

1 Viral meningitis in UK adults – a multicentre prospective observational cohort 2 study of incidence, aetiology and sequelae

3 4 **Research in context**

5 **Evidence before the study**

6 In recent years viral meningitis has been recognised increasingly, and can be a significant cause
7 of morbidity. Since the widespread introduction of conjugate vaccines against *Haemophilus*
8 *influenzae* type B in 1992, *Neisseria meningitidis* serogroup C in 1999 and *Streptococcus*
9 *pneumoniae* in 2002, the incidence of community acquired bacterial meningitis has been
10 declining. This, in combination with increased molecular testing, means viruses are growing in
11 relative importance as a cause of meningitis. Recent studies, using historical data, have also
12 suggested changes in the aetiology of childhood viral meningitis over several decades.

13 Variation in the incidence and aetiology of viral meningitis is reported. Some countries have a
14 high incidence of herpesviruses, mainly herpes simplex type 2 and varicella zoster virus, whilst
15 others rarely see them. We searched PubMed for “viral” AND “meningitis” AND “adults” with
16 no date or language restrictions. 307 publications were returned, 22 were cohort studies
17 looking at the aetiology of meningitis. Several papers describe the varying aetiology of
18 meningitis but only 1 attempted to determine the incidence – in a cohort of Israeli soldiers.
19 There has been a recent attempt to report the national incidence of viral meningitis in the UK,
20 but this study only included laboratory confirmed cases, and did not distinguish between
21 meningitis and encephalitis - where the aetiologies, treatment and prognoses are vastly
22 different. No UK study has examined the incidence and aetiology of viral meningitis in adults.
23 The outcomes following viral meningitis are also unclear, although subtle sequelae such as
24 neurocognitive and sleep disorders have been described.

25 **Added value of this study**

26 This study takes a unique approach that combines the benefits of a prospective clinical
27 epidemiological study with laboratory confirmed cases to estimate the incidence, aetiology
28 and sequelae of viral meningitis in UK adults. It is the largest clinical study of adults with viral
29 meningitis reported to date and gives us the first accurate incidence of viral meningitis, other
30 causes and those with no known cause. It also describes the significant longer-term impact
31 that viral meningitis has on quality of life, especially in regard to memory and mental health.

32 **Implications of all the available evidence**

33 Our findings demonstrate that viruses are the predominant cause of adult meningitis in the UK
34 with enteroviruses and herpesviruses responsible for the majority of cases where a cause is
35 found. Combined with previous studies this shows that there is significant geographical
36 variation in the aetiology of viral meningitis. We highlight the burden that viral meningitis
37 imposes on the health system and suggest areas where improvements could be made; a
38 reduction in the length of hospitalisation and an increase in those with an aetiological diagnosis
39 might be achieved through more rapid diagnostics. Additionally, we add to the literature
40 suggesting that viral meningitis has significant impact long after the patient has been
41 discharged.

42 **Viral meningitis in UK adults – a multicentre prospective observational cohort**
43 **study of incidence, aetiology and sequelae**

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65 ABSTRACT

66 **Background**

67 Viral meningitis is being recognised increasingly but little is known about the frequency with
68 which it occurs, or the causes and outcomes in the UK. We, therefore, aimed to determine the
69 incidence, aetiology and sequelae in UK adults. Understanding this will improve the
70 management of patients and assist in health service planning.

71 **Methods**

72 A multicentre prospective cohort study of adults with suspected meningitis was undertaken
73 between 2011 and 2014 in England. Nested within this, in the NHS Northwest region, was an
74 epidemiological study. We calculated the incidence of viral meningitis using Northwest patient
75 data and generalised to estimate UK data. Patients self-reported outcomes for one year after
76 admission.

77 **Findings**

78 1126 patients were enrolled. 638/1126 (57%) had meningitis: 231/1126 (36%) viral, 99/1126
79 (16%) bacterial and 267/1126 (42%) unknown aetiology. 41/1126 (6%) had other causes. The
80 estimated annual incidence of viral and bacterial meningitis was 2.73 and 1.24 per 100,000
81 respectively. The median (IQR) length of stay for patients with viral meningitis was 4 (3,7)
82 days, increasing to 9 (6,12) days in those treated with antivirals. Earlier lumbar puncture
83 resulted in more patients having a specific cause identified. Patients with viral meningitis
84 suffered a significantly decreased quality of life in the first year after illness.

85 **Interpretation**

86 Viruses are the most commonly identified cause of meningitis in UK adults, and led to
87 substantial long-term morbidity. Delays in performing LP and unnecessary antivirals were
88 associated with longer hospitalisations. Rapid diagnostics and rationalising treatments may
89 reduce the burden of meningitis on health services.

