Journal of Infection 89 (2024) 106223

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Viruses and Viral Diseases

Epidemiological trends in viral meningitis in England: Prospective national surveillance, 2013–2023

Seilesh Kadambari [a,b,*], Fariyo Abdullahi [c], Cristina Celma [d], Shamez Ladhani [c,e]

[a] Department of Paediatric Infectious Diseases, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[b] UCL Great Ormond Street Institute of Child Health, London, UK
[c] Immunisation and Vaccine Preventable Diseases Division, UK Health Security Agency, London, UK
[d] Enteric Virus Unit, UK Health Security Agency, Colindale, London, UK
[e] Paediatric Infectious Diseases Research Group and Vaccine Institute, Institute of Infection and Immunity, St George's University of London, London, UK

ARTICLE INFO

Article history:
Accepted 4 July 2024
Available online 8 July 2024

Keywords:
Viral
Meningitis
Enterovirus
Parechovirus
Herpes simplex virus
Epidemiology

SUMMARY

Background: In the conjugate vaccine era, viruses are the most common cause of meningitis. Here, we evaluated epidemiological trends in laboratory-confirmed viral meningitis across all age-groups over an 11-year period in England.

Methods: In England, hospital laboratories routinely report laboratory-confirmed infections electronically to the UK Health Security Agency. Records of positive viral detections in cerebrospinal fluid during 2013–2023 were extracted. Incidence rates with confidence intervals were calculated using mid-year resident population estimates.

Results: There were 22,114 laboratory-confirmed viral meningitis cases, including 15,299 cases during 2013–19 (pre COVID-19), with a gradual increase in incidence from 3.5/100,00 (95%CI: 3.3–3.6) to 3.9/100,000 (95%CI: 3.6–4.1). During 2020–21 when pandemic restrictions were in place, there were 2061 cases (1.8/100,000; 1.7–1.9), which increased to 4754 (4.2/100,000; 4.0–4.3) during 2022–23 (post pandemic restrictions).

Infants aged < 3 months accounted for 39.4% (8702/22,048) of all cases, with a stable incidence 2013–19 (504/100,000, 95%CI: 491–517), followed by a significant decline during 2020–21 (204/100,000; 188–221) and then an increase during 2022–23 (780/100,000; 749–812), with enteroviruses being the commonest cause (84.9%, 7387/8702; 424.74/100,000; 95%CI: 415.12–434.51), followed by parechoviruses (9.1%, 792/8702; 45.54/100,000; 95%CI: 42.42–48.82) and herpes simplex virus (4.4%, 380/8702; 21.85/100,000; 95%CI: 19.71–24.16). Pandemic restrictions were associated with significant declines in the incidence of enterovirus (77.7%) and parechoviruses (64% lower), with rebounds after societal restrictions were lifted.

Conclusions: Rates of viral meningitis have returned to pre-pandemic levels since societal restrictions were lifted. The highest incidence of viral meningitis remains in infants aged < 3 months and most commonly due to enteroviral infection.

Introduction

In the conjugate vaccine era, viruses account for the largest burden of meningitis across all groups.[1] In high-income countries, the widespread use of increasingly sensitive multiplex PCR assays, syndromic testing and uptake of recommendations in national guidelines have led to significant increases in the rates of detection of viruses in cerebrospinal fluid.[2–4]

In the UK, enteroviruses (EVs) account for more cases of childhood meningitis than all bacterial causes of meningitis combined.[5] Human Parechovirus (HPeV) are the second most common cause of viral meningitis in young infants. A British Paediatric Surveillance Unit found that 11% and 23% of infants younger than 90 days of age with EV and HPeV meningitis, respectively, required admission to a high dependency or intensive care unit.[6] There are, however, no preventive or therapeutic interventions for either EV or HPeV, in part due to a lack of epidemiological data to inform their development or use.

