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Trends in Paediatric Viral Meningitis and Encephalitis With Unconfirmed Aetiology: A Spanish Population-Based Study, 2016–2020

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ABSTRACT

Aim: The prevalence of meningitis and encephalitis of unknown aetiology in Spanish children has not been specifically documented before. The aim of this study is to describe the epidemiology and trends of these clinical conditions between 2016 and 2020.

Methods: Retrospective study analysing hospitalised children <15 years with meningitis and encephalitis/encephalomyelitis of unknown origin (ICD-10 codes) in Spain (2016–2020). Data from National Registry of Hospitalizations and National Institute for Statistics were used to calculate age-stratified hospitalisation rates (HR). Statistical analysis included Poisson regression to calculate hospitalisation rate ratios (HRR) by age groups and years and forecasting methods to predict 2020 HRs.

Results: Four thousand six hundred children were hospitalised with viral meningitis and encephalitis-encephalomyelitis of unknown origin, resulting in a HR of 7.8/10⁵ inhabitants. The highest HR was observed in children under 1 year (49.1/10⁵) and those aged 5–9 (10.4/10⁵). The global HR for viral meningitis (3.64/10⁵) was lower than for encephalitis-encephalomyelitis (4.2/10⁵). Hospitalisations decreased from 1475 (2016) to 452 (2020), attributed to enhanced pathogen detection methods and COVID-19 preventive measures.

Conclusion: Undiagnosed central nervous system entities remain a significant cause of paediatric hospitalisations in Spain, despite a declining incidence. Enhanced diagnostic strategies, including expanded microbiological testing and molecular epidemiology surveillance, could prove beneficial.

Abbreviations: CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; HRR, Hospitalisation Rate; HRR, Hospitalisation Rate Ratio; INE, National Institute of Statistics; NHR-CMBD, National Hospitalisation Registry—Minimum Basic Data Set.

Marina Pons-Espinal and Noemi López-Perea contributed equally to this work and share first authorship.

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Summary

- This study analyses paediatric encephalitis-encephalomyelitis and meningitis with unknown aetiology in Spain (2016–2020), showing significant hospitalisation decreases, particularly during the COVID-19 pandemic.
- Advanced diagnostic techniques and COVID-19 related interventions may have contributed to this declining trend.
- The findings underscore the importance of developing more accurate diagnostic methods for central nervous system infections.

1 | Introduction

Meningitis and encephalitis are infectious and/or immune-mediated diseases of the central nervous system (CNS) that can lead to serious consequences and potentially fatal outcomes. Infections, mostly caused by viruses, are often the cause or trigger of these episodes. The incidence and aetiology of meningitis and encephalitis vary by age and geographical location [1]. However, despite extensive diagnostic efforts, the cause remains unidentified in over half of cases [2, 3]. A wide range of pathogens can cause these diseases, consequently necessitating the use of multiple microbiological tests to establish the aetiological diagnosis [4]. Additionally, significant challenges remain in identifying causative microbiological agents. These include detecting unknown pathogens that may cause or contribute to disease development and monitoring emerging infectious outbreaks in new geographical regions.

Advances in vaccination and surveillance have significantly reduced the burden of infectious meningitis. Currently, viral meningitis is more prevalent than bacterial meningitis (accounting for nearly 30% of all cases) but is associated with lower mortality rates and fewer complications [5]. This condition is commonly characterised by the sudden onset of signs and symptoms of meningeal inflammation, cerebrospinal fluid (CSF) pleocytosis and the absence of microorganisms on Gram stain and/or on routine culture [6]. The global incidence of viral meningitis ranges from 0.26 to 17 cases per 10^5 [7]. A study in New Zealand reported an incidence of 9.6 per 10^5 of aseptic meningitis in children in 2020 [8]. Viral meningitis affects different age groups, with more severe consequences in paediatric patients compared to adults. These clinical entities typically have two peaks during childhood: first during the initial months of life, then again around age 5 [9]. Seasonality has been observed in temperate climates, with peaks occurring in summer and autumn. Higher incidence rates are seen in tropical climates, aligning with the distribution patterns of enterovirus infections [10, 11]. Parechovirus, herpes simplex virus and varicella zoster are also known etiologies [7, 8, 11]. Encephalitis is characterised by an altered mental state and is often accompanied by acute fever, seizures, and/or neurological deficits. Pleocytosis in CSF, in conjunction with neuroimaging and electroencephalographic abnormalities, supports the diagnosis. Encephalitis is an important cause of morbidity and mortality, with variable incidences across regions and a higher incidence in children (<15 years) and older adults

