

Trends in the diagnosis and management of infective meningitis at a tertiary centre over 10 years: a retrospective cohort study providing further evidence for culture-independent diagnostics

SC Williams, O Topping, G Tsermoulas, J Scriven & G Hassan-Smith

Abstract

Objective: This retrospective study analysed clinical characteristics, diagnosis, and management of infective meningitis patients at a UK-centre, aiming to identify emerging trends in the patient pathway.

Methods: A ten-year review of meningitis patients at a UK tertiary centre was conducted. Inclusion criteria encompassed signs/symptoms of meningitis with CSF WCC ≥ 4 cells/mm³ or causative pathogen identification.

Results: The study included 298 patients with infective meningitis were included (184 viral, 87 bacterial, 22 tuberculosis, 5 fungal). Key findings indicated underutilisation of culture-independent investigations, delayed administration of antibiotics, and lumbar puncture. Viral meningitis cases with a positively identified causative virus had shorter hospital stays.

Conclusion: Culture-independent investigations are under-utilised in meningitis diagnosis. Patients experience delays in essential interventions. Future advancements in rapid, point-of-care genomic sequencing could enhance diagnostic accuracy and speed.

Keywords

Meningitis, infective meningitis, bacterial meningitis, viral meningitis, TB, TB meningitis, fungal meningitis, CNS infection, meningoencephalitis

Introduction

Infective meningitis describes the pathological inflammation of the tissue coverings of the brain secondary to pathogenic infection. In recent decades, the picture of meningitis seen across the United Kingdom (UK) has changed. Widespread vaccination programmes have reduced the incidence of bacterial meningitis, the effects of this notably seen in paediatric populations.¹⁻³ However, mortality from bacterial meningitis remains high at 7 – 20% and is associated with significant neurological sequelae.^{1,4} Conversely, viral meningitis is typically a self-limiting condition with low risk of morbidity, mortality, or significant neurological sequelae.⁵ Rates of viral meningitis are increasing, in part due to increasing availability of molecular diagnostics.⁶ The impact of viral meningitis on healthcare systems is not benign, however - distinguishing between viral meningitis and bacterial meningitis can be challenging on initial presentation, and therefore patients often receive protracted courses

of empiric antibiotics and spend many days in hospital, exposing the patient to unnecessary treatment and accruing healthcare costs. The rapid identification of viral meningitis, and therefore the exclusion of a more sinister cause, may prevent prolonged and costly patient admissions.^{7,8} Fungal meningitis and mycobacterium tuberculosis (TB) meningitis are often devastating conditions, particularly amongst immunocompromised individuals, carrying high mortality and morbidity.¹

For all causes of infective meningitis, early identification of a causative pathogen is key to outcomes. This has been echoed in national guidelines produced by the British Infection Association.⁹ In the case of bacterial meningitis, this allows for rationalisation of antibiotic therapy, and enables a tailored therapeutic response. In the case of viral meningitis, early detection allows patients to be discharged promptly and empiric treatments stopped.

Immunisation programmes, novel diagnostic modalities, and improved treatments have caused

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Table 1. Final diagnosis and microbial cause of community acquired meningitis cases

Pathogen subgroup	N (% within subgroup)
Viral meningitis	184
• No viral pathogen identified ('likely viral')	102 (55%)
• Herpes Simplex Virus 2 (HSV2)	32 (17%)
• Enterovirus	30 (16%)
• Varicella Zoster Virus (VZV)	13 (7%)
• Epstein Barr virus (EBV)	3 (2%)
• Herpes Simplex Virus 1 (HSV1)	3 (2%)
• Enterovirus & EBV	1 (1%)
Bacterial meningitis	87
• Streptococcus pneumoniae	38 (44%)
• No bacterial pathogen identified ('likely bacterial')	29 (33%)
• Neisseria meningitidis	14 (16%)
• Streptococcus pyogenes	1 (1%)
• Escheria coli	1 (1%)
• Staphylococcus aureus	1 (1%)
• Staphylococcus cohnii	1 (1%)
• Streptococcus intermedius	1 (1%)
• Multiple	1 (1%)
TB meningitis	22
• Confirmed TB meningitis	13 (59%)
• No TB pathogen identified ('likely TB meningitis')	9 (41%)
Fungal meningitis	5
• Cryptococcus neoformans	5 (100%)

a paradigm shift in the diagnosis and management of meningitis in the UK.^{1,10} This retrospective study aimed to provide a snapshot of the clinical characteristics, diagnosis and management of infective meningitis, detailing emerging trends in diagnostic and management pathways, as well as providing epidemiological data regarding infective meningitis in the UK. Secondly, we aimed to compare our unit's performance with the British Infection Association's (BIA) 2016 guidelines on the diagnosis and management of meningitis.

Methods

This study comprised a retrospective cohort including all consecutive adult patients meeting diagnostic criteria for infective meningitis at a UK tertiary centre between 2010 and 2019. Where applicable, this study is reported in accordance with STROBE guidelines for the reporting of observational data.¹¹ Patient data was collected as part of a locally registered audit with the Clinical Governance and Patient Safety Team at the Healthcare Trust (registration code (CARMS-14502)). Patient data was inputted into an anonymised database.

An initial patient database was created through bioinformatic case extraction of patients with an ICD-10 diagnostic code for meningitis or meningoencephalitis, over a period of ten years from 2010 to 2019 inclusive, at a tertiary centre in the UK. Case notes were individually reviewed for suitability for inclusion to

a final patient database for analysis. Inclusion criteria were patients with signs and symptoms of meningitis (as determined by the research team), with a CSF WCC ≥ 4 cells/mm³ or a pathogen identified in CSF or blood. Exclusion criteria included patients aged <16 , repeat cases, and patients who were ultimately diagnosed with an alternative condition despite being coded as meningitis. Patients with a final diagnosis of chemical, carcinomatous, post-neurosurgical (within 50 days of neurosurgery), and chronic lymphocytic meningitis were excluded. Encephalitis, cerebral abscess, and subdural empyema patients were excluded.