Understanding long terms trends in viral meningitis could support clinical practice through planning healthcare services, monitor

* Correspondence to: Department of Paediatric Infectious Diseases, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK.
E-mail address: Seilesh.kadambari@gosh.nhs.uk (S. Kadambari).

https://doi.org/10.1016/j.jinf.2024.106223

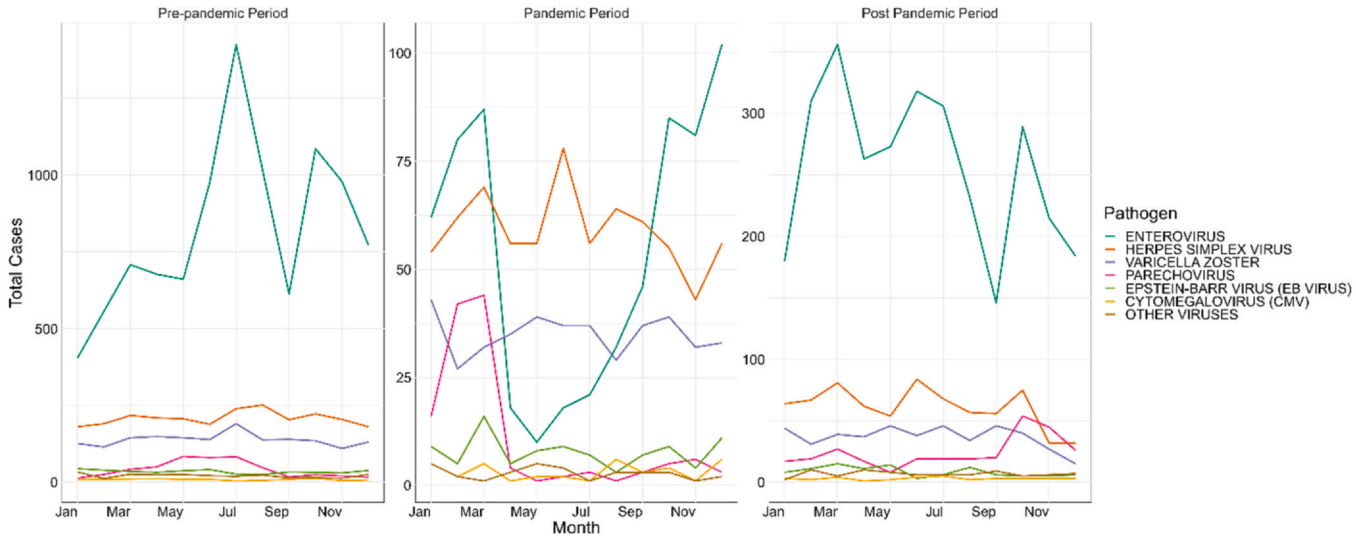

Fig. 1. Seasonal trends in viral meningoencephalitis during 2013–2023 and the impact of the COVID-19 pandemic on cyclicality.

circulating strains which have pandemic potential and also inform future development of antivirals and vaccines. Here, we use national laboratory surveillance data to describe trends in viral meningitis during 2013–2023 and understand the impact of the COVID-19 pandemic.

Methods

Data source

The UK NHS microbiology laboratories routinely report clinically significant infections electronically on a voluntary basis to the UK Health Security Agency (UKHSA) using the Second Generation Surveillance System (SGSS). For this study, demographic (age, gender, geographic region) and strain-specific (sample type, date of detection, molecular typing) records of all viruses detected in the cerebrospinal fluid (CSF) of patients of any age between 01 January 2013 and 01 November 2023 were extracted from SGSS. Duplicate records were removed, and reports of the same pathogen from the patient within 30 days were considered a single episode. SGSS does not include any clinical or outcome data.

We additionally interrogated the UKHSA laboratory information system, which contains information on EV detection status and typing data. NHS microbiology laboratories are requested to routinely submit all positive EV samples for EV typing, in part to fulfil the WHO commitment of demonstrating no circulating poliovirus. EV typing results were obtained from 01 January 2013 to 01 July 2023.

Statistical analysis

Data were analysed using R (version 4.3.2). Where age was available, cases were grouped into the eight age groups: < 3 months, 3–11 months, 1–4 years, 5–14 years, 15–24 years, 25–44 years, 45–64 years and ≥65 years. To compare case numbers and incidence rates before, during and after the COVID-19 pandemic, the pre-pandemic, pandemic and post-pandemic periods were defined as between 01 January 2013 and 31 December 2019, 01 January 2020 and 31 December 2021, and 01 January 2022 and 01 November 2023 respectively. Categorical variables were analysed as proportions and compared using the Chi-squared test or Fisher exact test where appropriate. Incidence rates of viral meningitis were calculated using age-specific mid-year population estimates from each relevant year of study and were obtained from the Office for National Statistics (www.statistics.gov.uk). Denominators for < 3-month-olds and 3- to 11-month-olds were calculated by dividing the population of infants aged < 1 year by 12 and multiplying by 3 and 9, respectively. The 95% confidence intervals (95%CI) for incidence rates were determined using the binomial distribution.

