusion of conductive (mild) hearing loss unrelated to the meningitis event. Second, some centres gave adjuvant steroids for the first 48 h of antibiotic treatment; however, this did not affect the outcome. Third, treating physicians decided not to allow some of the children to be randomly assigned on day 5, most of whom had seizures that were difficult to control, continuing fever, or deteriorating consciousness. It is probable that most of these children had sequelae rather than continuing infection, but since they were not assigned to treatment groups, we cannot conclude that a short antibiotic course would have been sufficient for these children. For conclusions to be applicable to typical settings in a developing country where good culture facilities are not available, and the differentiation between aseptic sequelae and possible untreated infection cannot be made, we would have preferred to include all children presenting with clinical meningitis. However, such a study would have been unethical. So, our study was done in circumstances as close as possible to routine clinical settings. Finally, our study sample size was insufficient for separate assessment by causative organism. Few children had persisting organisms on the second lumbar puncture. Equally less than 8% of children were not assigned because they were judged to be too ill. Other organisms were rarely found, with the exception of *Salmonella* spp in Malawi, which raises the issue of this organism for parts of sub-Saharan Africa. In conclusion, a 5-day course of ceftriaxone is not only clinically effective but also cost efficient, and we recommend this regimen for uncomplicated cases of meningitis in children, although our sample size was inadequate to answer this by individual bacteria.

Contributors

SAQ conceived the project. SAQ and MWW were involved in designing the study. SQN and SAQ supervised all analyses. EM, SAQ, MWW, and SQN wrote the paper with input from all the authors. All authors reviewed and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We acknowledge the involvement of Rafeza Khanam, Arifur, Maksuda Islam, Fahmida Zabeen, Jalal Ahmed, Amala Badiya, Rehana Begum (Bangladesh); Goenke Poerksen, Enitan Carroll, Sarah White, Mavuto Mukaka, Amos Phiri, Lorna Wilson (Malawi); and Chandiram, M Nand Lal (Hyderabad, Pakistan). We thank Medochemie Limited (Cyprus) for the donation, free of charge, of active and placebo ceftriaxone. The donor did not have any say in development of the protocol, interpretation of results, or the conclusions.

References

1 WHO. World Health Statistics 2006. Geneva: World Health Organization, 2006.
2 Ramakrishnan M, Ulland A, Sreinhardt LC, Moisi JC, Were F, Levine OS. Sequelae due to bacterial meninigitis among African children: a systematic literature review. *BMC Med* 2009; **7:** 47.
3 Lehmann D, Yeka W, Rongap T, et al. Aetiology and clinical signs of bacterial meningitis in children admitted to Goroka Base Hospital, Papua New Guinea, 1989–1992. *Ann Trop Paediatr* 1999; **19:** 21–32.
4 Palmer A, Weber M, Bojang K, McKay T, Adegbola RA. Acute bacterial meningitis in The Gambia. *J Trop Pediatr* 1999; **45:** 51–53.
5 Molyneux E, Walsh A, Phiri A, Molyneux M. Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996–97. *Trop Med Int Health* 1998; **3:** 610–18.
6 WHO. Antimicrobial and support therapy for meninigitis in children. Geneva: World Health Organization, 1998.
7 Hussey G, Schaaf H, Hanslo D, et al. Epidemiology of post-neonatal bacterial meningitis in Cape Town children. *S Afr Med J* 1997; **87:** 51–56.
8 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 893–902.
9 Watt JP, Wolfson LJ, O'Brien KL, et al. Burden of disease caused by *Haemophilus influenzae* in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 903–911.
10 Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349:** 1269–76.
11 Goetghebuer T, West TE, Wermenbol V, et al. Outcome of meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in The Gambia. *Trop Med Int Health* 2000; **5:** 207–13.
12 Goto H, Shimada K, Ikemoto H, Oguri P. Antimicorbial susceptibility of pathogens isolated from more than 10,000 patients with infectious respiratory diseases: a 25 year longitudinal study. *J Infect Chemother* 2009; **15:** 347–60.
13 Velasquez PA, Parussolo L, Cardoso CL, Togmin MC, Garcia LB. High prevalence of children colonized with penicillin-resistant *Streptococcus pneumoniae* in public day-care centers. *J Pediatr* (*Rio J*) 2009; **85:** 516–22 (in Portuguese).
14 Kisakye A, Makumbi I, Nansera D, et al. Surveillance for *Streptococcus pneumoniae* meningitis in children aged <5 years: implications for immunization in Uganda. *Clin Infect Dis* 2009; **48** (suppl 2)**:** S153–61.
15 Mudhune S, Wamae M, Network Surveillance Pneumococcal Disease in the East African Region. Report on invasive disease and meningitis due to *Haemophilus influenzae* and *Streptococcus pneumonia* from the Network for Surveillance of Pneumococcal Disease in the East African Region. *Clin Infect Dis* 2009; **48** (suppl 2)**:** S147–52.
16 Klugman KP. Pneumococcal resistance to the third generation cephalosporins: clinical, laboratory and molecular aspects. *Int J Antimicrob Agents* 1994; **4:** 63–67.
17 O'Neill E, Humphreys H, Phillips J, Smyth EG. Third-generation cephalosporin resistance among gram-negative bacilli causing meningitis in neurosurgical patients: significant challenges in ensuring effective antibiotic therapy. *J Antimicrob Chemother* 2006; **57:** 356–59.
18 Martin E, Koup JR, Paravicini U, Stoeckel K. Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. *J Pediatr* 1984; **105:** 475–81.
19 Girgis NI, Abu el Ella AH, Farid Z, Haberberger RL, Galal FS, Woody JN. Intramuscular ceftriaxone versus ampicillin-chloramphenicol in childhood bacterial meningitis. *Scand J Infect Dis* 1988; **20:** 613–17.
20 Radetsky M. Duration of treatment in bacterial meningitis: a historical inquiry. *Pediatr Infect Dis J* 1990; **9:** 2–9.
21 Lambert HP. Don't keep taking the tablets? *Lancet* 1999; **354:** 943–45.
22 Visintin C, Mugglestone MA, Fields EJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ* 2010; **340:** c3209.

