

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Clinical management of community-acquired meningitis in adults in the United Kingdom and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR).

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062698
Article Type:	Original research
Date Submitted by the Author:	21-Mar-2022
Complete List of Authors:	Ellis, Jayne; UCL, Harvey, David; Wirral University Teaching Hospital NHS Foundation Trust Defres, Sylviane; University of Liverpool; Royal Liverpool and Broadgreen Hospitals NHS Trust Chandna, Arjun ; Cambodia Oxford Medical Research Unit, Angkor Hospital for Children, ; University of Oxford Centre for Tropical Medicine and Global Health, MacLachlan, Eloisa; University of Leeds; National Student Association of Medical Research Solomon, Tom; University of Liverpool, Neurological Science, Medical Microbiology Heyderman, Robert; University College London, Division of Infection and Immunity; University of Malawi College of Medicine, Malawi Liverpool Wellcome Trust Clinical Research Programme McGill, Fiona; University of Liverpool, Institute of Infection and Global Health; Leeds Teaching Hospitals NHS Trust, Infectious Diseases study group, NAMM; British Infection Association, Collaborative authorship group
Keywords:	Diagnostic microbiology < INFECTIOUS DISEASES, Molecular diagnostics < INFECTIOUS DISEASES, Infectious disease/HIV < NEUROLOGY, INTERNAL MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Clinical management of community-acquired meningitis in adults in the United**

4
5
6 **Kingdom and Ireland in 2017: a retrospective cohort study on behalf of the National**

7
8 **Infection Trainees Collaborative for Audit and Research (NITCAR).**

9
10
11 Jayne Ellis, Specialty trainee¹, David Harvey, Consultant², Sylviane Defres, Consultant^{3,4,10},
12 Arjun Chandna, Specialty trainee^{5,6}, Eloisa Maclachlan, Medical Student^{7,8}, Tom Solomon,
13 Professor^{4,9,10}, Robert S Heyderman (0000-0003-4573-449X), Professor^{1,11}, Fiona McGill
14 (0000-0002-0903-9046), Consultant^{*4,10,12} on behalf of the NAMM (national audit of
15 meningitis management) group.

16
17 *Corresponding author: f.mcgill@nhs.net

- 18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
1. Hospital for Tropical Diseases, University College London Hospitals NHS Foundation Trust, London, UK.
 2. Wirral University Teaching Hospital NHS Foundation Trust, UK
 3. Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
 4. Institute of Infection, Veterinary and Ecological sciences, University of Liverpool, UK
Nuffield department of Medicine, University of Oxford
 5. Department of Clinical research, London School of Hygiene and Tropical Medicine, London, UK
 6. Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand
 7. University of Leeds, Leeds, UK
 8. National Student Association for Medical Research
 9. The Walton Centre NHS Foundation Trust, Liverpool, UK
 10. NIHR Health Protection Research Unit for Emerging and Zoonotic infections, University of Liverpool, Liverpool, UK
 11. Research Department of Infection, Division of Infection and Immunity, University College London, London, UK.
 12. Department of Infection and Travel Medicine and Department of Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

*Corresponding author: f.mcgill@nhs.net.

Corresponding author: Dr Fiona McGill, Leeds Teaching Hospitals NHS Trust, Beckett

Street, Leeds, LS9 7TF

f.mcgill@nhs.net.

COI: None to declare

Key words: meningitis, adults, bacteria, antibiotics, management, guidelines

Word Count: 2901

1
2
3 40 **Abstract**

4 41 **Objectives:** To assess current practice of suspected community acquired bacterial meningitis
5
6 42 in adults in the UK.

7
8
9 43 **Design:** Retrospective cohort

10
11 44 **Setting:** 64 UK and Irish hospitals

12
13 45 **Participants:** 1,471 adults with community acquired meningitis of any aetiology, admitted in
14
15
16 46 2017.

17
18 47 **Results:** None of the audit standards, from the 2016 UK Joint Specialists Societies guideline
19
20 48 on the diagnosis and management of meningitis, were met in all cases. With respect to 20 of
21
22 49 the 30 assessed standards, the clinical management provided for patients was in line with
23
24 50 recommendations in less than 50% of cases. 45% of patients had blood cultures taken within
25
26 51 an hour of admission, 0.5% had a lumbar puncture within one hour, 26% within 8 hours. 28%
27
28 52 had bacterial molecular diagnostic tests on CSF. Median time to first dose of antibiotics was
29
30 53 3.2 hours (IQR 1.3-9.2). 82% received empirical parenteral cephalosporins. 55% \geq 60 years
31
32 54 and 31% of immunocompromised patients received anti-*Listeria* antibiotics. 21% of patients
33
34 55 received steroids. Of the 1,471 patients, 21% had confirmed bacterial meningitis. Amongst
35
36 56 those with bacterial meningitis, pneumococcal aetiology, admission to intensive care and initial
37
38 57 Glasgow Coma Scale score less than 14 were associated with in-hospital mortality (aOR 2.08,
39
40 58 95% CI 0.96 – 4.48; aOR 4.28, 95% CI 1.81 – 10.1; aOR 2.90, 95% CI 1.26 – 6.71
41
42 59 respectively). Dexamethasone therapy was weakly associated with a reduction in mortality in
43
44 60 both those with proven bacterial meningitis (aOR 0.57, 95% CI 0.28 – 1.17) and with
45
46 61 pneumococcal meningitis (aOR 0.47, 95% CI 0.20 – 1.10).

47
48 62 **Conclusion:** This large study demonstrates that clinical care for patients with meningitis in the
49
50 63 UK is not in line with current evidence-based national guidelines. Diagnostics and therapeutics
51
52 64 should be targeted for quality improvement strategies. Additionally, work should be done to
53
54
55
56
57
58
59
60

1
2
3 65 improve the reach and impact of guidelines, once published, to ensure they translate into
4
5 66 changes in practice.
6
7

8 67
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

68 **Strengths and Limitations of this study**

- 69 • This is the largest national study of the management of meningitis in the UK
70 published to date
- 71 • The study includes all suspected community acquired bacterial meningitis, allowing
72 assessment of early clinical care prior to an aetiological diagnosis being made
- 73 • The study is widely translatable, and therefore representative of practice within the
74 UK and Ireland
- 75 • The study is limited by its retrospective design which brings associated recall bias and
76 some missing data
- 77 • The study may also be limited by the self-selection of the sites included

78 **Introduction**

79
80
81 Acute bacterial meningitis is a medical emergency associated with considerable death
82 and disability in the UK(1). Successful immunisation programmes targeting *Haemophilus*
83 *influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* means that
84 community acquired bacterial meningitis, particularly in children and adolescents, is now
85 relatively rare (2). The incidence of bacterial meningitis in adults in England is estimated to be
86 approximately 1-1.25 per 100,000 population overall, exceeding 9 per 100,000 in people over
87 70 years (2, 3).

88 Early recognition of meningitis, appropriate investigation, and treatment, saves lives
89 (4, 5). It is therefore essential that front-line clinicians, who may not encounter meningitis very
90 often, are vigilant and have a high index of suspicion to minimise poor outcomes. To help
91 frontline medical staff who are seeing patients with suspected meningitis, the UK guidelines
92 on the diagnosis and management of acute meningitis and meningococcal sepsis in
93 immunocompetent adults were published in 2016(6). The guidelines provide readily accessible,
94 comprehensive, evidenced-based recommendations. Previously published data suggest that
95 clinical care delivered in the UK is frequently non-adherent to guidelines(7, 8). A recent UK
96 study of viral meningitis also highlighted a large amount of inappropriate brain imaging prior
97 to lumbar punctures (LPs) and long delays in performing the LP (3, 9). Inadequate use of

1
2
3 98 molecular diagnostics and HIV-testing have also been highlighted as areas for improvement(3).
4
5 99 The increasing risk of multi-drug resistant bacteria, an ageing population susceptible to a wider
6
7
8 100 variety of bacteria (e.g. *Listeria monocytogenes*, *Escherichia coli* and *Klebsiella*
9
10 101 *pneumoniae*)(2) and the greater appreciation that viruses are a common cause of meningitis in
11
12 102 UK adults(10), make diagnostics essential. Reports from outside the UK have shown
13
14 103 improvements in outcomes following guideline publication and implementation (11). We
15
16 104 carried out a retrospective observational study with the dual aims of i) assessing current clinical
17
18 105 practice regarding diagnosis and management of adult patients with suspected community
19
20 106 acquired bacterial meningitis, and ii) to identify areas for improvement.

107 **Methods**

108
109 Hospitals in the UK were invited to take part in this study via the National Infection
110
111 Trainees Collaborative for Audit and Research (NITCAR) network, the UK Meningitis study
112
113 network, the British Infection Association (BIA) and through personal contacts. Eligible
114
115 patients were identified via hospital coding data, laboratory data, or a combination of both.
116
117 Data from patients aged 16 or over who presented with suspected acute community acquired
118
119 bacterial meningitis during 2017 were eligible for screening. Patients who met our case
120
121 definition for confirmed acute meningitis, regardless of aetiology, were eligible for inclusion
122
123 (box 1). Definitions are as previously published(3). Many interventions are performed prior
to knowing the final diagnosis, therefore, we included all types of meningitis in the analysis,
including viral and those in whom no pathogen was identified. This allowed us to assess the
entire clinical pathway of patients presenting with possible bacterial meningitis, although
some would be ultimately diagnosed with a different aetiology, or no confirmed aetiology at
all.

Box 1: Inclusion and exclusion criteria for cases of meningitis.A meningitis case was defined as:

- (1) Patients with a cerebrospinal fluid (CSF) WCC $>4 \times 10^6$ cells/L (regardless of whether a pathogen was identified or not) and a clinical suspicion of meningitis at the time OR
- (2) in the case of bacterial meningitis, symptoms and signs of meningitis with a significant pathogen in the CSF (culture or PCR) or blood regardless of CSF leukocyte count.

Patients with the following diagnoses were excluded:

- (1) Cryptococcal meningitis;
- (2) Tuberculous meningitis;
- (3) Nosocomial meningitis (defined as meningitis that occurs during a hospital admission or within 30 days of discharge or meningitis associated with indwelling devices in the central nervous system)
- (4) Encephalitis (defined as altered consciousness for >24 with no other cause found and two or more of the following signs: fever or history of fever ($\geq 38^\circ\text{C}$) during the current illness; seizures or focal neurological signs (with evidence of brain parenchyma involvement); CSF pleocytosis ($>4 \times 10^6$ cells per L); EEG suggesting encephalitis; and neuroimaging suggestive of encephalitis).

124 Standards indicative of good practice were taken from the 2016 UK Joint Specialists
125 Societies guideline on the diagnosis and management of meningitis and meningococcal sepsis
126 in immunocompetent adults, and the Standards in Microbiological Investigations on the
127 processing of cerebrospinal fluid (B27) (6, 12). For each standard, the number of patients as a
128 proportion of the total cohort who received clinical care in line with the standard is reported.
129 A second adjusted analysis taking account of missing data is also reported, whereby the number
130 of patients as a proportion of the cohort with available data who received clinical care in line
131 with the standard was reported.

1
2
3 132 Data were collected using electronic case report forms on REDcap™, a password
4
5 133 protected central web-based database system. All microbiological diagnostic procedures were
6
7 134 performed at the local hospital laboratory for each participating site using locally approved
8
9 135 procedures. All data were anonymised and recorded under a unique participant identification
10
11 136 number.

12
13
14 137 *Ethics approval:* As all data were anonymised individual patient consent and ethical
15
16 138 approval was not required. The study was registered with each site's clinical governance
17
18 139 department in line with local procedure.

19
20
21 140 *Statistical analyses:* Descriptive statistics were used to summarize data. Categorical
22
23 141 data were summarized using counts and percentages. Denominators presented are based on
24
25 142 available data, where incomplete case records were submitted by contributing sites. For
26
27 143 continuous variables, means and ranges or medians and inter-quartile ranges (IQRs) are
28
29 144 presented depending on the distribution of the data. Categorical data were analysed using Chi
30
31 145 squared or Fisher's exact test. Continuous data were analysed using t-tests, Mann Whitney U
32
33 146 or Kruskal Wallis depending on the distribution of the data. Regression analysis was used to
34
35 147 identify potential risk factors associated with poor outcomes.

36
37
38 148 Patient and Public Involvement. Although there was no direct involvement of patients
39
40 149 and public in this study the Meningitis Research Foundation, a key advocacy group for patients
41
42 150 are represented in the authorship of the original guidelines and will be key in the dissemination
43
44 151 of the results and the subsequent call to improve practice. Preliminary results have been shared
45
46 152 with the Meningitis Research Foundation and some of their members.

51 153 **Results**

52 154
53
54 155 1,471 patients from 64 hospitals throughout the UK and Ireland took part. The hospitals
55
56 156 ranged in size from small district generals to larger teaching hospitals. The mean number of
57
58 157 beds was 846 (range 230-2000). The hospitals who took part in England comprised 45% of the
59
60

1
2
3 158 total acute bed base in England, (42,612/94,827(13)). Females accounted for 57% and the
4
5 159 median age was 34 years (IQR 26,49). Confirmed viral meningitis occurred in 615 (42%) and
6
7 160 303 had confirmed bacterial meningitis (21%). More than one third of patients (n=553) fulfilled
8
9 161 the case definition (box 1) but had no confirmed microbiological diagnosis and were therefore
10
11 162 categorised as meningitis of unknown aetiology. *Streptococcus pneumoniae* and *Neisseria*
12
13 163 *meningitidis*, were the most common bacterial pathogens, where a cause was found, accounting
14
15 164 for 172 (57%) and 76 (25%) of cases respectively. *Haemophilus influenzae* (serotypes
16
17 165 unknown) was found in 14 cases. *Enteroviruses* were the most common viral pathogens
18
19 166 occurring in 429 (69%) of all confirmed viral meningitis. *Herpes simplex virus-2* was the
20
21 167 second most common viral pathogen detected in 97 (16%) of viral cases. Baseline
22
23 168 demographics and clinical characteristics are shown in table 1.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1: Baseline demographics, timing of key investigations and clinical outcomes of 1,471 adults presenting with suspected meningitis:

	<i>Total cohort</i>	<i>Bacterial meningitis</i>	<i>Viral meningitis</i>	<i>Other[†]</i>	<i>P value[‡]</i>
	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	
N	1,471 (100)	303 (21)	615 (42)	553 (38)	-
Median age (IQR)	34 (26 – 49)	54 (36 – 65)	31 (25 – 37)	34 (26 – 48)	< 0.001
Male	625 (43)	173 (57)	214 (35)	238 (43)	< 0.001
In patient mortality	48 (3)	38 (13)	2 (0.3)	8 (1.4)	< 0.001
ITU admission	192 (13)	157 (53)	4 (0.7)	31 (6)	< 0.001
Median Admission GCS (IQR)	15 (14-15)	13 (9 – 15)	15 (15-15)	15 (15-15)	< 0.001
Median time (hours) from admission to first antibiotics (IQR)	2.7 (0.9 – 8.3)	1.5 (0.4 – 5.3)	3.2 (1.3 – 8.3)	3.3. (1 – 12.5)	< 0.001
Median time (hours) from admission to blood cultures (IQR)	1 (0.3 – 4)	0.7 (0.2 – 2.4)	1 (0.3 – 3.7)	1.4 (0.3 – 6.1)	0.003
CT head prior to LP	1,094 (94)	207 (93)	459 (94)	428 (95)	0.55
Median time (hours) from admission to LP (IQR)	16.4 (7.9 – 26.7)	14.8 (7.7 – 29.8)	14.3 (7.5 – 22.6)	20 (8.8 – 35.8)	< 0.001
Adjunctive dexamethasone	300 (21)	150 (50)	69 (11)	81 (15)	< 0.001
Median CSF leucocyte count (IQR)	140 (44-399)	930 (235.5 – 3062.5)	122 (48 – 276)	85 (26.8 – 250.3)	< 0.001
Median CSF protein (IQR)	0.68 (0.46 - 1.21)	3.25 (1.4 – 5.8)	0.63 (0.45-0.9)	0.6 (0.4-1.0)	< 0.001
Median CSF glucose (IQR)	3.2 (2.8-3.7)	2.1 (0.95 – 3.45)	3.2 (2.9 – 3.6)	3.3 (3.0-3.8)	< 0.001

[†]= other meningitis category included all patients without a confirmed bacterial or viral pathogen

[‡] = for continuous variables, the Kruskal-Wallis test was used to compare medians across groups, and for categorical variables Chi squared tests were used.