Data regarding clinical presentation, diagnosis, management, and outcome was collected via in-house electronic patient records. Laboratory data such as white cell count (WCC), C-reactive protein (CRP), was taken from the presenting time of the meningitis episode. Patients who did not receive a blood culture within 7 days of meningitis episode / admission were listed as not having had a blood culture taken. Patients were considered immunocompromised if they had any of the following: active haematological malignancy; solid-organ or bone-marrow transplant; HIV infection with CD4 <200 cells/mm³; receipt of chemotherapy, radiotherapy, or other systemic immunosuppressive treatment; or any documented primary immunodeficiency. For patients who presented via A&E time of admission was recorded, along with time of other key steps in the meningitis pathway to enable analysis of time-to-intervention. Data regarding antimicrobial prescriptions were gathered using electronic prescribing records. Empiric antibiotic was defined as the antibiotics administered to the patient with the primary aim of treating meningitis prior to finding a causative organism. Definitive antibiotics were defined as those which the patient was treated with after causative pathogen identification.

Final diagnosis was divided into viral, bacterial, fungal, or TB meningitis. For meningitis cases in which an organism was not isolated, a final diagnosis of 'meningitis – unknown cause – likely 'pathogen'' was given, in-keeping with the audit tool derived from the British Infection Association.⁹ Final diagnosis of likely bacterial, likely viral, or likely TB was based upon clinical presentation, investigations, impression by the parent team at time of treatment, and the clinical research team. To minimise bias, cases were reviewed in duplicate by two authors (SW, OT) and any discrepancies were resolved through discussion with a third reviewer (GHS).

Quantitative data is presented descriptively. Missing data were excluded from analysis. Inferential statistical analysis was carried out using GraphPad Prism5 software (GraphPad Software, Inc.). Central tendency is described using median and interquartile range. Mann-Whitney statistical test was used when

*Infective Meningitis: 10 year retrospective cohort study***Table 2.** Demographics, symptomatology, investigations, and outcome for community acquired meningitis cases over a ten-year period.

	Bacterial meningitis (n = 87)	Viral meningitis (n=184)	TB meningitis (n = 22)	Fungal meningitis (n = 5)
Demographics				
% Female	52%	59%	41%	40%
Age (median+ IQR)	45 (30 – 62)	31 (IQR 25 – 41)	49 (IQR 25 – 57)	34 (IQR 20 – 57)
Immunocompromised	11%	8%	6%	80%
Symptomatic presentation				
Headache	76%	95%	60%	100%
Fever	69%	69%	30%	40%
Vomiting	54%	55%	35%	100%
Neck stiffness	39%	49%	0%	100%
Photophobia	26%	38%	15%	40%
Seizures	17%	9%	15%	0%
Rash	11%	9%	5%	0%
Time from symptom onset to admission Median + (IQR)	1.0 days (1 – 3)	2 days (IQR 1 – 4)	14 days (IQR 7 – 29)	14 days (IQR 6 – 52)
Laboratory data				
WCC at presentation (x10 ⁹ /L) Median + (IQR)	14.9 (10 – 22)	8.9 (IQR 7.2 – 10.7)	7.2 (IQR 6.1 – 9.6)	8.7 (IQR 5.0 – 9.6)
CRP at presentation (mg/L) Median + (IQR)	106 (27 – 246)	6 (IQR 1 – 16)	11 (IQR 5 – 42)	10 (IQR 2 – 25)
Lactate at presentation Median + (IQR)	3.2 (1.6 – 5.7)	1.5 (IQR 1.2 – 2.0)	-	-
CSF appearances				
Clear colourless fluid	43%	93%	52%	100%
Turbid fluid	39%	3%	0%	0%
Straw coloured fluid	10%	1%	24%	0%
Blood stained	7%	3%	24%	0%
Fibrin clot	1%	0%	0%	0%
CSF WCC cells/mm ³ Median + (IQR)	415 (104 – 1198)	124 (IQR 46 – 266)	36 (IQR 15 – 110)	34 (IQR 11 – 110)
CSF polymorphs cells/mm ³ Median + (IQR)	290 (55 – 978)	8 (IQR 1 – 20)	8 (IQR 2 – 16)	4 (IQR 2 – 62)
CSF mononuclear cells x10 ⁶ cells/mm ³ Median + (IQR)	30 (8 – 115)	94 (IQR 27 – 236)	27 (IQR 11 – 106)	13 (IQR 5 – 61)
CSF protein (g/L) Median + (IQR)	1.3 (0.7 – 4.8)	0.64 (IQR 0.49 – 0.99)	1.36 (IQR 0.77 – 2.22)	0.62 (IQR 0.43 – 1.02)
CSF:serum glucose ratio <0.5	73%	24%	82%	60%
Outcomes				
Length of stay Median + (IQR)	14 days (10 – 24)	4 days (IQR 2 – 9)	30 days (IQR 18 – 67)	63 days (IQR 35 – 133)
ITU admission (as direct result of meningitis)	47%	1.1%	50%	40%
Neurosurgical intervention required	16%	0%	55%	60%
Mortality rate	14%	2%	23%	0%

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comparing unpaired, nonparametric groups, whilst an unpaired *t* test was used when data was normally distributed. Shapiro-Wilk normality tests were used to determine whether data were parametrically or non-parametrically distributed.

Results

In total, 1546 patients matched the ICD-10 diagnostic code and were screened according to the inclusion/exclusion criteria. Of these, 298 cases met inclusion criteria (Table 1). In total, 140 cases (44% of total) of meningitis had no pathogen or underlying cause identified. These 'unknown cause' cases were deemed as likely viral (*n* = 102), likely bacterial (*n* = 29), or likely TB (*n* = 9).

Viral meningitis

184 cases of viral meningitis were identified (82 'confirmed' (viral pathogen identified), 102 likely) (Table 1). Demographic, clinical, laboratory, and outcome data can be found in Table 2, pathogen specific data can be found in Table 3. The most common causative virus was HSV2, detected in 32 patients (39% of identified viruses), followed by enterovirus (37%), and VZV (16%). HSV2 meningitis predominantly affected women (81% female), in contrast to other viral pathogens.

