Antibiotic Regimens in meningitis epidemics in sub-Saharan Africa:

Report for the WHO Meningitis Guideline Revision (May 2014)

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Recommendation question:

Should single dose antibiotic regimens continue to be recommended for suspected cases of meningitis during a meningococcal meningitis outbreak, and, if so, in what circumstances

Current WHO recommendations:

Presumptive treatment in a district with confirmed meningococcal meningitis epidemic is recommended as follows:

<2 months old: 7-day regimen (ceftriaxone) to cover Spn, Hib, NmA and enterobacteria

2-23 months old: 5-day regimen (ceftriaxone) to cover Spn, Hib, Nm

≥ 2 years old: single-dose regimen targeted to Nm, and continue treatment if not improving

As far as possible, the age groups displayed in this report match the current treatment guidelines.

PICO question:

Among cases in meningococcal meningitis outbreaks due to NmA before the introduction of MenAfriVac®, the MenA conjugate vaccine, compared with outbreaks due to other Nm serogroups, what is the proportion of cases receiving "sub-optimal" treatment, i.e. being caused by other pathogens than Nm?

May 3, 2014

I. Background

High case fatality is observed from pneumococcal meningitis in the meningitis belt. The internationally approved and gold standard presumptive treatment of bacterial meningitis is based on the administration of one or more antibiotics for at least 5 days, according to the local epidemiology of meningitis and patient characteristics. To ensure rapid and effective treatment at first contact, and given large volume of cases during past large scale meningitis outbreaks, a single dose regimen is currently recommended during epidemics of meningococcal meningitis in Africa for patients >23 months. This regimen is effective treatment for meningitis due to *N. meningitidis* but not for meningitis due to *S.pneumoniae (Spn)* and *H. influenzae type b (*Hib*)*. With fewer large scale epidemics of menininggococcal meningitis following the introduction of the serogroup A meningococcal conjugate vaccine, a higher proportion of meningitis cases due to *Spn* and Hib is expected.

II. Aim and objectives

The PICO 3 analysis aims to answer the following primary questions:

1) What is the distribution of causative organism (pathogen) among confirmed meningitis cases during *NmW /NmX epidemics compared with that during NmA epidemics?
2) What is the distribution of causative organism (pathogen) among different age groups of confirmed meningitis cases during *NmW /NmX epidemics compared with that during NmA epidemics?

As well as the following subsidiary questions to support the recommendations:

3) What it the case fatality of meningitis cases during *NmW /NmX epidemics compared with that during NmA epidemics?
4) What is the pathogen distribution during non-epidemic periods?

*Nm W and Nm X were the only Nm serogroups other than Nm A responsible for epidemics during the analysis period.

III. Methods

1. Evidence needed

Since data on antibiotic use is not routinely collected, evidence on patient outcome according to treatment protocol was not available. In order to infer the proportion of patients that would be treated sub-optimally during meningitis outbreaks, evidence on the incidence of meningitis due to Nm, Spn and Hib during outbreaks of meningococcal meningitis was gathered

2. Evidence gathering

We included events between 2002-2012, in all countries of the African meningitis belt

Data were retrieved from 3 main sources:

- Surveillance, from MoH, WHO country offices (enhanced and laboratory surveillance datasets).
- Partners (aggregated extracted on specific templates)
- Review of the literature (data extracted on specific templates)

Details on data collected (surveillance datasets and data from partners) are provided in Appendix 1.

3. Definitions

Current WHO case definitions were used for surveillance data[1,2].

An epidemic was defined based on alert/epidemic thresholds established in 2000[3]: Alert threshold > 5 cases/100,000 per week and epidemic threshold > 10 cases/100,000 per week.

An epidemic year at district level was defined as a year where cumulative attack rate (CAR)>100 cases/100,000 pop., as used in previous studies[4,5].

Epidemic period as time in weeks from first week alert threshold was crossed to last week before incidence declined below alert threshold, with crossing of the epidemic threshold in between.

Non-epidemic period is either a time when the epidemic threshold was not crossed during the "epidemic season" (ie from epidemiological weeks 1 to 26), or any time past week 26.

