Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study

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Summary

Background We studied causative pathogens, clinical characteristics, and outcome of adult community-acquired bacterial meningitis after the introduction of adjunctive dexamethasone treatment and nationwide implementation of paediatric conjugate vaccines.

Methods In this cohort study, we prospectively assessed adults (age >16 years) with community-acquired bacterial meningitis in the Netherlands, identified through the National Reference Laboratory for Bacterial Meningitis or individual physicians between Jan 1, 2006, and July 1, 2014. We identified independent predictors of an unfavourable outcome (Glasgow Outcome Scale score 1–4) by logistic regression.

Findings We assessed 1412 episodes of community-acquired bacterial meningitis. Incidence declined from 1·72 cases per 100 000 adults per year in 2007–08, to 0·94 per 100 000 per year in 2013–14. *Streptococcus pneumoniae* caused 1017 (72%) of 1412 episodes. Rates of adult bacterial meningitis decreased most sharply among pneumococcal serotypes included in paediatric conjugate vaccine, and in meningococcal meningitis. We found no evidence of serotype or serogroup replacement. The overall case fatality rate was 244 (17%) of 1412 episodes and unfavourable outcome occurred in 531 (38%) of 1412 episodes. Predictors of unfavourable outcome were advanced age, absence of otitis or sinusitis, alcoholism, tachycardia, lower score on the Glasgow Coma Scale, cranial nerve palsy, a cerebrospinal fluid white-cell count lower than 1000 cells per µL, a positive blood culture, and a high serum C-reactive protein concentration. Adjunctive dexamethasone was administered for 1234 (89%) of 1384 assessed episodes. The multivariable adjusted odds ratio of dexamethasone treatment for unfavourable outcome was 0·54 (95% CI 0·39–0·73).

Interpretation The incidence of adult bacterial meningitis has decreased substantially, which is partly explained by herd protection by paediatric conjugate vaccines. Adjunctive dexamethasone treatment was associated with substantially improved outcome.

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Introduction

Bacterial meningitis is associated with substantial mortality and morbidity.[1] The epidemiology and treatment of bacterial meningitis has changed over the past 15 years.[2,3] The routine use of protein–polysaccharide conjugate vaccines in childhood against common causative pathogens of bacterial meningitis has reduced the overall incidence, affecting the distributions of causative pathogens and the age groups most often affected.[2,4] The introduction of new treatments, such as dexamethasone as adjunctive treatment, might have affected national outcomes of bacterial meningitis.[5,6] In 2006, we started a prospective cohort study to identify and characterise host genetic traits and bacterial genetic factors controlling occurrence and outcome of bacterial meningitis (MeninGene).[7–19] Here, we report data from this study, including the incidence, causative pathogens, clinical features, and prognostic factors in adults with community-acquired bacterial meningitis in the Netherlands from 2006 to 2014.

Methods

Study population

We identified adults (patients older than age 16 years) who had bacterial meningitis in the Netherlands between Jan 1, 2006, and July 1, 2014, and who were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis. This laboratory receives cerebrospinal fluid and blood samples from roughly 85% of all patients with bacterial meningitis in the Netherlands (population 16·9 million).[20,21] The laboratory provided daily updates of the names of hospitals where patients with bacterial meningitis have been admitted in the preceding 2–6 days, and the names of the attending physicians, usually neurologists. Physicians were informed about the study by telephone. Physicians could also contact investigators at any time to include patients, without preceding report of the reference laboratory. Subsequently, patients or their legal representatives received written information about the study and were asked to give written informed consent for participation. Online case-record forms were used to collect data on patients' history, symptoms and signs on

Research in context

Evidence before this study

We searched PubMed for the terms "bacterial meningitis" and "community-acquired infections" or "immunity, herd" or "dexamethasone/therapeutic use". Serogroup A and C meningococcal conjugate vaccination reduces carriage and disease in both vaccinated and unvaccinated populations. The importance of herd protection has also become clear in meningitis due to *Haemophilus influenzae* type B and invasive pneumococcal disease. Serotype replacement by pneumococcal serotypes not included in the vaccine has been shown by several studies. In 2004, clinical features and prognostic factors for community-acquired bacterial meningitis were described in 696 Dutch adults. The mortality associated with bacterial meningitis was high, and the strongest risk factors for an unfavourable outcome were those that are indicative of systemic compromise, a low level of consciousness, and infection with *Streptococcus pneumoniae*. A randomised controlled study showed that adjunctive treatment with corticosteroids decreased the rate of unfavourable outcome and mortality in adults with community-acquired bacterial meningitis. In a meta-analysis of individual patient data from five clinical trials in bacterial meningitis, adjunctive dexamethasone did not significantly reduce death or neurological disability. A recent Cochrane review showed that corticosteroids were associated with decreased hearing loss and neurological sequelae.

Added value of this study

Our cohort study shows the epidemiology, clinical practice, prognostic factors, and outcomes in adults with community-acquired bacterial meningitis. After the introduction of conjugate vaccines in children, the incidence of serogroup C meningococcal meningitis and vaccine type pneumococcal meningitis has declined substantially in non-immunised adults. Contrary to previous publications, we found no evidence of pneumococcal serotype replacement. Outcome has improved substantially after the introduction of adjunctive dexamethasone treatment, and was associated with better outcome in both pneumococcal and non-pneumococcal episodes.