Ethics approval

UKHSA has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases, and, as such, individual patient consent is not required.

Results

There was a total of 22,114 laboratory confirmed viral meningitis cases during the surveillance period. Of these 15,299 (4.0/100,000, 95%CI: 3.9–4.0) were during 2013–19, which reduced to 2061 (1.8/100,000, 95%CI: 1.7–1.9) during 2020–21 and then increased to 4754 (4.2/100,000, 95%CI: 4.0–4.3) during 2022–23. The median age among 22,048 cases with a reported age was 19 years (IQR: 0–37), and 47.8% (10,530/22,048) were aged < 15 years. There was no difference in sex distribution, 49.9% (10,945/21,914) were female (p = 0.871), among the 21,914 cases with reported sex.

During 2013–2019, EVs were the only group of viral infections to demonstrate a seasonal trend with a characteristic peak in the summer and fall in the winter (Fig. 1). However, during 2020–2022, peaks in EV incidence were seen in the winter months and troughs in the summer months. In the post-pandemic era, it seems that typical seasonal trends in EV are being re-established, with a higher incidence during the summer of 2023. There was no significant disruption in long-term HPeV trends as a consequence of the COVID-19 pandemic (Fig. 2). Characteristic biennial peaks in HPeV were seen in even-numbered years but a smaller increase during 2020.

Infants aged < 3 months accounted for 39.4% (8702/22,048) of cases with known age (Fig. 3). The incidence was significantly higher in this age group, followed by 3- to 11-month-olds and 24- to 44-year-olds. Before the COVID-19 pandemic, the incidence of viral meningoencephalitis in infants < 3 months was 504/100,000 (95%CI: 491–517); during the pandemic, it fell to 204/100,000 (95%CI: 188–221) and post-pandemic increased to 780/100,000 (95%CI: 749–812). The rebound in incidence of viral meningoencephalitis was substantially higher after COVID-19 in infants less than 3 months old than in other age groups.