Single serogroup epidemic is defined as an epidemic with one single Nm serogroup representing >70% of all confirmed cases (minimum of 10 confirmed cases[6]).

Mixed serogroup epidemic is defined an epidemic with two or more Nm serogroups representing >70% of all confirmed cases (minimum of 10 confirmed cases[6]).

For the published papers, we used the definition provided by the authors. We noted if definitions were different than the above thresholds.

Inclusion criteria: Epidemic events had to meet the following criteria: i) ≥10 confirmed meningitis cases[6] ii) proportion of positive CSF samples out of CSF taken ≥20%, iii) single serogroup or mixed serogroup epidemic (defined above), iv) epidemic threshold crossed, v) Nm, Hi/Hib and Spn tested for.

NB Events could thus be included if not meeting the definition of epidemic year above (See Appendix 2).

4. Analysis

We conducted a descriptive analysis presenting a range of results for each of the questions asked. The results are based on confirmed cases (overall proportion) and on epidemic events (mean and median by event) regardless of the data source of the data (ie, using surveillance datasets and the data obtained from the literature review). They focus on the 3 main pathogens of interest for the revision of the guidelines for outbreak response (Nm, Hib and Spn), with emphasis on comparing the outputs obtained for Nm vs Hib/Spn in each of the situations summarized. Pooled proportions of Nm, Hb and Spn were calculated using a random effects model.

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[1] World Health Organization Regional Office for Africa (AFRO). Standard Operating Procedures for Enhanced Meningitis Surveillance in Africa. Ouagadougou, Burkina Faso; 2009.

[2] World Health Organization. Managing meningitis epidemics in Africa: A quick reference guide for health authorities and health-care workers 2010. Available from: http://www.who.int/csr/resources/publications/HSE_GAR_ERI_2010_4/en/index.html

[3] World Health Organization. Detecting meningococcal meningitis epidemics in highly endemic African countries. Wkly Epidemiol Rec 2000;75(38):306-9.

[4] Leake JAD, Kone ML, Yada AA, Barry LF, Traore G, Ware A, et al. Early detection and response to meningococcal disease epidemics in sub-Saharan Africa: appraisal of the WHO strategy. Bull World Health Organ 2002;80:342-349.

[5] Lewis R, Nathan N, Diarra L, Belanger F, Paquet C. Timely detection of meningococcal meningitis epidemics in Africa. Lancet. 2001;358(9278):287-93

[6] World Health Organization. The use of polysaccharide trivalent ACW vaccine for the control of epidemic meningococcal disease outbreaks in countries of the African meningitis belt. 2003

IV. Findings

1. Epidemic and non-epidemic events included in the analysis

A total of 22 epidemic events met the inclusion criteria: 11 NmW and/or NmX epidemics, and 11 NmA epidemics, used as a comparator. All events occurred in countries of the meningitis belt between 2002-2014. Focus was given to single serogroup epidemics and /or mixed epidemics without Nm A component (NmW and/or NmX) vs NmA. Mixed epidemics with NmA participation were not included in the main analysis for the two primary questions as the introduction of the MenA conjugate vaccine in Sub-Saharan Africa should limit the occurrence of such epidemics.

NmW epidemic events meeting the inclusion criteria occurred in Burkina Faso between 2002 and 2012. Records were also available for Benin, Cote d'Ivoire, Gambia, Ghana, Niger and Uganda, all of which occurred in 2010-2014 (Table 1). Two NmX epidemic events were documented in Burkina Faso, 2010 and Togo, 2007. Eleven NmA epidemic events were used for comparison purposes (NmA epidemics vs. non-NmA epidemics) (Table 2). All occurred in areas where the MenA conjugate vaccine had not yet been introduced.

Notes:

- In some rare instances, the type of Hi wasn't specified in the original datasets. Hi of "unspecified" or "any" type were included in the analysis as Hib.
- At the individual level, cases with more than one causal pathogen identified were discarded from the analysis. This situation occurred only in surveillance datasets.
- When the same events were described using different data sources, preference for inclusion was given to i) published data over surveillance datasets and ii) the largest and most comprehensive datasets.

