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ORIGINAL ARTICLE

Unusual Gram-negative bacteria cause more severe bacterial meningitis than the three classical agents in children

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Abstract

Aim: To compare the characteristics, mortality and sequelae at hospital discharge of childhood bacterial meningitis (BM) caused by the three "classical" agents *Neisseria meningitidis*, *Haemophilus influenzae* or *Streptococcus pneumoniae* versus BM due to other aetiology in Finland, Latin America and Angola.

Methods: This observational study is a secondary analysis of data from five prospective treatment trials on non-neonatal BM in Finland, Latin America and Angola in 1984–2017.

Results: Of the 1568 cases, 1459 (93%) were caused by the classics, 80 (5%) by other Gram-negative and 29 (2%) by other Gram-positive bacteria. Nonclassical Gram-negative disease was encountered especially in Angola ($p < 0.0001$). Overall, children in the nonclassical group presented later for treatment and were more often underweight and anaemic ($p < 0.001$). In multivariate analysis, even if the area was strongest predictor of poor outcome, nonclassical Gram-negative BM increased the odds for death twofold and the odds for death or severe sequelae 2.5-fold.

Conclusion: BM of a nonclassical aetiology is a particularly severe disease affecting especially Angolan children poorly armoured to fight infections. Since vaccinations are diminishing the role of classical agents, that of nonclassical agents is growing.

KEYWORDS
bacterial meningitis, child, Gram-negative bacteria, *Haemophilus influenzae*, *Streptococcus pneumoniae*

1 | INTRODUCTION

Numerous studies have examined the prevalence of childhood bacterial meningitis (BM) due to *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae*, the three "classical" BM agents. Our studies on 1568 patients with BM of known bacterial aetiology at age 2 months to 15 years in three continents[1–5] showed a 93% preponderance of the classical agents over other aetiology. A review on children aged 1–59 months from 48 studies in South Asia[6] found that meningococci, Hib and pneumococci caused a median of 78% of cases. The share of these agents in Mozambique was approximately 70%.[7]

Gram-negative rods that cause BM have long been known as a risk for severe disease in infants, especially those with neural tube or urinary tract anomalies.[8] However, information on Gram-positive bacteria, such as *Staphylococcus aureus* not following neurosurgery

Abbreviations: BM, bacterial meningitis; CI, confidence interval; CSF, cerebrospinal fluid; Hib, *Haemophilusinfluenzae*, type b; LatAm, Latin America; OR, odds ratio; PCR, polymerase chain reaction; WHO, World Health Organization.

(usually a shunt placement or revision),[9] *Streptococcus agalactiae* beyond the neonatal period[10] or *Listeria monocytogenes*,[11] is limited. A critical appraisal is warranted to examine the complex issue of the BM aetiology paying especial attention to the roles of classical meningococcal, Hib and pneumococcal meningitides versus the other less known agents in different study areas and clinical course and outcome of BM of different bacterial aetiologies. We compared the demographics, symptoms and signs, laboratory test results and outcome (mortality, hearing loss and neurological sequelae) at hospital discharge in children with BM caused by the "classical" versus "nonclassical" agents in Finland, Latin America and Angola, and in all the areas combined.

Key Notes

- We compared clinical characteristics and outcome of childhood bacterial meningitis (BM) caused by the three "classical" agents *Neisseria meningitidis*, *Haemophilus influenzae* or Streptococcus pneumoniae versus other aetiology in Finland, Latin America and Angola.
- Of cases, 93% were caused by the classics, 5% by other Gram-negative and 2% by other Gram-positive bacteria.
- Nonclassical disease, encountered especially in Angola in underweight and anaemic children, associated with particularly severe disease and poor outcome.

2 | METHODS

2.1 | Data collection

This study was an observational study, a secondary analysis of prospectively collected data during five prospective BM studies in Finland, LatAm and Angola in 1984–2017. The trial setups have been described earlier.[1–5] Importantly, all these studies were prospective, and the same data were collected uniformly using similar forms written in Finnish, Spanish or Portuguese. Thus, a large and comparable data set from three continents was gradually created. Hib vaccinations were introduced towards the end of the studies in Finland and LatAm and gradually in the beginning of the studies in Angola. Pneumococcal conjugate vaccine (PCV 13) was used only in the end of Angolan studies.

