Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study

N Nathan, T Borel, A Djibo, D Evans, S Djibo, J F Corty, M Guillerm, K P Alberti, L Pinoges, P J Guerin, D Legros

Lancet 2005; 366: 308–313
Published online July 5, 2005
DOI:10.1016/S0140-6736(05)66792-X

Epicentre, Paris, France (N Nathan MD, T Borel MD, D Evans MD, K P Alberti MSc, L Pinoges MSc, P J Guerin MD, D Legros MD); **Ministère de la Santé Publique et de la Lutte contre les Endémies, Niamey, Niger** (A Djibo MD); **Centre de Recherche Médicale et Sanitaire (CERMES), Niamey, Niger** (S Djibo MD); **and Médecins Sans Frontières (MSF), Paris, France** (J F Corty MD, M Guillerm DUT)

Correspondence to: Dr Philippe Jean Guerin, Epicentre, 8 rue Saint Sabin, 75011 Paris, France
philippe.guerin@epicentre.msf.org

Summary

Background **In sub-Saharan Africa in the 1990s, more than 600 000 people had epidemic meningococcal meningitis, of whom 10% died. The current recommended treatment by WHO is short-course long-acting oily chloramphenicol. Continuation of the production of this drug is uncertain, so simple alternatives need to be found. We assessed whether the efficacy of single-dose treatment of ceftriaxone was non-inferior to that of oily chloramphenicol for epidemic meningococcal meningitis.**

Methods **In 2003, we undertook a randomised, open-label, non-inferiority trial in nine health-care facilities in Niger. Participants with suspected disease who were older than 2 months were randomly assigned to receive either chloramphenicol or ceftriaxone. Primary outcome was treatment failure (defined as death or clinical failure) at 72 h, measured with intention-to-treat and per-protocol analyses.**

Findings **Of 510 individuals with suspected disease, 247 received ceftriaxone, 256 received chloramphenicol, and seven were lost to follow-up. The treatment failure rate at 72 h for the intention-to-treat analysis was 9% (22 patients) for both drug groups (risk difference 0·3%, 90% CI –3·8 to 4·5). Case fatality rates and clinical failure rates were equivalent in both treatment groups (14 [6%] ceftriaxone *vs* 12 [5%] chloramphenicol). Results were also similar for both treatment groups in individuals with confirmed meningitis caused by *Neisseria meningitidis*. No adverse side-effects were reported.**

Interpretation **Single-dose ceftriaxone provides an alternative treatment for epidemic meningococcal meningitis—its efficacy, ease of use, and low cost favour its use. National and international health partners should consider ceftriaxone as an alternative first-line treatment to chloramphenicol for epidemic meningococcal meningitis.**

Introduction

Epidemics of meningitis due to *Neisseria meningitidis* serogroup A are reported almost every year from sub-Saharan African countries, representing more than 600 000 affected individuals in the 1990s alone.[1,2] The case fatality ratio (CFR) is estimated to be 10%, with a further 10–20% of patients developing neurological sequelae.[3,4] During these epidemics with high numbers of people with meningitis, over-worked health staff often need effective, cheap, and easy-to-use antibiotics to handle the large influx of patients.

Long-acting chloramphenicol (oily suspension) was first proven effective against epidemic meningococcal meningitis in the mid-1970s,[5,6] and has been recommended by WHO as a regimen of one or two intramuscular injections since 1995·[7] Even though oily chloramphenicol remains active against *N meningitidis* serogroup A[8] and is critical for the management of meningitis epidemics, continuation of the production of the drug is uncertain, mainly because of the absence of financial market perspectives for this product.[9]