A past medical history of meningitis was noted in 10% of cases (18/184). This was notably greater in HSV2 meningitis cases, where 17% (5/32) of patients had a history of meningitis. Symptomatic onset to admission was a median of 2 days (IQR 1 - 4) in viral meningitis cases (data available for *n* = 165 patients). A short duration of onset was seen for HSV and enterovirus meningitis, with the notable exception being VZV meningitis, which had a median time from symptom onset to admission of 5 days (IQR 3 - 6) (*p* < 0.05) (*n* = 13). In total, 8% (14/184) of viral meningitis patients were immunocompromised; the proportion of patients who were immunocompromised was much greater for VZV meningitis patients at 31% (4/13).

Investigations and diagnostic methods

Laboratory data for viral meningitis patients is found in Table 2. Pathogen specific data is found in Table 3.

Treatment

Antiviral therapy was administered to 65% (120/184) of viral meningitis patients (median duration of therapy 6 days (IQR 3 - 11)). Patterns of antiviral treatment varied (Supplementary Material, Table 4) – 35% (64/184) were not prescribed any antivirals; 36% (66/184) were prescribed antivirals empirically which were then stopped once viral meningitis confirmed; 26% (48/184) were prescribed antivirals in both the

empiric and definitive period; and 3% (6/184) were prescribed antivirals upon discovery of an underlying viral pathogen. Empiric antibiotics were administered to 75% of viral meningitis patients (median treatment duration 4 days (IQR 2 - 6)). Duration of empiric antibiotic administration in viral meningitis was significantly less in cases where an underlying virus was identified (3 days (IQR 2 - 5) compared to likely viral cases (5 days (IQR 2 - 6)) (*p* < 0.05).

Outcomes

Outcomes measured for viral meningitis cases included length of stay (median 4 days (IQR 2 - 9)), intensive therapy unit (ITU) admission rate (1%, 2/184), and mortality rate (2%, 3/184). Pathogen-specific outcomes data can be found in Table 3.

Confirmed vs likely viral meningitis

In both groups, similar proportions of patients received antiviral therapy (67% vs 65%) and antimicrobial therapy (71% vs 77%). Duration of antibiotic treatment was greater for likely (5 days (IQR 2 - 8) compared to 'confirmed' (3 days (IQR 2 - 5)) (*p* < 0.05)). There was no statistically significant difference in the duration of antiviral treatment between the two groups. Length of stay was statistically significantly shorter in 'confirmed' cases (median 4 days (IQR 2 - 7)) compared to likely cases (median 5 days (IQR 2 - 10)) (*p* < 0.05, Mann-Whitney U)).

Bacterial meningitis

Demographics and final diagnosis

A total of 87 bacterial meningitis cases were identified (Table 1). Of these, 67% (58/87) had a causative pathogen identified, whilst 33% (29/87) had no pathogen identified throughout their admission. In cases where a bacterial pathogen was identified, streptococcus pneumoniae was most common (*n* = 38), accounting for 66% of confirmed bacterial meningitis cases, followed by Neisseria meningitidis (*n* = 14) (24% of cases). Median age was 45 (IQR 30 - 62) for all bacterial meningitis patients, 55 (IQR 32 - 64) for pneumococcal meningitis patients, and 27 (IQR 20 - 38) for meningococcal meningitis patients.

Diagnosis

Presenting features, laboratory data, and outcomes are shown in Table 2; pathogen specific data is shown in Table 3. Blood cultures were taken 84% (73/87) of the time (38% (28/73) were positive (excluding contaminants). CSF culture was sent in 80% (70/87, 66 LPs, 4 patients CSF sent via external ventricular drain) of cases and yielded a positive result 19% (13/70) of the time. CSF was sent for meningococcal/pneumococcal PCR analysis 45% (39/87) of the

*Infective Meningitis: 10 year retrospective cohort study***Table 3.** Pathogen-specific demographics, symptomatology, investigations, and outcome for community acquired meningitis cases over a ten year period. Pathogen-specific demographics, symptomatology, investigations, and outcome for community acquired meningitis cases over a ten year period.

	Bacterial meningitis		Viral meningitis		
	Pneumococcal meningitis (n=38)	Meningococcal meningitis (n=14)	HSV2 meningitis (n=32)	Enterovirus meningitis (n=30)	VZV meningitis (n=13)
Demographics					
% Female	50%	57%	81%	50%	46%
Age (median+ IQR)	55 (IQR 42 - 66)	27 (IQR 20 - 38)	31 (IQR 27 - 44)	31 (IQR 27 - 36)	54 (IQR 26 - 64)
Immunocompromised	8%	7%	3%	0%	31%
Symptomatic presentations					
Headache	58%	85%	100%	100%	100%
Fever	75%	75%	86%	79%	15%
Vomiting	48%	77%	57%	69%	46%
Neck stiffness	26%	54%	54%	62%	31%
Photophobia	26%	15%	25%	48%	62%
Seizures	19%	0%	14%	3%	0%
Rash	0%	46%	14%	0%	8%
Time from symptom onset to admission Median + (IQR)	1.0 day (1 - 2)	1 day (1 - 2)	1 day (1 - 3)	2 days (1 - 3)	5 days (3 - 6)
Laboratory data					
WCC at presentation (x10 ⁹ /L) Median + (IQR)	16 (6.9 - 23.7)	21.5 (16 - 28)	9.4 (8.1 - 10.4)	8.3 (6.5 - 9.3)	8.2 (6.5 - 9.5)
CRP at presentation (mg/L) Median + (IQR)	174 (64 - 318)	205 (125 - 348)	1* (1 - 5)	17* (5 - 36)	3 (1 - 16)
Lactate at presentation (mmol/L) Median + (IQR)	3.3 (2.1 - 5.6)	5.4 (3.4 - 7.5)	1.3 (1.2 - 1.7)	1.5 (1.1 - 2.1)	1.4 (1.38 - 1.5)
CSF appearances					
Clear colourless fluid	22%	33%	94%	97%	92%
Turbid fluid	48%	67%	3%	0%	0%
Straw coloured fluid	22%	0%	3%	0%	0%
Blood stained	4%	0%	0%	3%	8%
Fibrin clot	4%	0%	0%	0%	0%
CSF WCC (cells/mm ³) Median + (IQR)	663 (292 - 1757)	3223 (497 - 7267)	297 (143 - 404)	58 (41 - 97)	221 (87 - 335)
CSF polymorphs (cells/mm ³) Median + (IQR)	656 (208 - 1708)	2900 (401 - 7205)	9 (3 - 24)	12 (5 - 22)	12 (1.5 - 22)
CSF mononuclear cells (cells/mm ³) Median + (IQR)	35 (13 - 118)	89 (15 - 363)	270 (125 - 289)	34 (24 - 81)	217 (56 - 332)
CSF protein (g/L) Median + (IQR)	5 (3 - 7)	2.3 (0.68 - 4.2)	1.1* (0.7 - 1.4)	0.5* (0.35 - 0.65)	1.07 (0.84 - 1.74)
CSF:serum glucose ratio					
<0.5	90%	100%	5%	5%	56%
<0.3	60%	50%	0%	0%	0%
<0.2	60%	50%	0%	0%	0%
Outcomes					
Length of stay (days) Median + (IQR)	20† (14 - 26)	9† (6 - 11)	4 days (2 - 7)	3 days (2 - 4)	6 days (3 - 12)
ITU admission (as direct result of meningitis)	66%	57%	0%	0%	0%
Neurosurgical intervention required	21%	0%	0%	0%	0%
Mortality rate	18%	7%	0%	0%	0%