90 **Funding:** Meningitis Research Foundation; National Institute for Health Research

91 **Introduction**

92 As the incidence of bacterial meningitis decreases, the proportion of meningitis cases caused
93 by viruses is increasing.¹ The use of molecular diagnostics has also led to a greater recognition
94 of neurological viral infections.² A seven-fold rise in reports of viral meningitis and
95 encephalitis was seen in England and Wales between 2004 and 2013.² Enteroviruses and
96 herpesviruses are commonly reported causes of viral meningitis in adults, but their relative
97 incidence varies in different countries. Finland reports a high incidence of herpesvirus
98 meningitis, whereas Spain has a predominance of enteroviruses.^{3,4}

99 Identifying the cause of meningitis is important to improve clinical care, including reducing
100 unnecessary antibiotics and antivirals. Patients with suspected viral meningitis are often treated
101 with antibiotics whilst a diagnosis of bacterial meningitis is excluded. This results in patients
102 receiving needless antibiotics and may extend their hospital stay.⁵ Although aciclovir, which
103 has good *in-vitro* activity against many herpesviruses, is effective in encephalitis causes by
104 herpes simplex virus (HSV) and varicella zoster virus (VZV), its role in acute meningitis
105 caused by these viruses has never been determined.⁶ Aciclovir has no activity against
106 enteroviruses. Viral meningitis is traditionally considered a benign, self-limiting illness,⁷ but
107 there are increasing reports suggesting this may not be the case.⁸⁻¹⁰

108 Recent trends in bacterial, fungal, and mycobacterial meningitis in the UK have been
109 published,¹¹ but the clinical burden of viral meningitis remains unknown. We, therefore,
110 performed a national prospective observational study of adults admitted with suspected
111 meningitis to determine the incidence, aetiology and sequelae.

112 **Methods**

113 Patients were recruited from 42 hospitals, throughout England, between September 2011 and
114 September 2014, including all 24 acute hospitals in the Northwest administrative region of
115 England. Patients were eligible if they were aged ≥ 16 , had clinically suspected meningitis, and

116 either underwent a lumbar puncture (LP) or, if LP was contraindicated, had clinically suspected
117 meningitis and a significant pathogen identified in either blood culture or on blood polymerase
118 chain reaction (PCR). Those with ventricular devices were excluded. Case definitions are in
119 table 1.

120 Written informed consent was obtained. Clinical data were recorded on a secure online
121 database (OpenClinica™). Ethical approval was given by the North Wales multicentre research
122 ethics committee (reference 11/WA/0218). Research governance approval was given at each
123 hospital. The study protocol can be accessed at www.braininfectionsuk.org/ukmeningitis.

124 Estimation of meningitis incidence

125 Incidence rates were estimated by dividing the number of patients recruited in the Northwest
126 sites, in one year, by the total adult population of the same region. To estimate how many cases
127 of meningitis had been missed in the prospective study, a retrospective review of laboratory
128 records, spanning the first year of recruitment for each hospital, was performed in four hospitals
129 within the Northwest (representing the variation in recruitment rates throughout the whole
130 study). Cerebrospinal fluid (CSF) samples with a leukocyte count of $>4 \times 10^6$ cells/L were
131 identified from laboratory records and classified according to pathogen identified (or unknown
132 if none found). A proportional inflation, based on the total number of cases (those recruited
133 and those missed) divided by the actual number recruited into the Northwest sites in the
134 prospective study, was applied to the initial estimated Northwest incidence data. This was used
135 to estimate the population-standardised number of cases in the UK. Population data were
136 sourced from the Office for National Statistics.¹²

137 Outcomes

138 Clinical outcomes recorded included inpatient mortality and critical care use. Patient reported
139 outcome measures assessed quality of life, neuropsychological functioning and symptom
140 resolution. Quality of life was measured using EQ-5D-3L¹³ and SF-36¹⁴, both internationally
141 validated tools. Other outcome measures used were the Aldenkamp and Baker
142 neuropsychological assessment scale (ABNAS)¹⁵ and the Total Morbidity Score¹⁶ – both of
143 which were developed for neurological disorders, namely epilepsy and meningitis
144 (questionnaires in supplementary material). EQ-5D-3L, SF-36 and ABNAS were assessed at
145 6, 12, 24 and 48 weeks after admission. The Total Morbidity Score recorded resolution of
146 symptoms for 3 weeks after admission.¹⁷ Quality adjusted life years (QALYs) were calculated
147 from the EQ-5D-3L. There are no population level data for ABNAS, therefore questionnaires
148 were sent to family/friends of the patient to act as a control group.

149 Statistical Analysis

150 T-tests were used for normally distributed continuous data. Appropriate transformations were
151 applied in the case of non-normally distributed continuous data. If the transformed data were
152 still not normally distributed Mann Whitney U or Kruskal-Wallis tests were used. Categorical
153 data were analysed using Chi Square or Fisher's Exact test. 95% confidence intervals (CI) were
154 calculated using Byar's method.¹⁸ To obtain 95% CI for the UK incidence a proportional
155 inflation was applied to the Northwest data based on the retrospective data collection. Logistic
156 regression was used to assess relationship between time to LP and getting a microbiologically
157 proven diagnosis. The SF-6D, a single unit preference based measure, was obtained from the
158 SF-36 and non-parametric Bayesian analysis was used with permission from the University of
159 Sheffield, UK.^{19,20} A Bonferroni correction was applied to the ABNAS domains and a p-value
160 of <0.008 was considered statistically significant; last observation carried forward was used

161 for missing data. Variables associated with symptom resolution were determined in univariate
162 analyses using log-rank tests. Data were analysed using SPSS v21.