Implications of all the available evidence

Progress has been made in the prevention and treatment of community-acquired bacterial meningitis. Herd protection is a major part of the effectiveness of conjugate vaccines and can protect those with poor immunological response to vaccination—eg, infants and elderly people. The development of vaccines covering more pneumococcal serotypes, new potent anti-inflammatory treatments, immediate start of treatment, and aggressive supportive care might further improve the prognosis of patients with bacterial meningitis.

admission, laboratory findings at admission, clinical course, outcome and neurological findings at discharge, and treatment. Before the study, all Dutch neurologists received information about the study, which was followed up by periodic reminders.

We defined bacterial meningitis as a bacterial pathogen cultured in cerebrospinal fluid, or the combination of a positive PCR or antigen test in cerebrospinal fluid for *Streptococcus pneumoniae* or *Neisseria meningitidis* with at least one specific cerebrospinal fluid finding predictive of bacterial meningitis (according to the criteria of Spanos and colleagues:[22] glucose concentration <340 mg/L [1·9 mmol/L], cerebrospinal fluid glucose:blood glucose ratio <0·23, protein concentration >2200 mg/L, white cell count >2000 cells per µL, or >1180 polymorphonuclear leucocytes per µL). We excluded episodes of hospital-acquired meningitis, defined as bacterial meningitis that occurred while in hospital or within 1 week after discharge.[23] We also excluded patients with head trauma or neurosurgery in the previous month, or those with a neurosurgical device or missing outcome.

Procedures

Neurological examinations were done at admission and at discharge. Outcome was scored by the Glasgow Outcome Scale score:[24] 1=death, 2=vegetative state (unable to interact with the environment), 3=severe disability (unable to live independently but can follow commands), 4=moderate disability (capable of living independently but unable to return to work or school), and 5=mild or no disability (able to return to work or school). A favourable outcome was defined as a score of 5, and an unfavourable outcome as a score of 1–4.

Statistical analysis

We calculated the incidence of community-acquired meningitis as the number of new episodes per epidemiological year (July 1–June 30) per 100 000 adult patients (>16 years old on Jan 1). We tested bacterial susceptibility as previously described.[25] *N meningitidis* was considered susceptible to penicillin if the minimum inhibitory concentration (MIC) was 0·06 µg/mL or less. Reduced susceptibility was defined as a MIC of 0·06–1·0 µg/mL before 2010, and 0·06–0·25 µg/mL after 2010. Penicillin resistance was defined as a MIC of more than 1·0 µg/mL before 2010, and more than 0·25 µg/mL after 2010. *S pneumoniae* was considered to be sensitive to penicillin if the MIC was 0·06 µg/mL or less and resistant if MIC was more than 0·06 µg/mL. We did meningococcal serogrouping and multilocus sequence typing, and pneumococcal serotyping, as previously described.[21,26,27]

Categorical variables are expressed as counts (percentage) and we compared frequency distributions with the Fisher exact test. Continuous variables are expressed as median (IQR). We tested differences with the independent *t* test for normally distributed variables

or the Mann-Whitney *U* test otherwise. We tested trends in the incidence of pneumococcal serotypes with linear regression using incidence per 100 000 adults as the dependent variable and epidemiological year as the independent variable. We chose possible predictors of an unfavourable outcome on the basis of previous research, pathophysiological interest, and availability early in the course of the illness. We investigated the association between these predictors and outcomes with logistic regression, providing odds ratios (ORs) and 95% CIs. We assessed the linearity of the association between continuous predictors and outcome with the Hosmer-Lemeshow goodness of fit test and by visual inspection. If there was no linear relationship, the continuous predictor was categorised for further analyses. We estimated both univariable crude ORs and multivariable ORs corrected for all other variables in the model. We used multiple imputation for missing data in the multivariable analysis. We used all predictors together to impute missing values using the Mice package (version 2.22). We combined the coefficients of 60 rounds of imputation to obtain the final estimates for the multivariable model. The statistical tests were two-tailed, and we deemed p values of less than 0·05 as statistically significant. We did the imputation and all statistical analyses in R (version 3.0.1).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

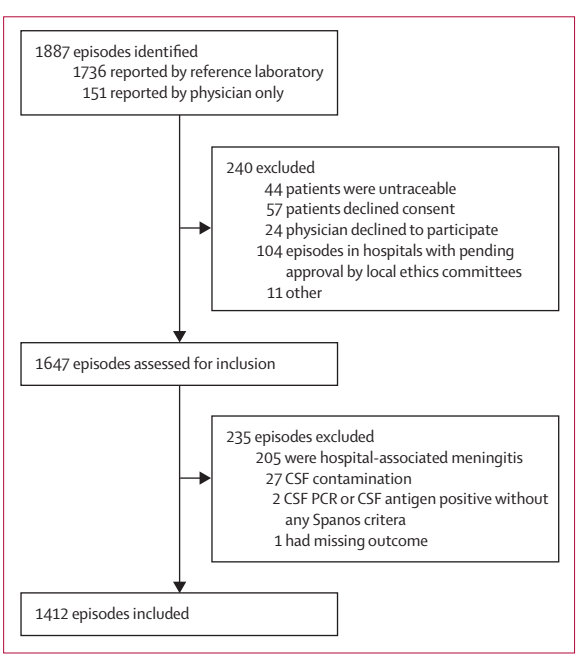

Figure 1: **Selection of patients**
CSF=cerebrospinal fluid.

