Adjunctive corticosteroids for acute bacterial meningitis in Africa – do we need more evidence?

YES!!

Matt Coldiron,

Epicentre – Médecins Sans Frontières

During an epidemic in meningitis belt

Other African studies

- Outside of 2 major trials in Malawi
  - 1 small trial (1989) Mozambique
  - 1 small trial (1979) in southern Nigeria
  - 2 observational studies (2010s) Ethiopia

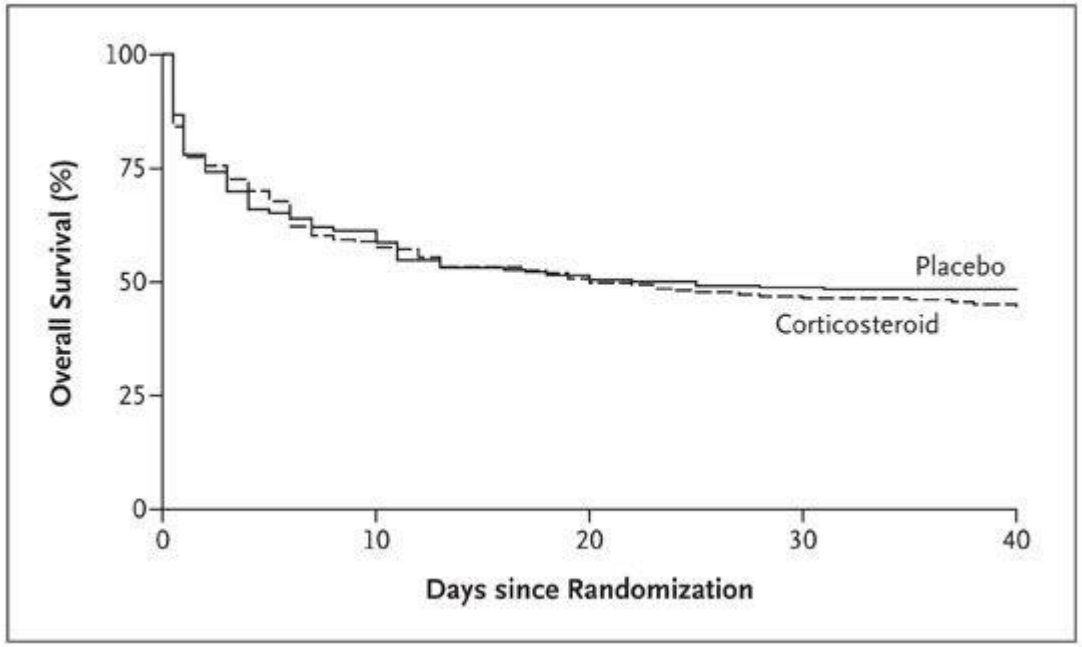
Malawi studies

	Children	Adults
Enrolled	598	465
Timing	Dexa prior to antiobiotics	Dexa prior to antiobiotics
Antiobiotic	Benzylpenicillin + chloramphenicol	Ceftriaxone
HIV	26%	90%
Presented within 48 hours of symptom onset	44%	26%
Primary outcome	Death	Death
Reference	Molyneux et al, Lancet 2002	Scarborough et al, NEJM 2007

Malawi results

	Overall*	
	Steroid (n=305)	Placebo (n=293)
Died	96 (31%)	91 (31%)
No neurological deficit†	141 (46%)	145 (49%)
Neurological sequelae	69 (23%)	56 (19%)
Cerebral palsy	17 (25%)	19 (34%)
Global delay	8 (12%)	6 (11%)
Hemiplegia,solitary	3 (4%)	4 (7%)
Speech disorder	4 (6%)	3 (5%)
Behaviour problem	7 (10%)	1 (2%)
Motor delay	9 (13%)	6 (11%)
Hydrocephalus	9 (13%)	2 (4%)
Cranial nerve palsy isolated	1 (1%)	0
Blind	0	1 (2%)
Balance problems	0	3 (5%)
Seizures	0	2 (4%)
Cerebral palsy and seizures	4 (6%)	7 (13%)
Cerebral palsy and blind	3 (4%)	3 (5%)
Cerebral palsy and hydrocephalus	2 (3%)	0
Hemiplegia with seizures	1 (1%)	0