163 **Microbiological testing**

164 All CSF samples had microscopy and culture performed. CSF PCR was performed in the
165 admitting hospitals, regional diagnostic centres, or University of Liverpool, for HSV-1 and 2,
166 VZV and enteroviruses, along with PCR for *Streptococcus pneumoniae* and *Neisseria*
167 *meningitidis*, following national recommendations.²¹

168 **Role of the funding source**

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

172 **Results**

173 1126 patients were enrolled, from throughout England, with 1113 included in the analysis
174 (figure 1). 638/1126 (57%) fitted the meningitis case definition. The cause was proven viral in
175 231/638 (36%), and bacterial in 99/638 (16%). The aetiology of all cases of meningitis are
176 given in table 2. Enteroviruses were the most frequent viruses (n=127), accounting for 55% of
177 all viral meningitis, and the single most common aetiology, accounting for 20% of all
178 meningitis (127/638). 101/231 cases (44%) were caused by herpesviruses [HSV type 2 (n=52),
179 VZV (n=43), HSV type 1 (n=3), Epstein-Barr virus (n=2) and cytomegalovirus (n=1)].
180 *Streptococcus pneumoniae* was the most common bacterial cause, responsible for 53/99
181 bacterial cases (54%), but only 8% of all meningitis. There were 29 cases of meningococcal
182 meningitis (48% serogroup B, 21% Y, 3% W and 28% unknown serogroup). There were four
183 patients with cryptococcal meningitis (all HIV positive), and 11 with tuberculous meningitis.

184 A total of 267/638 (42%) patients with meningitis had no cause identified, of these, 200/267
185 (75%) had a lymphocytic CSF (>50% lymphocytes) – classified as ‘*lymphocytic meningitis –*
186 *unknown aetiology*’, and 41/267 (15%) had neutrophil predominance (\geq 50% neutrophils) –
187 classified as ‘*neutrophilic meningitis – unknown aetiology*’. The predominant leukocyte type
188 was unknown in 26/267 patients with no identified cause (10%). Clinical features are shown in
189 table 3.

190 Using both the prospective and retrospective data, from the Northwest sites, the incidence of
191 viral meningitis and bacterial meningitis in UK adults was estimated to be 2.73 and 1.24 per
192 100,000 per year, respectively (table 4). When all cases were considered, including those with
193 no identified aetiology, the annual incidence of all meningitis in UK adults was 13.47 per
194 100,000.

195 Nine-hundred-and-one (81%) of 1113 patients had neurological imaging, with the majority
196 [776/1113 (70%)] before LP. Only 90/776 (12%) had an indication for imaging prior to LP, as
197 recommended in national guidelines (box).²² The most common indications were, Glasgow
198 coma scale \leq 12 in 54/776 (7%) and seizures in 36/776 (5%); five patients had papilloedema
199 and eight had focal neurological findings. The median (IQR) time from admission to
200 antibiotics, and to LP, were 2 [0,10 (n=237)] and 8 [3,22 (n=299)] hours respectively, in those
201 who did not have imaging prior to LP, compared with 3 [1,11 (n=563)] and 18 [9,30 (n=776)]
202 hours in those who did (p=0.004 and <0.0001 respectively). The median (IQR) time from
203 admission to LP was longer in the *lymphocytic meningitis – unknown aetiology* group [21
204 (9,37.5) hours] than those with proven viral meningitis [13 (7,23) hours], proven bacterial
205 meningitis [13 (4.5,23) hours] and *neutrophilic meningitis- unknown aetiology* [15 (7,22.5)
206 hours; p=<0.0001, <0.0001 and 0.008 respectively]. The median (IQR) time to LP for all
207 patients was 17 (8,29) hours. The chances of having a pathogen detected in viral meningitis
208 was reduced by 1% for every hour delay in LP after admission [OR 0.988 (95% CI 0.982-

209 10.995), $p=0.001$] (figure 2). For bacterial meningitis there was also a reduction of 1% for each
210 hour delay, but this was not statistically significant [OR 0.995 (95% CI 0.989-1.002), $p=0.16$].
211 24/99 (25%) patients with bacterial meningitis were diagnosed by molecular methods alone.
212 The role of different tests in diagnosing bacterial meningitis is shown in figure S1.

213 One-hundred-and-thirty-nine (60%) of 231 patients with viral meningitis had at least one dose
214 of an antiviral (aciclovir and/or valaciclovir) and 51/139 (37%) received a course, defined as \geq
215 five days. 42/98 (43%) of those with HSV or VZV meningitis received a course of antivirals
216 with a median (range) duration of ten (5-30) days. The treatment regime varied considerably
217 (figure S2). Patients in whom enterovirus meningitis was diagnosed were less likely to receive
218 antiviral drugs, where they would have no effect, than those where no aetiology was identified
219 [8/127 (6%) versus 50/248 (20%) ($p<0.0001$)]. Most patients [160/231 (69%)] with proven
220 viral meningitis also received at least one dose of antibiotics (median duration, one day) and
221 199/267 (75%) of those without an aetiological cause received at least a single dose. 328/454
222 (72%) patients who did not have meningitis received empirical antibiotics.

223 The median (IQR) length of stay for patients with viral meningitis was 4 (3,7) days. Patients
224 with herpesvirus meningitis stayed in hospital longer than patients with enteroviral meningitis
225 [6 (3.75,10) days vs, 3.5 (3,5) days, $p<0.0001$] and those with VZV meningitis stayed longer
226 than those with HSV [8 (5,11) days vs 5 (3,8) days, $p=0.02$]. Those who received antivirals
227 were in hospital longer than those who did not [8 (5,11) days vs. 3 (2,5) days, $p<0.0001$].
228 Those with *lymphocytic meningitis – unknown aetiology* stayed in hospital slightly longer than
229 those with proven viral meningitis [5 (3,8.5) days versus 4 (3,7), $p=0.09$]. Seven patients died
230 before discharge, five of whom had meningitis - three pneumococcal, one tuberculous and one
231 malignant meningitis. 91 patients required admission to intensive care; 52/91 (57%) had
232 bacterial meningitis, with 37/52 (71%) having pneumococcal disease. No patients with viral
233 meningitis died or required admission to intensive care.