170

171 Adherence to specific standards of good practice is shown in table 2. None were
 172 adhered to 100% of the time. Two thirds of the standards (n=20) had less than or equal to 50%
 173 adherence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Table 2. Adherence to audit standards[^]				
Immediate management				
	Number achieved standard/total number of patients analysed	% of total	Number achieved standard/total number of patients evaluable*	% of number evaluable
1. The patient's conscious level should be documented using the Glasgow coma scale.	1,283/1,471	87%	1283/1448	89%
2. Blood cultures should be taken as soon as possible and within 1 h of arrival at hospital	326/1,471 ¹	22%	326/767 ²	42%
3. LP should be performed within 1 h of arrival at hospital provided that it is safe to do so	8/1,471 ³	0.5%	8/1379 ⁴	0.6%
4. Antibiotic treatment should be commenced within the first hour	207/1471 ⁵	14%	207/1083 ⁶	19%
5. Patients with meningitis and meningococcal sepsis should be cared for with the input of an infection specialist such as a microbiologist or a physician with training in infectious diseases and/or microbiology	1,148/1,471 ⁷	78%	1148/1464	78%
Investigations				
6. Blood culture should be sent	977/1,471	66%	977/1469	67%
7. Blood Pneumococcal PCR should be sent	211/1,471	14%	211/1460	14%
8. Blood Meningococcal PCR should be sent	232/1,471	16%	232/1461	16%
9. CSF opening pressure should be documented	655/1,428 ⁸	46%	655/1361 ⁹	48%
10. CSF glucose with concurrent plasma glucose should be sent	607/1,428 ⁸	43%	607/1415	43%
11. CSF protein should be sent	1,358/1,428 ⁸	95%	1358/1420	96%
12. Microscopy of the CSF should take place within 2 hours of the lumbar puncture	596/1428 ⁸	42%	596/1203 ¹⁰	50%
13. CSF for pneumococcal PCR should be sent in all cases of suspected bacterial meningitis	412/1,428 ⁸	29%	412/1418	29%
14. CSF for Meningococcal PCR should be sent in all cases of suspected bacterial meningitis	434/1,428 ⁸	30%	434/1418	31%
15. A swab of the posterior nasopharyngeal wall should be obtained as soon as possible, and sent for meningococcal culture, in all cases of suspected meningococcal meningitis/sepsis	54/1,471	4%	54/1463 ¹¹	4%
16. All patients with meningitis should have an HIV test	646/1,471	44%	646/1459 ¹²	44%
Treatment				
17. All patients with suspected meningitis or meningococcal sepsis should be given ceftriaxone or cefotaxime	1039/1471 ¹³	71%	1039/1423 ¹⁴	73%
18. If the patient has, within the last 6 months, been to a country where penicillin resistant pneumococci are prevalent, IV vancomycin 15-20 mg/kg should be added 12-hourly (or 600 mg rifampicin 12-hourly IV or orally) ¹⁵	See footnote			

19. Those aged 60 or over should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].	55/233	24%	55/197 ¹⁶	28%
20. Immunocompromised patients (including diabetics and those with a history of alcohol misuse) should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin.	26/115 ¹⁷	23%	26/99 ¹⁸	26%
21. If there is a clear history of anaphylaxis to penicillins or cephalosporins give IV chloramphenicol 25 mg/kg 6- hourly	14/37	38%	14/30 ¹⁹	47%
22. If <i>Streptococcus pneumoniae</i> is identified continue with IV benzylpenicillin 2.4 g 4 hourly, 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly	114/172	66%	114/145 ²⁰	79%
23. If <i>N. meningitidis</i> is identified 2 g ceftriaxone IV 12 hourly, 2 g cefotaxime IV 6-hourly or 2.4 benzylpenicillin IV 4-hourly may be given as an alternative	52/76	68%	52/68 ²¹	76%
24. If the patient is not treated with ceftriaxone (in meningococcal disease), a single dose of 500 mg ciprofloxacin orally should also be given	0/2	0%	0/2	0%
25. If <i>Listeria monocytogenes</i> is identified Give 2 g ampicillin/amoxicillin IV 4-hourly and continue for at least 21 days. Co-trimoxazole 10-20 mg/kg or chloramphenicol are alternatives in cases of anaphylaxis to beta lactams.	4/7	57%	4/6	67% ²²
26. If <i>Haemophilus influenzae</i> is identified continue 2g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly for 10 days	9/14	64%	9/13	69% ²³
27. 10 mg dexamethasone IV 6 hourly should be started on admission, either shortly before or simultaneously with antibiotics.	67/1,471	5%	67/1435 ²⁴	5%
28. If pneumococcal meningitis is confirmed dexamethasone should be continued for 4 days.	34/172 ²⁵	20%	34/158 ²⁶	22%
Critical Care				
29. The following patients should be transferred to critical care - those with a rapidly evolving rash, those with a GCS of 12 or less and those with uncontrolled seizures	151/203 ²⁷	74%	151/203	74%
Notification				
30. All cases of meningitis (regardless of aetiology) should be notified to the relevant public health authority	236/1,471	16%	236/1465	16%
Notes. ^Only those audit standards that could be measured from the data collected. *excludes those where there was missing data and/or where not relevant. 1. Only 977 patients had blood cultures taken. 2. Excluding those who did not have blood cultures taken and where data was missing. 3. 1428 patients had a LP. 4. Excludes those who did not have an LP and where data was not available. 5. 82 patients had data consistent with having antibiotics prior to admission, this might be due to confusion about whether admission meant admission to the emergency department or admission to a ward, or it may represent data entry error therefore, these figures are not included. 6. 388 patients did not receive any antibiotics at all. 7. 310 (21%) of patients were admitted under an infection specialist, all others received consulting advice only. 8. 43 people did not have an LP. 9. Missing data on 67. 10. 43 had no LP, 97 missing data, 128 time of microscopy was before or at the same time as the LP. 11. Performed in 15/76 (20%) of proven meningococcal cases. 12. 9 known HIV positive and 3 missing data. 13. 285 patients were not given any antibiotics at all. 14. 48 patients who were definitely given antibiotics had missing data on which antibiotics they were given. 15. Using mainland Europe data only and with reference to ECDC data – 101 patients were documented to have travelled to a mainland European country within the previous 6 months. Travel history was not documented at all in 822 cases (56%). Of the 101 patients who had travelled to mainland Europe 54 (54%) had been to a country with a rate of penicillin resistant pneumococci of >5% (2017 data). 5/52 had no antibiotics. 0/47 had antibiotics to cover for penicillin resistant pneumococci. 16. 233 patients were aged over 60 but only 207 received antibiotics. Missing data for 10, 108 received amoxicillin at some point but only 55 received the correct dose. 17. Not including those >=60. 18. 15 did not received any antibiotics and missing data on 1. 19. 7 patients had no antibiotics at all. 20. 27 patients had insufficient antibiotic data. 21. 8 patient had insufficient antibiotic data. 22. 1 patient had insufficient antibiotic data. 23. Insufficient antibiotic data on 1 person. 24. Missing data on 36 – 11 on whether dexamethasone was received or not, 21 on the dose given and 4 on the timing. 25. Only 18 were given the correct dose (10mg). Some received dexamethasone for longer than 4 days. 26. Missing data on 14 individuals. 27. 7/11 patient with progressing rash, 131/176 patients with GCS <13 and 13/16 patients with uncontrolled seizures.				

1
2
3 175 Overall in-hospital mortality was 3% and was considerably higher in patients with
4
5 176 bacterial meningitis (13%), and pneumococcal meningitis in particular (16%). Mortality in
6
7 177 viral meningitis was 0.3% and 1.45% in those with meningitis of unknown aetiology. Just over
8
9 178 half (157) of those with confirmed bacterial meningitis required admission to an intensive care
10
11 179 unit (ICU).

12
13
14
15 180 *Use of diagnostics*

16 181 A few patients, 43, did not have an LP, of whom 26 (60%) had no contraindication (as
17
18 182 specified in the 2016 joint specialties guidelines and shown in box 2). Almost all these patients,
19
20 183 who did not have an LP, had either a positive blood culture (36, 84%) or a positive blood PCR
21
22 184 test (5, 12%).
23
24
25

26 185
27
28 **Box 2: Indications for neuroimaging before**
29 186 **lumbar puncture (LP) in suspected**
30 **meningitis.**

- 31 187
32 (1) Focal neurological signs
33 (2) Presence of papilloedema
34 188 (3) Continuous or uncontrolled seizures
35 (4) $GCS \leq 12$
36

37 189
38
39
40 190 Contra-indications for immediate LP were uncommon and occurred in 299 (20%)
41
42 191 patients. Glasgow coma score (GCS) ≤ 12 was the most common contra-indication for
43
44 192 immediate LP reported in 143 (10%), followed by focal neurological signs in 38 (3%). A
45
46 193 further 70 (7%) had other indications to delay LP. Neuroimaging prior to LP happened in 1094
47
48 194 of 1158 patients (94%), 911 (83%) of whom had no guideline-specified indication.
49
50 195 Neuroimaging was performed a median of 11 hours post arrival at hospital (IQR 4-21). Median
51
52 196 time from admission to LP was 16.5 hours (IQR 8 – 27). Only 6 patients had an LP within 1
53
54 197 hour of arrival at hospital and only 326 (26%) within 8 hours.
55
56
57
58
59
60

1
2
3 198 Median time from LP to CSF microscopy was 2 hours (IQR 1.1-3.2). Time from LP to
4
5 199 CSF analysis was significantly quicker when performed at on-site laboratories when compared
6
7
8 200 to centralised laboratory processing (median 1.65 hours (IQR 1.0 - 2.8) compared to 2.95 hours
9
10 201 (IQR 2.0 - 3.8) $p < 0.001$).

11
12 202 Fewer than one third of patients had pneumococcal (412, 28%) and meningococcal
13
14 203 polymerase chain reaction (PCR) (434, 29.5%) performed on their CSF. Pneumococcal PCR
15
16 204 was done on blood in 211 (14%) patients, and meningococcal PCR in 232 (16%). 646 patients
17
18 205 (44%) patients had a documented HIV test. Four of these were positive – two of whom had
19
20 206 pneumococcal meningitis, one of whom had enteroviral meningitis and one had meningitis of
21
22 207 unknown aetiology. Nine patients were previously known to be HIV positive.

23
24
25 208 Blood cultures were taken from 66% (n=977) of patients with 45% (n=438) having
26
27 209 them taken within one hour of arrival at hospital.

30 210 *Treatment*

31
32 211 285 patients (19%) did not receive antibiotics, most of whom had either viral meningitis
33
34 212 (163) or lymphocytic meningitis with no aetiology identified (105). The remaining 1,186
35
36 213 patients received at least one dose of antibiotics. The median time from hospital admission to
37
38 214 first dose of antibiotics was 3.2 hours (IQR 1.3,9.2). Amongst the patients who received
39
40 215 antibiotics the antimicrobials were commenced within an hour of arrival at hospital for
41
42 216 approximately one fifth of patients (207/1000). In confirmed bacterial meningitis cases, 92
43
44 217 patients (36%) received antibiotics within an hour of arrival.

45
46
47 218 Adherence with guideline specified empirical antibiotic regimens was good with 912
48
49 219 (80%) receiving a third-generation cephalosporin. Data is missing on antibiotic type for 47
50
51 220 patients. Of the 197 patients aged 60 years and over who received antibiotics, 108 (55%)
52
53 221 received ampicillin or amoxicillin; only 55 (28%) of those had the correct dose and dosing
54
55 222 frequency as recommended for *Listeria monocytogenes* meningitis. Similarly, only 36 (31%)
56
57
58
59
60

1
2
3 223 of the immunocompromised patients, who were aged under 60, (n=115) received any
4
5 224 ampicillin or amoxicillin for anti-*Listeria* cover. The supplementary table shows details
6
7
8 225 regarding risk factors for *Listeria*.

9
10 226 Only 300 patients (20%) received adjunctive steroids as recommended. Steroids were
11
12 227 given more frequently in patient with confirmed bacterial meningitis in 150 (50%) cases. In
13
14 228 patients with pneumococcal meningitis 97 patients (57%) received steroids.

15 229 *Clinical outcomes*

16
17
18
19 230 On multivariate analysis, having a confirmed diagnosis of bacterial meningitis was
20
21 231 strongly associated with in-hospital mortality. Adjusting for age and sex, confirmed bacterial
22
23 232 meningitis was associated with 26 times the odds of in-hospital mortality compared to those
24
25 233 with other forms of meningitis (aOR 25.9, 95% CI 5.93 – 113.0), including those with no
26
27 234 aetiology identified.

28
29
30 235 In patients with confirmed bacterial meningitis, on univariate analyses, in-hospital
31
32 236 mortality was associated with a positive blood culture (cOR 2.21, 95% CI 1.04 – 4.67); GCS \leq
33
34 237 13 (cOR 3.24, 95% CI 1.39 – 7.52), confirmed *Streptococcus pneumoniae* meningitis (cOR
35
36 238 2.37, 95% CI 1.10 – 5.11); and ICU admission (cOR 4.81, 95% CI 1.99 – 11.60). These
37
38 239 associations remained despite multivariate adjustment for age and sex (table 3).

39
40
41
42 240
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 3: Multivariate analysis of the association between baseline co-variates and in-hospital mortality in 303 patients with confirmed bacterial meningitis using logistic regression modelling:

Baseline co-variate	N	In-hospital mortality N (%) ¹	Crude OR for in-hospital mortality (95% CI)	P-value	Adjusted OR for in-hospital mortality (95% CI)*	P-value†
Sex						
Male	173	26 (15.1)	1			
Female	130	12 (9.23)	0.57 (0.27-1.18)	0.13		
Age group						
≤ 18 years	18	0 (0)				
19 – 59 years	159	18 (11.3)	1			
≥ 60 years	126	20 (16.0)	1.49 (0.75 – 2.96)	0.25		
Blood culture positive						
No	137	11 (8.09)	1		1	
Yes	166	27 (16.3)	2.21 (1.04 – 4.67)	0.03	1.87 (0.87 – 4.01)	0.10
GCS ≤ 13²						
No	124	8 (6.45)	1		1	
Yes	148	27 (18.2)	3.24 (1.39 – 7.52)	0.004	2.90 (1.26 – 6.71)	0.008
IV dexamethasone given³						
No	149	23 (15.4)	1		1	
Yes	150	14 (9.40)	0.57 (0.27 – 1.16)	0.11	0.57 (0.28 – 1.17)	0.12
IV dexamethasone given if <i>Strep.pneumoniae</i>⁴						
No	73	16 (21.9)	1		1	
Yes	97	11 (11.5)	0.46 (0.20 – 1.08)	0.07	0.47 (0.20 – 1.10)	0.08
Final diagnosis <i>S. pneumoniae</i>						
No	131	10 (7.63)	1		1	
Yes	172	28 (16.4)	2.37 (1.10 – 5.11)	0.02	2.08 (0.96 – 4.48)	0.05
ITU admission⁵						
No	144	7 (4.86)	1		1	
Yes	157	31 (19.7)	4.81 (1.99 – 11.60)	< 0.001	4.28 (1.81 – 10.1)	< 0.001

*adjusted for sex and age group

† P-value from LRT comparing models with and without primary exposure variable

1 = One participant had missing outcome data

2 = 31/303 (10%) participants did not have a GCS recorded

3 = 4/303 (1%) participants had missing data on IV dexamethasone administration

4 = 2/172 (1%) participants with confirmed *S. pneumoniae* meningitis had missing data on IV dexamethasone administration

5 = 1/303 (0.3%) participants had missing data on ITU admission

241

242 On both univariate and multivariate analyses (adjusted for age and sex), in patients with
 243 confirmed bacterial meningitis, the administration of dexamethasone was associated with a
 244 reduction in in-hospital mortality (aOR 0.57, 95% CI 0.28 – 1.17, p 0.12). When this analysis
 245 was restricted to include only those with confirmed *Streptococcus pneumoniae* meningitis,
 246 those who received dexamethasone had a reduced odds of in-hospital mortality (aOR 0.47,
 247 95% CI 0.20 – 1.10, p 0.08). Neither association reached statistical significance.

248 Discussion

249
250 This large national study evaluated the clinical management of adults with community
251 acquired meningitis throughout the UK and Ireland. Current practice falls short of the
252 recommendations in the 2016 UK guidelines(6). This is a concern for all patients but is of a
253 particular worry in bacterial meningitis. The management of bacterial meningitis is time
254 critical(4, 14). Delays in receiving antibiotics and having an LP, the unnecessary use of brain
255 imaging, a lack of appropriate antibiotics in those at risk of *Listeria* and the low rate of steroid
256 administration are areas for significant improvement.

257 Most patients in this study were given antibiotics prior to LP. Even taking this into
258 consideration, the median door to antibiotic time was still over three hours. The optimal timing
259 of antibiotics in bacterial meningitis is not known precisely but we do know that delays lead to
260 increased mortality (4, 5, 14). A delay of over three hours has previously been associated with
261 a 14-fold increase risk of death(14).

262 Delays in obtaining CSF are associated with a reduction in pathogen detection,
263 increased exposure to unnecessary anti-infectives, prolonged hospital stays and increased
264 mortality (4, 6, 15). In most cases brain imaging is not indicated in adults with suspected
265 community-acquired meningitis (4) however, in our cohort, a significant number of patients
266 had unnecessary scans. Although complications following LP are rare(16, 17), there may be an
267 unfounded fear of cerebral herniation following LP, even in those with no clinical features of
268 brain shift, which is leading to this excessive use of imaging(18). Education programs, along
269 with quality improvement measures, are essential to reduce the potentially harmful overuse of
270 neurological imaging. In addition, it is essential that we optimise meningitis care pathways to
271 ensure that clinicians have the time, space and equipment required to performed LPs in a timely
272 and safe manner (3, 19).