Results

1887 episodes of bacterial meningitis were identified, 1736 (92%) by the reference laboratory and 151 (8%) by physicians (figure 1). 240 (13%) of 1887 episodes were excluded from the cohort and 235 (12%) met exclusion criteria, resulting in 1412 (75%) episodes in 1391 patients (figure 1).

Median age was 61 years (table 1). A history of splenectomy or cerebrospinal fluid leak was present in

	Data
Age (years)	61 (47–69)
Men	707/1412 (50%)
History of meningitis	93/1396 (7%)
Symptoms <24 h	636/1353 (47%)
Seizures	98/1353 (7%)
Pretreatment with antibiotics	152/1377 (11%)
Otitis or sinusitis	480/1404 (34%)
Pneumonia	122/1347 (9%)
Endocarditis	17/1346 (1%)
Cerebrospinal fluid leak	39/1374 (3%)
Immunosuppressive drugs	107/1391 (8%)
History of splenectomy	32/1412 (2%)
History of cancer	173/1407 (12%)
Diabetes	171/1394 (12%)
HIV positive	12/1412 (1%)
Alcoholism	82/1412 (6%)
Symptoms and signs on presentation	
Headache	1015/1223 (83%)
Nausea	713/1159 (62%)
Neck stiffness	977/1322 (74%)
Rash	116/1412 (8%)
Heart rate (beats per min)*	100 (84–112)
Systolic blood pressure (mm Hg)†	142 (125–163)
Diastolic blood pressure (mm Hg)†	80 (69–90)
Body temperature (°C)	38·9 (37·9–39·6)
≥38°C	1033/1391 (74%)
Score on Glasgow Coma Scale	11 (9–14)
<14 (altered mental status)	996/1403 (71%)
<8 (coma)	185/1403 (13%)
Triad fever, neck stiffness, or altered mental status	563/1389 (41%)
Cranial nerve palsy	109/1245 (9%)
Aphasia, hemiparesis, or monoparesis	268/1221 (22%)
Indices of CSF inflammation	
Opening pressure >400 mm water	253/480 (53%)
White cell count (cells per µL)	2310 (547–6840)
<100	149/1352 (11%)
100–999	316/1352 (23%)
≥999	887/1352 (66%)
Protein (g/L)‡	3·9 (2·3–6·0)
CSF:blood glucose ratio§	0·04 (0·0–0·3)
Positive Gram stain	1057/1245 (85%)
Positive blood culture	927/1243 (75%)

(Table 1 continues on next page)

	Data
(Continued from previous page)	
Blood chemical tests	
C-reactive protein (mg/L)	194 (87–311)
<40	162/1353 (12%)
>80	1040/1353 (77%)
Thrombocyte count (per μL)	199 (151–253)
<150	322/1345 (24%)
Clinical course	
Seizures	185/1353 (14%)
Pneumonia	221/1311 (17%)
Cardiorespiratory failure	530/1412 (38%)
Score on Glasgow Outcome Scale	
1 (death)	244/1412 (17%)
2 (vegetative state)	2/1412 (<1%)
3 (severe disability)	64/1412 (5%)
4 (moderate disability)	221/1412 (16%)
5 (mild or no disability)	881/1412 (62%)

Data are median (IQR) or n/N (%). CSF=cerebrospinal fluid. *Evaluated in 1363 episodes. †Evaluated in 1381 episodes. ‡Evaluated in 1344 episodes. §Evaluated in 1309 episodes.

***Table 1*: Characteristics of the study population**

71 (5%) of 1374 episodes. For 457 (33%) of 1380 episodes, the patient had used immunosuppressive drugs or had a history of cancer, diabetes, HIV, or alcoholism. Extrameningeal foci of infection (otitis, sinusitis, pneumonia, or endocarditis) were present in 598 (42%) of 1412 episodes, and were more likely to occur in episodes of pneumococcal meningitis (518 [51%] of 1008) than in meningococcal meningitis (nine [6%] of 150) or listeria meningitis (eight [11%] of 74). Headache, neck stiffness, fever, and a change in mental status were common symptoms at presentation (table 1). The classic triad of fever, altered mental status, and neck stiffness was present in 563 (41%) of 1389 episodes. Rash was noted in 116 (8%) of 1412 episodes, of which 70 (60%) episodes were meningococcal meningitis and 34 (29%) were pneumococcal meningitis. The rash was petechial or consisted of purpura or ecchymosis in 69 (99%) of the 70 meningococcal cases and in 25 (74%) of 34 pneumococcal cases with a rash.