(>70 years). The range of encephalitis in children in western countries can vary from 10.5 to 13.8 per 10^5 inhabitants, with a median incidence rate of 2.2 per 10^5 in adults [12]. Globally, Japanese encephalitis remains the single largest cause of viral encephalitis. In western countries, herpes simplex virus is the most common cause, followed by enteroviruses, although their incidence is likely underestimated [2, 13]. Notably, enteroviruses cause periodic epidemics of brainstem encephalitis in paediatric cohorts, especially in East and Southeast Asia. Outbreaks of brainstem encephalitis caused by enterovirus A71 have also occurred in France [14], Germany [15, 16] and Spain [17, 18]. In European countries, the tick-borne encephalitis virus is an important emerging cause of viral encephalitis [19].

Although the incidence and epidemiology of meningitis and encephalitis have been extensively studied in other settings [8, 12], to the best of our knowledge, there are no studies that characterise the cases of these clinical entities of unknown aetiology in the paediatric population in Spain. Therefore, this study aims to describe the epidemiological characteristics and temporal trends of paediatric encephalitis-encephalomyelitis and meningitis cases with suspected viral aetiology but unidentified specific pathogens in Spain from 2016 to 2020.

2 | Material and Methods

2.1 | Study Design and Data Sources

A retrospective descriptive study was conducted using data from the National Hospitalisation Registry—Minimum Basic Data Set (NHR-CMBD) for the period January 2016–December 2020 in Spain. The NHR-CMBD is an integral part of Spain's Health Information System. This database holds anonymized standardised clinical-administrative data from hospitalizations in both public and private hospitals, providing insights into patient morbidity. It is estimated to cover 99.5% of the Spanish population. The following data were extracted for each hospitalisation: age, sex, date of hospital admission and primary and secondary diagnoses codes (1–14) from January 1st, 2016 to December 31st, 2020. Diagnostic registration was performed by clinicians, without prior inter-hospital diagnostic consensus due to the study's retrospective nature. Population data stratification by age group and calendar year were obtained from the National Institute of Statistics (INE).

2.2 | Case Definition and Diagnostic Coding

The diagnostic code selection using the International Classification of Diseases, 10th edition (ICD-10), encompassed suspected viral cases of central nervous system infection where the aetiology was not specified or sufficiently characterised. Cases of meningitis of unknown origin were defined as those hospitalisations including one or more codes as their primary or secondary diagnosis: A87.8, A87.9, G02.0, G03.0 or G03.9. Similarly, encephalitis and encephalomyelitis of unknown origin cases were defined as hospitalisations with any of these codes: A83.8, A83.9, A85.2, A85.8, A86, G04.00, G04.01, G04.81, G04.90 or G05.3 [20]. The Technical Unit of ICD-10-ES, operating under the Spanish Ministry of Health, maintains a

comprehensive quality control system for diagnostic coding. This centralised unit oversees the development and implementation of coding materials, including standardised manuals, guidelines and regulations.

2.3 | Statistical Analysis

Descriptive analysis was conducted by year, age group (<12 months; 1–4 years; 5–9 years; and 10–14 years) and diagnosis group according to the mentioned ICD-10 codes (meningitis, encephalitis and encephalomyelitis of unknown origin).

Hospitalisation rates (HR) per 10⁵ population were calculated by year and age group. To compare among the study years, rate ratios for hospitalisation (HRR) were calculated using Poisson regression. The first year, 2016, was taken as the reference, then the HRR were expressed as the ratio between the year rate (overall and by age group) and the rate for 2016 in the same group. Confidence intervals (95% CI) were also calculated through Poisson regression, and *p*-values were defined as statistically significant if <0.05 for both tails. HRs between age groups were compared using the chi-square test, and results with *p* < 0.05 were considered statistically significant. Statistical analyses were performed using Stata -version 17 (StataCorp, Texas, USA).

