Global and regional risk of disabling sequelae from bacterial meningitis

a systematic review and meta-analysis

Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis

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Few data sources are available to assess the global and regional risk of sequelae from bacterial meningitis. We aimed to estimate the risks of major and minor sequelae caused by bacterial meningitis, estimate the distribution of the different types of sequelae, and compare risk by region and income. We systematically reviewed published papers from 1980 to 2008. Standard global burden of disease categories (cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus) were labelled as major sequelae. Less severe, minor sequelae (behavioural problems, learning difficulties, unilateral hearing loss, hypotonia, diplopia), and multiple impairments were also included. 132 papers were selected for inclusion. The median (IQR) risk of at least one major or minor sequela after hospital discharge was 19·9% (12·3–35·3%). The risk of at least one major sequela was 12·8% (7·2–21·1%) and of at least one minor sequela was 8·6% (4·4–15·3%). The median (IQR) risk of at least one major sequela was 24·7% (16·2–35·3%) in pneumococcal meningitis; 9·5% (7·1–15·3%) in *Haemophilus influenzae* type b (Hib), and 7·2% (4·3–11·2%) in meningococcal meningitis. The most common major sequela was hearing loss (33·9%), and 19·7% had multiple impairments. In the random-effects meta-analysis, all-cause risk of a major sequela was twice as high in the African (pooled risk estimate 25·1% [95% CI 18·9–32·0%]) and southeast Asian regions (21·6% [95% CI 13·1–31·5%]) as in the European region (9·4% [95% CI 7·0–12·3%]; overall I^2=89·5%, p<0·0001). Risks of long-term disabling sequelae were highest in low-income countries, where the burden of bacterial meningitis is greatest. Most reported sequelae could have been averted by vaccination with Hib, pneumococcal, and meningococcal vaccines.

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Introduction

Published reviews of bacterial meningitis incidence and case fatality hide the true impact of bacterial meningitis on families and communities. Survivors of bacterial meningitis are at risk from long-term disabling sequelae and impaired quality of life,[1] but disabled children and adults are hidden from view in many societies, subjected to stigma and neglect, and undercounted in national and international statistics.[2]

Few data sources are available for paediatricians and public-health researchers to assess the long-term risk of disability associated with bacterial meningitis across countries and regions. There is also little information about the severity and distribution of the different types of sequelae. Additionally, the financial burden that families incur in caring for disabled individuals is commonly not calculated or is underestimated.[3] Data are especially poor from low-income countries, where the risks of infection are highest and care is least accessible. Indeed, previous systematic reviews of the long-term outcomes from bacterial meningitis focused on studies from high-income countries.[1,4]

The risk of sequelae from bacterial meningitis has probably changed since these systematic reviews were published because of improvements in antibiotics and supportive therapies to treat acute episodes of bacterial meningitis. Clinicians are now using highly sensitive tests to diagnose long-term disabling sequelae that would have previously remained undetected. Additionally, coverage of conjugate vaccines against the main causes of bacterial meningitis (*Haemophilus influenzae* type b [Hib], *Streptococcus pneumoniae* [pneumococcus], and *Neisseria meningitidis* [meningococcus]) has increased.[5] These factors might influence risks of sequelae in different ways.

Our aims were to estimate the risks of major and minor sequelae caused by bacterial meningitis, to estimate the distribution of the different types of sequelae, and to compare sequelae risk by region and gross national income (GNI).

Methods

Search strategy and selection criteria

The initial search of Medline and WHOLIS databases aimed to be as inclusive as possible, and used the search terms "meningitis, bacterial"[Mesh] AND "complications"[Subheading], limited to human studies published between Jan 1, 1980 and Mar 1, 2008 (figure 1). We restricted our search up to March, 2008, to maintain consistency and comparability with other WHO Global Burden of Disease (GBD) and Child Health Epidemiology Reference Group publications aimed at producing estimates for the year 2008.[6,7,8] We also contacted experts and searched reference lists of articles to obtain unpublished data. There were no language restrictions.

We defined bacterial meningitis according to the 2001 GBD Disease Control Priorities Project (DCPP)[9] as an acute bacterial disease with sudden onset of fever, intense headache, nausea, vomiting, or neck stiffness. The clinical diagnosis of meningitis had to be accompanied by laboratory evidence (in cerebrospinal fluid or blood) of a recognised bacterial pathogen (eg, Hib, pneumococcus, or meningococcus).[9] We did not include tuberculous or viral diseases, because their natural history and sequelae risks are substantially different from those of bacterial pathogens such as Hib, pneumococcus, and meningococcus.

A sequela was defined according to the GBD DCPP as a health state resulting from meningitis for which