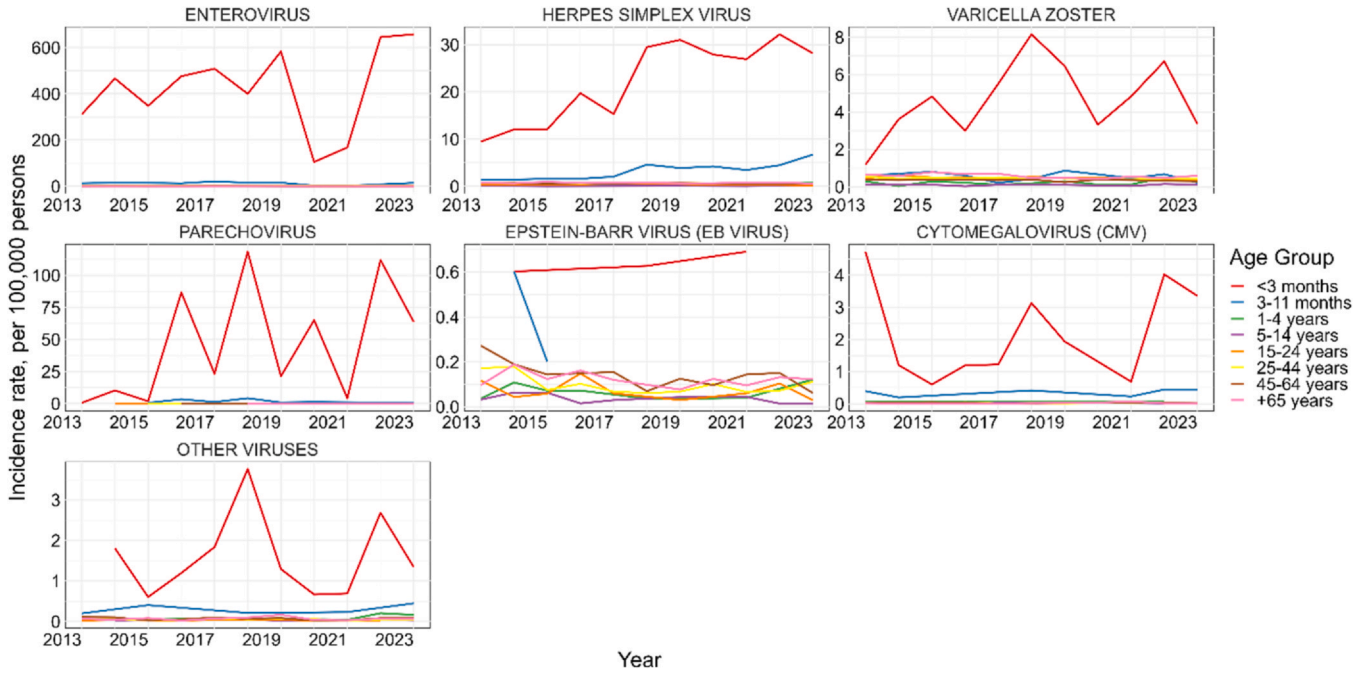

Fig. 2. Annual trends in incidence of viral meningitis across all age groups during 2013–2023.

EVs caused the majority of all cases of viral meningoencephalitis (13,585/22,114; 61.4%), followed by HSV (3943/22,114; 17.8%) and VZV (2527/22,114; 11.4%). In infants younger than 3 months, EV's caused the great majority of disease and accounted for 84.9% (7387/8702) of all cases in this age group followed by HPeV (792/8702; 9.1%) and HSV (380/8702; 4.4%) (Fig. 4). In total, 86.5% (792/916) of all cases of HPeV were seen in infants less than 3 months. In 2013, the incidence of HPeV meningitis in infants less than 3 months was 0.6/100,000 (95%CI: 0.0–3.3) and increased in 2023 to 63.7/100,000 (95%CI: 51.6–78.0) (Table 1).

In 2023, the incidence of neonatal (i.e., < 31 days old) EV meningoencephalitis was 80.8/100,000 live births (95%CI: 73.6–88.4), HPeV meningoencephalitis was 9.0/100,000 live births (95% CI: 6.7–11.8) and VZV meningoencephalitis was 0.4/100,000 live births (95% CI: 0.0–1.3). During the 10-year surveillance period, the incidence of neonatal HSV meningoencephalitis has increased in 2013 from 2.0/100,000 live births (95%CI: 1.0–3.4) to 4.9/100,000 live births (95% CI: 3.2–7.0) in 2023.

During the COVID-19 pandemic, there were significant declines in the incidence of EV (77.7% decline, 2.6/100,000 in the pre-pandemic period vs 0.6/100,000 during the pandemic period) and HPeV (64% decrease, 0.1/100,000 in 2019 vs 0.2/100,000 in 2021)) with rebounds to pre-pandemic levels after societal restrictions lifted. There was little to no change in the incidence of CMV, EBV and VZV prior to, during and post COVID-19 pandemic (Fig. 3). Incidence of CMV remained at 0.03/100,000 (pre-pandemic 95%CI: 0.02–0.03, pandemic 95% CI: 0.02–0.05 and post-pandemic 95%CI: 0.02–0.04), VZV at 0.4/100,000 (pre-pandemic 95%CI: 0.3–0.4, pandemic 95% CI: 0.3–0.4 and post-pandemic 95%CI: 0.3–0.4) and EBV at 0.1/100,000 (pre-pandemic 95%CI: 0.1–0.1, pandemic 95% CI: 0.1–0.1 and post-pandemic 95%CI: 0.1–0.1) within all three periods.

During the 10-year surveillance period, 27.7% (6573/23,662, 27.7%) of EV samples were genotyped (Table 2). The five most common EV genotypes across the surveillance period were E30 (n = 1041), E6 (n = 765), CV-B5 (n = 746), E9 (n = 552) and E18 (n = 542). In 2017, there were 337 cases of viral meningoencephalitis due to E30. There was no dominant EV type in any of the other years or age groups across the ten-year surveillance period. Notably, 132 cases of EV-71 were identified and only two cases of EV-68 during the decade long surveillance.