234 Quality of life was reduced in all aetiological groups, at all times points, when compared with
235 the UK population (figure 3). EQ-5D-3L utility scores were similar for both viral and bacterial
236 meningitis. They were significantly lower for HSV meningitis, compared with the other viral
237 aetiologies, at 6 weeks after discharge ($p=0.004$). 12/14 (86%) patients with HSV meningitis
238 who returned the questionnaires, had problems with anxiety or depression at six weeks (figure
239 S3). Supporting, and confirming, the EQ-5D-3L data, all groups had worse SF-6D scores than
240 UK norms (Figures S4 and S5). The average QALY for patients with viral meningitis, over the
241 first year, was 0.72. Compared with the age matched UK population, patients with viral
242 meningitis suffered a loss of 0.2 QALYs in that first year (figure S6). There was no significant
243 difference in time to resolution of headache between viral meningitis and bacterial, as measured
244 by the Total Morbidity Score (7 versus 8 days, $p= 0.09$) (table S1). Patients with viral
245 meningitis had significantly worse ABNAS scores than healthy controls at all four time points
246 in the year after illness (figure S7 and table S2).

247 Discussion

248 This study provides the first estimate of the incidence of viral meningitis in UK adults. Using
249 clinical and laboratory data we estimate the annual incidence of confirmed viral meningitis in
250 UK adults to be almost 3 per 100,000. Previous UK studies of meningitis have been based on
251 coding data or laboratory reports, missing those that have no aetiological diagnosis.^{1,2,11} We
252 have estimated the incidence of all meningitis to be 13.47 per 100,000. Previously, a similar
253 estimate of the incidence of meningitis in the US was estimated to be 27.9 per 100,000.²³ This
254 was in the late 20th century and included adults and children. It is likely to be substantially
255 lower now, given the impact of immunisation.²⁴

256 Enteroviruses were the most common aetiology, accounting for just over 50% of all confirmed
257 viral meningitis. Herpesviruses accounted for just under 50%, significantly more than in

258 previous studies from other countries.⁴ This may, in part, be explained by different rates of
259 HSV-2 seroprevalence – known to be higher in northern Europe than southern.²⁵

260 In line with other studies a significant proportion of our patients had no cause identified.^{3,4} This
261 poses a challenge on how to categorise them. There have been several attempts at diagnostic
262 algorithms each of which has its limitations, and none of which has become routine clinical
263 practice.²⁶ We chose a pragmatic and objective classification, used on the wards daily, based
264 on predominant CSF leukocyte type. We recognise this does not equate to presumed viral or
265 bacterial meningitis, and indeed, 18% of patients with bacterial meningitis had a lymphocytic
266 CSF and 7% of viral meningitis (mostly enteroviral) had a neutrophil predominance.
267 Nevertheless, it is a helpful way of providing an initial patient classification. The patients with
268 *lymphocytic meningitis – unknown aetiology* had a significantly longer time from admission to
269 LP, suggesting that an early LP may increase the number of patients having an aetiology
270 identified. It may be, as is known in enterovirus meningitis, that there is a change in the immune
271 response from neutrophils early on, to lymphocytes later.

272 Diagnosing a specific virus is known to reduce inappropriate antibiotic usage, length of hospital
273 stay, and hospitalisation costs.^{5,7} We have also shown it reduces the unnecessary use of
274 antivirals. 21% of patients with *lymphocytic meningitis – unknown aetiology* received a course
275 of aciclovir or valaciclovir compared with 6% of patients diagnosed with enteroviral
276 meningitis, where aciclovir would have no effect. With no evidence base to support aciclovir
277 treatment in HSV or VZV meningitis, as has been highlighted previously, there was much
278 variation in practice.⁶ Almost half of these patients received antivirals, resulting in longer
279 hospital admissions. Most patients who had antivirals had intravenous treatment, necessitating
280 inpatient care. A trial of aciclovir, or valaciclovir, in acute herpesvirus meningitis would help
281 determine best practice. Improving diagnostic testing so more patients can have a specific
282 aetiology determined quickly could reduce unnecessary antimicrobials and therefore, reduce

283 hospital stays and other investigations⁷. Full diagnostic accuracy and cost-effectiveness studies
284 should be performed before any new tests are introduced.

285 Once viral meningitis is diagnosed efforts should focus on symptomatic treatment and
286 expediting discharge. Theoretically this can happen quickly; a LP and the diagnostic PCR can
287 be done within a few hours. However, in our study the median time from admission to LP was
288 17 hours, and the median length of hospitalisation, four days. The prolonged time from
289 admission to LP is concerning. International guidelines all stress the urgency of the diagnostic
290 LP;^{26,27,28} delays decrease pathogen yield and can increase mortality.²⁹⁻³¹ The length of time it
291 took to get an LP may explain why a large proportion of patients had no aetiological cause
292 identified in our study, especially those with viral meningitis where there was a highly
293 significant association between time to LP and likelihood of getting a definitive diagnosis.
294 Unnecessary neuroimaging may have contributed to the delays. This has been highlighted
295 previously as a risk factor for increased mortality in bacterial meningitis.^{31,32} In the UK the
296 requirement for all patients to be transferred out of the emergency department within four hours
297 creates an unintended pressure causing key investigations such as LP, to be deferred until
298 patients have been admitted to a ward. Additional delays in diagnosis occur if the CSF is sent
299 to an offsite laboratory for analysis. Because of sample batching and transport it may take
300 several days from LP to result, despite the actual rapidity of the test. If PCR is performed
301 locally, seven days a week on receipt of a single CSF sample, the length of hospitalisation can
302 be reduced to less than a day, resulting in significant cost savings.⁷ In order to make this saving
303 relatively simple changes are required, such as doing LPs in the emergency department, and
304 having diagnostics available on-site .