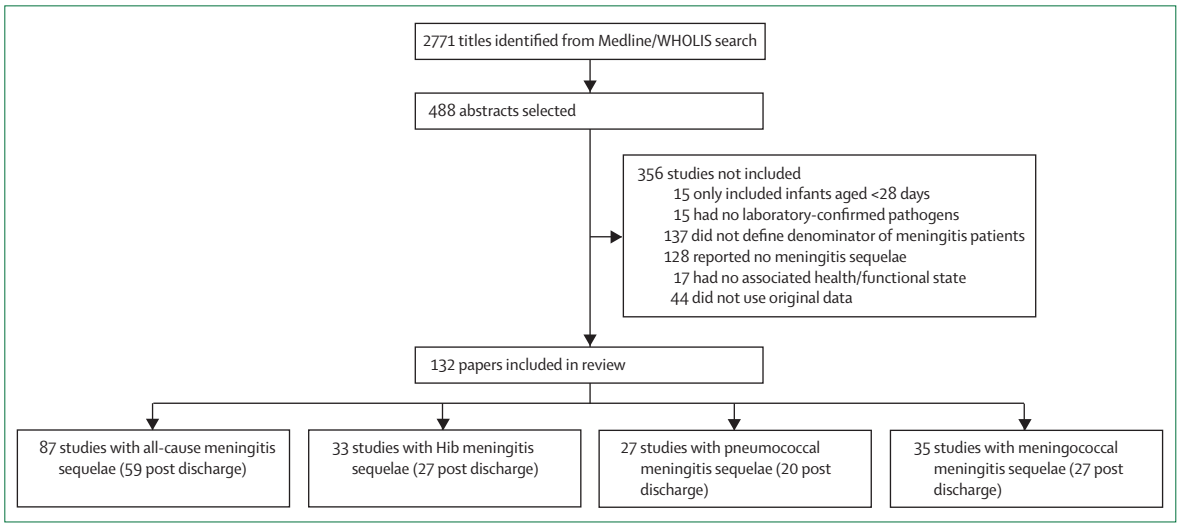


Figure 1: **Search results**
Numbers in final row do not sum to the total number of papers included (n=132) because some papers are included in more than one category.

epidemiological estimates (incidence, prevalence, average duration) and a single average disability weight could be calculated.[9] It included all current and future functional health states (until remission to full health or death) in the natural history of the disease that impaired quality of life or activities of daily living.

The GBD DCPP has defined a group of severe sequelae (table 1), which we retained for use in this study and labelled as major sequelae.[9] We also developed a set of other commonly reported minor sequelae that were less severe but still impaired quality of life and activities of daily living (table 1). A separate category was also created to identify individuals with more than one sequela (multiple impairments), because bacterial meningitis results in parenchymal brain damage and deficits in many different domains. Multiple impairments were also stratified into major and minor categories. All sequelae were allocated an International Classification of Diseases, 10th edition (ICD-10) code.[10]

Papers were excluded if they did not report the following: numbers of laboratory-confirmed pathogens, a defined denominator of meningitis patients, sequelae of meningitis, associated health/functional states, original data; or if the papers only included neonates (ie, newborns up to 1 month of age). Neonates were excluded because the causal organisms, potential interventions (including maternal health care), and policy implications are different to those for older infants, children, and adults.

	GBD, major sequelae		Non-GBD, minor sequelae	
	Case definition	ICD10 codes	Case definition	ICD10 codes
Cognitive	Mental retardation with IQ <70	F70–F79, F06.7	Learning difficulties or deficits in IQ with IQ >70 or speech/language impairment	F06.7, F80.0, F81.0, F81.2, F81.8, F81.9
Seizures	Seizures of any type	G40	..	..
Hearing	Bilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0·5 kHz, 1 kHz, 2 kHz, 4 kHz in the better ear) of >26 dB hearing level	H90.3, H90.5	Unilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0·5 kHz, 1 kHz, 2 kHz, 4 kHz) of >26 dB hearing level	H90.4, H90.7
Motor	Impairment, spasticity or paresis of one or more limbs	G80, G81.1, G82.1, G83.0–G83.3 G24.9, G25.3, G25.5, G25.9	Isolated hypotonia, motor delay, ataxia, gait or coordination difficulties	F82, R26–R27
Vision	Presenting visual acuity in the best eye of less than 6/12 or corresponding visual field loss	H47, H53.4	Unilateral visual disturbance, diplopia, nystagmus, or cranial nerve dysfunction	H49-51, H53.0, H53.2, H53.4, H54.4–H54.7
Behaviour	..	..	Any behavioural disorder attributed to the meningitis episode	F90–98
Clinical	Distinct pathological entity with any impairment to activities of daily living (ie, hydrocephalus)	G91.1, T85.0	Distinct pathological entity with no impairment to activities of daily living (ie, mild cerebral dilatation)	G91.2
Multiple impairments	At least two of above domains	..	At least two of above domains, or developmental delay not otherwise specified	..

GBD=Global Burden of Disease Project.[9] ICD10=International Classification of Diseases, 10th edition.[10] IQ=intelligence quotient.

Table 1: **Case definitions and domains**

Data extraction

Two reviewers (KE and VSK) examined titles, abstracts, and papers independently with identical case definitions (table 1), data abstraction forms, and selection criteria. Reviewers also classified the studies according to WHO region (African, South East Asian, Western Pacific, Eastern Mediterranean, European, and American regions) and WHO mortality strata.[11] Disagreements were resolved by consensus between the two reviewers and the lead authors (KE, VSK, AC, CS).

An initial review of bacterial meningitis studies indicated that sequelae were reported at either the time of discharge from hospital ("at discharge") or during the follow-up period after discharge home from hospital ("post discharge"). We decided to describe both sets of data, but to focus the main analysis on the post-discharge sequelae. This is because symptoms (eg, malaise) from acute meningitis infection persist until hospital discharge, and patients' responses to hospital neurological examinations are often suboptimum (especially cognitive and hearing examinations). More representative examinations occur after patients have had time to recover from the acute illness and return home to a familiar environment (post discharge).[12,13]

Analyses

We first described the results using medians (IQR) of the proportion of individuals with any (at least one) sequelae resulting from bacterial meningitis. Major, minor, and total (major or minor) sequelae risks were calculated separately for all-cause and pathogen-specific (Hib, pneumococcus, and meningococcus) meningitis.

Two types of adjustment were required to estimate the median (IQR) risk by domain (ie, risk of the different types of sequelae). First, many studies reported person counts for each domain independently (eg, percentage with hearing loss, percentage with motor deficit) and did not report the number of people with multiple impairments (eg, percentage with both hearing loss and motor deficit). We decided to retain these studies to avoid unnecessary data loss, but to convert the counts into mutually exclusive categories (eg, percentages with only hearing loss, with only motor deficit, with both hearing loss and motor deficit). To do this, we selected all studies that reported both independent and mutually exclusive counts and identified the mean ratio between these two indicators. These ratios were then applied to all studies that reported only independent counts so that mutually exclusive counts could be generated for all studies.