1
2
3 273 CSF culture positivity rates decline substantially when LP is delayed (3, 15). PCR can
4
5 274 detect bacterial DNA in CSF for several days after antibiotics have been administered. In the
6
7 275 UK 50% of meningococcal disease is diagnosed on PCR alone(20). Therefore, it is alarming
8
9 276 that PCR was used, in our cohort, as a diagnostic modality in so few patients. Meningitis
10
11 277 specific investigation order-sets using electronic ordering, and/or reflex laboratory testing to
12
13 278 increase use of molecular diagnostics should be considered to reduce opportunities for missed
14
15 279 microbiological diagnoses. There is the potential for increased use of rapid technologies that
16
17 280 can be used on site with minimal technical skill required(21). Having a rapid tests on site has
18
19 281 been shown to reduce bed days with significant cost savings in enteroviral meningitis (22).
20
21 282 Further research evaluating rapid diagnostic tests in other types of meningitis with clinically
22
23 283 relevant outcomes is needed. We also need to increase the offer of HIV testing in patients with
24
25 284 meningitis, as less than half the patients had a documented HIV test. Incident HIV diagnoses
26
27 285 were made in our cohort amongst patients presenting with bacterial, viral, and unknown cause
28
29 286 meningitis.
30
31
32
33
34

35 287 Corticosteroids have been shown to reduce mortality in pneumococcal meningitis (23).
36
37 288 We saw a 50% reduction in mortality in patients with pneumococcal meningitis who were
38
39 289 given steroids, albeit not reaching statistical significance. It is of concern that well-evidenced,
40
41 290 well-established therapies known to improve outcome, including mortality, are only being
42
43 291 given to just over half of those who might benefit. A protocolised, goal-directed therapy bundle,
44
45 292 including the use of corticosteroids and appropriate antibiotics warrants evaluation in the UK.
46
47
48

49 293 Although this is a large multi-national study, there are some limitations. NHS trusts
50
51 294 self-selected themselves for inclusion and we cannot rule out any significant differences with
52
53 295 trusts that did not. However, given that 64 hospitals were involved and good representation
54
55 296 from throughout the nations of the UK (and Ireland) we don't think this selection bias limits
56
57 297 the generalisability of our findings. We used well-established, published case definitions of
58
59
60

1
2
3 298 meningitis to minimise information bias, however misclassification of cases remains possible
4
5 299 especially in the cases without a confirmed microbiological diagnosis. Our case definitions
6
7
8 300 allowed us to include anyone suspected of having meningitis (of any cause) as objectively it is
9
10 301 often difficult to differentiate between viral and bacterial meningitis at the point of initial
11
12 302 assessment. However, it is possible that there may have been differences in presentation
13
14 303 between those with confirmed bacterial meningitis, those with confirmed viral meningitis and
15
16 304 those with no confirmed aetiology that meant they were managed in different ways. This study
17
18 305 was not powered to look at the differences between all the different aetiologies. Finally,
19
20 306 because this was a retrospective study, our analysis may have been subject to errors resulting
21
22 307 from recall bias and missing data. A prospective national study would have been challenging
23
24 308 to execute and it is likely that there would have been ascertainment bias in time and geography.
25
26 309 We therefore believe that, due the large sample size along with the use of electronic hospital
27
28 310 coding and laboratory data to ascertain cases, the risk of recall bias is low, and our retrospective
29
30 311 data is representative of practice within the UK.

31
32
33
34
35 312 In conclusion this is, to our knowledge, the largest UK study of adult patients with
36
37 313 meningitis. Awareness of practice guidelines for relatively rare acute medical conditions such
38
39 314 as meningitis is low and this study has demonstrated that despite clear, freely accessible
40
41 315 guidelines, clinical care is not in line with evidence-based recommendations. There is
42
43 316 considerable room for improvement. Whilst we recognise that guidelines do not improve
44
45 317 practice on their own, we do recommend that the findings from this study are strongly
46
47 318 considered in the development of the new National Institute for Clinical Excellence (NICE)
48
49 319 guideline on meningitis currently being developed, which for the first time, will include adults
50
51 320 as well as children. Given the widespread adoption of NICE endorsed guidelines and quality
52
53 321 standards to improve the quality of clinical practice, we anticipate that a NICE guideline will
54
55 322 improve awareness and uptake of good practice in the short term. In addition to education,
56
57
58
59
60

1
2
3 323 which has limited impact on changing behaviour, UK hospitals should use quality improvement
4
5 324 methods to improve management of patients with suspected meningitis. We suggest a national
6
7 325 strategic improvement plan should focus on the following key areas: timely use of diagnostics;
8
9 326 appropriate antibiotics in at risk populations and the use of adjunctive steroids. The integrated
10
11 327 use of electronic systems to standardize optimal use of diagnostics, and management bundles
12
13 328 may offer additional opportunities to improve outcomes. Each site that has been involved in
14
15 329 this study has been asked to implement site specific changes and re-evaluate for any
16
17 330 improvements in practice.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 332 Author contributions

5 333 Ellis J: Methodology, Data collection and curation, formal analysis, Investigation, Writing –
6
7 334 Original Draft Preparation. Harvey D: Methodology including pilot data, data collection,
8
9 335 reviewing and approving final draft. Defres S: Methodology including development of original
10
11 336 audit tool and guidelines, data collection, reviewing and approving final draft. Chandna A:
12
13 337 Methodology, reviewing and approving final draft. Maclachlan E: Methodology, data
14
15 338 collection, reviewing and approving final draft. Solomon T: Methodology including
16
17 339 development of original guidelines and audit tool, reviewing and approving final draft.
18
19 340 Heyderman RS: Conceptualization, Methodology, Supervision, Writing – Review & Editing.
20
21 341 McGill F: Conceptualization, Methodology, Data collection and curation, Investigation, formal
22
23 342 analysis, Writing –Original Draft Preparation. Responsible for overall content as guarantor.
24
25 343 The corresponding author attests that all listed authors meet authorship criteria and that no
26
27 344 others meeting the criteria have been omitted.

28
29 345
30
31 346 The Corresponding Author has the right to grant on behalf of all authors and does grant on
32
33 347 behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in
34
35 348 all forms, formats and media (whether known now or created in the future), to i) publish,
36
37 349 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other
38
39 350 languages, create adaptations, reprints, include within collections and create summaries,
40
41 351 extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on
42
43 352 the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of
44
45 353 electronic links from the Contribution to third party material where-ever it may be located; and,
46
47 354 vi) licence any third party to do any or all of the above.

48
49 355
50
51 356
52
53 357 Competing interests: All authors have completed the ICMJE uniform disclosure form
54
55 358 at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
56
57 359 submitted work; no financial relationships with any organisations that might have an interest
58
59 360 in the submitted work in the previous three years; no other relationships or activities that
60
61 361 could appear to have influenced the submitted work.

62
63 362 The lead author and corresponding author affirm that the manuscript is an honest, accurate,
64
65 363 and transparent account of the study; no important aspects of the study have been omitted.

66
67 364 Original data can be shared on request.

1
2
3
4 366 Acknowledgements

5 367 TS is supported by the National Institute for Health Research (NIHR) Health Protection
6
7 368 Research Unit in Emerging and Zoonotic Infections (Grant No. NIHR200907), NIHR Global
8
9 369 Health Research Group on Brain Infections (No. 17/63/110), and the UK Medical Research
10 370 Council's Global Effort on COVID-19 Programme (MR/V033441/1)

11
12 371

13
14 372 Funding

15 373 This research received no specific grant from any funding agency in the public, commercial
16
17 374 or not-for-profit sector.

18
19 375

20 376 Data Availability Statement

21
22 377 Data can be made available to other researchers on reasonable request to the authors.

23
24 378
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

379 List of contributors in NAMM

380

Site of Data collection	Names and Grades (at time of data collection) of contributors	Number of patients' data contributed
Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust	Amy Chue, SpR Ed Moran, Consultant Karishma Gokani, CMT	60
North Manchester General Hospital	Joseph Thompson, SpR	54
North Manchester General Hospital	Katherine Ajdukiewicz, Consultant	54
Oxford University Hospitals	Victoria Ward, SpR	50
Oxford University Hospitals	Lucinda Barrett, Consultant	50
Cheltenham General Hospital	Frances Edwards, CMT	47
Cheltenham General Hospital	Adam Usher, Consultant	47
Royal Alexandra Hospital, Paisley	Mairi McLeod, Consultant	45
Royal Alexandra Hospital, Paisley	Ramandeep Singh, medical student	45
Royal Alexandra Hospital, Paisley	Su su Htwe, SpR	45
Leicester Royal Infirmary, Leicester	Benedict Rogers, SpR	42
Leicester Royal Infirmary, Leicester	Grace Duane, Medical Student	42
Leicester Royal Infirmary, Leicester	Martin Wiselka, Consultant	42
Leicester Royal Infirmary, Leicester	Nicholas Wong, SpR	42
NHS Lothian	Elen Vink, SpR	42
NHS Lothian	Jennifer Poyner, SpR	42
NHS Lothian	Jenni Crane, Consultant	42
NHS Lothian	Ollie Lloyd, SpR	42
NHS Lothian	Emma Chisholm, SpR	42
Countess of Chester Hospital	Ildiko Kustos, Consultant	40
Countess of Chester Hospital	Ruth McEwen, Consultant	40
Countess of Chester Hospital	Sam Sutton, CMT	40
University Hospitals Plymouth Trust	Lewis Jones, Consultant	38
University Hospitals Plymouth Trust	Robert Tilley, Consultant	38
Addenbrookes hospital, Cambridge University Hospitals NHS Foundation Trust	M. Estee Torok, Honorary Consultant	37
Addenbrookes hospital, Cambridge University Hospitals NHS Foundation Trust	Isobel Ramsay, SpR	37
Hull University Teaching Hospitals NHS Trust	Monica Ivan, Consultant	36
Hull University Teaching Hospitals NHS Trust	Joshua York	36
Hull University Teaching Hospitals NHS Trust	Jennifer Ansett	36
Hull University Teaching Hospitals NHS Trust	Maithili Varadarajan	36
Hull University Teaching Hospitals NHS Trust	Celestine Eshiwe, SpR	36
London King's College	Amanda Fife, Consultant	36
London King's College	Stephanie Harris, SpR	36
London King's College	Ryan Jayesinghe, medical student	36
London King's College	Priya Sekhon	36
Aintree University Hospital, Liverpool	James Cruise, SpR	35
Aintree University Hospital, Liverpool	Susan Larkin, Consultant	35
Worcestershire Royal Hospital	Shivani Kanabar, Medical student	35
Worcestershire Royal Hospital	Ernest Mutengesa, Medical Student	35
Worcestershire Royal Hospital	Mirella Ling, Consultant	35

1			
2			
3	Worcestershire Royal Hospital	Christopher Green, Consultant	35
4	Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust	Martin Williams, Consultant	33
5	Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust	Matthew Stevens, CMT	33
6	Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust	Matthew Stevens, CMT	33
7	Victoria hospital, Kirkcaldy	David Griffith, Consultant	32
8	Victoria hospital, Kirkcaldy	David Griffith, Consultant	32
9	Victoria hospital, Kirkcaldy	Naomi Bulteel, SpR	32
10	Northumbria Healthcare NHS Foundatio Trust	Charlotte Milne, SpR	30
11	Northumbria Healthcare NHS Foundatio Trust	Jayanta Sarma, Consultant	30
12	Northumbria Healthcare NHS Foundatio Trust	Jayanta Sarma, Consultant	30
13	Ninewells hospital, Dundee	Aline Wilson, SpR	29
14	Ninewells hospital, Dundee	John Shone, Consultant	29
15	Ninewells hospital, Dundee	Lynn Urquhart, Consultant	29
16	Ninewells hospital, Dundee	Lynn Urquhart, Consultant	29
17	Ninewells hospital, Dundee	Sahar Eldirdiri, SpR	29
18	Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust	Alison Muir, Consultant	28
19	Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust	Alison Muir, Consultant	28
20	Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust	Leila White, Clinical Scientist	28
21	Sheffield teaching Hospitals	Jody Aberdein, Consultant	28
22	Sheffield teaching Hospitals	Jody Aberdein, Consultant	28
23	Sheffield teaching Hospitals	Phillip Simpson, SpR	28
24	Shrewbury and Telford Hospital NHS Trust	Hnin Hay Mar	26
25	Shrewbury and Telford Hospital NHS Trust	John Bowen	26
26	Shrewbury and Telford Hospital NHS Trust	Keying Tan	26
27	Shrewbury and Telford Hospital NHS Trust	Keying Tan	26
28	Shrewbury and Telford Hospital NHS Trust	Eint Shwe Zin thein	26
29	Shrewbury and Telford Hospital NHS Trust	Eint Shwe Zin thein	26
30	Shrewbury and Telford Hospital NHS Trust	Mahmoud Aziz	26
31	University Hospital North Midlands	Anthony Cadwgan, Consultant	25
32	University Hospital North Midlands	Brendan Davies, Consultant	25
33	University Hospital North Midlands	Daniel White, SpR	25
34	University Hospital North Midlands	Natasha Weston, SpR	25
35	University Hospital North Midlands	Salman Zeb, CMT	25
36	St George's Hospital, London	Angela Houston, Consultant	24
37	St George's Hospital, London	Imogen Fordham, clinical fellow	24
38	St George's Hospital, London	Imogen Fordham, clinical fellow	24
39	St George's Hospital, London	Terry John Evans, SpR	24
40	St George's Hospital, London	Terry John Evans, SpR	24
41	St George's Hospital, London	Louise Wootton, Physician's associate	24
42	Nottingham University Hospitals NHS Trust	David Turner, Consultant	24
43	Nottingham University Hospitals NHS Trust	David Turner, Consultant	24
44	Nottingham University Hospitals NHS Trust	Iona Willingham, SpR	24
45	Birmingham Queen Elizabeth Hospital	Aimee Johnson, SpR	23
46	Birmingham Queen Elizabeth Hospital	Nimal Wickramasinghe, Consultant	23
47	Birmingham Queen Elizabeth Hospital	Nimal Wickramasinghe, Consultant	23
48	Salford Royal Infirmary, Salford	Ashley Horsley, SpR	23
49	Salford Royal Infirmary, Salford	Ashley Horsley, SpR	23
50	Salford Royal Infirmary, Salford	Eamonn Trainor, Consultant	23
51	Salford Royal Infirmary, Salford	Olivier Gaillemin, Consultant	23
52	University Hospital Southampton NHS Foundation Trust	Andrew Rosser, Consultant	23
53	University Hospital Southampton NHS Foundation Trust	Andrew Rosser, Consultant	23
54	University Hospital Southampton NHS Foundation Trust	Nicholas J Norton, SpR	23
55	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Iain Crossingham, Consultant	22
56	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Katie Cheung, Medical Student	22
57	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Katie Cheung, Medical Student	22
58	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Megan Duxbury, CMT	22
59	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Ashutosh Deshpande, Consultant	22
60	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Ashutosh Deshpande, Consultant	22
61	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Emilie Bellhouse, FY2	22
62	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Kamaljit Khalsa, SpR	22