Discussion

In this prospective national population-based surveillance study, we found that the rates of viral meningitis reduced significantly when COVID-19 pandemic restrictions were in place, mainly because of large reductions in EV and HPeV infections across all age groups. After pandemic restrictions were removed, the rates of viral meningo-encephalitis have rebounded and appear to have stabilised, including the seasonal trends with pre-pandemic summer peaks in EV disease and biennial peaks in HPeV disease.

During the COVID-19 pandemic, a range of behavioural measures and societal restrictions contributed to huge reductions in the transmission of respiratory pathogens, including viruses that can cause meningitis.[7–10] In the USA, there have been resurgences in the rates of EV and HPeV meningitis in young infants since social restrictions lifted which led to the Centre for Disease Control issuing an advisory notice in July 2022 due to a resurgence of severe HPeV disease in young infants.[11] In England, we found a disproportionate rebound in the rates of EV and HPeV meningitis in infants younger than three months compared with increases in other age groups post-pandemic. There are potentially environmental (i.e. increased social mixing with high rates of circulating infection in older siblings who transmit infection in the household), immunological (i.e. loss of maternal antibody, which may confer transplacental protection in newborn infants, due to lack of exposure to the viruses during pandemic restrictions) and virological (i.e. the potential emergence of more pathogenic EV and HPeV strains) reasons for the observed increase in younger infants and these trends should continue to be carefully monitored through enhanced surveillance mechanisms.

We showed that EV's cause 85% of all disease in infants under three of months of age and account for more than double all the cases of laboratory confirmed bacterial meningitis in this age group in England.[12] In the U.K, 11% of all young infants with EV meningitis are admitted to an intensive care setting. Moreover, EV infection can cause severe sepsis-like syndrome, catastrophic neurological disease and occasional mortality in heavily immunosuppressed adults and children. To our knowledge, there are no phase 1 – 3 non-EV-71 antiviral or vaccine trials evaluating clinical efficacy in infants, young children or immunosuppressed populations. Our data should