Molyneux et al, Lancet 2002



Scarborough et al, NEJM 2007

Blantyre vs Niger in April

Mozambique vs Niger in March

Multi-centric European results

TABLE 2. OUTCOMES EIGHT WEEKS AFTER ADMISSION, ACCORDING TO CULTURE RESULTS.*

OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
Streptococcus pneumoniae	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
Neisseria meningitidis	4/50 (8)	5/47 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20
Focal neurologic abnormalities				
All patients	18/143 (13)	24/119 (20)	0.62 (0.36–1.09)	0.13
S. pneumoniae	11/49 (22)	11/33 (33)	0.67 (0.33–1.37)	0.32
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	3/11 (27)	3/16 (19)	1.45 (0.36–5.92)	0.66
Negative bacterial culture	1/37 (3)	5/26 (19)	0.14 (0.02–1.13)	0.07
Hearing loss				
All patients	13/143 (9)	14/119 (12)	0.77 (0.38–1.58)	0.54
S. pneumoniae	7/49 (14)	7/33 (21)	0.67 (0.25–1.69)	0.55
N. meningitidis	3/46 (7)	5/44 (11)	0.57 (0.15–2.26)	0.48
Other bacteria	2/11 (18)	1/16 (6)	2.91 (0.30–28.3)	0.55
Negative bacterial culture	1/37 (3)	1/26 (4)	0.70 (0.05–10.7)	1.00

*The analyses of unfavorable outcome and death included all patients and were performed with a last-observation-carried-forward procedure. The analyses of neurologic abnormalities and hearing loss included all surviving patients who underwent neurologic examination at eight weeks.

†CI denotes confidence interval.

‡Included in this category are two patients in whom cerebrospinal fluid culture was not performed.

Causative agent of enrolled patients

Causative agent	Dexa-methasone	Placebo
Spn	37%	35%
Nm	32%	33%
Other	8%	12%
Culture-Negative	23%	21%

De Gans et al, NEJM 2002

Time to presentation

	Europe[16] (n=301)	Malawi (child)[15] (n=598)	Vietnam[13] (n=429)	Malawi (adult)[14] (n=465)	South America[12]		Total (n=2029)	Dexamethasone (n=1019)	Placebo (n=1010)
					Randomisation schedule 1 (n=126)	Randomisation schedule 2 (n=110)			
Age (years)									
<5	0	429	0	0	117	90	636	316	320
5–15	1	168	0	2	9	17	197	99	98
16–55	198	0	322	447	0	0	967	490	477
>55	102	0	106	16	0	0	224	112	112
Unknown	0	1	1	0	0	3	5	2	3
Sex									
Men	169 (56%)	337 (56%)	315 (73%)	230 (50%)	73 (58%)	63 (57%)	1187 (58%)	601 (59%)	586 (58%)
Symptoms <48 h									
Yes	233 (77%)	266 (44%)	121 (28%)	121 (26%)	91 (72%)	93 (84%)	925 (46%)	471 (46%)	454 (45%)
Unknown	2 (1%)	2 (0·3%)	2 (0·5%)	5 (1%)	15 (12%)	9 (8%)	35 (2%)	17 (2%)	18 (2%)

Van de Beek et al. *Lancet Neurol* 2010

Table. Characteristics of 369 suspected meningitis patients visited at home after the epidemic season, Dogondoutchi, Niger, September 2015

Characteristic	No. (%) patients
Sex	
M	220 (59.6)
F	149 (40.4)
Age, y	
<2	22 (6.0)
2–4	57 (15.5)
5–14	190 (51.5)
15–29	84 (22.8)
30–44	13 (3.5)
≥45	3 (0.8)
Positive by PCR	194 (62.2)
N. meningitidis serogroup C	144 (74.2)
N. meningitidis serogroup W	36 (18.6)
S. pneumococcus	12 (6.2)
N. meningitidis serogroup unspecified	2 (1.0)
Delay between symptom onset and visit to health center, d*	
0	90 (24.4)
1	176 (47.7)
2	63 (17.1)
3	23 (6.2)
≥4	14 (0.8)

*Data missing for 3 patients.