At least one specific cerebrospinal fluid finding predictive of bacterial meningitis was present in 1229 (96%) of 1277 episodes with data available. Cranial imaging was done on admission for 1206 (86%) of 1402 episodes with data available and abnormalities were recorded in 561 (47%) of 1206 episodes, most commonly

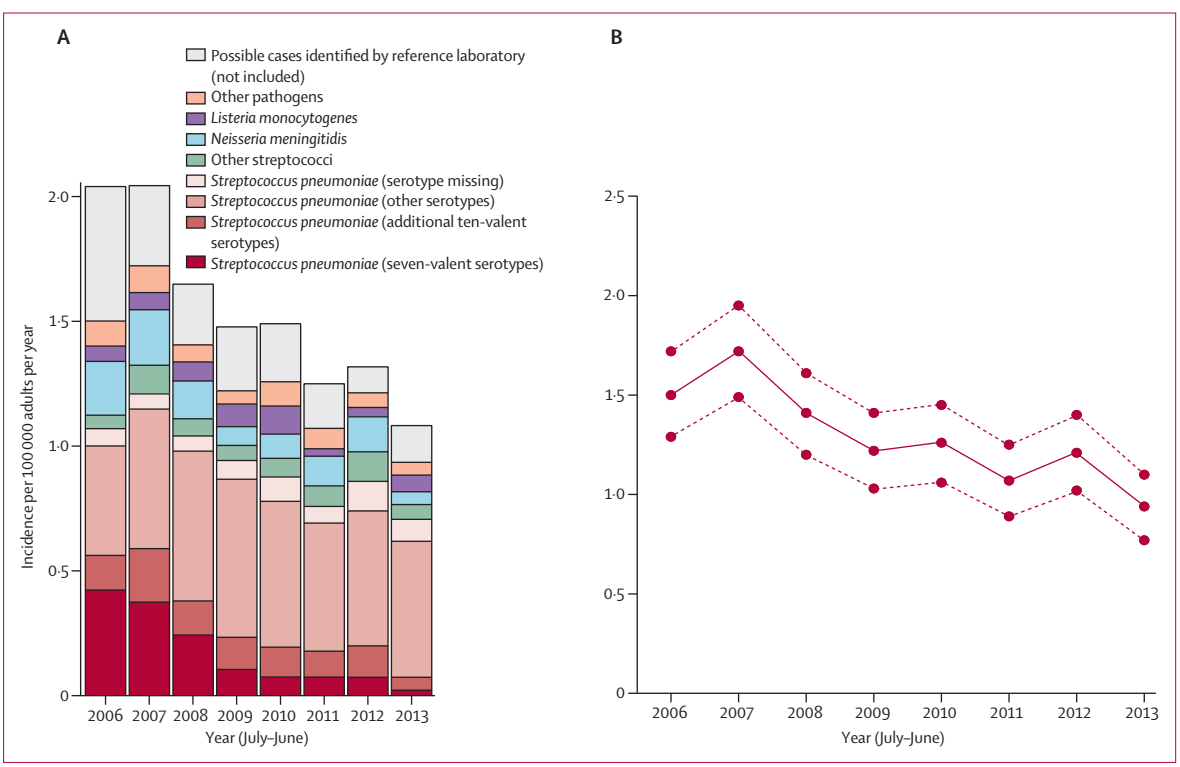

***Figure 2:* Incidence of community-acquired bacterial meningitis in the Netherlands for 2006–14**

(A) Incidence rate per 100 000 adults per year of all episodes reported to the Netherlands Reference Laboratory for Bacterial Meningitis. (B) Incidence rate with 95% CIs of all included episodes of community-acquired meningitis per 100 000 adults per year. Not all patients could be included in the first months of the study because of pending ethical approval in several hospitals. Routine vaccination against *S pneumoniae* at 2 months, 3 months, 4 months, and 11 months of age with the seven-valent conjugate vaccine was started in 2006, and replaced by a ten-valent conjugate vaccine in 2011. Children aged 1–19 years were offered a single meningococcal serogroup C vaccination in 2002, and routine vaccination at 14 months was subsequently introduced.

sinusitis or mastoiditis (386 [34%] of 1125 episodes in which otitis or sinusitis was evaluated), brain oedema (118 [10%] of 1165 episodes), and hydrocephalus (58 [5%] of 1177 episodes). Cranial imaging preceded lumbar puncture in 936 (86%) of 1092 episodes with neuroimaging data available. Treatment was started before imaging in 304 (36%) of 855 episodes for which we had data.

The most common pathogen was *S pneumoniae*, accounting for 1017 (72%) of 1412 isolates identified (figure 2, table 2). Pneumococcal serotype was available for 930 (91%) of 1017 episodes. Serotypes included those covered by the the seven-valent, ten-valent, and 13-valent conjugate vaccines (figure 2, table 2). 763 (82%) of 930 episodes were due to a pneumococcal serotype included in the 23-valent polysaccharide vaccine. In patients aged older than 65 years, 79 (22%) of 359 episodes were of serotypes covered by the seven-valent vaccine, 129 (36%) were of serotypes covered by the ten-valent vaccine, 181 (50%) were of serotypes covered by the 13-valent vaccine, and 283 (79%) were of serotypes covered by the 23-valent vaccine.

The incidence of community-acquired bacterial meningitis was highest in 2007–08, with 1·72 cases per 100 000 adults per year, and subsequently declined to 0·94 per 100 000 adults per year in 2013–14 (figure 2). There was a reduction in both the absolute number of pneumococcal cases per year and the proportion of cases caused by the seven-valent vaccine serotypes (figure 2). The incidence of pneumococcal serotypes included in the seven-valent vaccine decreased from 0·42 per 100 000 adults per year in 2006, to 0·02 in 2013. There was no evidence of serotype replacement. The mean incidence of pneumococcal serotypes not included in the seven-valent vaccine was 0·68 per 100 000 adults per year excluding missing serotypes, and 0·76 per 100 000 adults per year including missing serotypes. The mean incidence of pneumococcal serotypes not included in the ten-valent vaccine was 0·55 per 100 000 adults per year excluding missing serotypes, and 0·63 including missing serotypes. There was no increasing trend in the incidence of non-seven-valent serotypes (β –0·01, p=0·45) or non-ten-valent serotypes (β 0·004, p=0·69) during the observation period.