After approval by the relevant ethical committees, children aged 2 months to 15 years with symptoms and signs compatible with BM were enrolled, provided the legal guardian's consent was obtained. In case of illiteracy, a fingerprint was required. Once international registration of such studies became common practice, the Angolan trials were registered with the International Standard Randomized Controlled Trial Number Register (number ISRCTN62824827) and ClinicalTrials.gov (identifier NCT 01540838).

The inclusion criterion for the present study was to have BM with a confirmed bacterial aetiology. The bacteria were identified with CSF culture, Gram stain, PCR, latex agglutination test or blood culture in 1228 (78%), 122 (8%), 99 (6%), 97 (6%) and 22 cases (1%) respectively. Of these, 329 cases were collected from twelve hospitals around Finland,[1,2] 522 cases from Latin America (LatAm; Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela),[3] and 717 cases from the Paediatric Hospital of Luanda, the capital of Angola[4,5] (Table 1, Appendix S1). The exclusion criteria were age <2 months, trauma, intracranial shunt, previous hearing impairment or neurological disease and immunosuppression, except potential HIV infection (mainly relevant in Angola). Pretreatment with antimicrobials prevented enrolment if more than one parenteral dose had been administered. Nutritional status was graded according to WHO guidelines by using weight for age z-scores.[12]

2.2 | Laboratory, delineating outcomes, data analysis

All hospitals had a basic but sufficiently equipped on-site bacteriology and chemistry laboratory with trained personnel who followed standard textbook techniques. BM was a common diagnosis in those institutions, and appropriate handling of the specimens was part of their routine. Blood culture, CSF culture and Gram stain were performed in all hospitals. Resources permitting, the latex agglutination test in LatAm and Angola was performed when culture remained negative. Only some CSF samples were examined with PCR (in Finland or South Africa).

The course of illness was monitored by daily completion of specific study forms. Outcomes were assessed at discharge from hospital and categorised according to predefined criteria. Besides uneventful recovery and death, the outcomes in-between were graded as mild or severe neurological or audiological sequelae. Neurological sequelae were deemed severe in case of quadriplegia/paresis, hydrocephalus requiring a shunt, severe psychomotor retardation or blindness. Mild neurological sequelae consisted of any other abnormality, such as hemiparesis, monoparesis, psychomotor retardation or ataxia. Deafness was defined as the better ear's threshold of ≥80 dB, and milder hearing sequelae as a threshold >40 dB but <80 dB. Traditional audiometry was primarily used, while brain-evoked response audiometry (BERA) was the method of choice for small children. We also used Glasgow Outcome Scale to classify the patients by severity of audiological and neurological sequelae. Score 1 signifies death, score 2 vegetative state, score 3 severe disability, score 4 moderate disability and score 5 low or no disability.

All data were computed and analysed using JMP® Pro 14.1.0 (SAS Institute Inc, Cary, NC, USA) for Windows. Contingency analysis was used to examine relationships between two categorial variables. Pearson's chi-squared test was used to calculate *p* values. Associations with continuous characteristics were assessed using one-way ANOVA. We calculated odds ratios (OR) with 95% confidence intervals (CI) when comparing the nonclassical versus the classical agents in univariate analysis, overall and for each study site. To examine if type of bacteria was independent predictor of