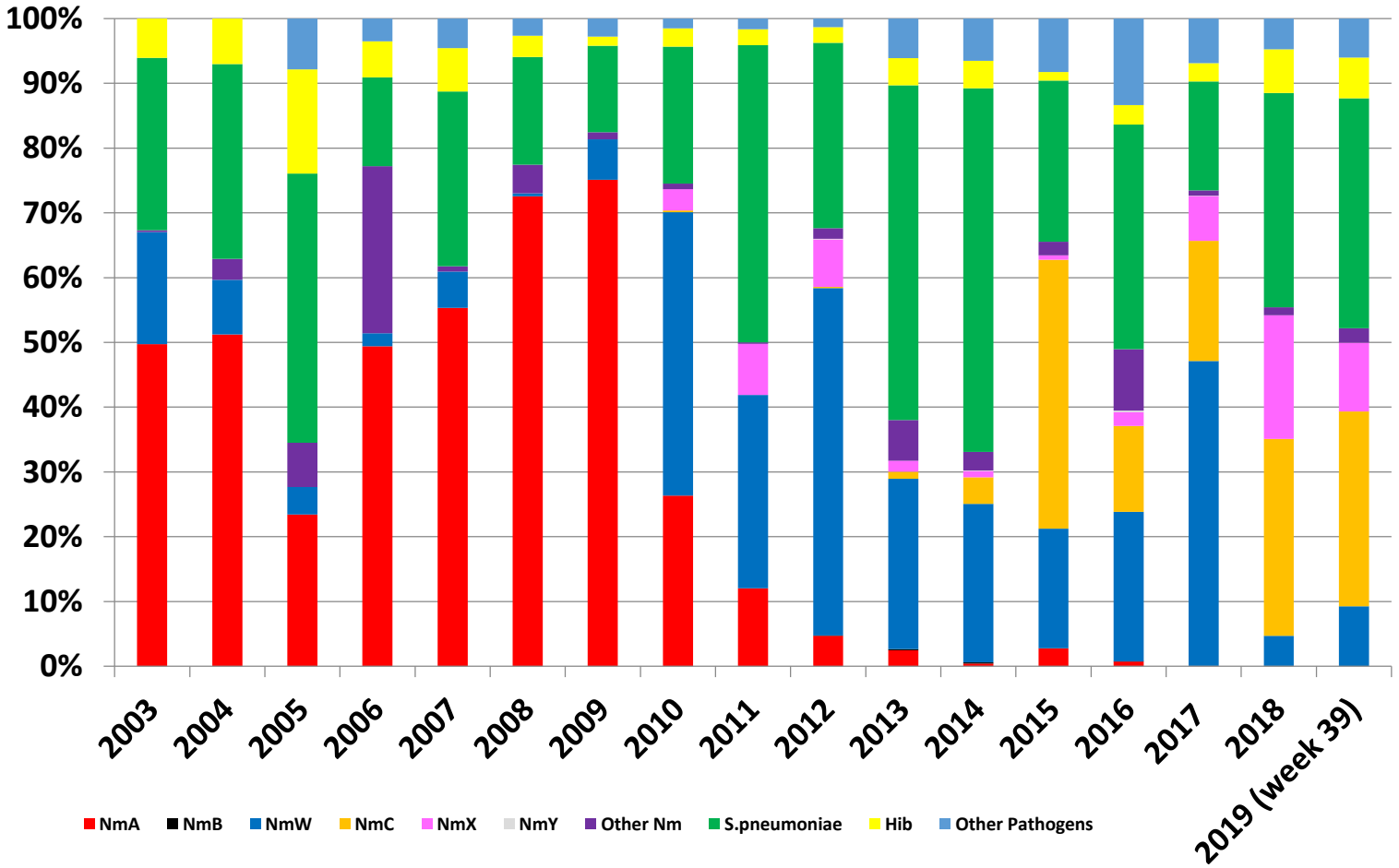
Coldiron et al, EID 2016

Table 1. Baseline characteristics of villages.