Alternative antimicrobial drugs with proven efficacy against *N meningitidis* include intravenous benzylpenicillin, ampicillin, and intravenous or intramuscular chloramphenicol or ceftriaxone.[10] However, protocols using multiple injections every day are impractical to use in epidemics and only drugs with simple treatment schedules provide an alternative to oily chloramphenicol. Several studies have shown the efficacy of a daily dose of ceftriaxone for 4 days in the treatment of bacterial meningitis.[11–14] Short-course protocols could also be effective because of the pharmacological properties of ceftriaxone that include a long half-life in blood (8 h) and in cerebrospinal fluid (CSF; 14 h), as well as residual amounts in CSF above the minimal inhibitory concentration of most of the organisms 24–48 h after injection.[11,15–18] Short-course protocols have been tested in two randomised trials. In a study undertaken by Epicentre in 1995, 47 children aged 2–35 months with meningococcal meningitis did not show any substantial difference in clinical failure rates among those receiving a two-injection regimen of ceftriaxone (9%) or oily chloramphenicol (8%).[19] The second small trial compared 2 days of ceftriaxone with 6 days of benzylpenicillin in 36 adults with bacterial meningitis. Recovery rates were 81% and 95%, respectively, with no significant difference shown.[20]

We undertook a multicentre, randomised, open-label, non-inferiority trial comparing the efficacy of short-course treatment of ceftriaxone with that of oily chloramphenicol in individuals with meningitis recruited during an epidemic in Niger in 2003.

Methods

Patients

The study was undertaken for 1 month (from March 24 to April 27, 2003) during a meningitis epidemic affecting Maradi and Zinder regions in eastern Niger. Our main objective was to compare the clinical effectiveness of one intramuscular injection of ceftriaxone with that of one intramuscular injection of oily chloramphenicol in the treatment of *N meningitidis* meningitis in an epidemic context. We tested the hypothesis that treatment outcome with ceftriaxone was non-inferior to that of chloramphenicol.

An individual with suspected meningitis was defined as a person admitted to one of eight peripheral health centres or to the Zinder regional hospital with sudden onset of fever or history of fever in the past 24 h associated with at least one of the following symptoms: neck stiffness, impaired consciousness, or petechial rash for patients older than 1 year; or bulging fontanel, axial hypotonia, upwardly turned gaze, or petechial rash for patients younger than 1 year. An individual with confirmed meningitis was defined as having suspected disease with a CSF white-blood-cell count of more than 50 cells per mL and a biological confirmation of *N meningitidis* meningitis by: pathogen identification in the CSF by gram staining, presence of soluble antigens in the CSF detected by direct agglutination test (Pastorex, Bio-rad Laboratories, CA, USA), pathogen identification in CSF culture, or detection of bacterial DNA of pathogen by PCR. Apart from PCR, laboratory testing was undertaken every day in a study laboratory in Zinder Hospital, Niger. PCR testing was undertaken at the CERMES laboratory in Niamey, Niger.

Individuals with suspected meningitis were included after written informed consent (or oral consent otherwise) was obtained. Patients were excluded if they were younger than 2 months, had a known allergy to one of the two trial drugs, had a recurrent history of meningitis since the beginning of the epidemic, or presented with non-reactive coma or cardiovascular shock. Pregnant and breastfeeding women were also excluded. Standardised data on clinical signs and symptoms were recorded at admission and throughout the follow-up for all patients. The study was approved by the Ministry of Health of Niger and reviewed by an independent ethics committee in France (Comité Consultatif de Protection des Personnes dans Recherche Biomédicale [CCPPRB], St Germain en Laye, France).

Procedures

At inclusion (0 h), medical doctors who were assigned to the study obtained CSF samples by lumbar puncture, undertook a rapid test for malaria diagnosis (Optimal, Diamed, Switzerland), and randomly assigned patients to receive either ceftriaxone (100 mg/kg to a maximum of 4 g, one intramuscular dose) or oily chloramphenicol (100 mg/kg to a maximum of 3 g, one intramuscular dose). Because of field conditions, our trial was not masked—the vials had different appearances and the treating doctors were not masked to which treatment was given. Block randomisation was done with a computer-generated list and the treatment group was allocated with individually sealed envelopes. Principal investigators undertook the randomisation in Paris before the trial began. They did not assign patients to treatment groups in the field. A second single dose (ceftriaxone 75 mg/kg or chloramphenicol 100 mg/kg) was given after 24–48 h in case of clinical failure, which was defined as: state of consciousness remaining severely altered (Glasgow coma score <11 at 24 h or <13 at 48 h), no improvement in the state of consciousness since 0 h, appearance or worsened neurological symptoms since 0 h, repeated or persistent convulsions, or axillary temperature above 38·5°C in the absence of other evident infectious pathological changes. In case of a positive malaria test, artemisinin-based combination therapy was given. Steroids were not used.