1			
2			
3	Imperial College School of Medicine	Helena Brezovjakova, Medical Student	22
4	Imperial College School of Medicine	Emma McLean, medical student	22
5	Imperial college healthcare NHS trust	Tanmay, Kanitkar, CMT	22
6	Imperial college healthcare NHS trust	Nicholas Davies, Consultant	22
7	Imperial College School of Medicine	Alexsander Dawidziuk, Medical Student	22
8	St James University hospital, Leeds	Eloisa Mclaughlin, Medical student	22
9	St James University hospital, Leeds	Joanna Allen, Consultant	22
10	St James University hospital, Leeds	Razan Saman, SpR	22
11	St James University hospital, Leeds	Sarah Kelly, SpR	22
12	Royal Liverpool University Hospital, Liverpool	Hugh Adler, SpR	22
13	Royal Liverpool University Hospital, Liverpool	Sylviane Defres, Consultant	22
14	Arrowe Park Hospital, Wirral	David Harvey, Consultant	21
15	Arrowe Park Hospital, Wirral	Elshadai Ejere, FY2	21
16	Queen's hospital, Romford	Aarti Shah, Consultant	21
17	Queen's hospital, Romford	Yiwen Soo, FY1	21
18	Raigmore Hospital, Inverness	Wendy Beadles, Consultant	21
19	Raigmore Hospital, Inverness	Heather Sturgeon, Medical student	21
20	Raigmore Hospital, Inverness	Brodie Cameron, Medical Student	21
21	James Cook University Hospital, Middlesbrough	Ben Tomlinson, SpR	20
22	James Cook University Hospital, Middlesbrough	David Chadwick, Consultant	20
23	University Hospital Monklands	Claire McGoldrick, Consultant	20
24	University Hospital Monklands	Katie McDowell, FY2	20
25	Cumberland infirmary, Carlisle	Alastair Miller, Consultant	19
26	Cumberland infirmary, Carlisle	Clive Graham, Consultant	19
27	Cumberland infirmary, Carlisle	Mpho Molosiwa, FY2	19
28	Newcastle Upon Tyne NHS Foundation Trust	Ewan Hunter, Consultant	19
29	Newcastle Upon Tyne NHS Foundation Trust	Ruth Owen, Medical Student	19
30	Newcastle Upon Tyne NHS Foundation Trust	Katherine Flack	19
31	Airedale hospital, Airedale	Adrian Kennedy, Consultant	18
32	Bradford Royal Infirmary, Bradford	Amy Robinson, Consultant	16
33	Bradford Royal Infirmary	Phoebe Cross, SpR	16
34	Bradford Royal Infirmary	Fay Perry	16
35	University Hospital Wales	Vithusha Inpadhas	16
36	Aberdeen Royal Infirmary	Ali Khan, SpR	15
37	Aberdeen Royal Infirmary	Sarathy Selvam, FY2	15
38	Aberdeen Royal Infirmary	Vhairi Bateman, Consultant	15
39	Aberdeen Royal Infirmary	Jeremy Wong, Medica Student	15
40	Lancaster Royal Infirmary	Henry Wu, FY2	15
41	Lancaster Royal Infirmary	Monika Pasztor, Consultant	15
42	Whittington Hospital, London	Trupti Patel, Consultant	14
43	Whittington Hospital, London	Ajanthiha Karunakaran, Medical Student	14
44	Russells Hall Hospital, Dudley	Basma Soliman, CT1	13
45	Russells Hall Hospital, Dudley	Hassan Paraiso, Consultant	13
46	Glasgow Royal Infirmary	Mairi McLeod, Consultant	13
47	Glasgow Royal Infirmary	Su su Htwe, SpR	13
48	Glasgow Royal Infirmary	Anna Smith	13
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1			
2			
3	James Paget University Hospitals NHS Foundation Trust	Andrew Blanshard, CMT	12
4	James Paget University Hospitals NHS Foundation Trust	Harish Reddy, Consultant	12
5	Portsmouth Hospitals University NHS Trust	Avneet Shahi, SpR	12
6	Portsmouth Hospitals University NHS Trust	Helen Chesterfield, Consultant	12
7	Portsmouth Hospitals University NHS Trust	Oliver Bannister, CMT	12
8	Portsmouth Hospitals University NHS Trust	Oliver Bannister, CMT	12
9	Withybush hospital, Haverford West	Ben Schroeder, Medical Student	12
10	Withybush hospital, Haverford West	Ken Woodhouse, Consultant	12
11	Ashford and St Peter's NHS Foundation Trust	Jan Coebergh, Consultant	11
12	Ashford and St Peter's NHS Foundation Trust	Jan Coebergh, Consultant	11
13	Ashford and St Peter's NHS Foundation Trust	Viva Levee, FY2	11
14	Mater Misericordiae University Hospital, Dublin	Eavan Muldoon, Consultant	11
15	Mater Misericordiae University Hospital, Dublin	Rhea O'regan, SPR	11
16	Mater Misericordiae University Hospital, Dublin	Rhea O'regan, SPR	11
17	Mater Misericordiae University Hospital, Dublin	Tee Keat Teoh, SpR	11
18	Newham Hospital, Barts Health NHS Trust	Sathyavani Subbarao, SpR	11
19	Newham Hospital, Barts Health NHS Trust	Sathyavani Subbarao, SpR	11
20	Newham Hospital, Barts Health NHS Trust	Simon Tiberi, Consultant	11
21	Newham Hospital, Barts Health NHS Trust	Caryn Rosmarin	11
22	London UCL and Hospital for Tropical diseases at University	Jayne Ellis, SpR	10
23	College London Hospitals NHS Foundation Trust.	Jayne Ellis, SpR	10
24	London UCL and Hospital for Tropical diseases at University	Lucy Bell, CMT	10
25	College London Hospitals NHS Foundation Trust.	Lucy Bell, CMT	10
26	London UCL and Hospital for Tropical diseases at University	Robert Heyderman, Consultant	10
27	College London Hospitals NHS Foundation Trust.	Robert Heyderman, Consultant	10
28	Barts Health NHS Trust	Jonathan Lambourne, Consultant	10
29	Barts Health NHS Trust	Jonathan Lambourne, Consultant	10
30	Barts Health NHS Trust	Emma McGuire, SpR	10
31	Guy's and St Thomas' NHS Foundation Trust	Robert Serafino, Consultant	10
32	Guy's and St Thomas' NHS Foundation Trust	Anna Goodman, Consultant	9
33	Guy's and St Thomas' NHS Foundation Trust	Ishaan Bhide, FY1	
34	Guy's and St Thomas' NHS Foundation Trust	Karanjeet Sagoo, Medical Student	
35	Whipps Cross, Barte Health NHS Trust	Mark Melzer, Consultant	8
36	Whipps Cross, Barte Health NHS Trust	Mark Melzer, Consultant	8
37	Whipps Cross, Barte Health NHS Trust	Maria Krutikov, SpR	8
38	The Royal Free Hospital, London	Indran Balakrishnan, Consultant	6
39	The Royal Free Hospital, London	Susan Hopkins, Consultant	6
40	The Royal Free Hospital, London	Susan Hopkins, Consultant	6
41	Trafford General Hospital, Manchester University NHS Foundation	Tim Jones, SpR	6
42	Trust	Kajal Patel, Medical Student	4
43	Trafford General Hospital, Manchester University NHS Foundation	Barzo Faris, Consultant	
44	Trust	Barzo Faris, Consultant	
45	William Harvey Hospital, East Kent	Graeme Calver, Consultant	3
46	William Harvey Hospital, East Kent	Ricky Singh, Medical Student	3
47	William Harvey Hospital, East Kent	Hazel Sanghvi, Medical Student	3
48	Tameside General Hospital	Mohamed Eltayeb, Clinical Fellow	2
49	Tameside General Hospital	Rathur Haris, Consultant	2

381

382

References

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis. *N Engl J Med*. 2004;351:1849-59.
2. Okike IO, Ribeiro S, Ramsay M, Heath PT, Sharland M, Ladhani SN. Trends in bacterial, mycobacterial and fungal meningitis in England and Wales 2004-11: an observational study. *Lancet Infect Dis*. 2014;14:301-7.
3. McGill F, Griffiths MJ, Bonnett LJ, Geretti AM, Michael BD, Beeching NJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis*. 2018;18(9):992-1003.
4. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from acute bacterial meningitis. *QJM*. 2005;98:291-8.
5. Bodilsen J, Dalager-Pedersen M, Schonheyder HC, Nielsen H. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. *BMC Infect Dis*. 2016;16(392):1-7.
6. McGill F, Heyderman RS, Michael BD, Defres S, Beeching NJ, Borrow R, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. 2016;72(4):405-38.
7. Stockdale AJ, Weekes MP, Aliyu SH. An audit of acute bacterial meningitis in a large teaching hospital 2005-10. *QJM*. 2011;104(12):1055-63.
8. Cullen MM. An audit of the investigation and initial management of adults presenting with possible bacterial meningitis. *J Infect*. 2005;50:120-4.
9. Brouwer M, van de Beek D. Viral meningitis in the UK: time to speed up. *Lancet Infectious Diseases*. 2018;18(9):930-1.
10. Kadambari S, Okike I, Ribeiro S, Ramsay ME, Heath PT, Sharland M, et al. Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004-2013. *J Infect*. 2014;69(4):326-32.
11. Glimåker M, Johansson B, Grindborg Ö, Bottai M, Lindquist L, Sjölin J. Adult Bacterial Meningitis: Earlier Treatment and Improved Outcome Following Guideline Revision Promoting Prompt Lumbar Puncture. *Clin Infect Dis*. 2015;60(8):1162-9.
12. Public Health England. UK Standards for Microbiology Investigations. Investigation of Cerebrospinal fluid. 2017.
13. The Kings Fund. NHS hospital bed numbers: past, present, future 2021 [Available from: <https://www.kingsfund.org.uk/publications/nhs-hospital-bed-numbers>].
14. Auburtin M, Wolff M, Charpentier J, Varon E, Tulzo YL, Girault C, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study. *Crit Care Medicine*. 2006;34:2758-65.
15. Michael B, Menezes BF, Cunniffe J, Miller A, Kneen R, Francis G, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J*. 2010;27(6):433-8.
16. Costerus JM, Brouwer MC, Sprengers MES, Roosendaal SD, van der Ende A, van de Beek D. Cranial Computed Tomography, Lumbar Puncture, and Clinical Deterioration in Bacterial Meningitis: A Nationwide Cohort Study. *Clin Infect Dis*. 2018;67(6):920-6.
17. Costerus JM, Brouwer MC, van de Beek D. Technological advances and changing indications for lumbar puncture in neurological disorders. *Lancet Neurol* 2018;17(3):268-78.
18. Glimaker M, Johansson B, Bell M, Ericsson M, Blackberg J, Brink M, et al. Early Lumbar Puncture in adult bacterial meningitis - rationale for revised guidelines. *Scand J Infect Dis*. 2013;45:657-63.
19. Defres S, Mayer J, Backman R, Kneen R. Performing lumbar punctures for suspected CNS infections: experience and practice of trainee doctors. *Br J Hosp Med*. 2015;76(11):658-62.

- 1
2
3 435 20. Heinsbroek E, Ladhani SN, Gray S, Guiver M, Kaczmarski E, Borrow R, et al. Added value of
4 436 PCR testing for confirmation of invasive meningococcal disease in England. *J Infect.* 2013;67:385-90.
5 437 21. Bouzid D, Zanella MC, Kerneis S, Visseaux B, May L, Schrenzel J, et al. Rapid diagnostic tests
6 438 for infectious diseases in the emergency department. *Clinical microbiology and infection : the official
7 439 publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2020.
8 440 22. Giuleri SG, Chapuis-Taillard C, Manuel O, Hugli O, Pinget C, Wasserfallen JB, et al. Rapid
9 441 detection of enterovirus in cerebrospinal fluid by a fully automated PCR assay is associated with
10 442 improved management of aseptic meningitis in adult patients. *J Clin Virol.* 2015;62:58-62.
11 443 23. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study
12 444 Investigators. Dexamethasone in Adults with Bacterial Meningitis. *N Engl J Med.* 2002;347(20):1549-
13 445 56.
14
15
16 446

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

447

For peer review only

Supplementary table.

Supplementary table . Risk factors for Listeria stratified by aetiology.

	Total cohort	Bacterial meningitis	Viral meningitis	Other meningitis[†]	P value
	N (%)	N (%)	N (%)	N (%)	
N	1,471 (100)	302 (21)	615 (42)	553 (38)	-
Age >60 years	235 (16)	126 (42)	27 (4)	79 (14)	<0.001
Number immunocompromised by disease/medication*	60 (4)	14 (5)	18 (3)	28 (5)	0.23
Number with Diabetes mellitus	64 (4)	30 (10)	11 (2)	22 (4)	<0.001
Number with a history of alcohol excess	36 (2)	21 (7)	3 (0.5)	12 (2)	<0.001

[†]= other meningitis category included all patients without a confirmed bacterial or viral pathogen

*=Conditions listed as immunocompromising conditions included haematological malignancy (n=8), Other malignancy (n=8), solid organ transplant (n=6), liver cirrhosis (n=1), HIV (n=9), Pregnancy (n=2). Medication listed included Steroids (n=7), tocilizumab, ecolizumab and infliximab (n=6), Methotrexate (n=8), Mycophenolate (n=2), Azathioprine (n=3), 'chemotherapy' (n=4). (some patients had more than one immunocompromising condition/ medication).

1 STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Location in paper
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title, page 1, line 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, page 2, line 40 onwards
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 4 line 80 onwards
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 5, line 104
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, page 5, line 108 onwards
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, page 5, line 108 onwards
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, page 6, box 1
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6, box 1 and line 125 onwards
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5, line 110 onwards
Bias	9	Describe any efforts to address potential sources of bias	Methods, page 5, line 117 onwards
			Discussion, page 17, line 294 onwards
Study size	10	Explain how the study size was arrived at	Methods, page 5, line 110 onwards
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, page 7, line 141 onwards
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods, page 7, line 141 onwards
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	Methods, page 6, line 130
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA

2 **Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, page 7, line 156
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Page 10, Table 2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9 Table 1, page 10, table 2 and page 15, table 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, page 14, line 230 onwards
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, page 16 line 249 onwards
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, page 17, line 294 onwards
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 18, line 313 onwards
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, page 17 line 296-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22, Line 439

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

Clinical management of community-acquired meningitis in adults in the United Kingdom and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062698.R1
Article Type:	Original research
Date Submitted by the Author:	31-May-2022
Complete List of Authors:	Ellis, Jayne; UCL, Harvey, David; Wirral University Teaching Hospital NHS Foundation Trust Defres, Sylviane; University of Liverpool; Royal Liverpool and Broadgreen Hospitals NHS Trust Chandna, Arjun ; Cambodia Oxford Medical Research Unit, Angkor Hospital for Children, ; University of Oxford Centre for Tropical Medicine and Global Health, MacLachlan, Eloisa; University of Leeds; National Student Association of Medical Research Solomon, Tom; University of Liverpool, Neurological Science, Medical Microbiology Heyderman, Robert; University College London, Division of Infection and Immunity; University of Malawi College of Medicine, Malawi Liverpool Wellcome Trust Clinical Research Programme McGill, Fiona; University of Liverpool, Institute of Infection and Global Health; Leeds Teaching Hospitals NHS Trust, Infectious Diseases study group, NAMM; British Infection Association, Collaborative authorship group
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Emergency medicine, Neurology
Keywords:	Diagnostic microbiology < INFECTIOUS DISEASES, Molecular diagnostics < INFECTIOUS DISEASES, Infectious disease/HIV < NEUROLOGY, INTERNAL MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, BACTERIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Clinical management of community-acquired meningitis in adults in the United**
4
5 2 **Kingdom and Ireland in 2017: a retrospective cohort study on behalf of the National**
6
7 3 **Infection Trainees Collaborative for Audit and Research (NITCAR)**
8
9

10 4
11 5 Jayne Ellis, Specialty trainee¹, David Harvey, Consultant², Sylviane Defres, Consultant^{3,4,10},
12 6 Arjun Chandna, Specialty trainee^{5,6}, Eloisa Maclachlan, Medical Student^{7,8}, Tom Solomon,
13 7 Professor^{4,9,10}, Robert S Heyderman (0000-0003-4573-449X), Professor^{1,11}, Fiona McGill
14 8 (0000-0002-0903-9046), Consultant^{4,10,12} on behalf of the National Audit of Meningitis
15 9 Management (NAMM) group
16

- 17 10
18 11
19 12 1. Hospital for Tropical Diseases, University College London Hospitals NHS
20 13 Foundation Trust, London, UK.
21 14 2. Wirral University Teaching Hospital NHS Foundation Trust, UK.
22 15 3. Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK.
23 16 4. Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool,
24 17 Liverpool, UK.
25 18 Nuffield department of Medicine, University of Oxford, Oxford, UK.
26 19 5. Department of Clinical Research, London School of Hygiene and Tropical Medicine,
27 20 London, UK.
28 21 6. Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok,
29 22 Thailand.
30 23 7. University of Leeds, Leeds, UK.
31 24 8. National Student Association for Medical Research.
32 25 9. The Walton Centre NHS Foundation Trust, Liverpool, UK
33 26 10. NIHR Health Protection Research Unit for Emerging and Zoonotic Infections,
34 27 University of Liverpool, Liverpool, UK.
35 28 11. Research Department of Infection, Division of Infection and Immunity, University
36 29 College London, London, UK.
37 30 12. Department of Infection and Travel Medicine and Department of Microbiology,
38 31 Leeds Teaching Hospitals NHS Trust, Leeds, UK.
39 32
40 33
41
42
43
44

45 34 **Correspondence to:** Dr Fiona McGill, Leeds Teaching Hospitals NHS Trust, Beckett Street,
46 35 Leeds, LS9 7TF
47
48 36 f.mcgill@nhs.net
49
50
51
52
53
54

55 38 Word count: 2901
56
57
58
59
60

1
2
3 40 **Abstract**

4 41 **Objectives:** To assess practice in the care of adults with suspected community acquired
5
6 42 bacterial meningitis in the UK and Ireland.

8 43 **Design:** Retrospective cohort study.

10 44 **Setting:** 64 UK and Irish hospitals.

12 45 **Participants:** 1,471 adults with community acquired meningitis of any aetiology in 2017.

14 46 **Results:** None of the audit standards, from the 2016 UK Joint Specialists Societies guideline
15
16 47 on diagnosis and management of meningitis, were met in all cases. With respect to 20 of 30
17
18 48 assessed standards, clinical management provided for patients was in line with
19
20 49 recommendations in less than 50% of cases. 45% of patients had blood cultures taken within
21
22 50 an hour of admission, 0.5% had a lumbar puncture within one hour, 26% within 8 hours. 28%
23
24 51 had bacterial molecular diagnostic tests on CSF. Median time to first dose of antibiotics was
25
26 52 3.2 hours (IQR 1.3-9.2). 82% received empirical parenteral cephalosporins. 55% \geq 60 years
27
28 53 and 31% of immunocompromised patients received anti-*Listeria* antibiotics. 21% received
29
30 54 steroids. Of the 1,471 patients, 21% had confirmed bacterial meningitis. Amongst those with
31
32 55 bacterial meningitis, pneumococcal aetiology, admission to intensive care and initial Glasgow
33
34 56 Coma Scale score less than 14 were associated with in-hospital mortality (adjusted odds ratio
35
36 57 [aOR] 2.08, 95% CI 0.96 – 4.48; aOR 4.28, 95% CI 1.81 – 10.1; aOR 2.90, 95% CI 1.26 – 6.71
37
38 58 respectively). Dexamethasone therapy was weakly associated with a reduction in mortality in
39
40 59 both those with proven bacterial meningitis (aOR 0.57, 95% CI 0.28 – 1.17) and with
41
42 60 pneumococcal meningitis (aOR 0.47, 95% CI 0.20 – 1.10).