Characteristic	Control (n = 17 villages; population = 25,510)	Household prophylaxis (n = 17 villages; population = 23,621)	Village-wide prophylaxis (n = 15 villages; population = 22,177)
Sex, *n* (%)			
Male	12,473 (49%)	11,477 (49%)	10,889 (49%)
Female	13,037 (51%)	12,144 (51%)	11,288 (51%)
Village population, median (IQR)	1,135 (903–1,594)	1,169 (716–2,045)	1,399 (924–1,879)
Total population <30 years, *n* (%)	19,748 (77%)	18,293 (77%)	17,031 (76%)
Villages targeted by vaccination campaign, *n* (%)	17 (100%)	16 (94%)	14 (93%)
Days between inclusion and vaccination, mean (SD)	11.5 (7.8)	10.8 (9.5)	12.2 (8.8)
Days between inclusion and first rainfall, mean (SD)	7.8 (6.9)	6.4 (8.1)	7.1 (6.5)
Case triggering inclusion of village			
Age in years, mean (SD)	14.5 (13.0)	11.0 (11.2)	21.4 (19.9)
Sex, *n/N* (%)			
Male	8/17 (47%)	8/17 (47%)	7/15 (47%)
Female	9/17 (53%)	9/17 (53%)	8/15 (53%)
Days between symptom onset and consultation, mean (SD)	1.4 (1.2)	1.9 (1.5)	1.9 (2.6)
All cases notified in village			
Age in years, mean (SD)	17.8 (12.6)	17.1 (14.9)	17.8 (17.3)
Sex, *n/N* (%)			
Male	55/132 (42%)	48/108 (44%)	28/57 (49%)
Female	77/132 (58%)	60/108 (56%)	29/57 (51%)
Days between symptom onset and consultation, mean (SD)	1.1 (1.1)	1.3 (1.3)	1.3 (1.6)