Primary outcome was treatment failure, defined by death or clinical failure (as defined above) at 72 h.

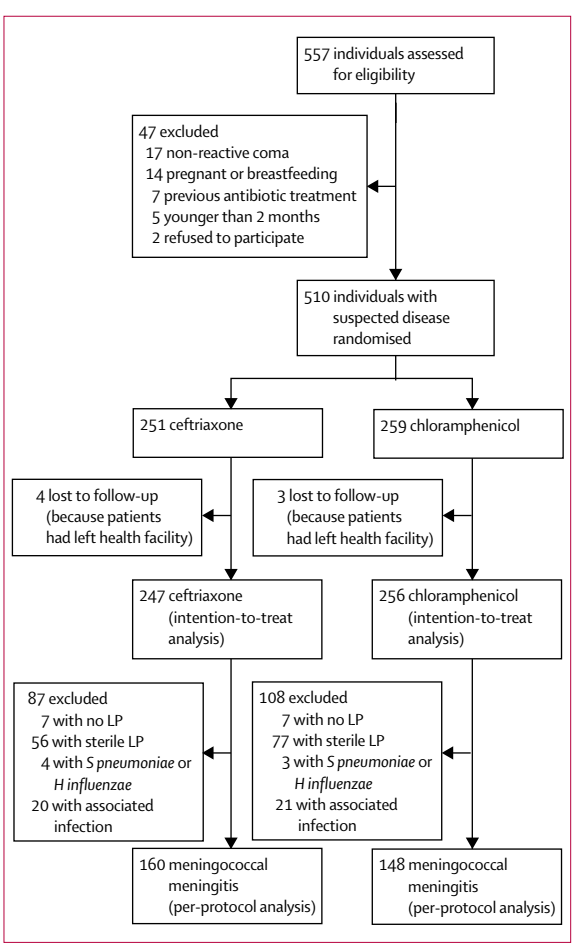

***Figure*: Trial profile**
LP=lumbar puncture.

	Intention-to-treat analysis		Per-protocol analysis	
	Chloramphenicol	Ceftriaxone	Chloramphenicol	Ceftriaxone
Age (years)				
<5	79 (31%)	81 (33%)	35 (24%)	33 (21%)
5–14	145 (57%)	136 (55%)	96 (65%)	108 (67%)
≥15	32 (12%)	30 (12%)	17 (11%)	19 (12%)
Median (IQR)	7·0 (4-11)	7·0 (3-10)	7·0 (5-11)	8·0 (5-12)
Sex (male)	132 (52%)	133 (54%)	67 (45%)	89 (57%)
Duration of fever (h)				
Mean (SD)	45·5 (40·4)	42·6 (32·4)	45·5 (35·5)	42·6 (34·9)
>48 h	51 (20%)	43 (17%)	29 (20%)	26 (16%)
Temperature ≥38°C	183 (71%)	187 (76%)	100 (67%)	117 (74%)
Dehydration	22 (9%)	19 (8%)	11 (7%)	15 (10%)
Convulsions				
All types	69 (27%)	68 (28%)	29 (20%)	37 (24%)
Severe	47 (19%)	54 (23%)	22 (15%)	30 (19%)
Impaired consciousness	49 (19%)	50 (20%)	24 (16%)	33 (21%)
Glasgow score ≤12 (in participants older than 4 years)	30 (17%)	23 (14%)	20 (18%)	19 (15%)
Petechial rash	2 (1%)	2 (1%)	1 (1%)	1 (1%)
Positive malaria test result	23 (9%)	22 (9%)	0	0
Cause				
N meningitidis	169 (66%)	180 (73%)	n/a	n/a
S pneumoniae	2 (1%)	2 (1%)	n/a	n/a
H influenzae	1	2 (1%)	n/a	n/a
Negative	77 (30%)	56 (23%)	n/a	n/a
No lumbar puncture	7 (3%)	7 (3%)	n/a	n/a
Diagnosis of meningococcal meningitis only	148 (58%)	160 (65%)	n/a	n/a

Data are number (%) unless indicated otherwise. Totals differ because of missing values. n/a=not applicable.