43
44 61 **Conclusion:** This study demonstrates that clinical care for patients with meningitis in the UK
45
46 62 is not in line with current evidence-based national guidelines. Diagnostics and therapeutics
47
48 63 should be targeted for quality improvement strategies. Work should be done to improve the
49
50 64 impact of guidelines, understand why they are not followed and, once published, ensure they
51
52 65 translate into changed practice.

1
2
3 66
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

67 **Keywords:** meningitis, adults, bacteria, antibiotics, management, guidelines

For peer review only

68 **Strengths and limitations of this study**

- 69 • To our knowledge, this is the largest national study of the management of meningitis
70 in the UK published to date.
- 71 • The study includes all suspected community acquired bacterial meningitis, allowing
72 assessment of early clinical care prior to an aetiological diagnosis being made.
- 73 • The study is widely translatable and representative of practice within the UK and
74 Ireland.
- 75 • The study is limited by its retrospective design which brings associated recall bias and
76 some missing data.
- 77 • The study may also be limited by the self-selection of the sites included.

79 **Introduction**

81 Acute bacterial meningitis is a medical emergency associated with considerable death and
82 disability in the UK(1). Successful immunisation programmes targeting *Haemophilus*
83 *influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* means that
84 community acquired bacterial meningitis, particularly in children and adolescents, is now
85 relatively rare (2). The incidence of bacterial meningitis in adults in England is estimated to be
86 approximately 1-1.25 per 100,000 population overall, exceeding 9 per 100,000 in people over
87 70 years (2, 3).

88 Early recognition of meningitis, appropriate investigation, and treatment, saves lives
89 (4, 5). It is essential that front-line clinicians, who may not encounter meningitis very often,
90 are vigilant and have a high index of suspicion to minimise poor outcomes. To help staff who
91 are seeing patients with suspected meningitis, the UK guidelines on the diagnosis and
92 management of acute meningitis and meningococcal sepsis in immunocompetent adults were
93 published in 2016(6). The guidelines provide readily accessible, comprehensive, evidenced-
94 based recommendations. Previous studies show that clinical care delivered in the UK is
95 frequently non-adherent to guidelines(7, 8). A more recent UK study highlighted a large
96 amount of inappropriate brain imaging prior to lumbar punctures (LPs) and long delays in
97 performing LPs (3, 9). Inadequate use of molecular diagnostics and HIV-testing have also been

1
2
3 98 highlighted as areas for improvement(3). The increasing risk of multi-drug resistant bacteria,
4
5 99 an ageing population susceptible to a wider variety of bacteria (e.g. *Listeria monocytogenes*,
6
7
8 100 *Escherichia coli* and *Klebsiella pneumoniae*)(2) and a greater appreciation that viruses are
9
10 101 common causes of meningitis(10, 11), make diagnostics essential. Reports from outside the
11
12 102 UK have shown improvements in outcomes following guideline publication and
13
14 103 implementation (12). We carried out a retrospective observational study with the dual aims of
15
16 104 i) assessing current clinical practice regarding diagnosis and management of adult patients with
17
18 105 suspected community acquired bacterial meningitis, and ii) to identify areas for improvement.
19
20
21

22 106 **Methods**

23 107
24 108 Hospitals in the UK were invited to take part in this study via the National Infection Trainees
25
26 109 Collaborative for Audit and Research (NITCAR) network, the UK Meningitis study network,
27
28 110 the British Infection Association (BIA) and through personal contacts. Eligible patients were
29
30 111 identified via hospital coding data, laboratory data, or a combination of both. Data from
31
32 112 patients aged 16 or over who presented with suspected acute community acquired bacterial
33
34 113 meningitis during 2017 were eligible for screening. Patients who met our case definition for
35
36 114 confirmed acute meningitis, regardless of aetiology, were eligible for inclusion (box 1).
37
38 115 Definitions are as previously published(3). Many interventions are performed prior to
39
40 116 knowing the diagnosis, therefore, we included all meningitis in the analysis, including viral
41
42 117 and those in whom no pathogen was identified. This allowed us to assess the entire clinical
43
44 118 pathway of patients presenting with possible bacterial meningitis, although some would be
45
46 119 ultimately diagnosed with a different aetiology.
47
48
49
50
51

52 120

53
54
55 121

Box 1: Inclusion and exclusion criteria for cases of meningitisA meningitis case was defined as:

- (1) Patients with a cerebrospinal fluid (CSF) WCC $>4 \times 10^6$ cells/L (regardless of whether a pathogen was identified or not) and a clinical suspicion of meningitis at the time OR
- (2) in the case of bacterial meningitis, symptoms and signs of meningitis with a significant pathogen in the CSF (culture or PCR) or blood regardless of CSF leukocyte count.

Patients with the following diagnoses were excluded:

- (1) Cryptococcal meningitis;
- (2) Tuberculous meningitis;
- (3) Nosocomial meningitis (defined as meningitis that occurs during a hospital admission or within 30 days of discharge or meningitis associated with indwelling devices in the central nervous system)
- (4) Encephalitis (defined as altered consciousness for >24 with no other cause found and two or more of the following signs: fever or history of fever ($\geq 38^\circ\text{C}$) during the current illness; seizures or focal neurological signs (with evidence of brain parenchyma involvement); CSF pleocytosis ($>4 \times 10^6$ cells per L); EEG suggesting encephalitis; and neuroimaging suggestive of encephalitis).

Standards indicative of good practice were taken from the 2016 UK Joint Specialists Societies guideline on the diagnosis and management of meningitis and meningococcal sepsis in immunocompetent adults, and the Standards in Microbiological Investigations on the processing of cerebrospinal fluid (B27) (6, 13). For each standard, the number of patients as a proportion of the total cohort who received clinical care in line with the standard is reported. A second adjusted analysis taking account of missing data is also reported, whereby the number of patients as a proportion of the cohort with available data who received clinical care in line with the standard was reported.

1
2
3 130 Data were collected using electronic case report forms on REDcap™, a password
4
5 131 protected central web-based database system. All microbiological diagnostic procedures were
6
7 132 performed at the local hospital laboratory for each participating site using locally approved
8
9 133 procedures. All data were anonymised and recorded under a unique participant identification
10
11 134 number.

15 135 *Ethics approval*

17 136 As all data were anonymised individual patient consent and ethical approval was not required.
18
19 137 The study was registered with each site's clinical governance department in line with local
20
21 138 procedure.

24 139 *Statistical analyses*

26 140 Descriptive statistics were used to summarize data. Categorical data were summarized using
27
28 141 counts and percentages. Denominators presented are based on available data, where incomplete
29
30 142 case records were submitted by contributing sites. For continuous variables, means and ranges
31
32 143 or medians and inter-quartile ranges (IQRs) are presented depending on the distribution of the
33
34 144 data. Categorical data were analysed using Chi squared or Fisher's exact test. Continuous data
35
36 145 were analysed using t-tests, Mann Whitney U or Kruskal Wallis depending on the distribution
37
38 146 of the data. Regression analysis was used to identify potential risk factors associated with poor
39
40 147 outcomes.

44 148 *Patient and public involvement*

46 149 Although there was no direct involvement of patients and public in this study the Meningitis
47
48 150 Research Foundation, a key advocacy group for patients are represented in the authorship of
49
50 151 the original guidelines and will be key in the dissemination of the results and the subsequent
51
52 152 call to improve practice. Preliminary results have been shared with the Meningitis Research
53
54 153 Foundation and some of their members.

58 154 **Results**

59 155

1
2
3 156 1,471 patients from 64 hospitals throughout the UK and Ireland took part (see appendix). The
4
5 157 hospitals ranged in size from small district generals to larger teaching hospitals. The mean
6
7 158 number of beds was 846 (range 230-2000). The hospitals who took part in England comprised
8
9 159 45% of the total acute bed base in England, (42,612/94,827(14)). Females accounted for 57%
10
11 160 (n=838) and the median age was 34 years (IQR 26,49). Confirmed viral meningitis occurred in
12
13 161 615 (42%) and 303 had confirmed bacterial meningitis (21%). More than one third of patients
14
15 162 (n=553) fulfilled the case definition (box 1) but had no confirmed microbiological diagnosis
16
17 163 and were therefore categorised as meningitis of unknown aetiology. Using the criteria proposed
18
19 164 by Spanos et al(15) 56 of those without a confirmed aetiology could be assumed to have
20
21 165 bacterial meningitis. *Streptococcus pneumoniae* and *Neisseria meningitidis*, were the most
22
23 166 common bacterial pathogens, where a cause was found, accounting for 172 (57%) and 76
24
25 167 (25%) of cases respectively. *Haemophilus influenzae* (serotypes unknown) was found in 14
26
27 168 cases. *Enteroviruses* were the most common viral pathogens occurring in 429 (69%) of all
28
29 169 confirmed viral meningitis. *Herpes simplex virus-2* was the second most common viral
30
31 170 pathogen detected in 97 (16%) of viral cases. Baseline demographics and clinical
32
33 171 characteristics are shown in table 1.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1: Baseline demographics, timing of key investigations and clinical outcomes of 1,471 adults presenting with suspected meningitis

	<i>Total cohort</i>	<i>Bacterial meningitis</i>	<i>Viral meningitis</i>	<i>Other†</i>	<i>P value¹</i>
	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	
N	1,471 (100)	303 (21)	615 (42)	553 (38)	-
Median age (IQR)	34 (26 – 49)	54 (36 – 65)	31 (25 – 37)	34 (26 – 48)	< 0.001
Male	625 (43)	173 (57)	214 (35)	238 (43)	< 0.001
In patient mortality	48 (3)	38 (13)	2 (0.3)	8 (1.4)	< 0.001
ITU admission	192 (13)	157 (53)	4 (0.7)	31 (6)	< 0.001
Median Admission GCS (IQR)	15 (14-15)	13 (9 – 15)	15 (15-15)	15 (15-15)	< 0.001
Median time (hours) from admission to first antibiotics (IQR)	2.7 (0.9 – 8.3)	1.5 (0.4 – 5.3)	3.2 (1.3 – 8.3)	3.3. (1 – 12.5)	< 0.001
Median time (hours) from admission to blood cultures (IQR)	1 (0.3 – 4)	0.7 (0.2 – 2.4)	1 (0.3 – 3.7)	1.4 (0.3 – 6.1)	0.003
CT head prior to LP	1,094 (94)	207 (93)	459 (94)	428 (95)	0.55
Median time (hours) from admission to LP (IQR)	16.4 (7.9 – 26.7)	14.8 (7.7 – 29.8)	14.3 (7.5 – 22.6)	20 (8.8 – 35.8)	< 0.001
Adjunctive dexamethasone	300 (21)	150 (50)	69 (11)	81 (15)	< 0.001
Median CSF leucocyte count (IQR)	140 (44-399)	930 (235.5 – 3062.5)	122 (48 – 276)	85 (26.8 – 250.3)	< 0.001
Median CSF protein (IQR)	0.68 (0.46 - 1.21)	3.25 (1.4 – 5.8)	0.63 (0.45-0.9)	0.6 (0.4-1.0)	< 0.001
Median CSF glucose (IQR)	3.2 (2.8-3.7)	2.1 (0.95 – 3.45)	3.2 (2.9 – 3.6)	3.3 (3.0-3.8)	< 0.001

† = other meningitis category included all patients without a confirmed bacterial or viral pathogen

¹ = for continuous variables, the Kruskal-Wallis test was used to compare medians across groups, and for categorical variables Chi squared tests were used.

173

174 Adherence to specific standards of good practice is shown in table 2. None were
 175 adhered to 100% of the time. Two thirds of the standards (n=20) had less than or equal to 50%
 176 adherence.

Table 2: Adherence to audit standards[^]				
Immediate management				
	Number achieved standard/total number of patients analysed	% of total	Number achieved standard/total number of patients evaluable*	% of number evaluable
1. The patient's conscious level should be documented using the Glasgow coma scale.	1,283/1,471	87%	1283/1448	89%
2. Blood cultures should be taken as soon as possible and within 1 h of arrival at hospital	326/1,471 ¹	22%	326/767 ²	42%
3. LP should be performed within 1 h of arrival at hospital provided that it is safe to do so	8/1,471 ³	0.5%	8/1379 ⁴	0.6%
4. Antibiotic treatment should be commenced within the first hour	207/1471 ⁵	14%	207/1083 ⁶	19%
5. Patients with meningitis and meningococcal sepsis should be cared for with the input of an infection specialist such as a microbiologist or a physician with training in infectious diseases and/or microbiology	1,148/1,471 ⁷	78%	1148/1464	78%
Investigations				
6. Blood culture should be sent	977/1,471	66%	977/1469	67%
7. Blood Pneumococcal PCR should be sent	211/1,471	14%	211/1460	14%
8. Blood Meningococcal PCR should be sent	232/1,471	16%	232/1461	16%
9. CSF opening pressure should be documented	655/1,428 ⁸	46%	655/1361 ⁹	48%
10. CSF glucose with concurrent plasma glucose should be sent	607/1,428 ⁸	43%	607/1415	43%
11. CSF protein should be sent	1,358/1,428 ⁸	95%	1358/1420	96%
12. Microscopy of the CSF should take place within 2 hours of the lumbar puncture	596/1428 ⁸	42%	596/1203 ¹⁰	50%
13. CSF for pneumococcal PCR should be sent in all cases of suspected bacterial meningitis	412/1,428 ⁸	29%	412/1418	29%
14. CSF for Meningococcal PCR should be sent in all cases of suspected bacterial meningitis	434/1,428 ⁸	30%	434/1418	31%
15. A swab of the posterior nasopharyngeal wall should be obtained as soon as possible, and sent for meningococcal culture, in all cases of suspected meningococcal meningitis/sepsis	54/1,471	4%	54/1463 ¹¹	4%
16. All patients with meningitis should have an HIV test	646/1,471	44%	646/1459 ¹²	44%
Treatment				
17. All patients with suspected meningitis or meningococcal sepsis should be given ceftriaxone or cefotaxime	1039/1471 ¹³	71%	1039/1423 ¹⁴	73%
18. If the patient has, within the last 6 months, been to a country where penicillin resistant pneumococci are prevalent, IV vancomycin 15-20 mg/kg should be added 12-hourly (or 600 mg rifampicin 12-hourly IV or orally) ¹⁵	See footnote			

19. Those aged 60 or over should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].	55/233	24%	55/197 ¹⁶	28%
20. Immunocompromised patients (including diabetics and those with a history of alcohol misuse) should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin.	26/115 ¹⁷	23%	26/99 ¹⁸	26%
21. If there is a clear history of anaphylaxis to penicillins or cephalosporins give IV chloramphenicol 25 mg/kg 6- hourly	14/37	38%	14/30 ¹⁹	47%
22. If <i>Streptococcus pneumoniae</i> is identified continue with IV benzylpenicillin 2.4 g 4 hourly, 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly	114/172	66%	114/145 ²⁰	79%
23. If <i>N. meningitidis</i> is identified 2 g ceftriaxone IV 12 hourly, 2 g cefotaxime IV 6-hourly or 2.4 benzylpenicillin IV 4-hourly may be given as an alternative	52/76	68%	52/68 ²¹	76%
24. If the patient is not treated with ceftriaxone (in meningococcal disease), a single dose of 500 mg ciprofloxacin orally should also be given	0/2	0%	0/2	0%
25. If <i>Listeria monocytogenes</i> is identified Give 2 g ampicillin/amoxicillin IV 4-hourly and continue for at least 21 days. Co-trimoxazole 10-20 mg/kg or chloramphenicol are alternatives in cases of anaphylaxis to beta lactams.	4/7	57%	4/6	67% ²²
26. If <i>Haemophilus influenzae</i> is identified continue 2g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly for 10 days	9/14	64%	9/13	69% ²³
27. 10 mg dexamethasone IV 6 hourly should be started on admission, either shortly before or simultaneously with antibiotics.	67/1,471	5%	67/1435 ²⁴	5%
28. If pneumococcal meningitis is confirmed dexamethasone should be continued for 4 days.	34/172 ²⁵	20%	34/158 ²⁶	22%
Critical Care				
29. The following patients should be transferred to critical care - those with a rapidly evolving rash, those with a GCS of 12 or less and those with uncontrolled seizures	151/203 ²⁷	74%	151/203	74%
Notification				
30. All cases of meningitis (regardless of aetiology) should be notified to the relevant public health authority	236/1,471	16%	236/1465	16%
<p>Notes.</p> <p>^Only those audit standards that could be measured from the data collected. *excludes those where there was missing data and/or where not relevant. 1. Only 977 patients had blood cultures taken. 2. Excluding those who did not have blood cultures taken and where data was missing. 3. 1428 patients had a LP. 4. Excludes those who did not have an LP and where data was not available. 5. 82 patients had data consistent with having antibiotics prior to admission, this might be due to confusion about whether admission meant admission to the emergency department or admission to a ward, or it may represent data entry error therefore, these figures are not included. 6. 388 patients did not receive any antibiotics at all. 7. 310 (21%) of patients were admitted under an infection specialist, all others received consulting advice only. 8. 43 people did not have an LP. 9. Missing data on 67. 10. 43 had no LP, 97 missing data, 128 time of microscopy was before or at the same time as the LP. 11. Performed in 15/76 (20%) of proven meningococcal cases. 12. 9 known HIV positive and 3 missing data. 13. 285 patients were not given any antibiotics at all. 14. 48 patients who were definitely given antibiotics had missing data on which antibiotics they were given. 15. Using mainland Europe data only and with reference to ECDC data – 101 patients were documented to have travelled to a mainland European country within the previous 6 months. Travel history was not documented at all in 822 cases (56%). Of the 101 patients who had travelled to mainland Europe 54 (54%) had been to a country with a rate of penicillin resistant pneumococci of >5% (2017 data). 5/52 had no antibiotics. 0/47 had antibiotics to cover for penicillin resistant pneumococci. 16. 233 patients were aged over 60 but only 207 received antibiotics. Missing data for 10, 108 received amoxicillin at some point but only 55 received the correct dose. 17. Not including those >=60. 18. 15 did not received any antibiotics and missing data on 1. 19. 7 patients had no antibiotics at all. 20. 27 patients had insufficient antibiotic data. 21. 8 patient had insufficient antibiotic data. 22. 1 patient had insufficient antibiotic data. 23. Insufficient antibiotic data on 1 person. 24. Missing data on 36 – 11 on whether dexamethasone was received or not, 21 on the dose given and 4 on the timing. 25. Only 18 were given the correct dose (10mg). Some received dexamethasone for longer than 4 days. 26. Missing data on 14 individuals. 27. 7/11 patient with progressing rash, 131/176 patients with GCS <13 and 13/16 patients with uncontrolled seizures.</p>				

1
2
3 178 Overall in-hospital mortality was low [48/1471 (3%)]. The mortality was higher in
4
5 179 bacterial meningitis (28/302, 13%), and pneumococcal meningitis in particular (28/172, 16%).
6
7
8 180 Mortality in viral meningitis was 0.3% (2/615) and 1.5% (8/548) in those with meningitis of
9
10 181 unknown aetiology. Just over half (157) of those with confirmed bacterial meningitis required
11
12 182 admission to an intensive care unit (ICU).

