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

Research in context

Evidence before the study

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

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

Added value of this study

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

Implications of all the available evidence

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

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

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ABSTRACT

Background

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

Methods

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

Findings

1126 patients were enrolled. 638/1126 (57%) had meningitis: 231/1126 (36%) viral, 99/1126 (16%) bacterial and 267/1126 (42%) unknown aetiology. 41/1126 (6%) had other causes. The estimated annual incidence of viral and bacterial meningitis was 2·73 and 1·24 per 100,000 respectively. The median (IQR) length of stay for patients with viral meningitis was 4 (3,7) days, increasing to 9 (6,12) days in those treated with antivirals. Earlier lumbar puncture resulted in more patients having a specific cause identified. Patients with viral meningitis suffered a significantly decreased quality of life in the first year after illness.

Interpretation

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

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Introduction

As the incidence of bacterial meningitis decreases, the proportion of meningitis cases caused by viruses is increasing.[1] The use of molecular diagnostics has also led to a greater recognition of neurological viral infections. [2] A seven-fold rise in reports of viral meningitis and encephalitis was seen in England and Wales between 2004 and 2013.[2] Enteroviruses and herpesviruses are commonly reported causes of viral meningitis in adults, but their relative incidence varies in different countries. Finland reports a high incidence of herpesvirus meningitis, whereas Spain has a predominance of enteroviruses.[3,4]

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

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

Methods

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

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

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

Estimation of meningitis incidence

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

Outcomes

Clinical outcomes recorded included inpatient mortality and critical care use. Patient reported outcome measures assessed quality of life, neuropsychological functioning and symptom resolution. Quality of life was measured using EQ-5D-3L[13] and SF-36[14], both internationally validated tools. Other outcome measures used were the Aldenkamp and Baker neuropsychological assessment scale (ABNAS)[15] and the Total Morbidity Score[16] – both of which were developed for neurological disorders, namely epilepsy and meningitis (questionnaires in supplementary material). EQ-5D-3L, SF-36 and ABNAS were assessed at 6, 12, 24 and 48 weeks after admission. The Total Morbidity Score recorded resolution of symptoms for 3 weeks after admission.[17] Quality adjusted life years (QALYs) were calculated from the EQ-5D-3L. There are no population level data for ABNAS, therefore questionnaires were sent to family/friends of the patient to act as a control group.

Statistical Analysis

T-tests were used for normally distributed continuous data. Appropriate transformations were applied in the case of non-normally distributed continuous data. If the transformed data were still not normally distributed Mann Whitney U or Kruskal-Wallis tests were used. Categorical data were analysed using Chi Square or Fisher's Exact test. 95% confidence intervals (CI) were calculated using Byar's method.[18] To obtain 95% CI for the UK incidence a proportional inflation was applied to the Northwest data based on the retrospective data collection. Logistic regression was used to assess relationship between time to LP and getting a microbiologically proven diagnosis. The SF-6D, a single unit preference based measure, was obtained from the SF-36 and non-parametric Bayesian analysis was used with permission from the University of Sheffield, UK.[19,20] A Bonferroni correction was applied to the ABNAS domains and a p-value of <0·008 was considered statistically significant; last observation carried forward was used

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

Microbiological testing

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

Role of the funding source

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

Results

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

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

Using both the prospective and retrospective data, from the Northwest sites, the incidence of viral meningitis and bacterial meningitis in UK adults was estimated to be 2·73 and 1·24 per 100,000 per year, respectively (table 4). When all cases were considered, including those with no identified aetiology, the annual incidence of all meningitis in UK adults was 13·47 per 100,000.