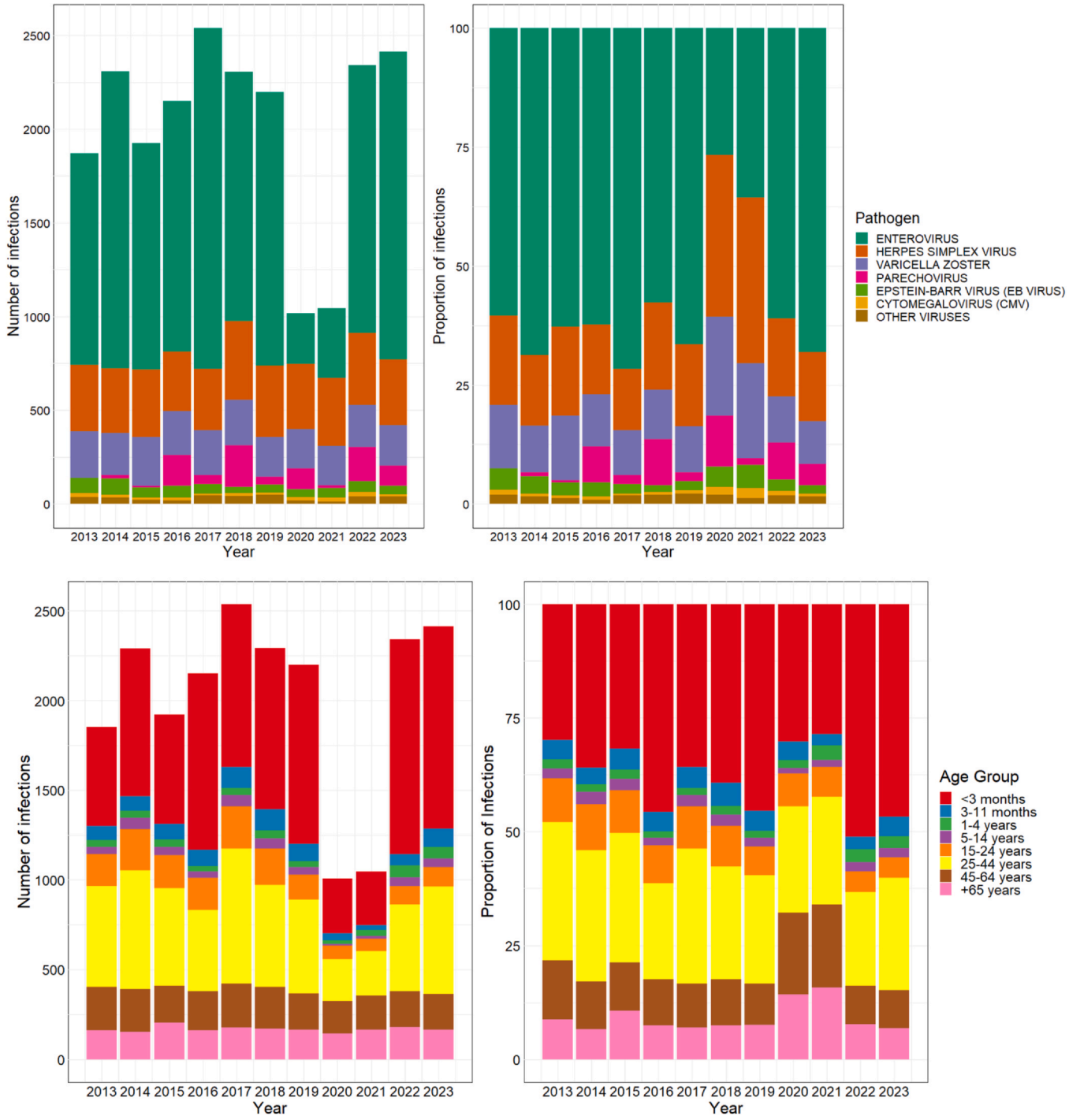

Fig. 3. Trends in age and pathogen in viral meningoencephalitis during 2013–2023.

encourage the development of novel and repurposed antiviral agents using pragmatic randomised controlled trials and large treatment registries.

In a previous national surveillance study of viral meningitis conducted in England during 2004–2013, we observed a sevenfold increase in the rates of viral meningitis across all age groups,[2] which was driven by increased detection through widespread use of PCR-testing across NHS microbiology laboratories. In the current surveillance, the overall rates of viral meningitis seem to have broadly stabilised over the last decade which implies molecular testing for the commonest viruses causing meningitis have been integrated across England. However, we found over a 60-fold increase in the rates of HPeV meningitis between 2013 and 2023. This is most likely due to increasing inclusion of HPeV as a target in multiplex PCR assays, especially in infants with suspected meningitis.[13,14] The increase in HPeV meningitis also suggests that clinicians are aware that HPeV should be routinely tested as part of a syndromic panel in young infants with suspected meningitis. It is not possible to distinguish HPeV as a cause of meningitis compared with EV or other bacterial pathogens. Moreover, the vast majority of infants with HPeV meningitis have absent CSF pleocytosis, which emphasises the importance of routine HPeV testing in any young infant who has an LP done to rule out meningitis.[6] Consequently, it is likely that HPeV meningitis continues to be underdiagnosed, especially in young infants.