N meningitidis was responsible for 150 (11%) of 1412 episodes (table 2). Meningococcal clonal complex by multilocus sequence typing was available for 119 (79%) of 150 episodes and the most common clonal complexes were ST-41/44 (42 [35%] of 119 episodes), ST-32 (28 [24%] of 119 episodes), and ST-269 (12 [10%] of 119 episodes). Patients with meningococcal meningitis were generally younger (median age 32 years, IQR 19–54) than were patients with other causative bacteria (median 61 years, IQR 46–71; p<0·0001).

Gram staining of cerebrospinal fluid yielded a positive result in 848 (92%) of 919 episodes of pneumococcal meningitis, 109 (83%) of 132 episodes of meningococcal meningitis, and 24 (41%) of 59 episodes of listeria meningitis in which Gram staining was done. Gram stain results led to a change in antimicrobial treatment for 560 (43%) of 1316 episodes. Blood cultures were positive for 927 (75%) of 1243 episodes in which cultures were done. Penicillin susceptibility was tested in 928 (91%) of 1017 episodes of pneumococcal meningitis; 15 (2%) of 928 pneumococcal isolates showed penicillin resistance, and three (20%) of these 15 isolates showed reduced susceptibility to ceftriaxone. Antibiotic susceptibility was tested for 134 (89%) of 150 episodes of meningococcal meningitis; 16 (12%) isolates showed intermediate penicillin resistance, all were susceptible to ceftriaxone and rifampicin.

Initial antibiotic treatment included a combination of amoxicillin with a third-generation cephalosporin in

	n/N (%)
*Streptococcus pneumoniae**	1017/1412 (72%)
7F	110/930 (12%)
3	106/930 (11%)
8	78/930 (8%)
22F	68/930 (7%)
23F	44/930 (5%)
19A	40/930 (4%)
19F	34/930 (4%)
39 other serotypes†	450/930 (48%)
Neisseria meningitidis	150/1412 (11%)
Serogroup B	113/137 (82%)
Serogroup Y	10/137 (7%)
Serogroup C	10/137 (7%)
Other serogroups	4/137 (3%)
Listeria monocytogenes	74/1412 (5%)
Haemophilus influenzae	47/1412 (3%)
Streptococcus pyogenes	24/1412 (2%)
Streptococcus agalactiae	21/1412 (1%)
Other streptococcal species‡	35/1412 (2%)
Staphylococcus aureus	21/1412 (1%)
Other§	23/1412 (2%)

*Of the 930 episodes with an identified pneumococcal serotype, 193 episodes were due to serotypes included in the seven-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) and 329 episodes were due to serotypes included in the ten-valent vaccine (1,5, and 7F, in addition to serotypes included in the seven valent vaccine). †Serotype (number): 10A (30), 23B (30), 4 (28), 12F (27), 6B (25), 14 (23), 18C (23), 1 (23), 9N (21), 11A (20), 23A (20), 6A (18), 24F (17), 33F (17), 9V (16), 15B (15), 6C (12), 35F (10), 16F (10), 15A (8), 17F (8), 15C (6), 31 (6), 38 (6), 18B (4), 20 (4), 37 (4), 5 (3), 34 (3), 35B (3), 22A (2), 7A (1), 7B (1), 10B (1), 13 (1), 24B (1), 25A (1), 27 (1), 28F (1). ‡*Streptococcus suis* (n=7), *Streptococcus salivarius* (n=5), *Streptococcus mitis* (n=4), *Streptococcus anginosus* (n=3), *Streptococcus dysgalactiae* subspecies *equisimilis* (n=3), *Streptococcus intermedius* (n=3), *Streptococcus equi* subspecies *zooepidemicus* (n=2), *Streptococcus parasanguinis* (n=2), *Streptococcus constellatus* subspecies *constellatus* (n=1), *Streptococcus gallolyticus* subspecies *gallolyticus* (n=1), *S gallolyticus* subspecies *pasteurianus* (n=1), *Streptococcus gordonii* (n=1), *Streptococcus oralis* (n=1), *Streptococcus sanguinis* (n=1) §*Escherichia coli* (n=10), *Capnocytophaga canimorsus* (n=3), *Klebsiella pneumoniae* (n=3), *Haemophilus parainfluenzae* (n=2), *Aggregatibacter aphrophilus* (n=1), *Campylobacter fetus* (n=1), *Nocardia farcinica* (n=1), *Pseudomonas aeruginosa* (n=1), *Salmonella enterica* (n=1).