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time, and these positively identified meningococcal/pneumococcal species 46% (18/39) of the time. Serum meningococcal/pneumococcal PCR was sent in 22% (19/87) of bacterial meningitis patients and of these, 42% (8/19) were positive for a pathogen. Figure 1 shows the diagnostic investigations performed and their percentage rate of pathogen detection.

For bacterial meningitis with a confirmed pathogen (58/87), the means of detection was varied. Meningococcal meningitis cases were predominantly diagnosed through PCR means, with 71% (10/14) of diagnoses made exclusively through PCR detection. In 50% of meningococcal meningitis cases, CSF meningococcal PCR was positive when CSF culture failed to generate a positive result.

Of the 66 patients who had LPs performed, 54% (36/66) had clinical contraindications to LP, for which the BIA state neuroimaging should be performed prior. All of these patients were appropriately imaged prior to LP. Overall, 97% (60/66) of patients undergoing LP had pre-procedure neuroimaging (typically CT head). Twenty-seven patients had no contraindication to LP, yet 21/27 (77%) of these patients still had a CT or MRI head prior to LP.

Management

Pre-hospital antibiotics were administered to 5% (4/87) of bacterial meningitis patients. For patients who presented via A&E, ceftriaxone was prescribed in 63% (40/64) patients (in line with national guidance), and aciclovir was co-prescribed in 45% (29/64) patients. Once admitted, prescription of ceftriaxone rose to 75% (61/81), and aciclovir was co-prescribed in 57% (46/81). For bacterial meningitis cases in which a pathogen was identified, definitive antibiotics were in line with local guidance in 92% (26/34) cases. Patients who met the criteria for *Listeria monocytogenes* cover ($n = 38$) were prescribed amoxicillin in 61% (26/34) of cases (criteria for *Listeria* cover includes age >60, diabetic patients, pregnant patients, and immunocompromised state). For bacterial meningitis patients presenting via A&E, time to first antibiotic administration was 98 minutes (IQR 41 – 242), with 33% (20/61) of patients receiving antibiotics within the first hour. The median duration of antibiotic therapy was 10 days (IQR 9 – 14) for all bacterial meningitis patients, 14 days (IQR 14 – 18) for pneumococcal meningitis patients, and 8 days (IQR 8 – 10) for meningococcal meningitis patients. Neurosurgical input was required in 16% (14/87) of bacterial meningitis patients (21% of pneumococcal meningitis patients (16% required EVD insertion) and 0% of meningococcal meningitis patients). Additional data regarding management of bacterial meningitis patients can be found in Supplementary Material 1, Table 5.

Outcomes

Median length of stay for bacterial meningitis patients was 14 days (IQR 10 – 24). ITU admission rate for bacterial meningitis was 47% (41/87). ITU admission rates were notably greater in the pneumococcal (66%, 25/38) and meningococcal (57%, 8/14) groups. Mortality rate was 14% (12/87); subgroup mortality rate was 18% (7/38) for pneumococcal and 7% (1/14) meningococcal meningitis group.

Tuberculosis meningitis

Twenty-two TB meningitis patients were included (13 confirmed, 9 likely). Demographic, clinical, laboratory, and outcome data can be found in Table 2. Diagnostic means of TB identification were AFB CSF microscopy (sent in 91% (20/22) of cases, of which 0% (0/20) were positive), MTB CSF PCR (sent in 77% (17/22) of cases, of which 41% positive (7/17)), and mycobacterial CSF culture (sent in 91% (20/22) of cases, of which 30% (6/20) positive). For cases diagnosed through mycobacterial culture, the median time to positive culture was 27 days (IQR 20.5 – 33).

Adjunctive steroids were administered in 68% (15/22) of patients. Outcomes measured included length of stay (median 30 days (IQR 18 – 67)), ITU admission rate (50%, 11/22), and mortality rate (23%, 4/22). Notably, for confirmed cases of TB meningitis, the ITU admission rate was 69% (9/13) and the mortality rate was 31% (4/13). Neurosurgical intervention was required in 55% (12/22) of cases, with 32% (7/22) requiring ≥ 2 neurosurgical procedures.

Fungal meningitis

Five cases of fungal meningitis were recorded, all of which were caused by *Cryptococcus neoformans* (Table 2). Four out of five cases were known to be immunosuppressed - one patient was HIV positive with a CD4 count of 51 cells/mm³; and three patients were on long term immunosuppressants.

Blood cultures were taken in all patients and were positive in 1/5 patients. CSF cryptococcal antigen was sent in all patients and was positive in all patients. CT/MRI head was normal in two patients, whilst three patients had positive signs on MRI including areas of leptomeningeal enhancement, infective focal lesions, and focal areas of inflammation.

One patient had no empiric phase. The remaining four were managed empirically with ceftriaxone (two of which also received aciclovir, and three of which received amoxicillin for *Listeria* cover). For patients with an empiric phase, antifungals were started on day 3 for two patients, day 4 for one patient, and day 12 for another. All patients were started on an induction phase of amphotericin and flucytosine, before a consolidation and prolonged maintenance phase of fluconazole.