2. Overall pathogen distribution

In NmW and NmX epidemics, about 90% of the cases were of meningococcal origin (overall proportion, as well as mean and median by epidemic; Table 1). In NmA epidemics, about 88% of the cases were of meningococcal origin with a mean and a median both greater than 90% (Table 2). The pooled proportions showed similar differences with wide confidence intervals. Details by event are provided in Appendix 3.

Conclusion: The overall pathogen distribution in NmW and NmX epidemics appears to be close to that of NmA epidemics.

Limitations: These findings may be influenced by the timing of epidemics in relation to the introduction of the Hib and Spn vaccines, and by reactive vaccination in NmW and NmA epidemics. Published reports of outbreaks are likely to be biased towards reporting of larger epidemics.

Table 1: Pathogen distribution in NmW, NmX and mixed Nm W/X epidemics

Country	Dates[7]	Number of districts	Predominant pathogen(s)	Pathogens identified % of total (n)				Data source
				Nm of all serogroups	Hib and Spn	Hib	Spn	
Benin	2012, W 1-26	5	NmW	95.9% (71)	4.1% (3)	4.1% (3)	0%	(Njanpop-Lafourcade, Hugonnet et al. 2013)
Burkina Faso	2002 W 1-23	30	NmW	91% (183)	9% (18)	2% (3)	7% (15)	(Bertherat, Yada et al. 2002)
Burkina Faso	2012, W 1-17	14	Nm W/X	71% (318)	29% (132)	3% (12)	26% (120)	(Savadogo, Kyelem et al. 2013)
Burkina Faso	2012	12	NmW	93% (652)	7% (49)	0.1% (1)	6.8% (48)	Surveillance datasets
Cote d'Ivoire*	2012	1	NmW	88.6% (31)	11.4% (4)	0% (0)	11.4% (4)	Surveillance datasets
Gambia**	2012, W 6-27	2	NmW	85 % (103)	15% (18)	0% (0)	15% (18)	(Hossain, Roca et al. 2013)
Ghana	2010	1	NmW	100% (13)	0% (0)	0% (0)	0% (0)	Surveillance datasets
Niger	2011	8	NmW	85% (408)	15% (72)	0.4% (2)	15% (70)	(Collard, Issaka et al. 2013)
Uganda	2014	1	NmW	93.3% (14)	6.7% (1)	0% (0)	6.7% (1)	Surveillance datasets
Burkina Faso	2010	4	NmX	96.5% (137)	3.5% (5)	0% (0)	3.5% (5)	Surveillance datasets
Togo	2007	1	NmX	90.8% (89)	9.2% (9)	2% (2)	7.1% (7)	(Delrieu, Yaro et al. 2011)
Distribution based on confirmed cases N=1880			**Number of confirmed cases**	**1701**	**179**	**11**	**168**	
			Pooled proportion (95%-CI)	**90.5%**	**9.5%**	**0.6%**	**8.9%**	
Distribution based on epidemic events N=10			**Mean (SD[8])**	**91.9% (4.9%)**	**8.1% (4.9%)**	**0.9% (1.4%)**	**7.3% (5.3%)**	
			Median (Range)	**92% (85-100%)**	**8% (0-15%)**	**0.05% (0-4.1%)**	**6.9% (0-15%)**	

*The pathogens identified as Nm Y/W via latex agglutination were considered as potentially of W serogroup, with a total hence greater than 70%

**Although the investigation of the epidemic was published in the paper referenced, the estimates presented above were obtained directly from the authors of the paper for the Feb 1, 2012-June 25, 2012 period

[7] When dates are not specified, the epidemic event is described from crossing the alert threshold up to crossing it down, as opposed to specified dates based on information provided by authors