TABLE 1 Patient characteristics and outcomes from meningitis

Variable	Total	Classical agents[a]	Other Gram-negatives	Other Gram-positives	*p*value
All	1568	1459 (93)	80 (5)	29 (2)	
Finland	329	326 (99)	0	3 (1)	
Latin America	522	502 (96)	14 (3)	6 (1)	
Angola	717	631 (88)	66 (9)	20 (3)	
Patient characteristics					
Glasgow Coma Score	12 (8–15)	12 (8–15)	11 (7–15)	12 (11–15)	0.24
Weight for age Z-score < −2	291/1536 (19)	246/1428 (17)	36/79 (46)	9/29 (31)	<0.0001
Ill >3 days before admission	577/1279 (45)	507/1181 (43)	57/73 (78)	13/25 (52)	<0.0001
Previous antibiotics	506/1466 (35)	456/1368 (33)	40/71 (56)	10/27 (37)	0.0004
B-haemoglobin, g/dl	8.7 (7.0–10.9)	8.8 (7.1–11.0)	7.6 (5.6–9.7)	8.4 (7.6–9.7)	<0.0001
Seizures before arrival	593/1525 (39)	539/1420 (38)	42/77 (55)	12/28 (43)	0.013
Seizures at ward	610/1200 (51)	539/1096 (49)	57/79 (72)	14/25 (56)	0.0004
Dyspnoea	444/1023 (43)	389/932 (42)	45/67 (67)	10/24 (42)	0.0003
Outcomes					
Glasgow outcome scale score	4 (3–5)	4 (3–5)	2 (1–5)	3 (1–5)	<0.0001
Severe neurological sequelae	103/1209 (9)	90/1152 (8)	9/41 (22)	4/16 (25)	0.0004
Death or severe neurological sequelae	446/1552 (29)	382/1444 (26)	48/80 (60)	16/28 (57)	<0.0001
Deafness	92/1036 (9)	88/996 (9)	4/30 (13)	0/10 (0)	0.42
Death or any severe sequelae	517/1387 (37)	450/1291 (35)	51/72 (71)	16/24 (67)	<0.0001
Death	343/1568 (22)	292/1459 (20)	39/80 (49)	12/29 (41)	<0.0001

Note: Data are presented as *n* (%) or median (interquartile range).

[a] Cases due to *Neisseria meningitidis*, *Haemophilus influenzae* or *Streptococcus pneumoniae*.

poor outcome, multivariate analysis was performed with type of bacteria and background characteristics that affect the prognosis of BM, namely area, weight-for-age Z-score < −2, treatment delay over 3 days and blood haemoglobin ≤ 8.7 g/dl (median).

3 | RESULTS

3.1 | Classical versus other BM types

Figure 1 displays the specific aetiology and it´s dissimilar distribution at our three study sites. Regarding the classical agents, 1459 cases in all, *H. influenzae* BM (total number 669) was represented by 218, 244 and 207 cases in Finland, LatAm and Angola, those numbers being 28, 143 and 334 (505 in all) for *S. pneumoniae*, and 80, 115 and 90 (285 in all) for *N. meningitidis* respectively. For the unusual Gram-negatives the numbers were 0, 14 and 66 (80 in all), and for Gram-positives 3, 6 and 20 (29 in all), correspondingly.

The overall share (Table 1, Appendix S1) of the nonclassical Gram-negatives compared to the total number in a particular site was no cases in Finland, 2.7% (14/522) in LatAm and 9% (66/717) in Angola. *Klebsiella* spp. and *Proteus* spp. were the most common fully identified Gram-negatives in Angola (Figure 1). However, of nonclassical Gram-negatives, 36% (5/14 in LatAm and 24/66 in Angola) were unidentified rods.

When compared with the total number (Table 1, Appendix S1), Gram-positive aetiology was identified 0.9% (3/329) in Finland, in 1.1% (6/522) in LatAm and in 2.8% (20/717) in Angola. Gram-negative BM was more than twice that common as Gram-positive BM in Angola and LatAm, this being almost nonexistent (N 3) in Finland. A few cases of *S. aureus* meningitis and some non-neonatal *S. agalactiae* meningitides were found in Angola. Slightly unexpectedly, solely one case of *Listeria* spp. in Finland was detected among all Gram-positive cases.