13
14
15 183 *Use of diagnostics*

16 184 A few patients, 42, did not have an LP, of whom 26 (62%) had no contraindication (as specified
17
18 185 in the 2016 joint specialties guidelines and shown in box 2). Five had meningococcal sepsis
19
20 186 without clinical evidence of meningitis. The remaining 37 had clinical symptoms of meningism
21
22 187 as well as a positive blood culture (n=35, 83%) and/or a positive blood PCR (n=16, 38%) for
23
24 188 either *Streptococcus pneumoniae* (n=23, 55%), *Neisseria meningitidis* (n=18, 43%) or *Listeria*
25
26 189 *monocytogenes* (n=1, 2%).
27
28
29
30
31

32
33 191 **Box 2: Indications for neuroimaging before**
34 **lumbar puncture (LP) in suspected**
35 **meningitis**

- 36 192 (1) Focal neurological signs
37 (2) Presence of papilloedema
38 (3) Continuous or uncontrolled seizures
39 193 (4) GCS \leq 12
40
41

42 194
43
44 195 Contra-indications for immediate LP were uncommon and occurred in 299 (20%)
45
46 196 patients. Glasgow coma score (GCS) \leq 12 was the most common contra-indication for
47
48 197 immediate LP reported in 143 (10%), followed by focal neurological signs in 38 (3%). A
49
50 198 further 70 (7%) had other indications to delay LP. Neuroimaging prior to LP happened in 1094
51
52 199 of 1158 patients (94%), 911 (83%) of whom had no guideline-specified indication.
53
54 200 Neuroimaging was performed a median of 11 hours post arrival at hospital (IQR 4-21). Median
55
56
57
58
59
60

1
2
3 201 time from admission to LP was 16.5 hours (IQR 8 – 27). Only 6 patients had an LP within 1
4
5 202 hour of arrival at hospital and only 326 (26%) within 8 hours.
6
7

8 203 Median time from LP to CSF microscopy was 2 hours (IQR 1.1-3.2). Time from LP to
9
10 204 CSF analysis was significantly quicker when performed at on-site laboratories when compared
11
12 205 to centralised laboratory processing (median 1.65 hours (IQR 1.0 - 2.8) compared to 2.95 hours
13
14 206 (IQR 2.0 - 3.8) $p < 0.001$).
15
16

17 207 Fewer than one third of patients had pneumococcal (412, 28%) and meningococcal
18
19 208 polymerase chain reaction (PCR) (434, 29.5%) performed on their CSF. Pneumococcal PCR
20
21 209 was done on blood in 211 (14%) patients, and meningococcal PCR in 232 (16%). 646 patients
22
23 210 (44%) patients had a documented HIV test. Four of these were positive – two of whom had
24
25 211 pneumococcal meningitis, one of whom had enteroviral meningitis and one had meningitis of
26
27 212 unknown aetiology. Nine patients were previously known to be HIV positive.
28
29

30
31 213 Blood cultures were taken from 66% (n=977) of patients with 45% (n=438) having
32
33 214 them taken within one hour of arrival at hospital.
34
35

36 215 *Treatment*

37
38 216 285 patients (19%) did not receive antibiotics, most of whom had either viral meningitis
39
40 217 (163) or lymphocytic meningitis with no aetiology identified (105). The remaining 1,186
41
42 218 patients received at least one dose of antibiotics. The median time from hospital admission to
43
44 219 first dose of antibiotics was 3.2 hours (IQR 1.3,9.2). Amongst the patients who received
45
46 220 antibiotics the antimicrobials were commenced within an hour of arrival at hospital for
47
48 221 approximately one fifth of patients (207/1000). In confirmed bacterial meningitis cases, 92
49
50 222 patients (36%) received antibiotics within an hour of arrival.
51
52

53
54 223 Adherence with guideline specified empirical antibiotic regimens was good with 912
55
56 224 (80%) receiving a third-generation cephalosporin. Data is missing on antibiotic type for 47
57
58 225 patients. Of the 197 patients aged 60 years and over who received antibiotics, 108 (55%)
59
60

1
2
3 226 received ampicillin or amoxicillin; only 55 (28%) of those had the correct dose and dosing
4
5 227 frequency as recommended for *Listeria monocytogenes* meningitis. Similarly, only 36 (31%)
6
7
8 228 of the immunocompromised patients, who were aged under 60, (n=115) received any
9
10 229 ampicillin or amoxicillin for anti-*Listeria* cover. Supplementary table 1 shows details regarding
11
12 230 risk factors for *Listeria*.

14 231 Only 300 patients (20%) received adjunctive steroids as recommended. Steroids were
16
17 232 given more frequently in patient with confirmed bacterial meningitis in 150 (50%) cases. In
18
19 233 patients with pneumococcal meningitis 97 patients (57%) received steroids.

21 234 *Clinical outcomes*

23
24 235 On multivariate analysis, having a confirmed diagnosis of bacterial meningitis was strongly
25
26 236 associated with in-hospital mortality. Adjusting for age and sex, confirmed bacterial meningitis
27
28 237 was associated with 26 times the odds of in-hospital mortality compared to those with other
29
30 238 forms of meningitis (adjusted odds ratio [aOR] 25.9, 95% CI 5.93 – 113.0), including those
31
32 239 with no aetiology identified.

35 240 In patients with confirmed bacterial meningitis, on univariate analyses, in-hospital
36
37 241 mortality was associated with a positive blood culture (crude odds ratio [cOR] 2.21, 95% CI
38
39 242 1.04 – 4.67); GCS \leq 13 (cOR 3.24, 95% CI 1.39 – 7.52), confirmed *Streptococcus pneumoniae*
40
41 243 meningitis (cOR 2.37, 95% CI 1.10 – 5.11); and ICU admission (cOR 4.81, 95% CI 1.99 –
42
43 244 11.60). These associations remained despite multivariate adjustment for age and sex (table 3).

46 245 The analysis was also conducted using only data from those who had had an LP
47
48 246 (supplementary table 2). The association between a positive blood culture and mortality was
49
50 247 lost. The association between confirmed pneumococcal aetiology and mortality was
51
52 248 approaching statistical significance and the association of ITU admission was maintained.
53
54
55

56 249
57
58
59
60

Table 3: Multivariate analysis of the association between baseline co-variates and in-hospital mortality in 303 patients with confirmed bacterial meningitis using logistic regression modelling

Baseline co-variate	N	In-hospital mortality N (%) ¹	Crude OR for in-hospital mortality (95% CI)	P-value	Adjusted OR for in-hospital mortality (95% CI)*	P-value†
Sex						
Male	173	26 (15.1)	1			
Female	130	12 (9.23)	0.57 (0.27-1.18)	0.13		
Age group						
≤ 18 years	18	0 (0)				
19 – 59 years	159	18 (11.3)	1			
≥ 60 years	126	20 (16.0)	1.49 (0.75 – 2.96)	0.25		
Blood culture positive						
No	137	11 (8.09)	1		1	
Yes	166	27 (16.3)	2.21 (1.04 – 4.67)	0.03	1.87 (0.87 – 4.01)	0.10
GCS ≤ 13²						
No	124	8 (6.45)	1		1	
Yes	148	27 (18.2)	3.24 (1.39 – 7.52)	0.004	2.90 (1.26 – 6.71)	0.008
IV dexamethasone given³						
No	149	23 (15.4)	1		1	
Yes	150	14 (9.40)	0.57 (0.27 – 1.16)	0.11	0.57 (0.28 – 1.17)	0.12
IV dexamethasone given if <i>Strep.pneumoniae</i>⁴						
No	73	16 (21.9)	1		1	
Yes	97	11 (11.5)	0.46 (0.20 – 1.08)	0.07	0.47 (0.20 – 1.10)	0.08
Final diagnosis <i>S. pneumoniae</i>						
No	131	10 (7.63)	1		1	
Yes	172	28 (16.4)	2.37 (1.10 – 5.11)	0.02	2.08 (0.96 – 4.48)	0.05
ITU admission⁵						
No	144	7 (4.86)	1		1	
Yes	157	31 (19.7)	4.81 (1.99 – 11.60)	< 0.001	4.28 (1.81 – 10.1)	< 0.001

*adjusted for sex and age group
† P-value from LRT comparing models with and without primary exposure variable
1 = One participant had missing outcome data
2 = 31/303 (10%) participants did not have a GCS recorded
3 = 4/303 (1%) participants had missing data on IV dexamethasone administration
4 = 2/172 (1%) participants with confirmed *S. pneumoniae* meningitis had missing data on IV dexamethasone administration
5 = 1/303 (0.3%) participants had missing data on ITU admission

250

251 On both univariate and multivariate analyses (adjusted for age and sex), in patients with
252 confirmed bacterial meningitis, the administration of dexamethasone was associated with a
253 reduction in in-hospital mortality (aOR 0.57, 95% CI 0.28 – 1.17, p 0.12). When this analysis
254 was restricted to include only those with confirmed *Streptococcus pneumoniae* meningitis,
255 those who received dexamethasone had a reduced odds of in-hospital mortality (aOR 0.47,
256 95% CI 0.20 – 1.10, p 0.08). Neither association reached statistical significance. This analysis

1
2
3 257 was also performed including the patients assumed to have bacterial meningitis according to
4
5 258 the Spanos criteria (supplementary table 3).

7
8 259 **Discussion**

9 260
10 261 This large national study evaluated clinical management of adults with community acquired
11
12 262 meningitis throughout the UK and Ireland. Current practice falls short of the recommendations
13
14 263 in the 2016 UK guidelines(6). This is a concern for all patients but is of a particular worry in
15
16 264 bacterial meningitis. The management of bacterial meningitis is time critical(4, 16). Delays in
17
18 265 receiving antibiotics and having an LP, the unnecessary use of brain imaging, a lack of
19
20 266 appropriate antibiotics in those at risk of *Listeria* and the low rate of steroid administration are
21
22 267 areas for significant improvement.

23
24
25
26 268 Most patients were given antibiotics prior to LP. Even taking this into consideration,
27
28 269 the median door to antibiotic time was over three hours. The optimal timing of antibiotics in
29
30 270 bacterial meningitis is not known precisely but we do know that delays lead to increased
31
32 271 mortality (4, 5, 16). A delay of over three hours has been associated with a 14-fold increase
33
34 272 risk of death(16).

35
36
37 273 Delays in obtaining CSF are associated with a reduction in pathogen detection,
38
39 274 increased exposure to unnecessary anti-infectives, prolonged hospital stays and increased
40
41 275 mortality (4, 6, 17). In most cases brain imaging is not indicated in adults with suspected
42
43 276 community-acquired meningitis (4) however, in our cohort, a significant number of patients
44
45 277 had unnecessary scans. Although complications following LP are rare(18, 19), there may be an
46
47 278 unfounded fear of cerebral herniation following LP, even in those with no clinical features of
48
49 279 brain shift, which is leading to excessive use of imaging(20). Education programs, along with
50
51 280 quality improvement measures, are essential to reduce the potentially harmful overuse of
52
53 281 neuroloimaging. Additionally, it is essential that we optimise care pathways to ensure that
54
55
56
57
58
59
60

1
2
3 282 clinicians have the time, space and equipment required to performed LPs in a timely and safe
4
5 283 manner (3, 21).
6

7
8 284 CSF culture positivity rates decline substantially when LP is delayed (3, 17). PCR can
9
10 285 detect bacterial DNA in CSF for several days after antibiotics have been administered. In the
11
12 286 UK half of meningococcal disease is diagnosed on PCR alone(22). It is alarming that PCR was
13
14 287 used, in our cohort, as a diagnostic modality in so few patients. Meningitis specific
15
16 288 investigation order-sets using electronic ordering, and/or reflex laboratory testing to increase
17
18 289 use of molecular diagnostics should be considered to reduce opportunities for missed
19
20 290 microbiological diagnoses. There is the potential for increased use of rapid technologies that
21
22 291 can be used on site with minimal technical skill required(23). Having rapid tests on site has
23
24 292 been shown to reduce bed days with significant cost savings(24). Further research evaluating
25
26 293 rapid diagnostic tests in other types of meningitis with clinically relevant outcomes is needed.
27
28 294 We also need to increase the offer of HIV testing in patients with meningitis, as less than half
29
30 295 the patients had a documented HIV test. Incident HIV diagnoses were made in our cohort
31
32 296 amongst patients presenting with bacterial, viral, and unknown cause meningitis.
33
34
35
36

37 297 There is good evidence that corticosteroids reduce mortality in pneumococcal
38
39 298 meningitis with no clinically significant increase in adverse events in other causes of meningitis
40
41 299 (25). Empirical steroids should be given for all adults with suspected bacterial meningitis. In
42
43 300 our study, we saw a reduction in mortality in patients with pneumococcal meningitis who were
44
45 301 given steroids, whilst this survival benefit did not reach statistical significance, this was likely
46
47 302 due to a type two error and the small sample of confirmed pneumococcal meningitis cases. It
48
49 303 is of concern that well-evidenced, well-established therapies known to improve outcome,
50
51 304 including mortality, are only being given to just over half those who might benefit. A
52
53 305 protocolised, goal-directed bundle, including the use of corticosteroids and appropriate
54
55 306 antibiotics warrants evaluation in the UK. There were clear differences between centres in our
56
57
58
59
60

1
2
3 307 study with one centre administering steroids to 26/42 (63%) of their patients and another giving
4
5 308 them to none. It is possible that those centres that adhered to the recommendation to give
6
7 309 steroids may also have adhered to other aspects of the guidelines more often as well,
8
9
10 310 contributing to improved outcomes.

11
12 311 Although this is a large multi-national study, there are limitations. NHS trusts self-
13
14 312 selected themselves for inclusion, we cannot rule out any significant differences with trusts that
15
16 313 did not. However, 64 hospitals were included with good representation throughout the nations
17
18 314 of the UK (and Ireland). We don't think any potential selection bias limits the generalisability
19
20 315 of our findings. We used well-established, published case definitions of meningitis to minimise
21
22 316 information bias, however misclassification of cases remains possible especially in the cases
23
24 317 without a confirmed microbiological diagnosis. Our case definitions allowed us to include
25
26 318 anyone suspected of having meningitis (of any cause) as objectively it is often difficult to
27
28 319 differentiate between viral and bacterial meningitis at the point of initial assessment. However,
29
30 320 it is possible that there may have been differences in presentation between those with confirmed
31
32 321 bacterial meningitis, those with confirmed viral meningitis and those with no confirmed
33
34 322 aetiology that meant they were managed in different ways. This study was not powered to look
35
36 323 at the differences between all the different aetiologies. Finally, because this was a retrospective
37
38 324 study, our analysis may have been subject to errors resulting from recall bias and missing data.
39
40 325 A prospective national study would have been challenging to execute and it is likely that there
41
42 326 would have been ascertainment bias in time and geography. We therefore believe that, due to
43
44 327 the large sample size along with the use of electronic hospital coding and laboratory data to
45
46 328 ascertain cases, the risk of recall bias is low, and our retrospective data is representative of
47
48 329 practice within the UK.