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Median length of stay was 63 days (IQR 35 - 133). Neurosurgical intervention was required in 3/5 (60%). ITU admission was seen in 2/5 (40%); no patients died during their admission. Two of five made a complete recovery; one patient developed chronic kidney disease (CKD) secondary to antifungal induced AKI; two patients ended up with significant disability requiring full time care, of which one of these patients died one-month post-discharge.

'Time to intervention' in suspected meningitis cases

Seventy-nine percent (235/298) of included patients were admitted via A&E. Of these, 132 had 'meningitis' recorded as a differential during clerking. Subgroup analysis of this group enables us to review time to key interventions in patients for whom meningitis was suspected 'at the front door' (Figure 2).

It has been reported that CT scans delay time to LP. BIA guidelines advise that CT should only be performed if there are signs of raised ICP (focal neurological signs, uncontrolled seizures, GCS $\leq$ 12, or papilloedema).⁹ The earliest LP performed was 4.8 hours post-admission. Further analysis of three subgroups reveals no link between undergoing CT and delay in LP; those who did not undergo neuroimaging had LP after median 13.4 hours (IQR 10.5 - 25.6); those who received neuroimaging within two hours of admission (i.e. no feasible reason why this would delay LP) underwent LP after a median of 13.7 hours (IQR 8.7 - 21); and analysis of all patients showed a median time to LP of 16.5 hours (IQR 11.2 - 23.1). There was no statistically significant difference in time to LP between these groups.

Discussion

Principal Findings and Comparison to Current Literature

This study presents a retrospective analysis of the management of 298 meningitis patients at a single centre over a ten-year period.

Viral meningitis patients tended to be young; present with headache, fever, vomiting; have low inflammatory markers, with clear CSF with an elevated mononuclear cell count; and tended to have short admissions and good outcomes, all of which is in keeping with the literature.^{5,12} Patients with viral meningitis who had a causative virus identified ('confirmed viral') had a statistically significantly reduced length of stay and received fewer antimicrobials when compared with those who did not (likely viral cases). This highlights the importance of early detection of causative pathogens to stakeholders in the patient pathway. McGill et al. report the healthcare cost of viral meningitis as £3,220,343 per annum

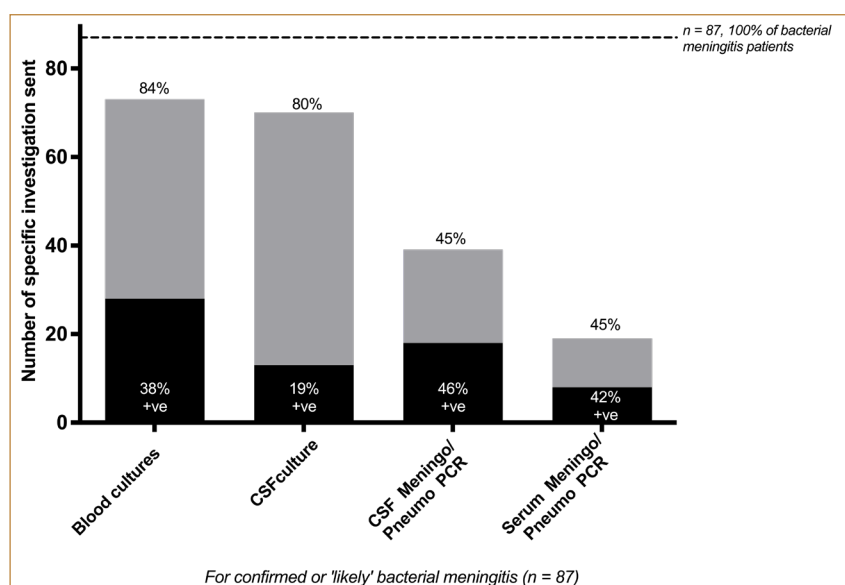


Figure 1. Diagnostic investigations performed in bacterial meningitis patients and their rate of pathogen detection. Culture-dependent means of diagnosis were sent in the majority of patients (blood cultures 84%; CSF culture 80%), and significantly more commonly than culture-independent investigations (CSF PCR 45%; Serum PCR 45%). Despite this, culture-independent techniques showed higher rates of pathogen detection. This may, in part, be due to the high rates of pre-investigation antibiotic administration seen in meningitis patients.

(95% CI £1,206,963 – £4,418,424) and noted that hospitalisation accounted for 79% of the total cost.¹³ Significant healthcare costs could be saved through early diagnosis and discharge, as well as reducing the burden of antibiotic over prescription associated with a microbial resistance.¹⁴

Prescribing pattern of both antibiotics and antivirals are a recurring issue in viral meningitis, which were echoed in our findings (Supplementary Material, Table 4).^{6,15,16} A similar split was seen between viral meningitis patients receiving no antivirals (35%), as empiric management only (i.e. antivirals stopped once virus identified, 36%), and those receiving aciclovir

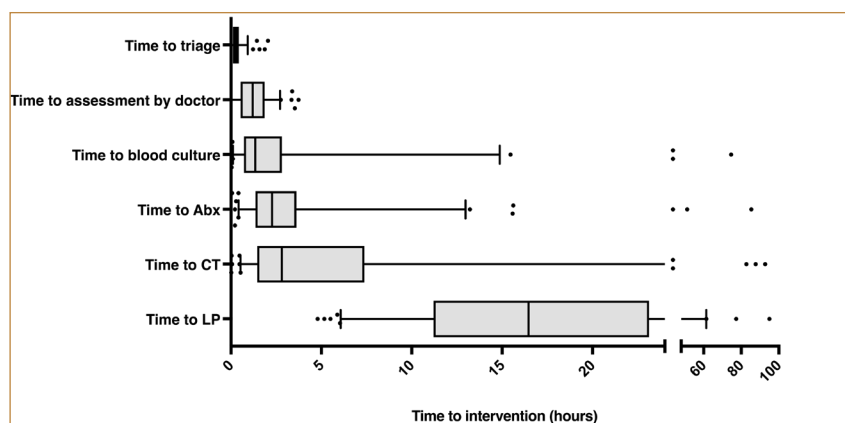


Figure 2. Time to intervention for patients with suspected meningitis presenting via the emergency department. Median, interquartile range, 5th – 95th percentile whiskers and outliers shown. Median time to triage was 16 minutes (IQR 6 – 26); median time to be seen by the clerking doctor was 72 minutes (IQR 32 – 112); median time to blood culture was 81 minutes (IQR 43 – 169); median time to empiric antibiotic administration was 136 minutes (IQR 82 – 217); median time to CT/MRI was 169 minutes (IQR 87 – 443); and median time to LP was 16.5 hours (IQR 11.2 – 23.1).