Table 1: **Baseline characteristics**

Rescue treatment for clinical failure at 72 h was intravenous ceftriaxone (100 mg/kg per day) for a minimum of 4 days. Secondary endpoints were: death within 72 h, clinical sequelae at 72 h (judged on gross clinical abnormality), and clinical failure between 24 h and 48 h needing a second injection.

Statistical analysis

The sample size was calculated to show non-inferiority in the proportion of treatment failure at 72 h in the ceftriaxone group compared with the oily chloramphenicol group, which was based on an estimated proportion of treatment failure in the chloramphenicol group of 15% and a difference of less than 10% between the two groups (beyond which non-inferiority could not be proven). We needed a sample size of 175 individuals with confirmed meningococcal meningitis per group to reject the null hypothesis of inferiority of ceftriaxone to oily chloramphenicol, if we considered a one-sided 5% significance level, 80% power, and 10% loss to follow-up.[21]

Primary and secondary endpoints were analysed according to intention-to-treat principles (all individuals with suspected disease included) as well as per-protocol principles (restricted to individuals with confirmed meningococcal meningitis without any additional infection or concomitant antibiotherapy). For each analysis, differences between groups in the distribution of baseline characteristics at admission were tested using the χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney or t test for continuous variables. We calculated the risk difference and 90% CIs of the primary and secondary outcomes.[21] The difference was regarded as equivalent if the upper limit of its 90% CI was below 10%.

A separate analysis assessing the risk of treatment failure at 72 h with suspected meningococcal meningitis was undertaken for all baseline characteristics using univariate and multivariate logistic regression. Data entry and analyses were undertaken by use of EpiInfo 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS 10·0 (SPSS, Chicago, IL, USA) software packages.

	Overall		Chloramphenicol		Ceftriaxone		Difference % (90% CI)
	n (%)	Total	n (%)	Total	n (%)	Total	
Intention-to-treat analysis							
Treatment failure at 72 h	44 (9%)	503	22 (9%)	256	22 (9%)	247	0·3% (−3·8 to 4·5)
Death at 72 h	26 (5%)	503	12 (5%)	256	14 (6%)	247	1·0% (−2·3 to 3·8)
Second injection between 24 h and 48 h	35 (7%)	481	19 (8%)	247	16 (7%)	234	−0·9% (−4·7 to 3·0)
Neurological sequelae at 72 h	29 (6%)	477	13 (5%)	244	16 (7%)	233	1·6% (−2·1 to 5·1)
Per-protocol analysis							
Treatment failure at 72 h	16 (5%)	308	8 (5%)	148	8 (5%)	160	−0·4% (−4·6 to 3·8)
Death at 72 h	11 (4%)	308	5 (3%)	148	6 (4%)	160	0·4% (−3·1 to 3·8)
Second injection between 24 h and 48 h	20 (7%)	298	9 (6%)	144	11 (7%)	154	0·8% (−3·9 to 5·7)
Neurological sequelae at 72 h	23 (8%)	297	9 (6%)	143	14 (9%)	154	2·8% (−2·3 to 7·9)

Table 2: **Proportion of primary and secondary endpoints**

Role of the funding source

MSF was the main source of funding for this study. MSF staff reviewed the manuscript and provided suggestions to clarify methods and results. Members of MSF were on the scientific committee and participated in the field study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 557 patients screened, 510 were randomly assigned to receive ceftriaxone or chloramphenicol. Of these individuals, 47 (9%) were excluded because they were ineligible and another seven (1%) were lost to follow-up after treatment allocation (figure). At the time of inclusion for the intention-to-treat analysis, 99 (20%) patients had impaired consciousness and 101 (20%) reported a history of severe convulsions (table 1). Body temperature was more than 38°C in 370 (74%) patients. A rapid test for malaria diagnosis was positive for 45 (9%) of individuals tested.