49
50 330 There is a clear need to better understand the sub-optimal guideline adherence reported
51
52 331 here. Although there has been research regarding primary care practice there has not been any
53
54
55
56
57
58
59
60

1
2
3 332 evaluation of exactly where delays occur and what the barriers are to achieving good practice
4
5 333 in secondary care(26, 27). A small questionnaire based study identified the inability to find
6
7 334 correct equipment, lack of time and/or paucity of appropriately trained staff as potential barriers
8
9 335 to performing timely lumbar puncture for the investigation of neurological infections(21).
10
11

12 336 Non-meningitis specific research evaluating barriers and facilitators to adhering to
13
14 337 clinical guidelines, report a lack of awareness or familiarity with the guidelines, as well as
15
16 338 disagreement with the content may both be important(28). External barriers such as equipment
17
18 339 and staffing were also identified which agrees with the limited research that there is in
19
20 340 neurological infections. There is observational evidence from other countries of improvements
21
22 341 in practice and outcome following implementation of guidelines (12, 29).
23
24

25 342 The patient journey in the UK normally starts with being admitted via an emergency
26
27 343 department or acute medical unit where clinicians may not be as familiar with the guidelines
28
29 344 and evidence as specialists. There is some evidence, both within meningitis and other infectious
30
31 345 diseases that management is improved by being looked after by a specialist. There is an expert
32
33 346 recommendation within the current UK guidelines that patients with meningitis should be
34
35 347 looked after with input of an infection specialist.
36
37
38
39

40 348 In conclusion this is, to our knowledge, the largest UK study of adult patients with
41
42 349 meningitis. Awareness of practice guidelines for relatively rare acute medical conditions such
43
44 350 as meningitis is low and this study has demonstrated that despite clear, freely accessible
45
46 351 guidelines, clinical care is not in line with evidence-based recommendations. There is
47
48 352 considerable room for improvement. Whilst we recognise that guidelines do not improve
49
50 353 practice on their own, we do recommend that the findings from this study are strongly
51
52 354 considered in the development of the new National Institute for Clinical Excellence (NICE)
53
54 355 guideline on meningitis currently being developed, which for the first time, will include
55
56 356 guidance for adult patients as well as children. Given the widespread adoption of NICE
57
58
59
60

1
2
3 357 endorsed guidelines and quality standards to improve the quality of clinical practice in the UK,
4
5 358 we anticipate that a NICE guideline will improve awareness and uptake of good practice in the
6
7
8 359 short term. In addition to education, which has limited impact on changing behaviour, UK
9
10 360 hospitals should use quality improvement methods to improve management of patients with
11
12 361 suspected meningitis. Good qualitative research to identify what the barriers to implementing
13
14 362 the guidelines should also be done.

15
16
17 363 We suggest a national strategic improvement plan should focus on the following key
18
19 364 areas: timely use of diagnostics; appropriate antibiotics in at risk populations and the use of
20
21 365 adjunctive steroids. The integrated use of electronic systems to standardize optimal use of
22
23 366 diagnostics, and management bundles may offer additional opportunities to improve outcomes.
24
25
26 367 Each site that has been involved in this study has been asked to implement site specific changes
27
28 368 and re-evaluate for any improvements in practice.

29
30
31 369
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

370 **Contributors**

371 Ellis J: Methodology, Data collection and curation, formal analysis, Investigation, Writing –
372 Original Draft Preparation. Harvey D: Methodology including pilot data, data collection,
373 reviewing and approving final draft. Defres S: Methodology including development of original
374 audit tool and guidelines, data collection, reviewing and approving final draft. Chandna A:
375 Methodology, reviewing and approving final draft. Maclachlan E: Methodology, data
376 collection, reviewing and approving final draft. Solomon T: Methodology including
377 development of original guidelines and audit tool, reviewing and approving final draft.
378 Heyderman RS: Conceptualization, Methodology, Supervision, Writing – Review & Editing.
379 McGill F: Conceptualization, Methodology, Data collection and curation, Investigation, formal
380 analysis, Writing –Original Draft Preparation. Responsible for overall content as guarantor.
381 The corresponding author attests that all listed authors meet authorship criteria and that no
382 others meeting the criteria have been omitted. The lead author and corresponding author affirm
383 that the manuscript is an honest, accurate, and transparent account of the study; no important
384 aspects of the study have been omitted.

385 The appendix includes a list of other contributors in the National Audit of Meningitis
386 Management (NAMM) group.

387 The Corresponding Author has the right to grant on behalf of all authors and does grant
388 on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity,
389 in all forms, formats and media (whether known now or created in the future), to i) publish,
390 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other
391 languages, create adaptations, reprints, include within collections and create summaries,
392 extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on
393 the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of
394 electronic links from the Contribution to third party material where-ever it may be located; and,
395 vi) licence any third party to do any or all of the above.

396

397 **Competing interests**

398 All authors have completed the ICMJE uniform disclosure form
399 at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
400 submitted work; no financial relationships with any organisations that might have an interest
401 in the submitted work in the previous three years; no other relationships or activities that
402 could appear to have influenced the submitted work.

403

1
2
3
4 404 **Acknowledgments**

5 405 TS is supported by the National Institute for Health Research (NIHR) Health Protection
6
7 406 Research Unit in Emerging and Zoonotic Infections (Grant No. NIHR200907), NIHR Global
8
9 407 Health Research Group on Brain Infections (No. 17/63/110), and the UK Medical Research
10 408 Council's Global Effort on COVID-19 Programme (MR/V033441/1)
11

12 409
13
14 410 **Funding**

15 411 This research received no specific grant from any funding agency in the public, commercial
16
17 412 or not-for-profit sector.
18

19 413
20 414 **Data availability statement**

21
22 415 Data can be made available to other researchers on reasonable request to the authors.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

416

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis. *N Engl J Med*. 2004;351:1849-59.
2. Okike IO, Ribeiro S, Ramsay M, Heath PT, Sharland M, Ladhani SN. Trends in bacterial, mycobacterial and fungal meningitis in England and Wales 2004-11: an observational study. *Lancet Infect Dis*. 2014;14:301-7.
3. McGill F, Griffiths MJ, Bonnett LJ, Geretti AM, Michael BD, Beeching NJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis*. 2018;18(9):992-1003.
4. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from acute bacterial meningitis. *QJM*. 2005;98:291-8.
5. Bodilsen J, Dalager-Pedersen M, Schonheyder HC, Nielsen H. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. *BMC Infect Dis*. 2016;16(392):1-7.
6. McGill F, Heyderman RS, Michael BD, Defres S, Beeching NJ, Borrow R, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. 2016;72(4):405-38.
7. Stockdale AJ, Weekes MP, Aliyu SH. An audit of acute bacterial meningitis in a large teaching hospital 2005-10. *QJM*. 2011;104(12):1055-63.
8. Cullen MM. An audit of the investigation and initial management of adults presenting with possible bacterial meningitis. *J Infect*. 2005;50:120-4.
9. Brouwer M, van de Beek D. Viral meningitis in the UK: time to speed up. *Lancet Infectious Diseases*. 2018;18(9):930-1.
10. Kadambari S, Okike I, Ribeiro S, Ramsay ME, Heath PT, Sharland M, et al. Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004-2013. *J Infect*. 2014;69(4):326-32.
11. McGill F, Tokarz R, Thomson EC, Filipe A, Sameroff S, Jain K, et al. Viral capture sequencing detects unexpected viruses in the cerebrospinal fluid of adults with meningitis. *Journal of Infection*. 2022;84(4):499-510.
12. Glimåker M, Johansson B, Grindborg Ö, Bottai M, Lindquist L, Sjölin J. Adult Bacterial Meningitis: Earlier Treatment and Improved Outcome Following Guideline Revision Promoting Prompt Lumbar Puncture. *Clin Infect Dis*. 2015;60(8):1162-9.
13. Public Health England. UK Standards for Microbiology Investigations. Investigation of Cerebrospinal fluid. 2017.
14. The Kings Fund. NHS hospital bed numbers: past, present, future 2021 [Available from: <https://www.kingsfund.org.uk/publications/nhs-hospital-bed-numbers>].
15. Spanos A, Harrell FE, Durack DT. Differential Diagnosis of Acute Meningitis. An Analysis of the Predictive Value of Initial Observations. *JAMA*. 1989;262(19):2700-7.
16. Auburtin M, Wolff M, Charpentier J, Varon E, Tulzo YL, Girault C, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study. *Crit Care Medicine*. 2006;34:2758-65.
17. Michael B, Menezes BF, Cunniffe J, Miller A, Kneen R, Francis G, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J*. 2010;27(6):433-8.
18. Costerus JM, Brouwer MC, Sprengers MES, Roosendaal SD, van der Ende A, van de Beek D. Cranial Computed Tomography, Lumbar Puncture, and Clinical Deterioration in Bacterial Meningitis: A Nationwide Cohort Study. *Clin Infect Dis*. 2018;67(6):920-6.
19. Costerus JM, Brouwer MC, van de Beek D. Technological advances and changing indications for lumbar puncture in neurological disorders. *Lancet Neurol* 2018;17(3):268-78.

- 1
2
3 469 20. Glimaker M, Johansson B, Bell M, Ericsson M, Blackberg J, Brink M, et al. Early Lumbar
4 470 Puncture in adult bacterial meningitis - rationale for revised guidelines. *Scand J Infect Dis.*
5 471 2013;45:657-63.
6 472 21. Defres S, Mayer J, Backman R, Kneen R. Performing lumbar punctures for suspected CNS
7 473 infections: experience and practice of trainee doctors. *Br J Hosp Med.* 2015;76(11):658-62.
8 474 22. Heinsbroek E, Ladhani SN, Gray S, Guiver M, Kaczmarski E, Borrow R, et al. Added value of
9 475 PCR testing for confirmation of invasive meningococcal disease in England. *J Infect.* 2013;67:385-90.
10 476 23. Bouzid D, Zanella MC, Kerneis S, Visseaux B, May L, Schrenzel J, et al. Rapid diagnostic tests
11 477 for infectious diseases in the emergency department. *Clinical microbiology and infection : the official
12 478 publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2020.
13 479 24. Giuleri SG, Chapuis-Taillard C, Manuel O, Hugli O, Pinget C, Wasserfallen JB, et al. Rapid
14 480 detection of enterovirus in cerebrospinal fluid by a fully automated PCR assay is associated with
15 481 improved management of aseptic meningitis in adult patients. *J Clin Virol.* 2015;62:58-62.
16 482 25. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study
17 483 Investigators. Dexamethasone in Adults with Bacterial Meningitis. *N Engl J Med.* 2002;347(20):1549-
18 484 56.
19 485 26. Brennan CA, Somerset M, Granier SK, Fahey TP, Heyderman RS. Management of diagnostic
20 486 uncertainty in children with possible meningitis: a qualitative study. *Br J Gen Pract.* 2003;53:626-31.
21 487 27. Granier S, Owen P, Pill R, Jacobson L. Recognising meningococcal disease in primary care:
22 488 qualitative study of how general practitioners process clinical and contextual information. *BMJ.*
23 489 1998;316:276-9.
24 490 28. Barth JH, Misra S, Moberg Aakre K, Langlois MR, Watine J, Twomey PJ, et al. Why are clinical
25 491 practice guidelines not followed? *Clinical chemistry and laboratory medicine.* 2016;54(7):1133-39.
26 492 29. Costerus JM, Brouwer MC, Bijlsma MW, Tanck MW, van der Ende A, van de Beek D. Impact
27 493 of an evidence-based guideline on the management of community-acquired bacterial meningitis: a
28 494 prospective cohort study. *Clinical microbiology and infection : the official publication of the
29 495 European Society of Clinical Microbiology and Infectious Diseases.* 2016;22(11):928-33.

30
31
32
33
34 496
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplementary table 1 . Risk factors for Listeria stratified by aetiology.

	Total cohort N (%)	Bacterial meningitis N (%)	Viral meningitis N (%)	Other meningitis [†] N (%)	P value
N	1,471 (100)	302 (21)	615 (42)	553 (38)	-
Age >60 years	235 (16)	126 (42)	27 (4)	79 (14)	<0.001
Number immunocompromised by disease/medication*	60 (4)	14 (5)	18 (3)	28 (5)	0.23
Number with Diabetes mellitus	64 (4)	30 (10)	11 (2)	22 (4)	<0.001
Number with a history of alcohol excess	36 (2)	21 (7)	3 (0.5)	12 (2)	<0.001

[†]= other meningitis category included all patients without a confirmed bacterial or viral pathogen

*=Conditions listed as immunocompromising conditions included haematological malignancy (n=8), Other malignancy (n=8), solid organ transplant (n=6), liver cirrhosis (n=1), HIV (n=9), Pregnancy (n=2). Medication listed included Steroids (n=7), tocilizumab, ecolizumab and infliximab (n=6), Methotrexate (n=8), Mycophenolate (n=2), Azathioprine (n=3), 'chemotherapy' (n=4). (some patients had more than one immunocompromising condition/medication).

Supplementary table 2: Multivariate analysis of the association between baseline co-variables and in-hospital mortality in 266 patients with bacterial meningitis confirmed by CSF analysis using logistic regression modelling:

Baseline co-variate	N	In-hospital mortality N (%) ¹	Crude OR for in-hospital mortality (95% CI)	P-value	Adjusted OR for in-hospital mortality (95% CI)*	P-value†
Sex						
Male	147	15 (10.2)	1			
Female	118	7 (5.93)	0.55 (0.22-1.42)	0.21		
Age group						
≤ 18 years	16	0 (0)	-			
19 – 59 years	136	10 (7.35)	1			
≥ 60 years	113	12 (10.6)	1.50 (0.62-3.61)	0.37		
Blood culture positive						
No	130	8 (6.15)	1		1	
Yes	135	14 (10.4)	1.76 (0.71-4.38)	0.21	1.46 (0.58-3.71)	0.42
GCS ≤ 13²						
No	106	3 (2.83)	1		1	
Yes	132	17 (12.9)	5.05 (1.41-18.2)	0.006	4.41 (1.24-15.7)	0.009
IV dexamethasone given³						
No	124	10 (8.06)	1		1	
Yes	137	11 (8.03)	0.99 (0.41-2.43)	0.99	1.02 (0.41-2.52)	0.96
IV dexamethasone given if <i>Strep.pneumoniae</i>⁴						
No	62	8 (12.9)	1		1	
Yes	89	8 (8.99)	0.67 (0.23-1.89)	0.44	0.68 (0.24-1.94)	0.48
Final diagnosis <i>S. pneumoniae</i>						
No	107	5 (4.46)	1		1	
Yes	136	17 (11.1)	2.67 (0.95-7.55)	0.05	2.37 (0.84-6.67)	0.08
ITU admission⁵						
No	129	4 (3.01)	1		1	
Yes	113	18 (13.7)	5.14 (1.65-16.0)	0.002	4.44 (1.44-13.6)	0.003

*adjusted for sex and age group

† P-value from LRT comparing models with and without primary exposure variable

1 = One participant had missing outcome data

2 = 28/266 (10%) participants did not have a GCS recorded

3 = 4/266 (1%) participants had missing data on IV dexamethasone administration

4 = 2/154 (1%) participants with confirmed *S. pneumoniae* meningitis had missing data on IV dexamethasone administration

5 = 2/266 (0.7%) participants had missing data on ITU admission

Supplementary table 3: Multivariate analysis of the association between baseline co-variates and in-hospital mortality in 359 patients with bacterial meningitis using the Spanos criteria[^] using logistic regression modelling:

Baseline co-variant	N	In-hospital mortality N (%) ¹	Crude OR for in-hospital mortality (95% CI)	P-value	Adjusted OR for in-hospital mortality (95% CI)*	P-value [†]
Sex						
Male	199	28 (14.1)	1			
Female	159	13 (8.18)	0.54 (0.27-1.09)	0.08		
Age group						
≤ 18 years	21	0 (0)	-			
19 – 59 years	192	18 (9.38)	1			
≥ 60 years	145	23 (15.9)	1.82 (0.94-3.52)	0.07		
Blood culture positive						
No	188	14 (7.45)	1		1	
Yes	170	27 (15.9)	2.35 (1.18-4.68)	0.01	1.93 (0.96-3.89)	0.06
GCS ≤ 13²						
No	163	9 (5.52)	1		1	
Yes	156	28 (17.9)	3.74 (1.67-8.36)	<0.001	3.19 (1.44-7.09)	0.003
IV dexamethasone given³						
No	189	26 (13.8)	1		1	
Yes	162	14 (8.64)	0.59 (0.30-1.18)	0.13	0.57 (0.28-1.14)	0.11
IV dexamethasone given if <i>Strep.pneumoniae</i>⁴						
No	73	16 (21.9)	1		1	
Yes	96	11 (11.5)	0.46 (0.19-1.08)	0.07	0.47 (0.20-1.10)	0.08
Final diagnosis <i>S. pneumoniae</i>						
No	187	13 (6.95)	1		1	
Yes	171	28 (16.4)	2.62 (1.30-5.29)	0.005	2.29 (1.14-4.63)	0.02
ITU admission⁵						
No	192	9 (4.69)	1		1	
Yes	163	32 (19.6)	4.97 (2.24-11.0)	<0.001	4.43 (2.03-9.68)	<0.001

*adjusted for sex and age group

[†] P-value from LRT comparing models with and without primary exposure variable

1 = One participant had missing outcome data

2 = 40/359 (11%) participants did not have a GCS recorded

3 = 7/359 (2%) participants had missing data on IV dexamethasone administration

4 = 2/172 (1%) participants with confirmed *S. pneumoniae* meningitis had missing data on IV dexamethasone administration