Nine-hundred-and-one (81%) of 1113 patients had neurological imaging, with the majority [776/1113 (70%)] before LP. Only 90/776 (12%) had an indication for imaging prior to LP, as recommended in national guidelines (box).[22] The most common indications were, Glasgow coma scale ≤12 in 54/776 (7%) and seizures in 36/776 (5%); five patients had papilloedema and eight had focal neurological findings. The median (IQR) time from admission to antibiotics, and to LP, were 2 [0,10 (n=237)] and 8 [3,22 (n=299)] hours respectively, in those who did not have imaging prior to LP, compared with 3 [1,11 (n=563)] and 18 [9,30 (n=776)] hours in those who did (p=0·004 and <0·0001 respectively). The median (IQR) time from admission to LP was longer in the *lymphocytic meningitis – unknown aetiology* group [21 (9,37·5) hours] than those with proven viral meningitis [13 (7,23) hours], proven bacterial meningitis [13 (4·5,23) hours] and *neutrophilic meningitis- unknown aetiology* [15 (7,22·5) hours; p=<0·0001, <0·0001 and 0·008 respectively]. The median (IQR) time to LP for all patients was 17 (8,29) hours. The chances of having a pathogen detected in viral meningitis was reduced by 1% for every hour delay in LP after admission [OR 0.988 (95% CI 0.982-

10.995), p=0·001] (figure 2). For bacterial meningitis there was also a reduction of 1% for each hour delay, but this was not statistically significant [OR 0.995 (95% CI 0.989-1.002), p=0·16]. 24/99 (25%) patients with bacterial meningitis were diagnosed by molecular methods alone. The role of different tests in diagnosing bacterial meningitis is shown in figure S1.

One-hundred-and-thirty-nine (60%) of 231 patients with viral meningitis had at least one dose of an antiviral (aciclovir and/or valaciclovir) and 51/139 (37%) received a course, defined as ≥ five days. 42/98 (43%) of those with HSV or VZV meningitis received a course of antivirals with a median (range) duration of ten (5-30) days. The treatment regime varied considerably (figure S2). Patients in whom enterovirus meningitis was diagnosed were less likely to receive antiviral drugs, where they would have no effect, than those where no aetiology was identified [8/127 (6%) versus 50/248 (20%) (p=<0·0001)]. Most patients [160/231 (69%)] with proven viral meningitis also received at least one dose of antibiotics (median duration, one day) and 199/267 (75%) of those without an aetiological cause received at least a single dose. 328/454 (72%) patients who did not have meningitis received empirical antibiotics.

The median (IQR) length of stay for patients with viral meningitis was 4 (3,7) days. Patients with herpesvirus meningitis stayed in hospital longer than patients with enteroviral meningitis [6 (3·75,10) days vs, 3·5 (3,5) days, p=<0·0001] and those with VZV meningitis stayed longer than those with HSV [8 (5,11) days vs 5 (3,8) days, p=0·02]. Those who received antivirals were in hospital longer than those who did not [8 (5,11) days vs. 3 (2,5) days, p=<0·0001]. Those with *lymphocytic meningitis – unknown aetiology* stayed in hospital slightly longer than those with proven viral meningitis [5 (3,8·5) days versus 4 (3,7), p=0·09]. Seven patients died before discharge, five of whom had meningitis - three pneumococcal, one tuberculous and one malignant meningitis. 91 patients required admission to intensive care; 52/91 (57%) had bacterial meningitis, with 37/52 (71%) having pneumococcal disease. No patients with viral meningitis died or required admission to intensive care.

Quality of life was reduced in all aetiological groups, at all times points, when compared with the UK population (figure 3). EQ-5D-3L utility scores were similar for both viral and bacterial meningitis. They were significantly lower for HSV meningitis, compared with the other viral aetiologies, at 6 weeks after discharge (p=0·004). 12/14 (86%) patients with HSV meningitis who returned the questionnaires, had problems with anxiety or depression at six weeks (figure S3). Supporting, and confirming, the EQ-5D-3L data, all groups had worse SF-6D scores than UK norms (Figures S4 and S5). The average QALY for patients with viral meningitis, over the first year, was 0.72. Compared with the age matched UK population, patients with viral meningitis suffered a loss of 0.2 QALYs in that first year (figure S6). There was no significant difference in time to resolution of headache between viral meningitis and bacterial, as measured by the Total Morbidity Score (7 versus 8 days, p= 0·09) (table S1). Patients with viral meningitis had significantly worse ABNAS scores then healthy controls at all four time points in the year after illness (figure S7 and table S2).