Compared to Finland and LatAm, relatively more nonclassical Gram-negative than classical meningitis was diagnosed in Angola, OR in univariate analysis being 6.18 (95% CI 3.44–11.11). A likewise difference was also observed for the nonclassical Gram-positive cases (OR 2.92, 95% CI 1.32–6.45). In Angola, the proportion of the nonclassical compared to classical aetiology of BM (Table 2) increased significantly in the 4 years between the first and the second study, both for Gram-negative and -positive bacteria ($p < 0.0001$ and $p = 0.007$, respectively).

3.2 | Patient characteristics in the nonclassical versus the classical aetiology groups

In general, the patients arrived clinically very ill in Finland, LatAm and Angola. Every second child (50%) with BM due to a classical

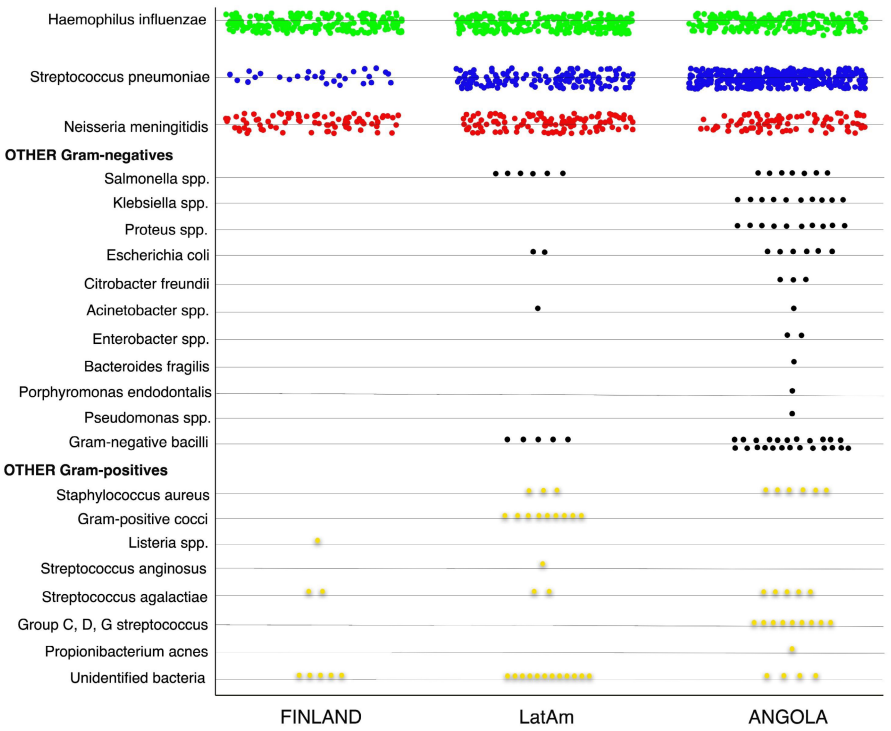

FIGURE 1 While the three classical agents *H. influenzae*, *S. pneumoniae* and *N. meningitidis* preponderated, the aetiology scene of BM in Finland, Latin America and Angola, Finland clearly stood out in terms of paucity of other causative agents

agent failed to score 13 on the age-adjusted Glasgow Coma Scale, this level indicating a clearly sick patient (Table 1). This was the case for 57% and 45% for children in the nonclassical Gram-negative and -positive groups respectively ($p = 0.39$). All aetiologies combined; the median overall age was 1.1 years; the median age was also the same for those with BM due to classical agents. Median age was 0.8 and 1.0 year for the Gram-negative and Gram-positive groups respectively ($p = 0.19$). The genders were presented fairly evenly (55% for boys, 45% for girls overall; $p = 0.41$).

Of the more than 100 analysed patient covariates we summarised in Table 1, those where the difference between the classical and the nonclassical Gram-negative and -positive meningitides was significant. Regarding children with nonclassical meningitis, when compared with patients with meningococcal, *H. influenzae* or pneumococcal meningitis, they showed poorer indices. The children with nonclassical Gram-negative meningitis were the most ill group.