305 Despite viral meningitis often being referred to as benign and self-limiting,⁷ we found long
306 term neuropsychiatric sequelae, particularly anxiety, depression and neurocognitive
307 dysfunction. Whilst patients with bacterial meningitis have more severe disease initially in

308 terms of critical care need and mortality, over the longer term all patients with meningitis, viral
309 and bacterial, had sequelae affecting quality of life including significant problems with memory
310 and mental health.

311 There are limitations to our study. Due to its prospective nature, we risked not recruiting all
312 eligible patients. We accounted for this by identifying cases retrospectively in the laboratories
313 and then applying an uplift. We extrapolated the incidence from the Northwest to the whole
314 country, which assumes there is minimal variation in incidence throughout the UK. We found
315 the incidence of pneumococcal, meningococcal and all viral meningitis was similar to other
316 UK based studies that used only laboratory data.^{2,11} Relying on CSF analysis excluded patients
317 who did not have a LP but allowed us to accurately define our cohort. Our definitions may have
318 missed some cases of viral meningitis with a CSF cell count of less than 5×10^6 cells/L or those
319 who did not have a LP. It is known that children, especially neonates, can have clinical features
320 of meningitis, with viruses detected in the CSF, without a CSF pleocytosis.³³ This is less well
321 recognised in adults. 58% of our patients who had a LP had meningitis, which is higher than
322 other studies,³⁴ and may indicate a higher threshold for LP in the UK. Given that we looked
323 only for the most common viruses we cannot exclude the possibility that other rare, novel or
324 emerging viruses might have been responsible for some cases. However, previous attempts
325 using novel techniques have failed to identify significantly more pathogens than routine
326 approaches.³⁵

327 In summary, this study shows that viruses are the major cause of meningitis in UK adults, and
328 impose a significant clinical burden – both acutely and longer term. To improve management
329 and reduce costs there is a pressing need for better diagnostic practices including rapid tests
330 and the delivery of high quality viral diagnostics locally. Treatments also need to be developed
331 and evaluated that may allow quicker recovery, and fewer longer term sequelae.

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361 Author contributions

362 TS, AJ, NJB, IH and DM devised the idea for the study.
363 FM wrote the protocol, submitted the ethics and Research and Development applications, co-
364 ordinated the multiple sites in the study, checked the data, analysed the data and wrote the
365 paper. FM was the recipient of an NIHR fellowship which funded part of the study.
366 FM, MJG, NJB, IH, DM, BDM, PS, AMG, KM, AM (Miller) and TS formed the steering
367 committee for the study. AM (Miller) was the chair of the steering committee. LB provided
368 statistical advice.
369 PS was a patient representative on the steering committee and gave advice regarding patient
370 recruitment and input to protocol and all patient facing material.
371 AM(Martin), KE, WW and AH provided help with quality of life analyses.
372 GA and AG analysed the neuropsychology data.
373 All authors contributed to, reviewed and approved the final draft of the paper.
374

375 Funding

376 This work was supported by the National Institute for Health Research (NIHR) Fellowship to
377 F.M [DRF-2013-06-168] and the Meningitis Research Foundation [0904.0]. TS was supported by a
378 UK Medical Research Council Senior Clinical Fellowship, an NIHR Programme Grant for Applied
379 Research (number RP-PG-0108-10,048), and the NIHR Health Protection Research Unit in Emerging
380 and Zoonotic Infections.

381

382 **Acknowledgements**

383

384 We acknowledge the initial help of Dr Bharam Ebrahimi who was a co-applicant on the
385 original grant application to the Meningitis Research Foundation.

386

387 **Conflict of Interest Statement**

388

389 FM was an NIHR Doctoral Research Fellow. BDM is an NIHR Academic Clinical Lecturer.
390 LB is an NIHR post-doctoral fellow. TS received support from the MRC and is an NIHR
391 senior investigator. This report is independent research arising from a doctoral research
392 fellowship supported by the National Institute for Health Research. FM, MJG, BDM, NJB
393 and TS are affiliated to the National Institute for Health Research Health Protection Research
394 Unit (NIHR HPRU) in Emerging and Zoonotic Infections at University of Liverpool in
395 partnership with Public Health England (PHE), in collaboration with Liverpool School of
396 Tropical Medicine. TS is also supported by the European Union's Horizon 2020 research and
397 innovation program under grant agreement No. 734584. FM, MJG, BDM and TS are based at
398 University of Liverpool and NJB is based at Liverpool School of Tropical Medicine. AM
399 (Martin) was supported by the NIHR collaboration for leadership in Applied Health Research
400 and Care North West. The views expressed are those of the author(s) and not necessarily
401 those of the NHS, the NIHR, the Department of Health or Public Health England. MJG and
402 TS have received support from FastTrack Diagnostics on projects unrelated to this. AMG
403 reports personal fees from Roche Pharma Research & Early Discovery, outside the submitted work.