[8] SD, standard deviation

Table 2: Pathogen distribution during NmA epidemics

Country	Dates[2]	Number of districts	Predominant serogroup	Pathogens identified % of total (n)				Data source
				Nm of all serogroups	Hib and Spn	Hib	Spn	
Burkina Faso	2006, W 1-18	1	NmA	75.5% (77)	24.5% (25)	9.8% (10)	14.7% (15)	(Sie, Pfluger et al. 2008)
Burkina Faso	2006	3	NmA	100% (16)	0% (0)	0% (0)	0% (0)	Surveillance datasets
Burkina Faso*	2006, W 1-14	3	NmA	100% (88)	0% (0)	0% (0)	0% (0)	(Tall, Hugonnet et al. 2012)
Burkina Faso*	2007, W 1-14	4	NmA	76.9% (20)	23.1% (6)	0%	23% (6)	(Tall, Hugonnet et al. 2012)
Burkina Faso*	2008, W 1-14	2	NmA	75% (15)	25% (5)	0%	25% (5)	(Tall, Hugonnet et al. 2012)
Cameroon*	2010, W 6-18	1	NmA	100% (34)	0% (0)	0%	0%	(Massenet, Vohod et al. 2011)
Chad	2010	1	NmA	100% (10)	0% (0)	0%	0%	Surveillance datasets
Niger	2008, W 1-28	4	NmA	87.7% (1072)	12.3% (150)	2.7% (33)	9.6% (117)	(Collard, Maman et al. 2011)
Nigeria	2008, W 1-13	Jigawa state	NmA	98.8% (84)	1.2% (1)	1.2% (1)	0%	(Akhimien and Akpan 2010)
South Sudan	2013	1	NmA	100% (13)	0% (0)	0%	0%	Surveillance datasets
Togo	2007	1	NmA	84.5% (218)	15.5% (40)	3.1% (8)	12.4% (32)	(Delrieu, Yaro et al. 2011)
Distribution based on confirmed cases N=1874			**Number of confirmed cases**	**1647**	**227**	**52**	**175**	
			Pooled proportion (95%-CI)	**87.1% (80.9% - 91.4%)**	**12.9% (8.6% - 19.1%)**	**3.3% (2.0% - 5.5%)**	**11.1% (7.5% - 16.1%)**	
Distribution based on events N=11			**Mean (SD)**	**90.8% (11.0%)**	**9.2% (11.0%)**	**1.5% (3.0%)**	**7.7% (9.8%)**	
			Median (Range)	**98.8% (75-100)**	**1.2% (0-25)**	**0.0% (0-9.8)**	**0.0% (0-25)**	

*localized epidemics

3. Pathogen distribution by age group

In NmW and NmX epidemics where the age categories could be matched to those of the recommendations (surveillance data sets only), the overall proportion of meningococcal cases by age group varied from 66.7% in cases younger than 2 months to 95% in cases between 2 and 14 years, with important variations by epidemic as represented by the mean (SD) and median (range). Values of the overall proportion of Hib and Spn cases were greater than 15% in cases aged <2-23 months and above 30 years (Table 3a). For NmW epidemics where the age categories did not match those of the recommendations, no case of Hib was identified and Spn was confirmed in cases younger than 4 years only (Table 3b).

Relevant data was available for 2 NmA epidemics but the age groups of only the Togo one matched the current recommendations (Table 4). In this event, less than 10% of Hib and Spn combined were found in all age groups, except the 2-23 months category. In the other event, proportions of Hib and Spn of less than 10% were observed in age groups from 5 to 29 year olds except the 15-19 year olds (17%). Hib cases were confirmed in cases younger than 4 years old only. See Appendix 4 for more details.

Conclusion: The proportion of pathogens per age group was similar between NmW/NmX epidemics and NmA epidemics (but see limitations). In NmW epidemics the proportion of other pathogens in 2-14 year olds was 5%, rising to 9% in 15-29 year olds, and higher in over 29 year olds though there were few cases in this older age group.