Overall (Table 1), approximately 46% of children with nonclassical Gram-negative BM arrived moderately to severely (z-score ≤2) underweight; this was the case for 31% and 17% for those in the Gram-positive and the classical BM groups respectively ($p < 0.001$). Further differences between the nonclassical Gram-negative groups versus the classical BM groups were a low (<8.5 g/dl) haemoglobin (OR 1.86, 95% CI 1.17–2.97), history of preadmission antimicrobials (OR 2.58, 95% CI 1.59–4.18), late arrival (after 3 days) for treatment (OR 4.74, 95% CI 2.69–8.34) and a more severe course reflected by seizures (OR 1.96, 95% CI 1.24–3.11) and dyspnoea (OR 2.86, 95% CI 1.69–4.83). The nonclassical Gram-positive BM patients differed significantly from classical BM only by living in Angola (OR 2.92, 95% CI 1.32–6.45).

In Angola (Table 3), the following characteristics were found more likely in children with Gram-negative nonclassical BM ($N = 66$) than in children with BM of classical aetiology: underweight (OR 2.04, 95% CI 1.22–3.41), treatment delay over three days (OR 3.49, 95% CI 1.79–6.81) and a history of preadmission antimicrobials (OR 2.27, 95% CI 1.30–3.96). During hospital stay, children with Gram-negative BM presented more frequently seizures (OR 1.80, 95% CI 1.01–3.19) and dyspnoea (OR 1.76, 95% CI 1.02–3.03). In regard to patients with Gram-positive nonclassical aetiology ($N = 20$) versus classical aetiology, no variable reached a significant difference.

In LatAm (Table 3), the results of a similar analysis showed that patients with nonclassical Gram-negative aetiology ($N = 14$) were 6.44 (95% CI 2.09–19.82) times more likely to be underweight and 3.34 (95% CI 1.07–10.37) times more likely to present seizures during hospital stay compared to classical aetiology. In Gram-positive nonclassical BM patients ($N = 6$), no variable reached a significant difference with classical aetiology. In Finland, a similar analysis was invalidated by the minimal number of patients (no Gram-negatives, three Gram-positives).

3.3 | Outcomes in the nonclassical versus the classical aetiology groups

Figure 2 gives a general picture of how the children from three continents with usual or unusual type of BM performed. The different treatments we tested in the original studies[1–5] did not improve the prognosis overall, except glycerol which diminished severe neurological sequelae in LatAm.[3]

Overall (Table 1), nonclassical meningitis left, more frequently, the patient with severe neurological sequelae (22–25%) than had he or she undergone meningococcal, *H. influenzae* or pneumococcal meningitis (8%). The case fatality was 60% in nonusual

TABLE 2 Causative bacteria of meningitides Angola during the two studies

	2005–2008 *n* = 520	2012–2017 *n* = 197	All
Classical bacteria	482 (92.7)	149 (75.6)	631 (88.0)
Haemophilus influenzae	199 (38.3)	8 (4.1)	207 (28.9)
Streptococcus pneumoniae	230 (44.2)	104 (52.8)	334 (46.6)
Neisseria meningitidis	53 (10.2)	37 (18.8)	90 (12.6)
Gram-negative bacteria	28 (5.4)	38 (19.3)	66 (9.2)
*Salmonella*spp.	3 (0.6)	4 (2.0)	7 (1.0)
*Klebsiella*spp.	4 (0.8)	6 (3.1)	10 (1.4)
*Proteus*spp.	6 (1.2)	4 (2.0)	10 (1.4)
Escherichia coli	2 (0.4)	4 (2.0)	6 (0.8)
Citrobacter freundii	1 (0.2)	2 (1.0)	3 (0.4)
*Acinetobacter*spp.	1 (0.2)	0	1 (0.1)
*Enterobacter*spp.	1 (0.2)	1 (0.5)	2 (0.3)
Bacteroides fragilis	1 (0.2)	0	1 (0.1)
Porphyromonas endodontalis	1 (0.2)	0	1 (0.1)
*Pseudomonas*spp.	1 (0.2)	0	1 (0.1)
Unidentified gram-negative bacteria	7 (1.4)	17 (8.6)	24 (3.4)
Gram-positive bacteria	10 (1.9)	10 (5.1)	20 (2.8)
Staphylococcus aureus	2 (0.4)	4 (2.0)	6 (0.8)
Streptococcus agalactiae	1 (0.2)	3 (1.5)	4 (0.6)
Group C streptococcus	4 (0.8)	3 (1.5)	7 (1.0)
Group D streptococcus	1 (0.2)	0	1 (0.1)
Group G streptococcus	1 (0.2)	0	1 (0.1)
Propionibacterium acnes	1 (0.2)	0	1 (0.1)