404

Table 1. Case Definitions

Meningitis	Patient with symptoms consistent with meningitis and a cerebrospinal fluid leukocyte count $>4 \times 10^6$ cells/L ^{*/**}
Viral meningitis	Meningitis AND Positive CSF PCR for a viral pathogen OR Detection of an appropriate pathogen by either throat swab, rectal swab or serology [^]
Bacterial meningitis	Meningitis ^{**} AND Detection of an appropriate pathogen from <i>either</i> blood or CSF by PCR, culture or gram stain. OR Patient with symptoms consistent with meningitis (who did not have an LP) AND Detection of an appropriate pathogen from blood by PCR, culture or gram stain
Lymphocytic meningitis – unknown aetiology	Meningitis AND CSF lymphocytes $> 50\%$ of total leucocyte count AND No cause identified
Neutrophilic meningitis – unknown aetiology	Meningitis AND CSF lymphocytes $\leq 50\%$ of total leucocyte count AND No cause identified
Undifferentiated meningitis	Meningitis AND No CSF leucocyte differential was performed, and no cause identified
Encephalitis (adapted from reference ³⁶)	Altered consciousness for >24 hours (including lethargy, irritability or a change in personality) with no other cause found With 2 or more of the following Fever or history of fever (≥ 38 degrees Celsius) during the current illness; Seizures and/or focal neurological signs (with evidence of brain parenchyma involvement); CSF pleocytosis ($>4 \times 10^6$ cells/L); EEG suggesting encephalitis; Neuroimaging suggestive of encephalitis (CT or MRI)
Tuberculous meningitis	Identification of <i>Mycobacterium tuberculosis</i> in the CSF or treated as tuberculous meningitis for ≥ 2 months
Fungal meningitis	Identification of fungus in the CSF with clinically suspected meningitis
Meningitis – other cause	Meningitis with a cause other than meningeal infection identified

*corrected for CSF red cell count by 1:700

** patients with bacterial and fungal meningitis who had symptoms consistent with meningitis and a pathogen identified in their CSF were classified as having meningitis even if there was no CSF pleocytosis

CSF – cerebrospinal fluid; PCR – polymerase chain reaction; EEG – electroencephalogram; CT – computed tomography; MRI – magnetic resonance imaging

[^] Cytomegalovirus, Epstein Barr virus and HIV serology

Table 2. Aetiology of meningitis in UK adults	N	%
Viral		
Enteroviruses	127	19.9
Herpes Simplex Virus type 2	52	8.2
Varicella Zoster Virus	43	6.7
Herpes Simplex Virus type 1	3	0.5
Epstein Barr Virus	2	0.3
Cytomegalovirus	1	0.2
Measles	1	0.2
Mumps	2	0.3
Total	231	36.2
Bacterial		
<i>Streptococcus pneumoniae</i>	53	8.3
<i>Neisseria meningitidis</i>	29	4.5
<i>Haemophilus influenzae</i>	5	0.8
<i>Listeria monocytogenes</i>	3	0.5
<i>Streptococcus pyogenes</i>	1	0.2
<i>Streptococcus agalactiae</i>	1	0.2
<i>Streptococcus oralis</i>	1	0.2
<i>Mycoplasma pneumoniae</i>	1	0.2
<i>Fusobacterium sp</i>	1	0.2
<i>Escherichia coli</i>	1	0.2
<i>Pseudomonas sp. And Klebsiella sp</i>	1	0.2
Positive 16S PCR with no product identified	2	0.3
Total	99	15.5
Mycobacterial		
<i>Mycobacterium tuberculosis</i>	11	1.7
Fungal		
<i>Cryptococcus neoformans</i>	4	0.6
Infectious causes originating outside the CNS		
Neurosyphilis	2	0.3
Endocarditis with cerebral emboli/epidural collection	2	0.3
Infected spinal stimulator	1	0.2
Subdural empyema	1	0.2
Total	6	1
Non-infectious causes of CSF pleocytosis		
Cerebral haemorrhage	3	0.5
Cerebral infarct	2	0.3
Idiopathic intracranial hypertension	2	0.3
Malignancy	2	0.3
Post-surgical	2	0.3
Cluster headache	1	0.2
Epidural haematoma	1	0.2
Lymphocytosis hypophysitis	1	0.2
Migraine	1	0.2
Miller Fisher Syndrome	1	0.2
Multiple Sclerosis	1	0.2
Neurosarcoidosis	1	0.2
Seronegative uveomeningeal syndrome	1	0.2
Sjogren's syndrome	1	0.2
Total	20	3
Unknown cause	267	41.8
Grand Total	638	100