FORECAST.ETS function implementation in Excel 2023 (Microsoft, USA) enabled hospitalisation rate (HR) value forecasting for 2020 based on 2016–2019 data. FORECAST.ETS utilises the AAA version of the Exponential Triple Smoothing (ETS) algorithm to project historical trends [21]. This helped elucidate the trends during the period 2016–2019 and visualise the discrepancies between the expected outcomes for 2020 and the actual occurrences due to the COVID-19 pandemic.

2.4 | Ethical Considerations

The study was approved by the institutional ethics committee of the Institut de Recerca Sant Joan de Déu (protocol PIC-104-21).

3 | Results

A total of 18427 hospitalizations due to meningitis and encephalitis-encephalomyelitis of unknown origin were reported in Spain during 2016–2020 (global HR: 11.10/10⁵ inhabitants). Children under 15 years of age represented 24.8% of the total cases (4600 hospitalizations), with a HR of 7.80/10⁵ inhabitants, with the highest rates for both combined entities observed in patients under 1 year of age (HR: 49.1/10⁵ inhabitants), followed by children aged 5–9 (HR: 10.4/10⁵ inhabitants) (Table 1). The differences in HR between infants under 1 year and all other age groups were statistically significant (*p* < 0.01).

Regarding meningitis of unknown origin, 2143 cases in children under 15 years were reported in Spain in the study period (HR 3.64/10⁵ inhabitants), with the highest rates documented in patients under 1 year (HR: 38.2/10⁵ inhabitants),

TABLE 1 | Meningitis and encephalitis-encephalomyelitis of unknown origin in children under 15 years of age: Hospitalizations, hospitalisation rates and ratio of hospitalisation rates by year and age group.

Year group	2016		2017		2018		2019		2020		2016–2020		2017 HRR ^b (95% CI)	2018 HRR ^b (95% CI)	2019 HRR ^b (95% CI)	2020 HRR ^b (95% CI)
	<i>n</i>	HR ^a	<i>n</i>	HR ^a	<i>n</i>	HR ^a	<i>n</i>	HR ^a	<i>n</i>	HR ^a	<i>n</i>	HR ^a				
<1 year	249	60.7	252	63.6	162	42.8	182	50.3	87	24.8	932	49.1	1.04 (0.88–1.24)	0.7 (0.58–0.86)	0.82 (0.68–1.00)	0.42 (0.32–0.52)
1–4 year	687	10.4	278	4.20	335	5.10	321	4.91	125	1.93	1746	5.33	0.40 (0.35–0.46)	0.49 (0.43–0.56)	0.47 (0.41–0.53)	0.18 (0.15–0.22)
5–9 years	379	15.4	264	10.8	236	9.88	227	9.69	141	6.10	1247	10.4	0.70 (0.60–0.82)	0.64 (0.54–0.75)	0.63 (0.53–0.74)	0.39 (0.32–0.48)
10–14 years	160	6.75	141	5.83	140	5.66	135	5.36	99	3.90	675	5.48	0.86 (0.69–1.08)	0.83 (0.66–1.05)	0.79 (0.63–0.99)	0.57 (0.45–0.74)
Total	1475	12.5	935	7.87	873	7.40	865	7.36	452	3.87	4600	7.80	0.63 (0.58–0.68)	0.59 (0.54–0.64)	0.59 (0.54–0.64)	0.31 (0.27–0.34)
<15 years																

Note: Spain, 2016–2020. Statistically significant values (*p* < 0.05) are highlighted in bold.

^aHospitalisation rate/10⁵.

^bHospitalisation rate ratio. Reference year 2016.

TABLE 2 | Meningitis of unknown origin in children under 15 years of age: Hospitalisations, hospitalisation rates and ratio of hospitalisation rates by year and age group.