Gram-negative, 51% in nonusual Gram-positive, and 24% in classical BM. Accurate assessment of hearing impairment was possible in 1036 cases. Deafness developed in classical BM in 9% (88/996) versus in 13% (4/30) and 0% in nonclassical Gram-negative and Gram-positive BM respectively ($p = 0.42$). Median Glasgow Outcome Scale Score was best in classical BM (4, IQR 3–5), worst in nonclassical Gram-negative BM (2, IQR 1–5), and in-between in nonclassical Gram-positive BM (3, IQR 1–5).

In Angola (Table 3, Appendix S1), the Gram-negative nonclassical BM patients ($N = 66$) were 2.18 (95% CI 1.31–3.64) times more likely to die than those with classical aetiology. Likewise, the combined outcome of death or any severe sequelae was 2.94 (95% CI 1.64–5.40) times more likely. For Gram-positive nonclassical BM ($N = 22$), none of the tested outcomes reached a significant difference with classical aetiology.

In LatAm (Table 3), a similar analysis showed that Gram-negative nonclassical BM patients ($N = 14$) were 4.92 (95% CI 1.22–19.88) times more likely to recover with severe neurological sequelae, whereas Gram-positive BM patients ($N = 6$) were 6.61 (95% CI 1.31–33.42) times more likely to die. In Finland, a similar analysis was invalidated by the minimal number of patients.

Table 4 presents multivariate analysis of predictors of death and the combined outcome of death or severe sequelae. Even if the area was the strongest predictor of poor outcome, nonclassical Gram-negative BM increased the odds for death 2.25-fold and for the combined outcome 2.63-fold. In unusual Gram-positive BM, no significant differences appeared. In severe neurological sequelae or deafness alone, no significant differences between the groups of bacteria were found.

4 | DISCUSSION

Our previous three-continent analysis of 2123 cases overviewed the children's general performance in BM,[13] while we here detailed the 1568 cases in which the causative agent was identified. Thus, we hereby availed the rather unique chance to figure out the pictures of meningococcal, *H. influenzae* and pneumococcal meningitis versus cases due to the nonclassical Gram-negative and -positive bacteria. Although data were collected over a large time span, the basic bacteriology at the study sites was virtually the same and remained unchanged.

Nonclassical Gram-positive bacteria comprised only a third (29 vs. 80) of the number of cases compared with the nonclassical Gram-negative bacteria, albeit this was not the case in Finland. *S. aureus* meningitis and disease due to various streptococci likely had their origin in the skin flora. Scratches and other superficial injuries are commonplace in children everywhere and given that suboptimal hygienic conditions increase the risk of secondary skin infections, occasional blood invasion is plausible.

In contrast, the multiplicity of most Gram-negative bacteria points toward the origin being in the gastrointestinal tract, sometimes perhaps the urinary tract. When intact, the junctions between gut epithelial cells are impermeable to enteric pathogens. In Africa, where diarrheal diseases are commonplace, this barrier is loosened and various Gram-negative bacteria gain access to blood and sometimes to the central nervous system. Severe malnutrition,[12,14,15] anaemia,[16,17] malaria,[18] sickle-cell disease[19] and HIV[18] increase the risk of bacteraemia. As we identified 19 bacterial pathogens in our Angolan series, no less than 28 different bacteria among 542 cerebrospinal specimens were found in Abuja, Nigeria.[20] Persistent intestinal inflammation, one manifestation of "an environmental enteric dysfunction",[21] is a plausible explanation behind these factors. *Salmonellae*, but not *Klebsiellae* or *Protei*, were fairly frequently