Rate of treatment failure at 72 h was about 9% both overall and for ceftriaxone and chloramphenicol separately (table 2); it was judged equivalent across the two treatment groups. Of the 44 treatment

failures at 72 h, 26 were caused by death and 18 by clinical failure. CFR at 72 h was about 5% in patients receiving chloramphenicol and 6% in those receiving ceftriaxone (table 2). Clinical failure took place in ten (4%) of 244 surviving participants in the chloramphenicol group and in eight (3%) of 233 in the ceftriaxone group (difference –0·8%, 90% CI –3·3 to 2·8). Of the 481 individuals with suspected disease at 48 h, 35 received a second injection; the re-injection rate in the chloramphenicol group was similar to that in the ceftriaxone group. Neurological sequelae at 72 h were reported in 29 (6%) surviving individuals, which included hearing impairment (n=14), and motor dysfunction (ie, ataxia, motor deficit, or both; n=15; table 2). Proportion of sequelae was comparable between chloramphenicol and ceftriaxone at about 7%.

In the per-protocol analysis, CSF samples were taken from 489 of the 503 individuals with suspected disease. Meningitis was diagnosed in 356 (73%) participants. Pathogens identified were: *N meningitidis* (98%, n=349 samples), *Streptococcus pneumoniae* (1%, n=4), and *Haemophilus influenzae* (1%, n=3). The 349 patients with confirmed meningococcal meningitis included 41 (12%) individuals who either presented with an associated infection at 0 h (n=27 [malaria], n=3 [bronchopneumonia]) or received concomitant antibiotherapy (n=11) and were excluded from per-protocol analysis.

Of the 308 patients with confirmed disease analysed per protocol, 160 received ceftriaxone and 148 received chloramphenicol. The distribution of characteristics on admission did not differ significantly between these groups (table 1). At 72 h, treatment failure was about 5% overall and in each treatment group. 11 (4%) patients died before 72 h and five (2%) of those who survived were classified as clinical failure. CFR was judged equivalent between the two treatment groups (table 2). The rate of second injection was about 6% in the chloramphenicol group compared with 7% in the ceftriaxone group. Of the patients with reported sequelae, nine (6%) were in the chloramphenicol group and 14 (9%) in the ceftriaxone group. No serious adverse events were reported during the study.

Univariate analysis of all individuals with suspected disease (table 3) showed a strong association between the risk of treatment failure at 72 h and (1) impaired consciousness, (2) either no confirmed disease or meningococcal meningitis associated with another infection, and (3) severe convulsion before admission. We did not record any association between ceftriaxone treatment and risk of treatment failure (odds ratio 1·0, 95% CI 0·6–1·9). However, an association was seen between the risk of treatment failure for children younger than 5 years and that for children older than 14 years, but this relation was not significant (3·0, 0·8–10·3; table 3). In the multiple logistic regression model, only impaired consciousness at 0 h or diagnosis of another disease (alone or associated with meningococcal meningitis) remained significant risk factors for treatment failure at 72 h.

	Treatment failure at 72 h		Univariate analysis (n=503), odds ratio (95% CI)	Multivariate analysis (n=478), odds ratio (95% CI)
	n (%)	Total		
Sex				
Male	25 (9%)	265	1·2 (0·6–2·2)	0·9 (0·5–1·8)
Female	19 (8%)	238	1	1
Age (years)				
<5	21 (13%)	160	3·0 (0·8–10·3)	1·4 (0·4–5·2)
5–14	20 (7%)	281	1·5 (0·4–5·2)	1·3 (0·3–4·7)
>15	3 (5%)	62	1	1
Duration of fever before admission (days)				
>2	17 (7%)	246	0·6 (0·3–1·2)	0·8 (0·4–1·8)
<2	27 (11%)	250	1	1
Temperature (°C) at admission				
>39·5	12 (11%)	105	1·8 (0·8–4·1)	1·5 (0·6–3·8)
38·6–39·5	18 (10%)	186	1·5 (0·7–3·1)	2·0 (0·9–4·5)
≤38·5	14 (7%)	212	1	1
Received antipyretic before admission				
Yes	18 (10%)	184	1·2 (0·6–2·2)	1·8 (0·9–3·7)
No	26 (8%)	313	1	1
Dehydration at admission				
Yes	4 (10%)	41	1·1 (0·4–3·3)	0·8 (0·2–2·7)
No	40 (9%)	461	1	1
Severe convulsion at or before admission				
Yes	17 (17%)	101	2·8 (1·5–5·4)	1·9 (0·9–4·1)
No	26 (7%)	388	1	1
Impaired consciousness at admission				
Yes	23 (23%)	99	5·5 (2·9–10·4)	5·0 (2·3–10·6)
No	21 (5%)	403	1	1
Diagnosis of another or meningitis-associated disease				
Yes	28 (14%)	195	3·1 (1·6–5·8)	3·3 (1·6–6·8)
No	16 (5%)	308	1	1