Discussion

This study provides the first estimate of the incidence of viral meningitis in UK adults. Using clinical and laboratory data we estimate the annual incidence of confirmed viral meningitis in UK adults to be almost 3 per 100,000. Previous UK studies of meningitis have been based on coding data or laboratory reports, missing those that have no aetiological diagnosis.[1,2,11] We have estimated the incidence of all meningitis to be 13·47 per 100,000. Previously, a similar estimate of the incidence of meningitis in the US was estimated to be 27·9 per 100,000.[23] This was in the late 20th century and included adults and children. It is likely to be substantially lower now, given the impact of immunisation.[24]

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

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

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

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

hospital stays and other investigations[7]. Full diagnostic accuracy and cost-effectiveness studies should be performed before any new tests are introduced.

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

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

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

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

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

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Author contributions

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

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Conflict of Interest Statement

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

Tables

Table 1. Case Definitions

Meningitis	Patient with symptoms consistent with meningitis and a cerebrospinal fluid leukocyte count >4 x 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 *either* 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 ≤ 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 x 10^6 cells/L); EEG suggesting encephalitis; Neuroimaging suggestive of encephalitis (CT or MRI)
Tuberculous meningitis	Identification of *Mycobacterium tuberculosis* 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		
Streptococcus pneumoniae	53	8.3
Neisseria meningitidis	29	4.5
Haemophilus influenzae	5	0.8
Listeria monocytogenes	3	0.5
Streptococcus pyogenes	1	0.2
Streptococcus agalactiae	1	0.2
Streptococcus oralis	1	0.2
Mycoplasma pneumoniae	1	0.2
Fusobacterium sp	1	0.2
Escherichia coli	1	0.2
Pseudomonas sp. And Klebsiella sp	1	0.2
Positive 16S PCR with no product identified	2	0.3
Total	**99**	**15.5**
Mycobacterial		
Mycobacterium tuberculosis	11	1.7
Fungal		
Cryptococcus neoformans	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 10^9/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 (x10^6/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)
***Streptococcus pneumoniae* meningitis**	26	13	0.23 (0.12-0.39)	4.5	1.04 (0.53-1.73)	529 (268-884)
***Neisseria meningitidis* 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 ≤ 12
Uncontrolled seizures
Papilloedema
Focal Neurological signs

References

1. Martin NG, Iro MA, Sadarangani M, Goldacre R, Pollard AJ, Goldacre MJ. Hospital admissions for viral meningitis in children in England over five decades: a population-based observational study. *Lancet Infect Dis* 2016; **16**(11): 1279-87.
2. Kadambari S, Okike I, Ribeiro S, et al. Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004-2013. *J Infect* 2014; **69**(4): 326-32.
3. Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology* 2006; **66**: 75-80.
4. de Ory F, Avellon A, Echevarria JE, et al. Viral Infections of the Central Nervous System in Spain: A Prospective Study. *J Med Virol* 2013; **85**: 554-62.
5. Robinson CC, Willis M, Meagher A, Gieseker KE, Rotbart H, Glode MP. Impact of rapid polymerase chain reaction results on management of pediatric patients with enteroviral meningitis. *Pediatr Infect Dis J* 2002; **21**: 283-6.
6. Landry ML, Greenwold J, Vikram HR. Herpes Simplex type-2 Meningitis: Presentation and Lack of Standardized Therapy. *Am J Med* 2009; **122**: 688-91.
7. Giuleri SG, Chapuis-Taillard C, Manuel O, et al. Rapid detection of enterovirus in cerebrospinal fluid by a fully automated PCR assay is associated with improved management of aseptic meningitis in adult patients. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2015; **62**: 58-62.
8. Schmidt H, Cohrs S, Heinemann T, et al. Sleep disorders are long-term sequelae of both bacterial and viral meningitis. *J Neurol Neurosurg Psychiatry* 2006; **77**(4): 554-8.
9. Schmidt H, Heimann B, Djukic M, et al. Neuropsychological sequelae of bacterial and viral meningitis. *Brain* 2006; **129**: 333-45.
10. Sittinger H, Muller M, Schweizer I, Merkelback S. Mild cognitive impairment after viral meningitis in adults. *J Neurol* 2002; **249**: 554-60.
11. 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.
12. Office for National Statistics. Office for National Statistics. 2016. https://www.ons.gov.uk/ (accessed 30th June 2016).
13. The Euroqol Group. EuroQoL - A new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199-208.
14. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical care* 1994; **32**(1): 40-66.
15. Brooks J BG, Aldenkamp A. . The A–B Neuropsychological Assessment Schedule (ABNAS): the further refinement of a patient-based scale of patient-perceived cognitive functioning. *Epilepsy Research* 2001; **43**: 227-37.
16. Desmond RA, Accortt NA, Talley L, Villano A, Soong SJ, Whitley RJ. Enteroviral Meningitis: Natural History and Outcome of Pleconaril Therapy. *Antimicrob Agents Ch* 2006; **50**(7): 2409-14.
17. Rotbart H, Webster DA. Treatment of potentially LIfe-Threatening Enterovirus Infections with Pleconaril. *Clin Infect Dis* 2001; **32**: 228-35.
18. Breslow NE, Day NE. Statistical Methods in Cancer Research, Volume II: The Design and Analysis of Cohort Studies. New York: Oxford University Press; 1987.
19. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of health economics* 2002; **21**(2): 271-92.
20. Kharroubi SA, Brazier JE, Roberts J, O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *Journal of health economics* 2007; **26**(3): 597-612.