Coldiron et al, Plos Med 2018

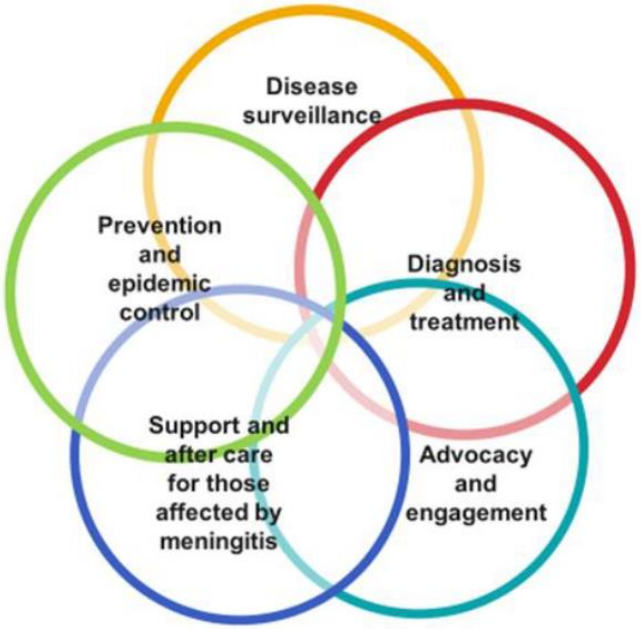
Changing patterns of causative agents



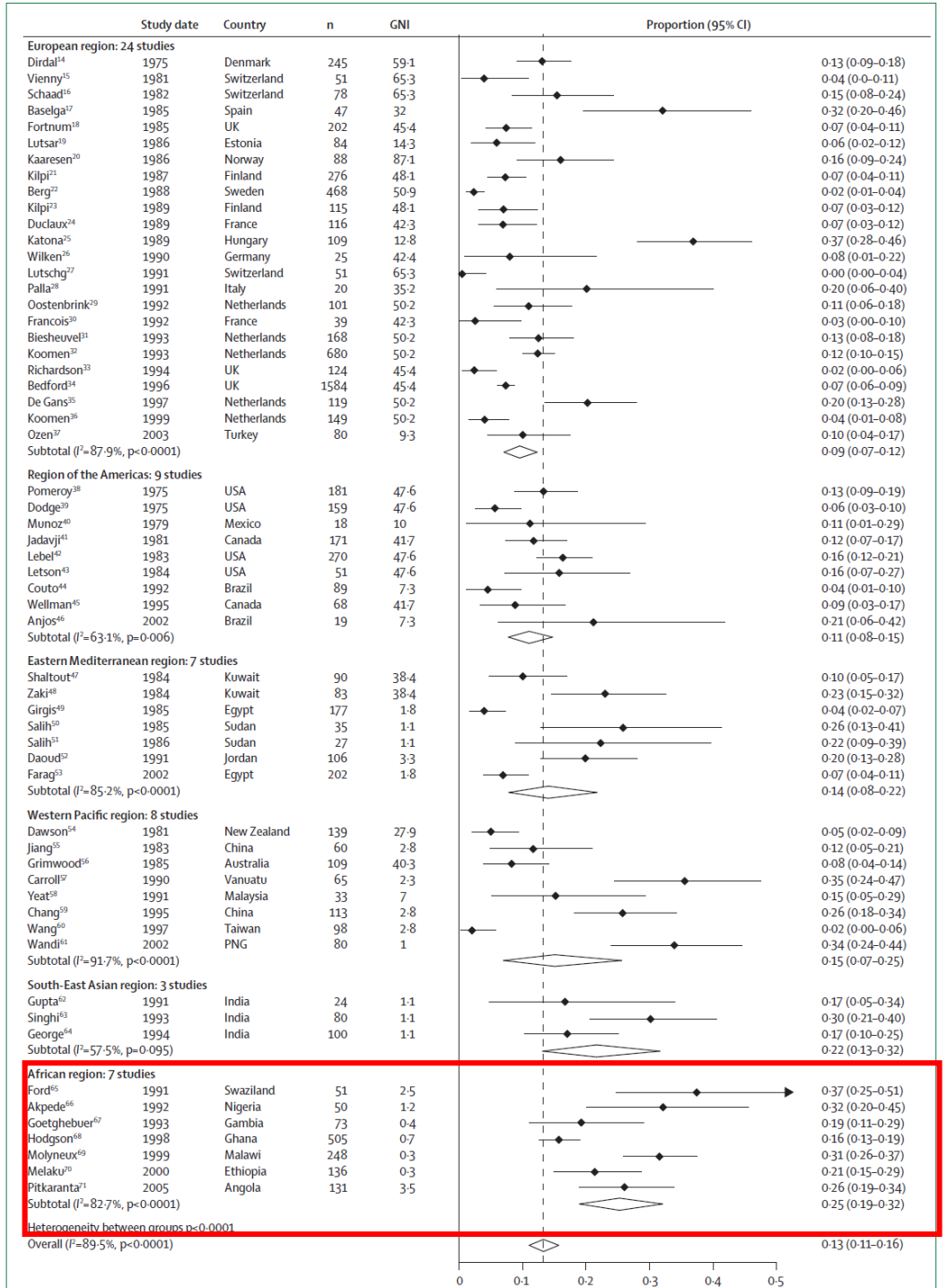
Defeating meningitis 2030

- Visionary goal 3: “Reduce disability and improve quality of life after meningitis due to any cause”