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definitively (29%). Present guidance states that aciclovir should only be commenced where encephalitis is a differential, and should not be routinely started in suspected meningitis patients. Clarification should be provided to local medical triaging teams to ensure adherence to recommended guidance.

Analysis of bacterial meningitis patients revealed several trends. Firstly, we note a reliance on culture-dependent investigations (CSF and blood culture), and an underutilisation of culture-independent investigations (CSF and serum PCR), despite culture-independent means showing a greater percentage pathogen detection rate (Figure 1). Reliance on culture-dependent investigations is reflected in current literature.¹⁰ This poses numerous issues in the diagnosis of meningitis, as research has demonstrated that CSF culture sensitivity is markedly reduced once empiric antibiotics have been administered (as was the case in 89% of our patients).¹⁰ Conversely, culture-independent techniques have been shown to maintain a high sensitivity and specificity many days after antimicrobial administration and offer a rapid and accurate means of identifying causative pathogens.^{9,10} Our data supports the increasing use of PCR and rapid-diagnostic tests in the management of bacterial meningitis.

Exploratory epoch analysis (Supplementary Material 2) revealed a modest increase in the use of viral CSF PCR and TB meningitis proportion over time, but no improvement in time-to-intervention metrics such as lumbar puncture or antibiotic administration. These findings suggest that despite advances in diagnostic capability, systemic delays persist. Future multicentre prospective audit cycles will be required to confirm these trends and evaluate whether changes in diagnostic practice translate to improved clinical outcomes.

While culture-independent techniques may reduce time to diagnosis overall, a core issue remains the time to CSF sampling through LP. Subgroup analysis of patients presenting via A&E who had meningitis listed as a differential enabled us to focus on the time-to-intervention for patients in whom clinicians suspected meningitis. Currently, BIA guidelines state that within the first hour the patient should receive antibiotics, have blood cultures taken, and undergo LP, amongst other interventions.⁹ Our data showed that these targets are not being met.

The reasons for delay to CSF collection are multifactorial. In the literature, the use of neuroimaging prior to LP has frequently been targeted as a cause for the observed delay. However, our data demonstrates that CT does not appear to be associated with increased time to LP. Given the widespread availability of CT in emergency departments, its utility in excluding differentials, and presented data suggesting it does not delay LP, our findings support current clinical practice

of obtaining of CT in suspected meningitis cases, where indicated. The root cause for delays in CSF sampling are likely attributable to systems-based delays rather than decision making and warrant dedicated process mapping.¹⁷ Going forward, diagnostic delay secondary to deferred CSF collection may be offset by early serum-based PCR diagnostics.

Quicker and more accurate diagnostic modalities are needed more than ever, highlighted by one third of our bacterial meningitis patients having no causative pathogen identified (29/87; 33%). Crucially, mortality rate within this group was high, at 7% - notably the same mortality rate as meningococcal meningitis. Rapid, accurate diagnostics are essential in enabling tailored antimicrobial therapy. Indeed, several centres have started integrating rapid multiplex PCR technology into their diagnostic workflows; however, many current screening sequencing tests are limited to tertiary centres or entail prolonged result turnaround times.¹⁸⁻²⁰ We envisage that further advancements in workflow development to optimise DNA/RNA extraction methods and subsequent bioinformatic analysis will enable development of point-of-care, unbiased genomic sequencing technologies in the future.²¹⁻²⁵ This is in line with the WHO 2030 roadmap to defeating meningitis, as well as enabling closer epidemiological mapping of local disease outbreaks.²⁶

TB meningitis patients included in this retrospective study were in keeping with expected clinical presentation and outcome.²⁷⁻²⁹ Again, the means of diagnosis highlight the importance of modern diagnostic modalities such as PCR. This finding is critical in the context of research consistently demonstrating that delayed diagnosis is associated with poor outcomes. In recent decades the diagnosis of TB meningitis has made several advances, particularly surrounding volume of CSF sampled, exploration of extracranial TB, and the use of novel rapid diagnostics.³⁰⁻³² Fungal meningitis is typically seen in immunocompromised individuals and incurs significant impact on patient outcomes, as well as generating healthcare costs.³³ Our dataset was small but mirrored these findings.

Our data closely mimic findings reported in a national audit of meningitis management.¹⁶ In particular, our data concurs on delay in key interventions, underuse of culture-independent investigations, and varied adherence to BIA guidance. We echo their conclusions that further steps need to be taken to ensure clinical translation of current BIA guidelines, and agree that the implementation of NICE guidelines will likely improve practice.

Strengths and limitations

Demographic and laboratory data from our bacterial, viral, TB, and fungal meningitis datasets were in-keeping with expected values, suggesting external

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validity of our dataset. Retrospective analysis of ten-years enables time for management changes to be observed and take effect, enabling a more holistic picture of meningitis management, in contrast to a cluster-based approach.

This study has several limitations. Firstly, retrospective data limits the conclusions that can be drawn from comparative statistical analysis. Selection of our patient dataset was subject to several limitations; initial identification of patients was based upon clinical coding which relies upon accurate coding; our study excluded patients with ventriculitis, cerebral abscess, and empyema, all of which can occur as a result of bacterial meningitis and may have resulted in exclusion of meningitis cases with such complications; patients who did not undergo CSF sampling (and who did not have a causative organism identified through other means such as blood culture or serum PCR) were excluded; all of which may have limited our initial dataset. These factors may also have led to inadvertent case misclassification or under-ascertainment of atypical presentations. We acknowledge that excluding patients who did not undergo lumbar puncture and had no microbiological confirmation may introduce selection bias, potentially under-representing patients who were too unwell or contraindicated for LP. Time-to-intervention data was based upon the time that interventions were recorded in clinical notes, which may not match reality. For instance, in the case of a patient with meningococcal sepsis, antibiotics may have been administered rapidly, and logged on a computer system once the patient was stabilised. Discrepancies such as this are not detected in our dataset, and therefore our time-to-intervention data may be viewed as a best-estimate.