Table 3. Clinical features of study population by aetiology

					Bacterial meningitis				Viral meningitis				Unknown aetiology			
	All patients (n=1117)	Not meningitis (n=454)	All meningitis (n=637)	P value*	All bacterial meningitis (n=99)	Pneumococcal meningitis (n=53)	Meningococcal meningitis (n=28)	P value **	All viral meningitis (n=231)	Enteroviral meningitis (n=127)	HSV meningitis (n=55)	VZV meningitis (n=43)	P value#	P value##	Purulent meningitis (n=41)	Lymphocytic meningitis (n=199)
Age	34 (25,49)	36 (25,48)	34 (25,49)	0.788	56 (34,65)	60 (42.5,65.5)	44 (19.5,57)	0.002	32 (24,42)	30 (24,36)	34 (26,50)	37 (25,53)	0.004	<0.001	33 (23,48.5)	33 (27,45.5)
Percentage female	704/1117 (63)	302/454 (66)	388/637 (61)	0.065	49/99 (49.5)	29/53 (55)	11/28 (39)	0.15	152/231 (66)	79/127 (62)	45/55 (82)	24/43 (56)	0.01	0.006	24/41 (58.5)	128/199 (64)
Neck stiffness	603/1079 (56)	238/436 (55)	348/616 (56.5)	0.571	39/92 (42)	19/47 (40)	11/29(38)	0.83	149/229 (65)	80/126 (63.5)	43/54 (80)	22/42 (52)	0.01	<0.001	20/36 (56)	100/179 (56)
Headache	1025/1096 (93.5)	415/446 (93)	587/623 (94)	0.445	82/92 (89)	43/47 (91.5)	26/29 (90)	1	229/231(99)	127/127 (100)	54/54 (100)	42/43 (98)	0.19	<0.001	36/41(88)	190/197 (96)
Photophobia	747/1083 (69)	320/443 (72)	415/613 (68)	0.119	39/91 (43)	18/47 (38)	14/29 (48)	0.39	185/231 (80)	111/127 (87)	42/55 (76)	28/43 (65)	0.004	<0.001	20/35(57)	121/178 (68)
History of rash	139/974 (14)	75/437 (17)	78/607 (13)	0.062	21/93 (23)	5/48 (10)	14/29 (48)	<0.001	29/228 (13)	11/125 (9)	6/54 (11)	11/43 (26)	0.02	0.03	2/33 (6)	14/175 (8)
Confusion	217/1077 (20)	65/436 (15)	145/615 (24)	<0.001	54/95 (57)	36/50 (72)	10/29 (34.5)	0.001	22/227 (10)	10/125(8)	5/53(9)	7/43(16)	0.28	<0.001	12/38 (32)	35/159 (18)
Sore throat	189/1048 (18)	109/427 (25.5)	77/594 (13)	<0.001	12/90 (13)	4/46 (9)	5/28 (18)	0.285	31/221 (14)	22/124(18)	6/50(12)	1/41 (2)	0.04	0.936	8/36 (22)	23/189 (12)
Vomiting	601/1088 (55)	229/441 (52)	359/622 (58)	0.061	62/94 (66)	28/48 (58)	24/29 (83)	0.03	123/229 (54)	66/126 (52)	26/54 (48)	29/43 (67)	0.14	0.051	24/39 (62)	118/196 (60)
Diarrhoea	107/1049 (10)	42/429 (10)	63/596 (11)	0.684	17/92 (18.5)	6/47 (13)	5/29 (17)	0.59	25/220 (11)	13/120 (11)	4/53 (8)	7/42 (17)	0.4	0.093	4/33 (12)	14/190 (7)
Myalgia	363/1029 (35)	173/420 (41)	182/585 (31)	0.001	21/90 (23)	4/46 (9)	12/29 (45)	<0.001	73/221 (33)	38/124 (31)	22/51 (43)	9/40 (23)	0.1	0.127	16/36 (44)	57/179 (32)
Genital Ulcers	8/941 (1)	3/369 (1)	5/550 (1)	0.878	0/88 (0)	0/44 (0)	0/29 (0)	n/a	5/206 (2)	0/112 (0)	5/48 (10)	0/40 (0)	0.001	0.188	0/32 (0)	0/167 (0)
Seizures	46/1069 (4)	25/432 (6)	20/613 (3)	0.048	8/96 (8)	6/51 (12)	1/29 (3)	0.41	0/226 (0)	0/126	0/51	0/43	n/a	<0.001	4/35 (10)	3/189 (2)
Previous history of meningitis	117/1077 (11)	44/437 (10)	72/615 (12)	0.396	11/95 (12)	9/50 (18)	1/29 (3)	0.08	24/226 (11)	7/126 (6)	15/53 (28)	2/41 (5)	<0.001	0.894	2/39 (5)	24/193 (12)
Fever (>38°C)	260/1117 (23)	110/454 (24)	143/618 (23)	0.511	39/99 (39)	26/53 (49)	7/29 (24)	0.03	43/226 (19)	28/127 (22)	8/55 (14.5)	6/43 (14)	0.33	<0.001	8/38 (21)	39/154 (20)
Kernig's positive	104/472 (22)	51/203 (25)	49/259 (19)	0.113	9/25 (36)	4/12 (33)	2/7 (29)	1	27/116 (23)	14/70 (20)	11/31 (35.5)	2/11 (18)	0.269	0.242	1/17 (6)	7/78 (9)
Brudzinski's positive	30/184 (16)	11/72 (15)	18/108 (17)	0.839	4/12 (33)	2/6 (33)	1/3 (33)	1	10/41 (24)	5/26 (19)	5/10 (50)	0/4 (0)	0.123	0.712	0/11 (0)	3/34 (9)
GCS	15 (15,15)	15 (15,15)	15 [15,15]	0.807	14 [10,15]	11 (9,14)	15 (14,15)	<0.001	15 [15,15]	15 (15,15)	15 (15,15)	15 (15,15)	0.25	<0.001	15 (15,15)	15 (15,15)
Blood WCC (x 10⁹/L)	9.4 (7.1,12.9)	9.3 (6.8,12.9)	9.45 (7.4,13)	0.252	16.39 (12.52,21.9)	16.9 (13.7,21.5)	17.8 (11.1,24.4)	0.74	8.8 (7.1,10.6)	8.8 (6.9,10.6)	9.4 (7.9,12)	8.6 (6.4,10.3)	0.07	<0.001	9.6 (7.9,13.9)	8.9 (7.1,11.8)
CRP (mg/L)	49.5 (22,122)	55 (28,120.5)	42.5 (19,123)	0.034	164 (67,261)	169 (69,263)	184 (111,295)	0.34	20 (14.5,37.5)	20 (16,38.5)	11 (10,28)	25.5 (18.5,76)	0.02	<0.001	38 (15,148)	31 (18,82)
CRP <10	41%	163/454 (36)	278/637 (44)		6/99 (6)	10%	0%	0.15	125/231 (54)	35%	83%	90%	<0.001	<0.001	24%	53%
CSF Opening Pressure (cm CSF)	20 (15,25.5)	18 (15,21)	22 (16,28)	1	30 (21,40)	36 (26,40)	30 (18,35)	0.07	21 (16.25,27)	21 (15,26)	22 (20,29)	25 (16,30)	0.34	<0.001	23.5 (21,29.5)	20 (15,25)
CSF leukocyte count (x10⁶/L)	77 (5,306)	n/a	155 (44,450)	<0.001	1800 (377,4850)	2180 (668,4340)	2000 (480,7175)	0.81	188 (67,355)	118 (44,218)	374 (225,718)	249 (106,450)	<0.001	<0.001	133 (29,730)	102 (34,255)
CSF neutrophil percentage	5 (0,37)	n/a	10 (0,47)	<0.001	90 (66,95)	90 (68,96)	90 (79,98)	0.62	5 (0,14.25)	8 (2,22)	1 (0,10)	0 (0,10)	<0.001	<0.001	80 (60,90)	4 (0,10)
CSF protein (g/L)	0.53 (0.32,0.98)	0.32 (0.25,0.45)	0.81 (0.53, 1.38)	<0.001	4 (2,6.68)	5.63 (3.1,8.12)	3.0 (1.17,6.67)	0.03	0.76 (0.54,1.12)	0.57 (0.45,0.75)	1.14 (0.9,1.32)	1.18 (0.89,1.4)	<0.001	<0.001	0.8 (0.5,1.44)	0.68 (0.49,1.0)
CSF glucose (mmol/L)	3.2 (2.8,3.7)	3.5 (3.2,3.9)	3 (2.5,3.5)	<0.001	1.1 (0.3,2.7)	0.5 (0.2,1.7)	1.1 (0.4,2.8)	0.02	3 (2.7,3.4)	3.1 (2.8,3.5)	3.0 (2.7,3.4)	2.85 (2.5,3.23)	0.009	<0.001	3.3 (2.7,3.9)	3.1 (2.8,3.4)
CSF: serum glucose ratio	0.58 (0.46,0.67)	0.63 (0.57,0.7)	0.52 (0.4,0.62)	<0.001	0.12 (0.03,0.41)	0.04 (0.01,0.26)	0.15 (0.05,0.42)	0.02	0.56 (0.49,0.63)	0.58 (0.53,0.64)	0.52 (0.48,0.61)	0.54 (0.45,0.63)	0.104	<0.001	0.57 (0.41,0.66)	0.57 (0.46,0.66)