Year group	2016		2017		2018		2019		2020		2016–2020		2017 HRR ^b (95% CI)	2018 HRR ^b (95% CI)	2019 HRR ^b (95% CI)	2020 HRR ^b (95% CI)
	n	HR ^a	n	HR ^a	n	HR ^a	n	HR ^a	n	HR ^a	n	HR ^a				
<1 year	188	45.8	211	53.24	123	32.5	141	39.0	61	17.4	724	38.2	1.16 (0.95–1.41)	0.70 (0.56–0.89)	0.84 (0.68–1.05)	0.37 (0.28–0.51)
1–4 years	288	4.37	102	1.54	126	1.92	92	1.41	25	0.39	633	1.93	0.35 (0.28–0.44)	0.43 (0.35–0.54)	0.32 (0.25–0.40)	0.08 (0.05–0.13)
5–9 years	208	8.44	128	5.25	104	4.36	84	3.59	31	1.34	555	4.65	0.62 (0.50–0.77)	0.51 (0.41–0.65)	0.42 (0.33–0.54)	0.16 (0.11–0.23)
10–14 years	59	2.49	61	2.52	45	1.82	43	1.71	23	0.91	231	1.88	1.01 (0.70–1.44)	0.73 (0.49–1.07)	0.68 (0.46–1.01)	0.34 (0.22–0.59)
Total <15 years	743	6.28	502	4.23	398	3.37	360	3.06	140	1.20	2143	3.64	0.67 (0.60–0.75)	0.53 (0.47–0.60)	0.48 (0.43–0.55)	0.19 (0.16–0.23)

Note: Spain, 2016–2020. Statistically significant values ($p < 0.05$) are highlighted in bold.

^aHospitalisation rate/ 10^5 .

^bHospitalisation rate ratio. Reference year 2016.

significantly exceeding the HR registered in older age groups (Table 2) ($p < 0.01$). For encephalitis-encephalomyelitis of unknown origin, 2457 hospitalisations were notified (overall HR: $4.17/10^5$), and the highest HR was also observed in children under 1 year of age (HR: $10.9/10^5$) (Table 3) which was statistically significantly higher than in all the other age groups ($p < 0.01$).

The meningitis, encephalitis and encephalomyelitis of unknown aetiology HR decreased from $12.5/10^5$ inhabitants in 2016 to $3.87/10^5$ inhabitants in 2020 (Table 1). Figure 1 illustrates the HR trends between 2016 and 2020. Hospitalisation rate ratios (HRR) showed a significant decrease between each year compared to 2016. The most marked decrease in HRR was observed in the age group of 1–4 years (HRR 2020 compared to 2016: 0.18 95% CI: 0.15–0.22), followed by the 5–9 years (HRR 2020 compared to 2016: 0.39; 95% CI: 0.32–0.48) and the <1 years (HRR 2020 compared to 2016: 0.42; 95% CI: 0.31–0.52). This decrease was largely attributed to changes in meningitis HR, dropping from $6.28/10^5$ in 2016 to $1.20/10^5$ in 2020 (HRR: 0.19 (95% CI: 0.16–0.23)) (Table 2). However, when examining encephalitis-encephalomyelitis specifically, the HR decreased from $6.18/10^5$ inhabitants in 2016 to $3.65/10^5$ in 2017, followed by an incremental increase through 2019 and a pronounced drop in 2020 to $2.67/10^5$, yielding a HRR: 0.43; 95% CI: 0.38–0.49. The major HRR decrease was again observed in the age group of 1–4 years (HRR 2020 compared to 2016: 0.25; 95% CI: 0.20–0.32) (Table 3).

The forecasting analysis revealed that the actual hospitalisation rates (HR) in 2020 for all entities were lower than predicted across all age groups, based on previous trends. Moreover, for infants under 1 year old and children aged 10–14 years, the actual HR fell below the lower confidence interval (Figure 1).

4 | Discussion

Our study demonstrates substantial declines in hospitalisation rates for paediatric encephalitis and meningitis of unknown origin in Spain from 2016 to 2020, with meningitis rates exhibiting a significant decrease from $6.28/10^5$ in 2016 to $1.20/10^5$ in 2020. The HRR analysis revealed consistent decreases across years, reaching its nadir in 2020 (HRR: 0.57, 95% CI: 0.45–0.74), representing a decrease of more than 70% in hospitalisations over the five-year study period. More specifically, meningitis hospitalisations decreased by 81%, while encephalitis hospitalisations showed a 57% reduction. Upon analysing the pre-pandemic period to mitigate the influence of the pandemic, the overall reduction was calculated at 40% (meningitis hospitalizations decreased by 52%, and encephalitis hospitalizations by 31%). These findings should be contextualised within the historical diagnostic challenges in CNS infections, as studies have shown that a significant proportion of cases remain undiagnosed—up to 64% of aseptic meningitis and between 27.5% and 79% of encephalitis cases [8, 22]. This high percentage of unknown aetiology has been gradually improving with the evolution of diagnostic methods, from basic testing to advanced techniques like PCR panels and metagenomics [23–26], though variations in diagnostic capabilities across different healthcare settings continue to influence reported rates.