Conclusions

This retrospective study identifies persistent weaknesses in the diagnostic and treatment pathways for infective meningitis. Over one-third of bacterial cases lacked a confirmed pathogen, reflecting underuse of culture-independent diagnostics. Broader implementation of rapid, point-of-care genomic testing could markedly improve detection and streamline management. In viral meningitis, early pathogen identification was associated with shorter hospital stay and reduced empiric antibiotic exposure. Delays in antibiotic administration and lumbar puncture remain common,

despite evidence that neuroimaging itself does not account for these delays.

These findings highlight three priorities for acute care pathways: (i) embed culture-independent testing (CSF/serum PCR) at first contact; (ii) reduce door-to-needle and door-to-LP times through workflow redesign; and (iii) standardise antimicrobial use, reserving aciclovir for suspected encephalitis and de-escalating antibiotics once a viral cause is confirmed. Addressing these targets could reduce admissions, antibiotic exposure, and inefficiency across meningitis care.

Abbreviations

LP = lumbar puncture

CSF = cerebrospinal fluid

TB = tuberculosis

CNS = central nervous system

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Ethics statement

Patient data was collected as part of a registered audit (CARMS-14502) with the Clinical Governance and Patient Safety Team at University Hospitals Birmingham NHS Foundation Trust. Patient data was inputted into an anonymised database utilising electronic health records.

Conflicts of interest

The authors report no conflicts of interest regarding this piece of work.

Author contribution statement:

SW – Study concepts and design, data curation, formal analysis, original draft, guarantor (data integrity).

OT – literature research, data analysis, manuscript preparation, manuscript editing.

GT – literature research, data analysis, manuscript preparation, manuscript editing.

JS – literature research, data analysis, manuscript preparation, manuscript editing.

GHS – Study concepts and design, manuscript review guarantor (overall study integrity).

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References

- Okike IO, Ribeiro S, Ramsay ME, 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(4):301-7.
- Bijlsma MW, Brouwer MC, Kasmaoentalib ES, Kloek AT, Lucas MJ, Tanck MW, *et al*. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. *Lancet Infect Dis*. 2016;16(3):339-47.
- Martin NG, Sadarangani M, Pollard AJ, Goldacre MJ. Hospital admission rates for meningitis and septicaemia caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* in children in England over five decades: a population-based observational study. *The Lancet Infectious Diseases*. 2014;14(5):397-405.
- 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(18):1849-59.
- Khetsuriani N, Quiroz ES, Holman RC, Anderson LJ. Viral meningitis-associated hospitalizations in the United States, 1988-1999. *Neuroepidemiology*. 2003;22(6):345-52.
- 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. *The Lancet infectious diseases*. 2018;18(9):992-1003.
- Robinson CC, Willis M, Meagher A, Giesecke KE, Rotbart H, Glodé MP. Impact of rapid polymerase chain reaction results on management of pediatric patients with enteroviral meningitis. *Pediatr Infect Dis J*. 2002;21(4):283-6.
- Chadwick DR, Lever AML. The impact of new diagnostic methodologies in the management of meningitis in adults at a teaching hospital. *QJM*. 2002;95(10):663-70.
- 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.
- McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. *Lancet*. 2016;388(10063):3036-47.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007 Nov;18(6):800-4.
- de Ory F, Avellón A, Echevarría JE, Sánchez-Seco MP, Trallero G, Cabrerizo M, *et al*. Viral infections of the central nervous system in Spain: a prospective study. *J Med Virol*. 2013;85(3):554-62.
- McGill F, Griffiths MJ, Bonnett L, Martin A, Geretti AM, Michael BD, *et al*. PO232 Incidence and healthcare costs of viral meningitis in adults – a multicentre prospective observational study in England. *J Neurol Neurosurg Psychiatry*. 2017 Dec 1;88(Suppl 1):A73-A73.
- Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf*. 2014 Dec;5(6):229-41.
- McGill F, Griffiths MJ, Solomon T. Viral meningitis: current issues in diagnosis and treatment. *Curr Opin Infect Dis*. 2017;30(2):248-56.
- Ellis J, Harvey D, Defres S, Chandna A, MacLachlan E, Solomon T, *et al*. Clinical management of community-acquired meningitis in adults in the UK and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR). *BMJ Open*. 2022 Jul 1;12(7):e062698.
- Hanrahan JG, Carter AW, Khan DZ, Funnell JP, Williams SC, Dorward NL, *et al*. Process analysis of the patient pathway for automated data collection: an exemplar using pituitary surgery. *Front Endocrinol (Lausanne)*. 2023;14:1188870.
- Milburn J, Lechiile K, Siamisang K, Williams CG, Owen L, Gwakuba E, *et al*. Human Herpesvirus-6 Detection in Cerebrospinal Fluid on the BioFire FilmArray Meningitis/Encephalitis Panel in a High Human Immunodeficiency Virus-Prevalence African Setting. *Open Forum Infect Dis*. 2022 Jul;9(7):ofac229.
- Enne VI, Aydin A, Baldan R, Owen DR, Richardson H, Ricciardi F, *et al*. Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. *Thorax*. 2022 Dec;77(12):1220-8.
- Markovich K, Wingler MJB, Stover KR, Barber KE, Wagner JL, Cretella DA. Analysis of the Clinical Impact of the BioFire FilmArray Meningitis Encephalitis Panel on Antimicrobial Use and Duration of Therapy at an Academic Medical Center. *Diseases*. 2022 Nov 20;10(4):110.
- Lipkin WI. The changing face of pathogen discovery and surveillance. *Nat Rev Microbiol*. 2013;11(2):133-41.
- Pérez-Ruiz M, Navarro-Marí JM, Sánchez-Seco MP, Gegúndez MI, Palacios G, Savji N, *et al*. Lymphocytic choriomeningitis virus-associated meningitis, southern Spain. *Emerg Infect Dis*. 2012;18(5):855-8.
- Nguyen NL, Zhao G, Hull R, Shelly MA, Wong SJ, Wu G, *et al*. Cache valley virus in a patient diagnosed with aseptic meningitis. *J Clin Microbiol*. 2013;51(6):1966-9.
- Cordey S, Bel M, Petty TJ, Docquier M, Sacco L, Turin L, *et al*. Toscana virus meningitis case in Switzerland: an example of the ezVIR bioinformatics pipeline utility for the identification of emerging viruses. *Clin Microbiol Infect*. 2015;21(4):387.e1-4.
- Wilson MR, Sample HA, Zorn KC, Arevalo S, Yu G, Neuhaus J, *et al*. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. *New England Journal of Medicine*. 2019 Jun 13;380(24):2327-40.
- Török ME, Peacock SJ. Rapid whole-genome sequencing of bacterial pathogens in the clinical microbiology laboratory—pipe dream or reality? *Journal of Antimicrobial Chemotherapy*. 2012;67(10):2307-8.
- Wilkinson RJ, Rohlwick U, Misra UK, van Crevel R, Mai NTH, Dooley KE, *et al*. Tuberculous meningitis. *Nat Rev Neurol*. 2017 Oct;13(10):581-98.
- Török ME. Tuberculous meningitis: advances in diagnosis and treatment. *Br Med Bull*. 2015 Mar;113(1):117-31.
- Marx GE, Chan ED. Tuberculous Meningitis: Diagnosis and Treatment Overview. *Tuberc Res Treat*. 2011;2011:798764.
- Donovan J, Cresswell FV, Thuong NTT, Boulware DR, Thwaites GE, Bahr NC, *et al*. Xpert MTB/RIF Ultra for the Diagnosis of Tuberculous Meningitis: A Small Step Forward. *Clinical Infectious Diseases*. 2020 Nov 5;71(8):2002-5.
- Ho J, Marais BJ, Gilbert GL, Ralph AP. Diagnosing tuberculous meningitis - have we made any progress? *Trop Med Int Health*. 2013 Jun;18(6):783-93.
- Riste M, Hobden D, Pollard C, Scriven JE. Diagnosis of tuberculous meningitis with invasive pulmonary sampling. *The Lancet Infectious Diseases*. 2018 Jan 1;18(1):25-6.
- Charalambous LT, Premji A, Tybout C, Hunt A, Cutshaw D, Elsamadicy AA, *et al*. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. *J Med Microbiol*. 2018 Feb;67(2):215-27.