Table 3: **Risk of treatment failure in individuals with suspected meningitis**

Discussion

Our results suggest non-inferiority of ceftriaxone to chloramphenicol when used as short-course (single-dose) treatment against epidemic meningococcal meningitis. 72 h after admission, we showed equivalency in the CFR, clinical failure rate, proportion of second injection, and proportion of sequelae between the treatment groups. Individuals with suspected disease represented more than 90% of those attending health facilities during the study. This exhaustive recruitment and the multiple inclusion sites (eight primary and one secondary health facilities) favour a highly representative sample of the population of individuals with meningitis who consult peripheral health structures during epidemics.

Our study was undertaken in peripheral health structures during the acute phase of an epidemic. Because of on-site constraints, the duration of follow-up was restricted to 72 h after admission, and information about long-term sequelae could not be extrapolated from our data. Patients in clinical failure at 72 h were followed through to complete recovery. Although the risk of relapse after discharge was regarded as low and all patients were advised to return to the clinic in the event

of clinical deterioration, no patients returned during the study period. Other studies testing short-course treatment (2–4 days) of ceftriaxone or chloramphenicol with longer follow-up periods than ours also failed to identify individuals with relapsed disease.[11–14,22–24] This scarcity of data could be explained by the fact that CSF is sterile 24–48 h after one injection of ceftriaxone or chloramphenicol.[11,15–18,25]

In both of our treatment groups, the CFR was lower than those reported from epidemiological surveillance or prospective studies undertaken during meningitis epidemics.[26–29] This difference might be due to the exclusion of individuals with the most severe disease and the study conditions that ensured full-time availability of medical staff and material. Previous studies have shown similar CFR and recovery rates without sequelae at 72 h to those in our study.[5,13,14,22,23] All deaths reported in our study took place within 30 h of admission, and all occurred in patients who presented with impaired consciousness at admission. Furthermore, two-thirds of the patients who died had been diagnosed with another infection, either alone or associated with meningococcal meningitis. Unconfirmed meningococcal meningitis or meningitis associated with another infection was one of the main risk factors for treatment failure at 72 h (table 3). Our results suggest that during a meningitis epidemic, if fever persists 48 h after a single injection of ceftriaxone or chloramphenicol with a second injection of antibiotics, other diseases such as malaria should be considered and treated immediately.

Antimicrobial drugs recommended during meningitis epidemics in sub-Saharan Africa should also be effective against other pathogens responsible for bacterial meningitis, and affordable for these countries. Resistance of *S pneumoniae* and *H influenzae* to chloramphenicol is increasing worldwide, but does not exceed 10% in African countries.[30–33] By contrast, only a few strains of *S pneumoniae* that are resistant to ceftriaxone have been isolated in Africa.[34,35] The cost of generic ceftriaxone has rapidly fallen, since patent rights for this drug expired in most countries. In our study, the average treatment dose was 2 g per person for both drugs. Treatment cost per patient was estimated as US$4–6 for chloramphenicol and $2–3 for ceftriaxone.