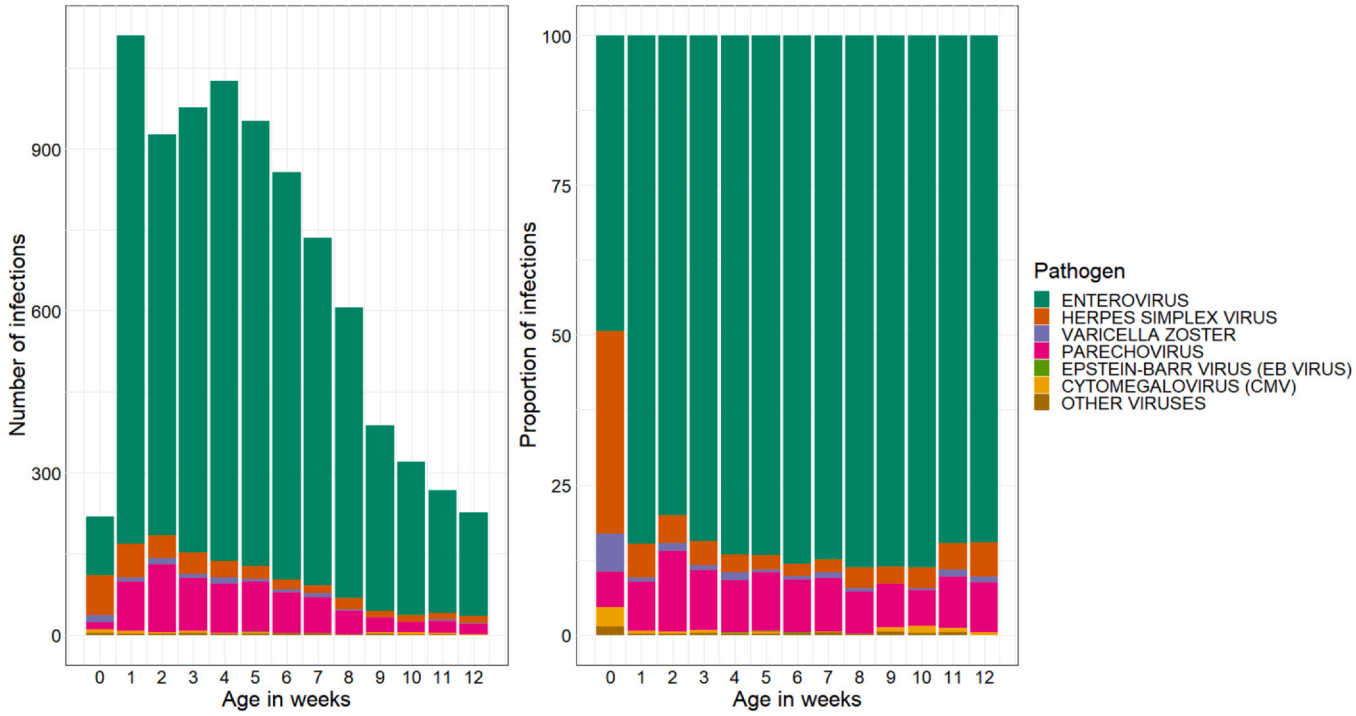

Fig. 4. Number and proportion of viral infections by pathogen and age in weeks.

Table 1
Incidence and number of cases (in parenthesis) of viral meningitis by age group in 2023.

Age group	Cytomegalovirus	Enterovirus	Epstein-Barr virus	Herpes simplex virus	Other viruses	Parechovirus	Varicella zoster	Overall
< 3 months	3.35 (5)	657.38 (980)	0.00 (0)	28.17 (42)	1.34 (2)	63.73 (95)	3.35 (5)	757.33 (1129)
3–11 months	0.45 (2)	14.31 (64)	0.00 (0)	6.71 (30)	0.45 (2)	0.45 (2)	0.22 (1)	22.58 (101)
1–4 years	0.00 (0)	1.34 (33)	0.12 (3)	0.69 (17)	0.16 (4)	0.00 (0)	0.28 (7)	2.59 (64)
5–14 years	0.00 (0)	0.41 (28)	0.01 (1)	0.12 (8)	0.03 (2)	0.01 (1)	0.12 (8)	0.7 (48)
15–24 years	0.00 (0)	1.05 (71)	0.03 (2)	0.19 (13)	0.00 (0)	0.01 (1)	0.33 (22)	1.62 (109)
25–44 years	0.00 (0)	2.72 (415)	0.11 (17)	0.58 (88)	0.05 (8)	0.01 (1)	0.45 (68)	3.91 (597)
45–64 years	0.02 (3)	0.23 (34)	0.06 (9)	0.62 (91)	0.1 (14)	0.03 (5)	0.29 (43)	1.36 (199)
+65 years	0.02 (2)	0.17 (18)	0.12 (13)	0.56 (60)	0.07 (7)	0.03 (3)	0.59 (63)	1.56 (166)
Total	0.02 (12)	2.88 (1643)	0.08 (45)	0.61 (349)	0.07 (39)	0.19 (108)	0.38 (217)	4.23 (2413)

EV-71 has been responsible for large outbreaks of hand foot and mouth disease (HFMD) in children across China, which led to the rapid development of vaccination to control the infection.[15] EV-68 and EV-71 have also caused outbreaks of acute flaccid paralysis (AFP) globally.[16,17] Interestingly, 132 cases of EV-71 infection were identified in our surveillance over the last decade. We found only two cases of EV-68 in the same period. Seroprevalence of EV-68 in the UK, however, approaches 100%, and increasing circulation may have contributed to an uptick in cases of AFP in 2018.[18,19] In our decade-long surveillance, there was an increase in the rates of E30 detection during 2017 which coincided with a European outbreak, and none of the other dominant genotypes seen in other years were observed other than in 2017.[20] In the aftermath of the COVID-19 pandemic, there have been outbreaks of novel EV-71 genogroups causing severe HFMD in China, E11 causing severe neonatal disease in France and coxsackie B causing myocarditis in young infants in

Table 2
EV genotype across all age groups during 2013–2023.