*Infective Meningitis: 10 year retrospective cohort study***Supplementary Material 1****Table 4.** Treatment for viral meningitis patients; with subgroup analysis of 'likely' and 'confirmed' viral meningitis cases.

	All viral meningitis (n=184)	'Likely' viral meningitis (n=102)	'Confirmed' viral meningitis (n=82)
Received antiviral treatment	65%	64%	67%
Duration of antiviral treatment (median + IQR)	6 days (IQR 3 – 11)	6 days (IQR 4 – 10)	7 days (IQR 3 – 14)
Patterns of antiviral treatment:			
Not prescribed at all	35%	36%	33%
Empiric only (stopped antivirals once viral meningitis confirmed / suspected)	36%	42%	29%
Empiric and definitive	26%	21%	32%
Definitive only	3%	1%	6%
Received antibiotics during admission	75%	77%	71%
Duration of antibiotic treatment (median + IQR)	4 days (IQR 2 – 6)	5 days* (IQR 2 – 8)	3 days* (IQR 2 – 5)

* = $P < 0.05$.**Table 5.** Treatment for bacterial meningitis.

	N (%)
Adjunctive dexamethasone prescribed?	38/87 (44%)
Pre-hospital antibiotics administered?	4/87 (5%)
A&E antibiotic management (data available for n = 64)	
Ceftriaxone prescribed	40/64 (63%)
Aciclovir prescribed within guidance (i.e. encephalitis a differential)	29/64 (45%)
Aciclovir prescribed outside guidance	16/64 (25%)
Ward empiric antibiotic management (data available for n = 81)	
Ceftriaxone prescribed	61/81 (75%)
Aciclovir prescribed within guidance (i.e. encephalitis a differential)	46/81 (57%)
Aciclovir prescribed outside guidance	32/81 (40%)
Definitive antibiotics in line with local guidelines (data available for n = 34)	26/34 (92%)
Percentage of patients who met need to for Listeria antibiotic cover*	38/87 (44%)
How many of these patients were correctly prescribed Listeria antibiotic cover?	23/38 (61%)
Time to first antibiotics (median + IQR)	98 minutes (41 – 242)
Antibiotics administered within the first hour? (data available for n = 61)	20/61 (33%)
Duration of antibiotic therapy (median + IQR):	
All bacterial meningitis	10 days (IQR 9 - 14)
Pneumococcal meningitis	14 days (IQR 14 – 18)
Meningococcal meningitis	8 days (IQR 8 – 10)
Neurosurgery required**	14/87 (16%)

*Amoxicillin antibiotic cover for Listeria should be provided to those deemed vulnerable. Local guidelines state that patients aged >60, diabetic patients, pregnant patients, and immunocompromised patients fall under this category.

**Neurosurgical input was required in 21% of pneumococcal meningitis patients (16% required EVD insertion) and 0% of meningococcal meningitis patients.

Supplementary Material 2**Epoch Analysis**

Our analysis demonstrated that CSF PCR utilisation (bacterial/ meningococcal/pneumococcal) decreased modestly from 25% to 20%, while viral CSF PCR use increased from 72% to 80%. The proportion of TB meningitis increased from 6% to 15%, whereas serum/blood PCR utilisation decreased from 14% to 10%. Median time to lumbar puncture increased from 13.9 hours (IQR 8.1–26.1) in the earlier epoch to 19.8 hours (IQR 12.6–27.7) in the later epoch, and median time to first antibiotic administration

rose from 2.3 hours (IQR 1.35–4.37) to 3.0 hours (IQR 1.66–7.41).

These findings suggest greater use of viral molecular diagnostics and an increasing proportion of TB meningitis cases in the latter half of the decade, but no temporal improvement in key time-to-intervention metrics. Importantly, there was no significant difference in ITU admission rate or mortality rate between epochs, suggesting that these workflow changes have not yet translated into measurable outcome improvements.