In conclusion, ceftriaxone is an equally effective alternative to oily chloramphenicol for the treatment of meningococcal meningitis during epidemics in resource-poor settings. The good efficacy and ease of use in an epidemic context, effectiveness against pathogens such as *S pneumoniae*, wide availability, and low cost are good arguments for ceftriaxone use. Future production of oily chloramphenicol is still uncertain. The potential for emergence of resistance of ceftriaxone if inappropriately used is a major concern. Public-health authorities should put mechanisms in place to ensure proper use of ceftriaxone to avoid rapid spread of resistance as seen previously with other broad-spectrum antibiotics. Recommendations for the conditions of ceftriaxone use, as well as strategies for its introduction and distribution during epidemics, should now be addressed by national and international health partners.

Contributors

N Nathan participated in the study conceptualisation, writing of the protocol, implementation of the study on site, overseeing the field study, data analysis, interpretation of results, and writing of the manuscript. T Borel participated in the study conceptualisation, writing of the protocol, implementation of the study on site, overseeing the field study, data cleaning and analysis, interpretation of results, and writing of the initial report and final manuscript. A Djibo and J-F Corty helped undertake the study and revise the manuscript. D Evans undertook and coordinated the study on site, collected data, and helped revise the manuscript. S Djibo analysed bacterial samples (PCR), and helped revise the manuscript. M Guillerm contributed to the laboratory aspects of protocol, implementation of site laboratory, analysis of bacterial samples, revision of manuscript. K P Alberti oversaw the field study and helped to write the manuscript. L Pinoges and P J Guerin helped with statistical analysis and writing of the manuscript. D Legros participated in the study conceptualisation, advised on field implementation, and helped write the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We dedicate this work to our friend and colleague Nicolas Nathan who passed away prematurely in May, 2004. We thank Siddou Moumouni Daouda (Zinder regional director of health), D'Mai Moctar Hassane (Maradi regional director of health), Suzanne Chanteau (director of CERMES), and MSF for their support and collaboration; Danielle Bonneville (laboratory technician) and all the medical personnel for their dedicated work in the study; the members of the scientific committee for their contribution—Michel Rey (CHRU Hôtel Dieu, Clermont Ferrand, France), Michel Cadoz (sanofi pasteur, Lyon, France), Xavier Nassif (CHU Necker, Paris, France), Michel Van Herp (MSF, Bruxelles, Belgium), and Francis Varaine (MSF, Paris, France); and Angela Rose (Epicentre), Dominique A Caugant (Norwegian Institute of Public Health, Norway), and William Perea (WHO, Geneva, Switzerland) for their valuable comments on the manuscript.

References

1 Molesworth AM, Thomson MC, Connor SJ, et al. Where is the meningitis belt? Defining an area at risk of epidemic meningitis in Africa. *Trans R Soc Trop Med Hyg* 2002; **96:** 242–49.

2 WHO. WHO report on global surveillance of epidemic-prone infectious diseases. WHO/CDS/CSR/ISR/2000.1 Geneva: World Health Organization, 2000.

3 Peltola H. Burden of meningitis and other severe bacterial infections of children in Africa: implications for prevention. *Clin Infect Dis* 2001; **32:** 64–75.

4 Baraff LJ. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993; **12:** 389–94.

5 Rey M, Ouedraogo L, Saliou F, Perino L. Traitement minute de la méningite cérébro-spinale épidémique par injection intramusculaire unique de chloramphénicol (suspension huileuse). *Med Mal Infect* 1976; **6:** 120–24.

6 Saliou F, Ouedraogo L, Muslin D, Rey M. L'injection unique de chloramphénicol dans le traitement de la méningite cérébro-spinale en Afrique tropicale. *Med Trop* 1977; **37:** 141–47.

7 WHO. Control of epidemic meningococcal disease. WHO practical guidelines. Lyon: Ed. Fondation Marcel Mérieux, 1995.

8 Tondella ML, Rosenstein NE, Mayer LW, et al. Lack of evidence for chloramphenicol resistance in *Neisseria meningitidis*, Africa. *Emerg Infect Dis* 2001; **7:** 163–64.