Second, many studies did not report on all domains. In some cases this was due to the design of the study (eg, some studies were only designed to assess audiological sequelae and individuals were not examined for motor deficit or other abnormalities). In other cases, no sequelae were reported for a given domain and it was not clear whether the study had been designed to examine this domain. Domain-specific risks were calculated based only on the studies that examined a given domain, but all domain-specific risks were adjusted to ensure they summed to the estimated overall risk of experiencing at least one sequela.

We used random-effects meta-analysis to investigate the impact of the following covariates on risk of sequelae: WHO region, WHO mortality strata, GNI band, decade of data collection, age-group (<5 years, ≥5 years), study design (prospective, retrospective), duration of follow-up after hospital discharge, and percentage of cases with laboratory confirmation of the pathogen. The only outcome considered in these analyses was the proportion of patients with bacterial meningitis who had at least one major sequela. Each covariate was categorical with clearly defined subgroups. Thus, for each covariate we first did a random-effects meta-analysis of all available studies within the subgroups to impute estimates (eg, for age-group, we imputed estimates for patients aged <5 years and ≥5 years separately). We then did a bivariate metaregression analysis in which we examined each covariate fitted individually as a single factor in isolation and compared estimates with the most prevalent subgroup (eg, for age-group, we compared estimates for patients aged 5 years with those aged ≥5 years). Finally, we did a multivariate analysis in which we included all important covariates (GNI band, decade of data collection, age-group, study design, duration of follow-up after hospital discharge, and percentage of cases with laboratory confirmation of the pathogen) in a multivariate metaregression model and obtained final estimates of the proportion of people with at least one major sequela adjusting for the effect of these covariates. WHO region, WHO mortality band, and GNI were highly correlated and therefore only GNI was included in this final model because it was a better predictor of sequelae risk than mortality band and region. Heterogeneity was assessed by use of standard meta-analytic methods.

Results

We selected 132 studies that were suitable for inclusion (figure 1).[14–145] The webappendix includes a full summary of the studies included. No unpublished data that satisfied our criteria were identified. Overall, 18 183 survivors of acute bacterial meningitis were examined for sequelae in the included studies (median number of survivors per study, 85 [IQR 47–148]). As shown in table 2, Hib was the most common cause of bacterial meningitis (35·5% of all the bacterial pathogens reported), followed by pneumococcus (19·6%), meningococcus (16·4%), and other pathogens (12·0%). Median age at meningitis episode was 29 months (IQR 13–67 months), and 106 (79%) papers reported sequelae risk in children aged under 5 years.

See Online for webappendix

53 (40%) papers were from the European region, followed by the Americas (n=32), Eastern Mediterranean (n=10), Western Pacific (n=16), Africa (n=13), and Asia (n=8). The median (IQR) year of data collection was 1989

	Studies (n)	Median (IQR)
At discharge (total 42 studies)		
Number of people with bacterial meningitis	42	101·0 (47·0–194·0)
Age at meningitis episode (months)	35	31·1 (13·1–50·0)
Cases laboratory confirmed (%)	42	100·0% (95·1–100·0%)
Pathogen identified (%)		
Hib	19	31·1% (20·0–72·0%)
Pneumococcus	25	23·6% (14·1–40·2%)
Meningococcus	21	9·4% (5·1–32·1%)
Other pathogens	24	13·4% (8·2–28·1%)
Loss to follow-up (%)	42	0
Number of people examined for sequelae	42	84·5 (38·0–166·0)
Post discharge (total 90 studies)		
Number of people with bacterial meningitis	90	89·0 (58·0–166·0)
Age at meningitis episode (months)	70	27·1 (13·8–72·4)
Cases laboratory confirmed (%)	90	100·0% (88·4–100·0%)
Pathogen identified (%)		
Hib	46	40·0% (16·2–53·1%)
Pneumococcus	50	15·5% (10·0–21·0%)
Meningococcus	47	23·4% (12·1–42·1%)
Other pathogens	40	10·6% (4·1–20·0%)
Loss to follow-up (%)	37	14·1% (8·3–26·3%)
Number of people examined for sequelae	90	85·0 (48·0–138·0)

Hib=*Haemophilus influenzae* type b.

Table 2: **Study characteristics, by timing and pathogen**

(1982–94). Six (10%) post-discharge studies reported sequelae risk based on data collected after 2000. Studies with a retrospective design (n=58) were retained to avoid unnecessary loss of data, although differences between retrospective and prospective studies were tested in the meta-regression analysis. The median follow-up time after hospital discharge was 24 months (IQR 6–63 months). Two studies followed individuals for 16 years after the meningitis episode.[59,127] The median loss to follow-up (14·0% [IQR 7·8–22·7%]) was similar in all WHO regions and mortality strata.

No studies reported sequelae risk in malnourished people. Two papers, from Malawi and South Africa, reported sequelae risk in HIV-infected children.[69,112] Both studies reported that sequelae risk was twice as high in HIV-infected than in non-HIV-infected children. We included the overall sequelae risk estimates (for HIV-infected and non-HIV-infected people) in our analysis. Sequelae risks were reported for all-cause bacterial meningitis (n=87), and for patients with only Hib (n=33), pneumococcal (n=27), and meningococcal meningitis (n=35).

Table 3 shows risks of sequelae at discharge and post discharge. Total (major or minor) median (IQR) risks of sequelae were similar in studies with patients assessed at hospital discharge (22·8% [12·1–29·2%]) compared with those assessed during the post-discharge follow-up period (19·9% [12·3–35·3%]). In the post-discharge studies in which major (n=58) and minor (n=37) risks were included, the median (IQR) risks of at least one sequela were 12·8% (7·2–21·1%) and 8·6% (4·4–15·3%), respectively.