TABLE 3 | Encephalitis and encephalomyelitis of unknown origin in children under 15 years of age: hospitalisations, hospitalisation rates and ratio of hospitalisation rates by year and age group.

Year group	2016		2017		2018		2019		2020		2017 HRR ^b (95% CI)	2018 HRR ^b (95% CI)	2019 HRR ^b (95% CI)	2020 HRR ^b (95% CI)
	n	HR ^a	n	HR ^a	n	HR ^a	n	HR ^a	n	HR ^a				
<1 year	61	14.9	41	10.3	39	10.3	41	11.3	26	7.41	0.69 (0.47–1.03)	0.69 (0.46–1.03)	0.76 (0.51–1.13)	0.49 (0.31–0.78)
1–4 years	399	6.05	176	2.66	209	3.18	229	3.50	100	1.55	0.43 (0.37–0.52)	0.52 (0.44–0.62)	0.58 (0.49–0.68)	0.25 (0.20–0.32)
5–9 years	171	6.93	136	5.58	132	5.53	143	6.11	110	4.76	0.80 (0.64–1.00)	0.79 (0.63–1.00)	0.88 (0.70–1.09)	0.68 (0.54–0.87)
10–14 years	101	4.26	80	3.31	95	3.84	92	3.65	76	3.00	0.77 (0.59–1.03)	0.90 (0.68–1.19)	0.86 (0.64–1.13)	0.70 (0.52–0.94)
Total	732	6.18	433	3.65	475	4.02	505	4.30	312	2.67	0.58 (0.52–0.66)	0.65 (0.59–0.73)	0.69 (0.62–0.78)	0.43 (0.38–0.49)
<15 years														

Note: Spain, 2016–2020. Statistically significant values ($p < 0.05$) are highlighted in bold.

^aHospitalisation rate/10⁵.

^bHospitalisation rate ratio. Reference year 2016.

Regarding demographic distribution, hospitalizations for meningitis or encephalitis in the paediatric population under 15 years of age constituted approximately one-quarter of all such hospitalizations across age groups. Age-stratified analysis revealed significantly higher rates in children under 1 year (49.1/10⁵ over the study period), while the 1–4 years age group showed the most pronounced decline (82% reduction between 2016 and 2020; 53% between 2016 and 2019). Our results align with data from other European countries reporting high incidence in infants (38.7/10⁵ in children younger than 6 months) and peak rates of 58.7/10⁵ just after birth [9]. Additionally, similar trends in incidence decline were observed in England [27], where viral meningitis rates among children aged 1–14 years decreased significantly from an average of 13.5/10⁵ during 1968–1985 to 5.2/10⁵ during 1989–2011, largely due to advancements in diagnostics and vaccination programmes. Interestingly, this decline was entirely restricted to children aged 1–14 years, while infants under 1 year exhibited stable or increasing rates during recent years. In fact, during the latter part of this period (2007–2011), infants accounted for 73% of all cases compared to only 11% during earlier decades (1968–1985). More recent data from England between 2013 and 2019 [28] showed that infants under 3 months had an incidence rate of viral meningitis as high as 504/10⁵, driven primarily by enteroviruses (84.9%), followed by parechoviruses and herpes simplex virus. These findings emphasise the biological vulnerability of young infants to first-time neurotropic viruses exposure, such as enteroviruses (EV) [18], and highlight how systematic screening protocols requiring lumbar punctures in febrile young infants improve case detection [8]. Again, the widespread implementation of syndromic molecular testing during recent years, especially the late 2010s, enables more detections and etiological diagnoses. This increased diagnostic capability likely explains part of the observed reduction in cases of unknown origin in our study.