TABLE 3 Odds ratios and 95% confidence intervals for children with meningitis caused by the nonclassical Gram-negative or -positive bacteria versus the three "classics," *N. meningitidis*, *H. influenzae* or *S. pneumoniae*

	Angola Nonclassical vs. classical bacteria		LatAm Nonclassical vs. classical bacteria	
Variable	**Gram-negative**	**Gram-positive**	**Gram-negative**	**Gram-positive**
Patient characteristics				
Age ≥ 1 year	1.09 (0.66–1.81)	1.38 (0.56–3.41)	1.49 (0.49–4.51)	1.21 (0.24–6.05)
Sex, female	1.44 (0.85–2.43)	1.39 (0.57–3.41)	0.97 (0.33–2.85)	0.68 (0.12–3.77)
Glasgow Coma Score < 13	0.96 (0.57–1.62)	0.85 (0.35–2.07)	1.01 (0.34–2.95)	0.66 (0.12–3.65)
Weight for age Z-score < −2	2.04 (1.22–3.41)	1.05 (0.40–2.77)	6.44 (2.09–19.82)	3.75 (0.67–20.96)
Ill >3 days before admission	3.49 (1.79–6.81)	1.09 (0.44–2.70)	1.20 (0.31–4.56)	–
Pretreatment antibiotics	2.27 (1.30–3.96)	1.14 (0.44–2.93)	1.08 (0.35–3.26)	0.39 (0.04–3.34)
B-haemoglobin <8.5 g/dl	0.67 (0.39–1.15)	0.70 (0.27–1.78)	1.24 (0.42–3.62)	0.41 (0.05–3.72)
Seizures before or at admission	1.29 (0.77–1.31)	1.11 (0.45–2.77)	1.59 (0.53–4.81)	0.93 (0.17–5.12)
Seizures at ward	1.80 (1.01–3.19)	1.16 (0.46–2.94)	3.34 (1.07–10.37)	0.52 (0.06–4.71)
Dyspnoea	1.76 (1.02–3.03)	0.70 (0.29–1.72)	2.08 (0.18–23.60)	–
Outcomes				
Death	2.18 (1.31–3.64)	1.58 (0.65–3.88)	2.64 (0.81–8.67)	6.61 (1.31–33.42)
Severe neurological sequelae	1.63 (0.64–4.16)	2.55 (0.66–9.90)	4.92 (1.22–19.88)	–
Deafness	1.22 (0.35–4.28)	–	0.99 (0.12–8.27)	–
Death or any severe sequelae[a]	2.94 (1.60–5.40)	2.41 (0.84–6.92)	2.40 (0.79–7.28)	3.09 (0.51–18.70)

Note: Univariate analysis of patient characteristics and outcome.

[a] Death or severe neurological sequelae or deafness.

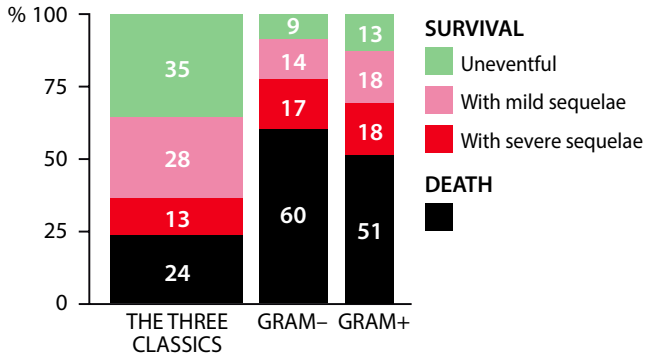

FIGURE 2 Children's outcomes from meningitis due to *N. meningitidis*, *H. influenzae* or *S. pneumoniae* (THE THREE CLASSICS) versus other Gram-negative (GRAM-) or Gram-positive (GRAM+) bacteria. All numbers indicate percentages

detected also in LatAm, being totally nonexistent in our series from Finland (Figure 1). Gram-negative organisms, classical and nonclassical, contributed the majority (72%) of cases of childhood BM in a small series (N 18) in Nepal,[22] whereas no difference to Gram-positives prevailed in a more recent study (N 52) from the same country.[23]