Limitations: The comparison of age group distribution for NmA epidemics is limited to one country. The numbers of samples available for comparison in some age groups were quite low with wide confidence intervals (See GRADE table)

Table 3: Pathogen distribution by age group during NmW, NmX and mixed Nm W/X epidemics[9]

a) From individual surveillance datasets

Country, year, epidemic type, number of confirmed cases	Age group	Number of confirmed cases	Pathogens identified % (n)			
			Nm of all serogroups	Hib and Spn	Hib	Spn
Burkina Faso, 2012 NmW epidemic N=697	<2Months	*7*	71.4% (5)	28.6% (2)	0	28.6% (2)
	2-23 Months	*125*	87.2% (109)	12.8% (16)	0	12.8% (16)
	2-4yrs	*165*	97.6% (161)	2.4% (4)	0.6% (1)	1.8% (3)
	5-14yrs	*308*	94.2% (290)	5.8% (18)	0	5.8% (18)
	15-29yrs	*67*	91% (61)	9.0% (6)	0	9.0% (6)
	>=30yrs	*25*	92% (23)	8.0% (2)	0	8.0% (2)
Burkina Faso, 2010 NmX epidemic N=125	<2m	*1*	100% (1)	0	0	0
	2-23 m	*6*	83.3% (5)	16.7% (1)	0	16.7% (1)
	2-4y	*22*	95.5% (21)	4.5% (1)	0	4.5% (1)
	5-14y	*89*	97.8% (87)	2.2% (2)	0	2.2% (2)
	15-29y	*6*	100% (6)	0	0	0
	≥30y	*2*	50% (1)	50% (1)	0	50% (1)
Burkina Faso, 2002 NmW epidemic N=104	<2Months	-				
	2-23 Months	*18*	88.9% (16)	11.1% (2)	0	11.1% (2)
	2-4yrs	*30*	96.7% (29)	3.3% (1)	0	3.3% (1)
	5-14yrs	*39*	100% (39)	0	0	0
	15-29yrs	*15*	93.3% (14)	6.7% (1)	0	6.7% (1)
	>=30yrs	*2*	100% (2)	0	0	0
Benin, 2012 NmW epidemic N=62	<2Months	*4*	50% (2)	50% (2)	0	50% (2)
	2-23 Months	*23*	56.5% (13)	43.9% (10)	8.7% (2)	34.8% (8)
	2-4yrs	*18*	72.2% (13)	28.4% (5)	11.1% (2)	16.7% (3)
	5-14yrs	*15*	100% (15)	0	0	0
	15-29yrs	-		-	-	-
	>=30yrs	*2*	50% (1)	50% (1)	0	50% (1)
Cote d'Ivoire, 2012 NmW epidemic N=34	<2Months	-	-	-	-	-
	2-23 Months	*2*	100% (2)	0	0	0
	2-4yrs	*11*	100% (11)	0	0	0
	5-14yrs	*5*	100% (5)	0	0	0

[9] Epidemics are presented by decreasing total number of confirmed cases

	15-29yrs	*12*	83.3% (10)	16.7% (2)	0	16.7% (2)
	>=30yrs	*4*	75% (3)	25% (1)	0	25.0 % (1)
Ghana, 2010 NmW epidemic N=13	<2Months	-	-	-	-	-
	2-23 Months	*2*	100% (2)	0	0	0
	2-4yrs	*3*	100% (3)	0	0	0
	5-14yrs	*4*	100% (4)	0	0	0
	15-29yrs	*2*	100% (2)	0	0	0
	>=30yrs	*2*	100% (2)	0	0	0
Uganda, 2014 NmW epidemic N=14	<2Months	-	-	-	-	-
	2-23 Months	*3*	100% (3)	0	0	0
	2-4yrs	*4*	100% (4)	0	0	0
	5-14yrs	*5*	100% (5)	0	0	0
	15-29yrs	-		0		
	>=30yrs	*2*	50% (1)	50% (1)	0	50% (1)

Distribution based on confirmed cases N=1094		**Pooled proportion of pathogens identified % (95%-CI)**			
		Nm of all serogroups	**Hib and Spn**	**Hib ***	**Spn**
<2Months	***12***	**0.649 0.364 0.856**	**0.351 0.144 0.636**		**0.351 0.144 0.636**
2-23 Months	***184***	**0.776 0.609 0.886**	**0.224 0.114 0.391**		**0.188 0.120 0.281**
2-4yrs	***261***	**0.916 0.798 0.968**	**0.084 0.032 0.202**		**0.054 0.026 0.108**
5-14yrs	***483***	**0.936 0.877 0.967**	**0.064 0.033 0.123**		**0.060 0.040 0.088**
15-29yrs	***111***	**0.899 0.827 0.943**	**0.101 0.057 0.173**		**0.101 0.057 0.173**
>=30yrs	***43***	**0.755 0.579 0.873**	**0.245 0.127 0.421**		**0.245 0.127 0.421**