Values are median [IQR] for continuous data and N/n. evaluable (%) for categorical data.

GCS – Glasgow Coma Scale; WCC – White cell count; CRP – C-reactive protein; CSF – cerebrospinal fluid; HSV – Herpes Simplex Virus; VZV –Varicella zoster virus.

*Significance values comparing all meningitis and not meningitis. #Significance values comparing HSV, VZV and enteroviral. ## Significance values comparing all proven bacterial and all proven viral

Table 4. Estimated incidence of community acquired meningitis in UK adults by aetiology						
Aetiology	Total number of patients recruited in Northwest sites over duration of study	Estimated number of patients in the Northwest in one year~	Estimated annual incidence (95% CI) in Northwest* based on numbers recruited (per 100,000)	Proportional increase #	Estimated annual corrected incidence (95% CI) (per 100,000 population)	Estimated number of cases a year in the UK (95% CI)
Enteroviral meningitis	85	39	0.70 (0.49-0.95)	2.25	1.57 (1.11-2.14)	802 (567-1091)
Herpes simplex virus meningitis	38	18	0.31 (0.19-0.51)	2.5	0.78 (0.48-1.27)	399 (242-647)
Varicella zoster virus meningitis	29	13	0.24 (0.12-0.4)	1.5	0.36 (0.19-0.59)	182 (94-303)
Total confirmed viral meningitis	154	71	1.27 (0.99-1.6)	2.15	2.73 (2.13-3.44)	1389 (1084-1750)
<i>Streptococcus pneumoniae</i> meningitis	26	13	0.23 (0.12-0.39)	4.5	1.04 (0.53-1.73)	529 (268-884)
<i>Neisseria meningitidis</i> meningitis	15	7	0.12 (0.04-0.25)	1	0.12 (0.04-0.25)	63 (23-125)
Total confirmed bacterial meningitis	47	22	0.39 (0.24-0.58)	3.2	1.24 (0.76-1.87)	631 (390-951)
Meningitis – unknown aetiology	176	81	1.45 (1.15-1.8)	7.3	10.58 (8.4-13.14)	5390 (4277-6695)
All meningitis**	385	178	3.17 (2.72-3.67)	4.25	13.47 (11.55-15.59)	6864 (5886-7944)
~based on sites recruiting patients for a median duration of 26 months *Calculated using Office of National Statistics mid-2012 population data and the Northwest having 11% of the UK population						
# based on number of cases missed in one year in Northwest sentinel sites **Includes unknown aetiology and causes other than bacteria and viruses						

Box. Indications for neuroimaging prior to lumbar puncture

Glasgow Coma Scale \leq 12

Uncontrolled seizures

Papilloedema

Focal Neurological signs

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