Concerning the variables associated with nonclassical BM (Table 3), our most reliable results come from Angola with most patients. These results underline how especially Gram-negative nonclassical BM affects children in many ways poorly prepared to fight the infection: underweight, partially treated and with delay to receive appropriate BM treatment. Not unexpectedly, considering the accumulation of risk factors for adverse outcome, they doubled the already high mortality figures of Angola. Results from LatAm differed somewhat from Angola, possibly due to the small number of patients, and should be controlled with more cases.

Once *H. influenzae* type b, pneumococcal and meningococcal vaccines become available, approximately a 90% reduction in childhood BM is possible. Now that the role of these three agents is diminishing, the role of nonclassical agents is growing. In our study, the proportion of nonclassical bacteria increased with time, being lowest in the first studies in Finland and highest in the last study in Angola. If new epidemiological studies confirm our findings, developing vaccines against unusual agents might become necessary. Accordingly, there would be an increasing need for effective *Klebsiella pneumoniae*, *Escherichia coli* and *S. aureus* vaccines. Initial steps have been taken towards this goal.[24–26]

This study has some limitations. Although major quality differences in the performance of our institution's bacteriology laboratories were unlikely, the laboratories were not uniformly standardised. Antibiotic resistance was not addressed. Particularly in Africa, common conditions such as sickle cell disease, HIV and parasitic infections (including malaria) likely affected the results.[14–19] We did not have the resources to routinely investigate these conditions. However, it is unlikely that these potentially confounding factors would have been significantly concentrated in only one aetiology group. We performed multivariate analysis to mitigate the effect of

TABLE 4 Multivariate analysis of factors associated with death and dismal outcome (death, severe neurological sequelae or deafness) in children with meningitis

	Death		Dismal outcome	
Variable	**OR (95% CI)[a]**	***p*value**	**OR (95% CI)**	***p*value**
Angola vs. Finland	11.02 (5.05–24.06)	<0.0001	11.76 (5.96–23.19)	<0.0001
Latin America vs. Finland	4.28 (1.91–8.59)	0.0004	8.51 (4.29–16.87)	<0.0001
Angola vs. Latin America	2.58 (1.71–3.88)	<0.0001	1.38 (0.98–1.94)	0.06
Weight for age Z-score < −2	1.24 (0.90–1.71)	0.19	1.20 (0.87–1.65)	0.26
Ill > 3 days before admission	1.31 (0.97–1.77)	0.075	1.44 (1.09–1.91)	0.010
B-haemoglobin ≤ 8.7 g/dl (median)	1.41 (1.00–2.01)	0.052	1.63 (1.19–2.24)	0.003
Nonclassical Gram-negative bacteria vs. classical bacteria	2.25 (1.35–3.75)	0.002	2.63 (1.47–4.70)	0.001
Nonclassical Gram-positive bacteria vs. classical bacteria	1.81 (0.18–4.28)	0.18	2.33 (0.88–6.18)	0.09

[a]Odds ratios and 95% confidence intervals.

area, underweight, treatment delay and anaemia in evaluating the effect of nonclassical bacteria in outcome. The study sites had the most effect on outcome of children. Even if one would think that the outcome would improve with time with improving healthcare, in the present study the outcome worsened with time as the studies were done first in Finland (a high-income country) thereafter in Latin America (upper middle-income area) and latest in Angola (lower middle-income country).

Despite these limitations, a very large series of practically every type of non-neonatal paediatric BM from multiple study sites were here compiled and patient clinical characteristics and outcome in unusual BM was directly compared with that in classical meningococcal, Hib or pneumococcal BM. Our results should encourage development of vaccines against these unusual agents.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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