Distribution based on epidemic events N=8		**Pathogens identified (mean (SD); median (range))**			
		Nm of all serogroups	**Hib and Spn**	**Hib***	**Spn**
<2Months	***12***	**73.8% (0.25); 71.4% (50-100)**	**26.2% (0.25); 28.6% (0-50)**		**26.2% (0.25); 28.6% (0-50)**
2-23 Months	***184***	**82% (0.22); 88% (50-100)**	**18.1% (0.22); 11.95% (0-60)**		**14.4% (0.16); 11.95% 0-40)**
2-4yrs	***261***	**92.1% (0.12); 97.2% (72.2-100%)**	**8.0% (0.12); 2.85 % (0-28.4)**		**3.3% (0.06) ; 0.9% (0-16.7)**
5-14yrs	***483***	**96.2% (0.08); 100% (77.8-100)**	**3.8% (0.08); 0% (0-22.2)**		**3.1% (0.06) ; 0% (0-16.7)**
15-29yrs	***111***	**92.8% (0.07); 92.2% (83.3-100)**	**7.3% 0.07) ; 7.9% (0-16.7)**		**7.3% 0.07) ; 7.9% (0-16.7)**
>=30yrs	***43***	**70.9% (0.24) ; 62.5% (50-100)**	**29.1% (0.24); 37.5% (0-50)**		**29.1% (0.24) ; 37.5% (0-50)**

*Data not given as numbers very small

b) From data extraction templates and literature review[10]

Country, year, Type of epidemic, Total number of confirmed cases*	**Age groups**	**Number of confirmed cases**	**Pathogens identified % (n)**				**Data source**
			Nm of all serogroups	**Hib and Spn**	**Hib**	**Spn**	
Burkina Faso, 2012	<2y	80	56.3% (45)	43.8% (35)	7.5% (6)	36.3% (29)	(Savadogo, Kyelem et

Nm W/X epidemic N=450	2y-4y	86	86.0% (74)	14.0% (12)	4.7% (4)	9.3% (8)	al. 2013)
	5y-14y	206	76.7% (158)	23.3% (48)	0.5% (1)	22.8% (47)	
	15y-29y	54	59.3% (32)	40.7% (22)	1.9% (1)	38.9% (21)	
	≥30y	24	37.5% (9)	62.5% (15)	0% (0)	62.5% (15)	
Gambia, 2012 NmW epidemic N=121	<1y	35	69% (24)	31% (11)	0%	31% (11)	Data extraction templates
	1y-4y	72	92% (66)	8% (6)	0%	8% (6)	
	5y-14y	13	100% (13)	0%	0%	0%	
	15y-29y	1	100% (1)	0%	0%	0%	
	≥30y	-	-	-	-	-	
Benin, 2012 N=69 NmW epidemic	<1y	6	100% (6)	0%	0%	0%	(Njanpop-Lafourcade, Hugonnet et al. 2013)
	1-4y	19	100% (19)	0%	0%	0%	
	5-14y	32	100% (32)	0%	0%	0%	
	15-29y	5	100% (5)	0%	0%	0%	
	≥30y	6	100% (6)	0%	0%	0%	
	Unknown	1	0%	100% (1)	0%	100% (1)	

*with age available

Table 4: Pathogen distribution by age group in NmA epidemics[10]