Table 2: **Typing and subtyping of causative pathogens**

459 (36%) of 1273 episodes. Monotherapy was started with a third-generation cephalosporin in 365 (29%) of 1273 episodes, and with either penicillin or amoxicillin in 259 (20%) of 1273 episodes. Other regimens were used in 190 (15%) of 1273 episodes. Initial antimicrobial treatment was appropriate for the pathogen cultured in

	Favourable outcome (n=881)	Unfavourable outcome (n=531)	Univariable odds ratio for unfavourable outcome (95% CI)	Multivariable odds ratio for unfavourable outcome (95% CI)	p value of multivariable analysis
Age (years)	58 (42–67)	64 (55–75)	..	..	..
16–39	194/881 (22%)	43/513 (8%)	Reference	Reference	..
40–70	542/881 (62%)	297/513 (56%)	2·47 (1·73–3·54)	1·55 (1·02–2·35)	0·041
>70	145/881 (17%)	191/513 (36%)	5·94 (4·01–8·81)	3·04 (1·89–4·89)	<0·0001
Symptoms <24 h	428/855 (50%)	208/498 (42%)	0·72 (0·57–0·90)	0·84 (0·65–1·10)	0·22
Seizures	48/857 (6%)	50/496 (10%)	1·89 (1·22–2·92)	1·50 (0·85–2·63)	0·16
Pretreatment with antibiotics	97/858 (11%)	55/519 (11%)	0·93 (0·64–1·34)	1·10 (0·72–1·68)	0·65
Otitis or sinusitis	338/876 (39%)	142/528 (27%)	0·59 (0·46–0·75)	0·74 (0·55–0·99)	0·041
Pneumonia	54/860 (6%)	68/487 (14%)	2·42 (1·63–3·60)	1·36 (0·81–2·27)	0·23
Immunosuppressive drugs	57/870 (7%)	50/521 (10%)	1·51 (1·00–2·29)	1·02 (0·62–1·67)	0·94
History of splenectomy	15/881 (2%)	17/531 (3%)	1·91 (0·89–4·14)	1·08 (0·47–2·48)	0·85
History of cancer	83/881 (9%)	90/526 (17%)	1·98 (1·42–2·77)	1·17 (0·80–1·72)	0·42
Diabetes	94/874 (11%)	77/520 (15%)	1·44 (1·03–2·02)	1·38 (0·93–2·04)	0·11
HIV positive	9/881 (1%)	3/531 (1%)	0·55 (0·10–2·22)	0·62 (0·14–2·63)	0·51
Alcoholism	34/881 (4%)	48/531 (9%)	2·47 (1·54–4·02)	1·98 (1·15–3·41)	0·013
Headache	716/819 (87%)	299/404 (74%)	0· 41 (0·30–0·56)	0·71 (0·49–1·01)	0·058
Nausea	495/762 (65%)	218/397 (55%)	0·66 (0·51–0·85)	0·86 (0·63–1·16)	0·32
Neck stiffness	636/837 (76%)	341/485 (70%)	0·75 (0·58–0·97)	0·82 (0·54–1·25)	0·36
Rash	85/881 (10%)	31/531 (6%)	0·58 (0·37–0·90)	0·88 (0·53–1·46)	0·63
Heart rate (beats per min)*	98 (82–110)	102 (89–120)	1·18 (1·12–1·24)	1·10 (1·03–1·17)	0·0030
Diastolic blood pressure (mm Hg)†	79 (68–88)	80 (70–92)	1·10 (1·03–1·17)	1·03 (0·95–1·11)	0·51
Temperature (°C)‡	39·0 (38·0–39·7)	38·8 (37·6–39·5)	0·87 (0·81–0·95)	0·89 (0·79–1·01)	0·070
Score on Glasgow Coma Scale§	12 (9–14)	10 (8–13)	0·85 (0·82–0·88)	0·91 (0·87–0·96)	0·00085
Triad of fever, neck stiffness, and Glasgow Coma Scale score <14	354/851 (42%)	209/496 (42%)	1·02 (0·81–1·29)	1·03 (0·68–1·56)	0·88
Aphasia, hemiparesis, or monoparesis	148/547 (27%)	120/257 (47%)	2·36 (1·71–3·25)	1·15 (0·83–1·58)	0·40
Cranial nerve palsy	43/747 (5%)	60/449 (13%)	2·68 (1·74–4·14)	2·55 (1·59–4·09)	0·00013
Cerebrospinal fluid white cell count (cells per µL)	3183 (950–7983)	1186 (249–5010)	..	..	..
<100	60/846 (7%)	89/506 (18%)	3·61 (2·50–5·22)	2·10 (1·34–3·29)	0·0012
100–999	157/846 (19%)	159/506 (31%)	2·47 (1·87–3·25)	2·04 (1·46–2·84)	<0·0001
1000–10 000	470/846 (56%)	193/506 (38%)	Reference	Reference	..
>10 000	159/846 (19%)	65/506 (13%)	1·00 (0·71–1·39)	0·81 (0·56–1·19)	0·29
CSF protein (g/L)¶	3·5 (2·1–5·7)	4·5 (2·7–6·5)	1·08 (1·04–1·11)	1·03 (0·99–1·07)	0·13
CSF:blood glucose ratio‖	0·1 (0–0·3)	0·01 (0–0·1)	..	..	..
<0·25	560/825 (68%)	407/484 (84%)	1·53 (0·88–2·64)	1·28 (0·63–2·58)	0·49
0·25–0·5	223/825(27%)	57/484 (12%)	0·54 (0·29–0·98)	0·71 (0·34–1·50)	0·36
>0·5	42/825 (5%)	20/484 (4%)	Reference	Reference	..
Positive blood culture	550/777 (71%)	377/466 (81%)	1·75 (1·31–2·34)	1·44 (1·02–2·05)	0·040
Thrombocyte count	207 (160–257)	185 (135–237)	..	..	..
<150	163/845 (19%)	159/500 (32%)	1·94 (1·50–2·50)	1·32 (0·96–1·81)	0·088
150–450	664/845 (79%)	334/500 (67%)	Reference	Reference	..
>450	18/845 (2%)	7/500 (1%)	0·77 (0·32–1·87)	0·46 (0·17–1·26)	0·13
C-reactive protein (mg/L)**	162 (72–272)	249 (134–370)	1·04 (1·03–1·05)	1·02 (1·01–1·03)	<0·0001