The median (IQR) risk of at least one major sequela was 24·7% (16·2–35·3%) in pneumococcal meningitis, 9·5% (7·1–15·3%) in Hib, and 7·2% (4·3–11·2%) in meningococcal meningitis (table 3). There was a 2·5 times greater risk of at least one major sequela in the nine studies that compared pneumococcal and Hib meningitis (risk ratio 2·49 [95% CI 1·87–3·31]).[14,17,34,39,43,47,49,52,67] However, there were no significant differences between meningococcal and Hib meningitis (risk ratio 0·92 [95% CI 0·66–1·29]).

Unadjusted and adjusted median (IQR) risks of the different types of major and minor sequelae are shown in table 3. Only 20 (15%) studies assessed all seven domains. 30 (23%) studies only assessed hearing and 81 (61%) did not assess cognitive deficit. All domain-specific risks were highest for pneumococcus, which was associated with a median (IQR) risk of major hearing loss of 9·9% (8·1–12·3%), which was higher than hearing loss due to Hib (4·5% [2·2–6·1%]) and meningococcus (4·1% [2·3–7·2%]).

The most common types of major sequelae were hearing loss (33·6%), followed by seizures (12·6%), motor deficit (11·6%), cognitive impairment (9·1%), hydrocephalus (7·1%), and visual disturbance (6·3%). 470 (19·7%) individuals were reported to have multiple sequelae. The most common multiple impairment combinations were cognitive deficit plus hearing loss (39·1%), cognitive deficit plus motor impairment (21·1%), and cognitive deficit plus motor deficit plus seizures (8·1%). 399 (85%) individuals were reported to have a cognitive deficit in combination with one or more other domains: 56·5% with a motor deficit, 61·1% with a hearing deficit.

The risk of at least one major sequela was almost three times greater in the WHO African region (pooled risk estimate 25·1% [95% CI 18·9–32·0%]) and southeast Asian region (21·6% [95% CI 13·1–31·5%]) compared with the European region (9·4% [95% CI 7·0–12·3%]; figure 2). There was also a progressively higher risk of major sequelae as WHO mortality strata increased (figure 3); risk of a major sequela was three times greater in countries in the highest mortality stratum (stratum E, 29·1% [95% CI 20·9–37·9%]) than in those in the lowest stratum (stratum A, 9·1% [95% CI 7·2–11·1%]).

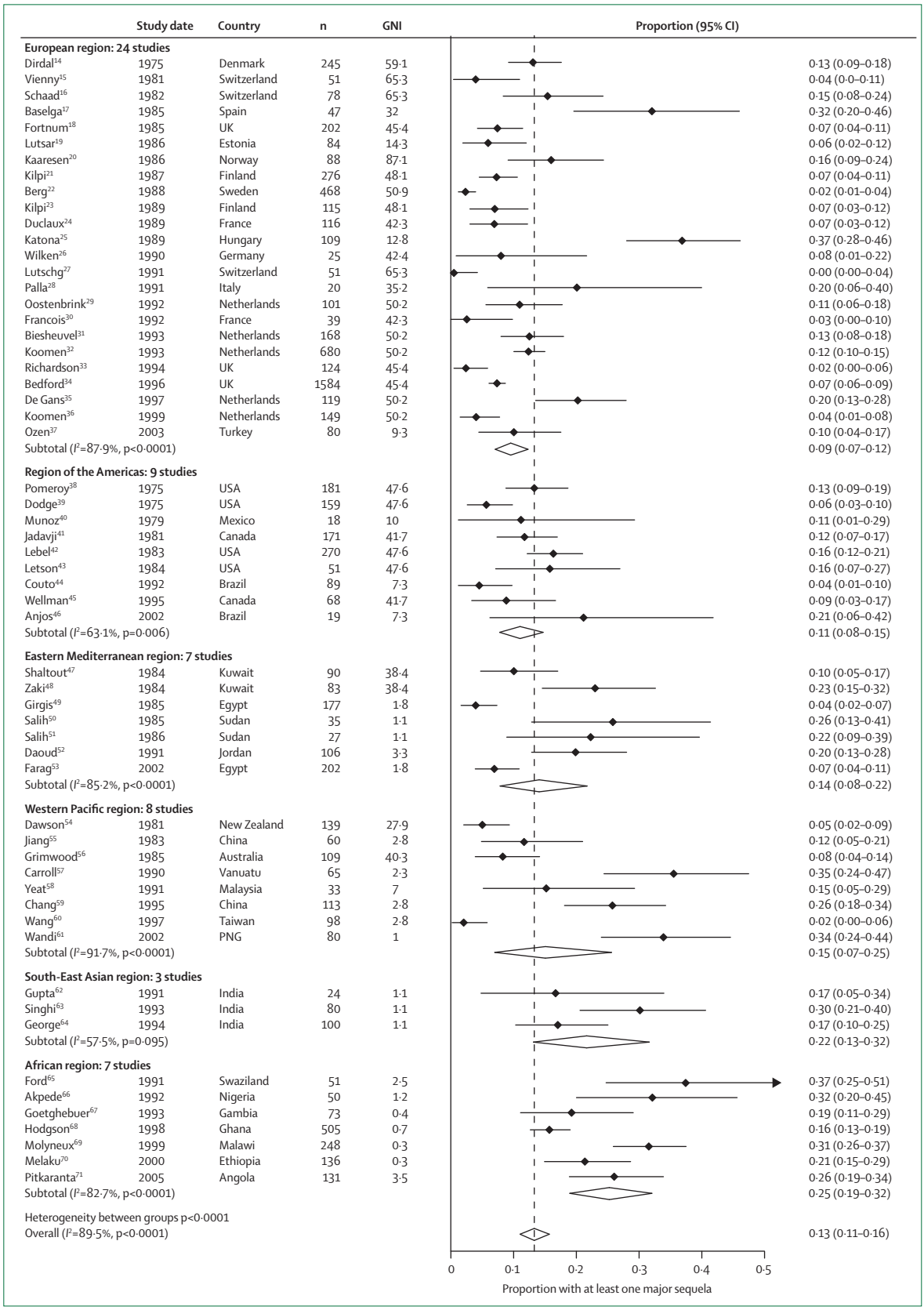
Table 4 shows the results from the meta-regression analysis of the effect of important covariates on the risk of at least one major sequelae. Because WHO region, WHO mortality band, and GNI were highly correlated, only GNI was included in the final analysis because it was a better predictor of sequelae risk than mortality band and region. Countries in the poorest GNI band (<US$1500 per head) had a much higher risk of major sequelae than the countries in the richest band (≥$45 000 per head). The risk of a major sequela was also significantly higher in people aged less than 5 years compared with those aged 5 years or more. There were