9 Lewis RF, Dorlencourt F, Pinel J. Long-acting oily chloramphenicol for meningococcal meningitis. *Lancet* 1998; **352:** 823.

10 WHO. Antimicrobial and support therapy for bacterial meningitis in children. Report of the meeting of 18–20 June 1997. Geneva: World Health Organization, 1997.

11 Scholtz 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.

12 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.

13 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.

14 Kavaliotis J, Manios SG, Kansouzidou A, Danielidis V. Treatment of childhood bacterial meningitis with ceftriaxone once daily: open, prospective, randomized, comparative study of short-course versus standard length therapy. *Chemotherapy* 1989; **35:** 296–303.

15 Garraffo R. Pharmacocinétique clinique de la ceftriaxone. *Lettre de l'infectiologue* 1995: 8–12.

16 Hohl P, Martin E, Kayser FH. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part II: bacteriological results. *Infection* 1990; **18:** 78–82.

17 Delsignore R, Baroni CM, Crotti G, et al. Absolute bioavailability of ceftriaxone after intramuscular administration to healthy volunteers. *Chemotherapy* 1983; **29:** 157–62.

18 Cadoz M, Denis F, Guerma T, Prince-David M, Diop Mar I. Comparaison bactériologique, pharmacologique et clinique de l'amoxycilline et du ceftriaxone dans 300 méningites purulentes. *Pathol Biol* 1982; **30:** 522–25.

19 Varaine F, Keita M, Kaninda AV, et al. Long acting chloramphenicol versus ceftriaxone for treatment of bacterial meningitis in children aged 2–35 months. Eighth International Congress for Infectious Diseases, Boston, MD USA, 15–18 May, 1998.

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

21 Com-Nougue C, Rodary C. Revue des procédures statistiques pour mettre en évidence l'équivalence de deux traitements. *Rev Epidemiol Sante Publique* 1987; **35:** 416–30.

22 Wali SS, Macfarlane JT, Weir WR, et al. Single injection treatment of meningococcal meningitis. 2. Long acting chloramphenicol. *Trans R Soc Trop Med Hyg* 1979; **73:** 698–702.

23 Puddicombe JB. A field trial of a single intramuscular injection of long acting chloramphenicol in the treatment of meningococcal meningitis. *Trans R Soc Trop Med Hyg* 1984; **78:** 399–403.

24 Pécoul B, Varaine F, Keita M, et al. Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. *Lancet* 1991; **338:** 862–66.

25 Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med* 1990; **322:** 141–47.

26 Greenwood BM, Bradley AK, Cleland PG, et al. An epidemic of meningococcal infection at Zaria, Northern Nigeria. 1. General epidemiological features. *Trans R Soc Trop Med Hyg* 1979; **73:** 557–62.

27 Mohammed I, Nassidi A, Alkali AS. A severe epidemic of meningococcal meningitis in Nigeria, 1996. *Trans R Soc Trop Med Hyg* 2000; **94:** 265–70.

28 Santaniello-Newton A, Hunter PR. Management of an outbreak of meningococcal meningitis in a Sudanese refugee camp in Northern Uganda. *Epidemiol Infect* 2000; **124:** 75–81.

29 Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. *Trans R Soc Trop Med Hyg* 1987; **81:** 536–38.

30 Bernardino L, Magalhães J, Simões MJ, Monteiro L. Bacterial meningitis in Angola. *Lancet* 2003; **361:** 1564–65.

31 Mwangi I, Berkley J, Lowe B, Peshu N, Marsh K, Newton CR. Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance and outcome. *Pediatr Infect Dis J* 2002; **21:** 1042–48.

32 Duke T, Michael A, Mokela D, Wal T, Reeder J. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? *Arch Dis Child* 2003; **88:** 536–39.

33 Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002; **360:** 211–18.

34 Karstaedt AS, Khoosal M, Crewe-Brown HH. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. *Pediatr Infect Dis J* 2000; **19:** 454–57.

35 Benbachir M, Benredjeb S, Boye CS, et al. Two-year surveillance of antibiotic resistance in *Streptococcus pneumoniae* in four African cities. *Antimicrob Agents Chemother* 2001; **45:** 627–29.