The study included 1412 episodes of community-acquired meningitis in 1391 patients; data are median (IQR) or n/N (%), unless stated otherwise. The multivariable analysis used an imputed dataset with 60 imputation rounds, all variables in the table were entered in the multivariable logistic regression model simultaneously. CSF=cerebrospinal fluid. *Evaluated in 1363 episodes; odds ratio is for an increase of ten beats per min. †Evaluated in 1381 episodes; odds ratio is for a 10 mm Hg increase. ‡Evaluated in 1391 episodes. §Evaluated in 1403 episodes; odds ratio is for a one point increase. ¶Evaluated in 1344 episodes. ‖Evaluated in 1309 episodes. **Evaluated in 1353 episodes; odds ratio is for a 10 mg/L increase.

Table 3: **Factors associated with an unfavourable outcome**

1247 (98%) of 1273 episodes; eight (11%) of 74 patients with listeria meningitis were initially treated with cephalosporin alone. Adjunctive dexamethasone was administered for 1234 (89%) of 1384 assessed episodes. Dexamethasone 10 mg intravenously, every 6 h for 4 days, was started before or with the first dose of parenteral antibiotics in 1075 (78%) of 1384 episodes.[5,28]

The overall case fatality rate was 244 (17%) of 1412 episodes and varied with the causative organism: 179 (18%) in 1017 episodes of pneumococcal meningitis, five (3%) in 150 episodes of meningococcal meningitis, and 26 (35%) in 74 episodes of listeria meningitis. An unfavourable outcome occurred in 531 (38%) of 1412 episodes: 413 (41%) of 1017 episodes of pneumococcal meningitis, 19 (13%) of 150 episodes of meningococcal meningitis, and 40 (54%) of 74 episodes of listeria meningitis. The appendix (p 1) shows characteristics of listeria meningitis episodes. In a multivariable analysis, several characteristics were associated with an unfavourable outcome in bacterial meningitis due to any pathogen: older age, absence of otitis or sinusitis, alcoholism, tachycardia, lower score on the Glasgow Coma Scale, cranial nerve palsy, a cerebrospinal fluid white blood cell count of less than 1000 cells per µL, a positive blood culture, and a high serum C-reactive protein concentration (table 3).

Pneumococcal serotype was not associated with outcome after correcting for multiple testing, neither with use of serotype 7F as a reference category, nor in dichotomised analyses between high-virulence and low-virulence serotypes or between serotypes included in conjugate vaccines versus those not included (data not shown).[29,30]

The proportion of patients with unfavourable outcome was lower in those treated with adjunctive dexamethasone according to guideline recommendations (10 mg four times per day for 4 days) than those who did not receive it according to guideline recommendations (360 [34%] of 1075 *vs* 157 [51%] of 309; p<0·0001). In a multivariable analysis including all baseline variables, the adjusted OR of dexamethasone treatment for unfavourable outcome was 0·54 (95% CI 0·39–0·73) and the adjusted OR for death was 0·46 (0·32–0·66). The adjusted OR for the association between dexamethasone treatment and unfavourable outcome was 0·55 (0·38–0·80) in patients with pneumococcal meningitis and 0·44 (0·23–0·85) for patients with meningitis caused by other pathogens. Hearing loss at discharge was present in 144 (16%) of 902 surviving patients and was not significantly affected by dexamethasone use (OR 1·32, 95% CI 0·80–2·23; p=0·30).

Discussion

Our findings show that the incidence of adult bacterial meningitis has decreased since the introduction of conjugate vaccines, primarily because of falls in pneumococcal and meningococcal meningitis. Incidence decreased most sharply among pneumococcal serotypes included in the seven-valent and ten-valent conjugate vaccines; these vaccines were introduced in the Netherlands in 2006 and 2011. A surveillance study[4] of 17·4 million people in the USA during 1998–2007, showed a similar effect of herd protection in adults. Our study included 16·8 million people, and by contrast with the US study, we observed no serotype replacement of non-vaccine serotypes. This difference between studies might only partly be explained by age differences. The US study showed that serotype replacement was age dependent, with an increase of 90% in children aged younger than 5 years, 61% at any age, and 18% in patients older than 65 years.[4] Dutch surveillance data has shown evidence of serotype replacement,[31,32] but only for all invasive pneumococcal disease combined, and not in the subgroup of patients with meningitis. Pneumococcal meningitis due to non-vaccine types did not increase during the observation period in adults or children aged 0–16 years (data not shown). The incidence of adult meningitis due to non-seven-valent or non-ten-valent serotypes in 2006–13 was not higher than in 1998–2002.[1]