5 = 4/359 (1%) participants had missing data on ITU admission

[^] - Spanos criteria use various parameters to allow patients who have not had an aetiological agent to be assumed to be likely bacterial in nature.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Site of Data collection	Names and Grades (at time of data collection) of contributors	Number of patients' data contributed
Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust	Amy Chue, SpR Ed Moran, Consultant Karishma Gokani, CMT	60
North Manchester General Hospital	Joseph Thompson, SpR	54
North Manchester General Hospital	Katherine Ajdukiewicz, Consultant	54
Oxford University Hospitals	Victoria Ward, SpR	50
Oxford University Hospitals	Lucinda Barrett, Consultant	50
Cheltenham General Hospital	Frances Edwards, CMT	47
Cheltenham General Hospital	Adam Usher, Consultant	47
Royal Alexandra Hospital, Paisley	Mairi McLeod, Consultant	45
Royal Alexandra Hospital, Paisley	Ramandeep Singh, medical student	45
Royal Alexandra Hospital, Paisley	Su su Htwe, SpR	45
Leicester Royal Infirmary, Leicester	Benedict Rogers, SpR	42
Leicester Royal Infirmary, Leicester	Grace Duane, Medical Student	42
Leicester Royal Infirmary, Leicester	Martin Wiselka, Consultant	42
Leicester Royal Infirmary, Leicester	Nicholas Wong, SpR	42
NHS Lothian	Elen Vink, SpR	42
NHS Lothian	Jennifer Poyner, SpR	42
NHS Lothian	Jenni Crane, Consultant	42
NHS Lothian	Ollie Lloyd, SpR	42
NHS Lothian	Emma Chisholm, SpR	42
Countess of Chester Hospital	Ildiko Kustos, Consultant	40
Countess of Chester Hospital	Ruth McEwen, Consultant	40
Countess of Chester Hospital	Sam Sutton, CMT	40
University Hospitals Plymouth Trust	Lewis Jones, Consultant	38
University Hospitals Plymouth Trust	Robert Tilley, Consultant	38
Addenbrookes hospital, Cambridge University Hospitals NHS Foundation Trust	M. Estee Torok, Honorary Consultant	37
Addenbrookes hospital, Cambridge University Hospitals NHS Foundation Trust	Isobel Ramsay, SpR	37
Hull University Teaching Hospitals NHS Trust	Monica Ivan, Consultant	36
Hull University Teaching Hospitals NHS Trust	Joshua York	36
Hull University Teaching Hospitals NHS Trust	Jennifer Ansett	36
Hull University Teaching Hospitals NHS Trust	Maithili Varadarajan	36
Hull University Teaching Hospitals NHS Trust	Celestine Eshiwe, SpR	36
London King's College	Amanda Fife, Consultant	36
London King's College	Stephanie Harris, SpR	36
London King's College	Ryan Jayesinghe, medical student	36
London King's College	Priya Sekhon	36
Aintree University Hospital, Liverpool	James Cruise, SpR	35
Aintree University Hospital, Liverpool	Susan Larkin, Consultant	35
Worcestershire Royal Hospital	Shivani Kanabar, Medical student	35
Worcestershire Royal Hospital	Ernest Mutengesa, Medical Student	35
Worcestershire Royal Hospital	Mirella Ling, Consultant	35
Worcestershire Royal Hospital	Christopher Green, Consultant	35
Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust	Martin Williams, Consultant	33

1			
2			
3	Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust	Matthew Stevens, CMT	33
4	Victoria hospital, Kirkcaldy	David Griffith, Consultant	32
5	Victoria hospital, Kirkcaldy	Naomi Bulteel, SpR	32
6	Northumbria Healthcare NHS Foundatio Trust	Charlotte Milne, SpR	30
7	Northumbria Healthcare NHS Foundatio Trust	Jayanta Sarma, Consultant	30
8	Ninewells hospital, Dundee	Aline Wilson, SpR	29
9	Ninewells hospital, Dundee	John Shone, Consultant	29
10	Ninewells hospital, Dundee	Lynn Urquhart, Consultant	29
11	Ninewells hospital, Dundee	Sahar Eldirdiri, SpR	29
12	Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust	Alison Muir, Consultant	28
13	Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust	Leila White, Clinical Scientist	28
14	Sheffield teaching Hospitals	Jody Aberdein, Consultant	28
15	Sheffield teaching Hospitals	Phillip Simpson, SpR	28
16	Shrewbury and Telford Hospital NHS Trust	Hnin Hay Mar	26
17	Shrewbury and Telford Hospital NHS Trust	John Bowen	26
18	Shrewbury and Telford Hospital NHS Trust	Keying Tan	26
19	Shrewbury and Telford Hospital NHS Trust	Eint Shwe Zin thein	26
20	Shrewbury and Telford Hospital NHS Trust	Mahmoud Aziz	26
21	University Hospital North Midlands	Anthony Cadwgan, Consultant	25
22	University Hospital North Midlands	Brendan Davies, Consultant	25
23	University Hospital North Midlands	Daniel White, SpR	25
24	University Hospital North Midlands	Natasha Weston, SpR	25
25	University Hospital North Midlands	Salman Zeb, CMT	25
26	St George's Hospital, London	Angela Houston, Consultant	24
27	St George's Hospital, London	Imogen Fordham, clinical fellow	24
28	St George's Hospital, London	Terry John Evans, SpR	24
29	St George's Hospital, London	Louise Wootton, Physician's associate	24
30	Nottingham University Hospitals NHS Trust	David Turner, Consultant	24
31	Nottingham University Hospitals NHS Trust	Iona Willingham, SpR	24
32	Birmingham Queen Elizabeth Hospital	Aimee Johnson, SpR	23
33	Birmingham Queen Elizabeth Hospital	Nimal Wickramasinghe, Consultant	23
34	Salford Royal Infirmary, Salford	Ashley Horsley, SpR	23
35	Salford Royal Infirmary, Salford	Eamonn Trainor, Consultant	23
36	Salford Royal Infirmary, Salford	Olivier Gaillemin, Consultant	23
37	University Hospital Southampton NHS Foundation Trust	Andrew Rosser, Consultant	23
38	University Hospital Southampton NHS Foundation Trust	Nicholas J Norton, SpR	23
39	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Iain Crossingham, Consultant	22
40	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Katie Cheung, Medical Student	22
41	Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust	Megan Duxbury, CMT	22
42	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Ashutosh Deshpande, Consultant	22
43	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Emilie Bellhouse, FY2	22
44	Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde	Kamaljit Khalsa, SpR	22
45	Imperial College School of Medicine	Helena Brezovjakova, Medical Student	22
46	Imperial College School of Medicine	Emma McLean, medical student	22
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1			
2			
3	Imperial college healthcare NHS trust	Tanmay, Kanitkar, CMT	22
4	Imperial college healthcare NHS trust	Nicholas Davies, Consultant	22
5	Imperial College School of Medicine	Alexsander Dawidziuk, Medical Student	22
6	Imperial College School of Medicine	Alexsander Dawidziuk, Medical Student	22
7	St James University hospital, Leeds	Eloisa McLaughlin, Medical student	22
8	St James University hospital, Leeds	Joanna Allen, Consultant	22
9	St James University hospital, Leeds	Razan Saman, SpR	22
10	St James University hospital, Leeds	Sarah Kelly, SpR	22
11	St James University hospital, Leeds	Sarah Kelly, SpR	22
12	Royal Liverpool University Hospital, Liverpool	Hugh Adler, SpR	22
13	Royal Liverpool University Hospital, Liverpool	Sylviane Defres, Consultant	22
14	Arrowe Park Hospital, Wirral	David Harvey, Consultant	21
15	Arrowe Park Hospital, Wirral	David Harvey, Consultant	21
16	Arrowe Park Hospital, Wirral	Elshadai Ejere, FY2	21
17	Queen's hospital, Romford	Aarti Shah, Consultant	21
18	Queen's hospital, Romford	Yiwen Soo, FY1	21
19	Raigmore Hospital, Inverness	Wendy Beadles, Consultant	21
20	Raigmore Hospital, Inverness	Wendy Beadles, Consultant	21
21	Raigmore Hospital, Inverness	Heather Sturgeon, Medical student	21
22	Raigmore Hospital, Inverness	Heather Sturgeon, Medical student	21
23	Raigmore Hospital, Inverness	Brodie Cameron, Medical Student	21
24	James Cook University Hospital, Middlesbrough	Brodie Cameron, Medical Student	21
25	James Cook University Hospital, Middlesbrough	Ben Tomlinson, SpR	20
26	James Cook University Hospital, Middlesbrough	Ben Tomlinson, SpR	20
27	James Cook University Hospital, Middlesbrough	David Chadwick, Consultant	20
28	University Hospital Monklands	David Chadwick, Consultant	20
29	University Hospital Monklands	Claire McGoldrick, Consultant	20
30	University Hospital Monklands	Claire McGoldrick, Consultant	20
31	University Hospital Monklands	Katie McDowell, FY2	20
32	Cumberland infirmary, Carlisle	Katie McDowell, FY2	20
33	Cumberland infirmary, Carlisle	Alastair Miller, Consultant	19
34	Cumberland infirmary, Carlisle	Alastair Miller, Consultant	19
35	Cumberland infirmary, Carlisle	Clive Graham, Consultant	19
36	Cumberland infirmary, Carlisle	Clive Graham, Consultant	19
37	Cumberland infirmary, Carlisle	Mpho Molosiwa, FY2	19
38	Newcastle Upon Tyne NHS Foundation Trust	Mpho Molosiwa, FY2	19
39	Newcastle Upon Tyne NHS Foundation Trust	Ewan Hunter, Consultant	19
40	Newcastle Upon Tyne NHS Foundation Trust	Ewan Hunter, Consultant	19
41	Newcastle Upon Tyne NHS Foundation Trust	Ruth Owen, Medical Student	19
42	Newcastle Upon Tyne NHS Foundation Trust	Ruth Owen, Medical Student	19
43	Newcastle Upon Tyne NHS Foundation Trust	Katherine Flack	19
44	Airedale hospital, Airedale	Katherine Flack	19
45	Airedale hospital, Airedale	Adrian Kennedy, Consultant	18
46	Bradford Royal Infirmary, Bradford	Adrian Kennedy, Consultant	18
47	Bradford Royal Infirmary, Bradford	Amy Robinson, Consultant	16
48	Bradford Royal Infirmary	Amy Robinson, Consultant	16
49	Bradford Royal Infirmary	Phoebe Cross, SpR	16
50	Bradford Royal Infirmary	Phoebe Cross, SpR	16
51	University Hospital Wales	Fay Perry	16
52	University Hospital Wales	Fay Perry	16
53	Aberdeen Royal Infirmary	Vithusha Inpadhas	16
54	Aberdeen Royal Infirmary	Vithusha Inpadhas	16
55	Aberdeen Royal Infirmary	Ali Khan, SpR	15
56	Aberdeen Royal Infirmary	Ali Khan, SpR	15
57	Aberdeen Royal Infirmary	Sarathy Selvam, FY2	15
58	Aberdeen Royal Infirmary	Sarathy Selvam, FY2	15
59	Aberdeen Royal Infirmary	Vhairi Bateman, Consultant	15
60	Aberdeen Royal Infirmary	Vhairi Bateman, Consultant	15
61	Aberdeen Royal Infirmary	Jeremy Wong, Medica Student	15
62	Lancaster Royal Infirmary	Jeremy Wong, Medica Student	15
63	Lancaster Royal Infirmary	Henry Wu, FY2	15
64	Lancaster Royal Infirmary	Henry Wu, FY2	15
65	Lancaster Royal Infirmary	Monika Pasztor, Consultant	15
66	Lancaster Royal Infirmary	Monika Pasztor, Consultant	15
67	Whittington Hospital, London	Trupti Patel, Consultant	14
68	Whittington Hospital, London	Trupti Patel, Consultant	14
69	Whittington Hospital, London	Ajanthiha Karunakaran, Medical Student	14
70	Whittington Hospital, London	Ajanthiha Karunakaran, Medical Student	14
71	Russells Hall Hospital, Dudley	Basma Soliman, CT1	13
72	Russells Hall Hospital, Dudley	Basma Soliman, CT1	13
73	Russells Hall Hospital, Dudley	Hassan Paraiso, Consultant	13
74	Russells Hall Hospital, Dudley	Hassan Paraiso, Consultant	13
75	Glasgow Royal Infirmary	Mairi McLeod, Consultant	13
76	Glasgow Royal Infirmary	Mairi McLeod, Consultant	13
77	Glasgow Royal Infirmary	Su su Htwe, SpR	13
78	Glasgow Royal Infirmary	Su su Htwe, SpR	13
79	Glasgow Royal Infirmary	Anna Smith	13
80	Glasgow Royal Infirmary	Anna Smith	13
81	James Paget University Hospitals NHS Foundation Trust	Andrew Blanshard, CMT	12
82	James Paget University Hospitals NHS Foundation Trust	Andrew Blanshard, CMT	12
83	James Paget University Hospitals NHS Foundation Trust	Harish Reddy, Consultant	12
84	James Paget University Hospitals NHS Foundation Trust	Harish Reddy, Consultant	12

1			
2			
3	Portsmouth Hospitals University NHS Trust	Avneet Shahi, SpR	12
4	Portsmouth Hospitals University NHS Trust	Helen Chesterfield, Consultant	12
5	Portsmouth Hospitals University NHS Trust	Oliver Bannister, CMT	12
6	Withybush hospital, Haverford West	Ben Schroeder, Medical Student	12
7	Withybush hospital, Haverford West	Ken Woodhouse, Consultant	12
8	Ashford and St Peter's NHS Foundation Trust	Jan Coebergh, Consultant	11
9	Ashford and St Peter's NHS Foundation Trust	Viva Levee, FY2	11
10	Mater Misericordiae University Hospital, Dublin	Eavan Muldoon, Consultant	11
11	Mater Misericordiae University Hospital, Dublin	Rhea O'regan, SPR	11
12	Mater Misericordiae University Hospital, Dublin	Tee Keat Teoh, SpR	11
13	Newham Hospital, Barts Health NHS Trust	Sathyavani Subbarao, SpR	11
14	Newham Hospital, Barts Health NHS Trust	Simon Tiberi, Consultant	11
15	Newham Hospital, Barts Health NHS Trust	Caryn Rosmarin	11
16	London UCL and Hospital for Tropical diseases at University College London Hospitals NHS Foundation Trust.	Jayne Ellis, SpR	10
17	London UCL and Hospital for Tropical diseases at University College London Hospitals NHS Foundation Trust.	Lucy Bell, CMT	10
18	London UCL and Hospital for Tropical diseases at University College London Hospitals NHS Foundation Trust.	Robert Heyderman, Consultant	10
19	Barts Health NHS Trust	Jonathan Lambourne, Consultant	10
20	Barts Health NHS Trust	Emma McGuire, SpR	10
21	Barts Health NHS Trust	Robert Serafino, Consultant	10
22	Guy's and St Thomas' NHS Foundation Trust	Anna Goodman, Consultant	9
23	Guy's and St Thomas' NHS Foundation Trust	Ishaan Bhide, FY1	
24	Guy's and St Thomas' NHS Foundation Trust	Karanjeet Sagoo, Medical Student	
25	Whipps Cross, Barte Health NHS Trust	Mark Melzer, Consultant	8
26	Whipps Cross, Barte Health NHS Trust	Maria Krutikov, SpR	8
27	The Royal Free Hospital, London	Indran Balakrishnan, Consultant	6
28	The Royal Free Hospital, London	Susan Hopkins, Consultant	6
29	The Royal Free Hospital, London	Tim Jones, SpR	6
30	Trafford General Hospital, Manchester University NHS Foundation Trust	Kajal Patel, Medical Student	4
31	Trafford General Hospital, Manchester University NHS Foundation Trust	Barzo Faris, Consultant	
32	William Harvey Hospital, East Kent	Graeme Calver, Consultant	3
33	William Harvey Hospital, East Kent	Ricky Singh, Medical Student	3
34	William Harvey Hospital, East Kent	Hazel Sanghvi, Medical Student	3
35	Tameside General Hospital	Mohamed Eltayeb, Clinical Fellow	2
36	Tameside General Hospital	Rathur Haris, Consultant	2
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Location in paper
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title, page 1, line 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, page 2, line 40 onwards
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, page 4 line 80 onwards
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 5, line 104
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, page 5, line 108 onwards
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, page 5, line 108 onwards
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, page 6, box 1
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6, box 1 and line 125 onwards
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5, line 110 onwards
Bias	9	Describe any efforts to address potential sources of bias	Methods, page 5, line 117 onwards
			Discussion, page 17, line 294 onwards
Study size	10	Explain how the study size was arrived at	Methods, page 5, line 110 onwards
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, page 7, line 141 onwards
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods, page 7, line 141 onwards
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	Methods, page 6, line 130
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA

Results

1	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, page 7, line 156	
2			(b) Give reasons for non-participation at each stage	NA	
3			(c) Consider use of a flow diagram	NA	
4	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 9, Table 1	
5			(b) Indicate number of participants with missing data for each variable of interest	Page 10, Table 2	
6			(c) Summarise follow-up time (eg, average and total amount)	NA	
7	Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 9 Table 1, page 10, table 2 and page 15, table 3	
8	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, page 14, line 230 onwards	
9			(b) Report category boundaries when continuous variables were categorized	NA	
10			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	
11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA	
12	Discussion				
13	Key results	18	Summarise key results with reference to study objectives	Discussion, page 16 line 249 onwards	
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, page 17, line 294 onwards	
15	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 18, line 313 onwards	
16	Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, page 17 line 296-8	
17	Other information				
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22, Line 439	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only