23 Feigin RD, Pearlman E. Bacterial meningitis beyond the neonatal period. In: Feigin RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases, 3rd edn. Philadelphia, PA: WB Saunders Co, 1992: 400–30.

24 Nathan N, Borel T, Djibo A, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet* 2005; **366:** 308–13.

25 Marhoum el Filali K, Noun M, Chakib A, Zahraoui M, Himmich H. Ceftriaxone versus penicillin G in short-term treatment of meningococcal meningitis in adults. *Eur J Clin Microbiol Infect Dis* 1993; **12:** 766–68.

26 Auvergnat JC, Le Tallec JY, Marchou B, Massip P, Carriere JP, Armengaud M. Shortened antibiotic therapy of menningococcal meningitis: 5-day administration of ceftriaxone. *Pathol Biol (Paris)* 1988; **36:** 735–37 (in French).

27 Viladrich PF, Pallares R, Ariza J, Rufi G, Gudiol F. Four days of penicillin therapy for meningococcal meningitis. *Arch Intern Med* 1986; **146:** 2380–82.

28 Lin TY, Chrane DF, Nelson JD, McCracken GH Jr. Seven days of ceftriaxone therapy is as effective as ten days' treatment for bacterial meningitis. *JAMA* 1985; **253:** 3559–63.

29 Martin E, Hohl P, Guggi T, Kayser FH, Fernex M. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part I: Clinical results. *Infection* 1990; **18:** 70–77.

30 Roine I, Ledermann W, Foncea LM, Banfi A, Cohen J, Peltola H. Randomized trial of four vs seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. *Pediatr Infect Dis J* 2000; **19:** 219–22.

31 Singhi P, Kaushal M, Singhi S, Ray P. Seven days vs 10 days ceftriaxone therapy in bacterial meningitis. *J Trop Pediatr* 2002; **48:** 273–79.

32 Sholtz H, Hofmann T, Noack R, Edwards DJ, Stoeckel K. Prospective comparison of ceftriaxone and cefotaxime for the short-term treatment of bacterial meningitis in children. *Chemotherapy* 1998; **44:** 142–47.

33 Lutsar I, Gontmachr A, Narska M, et al. Five days of antibacterial therapy for bacterial meningitis in children? *Infection* 1995; **23:** 113–18.

34 Lutsar I, Gontmachr A, Narska M, et al. Five days of antibacterial therapy for bacterial meningitis in children? *Infection* 1995; **23:** 113–18.

35 Jadavji T, Biggar WD, Gold R, Prober CG. Sequelae of acute bacterial meningitis in children treated for seven days. *Pediatrics* 1986; **78:** 21–25.

36 Martin E, Hohl P, Guggi T, Kayser FH, Fernex M. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results from a Swiss multicenter study. Part 1: Clinical results. *Infection* 1990; **18:** 70–77.

37 Simeonsson RJ, Lollar D, Hollowell M. Revision of the International Classification of Impairments, Disabilities, and Handicaps: developmental issues. *J Clin Epidemiol* 2000; **53:** 113–24.

38 Squires J, Bricker D, Potter LW. Revision of a parent-completed developmental screening tool: ages and stages questionnaires. *J Pediatr Psychol* 1997; **22:** 313–28.

39 WHO. Chapter 5: Bacteriological media—Guidelines on Standard Operating Procedures for Microbiology. Geneva: World Health Organization, 2006. http://www.searo.who.int/en/Section10/Section17/Section53/Section482_1782.htm (accessed April 4, 2011).

40 Wikler MA, Hindler JF, Cockerill FR, et al. Performance standards for antimicrobial disk susceptibility tests; approved standard—tenth edition. Wayne, PA: Clinical Laboratory Standard Institute, 2009.

41 Trunkel AR, Scheld WM. Pathogenesis and pathophysiology of bacterial meningitis. *Clin Microbiol Rev* 1993; **6:** 118–36.

42 Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. *Arch Dis Child* 2009; **94:** 607–14.

43 Kutz JW, Simon LM, Chennupati SK, Giannoni CM, Manolidis S. Clinical predictors for hearing loss in children with bacterial meningitis. *Arch Otolaryngol Head Neck Surg* 2006; **132:** 941–45.

44 Forsyth H, Kalumbi F, Mphaka E, et al. Hearing loss in Malawian children after bacterial meningitis: incidence and risk factors. *Audiol Med* 2004; **2:** 100–07.

45 Qazi SA, Khan MA, Mughal N, et al. Dexamethasone and bacterial meningitis in Pakistan. *Arch Dis Child* 1996; **75:** 482–88.

46 Fortnum HM. Hearing impairment after bacterial meningitis: a review. *Arch Dis Child* 1992; **67:** 1128–33.

47 Eisenhut M, Meehan T. Risk factors for hearing loss in bacterial meningitis: delay in treatment and clinical manifestations. *Audiol Med* 2002; **11:** 86–97.

48 Daza P, Banda R, Misoya K, et al. The impact of routine infant immunization with *Haemophilus influenzae* type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence. *Vaccine* 2006; **24:** 6232–39.

49 Price EH, de Louvois J, Workman MR. Antibiotics for *Salmonella* meningitis in children. *J Antimicrob Chemother* 2006; **46:** 653–55.

50 AAP. Salmonella infections. In: Peter G, ed. Report of the Committee on Infectious Diseases, 25th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2000.