Year	EV-A71	EV-A	CV-B4	CV-B5	E6	E9	E11	E18	E30	Other EV-B	EV-C	EV-D68	Total by year
2013	34	23	13	64	125	2	19	3	210	275	0		755
2014	8	15	31	127	16	210	43	90	197	269	0		975
2015	12	11	18	88	191	22	24	101	13	107	0		569
2016	2	15	10	88	105		37	9	51	211	0	2	520
2017	20	30	45	93	94	19	27	74	337	163	0		857
2018	12	20	8	56	181	22	45	91	124	164	0		715
2019	25	22	87	82	11	40	62	65	80	427	0		814
2020	4	1	4	31		8	3	6	10	57	0		120
2021	1	18	18	4	4	4	6	2		138	0		177
2022	2	33	27	105	22	122	87	27	4	281	3		686
2023*	12	0	3	8	16	103	13	74	15	143	1		385
Total by strain	132	188	264	746	765	552	366	542	1041	2235	4	2	6573

Only strains which represent > 5% or over throughout the surveillance period are reported, with minor strains grouped by species (A, B and C). We have reported EV-A71 and EV-D68 as exceptions due to their relevance as potentially outbreak causing strains.
* from 1/1/23 - 30/6/23

England.[21–23] These reports emphasise the importance of local microbiology laboratories submitting positive EV samples to the reference laboratories for genotyping to monitor circulating strains, identifying outbreaks early and informing public health measures.

The significant reduction in EV and HPeV meningoencephalitis during pandemic restrictions, both most often transmissible through respiratory secretions, contrasts with the relatively stable rate of latent human herpes viral infections (i.e. CMV, EBV and HSV) during the entire decade-long surveillance period. We did, however, find a 2.5-fold increase in the rates of neonatal HSV meningoencephalitis in 2023 compared with 2013. Neonatal systemic HSV infections are rare but potentially catastrophic, with a case-fatality rate of up to 30% mortality even with treatment.[24] The increase in neonatal HSV parallels the increase in sexually transmitted infections, including HSV, in women of childbearing age in England over the last decade.[25] The higher rates of HSV meningoencephalitis in young infants are also likely due to more timely testing for HSV in severely unwell neonates by clinicians because of increased awareness of the condition, wider integration of multiplex PCR testing which includes an HSV target and, potentially, adoption of US guidelines to test asymptomatic neonates born to women with a history of genital herpes compared with a more conservative approach recommended in the UK.[26] In the last five years, there have been various HSV vaccine candidates which have entered phase 2 trials in adults.[27] Improving our understanding of the epidemiology of HSV, especially neonatal HSV, including more precise estimates on clinical burden, genotyping and seroprevalence, will be important in order to inform vaccine trial development.

This study has some limitations. Only cases with a confirmed virus identified in CSF were included and cases of CSF pleocytosis (with no pathogen) or clinically diagnosed meningoencephalitis cases were excluded. SGSS does not contain any clinical or laboratory data. We are therefore unable to comment on risk factors, disease severity or clinical outcomes. CMV and EBV are carried in the lymphocytes of infected individuals so a positive isolate in CSF may represent either infection, reactivation or “bystander” without being responsible for the underlying disease process. In the absence of radiological data, it was not possible to distinguish cases of meningitis and encephalitis. In our previous national surveillance conducted during 2004 – 2013, only 2.6% of EV-positive samples had genotyping data compared with 27.7% in the current study. The majority of CSF samples, however, are still not genotyped, which means it is not possible to gain a more detailed understanding of the molecular epidemiology of EV meningitis in England.

This surveillance provides a national, population-based analysis of laboratory-confirmed viral meningitis across all age groups over a decade-long surveillance period. We found that the rates of viral meningitis are currently stable and returned to pre-pandemic levels. Our findings highlight the very high burden of enterovirus infections, especially in young infants and should encourage the development of vaccines and effective therapeutic interventions against EVs especially given their ability to cause large outbreaks of severe disease and their potential for future pandemics.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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