no clear differences in major sequelae risk associated with duration of follow-up, type of study design, percentage of isolates with laboratory confirmation, or decade of data collection. Additionally, a metaregression analysis of major sequelae risk by year of data collection from 1980 to 2008 revealed negligible correlation for all causes (coefficient 0·0015, 95% CI –0·0051 to 0·0080) and specific causes (Hib, 0·0030, –0·0073 to 0·0133; pneumococcus, 0·0079, 95% CI –0·0011 to 0·017; meningococcus, 0·0037, 95% CI –0·0023 to 0·0098).

	All-cause at discharge			Post discharge											
				All-cause			Hib			Pneumococcus			Meningococcus		
	n	Median (IQR) risk (%)	Adjusted median*	n	Median (IQR) risk (%)	Adjusted median*	n	Median (IQR) risk (%)	Adjusted median*	n	Median (IQR) risk (%)	Adjusted median*	n	Median (IQR) risk (%)	Adjusted median*
At least one sequela (major or minor)	28	22·8% (12·1–29·2%)	22·8%	59	19·9% (12·1–35·2%)	19·9%	27	14·5% (0·1–27·1%)	14·5%	20	34·7% (28·2–45·1%)	34·7%	27	9·5% (5·1–15·1%)	9·5%
Cognitive difficulties	7	2·3% (1·1–3·1%)	1·5%	21	2·8% (2·2–10%)	2·2%	11	1·6% (1·0–13·1%)	1·1%	9	6·3% (4·1–7·2%)	4·2%	6	2·9% (1·0–7·2%)	1·6%
Seizure disorder	5	5·4% (4·3–5·1%)	3·7%	27	2·0% (1·0–4·1%)	1·6%	9	2·2% (2·1–3·2%)	1·5%	8	3·7% (3·1–5·1%)	2·5%	5	0·9% (0·1–2·0%)	0·5%
Hearing loss	21	6·1% (3·1–17·1%)	4·1%	54	7·7% (3·1–13·2%)	6·0%	18	4·6% (3·1–8·2%)	3·2%	15	11·2% (9·1–19·2%)	7·5%	17	4·6% (3·0–7·3%)	2·6%
Motor deficit	9	6·6% (1·1–9·1%)	4·5%	30	3·0% (1·0–8·1%)	2·3%	14	3·2% (2·2–8·1%)	2·2%	8	8·7% (5·1–11·0%)	5·8%	9	1·8% (1·0–4·1%)	1·0%
Visual disturbance	2	4·1% (4·1–4·4%)	2·8%	14	1·2% (1·1–2·3%)	0·9%	2	0·7% (0·1–1·0%)	0·5%	5	1·7% (1·1–2·1%)	1·1%	4	2·7% (1·1–4·1%)	1·5%
Behavioural problems	1	1·0% (1·0–1·0%)	0·7%	5	3·3% (2·1–6·1%)	2·6%	2	3·0% (3·0–3·4%)	2·1%	2	6·8% (4·0–10·1%)	4·6%	2	1·0% (0·6–1·1%)	0·6%
Clinical impairments	7	2·5% (2·3–6·1%)	1·7%	11	1·1% (1·0–3·1%)	0·9%	3	1·7% (1·0–2·0%)	1·2%	1	5·1% (5·0–5·2%)	3·3%	1	0·4% (0·1–0·5%)	0·2%
Multiple impairments	28	5·5% (3·1–7·2%)	3·8%	27	4·4% (2·1–8·2%)	3·5%	24	3·7% (3·1–8·3%)	2·6%	20	8·6% (6·1–11·2%)	5·7%	25	2·3% (1·1–4·0%)	1·3%
At least one major sequela	28	16·0% (7·1–21·2%)	16·0%	58	12·8% (7·1–21·1%)	12·8%	27	9·5% (7·1–15·2%)	9·5%	20	24·7% (16·2–35·4%)	24·7%	26	7·2% (4·1–11·0%)	7·2%
Major cognitive difficulties	3	2·8% (2·3–3·3%)	2·0%	17	1·5% (1·2–2·2%)	1·1%	8	1·4% (1·0–2·1%)	1·0%	7	4·5% (4·1–6·2%)	3·1%	3	0·7% (0·0–3·1%)	0·4%
Major seizure disorder	5	5·4% (4·1–5·3%)	3·8%	27	2·0% (1·0–4·3%)	1·6%	11	2·1% (1·1–3·0%)	1·5%	8	3·7% (3·1–5·2%)	2·5%	5	0·9% (0·0–2·0%)	0·5%
Major hearing loss	21	5·9% (3·1–9·3%)	4·2%	54	5·6% (3·1–10·1%)	4·3%	19	4·5% (2·1–6·3%)	3·2%	15	9·9% (8·1–12·3%)	6·7%	16	3·8% (1·2–7·3%)	2·1%
Major motor deficit	9	1·2% (1·0–4·1%)	0·8%	29	2·0% (1·1–3·2%)	1·5%	14	1·7% (1·1–3·2%)	1·2%	7	4·8% (4·1–5·2%)	3·3%	9	1·4% (1·1–4·0%)	0·8%
Major visual disturbance	1	0·9% (1·0–1·0%)	0·7%	11	1·1% (1·1–2·3%)	0·8%	4	0·1% (0·1–0·1%)	0·1%	5	1·7% (1·0–2·3%)	1·1%	3	3·7% (2·1–4·2%)	2·1%
Major clinical impairments	7	2·5% (2·1–6·2%)	1·8%	11	1·1% (1·0–3·1%)	0·9%	4	1·0% (0·0–2·1%)	0·7%	1	5·0% (5·0–5·0%)	3·4%	1	0·4% (0·1–0·5%)	0·2%
Major multiple impairments	28	3·7% (2·1–6·1%)	2·6%	27	3·3% (2·1–5·2%)	2·5%	24	2·7% (2·0–4·1%)	1·9%	20	6·6% (3·1–9·4%)	4·5%	24	1·7% (1·0–2·1%)	1·0%
At least one minor sequela	17	9·4% (5·2–14·1%)	9·4%	37	8·6% (4·1–15·2%)	8·6%	17	5·7% (2·1–15·2%)	5·7%	10	18·6% (11·0–23·1%)	18·6%	11	2·3% (1·1–12·1%)	2·3%
Minor cognitive difficulties	4	2·1% (2·0–5·2%)	0·8%	13	4·8% (2·1–10%)	2·2%	6	8·8% (2·1–15·1%)	2·4%	4	5·1% (2·1–8·0%)	3·0%	3	7·1% (4·1–13·3%)	0·9%
Minor hearing loss	8	6·4% (1·0–9·1%)	2·7%	20	4·5% (3·1–7·1%)	2·1%	4	2·2% (2·1–3·2%)	0·6%	6	7·8% (6·1–12·1%)	4·6%	5	4·1% (1·1–5·0%)	0·5%
Minor motor deficit	4	7·6% (5·1–9·2%)	3·2%	10	3·0% (2·1–6·2%)	1·4%	7	4·8% (2·1–5·3%)	1·3%	5	4·6% (4·0–9·1%)	2·7%	1	3·0% (3·1–3·4%)	0·4%
Minor visual disturbance	2	3·6% (3·1–4·2%)	1·5%	4	1·0% (0·0–2·3%)	0·5%	1	0·1% (0·1–0·1%)	0·1%	1	3·1% (3·1–3·1%)	1·8%	1	1·8% (2·1–2·2%)	0·2%
Minor behavioural problems	1	1·0% (1·0–1·0%)	0·4%	5	3·3% (2·1–6·2%)	1·5%	2	3·0% (3·0–3·1%)	0·8%	2	6·8% (4·0–10·2%)	4·0%	2	1·0% (1·0–1·1%)	0·1%
Minor multiple impairments	17	2·1% (1·0–3·0%)	0·9%	27	1·9% (1·0–3·1%)	0·9%	14	2·0% (1·0–6·1%)	0·6%	10	4·0% (2·0–5·1%)	2·4%	9	1·3% (0·0–4·0%)	0·2%