- Strategic goal 9, landmark 1: Perform a review of adjunctive therapies in LMICs by 2022



Sequelae in Africa



	Study date	Country	n	GNI	Proportion (95% CI)
European region: 24 studies					
Dirdal[14]	1975	Denmark	245	59·1	0·13 (0·09–0·18)
Vienny[15]	1981	Switzerland	51	65·3	0·04 (0·0–0·11)
Schaad[16]	1982	Switzerland	78	65·3	0·15 (0·08–0·24)
Baselga[17]	1985	Spain	47	32	0·32 (0·20–0·46)
Fortnum[18]	1985	UK	202	45·4	0·07 (0·04–0·11)
Lutsar[19]	1986	Estonia	84	14·3	0·06 (0·02–0·12)
Kaaresen[20]	1986	Norway	88	87·1	0·16 (0·09–0·24)
Kilpi[21]	1987	Finland	276	48·1	0·07 (0·04–0·11)
Berg[22]	1988	Sweden	468	50·9	0·02 (0·01–0·04)
Kilpi[23]	1989	Finland	115	48·1	0·07 (0·03–0·12)
Duclaux[24]	1989	France	116	42·3	0·07 (0·03–0·12)
Katona[25]	1989	Hungary	109	12·8	0·37 (0·28–0·46)
Wilken[26]	1990	Germany	25	42·4	0·08 (0·01–0·22)
Lutschg[27]	1991	Switzerland	51	65·3	0·00 (0·00–0·04)
Palla[28]	1991	Italy	20	35·2	0·20 (0·06–0·40)
Oostenbrink[29]	1992	Netherlands	101	50·2	0·11 (0·06–0·18)
Francois[30]	1992	France	39	42·3	0·03 (0·00–0·10)
Biesheuvel[31]	1993	Netherlands	168	50·2	0·13 (0·08–0·18)
Koomen[32]	1993	Netherlands	680	50·2	0·12 (0·10–0·15)
Richardson[33]	1994	UK	124	45·4	0·02 (0·00–0·06)
Bedford[34]	1996	UK	1584	45·4	0·07 (0·06–0·09)
De Gans[35]	1997	Netherlands	119	50·2	0·20 (0·13–0·28)
Koomen[36]	1999	Netherlands	149	50·2	0·04 (0·01–0·08)
Ozen[37]	2003	Turkey	80	9·3	0·10 (0·04–0·17)
Subtotal (I^2=87·9%, p<0·0001)					0·09 (0·07–0·12)
Region of the Americas: 9 studies					
Pomeroy[38]	1975	USA	181	47·6	0·13 (0·09–0·19)
Dodge[39]	1975	USA	159	47·6	0·06 (0·03–0·10)
Munoz[40]	1979	Mexico	18	10	0·11 (0·01–0·29)
Jadavji[41]	1981	Canada	171	41·7	0·12 (0·07–0·17)
Lebel[42]	1983	USA	270	47·6	0·16 (0·12–0·21)
Letson[43]	1984	USA	51	47·6	0·16 (0·07–0·27)
Couto[44]	1992	Brazil	89	7·3	0·04 (0·01–0·10)
Wellman[45]	1995	Canada	68	41·7	0·09 (0·03–0·17)
Anjos[46]	2002	Brazil	19	7·3	0·21 (0·06–0·42)
Subtotal (I^2=63·1%, p=0·006)					0·11 (0·08–0·15)
Eastern Mediterranean region: 7 studies					
Shaltout[47]	1984	Kuwait	90	38·4	0·10 (0·05–0·17)
Zaki[48]	1984	Kuwait	83	38·4	0·23 (0·15–0·32)
Girgis[49]	1985	Egypt	177	1·8	0·04 (0·02–0·07)
Salih[50]	1985	Sudan	35	1·1	0·26 (0·13–0·41)
Salih[51]	1986	Sudan	27	1·1	0·22 (0·09–0·39)
Daoud[52]	1991	Jordan	106	3·3	0·20 (0·13–0·28)
Farag[53]	2002	Egypt	202	1·8	0·07 (0·04–0·11)
Subtotal (I^2=85·2%, p<0·0001)					0·14 (0·08–0·22)
Western Pacific region: 8 studies					
Dawson[54]	1981	New Zealand	139	27·9	0·05 (0·02–0·09)
Jiang[55]	1983	China	60	2·8	0·12 (0·05–0·21)
Grimwood[56]	1985	Australia	109	40·3	0·08 (0·04–0·14)
Carroll[57]	1990	Vanuatu	65	2·3	0·35 (0·24–0·47)
Yeat[58]	1991	Malaysia	33	7	0·15 (0·05–0·29)
Chang[59]	1995	China	113	2·8	0·26 (0·18–0·34)
Wang[60]	1997	Taiwan	98	2·8	0·02 (0·00–0·06)
Wandi[61]	2002	PNG	80	1	0·34 (0·24–0·44)
Subtotal (I^2=91·7%, p<0·0001)					0·15 (0·07–0·25)
South-East Asian region: 3 studies					
Gupta[62]	1991	India	24	1·1	0·17 (0·05–0·34)
Singhi[63]	1993	India	80	1·1	0·30 (0·21–0·40)
George[64]	1994	India	100	1·1	0·17 (0·10–0·25)
Subtotal (I^2=57·5%, p=0·095)					0·22 (0·13–0·32)
African region: 7 studies					
Ford[65]	1991	Swaziland	51	2·5	0·37 (0·25–0·51)
Akpede[66]	1992	Nigeria	50	1·2	0·32 (0·20–0·45)
Goetghebuer[67]	1993	Gambia	73	0·4	0·19 (0·11–0·29)
Hodgson[68]	1998	Ghana	505	0·7	0·16 (0·13–0·19)
Molyneux[69]	1999	Malawi	248	0·3	0·31 (0·26–0·37)
Melaku[70]	2000	Ethiopia	136	0·3	0·21 (0·15–0·29)
Pitkaranta[71]	2005	Angola	131	3·5	0·26 (0·19–0·34)
Subtotal (I^2=82·7%, p<0·0001)					0·25 (0·19–0·32)
Heterogeneity between groups p<0·0001					
Overall (I^2=89·5%, p<0·0001)					0·13 (0·11–0·16)