21. Public Health England. Meningoencephalitis. UK Standards for Microbiology Investigations.; 2014.
22. Begg N, Cartwright KAV, Cohen J, et al. Consensus Statement on Diagnosis, Investigation, Treatment and Prevention of Acute Bacterial Meningitis in Immunocompetent Adults. *J Infect* 1999; **39**: 1-15.
23. Khetsuriani N, Quiroz ES, Holman R, Anderson LJ. Viral Meningitis-Associated Hospitalisations in the United States, 1988-1999. *Neuroepidemiology* 2003; **22**: 345-52.
24. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. *Lancet Infect Dis* 2014; **14**(9): 813-9.
25. Smith J, Robinson J. Age-Specific Prevalence of Infection with herpes Simplex Types 2 and 1: A Global Review. *J Infect Dis* 2002; **186 (Suppl1)**: S3-S28.
26. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clinical Microbiology and Infection* 2016; **22**: S37-S62.
27. McGill F, Heyderman RS, Michael BD, et al. The UK Joint specialist societies guideline on the management of community acquired bacterial meningitis in immunocompetent adults. *J Infect* 2016; **72**(4): 405-38.
28. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice Guidelines for the management of Bacterial Meningitis. *Clin Infect Dis* 2004; **39**: 1267-84.
29. Michael B, Menezes B, Cunniffe J, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J* 2010; **27**: 433-8.
30. Kupila L, Vuorinen T, Vainionpaa R, Marttila R J, Kotilainen P. Diagnosis of Enteroviral Meningitis by Use of Polymerase Chain Reaction of Cerebrospinal fluid, stool and serum specimens. *Clin Infect Dis* 2005; **40**: 982-7.
31. 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.
32. 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.
33. Tan NWH, Lee EY, Khoo GMC, Tee NWS, Krishnamoorthy S, Choong CT. Cerebrospinal fluid white cell count: discriminatory or otherwise for enteroviral meningitis in infants and young children? *Journal of NeuroVirology* 2016; **22**(2): 213-7.
34. Thomas KE, Hasbun R, Jekel J, Quagliarello VJ. The Diagnostic Accuracy of Kernig's Sign, Brudzinski's Sign, and Nuchal Rigidity an Adults with Suspected Meningitis. *Clin Infect Dis* 2002; **35**: 46-52.
35. Hsu CC, Tokarz R, Briese T, Tsai HC, Quan PL, Lipkin WI. Use of staged molecular analysis to determine causes of unexplained central nervous system infections. *Emerg Infect Dis* 2013.
36. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013; **57**: 1114-28.