Concerning encephalitis, our findings align with studies from Australia and the United States reporting similar encephalitis incidence rates of 4.17–7.3/10⁵ in children [29, 30]. After an initial decline (2016–2017), our data show steady rates through 2017–2019. The 2019 Global Burden of Disease Study similarly documented a reduction in the age-standardised incidence rate, mortality rates, and disability-adjusted life years rate for encephalitis over the last 30 years [5]. However, this decline reached an inflection point during 2011–2013 and subsequently plateaued. Several complex factors contribute to this observed trend: climate change affecting vector-borne transmission patterns, the emergence of new pathogens (particularly EV-A71 and West Nile virus), and the increasing utilisation of immunosuppressive therapy in medical treatment [31, 32]. Upon examination of trends across different settings, variations emerge due to local epidemiological patterns, differences in diagnostic capabilities between healthcare systems and distinct viral circulation patterns [27, 33, 34].

Notably, hospitalisation rates reached their lowest levels across all groups in 2020, coinciding with COVID-19 non-pharmaceutical interventions. This reduction mirrors findings from other studies documenting dramatic decreases in invasive infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*, all of which share respiratory transmission routes [35]. Similarly, viral diseases such as respiratory syncytial virus and influenza saw marked

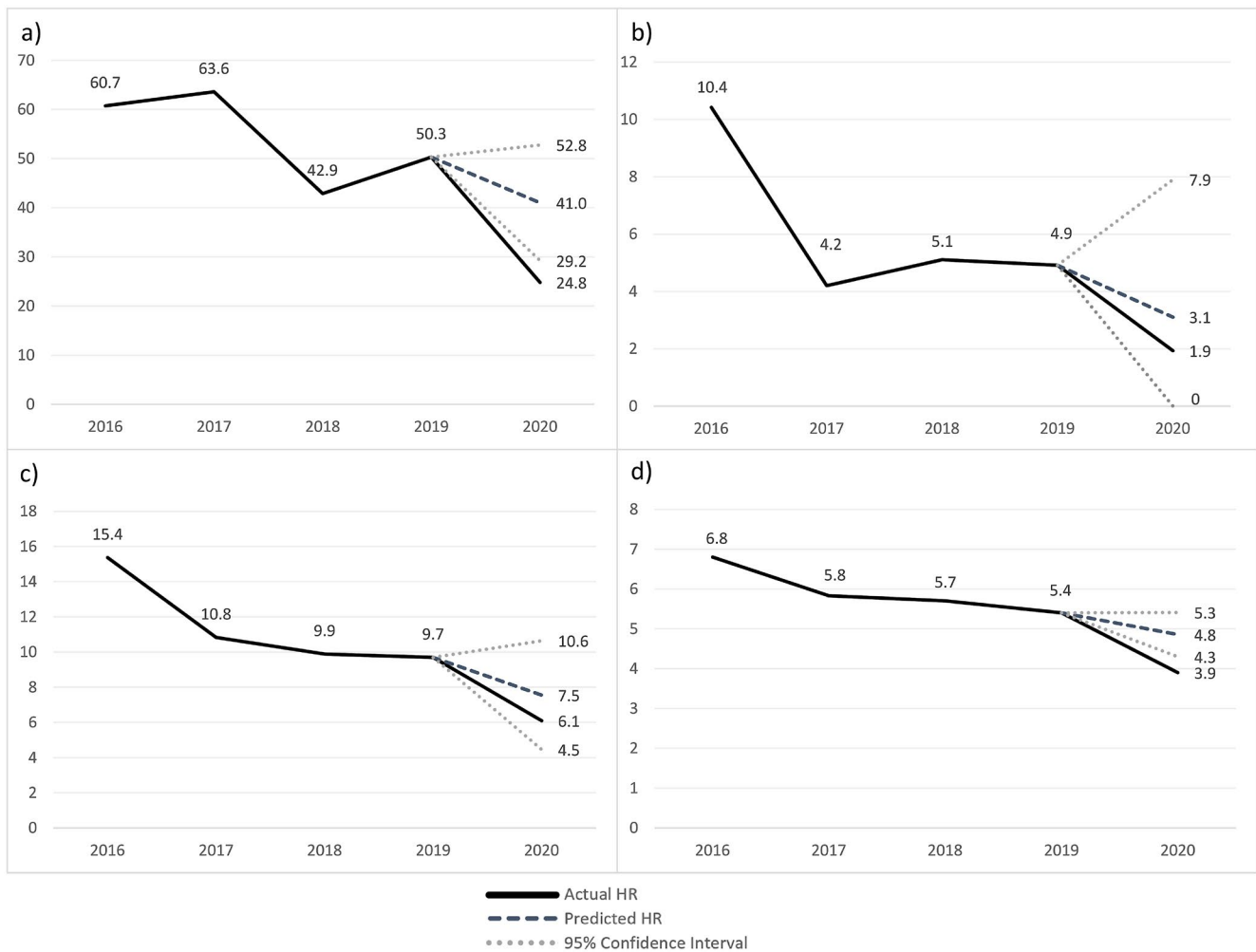


FIGURE 1 | Forecasting hospitalisation rates in Spain for paediatric meningitis and encephalitis-encephalomyelitis of unknown origin by age group in 2020. (a) < 1 year (b) 1–4 years (c) 5–9 years (d) 10–14 years.

declines during this period [36]. The implementation of school closures significantly contributed to this decline by limiting transmission opportunities among children, while broader containment measures provided additional protection against various infectious agents. However, it is important to note that our study's endpoint in 2020 precludes us from analysing potential rebounds following the lifting of COVID-19 restrictions. In England, for instance, a significant increase in paediatric viral meningitis post-pandemic has been reported (from $1.8/10^5$ during restrictions to $4.2/10^5$ after restrictions were lifted) [28]. In our opinion, the marked reduction observed during the pandemic period highlights significant opportunities for improving diagnostic capabilities in cases of CNS infections that currently lack clear diagnoses. Particularly, advances in metagenomics technology, along with better methods for diagnosing immune-mediated encephalitis that mimics viral CNS infections, should help increase the proportion of patients who receive definitive etiologic diagnoses [26, 33].

Several limitations merit consideration in our study. First, the use of ICD-10 codes for case identification presents inherent challenges in classification accuracy. While we carefully selected codes that indicate unspecified or incompletely characterised aetiology, some codes (particularly A87.8) could