*Median adjusted for incomplete reporting of mutually exclusive risk. Hib=*Haemophilus influenzae* type b.

Table 3: **Sequelae risk, by timing and pathogen**


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
Proportion with at least one major sequela

Discussion

We reported a median overall risk of long-term disabling sequelae in meningitis survivors after discharge from hospital of 20%. Risks of at least one major post discharge sequela ranged from 9% to 25% across the WHO regions, and were almost three times higher in Africa and Asia than in Europe. Major sequelae risk also increased significantly as GNI per head decreased. The overall global risk was similar to that found in previous reviews,[1,4] but our study differed by reporting disparities in risk between high-income and low-income countries.

Hearing loss was the most common type of sequela. Motor deficit, seizures, and cognitive deficits were also important. 20% of the impairments were reported to involve multiple domains; cognitive deficit plus hearing loss or motor deficit was the most commonly reported combination. Paediatricians are well aware that bacterial meningitis can result in complex, multifaceted syndromes; parenchymal brain injury can result in normal structural appearance, diffuse oedema, focal lesions, and gross cerebral necrosis.[13] However, no other studies have reported such high risks of multiple impairments from bacterial meningitis. The distribution of the different types of sequelae seemed similar for Hib, pneumococcus, and meningococcus, suggesting that the organisms might cause similar intracranial pathological processes.

Long-term disabling sequelae were particularly common in people with pneumococcal meningitis. This has been reported in other studies,[1,4,130] and is due to the particular virulence of the pneumococcal organism.[13] Hib was the most common cause of bacterial meningitis, because many studies included data from the pre-Hib-vaccination era. The risks of sequelae for Hib and meningococcal meningitis differed little.

There also seems to have been little change in the risk of long-term disabling sequelae over the past three decades. In particular, there was no change in risk over time for specific causes (Hib, pneumococcus, and meningococcus). This might be due to the increased use of highly sensitive tests to diagnose long-term disabling sequelae. An alternative explanation is that advances in medical care and new technologies (which should be reducing sequelae risk) are not reaching the people most in need. Further research and investigation into these issues is needed.

Our review had several limitations. First, only 60% of studies were prospective, and almost 20% of individuals in these studies were lost to follow-up. Families of disabled people might be more likely to suffer from financial or emotional stresses than families of non-disabled people, and so might be more likely to move or migrate out of the study area and become lost to follow-up.[146] Conversely, those who have few or no sequelae might be more likely to become lost to follow-up due to lack of interest in the study or no perceived benefit in continued participation.