See Online for appendix

Serogroup C meningococcal meningitis virtually disappeared after routine vaccination against this bacterium in 2002.[33] Herd protection was responsible for more than 36% of the effect of meningococcal conjugate serogroup C vaccine and lasted for more than 10 years.[34] Serogroup B meningococcal meningitis has probably decreased because of a natural fluctuation in incidence.[21]

The relative contribution of pneumococcal meningitis to adult bacterial meningitis has increased and has led to a change in population characteristics of those with bacterial meningitis. Patients with bacterial meningitis are older and more likely to have risk factors for pneumococcal meningitis, such as otitis, sinusitis, and an immunocompromised state, than were patients in 1998–2002.[1] For the subgroup of pneumococcal meningitis, the proportions of patients with an unfavourable outcome or death have decreased substantially over this period (unfavourable outcome from 50% to 41%, absolute risk reduction –9%, 95% CI –7 to –11; death from 30% to 18%, absolute risk reduction –12%, 95% CI –10 to –14).[1] The strongest risk factors for an unfavourable outcome were those that suggested systemic compromise, a low level of consciousness, and infection with *S pneumoniae*.

Dexamethasone treatment has been used widely as adjunctive treatment for adults with bacterial meningitis. In our study, it was administered to about 90% of patients, irrespective of the causative pathogen. Dexamethasone treatment was independently associated with favourable outcome and increased survival in patients with both pneumococcal and non-pneumococcal meningitis. These findings are consistent with the results of a Cochrane review.[35] We previously wrote that it seems unlikely that a study could have enough power to prove or disprove an effect of adjunctive dexamethasone treatment on meningococcal meningitis.[18] The use of observational data precludes making strong conclusions

about treatment effects, but the present findings in combination with a randomised study in the same population,[5] and meta-analysis of randomised clinical trials[35,36] showing a similar effect, suggest that implementation of dexamethasone treatment has improved the prognosis of bacterial meningitis, both pneumococcal and non-pneumococcal.

A history of meningitis was reported for 7% of episodes. This proportion is similar to previous studies.[37,38] Causes of recurrent meningitis are cerebrospinal fluid leakage and immunodeficiency, which should carefully be assessed in patients with recurrent meningitis.[37–39] Because of the large number of patients with a history of meningitis in our cohort, physicians could consider vaccinating against the most common causes of bacterial meningitis in their region in any patient with bacterial meningitis.

Our study has several limitations. Patients who underwent lumbar puncture and who had a positive cerebrospinal fluid culture were over-represented. 11–22% of patients with bacterial meningitis have negative cerebrospinal fluid cultures.[40] Lumbar puncture might be postponed in patients with coagulation disorders or severe septic shock, which can result in negative cerebrospinal fluid cultures. Additionally, patients with bacterial meningitis who have space-occupying lesions on CT might not undergo lumbar puncture. Another limitation of our study was that we had little information about comorbidity and the timing of systemic and neurological complications. The vaccination status of patients was also not available. Theoretically, decreased incidence rates among serotypes included in the seven-valent vaccine could be, at least partly, due to vaccination of Dutch adults. However, in the Netherlands, routine pneumococcal vaccination for adults is not advised by the Health Council of the Netherlands, with the exception of high-risk groups (eg, those with hyposplenia or asplenia, sickle cell disease, and cerebrospinal fluid leakage). Based on sales records from Dutch pharmacies, pneumococcal vaccine coverage is low among adults aged older than 65 years in the Netherlands.[32] Finally, antibiotic resistance among pneumococcal isolates was rare. Adding dexamethasone has the potential to reduce cerebrospinal fluid penetration of vancomycin, a drug that has become the standard empirical antimicrobial treatment for pneumococcal strains that, on the basis of local epidemiology, are likely to be highly resistant to penicillin or cephalosporin.[41] Although a prospective multicentre observational study[42] has shown that appropriate concentrations of vancomycin in cerebrospinal fluid can be achieved even when concomitant steroids are used, some experts have advised the addition of rifampicin to vancomycin and ceftriaxone or cefotaxime regimens in areas with high rates of pneumococcal drug resistance.[3,41]

Our findings show the substantial improvement in the prognosis of pneumococcal meningitis over the past two decades and the effect of paediatric conjugate vaccines on adult bacterial meningitis. Herd protection is a major part of the effectiveness of conjugate vaccines and can protect those with poor immunological response to vaccination—eg, infants and elderly people. The development of vaccines covering more pneumococcal serotypes, new potent anti-inflammatory treatments,[14] starting treatment immediately after blood cultures are obtained, and aggressive supportive care might further improve the prognosis of patients with bacterial meningitis.

Contributors

MWB collected, analysed, and interpreted data, and wrote the first draft of the report. MCB designed the study, collected and interpreted data, and reviewed the report. ESK, ATK, and MJL collected data and reviewed the report. AvdE designed the study, collected and interpreted data, and reviewed the report. DvdB designed the study, collected, analysed, and interpreted data, and reviewed the report. MWT analysed and interpreted data and reviewed the report.

Declaration of interests

We declare no competing interests.

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