potentially include cases where partial etiological information exists. Our inclusive approach might have captured some cases where the pathogen was partially characterised, though not definitively identified. Second, variations in coding practices across different hospitals and regions could affect case classification. This is particularly relevant for codes like A87.8 versus G03.8, where the distinction between “other specified” and “unspecified” causes might be interpreted differently across institutions. Third, our study's focus on cases with suspected viral aetiology might underestimate the total burden of central nervous system infections of unknown origin, as some cases might be coded under more general categories. However, this approach enhances specificity in tracking cases where viral aetiology is suspected but unconfirmed, aligning with our primary research objective. Finally, while the Spanish Hospitalisation Registry provides comprehensive coverage, changes in diagnostic capabilities and coding practices over the study period might influence temporal trends. Nevertheless, these limitations are inherent to large-scale epidemiological studies using administrative data and do not substantially impact our main findings regarding age-related differences and epidemiological trends.

In conclusion, while paediatric meningitis and encephalitis remain significant concerns in Spain, our findings demonstrate

important epidemiological shifts. The implementation of advanced surveillance systems incorporating molecular diagnostics will be essential for future disease management [30]. Future research should focus on identifying specific etiological agents and optimising intervention strategies, particularly in the context of evolving diagnostic capabilities and changing patterns of disease transmission.

Author Contributions

Marina Pons-Espinal: conceptualization, data curation, investigation, writing – review and editing, writing – original draft. **Noemi López-Perea:** writing – review and editing, methodology, data curation, validation, formal analysis, investigation, writing – original draft, conceptualization. **Josefa Masa-Calles:** methodology, data curation, formal analysis, writing – review and editing, conceptualization. **Carmen Muñoz-Almagro:** conceptualization, investigation, writing – review and editing. **David Tarragó:** investigation, methodology, writing – review and editing, project administration, funding acquisition. **Cristian Launes:** writing – review and editing, writing – original draft, investigation, methodology, formal analysis, supervision, project administration, funding acquisition.

Ethics Statement

This study involves the use of patient medical data from the NHR-CMBD. These data are hosted by the Spanish Ministry of Health. Researchers working in public and private institutions can request the databases by completing, signing, and sending a questionnaire available on the Ministry website. In this questionnaire, a signed confidentiality commitment is required. According to this confidentiality commitment, researchers cannot provide the data to other researchers, who must request the data directly from the Ministry. All data are anonymized and de-identified by the Ministry before being provided to applicants. Thus, no ethical approval or informed consent was required by the Spanish human research act to conduct this data analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

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