Figure 2: **Meta-analysis of the risk of developing at least one major post-discharge sequela by study and WHO region (all-cause meningitis)**
Analysis was by random-effects meta-analysis. GNI=gross national income.

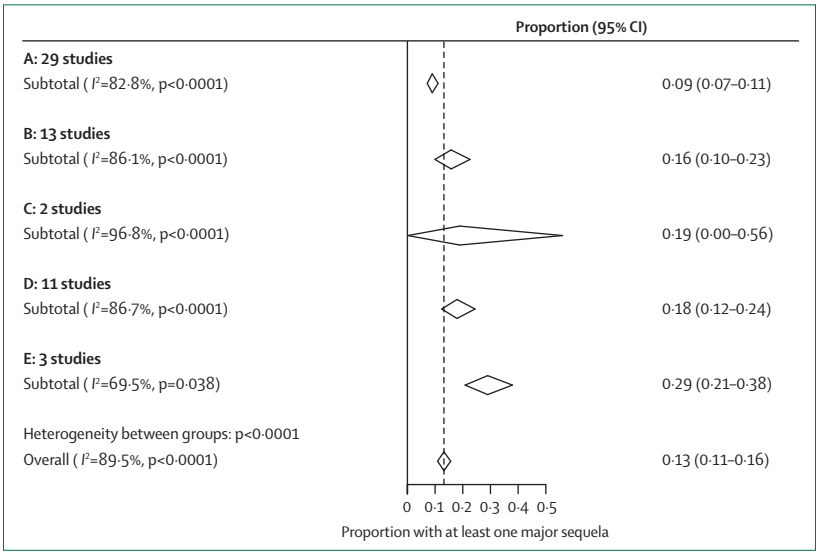


Figure 3: **Meta-analysis estimates of the risk of developing at least one major post-discharge sequela by WHO mortality strata (all-cause meningitis)**
Analysis was by random-effects meta-analysis. Mortality strata were created by WHO[11] to define countries in terms of health status and mortality rather than income: A=very low child mortality; B=low child mortality plus low adult mortality; C=low child mortality plus high adult mortality; D=high child mortality plus high adult mortality; E=high child mortality plus very high adult mortality.

Additionally, disabled people have a higher mortality risk than non-disabled people, and some will have died before follow-up, leaving the survivors with a spuriously low occurrence of sequelae.[146] This survivor bias is particularly important for African and Asian countries with high case fatality after hospital discharge.[147] Furthermore, all studies included in our study were hospital based. Hospital studies are biased towards patients with better access to acute and long-term health care.[148] These people tend to have higher socioeconomic status and lower sequelae risk than those with poor access to care.[4]

Second, our studies were very heterogeneous and this was obvious in our metaregression analysis. This was due to the wide range of data sources retained, particularly in studies from low-income countries. However, we did adjust our meta-analyses for important variables (ie, age, study design, GNI, duration of follow-up, year of data collection, percentage of cases laboratory confirmed) and presented both unadjusted and adjusted estimates.

Third, observational studies are prone to problems with misclassification.[149] Only 15% of the studies examined all the sequelae domains; thus, the number of individuals with multiple impairments is likely to have been underestimated. Moreover, only two studies assessed cognitive and visual domains in the African and Asian regions, and these risks are likely to have been underestimated. However, our abstractors used strict case definitions, and we adjusted the domain-specific sequelae so that they represented mutually exclusive counts of children.

Finally, few studies assessed the influence of important potential risk factors. No studies documented the effect of malnutrition and only two studies examined the role

	Studies (n)	Participants (N)	Pooled risk within each subgroup (95% CI)	Bivariate meta-regression		Multivariate meta-regression	
				Difference in risk from most prevalent stratum*	p†	Difference in risk from most prevalent stratum*‡	p†
Gross national income (US$ per head)							
>45 000	20	5160	0·088 (0·067–0·113)	..	..	..	..
25 000–44 999	11	907	0·109 (0·071–0·154)	0·022	0·45	–0·11	0·06
5000–24 999	7	432	0·135 (0·054–0·247)	0·046	0·21	0·047	0·18
1500–4999	9	1003	0·164 (0·086–0·260)	0·073	0·031	0·07	0·028
<1500	11	1358	0·238 (0·190–0·290)	0·150	0·000	0·15	0·000
Data collection period							
1970–1979	4	603	0·105 (0·066–0·153)	–0·034	0·51	0·054	0·21
1980–1989	22	2846	0·117 (0·084–0·155)	–0·022	0·44	0·5	0·81
1990–1999	26	4763	0·139 (0·104–0·178)	..	..	..	..
2000–2006	6	648	0·187 (0·103–0·289)	0·048	0·34	–0·026	0·42
Age-group							
<5 years	52	8135	0·140 (0·117–0·165)	..	..	..	..
>5 years	6	725	0·072 (0·017–0·163)	–0·068	0·072	–0·057	0·017
Study design							
Prospective	42	6261	0·142 (0·112–0·175)	..	..	..	..
Retrospective	16	2599	0·109 (0·082–0·140)	–0·033	0·27	–0·001	0·95
Duration of follow-up							
<1 year	22	2651	0·116 (0·079–0·159)	..	..	..	..
1–1·9 years	8	629	0·137 (0·107–0·171)	0·021	0·53	0·054	0·09
2–4·9 years	11	1342	0·230 (0·165–0·301)	0·114	0·004	–0·005	0·86
5–9·9 years	10	2458	0·099 (0·065–0·140)	–0·017	0·68	–0·044	0·07
>10 years	7	1780	0·097 (0·049–0·159)	–0·019	0·60	0·01	0·70
Percentage of cases laboratory confirmed							
100%	32	4723	0·097 (0·077–0·120)	..	..	..	..
80–99%	7	873	0·114 (0·047–0·204)	0·017	0·60	–0·009	0·73
60–79%	8	2071	0·232 (0·125–0·360)	0·135	0·001	0·0118	0·001
40–59%	3	147	0·312 (0·240–0·389)	0·215	0·003	0·0180	0·01
0–39%	7	915	0·159 (0·095–0·235)	0·062	0·10	–0·005	0·88

*Compared to the most prevalent stratum. †Student's t-test for difference from the most prevalent stratum. ‡Adjusted for GNI band, data collection period, age-group, study design, duration of follow-up, percentage of cases laboratory confirmed.