0 0·1 0·2 0·3 0·4 0·5

Edmond et al, Lancet ID 2010

Follow-up in Dakar

- 66 children who survived to hospitalization between 2001-2007 visited at home in 2007
  - 71% had minor or major sequelae
  - No family could afford the care they desired for their child

TABLE 7. Mean Discounted Lifetime Costs Per Child Among All Study Children With Meningitis Sequelae (2010 US$)

	No. of Children	Mean	SD	95% CI	Minimum	Maximum
Meningitis episode costs	47	1441	1158	435–3165	392	7076
Sequelae costs						
Rehospitalization	47	275	640	0–1809	0	2572
Lifetime outpatient visits	47	185	164	16–503	0	753
Lifetime child care	47	3158	6326	0–14,506	0	29,012
Lifetime productivity costs	47	31,276	28,033	0–96,709	0	96,709
Subtotal: lifetime sequelae costs	47	34,895	29,589	67–96,755	49	111,380
Total lifetime costs	47	36,336	30,030	775–97,387	477	99,528

SD indicates standard deviation.

Griffiths, Pediatr Infect Dis J 2012

To summarize

- Best-quality current data is difficult to generalize to African meningitis belt, which still has the highest burden of disease
  - Health-seeking behaviors different in meningitis belt?
- Epidemiology of meningitis is changing, with a higher proportion of pneumococcal disease
- Sequelae are expensive (and largely forgotten) in Africa

- Given the lack of harm, further research into adjunctive dexamethasone (powered to look at sequelae) should be performed in the African meningitis belt.
- VOTE YES!