Country, Year Predominant pathogen Total number of confirmed cases	**Age groups**	**Number of confirmed cases**	**Pathogens identified % (n)**				**Data source**
			Nm of all serogroups	**Hib and Spn**	**Hib**	**Spn**	
Burkina Faso, 2006 NmA epidemic N=103	<1y	*8*	62.5% (5)	37.5% (3)	25% (2)	12.5% (1)	(Sie, Pfluger et al. 2008)
	1-4y	*25*	60% (15)	40% (10)	28% (7)	12% (3)	
	5-9y	*37*	95% (35)	5% (2)	0% (0)	5% (2)	
	10-15y	*16*	94%(15)	6% (1)	0% (0)	6% (1)	
	15-19y	*6*	83% (5)	17% (1)	0% (0)	17% (1)	
	20-29y	*5*	100% (5)	0% (0)	0% (0)	0% (0)	
	30-39y	-	-	-	-	-	
	>40y	*6*	50% (3)	50% (3)	0% (0)	50% (3)	
Togo, 2007 NmA epidemic N=180	<2m	*3*	100% (3)	0% (0)	0% (0)	0% (0)	Individual surveillance datasets
	2-23 m	*21*	81% (17)	19% (4)	9.5% (2)	9.5% (2)	
	2-4y	*28*	92.9% (26)	7.1% (2)	3.5% (1)	3.5% (1)	
	5-14y	*79*	93.7% (74)	6.3% (5)	0% (0)	6% (5)	
	15-29y	*39*	100% (39)	0% (0)	0% (0)	0% (0)	
	≥30y	*10*	100% (10)	0% (0)	0% (0)	0% (0)	

Notes:

- Data in Tables 3b and 4 were not combined as i) there were only two events in each, and ii) the age groups did not match the age groups for the comparative analysis apart from the Togo data in Table 4.

[10] Age groups could not be matched with the treatment guidelines for part of these data; summary data are therefore not presented

- There are several epidemics without confirmed cases < 2 months

4. Severity of bacterial meningitis: case fatality

Relevant information on case fatality was available for 3 different NmW epidemics (Table 5). In those epidemics, the mean case fatality across epidemics was 8.6%. The case fatality of confirmed cases was 16.5% in the epidemic where such information was available, without specification of the causal pathogen (Gambia, 2012). In NmA epidemics, the case fatality of suspected cases was 3.9% (Table 6). It was 13.5% for confirmed cases in the only study where available, with pathogen-specific values of 46.7% for Spn and 7.4% for Nm (all being of serogroup A). No case fatality was recorded for Hib cases in this study. The span of case fatality values is wide and may also depend on the quality of the underlying surveillance and healthcare systems, as well as the virulence of the strains involved.

Limitations: Very limited information is available on the outcome of confirmed cases, overall and by pathogen (Hib in particular) regardless of the data source.

Table 5. Case fatality of confirmed meningitis cases during NmW epidemics

Country, year	Case fatality of suspected cases	Case fatality of confirmed cases**	Pathogen-specific mortality	Data source
Burkina Faso, 2002	1510/13124=12%	n/a	n/a	(Bertherat, Yada et al. 2002)
Gambia, 2012	36/469=8%*	14/85= 16.5%	n/a	(Hossain, Roca et al. 2013)
Niger, 2011	1260/22046=5.7%	n/a	n/a	(Collard, Issaka et al. 2013)
Mean (SD)	**8.6% (3.2%)**	**16.5% (one epidemic)**	**n/a**	
Median (Range)	**8% (5.7-12%)**	**-**	**n/a**	

*confirmed and suspected cases (Hossain, Roca et al. 2013)
**details by pathogen were not available in all instances

Table 6. Case fatality of meningitis cases during NmA epidemics

Country, year	Case fatality of suspected cases	Case fatality of confirmed cases**	Pathogen-specific mortality	Data source
Burkina Faso, 2006	n/a	13/96=13.5%	NmA: 6/81=7.4% Spn: 7/15=46.7% Hib: 0%	(Sie, Pfluger et al. 2008)
Niger, 2009	561*/13357= 4.2%	n/a	n/a	(Collard, Maman et al. 2011)
Nigeria, 2008	306/8616=3.6%	n/a	n/a	(Akhimien and Akpan 2010)
Mean (SD)	**3.9% (0.4%)**	**13.5% (one study)**	**NmA: 6/81=7.4% Spn: 7/15=46.7% Hib: 0% (one study)**	
Median (Range)	**3.9% (3.6-4.2%)**	**-**	**-**	

*numerator estimated to 561 based on provided mortality and denominator

5. Non-epidemic periods

The events included represent endemic data with seasonal fluctuations without crossing of the epidemic threshold as currently defined and rely on published studies, where age groups could not be matched to

these of the current treatment guidelines (Table 8). Of the 827 confirmed cases pooled from the 5 studies included, 72.7% cases were of Hib or Spn origin, with a mean by study of 75.8%. The proportion of Hib and Spn cases was highest in cases <5 years (80.9%).