Table 4: **Metaregression analysis of the effect of important explanatory variables on the risk of major post discharge sequelae (all-cause meningitis)**

of HIV in the development of neurodevelopmental sequelae. We were not able to examine the effect of other important risk factors, such as prematurity or low birth weight, because few studies provided sufficient data to examine these issues separately. We were also unable to report on the underlying level of neurodevelopmental disability in specific regions because most studies did not report disability risk in healthy community control groups, nor the developmental status of participants before the acute attack of meningitis.

Our analyses focused on the risk of major sequelae in patients after they were discharged home from hospital. The natural healing process after the acute meningitis episode leads clinicians to expect a decrease in the proportion of people with sequelae from bacterial meningitis over time. However, we found little change in sequelae risk during the post-discharge follow-up period. Other systematic reviews have also reported similar findings,[1] and this might be due to problems with sequelae ascertainment in the included studies. Indeed, the longer the follow-up period, the longer the time available for disabled people to migrate or die or refuse to participate (ie, become lost to follow-up). Additionally, as people (especially children) become older, they become easier to examine and several sequelae that are not able to be ascertained in younger people can become evident at an older age (eg, motor impairments can manifest as floppiness in infants but spasticity in older children, tests for cognitive deficits and hearing loss are very difficult to administer in young children). Prospective studies with long-term follow-up and repeat examinations of the same people provide the most useful data. A large prospective UK study reported that almost 16% of children followed up to age 5 years had a significant disability.[34] Studies from Australia and the UK reported up to 12% of children with major

impairments and 30% of children with cognitive and behavioural problems at 12 years after the meningitis episode.[57,98] However, an older US study reported a sharp decrease in neurological and audiological abnormalities as duration of follow-up increased (42% of children at hospital discharge, 38% at 1 month, and 5% at 12 months after the acute meningitis episode).[150]

We also reported that the risk of sequelae in children aged less than 5 years was twice as high as for older people. This finding is consistent with other studies that used multivariate regression models and reported increased odds of meningitis sequelae in infants compared to older people.[151] Other researchers have described high risk of sequelae in infants who develop acute bacterial meningitis in the early months of life.[4,34,152]

This study has important implications for policy development. We have emphasised the differentials in the risk of sequelae after bacterial meningitis between high-income and low-income countries. There are many reasons for these disparities, including delay in receiving effective hospital antibiotic treatment for the acute meningitis episode.[21,153] People in low-income countries often have to travel much further to a health-care facility than those in high-income countries.[154] Costs of hospital care can be prohibitive for many families and might result in significant delays in presentation to hospital.[154] There is also an increasing problem of suboptimum quality of care once people are admitted to hospital in low-income countries.[155] Reasons include emerging antibiotic resistance and increased use of low-cost generic parenteral antibiotics of low potency (ie, third-generation cephalosporins).[155,156] Treatment failures from prescribed antibiotics are becoming increasingly common and must be addressed by tighter manufacturing regulations.[156]

The results of this study highlight the importance of both primary and secondary prevention. Many of the reported disabilities could have been averted. Highly efficacious conjugate vaccines are now available for the three major causes of bacterial meningitis in children aged less than 5 years (Hib, pneumococcus, and meningococcus). Vaccines for other important causes of meningitis are also needed (eg, group B streptococcus). Additionally, timely access to follow-up services for disabled people (such as antiepileptics, hearing assessment, speech therapy, physiotherapy, and occupational therapy) can reduce the severity of sequelae and improve quality of life.[2] However, these services are often not available in low-income countries. For example, a recent study in Senegal reported that no children with bacterial meningitis received post-discharge follow-up care from a health-care professional 12 months after the acute bacterial meningitis episode (Griffiths UK, unpublished). All people who are admitted to hospital with a serious neurological infection such as bacterial meningitis require close long-term follow-up after hospital discharge.[13] Inpatient hospital audit and peer review has improved markedly over the past decade,[157] but post-discharge care has not received the same attention.

Global, regional, and national estimates should be revised to indicate the true burden of long-term disabling sequelae from bacterial meningitis. These data should be disseminated so that appropriate services and follow-up care can be planned and implemented. This information should also be used in advocacy to improve basic services such as vaccination, timely access to hospital care, hospital treatment, and long-term community-based follow-up for people with meningitis sequelae.

Search strategy and selection criteria

These are described in detail in the Methods section.

Contributors

KE took the lead role in the design and conceptualisation of all aspects of this study, was the second data abstractor on the paper, oversaw the study's conduct, wrote all drafts of the paper, and was responsible for the final version. AC assisted in the conceptualisation of the methods and results sections, designed the data analysis plan, did much of the data analysis, and provided substantial inputs into all versions of the paper. VSK designed all the literature searches, created the data abstraction forms, was the first data abstractor, and provided substantial inputs into all versions of the paper. CS commented on different drafts of the paper and was responsible for the meta-analyses. UKG conceived the initial idea for this study and provided inputs into all versions of the paper. IR provided important objective advice about the design, conduct, analyses, and synthesis of the study, and provided substantial inputs into the final versions of the paper. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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