Conclusion: The proportion of Hib and Spn was much higher (72.7%) than in Nm epidemic periods (9.9% for NmW) (p<0.0001).

Limitations: Limited information is available on case fatality of confirmed cases during non-epidemic periods and important fluctuations exist (Appx B: Mortality and morbidity).

There was no information on case fatality by pathogen and by age. One study included adult cases only. Data from sentinel surveillance (PBM, CVD-Mali) were not included in this part of the analysis because i) they are paediatric only ii) they could not always be matched with surveillance data, hence leaving uncertainty about epidemic classification.

Table 7: Summary findings for non-epidemic periods

	Pathogens identified				Data source
Overall pathogen distribution	Nm of all serogroups	Hib and Spn	Hib	Spn	(Adjogble, Lourd et al. 2007); (Mbelesso, Tatangba-Bakozo et al. 2006)*; (Guindo, Coulibaly et al. 2011) ; (Ouedraogo, Yameogo et al. 2012) ; (Sie, Pfluger et al. 2008)**
Based on confirmed cases (N=827)					
% (n)	27.3% (226)	72.7% (601)	18.7% (154)	54% (447)	
Based on studies (N=5)					
Mean (SD)	24.2% (10%)	75.8% (10%)	22.3% (15%)	49.1% (16%)	
Median (Range)	24.7% (7-33.4)	75.3% (66.6-93%)	26.8% (2-39%)	44.2% (34.4-74.2%)	
Pathogen distribution by age group, in studies where available					
Based on confirmed cases (N=497)					
% (n)	Nm of all serogroups	Hib and Spn	Hib	Spn	
<5 years	19.1% (58)	80.9% (245)	45.5% (138)	35.3% (107)	
5-14 years	60.3% (108)	39.7% (71)	10.6% (19)	29.1% (52)	
>=15 years	46.9% (97)	53.1% (110)	4.3% (9)	48.8% (101)	

*adult population, ie >15 years

**between January and April 2005

GRADE Evidence Profile

Quality assessment						Summary of findings: Proportion of Spn and Hib in NmA cf NmW and NmX epidemics					
Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	**Combined % Spn and Hib in Nm epidemics**	**NmA epidemics Overall % (95% CI)**	**NmW/X epidemics Overall % (95% CI)**	**Difference * (NmW/X-NmA)**	**Certainty of the evidence**	Importance
Surveillance data and literature review	No serious limitations	Serious inconsistency (wide variability between studies)	Serious indirectness (changing epidemiology, changing vaccination status)	No Serious imprecision	Serious risk of bias (towards reporting of larger epidemics;	*All ages***	12.9% (8.6-19.1%) (n=1874)	9.9% (6.9-14.0%) (n=1924)	**-3.0%**	⊕◯◯◯ VERY LOW	IMPORTANT
						2-23 months	19%*** (7-41%) (n=21)	22.4% (11-39%) (n=184)	**3.4%**	⊕◯◯◯ VERY LOW	
						2-4 years	7.1%*** (1-24%) (n=28)	8.4% (3-20%) (n=261)	**1.3%**		
						5-14 years	6.3%*** (2-14%) (n=79)	6.4% (3-12%) (n=483)	**0.1%**		
						15-29 years	0%*** (0-11%) (n=39)	10.1% (5-17%) (n=111)	**10.1%**		
						>=*30 years*	0%*** (0-32%) (n=10)	24.5% (12-42%) (n=43)	**24.5%**		
						Adverse effects of 5 days ceftriaxone	Not considered serious				

*No differences statistically significant

** Different numerators and denominators used for all age analysis and for those with age breakdown according to availability of age specific data.

*** Only one study

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